NSAID complications
the balance of risks

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Promotor: Prof. dr. M.A.F.J. van de Laar
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Aan mijn ouders
Aan Daniëlle en Erik

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and associated treatment complications:

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Harald E Vonkeman, Mart A F J van de Laar

Submitted for publication

THE AGE OF ASPIRIN

The use of non-steroidal anti-inflammatory substances predates the dawn of modern medicine. The earliest known references to the medicinal use of myrtle and willow tree bark, original sources of aspirin-like compounds, can be traced back to the ancient Egyptians. The application of willow tree bark for stiff and painful joints is recommended in Ebers papyrus, a comprehensive one hundred and ten page medical text, containing 877 treatises on various physical, mental and spiritual diseases, which is dated to the reign of Amenhotep I around 1534 BC.[1] Hippocrates of Cos (460-377 B.C.), who had spent several years in Egypt studying medicine, also noted that chewing the bitter leaves of the willow tree reduces pain, and he recommended this remedy for women in labour. Subsequent ancient Greek physicians recommended willow tree preparations, especially from the inner bark, for alleviating pain, fever and inflammation.[1-4]

Advocates of the Doctrine of Signatures attributed the healing force of nature to Divine Providence, which often placed the cure next to the malady and left clues for its discovery. Christian metaphysics expanded this early european philosophy in theology. According to the Christian version, God had so set his mark upon Creation, that by careful observation one could find all right doctrine represented and even learn the uses of a plant from some aspect of its form or place of growing.[5] The willow tree grows in damp regions where fever (possibly malaria) was endemic and the flexibility of its "weeping" branches might suggest a further effect in reducing stiffness and inflammation of joints.[2] As late as 1763 AD, the reverend Edward Stone, a vicar from Chipping Norton in Oxfordshire, England, in following the Doctrine of Signatures successfully treated fever in fifty patients using "twenty grains (1 gram) of powdered willow bark in a dram of water every four hours". In a letter to the Earl of Macclesfield, then president of the Royal Society in London, he subsequently presented the first scientific description of the effects of willow bark. However, the report was regretfully attributed to the mathematician Edmund Stone, due to a misprint.[6]

The following one hundred years brought the industrial revolution and in its wake the birth of modern pharmaceutical medicine. In 1828 Johann Andreas Buchner first isolated salacin from willow bark. It was named after its source (Salix alba; the white willow), and was also discovered in other Salicaea, such as poplars and aspens.[1,3] In 1838 Raffaelle Piria treated salacin to yield salicylic acid, which was also found to occur naturally in some species of Spiraea (Spiraea ulmaria; meadowsweet). Salicylic acid was found to possess profound medicinal properties and soon became a panacea despite causing severe gastric irritation, bleeding and diarrhea.[2] In 1853 a French chemist called Charles Frederic Gerhardt managed to buffer salicylic acid to make it less gastrotoxic, a discovery that remained obscure for nearly 50 years. In 1857 Hammond Kolbe discovered how to synthesise salicylic acid de novo, and salicylic acid could subsequently be produced on an industrial scale by 1874.[1,3]

Meanwhile, in 1863 Friedrich Bayer and Friedrich Weskott had founded a dye manufacturing company in Wuppental-Barmen. In 1886, the Bayer company started producing phenacetin from dye manufacturing by-products. Phenacetin was the first real analgesic to be marketed and Bayer's pharmaceutical branch would eventually become the company's core business.[7] Phenacetin use however proved to be associated with increased risk of death due to urologic or renal disease and cancers, and its use was temporarily banned, but is restrictedly allowed at present. In 1948 paracetamol was discovered to be phenacetin's major metabolite.[8]

In 1899, a German chemist working for the Bayer company called Felix Hoffmann, rediscovered and perfected Gerhardt's formula for acetylating salicylic acid. After trying the result on his father who was suffering from arthritic pain, Hoffmann convinced Heinrich Dreser, head of Bayer's pharmacological Division, to conduct animal experiments to establish the drug's analgesic and anti-inflammatory properties, properties which were confirmed by subsequent tests on patients at the Deaconess Hospital in Halle an der Saale.[9] Acetyl salicylic acid, the world's first truly synthetic drug, was patented on March 6, 1899 and was called Aspirin; "A" from Acetyl, "spir" from spiraea ulmaria, and "in" as a then typical name-ending for medicines.[10] Heinrich Dreser was initially reluctant to support aspirin, preferring to push another of Hoffmann's discoveries. As it happened, 11 days after discovering aspirin, in an attempt to manufacture codeine, again by acetylation Hoffmann produced a potent acetylated synthetic of morphine, which Bayer called heroin, after the "heroic" feeling it induced in volunteering Bayer employees.[1] Aspirin and heroin were initially marketed side by side, heroin being the more successful painkiller, and commonly believed to be the healthier of the two. Heroin found a large market share as a supposedly non-addictive morphine substitute and as children's cough remedy. By 1899, Bayer was producing a ton of heroin yearly, with exports to 23 countries. Eventually in 1913, heroin's obvious addictiveness and a sharp increase in heroin related hospitalisations caused Bayer to end production. Recreational use however continued to expand. Supposedly, the term "junky" was coined to describe recreational heroin users who financed their addition by selling scrap (junk) metal.

As aspirin became ever more popular, Bayer opened a production plant in Albany, New York, in 1903. As a first example of mass marketing of a pharmaceutical product, Bayer energetically promoted the drug to more than 30,000 doctors and also introduced the concept of celebrity endorsement by recruiting Caruso and Kafka, the latter claiming that aspirin "eased the unbearable pain of being".[7] At first aspirin was relatively expensive, being sold as a powdered drug only, available over the counter from 1911, but cheaper mass produced aspirin tablets were introduced in 1915. From 1914 through 1916, pending the 1917 loss of patent, Bayer introduced aggressive direct to consumer marketing to establish the brand name, but U.S. sales collapsed when the U.S. entered the first World War and Bayer was accused of secretly attempting to poison the American people. Under the "Trading with the Enemy" Act, Bayer US was sold for $ 5.31 million to Sterling Products, a company that would ultimately be acquired by Bayer in 1994.[1] In the interim however, the U.S. trademark was lost after a 1921 U.S. federal court ruled "aspirin" a genericized trademark. None the less, aspirin continued generating huge revenues. In 1940 Bayer aspirin sold approximately 100 million DM a year, in 1990 800 million, while current estimates approximate € 2 billion a year. The Aspirin Foundation states that annual production is approximately 35,000 metric tonnes, equivalent to over 100 billion standard aspirin tablets every year, and that since it was patented a trillion (a million billion) tablets have been consumed.[11]

However, aspirin's inventor Felix Hoffmann reaped little rewards. The German patent office had refused to patent aspirin in 1900, considering the industrial process to be insufficiently novel. Hoffmann's contract with Bayer stated that royalties would only be paid on patented products, and therefore he received none. Conversely, Heinrich Dreser's contract stated payment of royalties on marketed products, allowing him to retire early a rich man.[3]

Aspirin's road to pharmaceutical glory was interrupted by a 1938 publication in the Lancet by Douthwaite and Lintott, who used rigid endoscopy to demonstrate aspirin induced gastric damage in

a series of patients.[12] Concern was raised further by subsequent reports on increased bleeding during aspirin use. However, aspirin's emergent side effects were soon to be overshadowed by a huge unexpected benefit; inhibition of platelet aggregation. In the late 1940s, Lawrence L. Craven, a general practitioner from Glendale, California, observed increased bleeding in children who chewed aspirin-gum after tonsillectomy. Craven inferred aspirin to be an effective prophylaxis of cardiovascular events and started prescribing an aspirin a day to overweight middle-aged men with sedentary lifestyles and also to patients who had recovered from previous heart attacks. After having treated nearly 8000 patients, and noting not a single heart attack or stroke among them, Craven recommended aspirin as "a safe and effective method of preventing coronary thrombosis".[13] His recommendations were largely ignored by the medical profession, partly because they were published in rather obscure medical journals, such as the Mississippi Valley Medical Journal. In 1968 O'Brian showed aspirin to inhibit human platelet aggregation,[14] and in 1974 systematic data showed that aspirin use was associated with a reduction in myocardial infarction and stroke,[15] but it would not be until the 1980s that the U.S. Food and Drug Administration (FDA) would finally endorse Craven's recommendation.[1]

A NOBEL MODE OF ACTION

While aspirin's analgesic, anti-pyretic and anti-inflammatory properties had been well recognized by the beginning of the 20th century, it's mode of action remained obscure until the 1970s. Several pieces of the puzzle were still missing. In 1935 the eminent Swedish physiologist Ulf von Euler, and independently the British pharmacologist M.W. Goldblatt, had isolated prostaglandin from seminal fluid.[16,17] Although in actuality produced in the seminal vesicles, prostaglandin was initially thought to be a prostatic secretion and thus acquired its name. In 1945 von Euler met the young biochemist Sune Bergström at a meeting of the Physiological Society of the Karolinska Institute in Stockholm, Sweden, and asked if he might be interested in studying some of his lipid extracts of sheep vesicular glands.[18] Bergström purified the crude extract and in 1957, with his graduate student Bengt Ingemar Samuelsson, was able to isolate small amounts of prostaglandin E_1 and prostaglandin F_1. By 1962, Bergström and Samuelsson had isolated and determined the structure of six different prostaglandins. They showed that the rapidly metabolized prostaglandins act locally and are involved in many processes that cause inflammation after injury or illness, affect constriction and relaxation of blood vessels, regulate the constriction of the uterus, and help to clot blood. Some unusual features were found, namely that the same prostaglandins may act differently in different tissues, and that prostaglandins often come in pairs with opposite actions. Bergström and Samuelsson went on to demonstrate how prostaglandins were produced in the body from essential fatty acids; gamma-linolenic acid, arachidonic acid, and eicosapentaenoic acid. Progress was slow, as prostaglandins were in limited supply and their production time consuming. Fortunately, Bergström's efforts were greatly enhanced by a generous mode of international collaboration.[19] In the early 1960s David van Dorp and Henk Vonkeman working at Unilever Research Laboratories in The Netherlands had elucidated the biosynthesis of prostaglandins from their essential fatty acid precursors, findings which they agreed to share and simultaneously publish with Bergström in 1964.[20,21]
In 1971, Sir John Robert Vane, then at the Royal College of Surgeons in London and not yet Sir, showed that aspirin-like compounds act by the inhibition of the production of prostaglandins.[22] For this discovery he shared the 1982 Nobel Prize in Physiology or Medicine with Bergström and Samuelsson,

and received his subsequent knighthood. Essentially, in humans arachidonic acid is mobilized from cell-membrane glycerophospholipids by phospholipase A_2. The subsequent biotransformation of arachidonic acid is catalyzed by prostaglandin G_2/H_2 synthase, resulting in the sequential formation of prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2) via the cyclooxygenase (COX) activities of the protein. Additional tissue specific prostaglandin synthases subsequently convert PGH_2 into other prostaglandins and thromboxane, each with different functions in different tissues. For example, PGD_2 is involved in sleep regulation and allergic reactions, PGF_2 controls the contraction of the uterus during birth and menstruation, thromboxane A_2 (TXA_2) stimulates the constriction of blood vessels and induces platelet aggregation, prostacyclin (PGI_2) dilates blood vessels, inhibits platelet aggregation and may protect against damage to the stomach lining, and prostaglandin E_2 (PGE_2) is involved in pain, inflammation and fever and also protects against damage to the stomach. John Vane and ensuing researchers demonstrated that by blocking the COX enzyme and consequently inhibiting the biotransformation of arachidonic acid into prostaglandin H_2, aspirin effectuates its analgesic, anti-pyretic and anti-inflammatory properties while conversely causing gastric damage and increased bleeding.[23,24]

NON STEROIDAL ANTI-INFLAMMATORY DRUGS

In 1959 John Nicholson from the Boots Company had, in collaboration with Stuart Adams, synthesized a drug with analgesic, anti-pyretic and anti-inflammatory properties similar to aspirin. The drug was named ibuprofen and was marketed in 1969 under the brand name Brufen, despite performing no better than placebo in an initial clinical trial among 18 rheumatoid arthritis patients.[25,26] Ibuprofen would however prove to be one in a long series of very successful non-aspirin, non steroidal-anti-inflammatory drugs (NSAIDs). Currently, approximately 50 different NSAID preparations are available and, as a class, they are among the most commonly prescribed drugs world-wide. NSAIDs may be grouped as salicylates (with as prominent member aspirin itself), arylalkanoic acids (diclofenac, indometacine, nabumetone, sulindac), 2-arylpropionic acids or profens (ibuprofen, flurbiprofen, ketoprofen, naproxen), N-Arylanthranilic acids or fenamic acids (Mefenamic acid, Meclofenamic acid), pyrazolidine derivates (phenylbutazone), oxicams (piroxicam, meloxicam), sulphonanilides (nimesulide), and others. As a group, NSAIDs are structurally diverse and differ in pharmacokinetic and pharmacodynamic properties, but ultimately share the same mode of action. Like aspirin, non-aspirin NSAIDs inhibit the production of prostaglandins by blocking the COX enzyme, causing analgesic, anti-pyretic and anti-inflammatory benefits, but at a risk for increased gastric bleeding.[27]

However, aspirin and non-aspirin NSAIDs differ fundamentally in the way the COX enzyme is inhibited. Aspirin inhibits COX by non-competitive and irreversible acetylation, where an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme, rendering the COX enzyme permanently inaccessible for the biotransformation of arachidonic acid into prostaglandin H_2. Conversely, non-aspirin NSAIDs competitively and reversibly inhibit the COX enzyme during only part of their dosage interval. This distinction is exemplified by their differential effects on platelet aggregation. Blood platelets, unlike inflammatory cells, have no cellular nucleus and are therefore unable to newly synthesize COX. Aspirin will irreversibly block all COX on blood platelets, permanently preventing the production of thromboxane A_2 and subsequently inhibiting platelet aggregation for the duration of the platelets' life-cycle, making aspirin a potent cardiovascular protective agent. Conversely, as a result of their competitive reversible

binding of the COX enzyme, non-aspirin NSAIDs do not provide significant long-term inhibition of blood platelet aggregation.

THE COX-2 HYPOTHESIS

The suggestion of distinct isoforms of the COX enzyme, with differing sensitivities to NSAIDs, had been around for some time when in 1989 Phillip Needleman identified a second cyclooxygenase isozyme; COX-2.[28] Apparently, COX-1 was constitutionally present in low abundance in most human tissues, acting as a housekeeping enzyme by regulating normal physiological processes such as the maintenance of gastric mucosal integrity, kidney function and platelet aggregation. Conversely, COX-2 was undetectable in most tissues under normal physiological circumstances, and was selectively upregulated after exposition to inflammatory mediators or trauma, causing subsequent inflammatory responses and mediation of pain. If this "COX-1 good, COX-2 bad" hypothesis were true, then a COX-2 selective NSAID would be an ideal drug, with analgesic, anti-pyretic and anti-inflammatory benefits without gastric or other side effects.

In the early 1990s, X-ray crystallography clarified the COX three dimensional structure, showing a long narrow channel, ending in a hairpin bend.[29,30] Both COX isozymes are membrane-associated and internalise adjacent arachidonic acid which is released when membrane damage occurs. Arachidonic acid is bound high within the COX enzyme and is biotransformed via prostaglandin G_2 into prostaglandin H_2, which is a subsequent substrate for other cell and tissue specific terminal enzymes, such as prostacyclin synthase which produces prostacyclin, thromboxane synthase which produces thromboxane, and glutathione S-transferase for the conversion to prostaglandin E_2. Most non-aspirin NSAIDs inhibit prostaglandin G_2/H_2 synthase by blocking both COX-1 and COX-2 isozymes halfway up their channel by binding an arginine molecule at position 120, thereby inhibiting access of arachidonic acid to the catalytic site and thus ultimately inhibiting the synthesis of prostaglandin, prostacyclin and thromboxanes. The NSAID binding at the arginine 120 site is competitive and reversible, the extent and duration of COX inhibition depends on the drugs half-life and concentration. COX-1 and COX-2 share the arginine 120 site but differ with respect to position 523. In COX-1, position 523 is taken up by a bulky isoleucine molecule, while a smaller valine molecule at the same position in COX-2 leaves room for a gap, or side-pocket, in the channel's wall.[31] It was this side-pocket that provided the target for COX-2 selective NSAIDs. Specifically, rather bulky NSAIDs with a rigid side-extension that would bind within the side-pocket would be able to access and block COX-2 but not the narrower COX-1 enzyme. Also, the COX-2 selective covalent binding within the COX-2 side pocket would be semi-irreversible, thus lastingly inhibiting access of arachidonic acid to the catalytic site.[32] A number of pharmaceutical companies tested and developed this hypothesis and by 1995 the first generation of COX-2 selective NSAIDs entered clinical trials, with celecoxib (Celebrex®) and rofecoxib (Vioxx®).

NSAID INDUCED GASTRODUODENAL TOXICITY

NSAIDs are effective analgesic, anti-pyretic and anti-inflammatory drugs, especially in arthritic diseases. However, their use is limited by serious side effects, most common of which is gastroduodenal toxicity. The spectrum of NSAID related gastroduodenal toxicity may be categorised into three groups: (i) subjective symptoms like heartburn, dyspepsia, nausea, and abdominal pain are most common, occurring

in 15-40% of NSAID users and causing 10% to change or discontinue their NSAID use; (ii) superficial gastroduodenal mucosal lesions such as erosions and asymptomatic ulcers occur in 5-20% of NSAID users, and may heal spontaneously; (iii) serious gastroduodenal ulcers with life-threatening complications like perforation, symptomatic ulcers and bleeding (perforation, ulcer, bleeding; PUB) occur in 1-2% of chronic NSAID users, with an associated mortality rate of 10-15%.[33,34,35]

Although topical gastroduodenal injury may occur, post-absorptive inhibition of gastrointestinal COX probably plays a more central role in the pathogenesis of NSAID associated gastroduodenal ulcers. By inhibition of gastric COX, NSAIDs may reduce mucosal blood flow, causing local ischaemic injury. NSAIDs may also impair specific prostaglandin-dependent defences which protect the gastric mucosa, such as the thick bicarbonate containing mucous layer lining the interior of the stomach, which buffers luminal gastric acid and thus protects the stomach wall. When these defences have been weakened by NSAID inhibition of gastrointestinal COX-1, a second wave of injury caused by luminal gastric acid may facilitate deeper ulceration, bleeding and even perforation of the stomach wall.[36] Strategies aimed at preventing NSAID-gastropathy either help to maintain the integrity of the stomach wall and mucous lining, such as the use of COX-2 selective NSAIDs and the concomitant administration of prostaglandin analogues, or alternatively inhibit the secretion of gastric acid, such as concomitant histamine H2-receptor antagonists or proton-pump inhibitors.

Multiple studies have identified additional risk factors for the development of NSAID ulcers. Assessment of these risk factors is recommended for identifying patients who should be considered for ulcer prophylaxis.[37] Risk factors include; a prior history of gastrointestinal events (increases risk 4 to 5-fold), patient's age over 60 years (risk 5 to 6-fold), high dosage of NSAID (risk 10-fold), concomitant use of corticosteroids (risk 4 to 5-fold), anti-coagulants (risk 10 to 15-fold), aspirin, platelet inhibitors, and serotonin reuptake inhibitors (risk 12 to 15-fold), infection with Helicobacter pylori, and co-morbid conditions such as diabetes mellitus, heart failure and rheumatoid arthritis.[38] Several studies have ranked commonly prescribed NSAIDs for their relative gastrointestinal toxicity. The risk for gastrointestinal complications appears highest with indomethacin, followed by naproxen, diclofenac, piroxicam, tenoxicam, ibuprofen, and meloxicam.[39] The risk is also related to the duration of treatment.

THE ROLE OF HELICOBACTER PYLORI INFECTION

In the early 1980s, at a time that prevailing dogma stated "no acid, no ulcer", the Australian pathologist John Robin Warren observed the presence of proliferating bacteria on the gastric mucosa from mucosal biopsies and established its close relationship to active chronic gastritis. In 1982 a young gastroenterology fellow, Barry Marshall, successfully collaborated with Warren and cultured and classified the gastric pathogen as an S-shaped campylobacter-like organism, now known as Helicobacter pylori.[40,41] In fulfilling Koch's third and forth postulates, Marshall demonstrated that the bacteria could colonize normal mucosa and induce gastritis by ingesting an inoculum of H. pylori.[42] He duly developed acute gastritis, which was endoscopically and histologically confirmed 10 days later, after which he easily treated himself. The further association of H. pylori with peptic ulceration, and possibly with gastric adenocarcinoma, was first suggested by Marshall.[40] For their discovery Warren and Marshall were awarded the 2005 Nobel Prize in Physiology or Medicine.

The interaction between H. pylori and the use of NSAIDs in the development of gastroduodenal ulcers

is less clear. H. pylori infection and NSAID use may represent independent, but synergistic risk factors.[43,44] A recent meta-analysis of 21 studies which evaluated the relationship between H. pylori and NSAIDs in the development of gastroduodenal ulcers found that the risk for uncomplicated ulcers was four times as high in H. pylori positive compared with H. pylori negative patients, irrespective of NSAID use (odds ratio 4.03), and three times as high in NSAID users compared with non-users, irrespective of H. pylori status (odds ratio 3.10). Furthermore, the risk of uncomplicated ulcers was almost twice as high among H. pylori positive compared with H. pylori negative NSAID users (odds ratio 1.81), and 17.5 times higher among H. pylori positive NSAID users compared with H. pylori negative non-users.[44] Possible explanations for the increased risk of ulcers in H. pylori positive NSAID users are deterioration of the mucosal barrier caused by inflammation, increased acid secretion, a higher level of apoptosis in the infected mucosa, and decreased gastric adaptation to NSAIDs.[45]

Whether eradication of H. pylori prior to, or during, NSAID treatment can reduce the risk of gastroduodenal ulcers has yet to be determined. Several studies have addressed these issues but results are inconsistent.[46-50] In a study by Francis Chan, 100 H. pylori positive patients without previous exposure to NSAIDs and no pre-existing ulcers on endoscopy were randomized to naproxen 750 mg per day for 8 weeks or to a one-week course of triple therapy for H. pylori, followed by naproxen treatment. H. pylori eradication was successful in 89% in the eradication group, and 0% in the naproxen group. At repeated endoscopy after 8 weeks, 7% in the H. pylori eradication group and 26% in the naproxen-only group had ulcers ($p=0.01$). In the eradication group, 2 out of the 3 patients with ulcers had failure of H. pylori eradication.[46] In a second study by the same authors, 100 NSAID-naïve patients with a positive urea breath test, dyspepsia, or an ulcer history were randomized to omeprazole triple therapy or omeprazole with placebo for 1 week, and subsequent diclofenac slow release 100 mg per day for 6 months, followed by endoscopy. H. pylori was eradicated in 90% in the eradication group, and 6% in the placebo group. The 6-month probability of endoscopic ulcers was 12% in the eradication group and 34% in the placebo group ($p=0.009$). The 6-month probability of complicated ulcers was 4% in the eradication group and 27% in the placebo group ($p=0.003$).[47] In a third study, 660 H. pylori positive patients without previous or current ulcers received diclofenac 50 mg BID for 5 weeks and were randomized to 1 of 4 strategies; triple therapy for 1 week followed by placebo for 4 weeks, triple therapy for 1 week followed by omeprazole 20 mg per day for 4 weeks, omeprazole 20 mg per day for 5 weeks, or placebo for 5 weeks. At repeated endoscopy, all 3 active therapies were equally effective in reducing the occurrence of NSAID ulcers as compared with placebo ($p<0.05$).[48] In this study, lack of significant difference between the active therapy groups might have been due to the overall low incidence of ulcers (6% in the placebo group) and the short study duration. In a study by Chris Hawkey, 285 H. pylori positive NSAID users with current or previous ulcers or with dyspepsia were randomized to omeprazole triple therapy or omeprazole with placebo for 1 week. All patients were subsequently treated with omeprazole 20 mg daily for another 3 weeks, at which time ulcer healing was endoscopically confirmed. NSAID use was continued throughout the study and endoscopy was repeated at 3 and 6 months. Patients in both groups were equally likely to remain ulcer free at 6 months (56% on placebo and 53% on triple therapy), and time to treatment failure also did not differ. Unexpectedly, fewer baseline gastric ulcers healed among patients who underwent H. pylori eradication.[49] In a study by de Leest, 347 H. pylori positive long-term NSAID users were randomized to omeprazole triple therapy or placebo for 1 week. NSAID use was

continued throughout the study and 48% were on concomitant gastroprotective medication. At endoscopy after 3 months, 4% in the H. pylori eradication group and 5% in the placebo group had ulcers (p=0.65). During 12 months follow-up no symptomatic ulcers or ulcer complications occurred.[50] In this study, lack of significant difference between the active therapy and placebo groups might again have been due to the overall low incidence of ulcers.

The role of H. pylori seems to be different in NSAID-naïve patients than in those on long-term NSAID treatment. In NSAID-naïve patients, H. pylori increases the risk for ulcers, whereas in long-term NSAID users, ulcers occur irrespective of H. pylori status. Epidemiological studies have shown that the risk for ulcers is substantially increased during the first months of NSAID therapy. Possibly this excess risk occurs in a susceptible subgroup of H. pylori positive patients.[47] These susceptible H. pylori patients will likely discontinue their NSAID use, creating a population of those who can tolerate long-term NSAID treatment irrespective of their H pylori status. Consequently, eradication of H pylori does not affect the ulcer risk in patients who are already on long-term NSAIDs. However, H. pylori eradication prior to NSAID therapy might lower the ulcer risk in NSAID-naïve patients.

Current recommendations regarding H. pylori testing and treatment in patients requiring NSAIDs are that patients with a history of gastroduodenal ulcers should be tested for H. pylori prior to starting NSAID or aspirin therapy, and if present H. pylori should be eradicated. In asymptomatic patients with no ulcer history and not currently taking NSAIDs, physicians may consider H. pylori testing prior to starting long-term NSAID therapy. It is possible that successfully H. pylori eradication in such individuals will reduce the risk of NSAID-related ulcer complications. This "test-and-treat" approach may be more effective in populations with high prevalence of H. pylori infection.

PREVENTION OF NSAID GASTRODUODENAL TOXICITY

When reviewing the evidence for gastroprotective strategies in NSAID users, one has to make several distinctions. Firstly, efficacy may be proven for the prevention of subjective symptoms, for endoscopic ulcers, or for serious NSAID ulcer complications such as ulcer perforation and bleeding (PUBs). The prevention of subjective symptoms, such as dyspepsia and abdominal pain, is very relevant to clinical practice as it affects up to 40% of NSAID users and may influence adherence to NSAID therapy.[51] However, in NSAID users the occurrence of subjective symptoms is poorly correlated with the development of gastroduodenal ulcers. Most NSAID users with subjective symptoms have no endoscopic gastroduodenal damage, while up to 58% of patients who present with life threatening NSAID ulcer complications do not have prodromal symptoms.[52]

Many gastroprotective strategies have proven efficacy for the prevention of endoscopic ulcers. However, most endoscopic ulcers cause neither symptoms nor complications and may heal spontaneously, even during continued NSAID use. The clinically relevant target for gastroprotective strategies is therefore the prevention of serious NSAID ulcer complications (PUBs), as these are associated with significant morbidity, mortality and costs.[53] Conversely, one may argue that an endoscopic ulcer is an intermediate in the causal chain from NSAID use to PUBs. In that case, the prevention of endoscopic ulcers may be viewed as a pseudo-outcome for the prevention of PUBs. However, none of the preventive strategies entirely eliminates the risk for endoscopic ulcers and one may postulate that it is exactly these remaining ulcers that may perforate and bleed. In that case, the extrapolation of efficacy in preventing endoscopic ulcers to

preventing PUBs may be a fallacy. Efficacy for the prevention of serious NSAID ulcer complications has only been directly proven for a few strategies, as PUBs are relatively rare, making the necessary studies very large and expensive.

A second distinction to be made is the difference between primary and secondary prevention of NSAID ulcers. Primary prevention concerns the prevention of NSAID ulcers in all patients starting on NSAID therapy, or in those using NSAID therapy who have not had previous NSAID ulcers. Secondary prevention concerns the prevention of recurrent NSAID ulcers in those with a (recent) history of NSAID ulcers. Some of the studies proving the efficacy of gastroprotective strategies in preventing PUBs have been secondary prevention studies. Patients with a history of NSAID ulcers are by definition high risk patients. Extrapolation of results from secondary prevention studies to the primary prevention of NSAID ulcers may overestimate efficacy and underestimate costs.

PRIMARY PREVENTION OF NSAID ULCERS

NSAID induced depletion of local endogenous gastrocytoprotective prostaglandins may be reversed by co-administration of prostaglandin E analogues such as misoprostol. Concomitant use of misoprostol has been shown to decrease both the risk for endoscopic NSAID ulcers and for serious NSAID ulcer complications. In one large study, 8,843 elderly NSAID using rheumatoid arthritis patients were randomized to misoprostol 200 µg four times daily or placebo for 6 months.[36] Serious NSAID ulcer complications (perforation, gastric outlet obstruction, bleeding) were reduced by 40% (odds ratio 0.598, 95%CI 0.364 to 0.982, P=0.049, absolute risk reduction 0.57%, number needed to treat 175) among patients receiving misoprostol compared with those receiving placebo. However, during the first month of treatment more patients receiving misoprostol (20%) than placebo (15%) withdrew from the study, primarily because of diarrhea and abdominal discomfort. Other studies have demonstrated that efficacy and side effects of misoprostol are dose dependent. In one study, 1200 long-term NSAID users were randomized to one of four regimens; placebo four times daily, 200 µg of misoprostol twice daily and placebo twice daily, 200 µg of misoprostol three times daily and placebo once daily, and 200 µg of misoprostol four times daily, with upper gastrointestinal endoscopy for ulcers at 4, 8 and 12 weeks.[54] The incidence of gastric ulcers was 15.7% with placebo, 8.1% with 400 µg of misoprostol, 3.9% with 600 µg, and 4% with 800 µg. The incidence of duodenal ulcers was 7.5% with placebo, 2.6% with 400 µg of misoprostol, 3.3% with 600 µg, and 1.4% with 800 µg. Withdrawal due to adverse events was 20% with 800 µg of misoprostol, compared to 12% with 400 or 600 µg. In a 2002 Cochrane systematic review, all doses of misoprostol significantly reduced the risk of endoscopic NSAID ulcers.[55] Misoprostol 800 µg/day was superior to 400 µg/day for the prevention of endoscopic gastric ulcers, while a dose response relationship was not seen for duodenal ulcers. Misoprostol caused diarrhea at all doses, although significantly more at 800 µg/day than 400 µg/day.

Misoprostol 800 µg/day significantly reduced the risk of NSAID ulcer complications, such as perforation, bleeding or obstruction.[55] High dose misoprostol could be considered as the gold standard for the primary prevention of NSAID ulcer complications.

NSAID induced gastroduodenal damage partly depends on low intraluminal gastric pH, and elevation of the intragastric pH reduces the risk of gastroduodenal ulcers. The production of gastric acid can be inhibited with proton-pump inhibitors (PPIs) and histamine H_2-receptor antagonists (H2RAs). PPIs

are significantly more effective than H2RAs in achieving and sustaining an intragastric pH above 4.0.[56] Several studies have evaluated the efficacy of concomitant use of PPIs on reducing the risk of NSAID ulcers. Concomitant PPIs have been shown to prevent endoscopic NSAID ulcers.[55,57,58] PPIs are better tolerated but have lower efficacy than high dose misoprostol.[57,59] In one study, 537 long-term NSAID users were randomized for placebo, misoprostol 800 µg/day, lansoprazole 15 mg/day, or lansoprazole 30 mg/day, with upper gastrointestinal endoscopy for ulcers at 12 weeks.[57] The incidence of endoscopic ulcers was 49% with placebo, 20% with lansoprazole 15 mg, 18% with lansoprazole 30 mg, and 7% with misoprostol. However, if withdrawals were classified like ulcers as treatment failures, misoprostol and lansoprazole had equal efficacy. One study directly compared the pharmacodynamic efficacies of different PPIs in controlling intragastric acidity in NSAID users.[60] The mean percentage of time during a 24-hr pH monitoring period that the gastric pH was >4.0 was significantly greater with esomeprazole (74%) compared with lansoprazole (67%) and pantoprazole (61%). However, there have been few studies directly comparing the efficacies of different PPIs in reducing the risk of NSAID ulcers. In one study, 595 NSAID using rheumatoid arthritis patients were randomized for pantoprazole 20 mg once daily, pantoprazole 40 mg once daily, or omeprazole 20 mg once daily.[61] At 6 months, incidence of endoscopic ulcers was 10% with pantoprazole 20 mg, 7% with pantoprazole 40 mg, and 11% with omeprazole 20 mg.

There have been no studies demonstrating the efficacy of PPIs in the primary prevention of serious NSAID ulcer complications.

Several studies have evaluated the efficacy of concomitant use of H2RAs on reducing the risk of NSAID ulcers. Standard doses of H2RAs are not effective for the prevention of gastric NSAID ulcers, although they may prevent duodenal ulcers.[55,62] High doses of H2RAs may prevent both gastric and duodenal endoscopic NSAID ulcers.[55,63] In one study, 285 long-term NSAID users with rheumatoid arthritis or osteoarthritis were randomized for famotidine 40 mg twice daily, famotidine 20 mg twice daily, or placebo.[63] At 24 weeks, the incidence of endoscopic gastric ulcers was 8% with famotidine 80 mg, 13% with famotidine 40 mg, and 20% with placebo, and the incidence of duodenal ulcers was 2%, 4%, and 13%, respectively. Several studies have directly compared the effects of concomitant misoprostol and H2RAs on the risk of NSAID ulcers. Misoprostol 400 to 800 µg/day was shown to be more effective than ranitidine 150 mg twice daily in preventing endoscopic NSAID ulcers.[64,65] Furthermore, in direct comparison PPIs have also been shown to be more effective than H2RAs in preventing endoscopic NSAID ulcers.[66]

There have been no studies demonstrating the efficacy of H2RAs in the primary prevention of serious NSAID ulcer complications.

With the discovery of the two cyclooxygenase (COX) isoenzymes; COX-1 and COX-2, it was hypothesized that the continuous production of local gastroprotective prostaglandins is mainly COX-1 dependent, while the inducible production of inflammatory prostaglandins is mainly COX-2 dependent. Most traditional NSAIDs were found to be nonselective inhibitors of both COX isoforms.[67] An ideal NSAID would selectively inhibit the inducible COX-2 isoform, thereby reducing inflammation and pain, without acting on the constitutive COX-1 isoform, thereby minimizing toxicity. On the basis of this hypothesis, several COX-2 selective NSAIDs were developed in the 1990s. Celecoxib (Celebrex®), rofecoxib (Vioxx®), and valdecoxib (Bextra®) received FDA approval for use in rheumatoid arthritis

and osteoarthritis while celecoxib and rofecoxib were also approved for use in acute pain. Two other COX-2 selective NSAIDs, etoricoxib (Arcoxia®) and lumircoxib (Prexige®) received European approval for use in rheumatoid arthritis, osteoarthritis and acute gout or osteoarthritis, respectively.

COX-2 selective NSAIDs demonstrate comparable analgesia and anti-inflammatory effects to nonselective NSAIDs in patients with rheumatoid arthritis and osteoarthritis.[67-71] At their defined therapeutic doses, COX-2 selective NSAIDs show at least a 200 to 300-fold selectivity for inhibition of COX-2 over COX-1.[67] Many studies have evaluated the efficacy of COX-2 selective NSAIDs on reducing the risk of NSAID ulcers. In 2000, two pivotal outcome studies, the CLASS and VIGOR studies, demonstrated that COX-2 selective NSAIDs decrease both the risk for endoscopic NSAID ulcers and for serious NSAID ulcer complications when compared to nonselective NSAIDs.[72,73] In the Celecoxib Long-term Arthritis Safety Study (CLASS), 8059 rheumatoid arthritis and osteoarthritis patients were randomized for celecoxib 400 mg twice daily, ibuprofen 800 mg three times daily, or diclofenac 75 mg twice daily.[72] Prophylactic aspirin use was permitted. At 6 months, the annualized incidence rates of NSAID ulcer complications alone and combined with symptomatic ulcers for celecoxib vs. NSAIDs were 0.76% vs. 1.45% (P=0.09) and 2.08% vs. 3.54% (P=0.02), respectively. For patients not taking aspirin, the annualized incidence rates were 0.44% vs. 1.27% (P=0.04) and 1.40% vs. 2.91% (P=0.02), respectively. For patients taking aspirin, there were no significant differences.[72] However, at the final study endpoint after one year there was no statistically significant reduction in NSAID ulcers or ulcer complications among patients taking celecoxib, although there was substantial patient drop-out, making the final study endpoint difficult to interpret.

In the VIoxx Gastrointestinal Outcome Research study (VIGOR), 8076 rheumatoid arthritis patients were randomized for rofecoxib 50 mg daily or naproxen 500 mg twice daily.[73] During a median follow-up of 9.0 months, 2.1 gastrointestinal events per 100 patient-years (gastroduodenal perforation, obstruction, bleeding, and symptomatic ulcers) occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk 0.5, 95%CI 0.3 to 0.6, P<0.001). The rates of complicated events (perforation, obstruction, and severe bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years, respectively (relative risk 0.4, 95%CI 0.2 to 0.8, P=0.005). However, the incidence of myocardial infarction was higher in the rofecoxib group than in the naproxen group (0.4 percent vs. 0.1 percent).[73]

The Multinational Etoricoxib and Diclofenac Arthritis Long-term program (MEDAL) was a pooled intent-to-treat analysis of three randomised comparisons of etoricoxib (60 or 90 mg daily) and diclofenac (150 mg daily) in 34,701 rheumatoid arthritis or osteoarthritis patients.[74] Overall, gastrointestinal events were significantly less common with etoricoxib than with diclofenac (hazard ratio 0.69, 95%CI 0.57 to 0.83, P=0.0001). This was due to a significantly decrease in uncomplicated ulcers with etoricoxib (hazard ratio 0.57, 95%CI 0.45 to 0.74, P<0.0001), but there was no difference in perforation, obstruction, or bleeding (hazard ratio 0.91, 95%CI 0.67 to 1.24, P=0.561). PPIs were used concomitantly for at least 75% of the study period by 40% of the patients and low-dose aspirin by 33%, but treatment effects did not differ significantly in these subgroups.[74]

In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), 18,325 osteoarthritis patients were randomized for lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg three times daily for 52 weeks.[75] In the patients not taking aspirin, the cumulative incidence of serious NSAID ulcer complications (bleeding, perforation, or obstruction) was significantly lower

with lumiracoxib than with naproxen or ibuprofen (hazard ratio 0.21, 95%CI 0.12 to 0.37). However, there was no significant difference in the patients concurrently taking aspirin. Furthermore, there were more myocardial infarctions with lumiracoxib, especially as compared with naproxen (0.38% vs. 0.21%), although the differences were not statistically significant.[75]

Several tentative conclusions may be drawn from these and other studies. Firstly, the use of COX-2 selective NSAIDs significantly reduces the risk of NSAID ulcers and of serious NSAID ulcer complications. However, long-term efficacy remains debatable. Secondly, concurrent use of low dose aspirin for primary or secondary prevention of cardiovascular or cerebrovascular disease negates the gastroprotective effect of COX-2 selective NSAIDs. This observation may be directly related to effect of aspirin, which irreversibly blocks COX-1 in the gastrointestinal tract.[76] Thirdly, the use of COX-2 selective NSAIDs increases the risk of myocardial infarction, as compared with the nonselective NSAID naproxen.

TREATMENT OF NSAID ULCERS

The development of upper gastrointestinal ulcer disease in a patient on NSAID therapy should result in prompt discontinuation of the drug, followed by the initiation of medical therapy to promote ulcer healing. Treatment options include gastric acid suppressants such as PPIs or H2RAs, and cytoprotective drugs such as sucralfate and misoprostol. The patient's H. pylori status should also be assessed, and if present H. pylori should be eradicated.[37]

In certain patients discontinuation of NSAID therapy may not be possible. Several studies have evaluated the efficacy of medical therapy for ulcer healing during continued NSAID therapy. Ulcer healing may occur more rapidly with PPIs than with H2RAs, misoprostol, or sucralfate.[77,78,79] In one study, 541 patients with NSAID ulcers or multiple gastroduodenal erosions who required continuous NSAID therapy were randomized for treatment with omeprazole 20 mg daily, omeprazole 40 mg daily, or ranitidine 150 mg twice daily.[77] At eight weeks, the rates of endoscopic ulcer healing were 80% with omeprazole 20 mg, 79% with omeprazole 40 mg, and 63% with ranitidine 300 mg. In a second study, 935 patients with NSAID ulcers or multiple erosions who required continuous NSAID therapy were randomized for treatment with omeprazole 20 mg daily, omeprazole 40 mg daily, or misoprostol 200 µg four times daily.[78] At eight weeks, endoscopic healing rates were comparable in all three groups, with successful treatment in 76% with omeprazole 20 mg, 75% with omeprazole 40 mg, and 71% with misoprostol. In a third study, 98 patients with NSAID ulcers who required continuous NSAID therapy were randomized for treatment with omeprazole 20 mg daily or sucralfate 2 grams twice daily.[79] At eight weeks, the rates of gastric ulcer healing were 87% with omeprazole versus 52% with sucralfate, while the rates of duodenal ulcer healing were 95% versus 73%.

SECONDARY PREVENTION OF NSAID ULCERS

The aim of secondary prevention strategies is the prevention of recurrent NSAID ulcers in patients with a (recent) history of gastroduodenal ulcers who require continued NSAID therapy. A prior history of gastroduodenal ulcers is a strong predictor for the occurrence of NSAID ulcers, and careful assessment of alternative treatment options should be undertaken before NSAID therapy is reinitiated or continued.

Several studies have compared the efficacy of concomitant use of PPIs, H2RAs, and misoprostol on reducing the risk of recurrent endoscopic NSAID ulcers. In the previously mentioned study on NSAID

ulcer healing with omeprazole 20 mg, omeprazole 40 mg, or ranitidine 300 mg, the 432 patients in whom initial treatment had been successful were then randomized for six months of maintenance therapy with either omeprazole 20 mg daily or ranitidine 150 mg twice daily.[77] The proportion of patients who remained in remission at six months was significantly higher with omeprazole (72%) than with ranitidine (59%). Likewise, in the study on NSAID ulcer healing with omeprazole 20 mg, omeprazole 40 mg, or misoprostol 800 µg, the 732 patients in whom initial treatment had been successful were then randomized for six months of maintenance therapy with either omeprazole 20 mg daily, misoprostol 200 µg twice daily, or placebo.[78] The proportion of patients who remained in remission at six months was significantly higher with omeprazole (61%) than with misoprostol (48%) or placebo (27%). Halving the misoprostol dosage for the maintenance phase may have biased the study in favour of omeprazole. However, omeprazole was still better tolerated than misoprostol.

These two studies allow some interesting additional observations. Firstly, during continued NSAID use following successful initial treatment, the rate of recurrent endoscopic ulcers was very high at 73% in six months with placebo. Secondly, although the efficacy of omeprazole 20 mg daily was significantly better than ranitidine 150 mg twice daily or misoprostol 200 µg twice daily, the rate of recurrent endoscopic ulcers was still high at 28% and 39% in six months.

In two similarly designed studies, VENUS (United States) and PLUTO (multinational), 844 and 585 NSAID users, including COX-2 selective NSAIDs, were randomized for esomeprazole 20 mg, esomeprazole 40 mg, or placebo for 6 months.[80] Patients were 60 years or older and/or had documented ulcers in the previous 5 years (VENUS 20%, PLUTO 36%), but no ulcer complications in the 6 months before study entry, no endoscopic ulcers at baseline, and were H. pylori negative. At 6 months, the estimated proportions developing endoscopic ulcers were 20% and 12% with placebo, 5% and 5% with esomeprazole 20 mg, and 5% and 4% with esomeprazole 40 mg, for VENUS and PLUTO respectively. Interestingly, the pooled ulcer rates for the 400 COX-2 selective NSAID users and 978 nonselective NSAID users were 16.5% and 17% with placebo, 1% and 7% with esomeprazole 20 mg, and 4% and 5% with esomeprazole 40 mg. Patients using COX-2 selective NSAIDs did not have a higher risk for developing NSAID ulcers than those using nonselective NSAIDs. The COX-2 selective and nonselective groups had similar proportions of patients with an ulcer history (34% and 33%), mean age was slightly higher in the COX-2 selective group (mean 66.6 and 64.2 years), but there were fewer low dose aspirin users in the COX-2 selective group (3% and 12%).[80]

Several studies have compared efficacy of either a COX-2 selective NSAID or the combination of a nonselective NSAID with a PPI for the secondary prevention of NSAID ulcer complications.[81,82,83] In one study, 287 H. pylori negative arthritis patients who had presented with NSAID ulcer bleeding were randomized after endoscopically confirmed ulcer healing for celecoxib 200 mg twice daily plus placebo or diclofenac 75 mg twice daily plus omeprazole 20 mg.[81] The probability of endoscopically confirmed recurrent ulcer bleeding during six-month follow-up was 4.9% with celecoxib and 6.4% with diclofenac plus omeprazole. Therefore, among high risk patients with a recent history of ulcer bleeding, treatment with celecoxib was as effective as treatment with diclofenac plus omeprazole for the prevention of recurrent bleeding, but neither strategy completely eliminated the risk.[81] In an extension to the previous study, 222 (86%) of the patients without recurrent bleeding within the study period agreed to undergo follow-up endoscopy at their last study visit.[82] The probability of recurrent endoscopic ulcers in six months

was 19% with celecoxib and 26% with diclofenac plus omeprazole. With combined bleeding and endoscopic ulcers, 24% with celecoxib and 32% with diclofenac plus omeprazole had recurrent ulcers. Therefore, among high risk patients with a recent history of ulcer bleeding, neither celecoxib nor diclofenac plus omeprazole adequately prevented ulcer recurrence.[81,82] In another similar study, 224 H. pylori negative patients who had presented with NSAID ulcer bleeding were randomized after endoscopically confirmed ulcer healing for celecoxib 200 mg once daily or naproxen 250 mg three times daily plus lansoprazole 30 mg once daily.[83] The cumulative incidence of recurrent ulcer complications at 24 weeks was 3.7% with celecoxib and 6.3% with naproxen plus lansoprazole.

One study compared the efficacy of either H. pylori eradication or concomitant PPI treatment for the secondary prevention of NSAID ulcer bleeding.[84] This study enrolled 400 H. pylori positive patients, 150 with NSAIDs and 250 with low dose aspirin for cardiovascular prophylaxis, who had presented with ulcer bleeding. Only the data for the 150 NSAID users will be presented here. After endoscopically confirmed ulcer healing with omeprazole 20 mg daily for eight weeks or longer, patients were given naproxen 500 mg twice daily and then randomized for omeprazole 20 mg daily for six months or one week of H. pylori eradication therapy followed by placebo for six months. The probability of recurrent NSAID ulcer bleeding during the six-month period was 19% percent for patients receiving eradication therapy and 4% percent for those treated with omeprazole.[84]

One study evaluated the efficacy of combination treatment with a COX-2 selective NSAID and a PPI for the secondary prevention of NSAID ulcer complications in patients at very high risk for ulcer bleeding.[85] In this study, 441 H. pylori negative arthritis patients who had presented with NSAID ulcer bleeding were treated with celecoxib 200 mg twice daily after endoscopically confirmed ulcer healing and were randomized for additional esomeprazole 20 mg twice daily or placebo. The 13-month cumulative incidence of recurrent ulcer bleeding was 0% with celecoxib and esomeprazole combination therapy and 9% with celecoxib mono-therapy.[85] Therefore, patients at very high risk for recurrent ulcer bleeding who need continued NSAID treatment might benefit from combination treatment with a COX-2 selective NSAID and a PPI.

SECONDARY PREVENTION OF ASPIRIN ULCERS

Aspirin 75 mg to 325 mg daily has proven efficacy in secondary prevention and, in selected patients, the primary prevention of cardiovascular disease. However, patients using low dose aspirin have a small increase in risk of major gastrointestinal bleeding. A meta-analysis of adverse events of low dose aspirin in 22 randomized placebo-controlled trials found a relative risk of 2.07 for major gastrointestinal bleeding with aspirin, with an absolute annual increase of 0.12%.[86] With this low absolute risk increase, the number needed to treat with aspirin to cause one major gastrointestinal bleeding is 833. Therefore, strategies for the prevention of gastrointestinal bleeding should be targeted at high risk patients. However, the general increase in use of aspirin, and particularly the overuse of aspirin for primary prevention of cardiovascular disease, may now make it a bigger cause of ulcer bleeding than NSAIDs. Different strategies have been evaluated for the prevention of recurrent gastrointestinal bleeding in patients who continue aspirin therapy.[84,87,88] In one study, 123 H. pylori positive patients who had developed bleeding ulcers with low dose aspirin were treated with H. pylori eradication therapy and then randomized for lansoprazole 30 mg daily or placebo in addition to aspirin 100 mg daily. At 12 months

follow-up, the rate of recurrent ulcer complications was 1.6% with lansoprazole and 14.8% with placebo.[87] In another study, 320 H. pylori negative patients who presented with ulcer bleeding with low dose aspirin were randomized after endoscopically confirmed ulcer healing for aspirin 80 mg daily plus esomeprazole 20 mg daily or clopidogrel 75 mg daily plus placebo. Clopidogrel had previously been recommended as an alternative in patients with major gastrointestinal complications with aspirin. At 12 months follow-up, the rate of recurrent ulcer bleeding was 0.7% with aspirin plus esomeprazole and 8.6% percent with clopidogrel.[88] One previously mentioned study compared the efficacy of either H. pylori eradication or concomitant PPI treatment for the secondary prevention of aspirin ulcer bleeding.[84] This study enrolled 400 H. pylori positive patients, 250 with low dose aspirin and 150 with NSAIDs, who had presented with ulcer bleeding. Only the data for the 250 aspirin users will be presented here. After endoscopically confirmed ulcer healing with omeprazole 20 mg daily for eight weeks or longer, patients were given aspirin 80 mg daily and then randomized for omeprazole 20 mg daily for six months or one week of H. pylori eradication therapy followed by placebo for six months. The probability of recurrent ulcer bleeding during the six-month period was 1.9% percent for patients receiving eradication therapy and 0.9% percent for those treated with omeprazole.[84]

POSSIBLE NSAID PREVENTION OF COLON CANCER

A large body of evidence has shown that aspirin and NSAIDs may inhibit colorectal carcinogenesis.[89] The evidence derives from animal models, epidemiological studies, intervention trials with NSAIDs in patients with familial polyposis, and randomized controlled trials with aspirin and COX-2 selective NSAIDs. Aspirin and NSAIDs may inhibit colorectal carcinogenesis by increasing the rate of apoptosis in colon cancer cells, inhibiting tumour angiogenesis, inhibiting cell proliferation and tumour growth, and decreasing metastatic potential.

A systematic review of controlled and observational studies examining the use of aspirin for the primary prevention of colorectal cancer found that regular use of aspirin was associated with a significantly reduced incidence of colonic adenomas in randomized controlled trials (relative risk 0.82), case-control studies (relative risk 0.87), and cohort studies (relative risk 0.72).[90] In cohort studies, regular use of aspirin was associated with relative risk reductions of 22% for incidence of colorectal cancer. Benefits from chemoprevention were more evident when aspirin was used at a high dose and for periods longer than 10 years.[90]

A systematic review of controlled and observational studies examining the use of nonselective and COX-2 selective NSAIDs for primary prevention of colorectal cancer found that nonselective NSAIDs were associated with a significantly reduced incidence of colorectal adenomas in cohort studies (relative risk 0.64) and case-control studies (relative risk 0.54). COX-2 selective NSAIDs were also associated with a significantly reduced incidence of colorectal adenomas in randomized controlled trials (relative risk 0.72). Nonselective NSAIDs were associated with a significant reduction in colorectal cancer in cohort studies (relative risk 0.61) and in case-control studies (relative risk 0.70).[91]

NSAID INDUCED CARDIOVASCULAR TOXICITY

Within the endovascular lumen COX-1 and COX-2 appear to play important roles in thrombogenesis.[92] Activated blood platelets produce COX-1 dependent thromboxane A_2, which acts as a pro-thrombotic

platelet agonist and vasoconstrictor. Nearby endothelial and smooth muscle cells produce COX-2 dependent prostaglandin I_2 (prostacyclin), especially after cell damage has occurred.[93] Prostacyclin is an anti-thrombotic platelet inhibitor and vasodilator, and thus modulates the interaction between activated platelets and the endovascular wall. COX-2 selective NSAIDs may, by their irreversible covalent binding of COX-2, strongly impair the synthesis of anti-thrombotic prostacyclin while lacking COX-1 inhibiting effects, thus tipping the scales of homoeostasis in favour of thrombogenesis and vasoconstriction.[93] As their effect is temporary and reversible, only continuous high dosage of nonselective NSAIDs will considerably inhibit COX-1 and COX-2. Under normal circumstances, nonselective NSAIDs would not greatly influence the endovascular homeostasis. However, cell damage, atherosclerotic plaques and laminar shear forces selectively up-regulate the expression of COX-2 by endothelial cells in an attempt to maintain homoeostasis.[94] Therefore, in clinical syndromes of platelet activation, COX inhibition by any NSAID, but especially by COX-2 selective NSAIDs, could be expected to increase the risk for cardiovascular events.[93]

On 30 September 2004, Merck Sharp & Dohme removed its COX-2 selective NSAID rofecoxib (Vioxx®) from the market because of a raised risk for cardiovascular events, especially myocardial infarctions. Overnight, direct-to-consumer advertising was replaced by direct-to-litigant advertising. The VIoxx Gastrointestinal Outcome Research study (VIGOR) had already shown that rofecoxib, compared with naproxen, carried an increased risk for thrombotic cardiovascular events. In this study, the incidence of myocardial infarction was 0.4% with rofecoxib 50 mg and 0.1% with naproxen 1000 mg, but these results were heavily debated.[73]

The expectancy of a lower incidence of gastrointestinal side effects and a superior therapeutic index with COX-2 selective NSAIDs had led to studies assessing their efficacy for the prevention of adenomatous polyps in patients who had undergone endoscopic polypectomy. Although these studies showed COX-2 selective NSAIDs to be effective for colorectal neoplasia prevention, they also confirmed the suspected increase in cardiovascular risk. In the Adenomatous Polyp Prevention On Vioxx study (APPROVe), the 18-month rates of thrombotic events were 1.5 per 100 patient years with rofecoxib and 0.78 per 100 patient years with placebo (relative risk 1.92), prompting the withdrawal of rofecoxib.[95] Likewise, in the Adenoma Prevention with Celecoxib study (APC), which was terminated early by the National Institutes of Health, the risk for having major cardiovascular events was increased 2.3-fold with celecoxib 400 mg and 3.4-fold with celecoxib 800 mg, compared with placebo.[96]

In a study assessing the safety of parecoxib and valdecoxib after cardiac surgery, 1,671 patients were randomized for intravenous parecoxib or placebo for three days after coronary-artery bypass grafting, followed by oral valdecoxib or placebo for 10 days. All patients also received low dose aspirin and were followed for up to 30 days. Cardiovascular events occurred in 0.5% with placebo only, 1.1% with placebo followed by valdecoxib (relative risk 2.0), and 2.0% with parecoxib followed by valdecoxib (relative risk 3.7).[97]

In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), 18,325 osteoarthritis patients were randomly assigned to lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg three times daily and followed for one year.[98] Patients with prior myocardial infarction, stroke, coronary bypass grafting, angioplasty or stenting, angina, or significant heart failure were excluded. The rates of cardiovascular events were not significantly different for lumiracoxib and

nonselective NSAIDs (0.86 and 0.75 per 100 patient years, hazard ratio 1.14, 95% CI 0.78 to 1.66). Compared to naproxen, the relative risk for lumiracoxib was increased but did not reach statistical significance (hazard ratio 1.5, 95% CI 0.9 to 2.4).[98]

The Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme evaluated the cardiovascular safety of etoricoxib in a pre-specified analysis of three separate trials comparing etoricoxib with diclofenac in 24.913 osteoarthritis patients and 9787 rheumatoid arthritis patients.[99] After 18 months, 320 patients with etoricoxib (1.24 per 100 patient years) and 323 with diclofenac (1.30 per 100 patient years) had thrombotic cardiovascular events (hazard ratio 0.95, 95% CI 0.81 to 1.11).[99] However, interpretation of these results is problematic since diclofenac itself is strongly associated with an increased risk of cardiovascular outcomes.[100]

One meta-analysis assessed the effects of COX-2 selective and nonselective NSAIDs on the risk of vascular events in published and unpublished tabular data from 138 randomised trials that included a comparison of a COX-2 selective NSAID versus placebo or a COX-2 selective NSAID versus a nonselective NSAID, of at least four weeks' duration.[101] Selective COX 2 inhibitors were associated with a moderate increase in the risk of serious vascular events compared to placebo (rate ratio 1.42), which was chiefly attributable to an increased risk of myocardial infarction (rate ratio 1.86). High dose regimens of nonselective NSAIDs were associated with a similar increase in risk of vascular events compared to placebo (rate ratio was 1.51 for ibuprofen, and 1.63 for diclofenac), with the exception of high dose naproxen (rate ratio 0.92).[101]

One systematic review and meta-analysis assessed the risks of serious cardiovascular events with individual COX-2 selective and nonselective NSAIDs in 17 case-control and 6 cohort studies.[100] Rofecoxib was associated with a significant dose-related relative risk of serious cardiovascular events during the first month of treatment (relative risk 1.33 with 25 mg or less daily, relative risk 2.19 with more than 25 mg daily). Celecoxib was not associated with an elevated risk (relative risk 1.06). Among the nonselective NSAIDs, diclofenac had the highest risk (relative risk 1.40). Other nonselective NSAIDs had relative risks close to 1: ibuprofen (relative risk 1.07), piroxicam (relative risk 1.06). The risk appeared lowest for naproxen (relative risk 0.97).[100]

One meta-analysis assessed the comparative risk of myocardial infarctions with COX-2 selective and nonselective NSAIDs in case-control studies, cohort studies, and randomised controlled trials in colonic adenomas and arthritis.[102] Fourteen case-control studies with 74,673 myocardial infarction patients and 368,968 controls showed no significant association of NSAIDs with myocardial infarctions in a random effects model and a small risk in a fixed effects model (odds ratio 1.32). Six cohort studies with 387,983 patient years and 1,120,812 control years showed no significant risk of myocardial infarctions with NSAIDs, except for rofecoxib (relative risk 1.25). Four randomized controlled trials of NSAIDs in colonic adenomas with 6000 patients showed increased risks of myocardial infarctions with NSAIDs (relative risk 2.68). Fourteen randomized controlled trials in arthritis with 45,425 patients showed more myocardial infarctions with COX-2 selective NSAIDs (odds ratio 1.6), but fewer serious upper gastrointestinal events (odds ratio 0.40).[102]

Based on a review of available data from long-term placebo- and active-controlled clinical trials of NSAIDs, the U.S. Food and Drug Administration (FDA) has concluded that an increased risk of serious adverse cardiovascular events may be a class effect for all NSAIDs, COX-2 selective and nonselective

alike (excluding aspirin). The FDA has subsequently requested that the package insert for all NSAIDs be revised to include a boxed warning highlighting the potential increased risk of cardiovascular events and the well described risk of serious, and potentially life-threatening, gastrointestinal bleeding. The FDA has also requested that the package insert for all NSAIDs include a contraindication for use in patients immediately post-operative from coronary artery bypass graft surgery.[103]

NSAID INTERFERENCE WITH ASPIRIN

The beneficial effect of aspirin may be attenuated by concomitant administration of NSAIDs such as ibuprofen or naproxen.[104,105] In one study, patients were treated with aspirin two hours before or two hours after ibuprofen.[104] Serum thromboxane B_2 levels and platelet aggregation were maximally inhibited with aspirin before ibuprofen. In contrast, inhibition of serum thromboxane B_2 formation and platelet aggregation by aspirin was prevented with a single daily dose of ibuprofen before aspirin, as well as when multiple daily doses of ibuprofen were given. The concomitant administration of rofecoxib, acetaminophen or diclofenac before or after aspirin did not affect the pharmacodynamics of aspirin.[104] Similar effects have been described with naproxen. In one study, a single dose of naproxen two hours before aspirin interfered with the antiplatelet effect of aspirin.[105] Nonselective NSAIDs compete with aspirin for a common binding site on COX-1. The presence of a nonselective NSAID at this site prevents aspirin from binding and irreversibly acetylating a serine residue on COX-1.[106] This pharmacodynamic interaction is not seen with COX-2 selective NSAIDs. Aspirin causes an irreversible and nearly complete blockade of COX at low doses, while the blockade caused by ibuprofen at therapeutic doses is reversible and much less complete, declining rapidly between doses.[107] The inhibitory effect of naproxen on platelet function is greater than that of ibuprofen and its half-life is significantly longer. Whether these findings have clinical relevance in patients with cardiovascular disease has yet to be determined.

NSAID INDUCED EXACERBATION OF HEART FAILURE

NSAID use is not associated with a first occurrence of heart failure, but may exacerbate pre-existing disease. In patients with pre-existing heart failure, NSAID use may induce systemic vasoconstriction causing an increase in afterload with further reduction in cardiac contractility and cardiac output. Advanced heart failure is associated with increased secretions of antidiuretic hormone, angiotensin II, and norepinephrine. The ensuing renal ischemia may lead to water retention and hyponatremia, resulting in further worsening of heart failure and increased risk for acute renal failure.

In the prospective Rotterdam cohort study, 7277 subjects over 55 years of age were followed up from the interview date until a diagnosis of incident heart failure, death, or end of the follow-up period. During follow-up, 345 participants had incident heart failure. Current use of NSAIDs was associated with a relative risk of incident heart failure of 1.1 (95% CI 0.7 to 1.7). However, in NSAID users with prevalent heart failure the adjusted relative risk of a relapse was 9.9 (95% CI 1.7 to 57.0).[108] Another study found a similar 10-fold increased risk of exacerbating heart failure in elderly patients with recent NSAID use. In this study, the risk was related to the dose of NSAID consumed within the week prior to hospitalization for heart failure.[109]

One population-based retrospective cohort study compared the rates of hospital admission for heart failure in 38.882 elderly patients who were newly dispensed COX-2 selective or nonselective NSAIDs

and 100.000 randomly selected non-NSAID using controls. The crude rate of hospitalization for heart failure was 0.9 per 100 patient years for the controls, 1.3 per 100 patient years with celecoxib (adjusted rate ratio compared with controls 1.0), 1.6 per 100 patient years with nonselective NSAIDs (rate ratio 1.4), and 2.4 per 100 patient years with rofecoxib (rate ratio 1.8).[110]

NSAID INDUCED HYPERTENSION

Patients with hypertension may have increased activation of the renin-angiotensin and sympathetic nervous system, with subsequent release of vasodilator prostaglandins from the kidney, which act locally to lessen the degree of renal ischemia. When this compensatory response is inhibited by NSAIDs, the increase in renal and systemic vascular resistance can cause an elevation in blood pressure averaging 3 to 6 mmHg.[111] This effect may be most pronounced in patients who are salt-sensitive and ingesting a relatively high salt diet, and appears to be smallest in patients taking calcium channel blockers.

In the Nurses' Health Study II, a prospective study of over 80,000 women of 31 to 50 years of age without an initial history of hypertension, the relative risk for the development of hypertension after two years of follow-up was 1.86 with NSAIDs compared to non-NSAIDs, but not with aspirin.[112]

In a meta-analysis of 19 randomized trials with COX-2 selective NSAIDs involving 45,451 participants in whom blood pressure data were available, the rate of incident hypertension was 2.63 with rofecoxib compared to placebo.[111] The weighted mean increase in blood pressure was 5.66 mmHg with rofecoxib and 2.6 mmHg with celecoxib. However, celecoxib was associated with a 0.99 mmHg increase in diastolic blood pressure, whereas rofecoxib was not.[111]

NSAID INDUCED ACUTE RENAL FAILURE

In normal subjects the basal rate of renal prostaglandin synthesis is relatively low and does not play a major role in the regulation of renal hemodynamics. The release of renal prostacyclin and prostaglandin E_2 is increased by glomerular disease, renal insufficiency, hypercalcemia, and by increases in the vasoconstrictors angiotensin II and norepinephrine in states of effective volume depletion, such as heart failure, cirrhosis, and true volume depletion.[113] In these situations, renal vasodilator prostaglandins maintain renal blood flow and glomerular filtration rate by relaxing pre-glomerular resistance and antagonizing the vasoconstrictor effects of angiotensin II and norepinephrine. NSAID inhibition of prostaglandin synthesis in such conditions may cause reversible renal ischemia, a decline in glomerular hydraulic pressure and glomerular filtration rate, and acute renal failure.

Acute renal failure may occur with any COX-2 selective or nonselective NSAIDs. In one nested case-control study, hospitalization for acute renal failure was correlated with initiation of NSAID use among 121,722 patients older than 65 years of age.[114] The risk of acute renal failure was highest within 30 days of treatment initiation and receded thereafter. The relative risk of acute renal failure was comparable with rofecoxib (relative risk 2.31, 95% CI 1.73 to 3.08), naproxen (relative risk 2.42, 95% CI 1.52 to 3.85), and nonselective, non-naproxen NSAIDs (relative risk 2.30, 95% CI 1.60 to 3.32), but was slightly lower with celecoxib (relative risk 1.54, 95% CI 1.14 to 2.09). In another study, 60 elderly patients receiving a low-salt diet were randomized for rofecoxib 12.5 mg daily, rofecoxib 25 mg daily, indomethacin 50 mg three times daily, or placebo for five days.[115] Compared with placebo, glomerular filtration rate was significantly lowered with rofecoxib 12.5 mg (8.4 mL/min lower), with rofecoxib

25 mg (7.8 mL/min lower), and with indomethacin 150 mg (6.0 mL/min lower).
NSAID use is also associated with acute interstitial nephritis, membranous nephropathy, and nephrotic syndrome due to minimal change disease. The underlying pathophysiologic mechanisms are not known. Affected patients typically present with hematuria, pyuria, white cell casts, proteinuria, and acute renal insufficiency. Spontaneous recovery usually occurs within weeks to months after therapy is discontinued.[116] Subsequent administration of NSAIDs should be avoided as relapse may occur with rechallenge.

FUTURE DEVELOPMENTS

Most cells routinely make prostaglandins through the action of COX-1 on arachidonic acid. Arachidonic acid is converted to the endoperoxide PGH_2, which is subsequently converted by additional prostaglandin synthases into other prostaglandins such as; PGD_2, involved in sleep regulation and allergic reactions; PGF_2, involved in uterus contraction; PGI_2, involved in dilation of blood vessels, platelet inhibition, and stomach protection; PGE_2, involved in pain, inflammation and fever, and in stomach protection; and thromboxane; TXA_2, involved in constriction of blood vessels and platelet aggregation. When tissue injury occurs, a chemical signal instructs macrophages and inflammatory cells to increase the activity of COX-2, which subsequently increases the isomeration of PGH_2 to PGE_2 by PGE_2 synthases (PGES). Aspirin and nonselective NSAIDs act by blocking both COX isoforms, COX-1 and COX-2, early in the prostaglandin synthesis pathway, consequently inhibiting the entire synthesis of prostaglandins downstream of PGH_2. Inflammatory PGE_2 synthesis was found to be mainly COX-2 dependent, while gastroprotective PGE_2 synthesis was found to be mainly COX-1 dependent, prompting the development of the COX-2 selective NSAIDs. However, COX-2 selective NSAIDs still interact early in the prostaglandin synthesis pathway and inadvertently inhibit other COX-2 dependent prostaglandins, such as cardioprotective PGI_2, with the consequential elevated risk for cardiovascular events.
More specific targets for anti-inflammatory action would have to be sought downstream from the COX enzymes in the prostaglandin synthesis pathway.[117] Recent discoveries have found different forms of PGE_2 synthase (PGES).[118] A cytosolic form of PGES (cPGES) couples preferentially with COX-1 to convert PGH_2 into gastroprotective PGE_2, while one of two membrane-bound forms of PGES (mPGES-1) couples with COX-2 to convert PGH_2 into inflammatory PGE_2. Several agents, still under development, specifically block mPGES-1. Inhibiting mPGES-1 but not the enzymes that make normal levels of prostaglandins may thus control inflammatory PGE_2 levels, providing analgesic, anti-pyretic and anti-inflammatory benefits, without concurrent cardiovascular or gastrointestinal harms. Alternative strategies being developed for third generation NSAIDs involve drugs that would bind to PGE_2 receptors, directly blocking them from functioning.[117]

THE BALANCE OF RISKS

In summary, non-steroidal anti-inflammatory drugs (NSAIDs) are one of the oldest, most successful drugs known to modern medicine. NSAIDs are effective for alleviating pain, fever and inflammation, by inhibiting prostaglandin synthesis. Aspirin, by its irreversible inhibition of blood platelet function, is also effective in the secondary prevention and, in selected patients, primary prevention of cardiovascular disease. In addition, NSAIDs may also inhibit colorectal carcinogenesis.

NSAID use is associated with several serious treatment side effects, with considerable associated morbidity and mortality. NSAIDs may be considered the most fatal drugs for non-fatal diseases. NSAIDs may cause gastrointestinal ulcers, which may be complicated by ulcer bleeding, perforation and obstruction. Cyclooxygenase (COX)-2 selective NSAIDs and high dose nonselective NSAIDs may cause serious cardiovascular events, especially myocardial infarction, with the possible exception of naproxen. NSAIDs use is also associated with the development of hypertension, acute renal failure, and with worsening of pre-existing heart failure.

Concurrent use of low dose aspirin for primary or secondary prevention of cardiovascular disease may negate the gastroprotective effect of COX-2 selective NSAIDs. Conversely, the beneficial effect of aspirin may be attenuated by concomitant use of nonselective NSAIDs, such as ibuprofen or naproxen. Physicians must take into account both the gastrointestinal and cardiovascular risks of individual patients when prescribing NSAIDs. Interestingly, in a study among Canadian osteoarthritis patients, most patients were willing to accept some additional risk of ulcer bleeding and heart attacks or stroke to gain pain relief, but were generally willing to accept a greater additional risk of ulcer bleeding than of heart attacks or stroke.[119]

As a central dictum in NSAID treatment, physicians should always prescribe the lowest effective dose for the shortest possible time.

Patients with a history of gastroduodenal ulcers should be tested for H. pylori prior to starting NSAID or aspirin therapy, and if present H. pylori should be eradicated. In asymptomatic patients with no ulcer history and not currently taking NSAIDs, physicians may consider H. pylori testing prior to starting long-term NSAID therapy. This "test-and-treat" approach may be more effective in populations with high prevalence of H. pylori infection.

In patients with a low cardiovascular risk, NSAIDs can be prescribed according to the risk for gastrointestinal events.[120] Patients with a low gastrointestinal risk may be treated with a nonselective NSAID. Patients with a moderate gastrointestinal risk (one or two gastrointestinal risk factors) may be treated with a nonselective NSAID plus a PPI or misoprostol 800 µg, or with a COX-2 selective NSAID. In patients with a high gastrointestinal risk (more than two gastrointestinal risk factors or prior ulcer complications) alternative treatment options should be explored. If NSAID therapy is required, patients may be treated with a combination of a COX-2 selective NSAID and a PPI twice daily.

Patients with a high cardiovascular risk should receive prophylactic low dose aspirin. If additional NSAID therapy is required, naproxen is the preferred NSAID, in combination with a PPI or misoprostol 800 µg, irrespective of the presence of additional gastrointestinal risk factors.[120] Patients with a high cardiovascular risk and a high gastrointestinal risk should avoid NSAID therapy.

THIS THESIS

Several questions still remain to be answered. First, are PPIs and COX-2 selective NSAIDs effective for the primary prevention of serious NSAID ulcer complications in a general population of NSAID using patients? To answer this question, we designed a large nested case-control study in a cohort of NSAID users from the general population (*Chapter 3*). Second, how are gastroprotective strategies utilized in NSAID users according to their risk for gastrointestinal events? To answer this question, we determined the relationship between risk factors for gastrointestinal events and the likelihood of receiving adequate

gastroprotection in cases with serious NSAID ulcer complications and controls (*Chapter 4*). Third, are patients with a slow NSIAD metabolism associated with allele variants of the cytochrome P450 2C9 genotype at increased risk for serious NSAID ulcer complications? To answer this question we examined CYP 2C9 allele frequencies in cases with serious NSAID ulcer complications and compared them with frequencies in matched controls (*Chapter 5*). Fourth, are strategies which are effective for the primary prevention of serious NSAID ulcer complications in a general population of NSAID using patients also cost-effective? To answer this question, we conducted a cost-of-illness study to determine the direct medical costs associated with hospitalization and treatment of patients with serious NSAID ulcer complications (*Chapter 6*), and extended this analysis with data from the nested case-control study to estimate the cost-effectiveness of concomitant PPIs in relation to the occurrence of serious NSAID ulcer complications (*Chapter 7*). Fifth, is long-term use of COX-2 selective NSAIDs in H. pylori positive patients associated with a reduced incidence of NSAID ulcers compared to long-term use of nonselective NSAIDs? To answer this question, we conducted a post hoc analysis of the data from a recently conducted randomized, double blind, placebo controlled clinical trial which examined the effect of H. pylori eradication on the incidence of endoscopic ulcers in patients on long-term NSAID treatment (*Chapter 8*). Sixth, how should assess persistent H. pylori infection or success of eradication following triple therapy in NSAID users? To answer this question, we compared H. pylori IgG-antibody titers, hematoxylin and eosin stains, immunohistochemical stains, and H. pylori culture results in follow-up biopsies from H. pylori-positive long-term NSAID users who had been treated with triple therapy or placebo, to determine the sensitivity and specificity of these different detection methods (*Chapter 9*), and also measured H. pylori IgG-antibody titer changes (*Chapter 10*).

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CHAPTER II

Understanding the NSAID related risk of vascular events

Harald E Vonkeman, Jacobus R B J Brouwers, Mart A F J van de Laar

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Concern is growing about an increased risk of thrombotic events (including myocardial infarction and stroke) during the use of non-steroidal antiinflammatorydrugs (NSAIDs), in particular the so called selective cyclo-oxygenase-2 (COX 2) inhibitors. Although clinical trials give conflicting results with respect to the incidence of vascular events, increasing evidence shows that a class effect might exist for selective COX 2 inhibitors. Even before the massive introduction of selective COX 2 inhibitors, observational studies showed that the use of NSAIDs causes congestive heart failure in elderly patients.[1,2] Conversely, the discontinuation of NSAIDs has also been associated with increased risk of myocardial infarction, especially in the first several weeks after stopping chronic NSAID treatment.[3]
Many different mechanisms could explain the different effects of classic NSAIDs and selective COX 2 inhibitors in relation to thrombotic vascular events. In this review we link biochemical facts concerning NSAIDs and COX inhibitors with data from clinical trials.

KEY ENZYMES: COX 1 AND COX 2

The key step in the synthesis of prostaglandins, the transformation of arachidonic acid to prostaglandin H_2, is catalysed by two different isoenzymes – cyclooxygenase-1 and cyclo-oxygenase-2.[4] COX 1 is expressed constitutively at variable concentrations and regulates normal physiology, such as the maintenance of gastric mucosal integrity, kidney function, and platelet aggregation. Conversely, COX 2 is usually undetectable in most tissues and is selectively expressed after exposition to inflammatory mediators or trauma (*fig 1*).
The hypothesis formed is that the adverse gastrointestinal effects of NSAIDs are attributable to the inhibition of COX 1 and that selective inhibition of COX 2 would yield effective but gastrointestinally safer drugs. A number of pharmaceutical companies developed and tested this hypothesis and several selective COX 2 inhibitors were subsequently marketed.

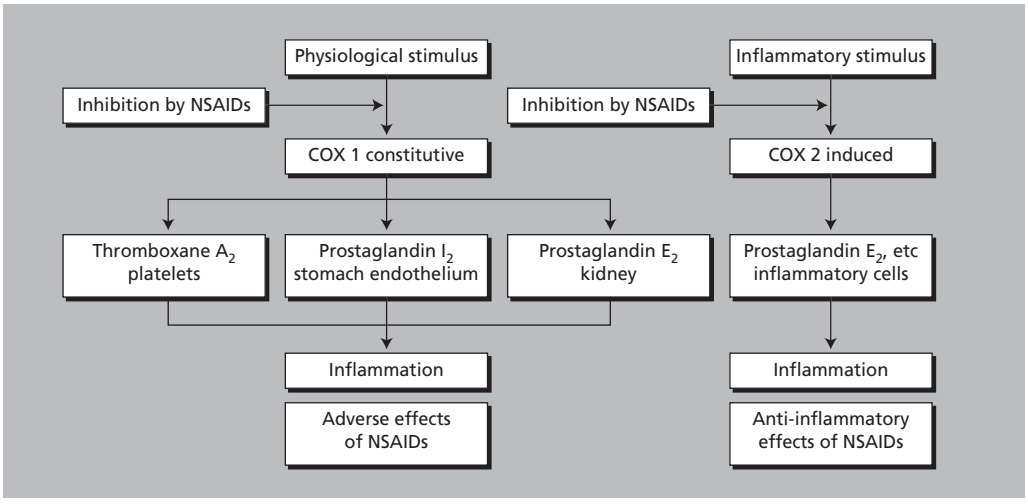

Figure 1 Differential prostanoid synthesis, showing differential prostanoid synthesis by different cells in different tissues. NSAIDs' anti-inflammatory effects are due to cyclo-oxygenase-2 (COX 2) inhibition, and adverse effects occur because of COX 1 and also COX 2 inhibition.

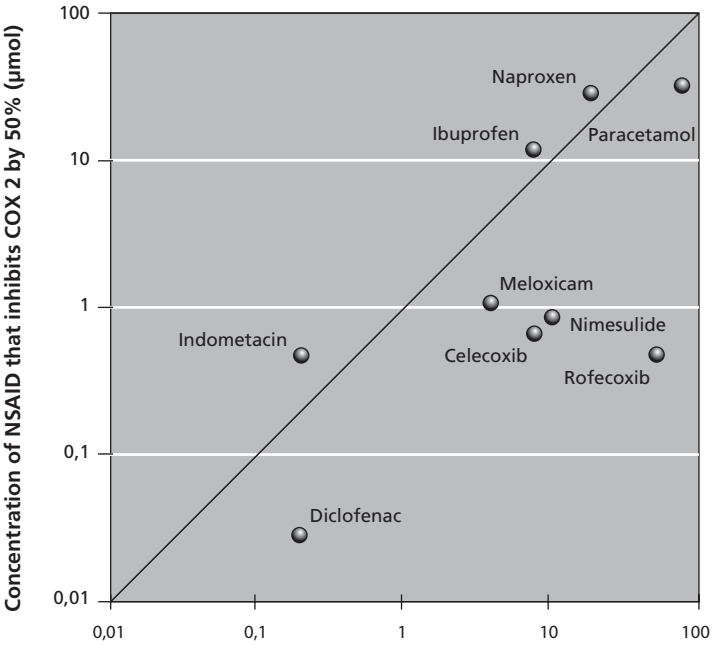

Figure 2 Inhibition of cyclo-oxygenase-1 (COX 1) and COX 2, showing the concentration of non-steroidal anti-inflammatory drugs needed to inhibit the activity of COX 1 and COX 2 by 50% in assays of whole blood. Diagonal line shows equivalence (adapted from FitzGerald and Patrono[10])

The COX 2 hypothesis does, however, have an unexpected and dark side. Within the endovascular lumen, COX 1 and COX 2 have an important role in the interaction between platelets and endothelial cells and in thrombogenesis.[5] Activated platelets produce COX 1 dependent thromboxane A_2. Thromboxane A_2 acts as a platelet agonist and vasoconstrictor, and its effects can be considered as prothrombotic. Nearby endothelial and smooth muscle cells produce COX 2 dependent prostaglandin I_2 (prostacyclin), especially after cell damage has occurred, as occurs in the formation of atherosclerotic plaques.[6] Prostacyclin is a natural platelet inhibitor and has vasodilatory effects. Prostacyclin thus modulates the interaction between platelets and the endovascular wall, inhibiting thrombogenesis and atherosclerosis.[7] Selective COX 2 inhibitors may, by their irreversible covalent binding, strongly impair the synthesis of the antithrombotic prostacyclin while lacking any antiplatelet effects, thus tipping the scales of homoeostasis in favour of thrombogenesis and vasoconstriction. As shown previously by our group and others, platelet function is inhibited by non-selective NSAIDs but not by selective COX 2 inhibitors.[8,9] These in vitro findings suggest that selective COX 2 inhibitors may increase the risk of vascular events, including myocardial infarction and stroke, especially in patients with pre-existing endothelial damage or a history of thromboembolic events – that is, elderly patients.

Using human whole blood assays, NSAIDs can be assessed and ranked for their in vitro level of COX 2 selectivity.[10] Some classic NSAIDs more or less equivalently inhibit COX 1 and COX 2; others show some COX 2 selectivity. Selective COX 2 inhibitors on the other hand, have shown a 200-300-fold selectivity for COX 2 (*fig 2*). As their effect is temporary and reversible, only continuous high dosage of classic NSAIDs will considerably inhibit COX 1 and COX 2. For selective COX 2 inhibitors, conversely, because of irreversible covalent binding, considerable inhibition of COX 2 (but not COX 1) might also be expected during intermittent use and at lower dosage. In inflammatory states like in synovitis this

irreversible COX 2 binding would be advantageous because of massive overexpression of COX 2. However, in the interaction between platelets and the endovascular wall, no continuous overabundant expression of COX 2 is to be expected. One could surmise that under normal circumstances, the use of classic NSAIDs would not greatly influence the production of platelet COX 1 dependent thromboxane A_2 or the concentrations of endothelial COX 2 dependent prostacyclin, thus retaining the endovascular prothrombotic and antithrombotic balance. However, cell damage, atherosclerotic plaques, and laminar shear forces selectively upregulate the expression of COX 2 by endothelial cells in an attempt to maintain homoeostasis.[11] In clinical syndromes of platelet activation, therefore, COX inhibition by any NSAID, but especially by selective COX 2 inhibitors, could be expected to upset the thrombotic equilibrium, increasing the risk of cardiovascular events.

CLINICAL DATA ON CARDIOVASCULAR EVENTS

On 7 April 2005, Pfizer agreed to suspend the marketing and sale of valdecoxib (Bextra) in the United States and European Union pending further discussions with the US Food and Drug Administration on the drug's overall risk versus benefit profile.[12] Previously, on 30 September 2004, Merck Sharp & Dohme removed its selective COX 2 inhibitor rofecoxib (Vioxx) from the market. The reason for this was a raised risk of cardiovascular events, especially myocardial infarctions. The Vioxx gastrointestinal outcome research study (VIGOR) had previously shown that rofecoxib, compared with naproxen, has noticeably less serious gastrointestinal side effects. The same study, however, also showed that rofecoxib, compared with naproxen, carried an increased risk for thrombotic cardiovascular events. In the group taking 50 mg of rofecoxib, 45 events occurred compared with 19 in the group taking 1000 mg of naproxen ($P < 0.002$).[13] Overall, there were more serious side effects with rofecoxib than with naproxen and the way in which the VIGOR data were presented has elicited an "expression of concern" as not all observed myocardial infarctions were reported, apparently purposely, resulting in an understatement of the difference in risk.[14–16]

Although many subsequent retrospective case control studies seemed to confirm this raised risk, it was the prospectively randomised adenomatous polyp prevention on Vioxx study (APPROVe) which definitively showed an increased risk for cardiovascular events, such as myocardial infarctions and stroke. In the APPROVe study, 46 of 1287 (3.6%) participants taking 25 mg of rofecoxib compared with 26 of 1299 (2.0%) taking placebo, had a confirmed thrombotic event after 18 months (relative risk 1.92, 95% confidence interval 1.19 to 3.11).[17] Although the risk was relatively low, at 1.50 per 100 patient years, this was reason for the voluntary worldwide withdrawal of rofecoxib. These series of events have led to greater scrutiny of the remaining selective COX 2 inhibitors and also of the NSAID group as a whole. Soon after the withdrawal of rofecoxib yet another selective COX 2 inhibitor – namely, celecoxib (Celebrex), came under fire. In the adenoma prevention with celecoxib study (APC), 2035 participants were randomised to either a daily dose of 400 mg or 800 mg of celecoxib or placebo. The study was designed to assess whether (high dose) celecoxib can prevent colon polyps. It was to finish in spring 2005 but was terminated early by the National Institutes of Health. In the APC study, participants who took 400 mg of celecoxib seemed to have 2.3 (0.9 to 5.5) times as much risk of having a major cardiovascular event, compared with participants who took placebo. In those taking a daily dose of 800 mg of celecoxib the risk was increased by 3.4 (1.4 to 7.8)-fold. After an aver-

age of 33 months, there were seven cardiovascular events in 679 subjects in the placebo group, 16 in 685 in the 400 mg group, and 23 in 671 in the 800 mg group.[18] However, in two other long term follow-up celecoxib studies, the celecoxib long term arthritis safety study (CLASS) and the prevention of spontaneous adenomatous polyps study (PreSAP) preliminary reports do not suggest an increased cardiovascular risk.[19]

A meta-analysis on two trials in high risk patients, who had recently undergone coronary artery bypass graft surgery, showed a significantly greater cardiovascular risk for the selective COX 2 inhibitor valdecoxib (Bextra) (relative risk 3.08; 1.20 to 7.87).[20] Likewise, in a study after coronary artery bypass graft surgery in which patients received intravenous parecoxib (Dynastat), a pro-drug which is converted into valdecoxib, followed by oral valdecoxib, patients receiving valdecoxib showed an increased risk of myocardial infarction compared with patients receiving placebo.[21] For the selective COX 2 inhibitor lumiracoxib (Prexige), no significant increase in cardiovascular events was found compared with non-selective NSAIDs. In the therapeutic arthritis research and gastrointestinal events trial (TARGET), 18 325 patients with osteoarthritis were randomly treated with lumiracoxib, naproxen, or ibuprofen for one year.[22] Event rates were similar, and the adjusted hazard ratio did not increase significantly (hazard ratio 1.14, 0.78 to 1.66). But absence of evidence is not evidence of absence, as in this trial patients with a high risk for cardiovascular events were excluded and the number of events was quite low.

Recently, Merck Sharp and Dohme discussed cardiovascular safety for the selective COX 2 inhibitor etoricoxib (Arcoxia) in their new drug application briefing. An increase of cardiovascular events was seen for etoricoxib, compared with placebo or non-selective NSAIDs. Furthermore, the marginal gastrointestinal advantage of etoricoxib compared with naproxen was entirely lost in users of low dose aspirin.[23] However, the original publications should be awaited before these results can be taken into consideration.

To confuse matters, preliminary results from the three year ongoing placebo controlled Alzheimer's disease anti-inflammatory prevention trial (ADAPT) also suggested an increased cardiovascular risk

Summary points

A significant increase in risk for cardiovascular events in non-steroidal anti-inflammatory drug (NSAID) users has been found in clinical trials and observational studies, especially in patients taking selective cyclo-oxygenase-2 (COX 2) inhibitors.

Two selective COX 2 inhibitors have subsequently been taken off the market, but others are still available.

Within the endovascular lumen platelet COX 1 dependent prothrombotic thromboxane-A_2 and endothelial COX 2 dependent antithrombotic prostacyclin are balanced and so prevent coagulation.

Selective COX 2 inhibitors impair prostacyclin synthesis but lack antiplatelet effects, tipping the scales in favour of thrombogenesis and increasing the risk of cardiovascular events. Patients at risk of cardiovascular events should not be treated with selective COX 2 inhibitors.

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Information for patients

Food and Drug Administration. www.fda.gov/cder/drug/infopage/COX2/default.htm.Website on cyclooxygenase-2 selective and non-selective nonsteroidal anti-inflammatory drugs

for the classic non-selective NSAID naproxen.[24] In the ADAPT trial, 2500 elderly patients had been taking 400 mg of naproxen, 400 mg of celecoxib, or placebo from 2001 onwards to test the hypothesis that NSAIDs might protect against the onset of Alzheimer's disease in those at risk. The National Institutes of Health recently terminated this study early, after finding that those taking naproxen had a 50% increase in cardiovascular events compared with placebo.

Surprisingly, no increase was seen in those taking celecoxib.[24] This is however consistent with results from a large case-control study in over 8000 patients taking selective COX 2 inhibitors, that showed that patients using rofecoxib were more likely to have a myocardial infarction than those that took celecoxib (odds ratio 2.72; 1.24 to 5.95).[25] These findings were confirmed in another very large nested case-control study. In 2 302 029 person years of follow-up, 8143 cases of acute myocardial infarction and sudden cardiac death occurred. Rofecoxib increased the risk compared with celecoxib, and naproxen use did not offer any protection.[26] Also, in a case-control study with 10 280 cases of first time admission to hospital for myocardial infarction and 102 797 population controls, risk for myocardial infarction was highest in users of rofecoxib, but was also raised in other selective and non-selective NSAID users, compared with non-users.[27]

CONCLUSION

A significant increase in risk of cardiovascular events in NSAID users has been found in clinical trials and observational studies, especially in patients taking selective COX 2 inhibitors. Two selective COX 2 inhibitors have subsequently been taken off the market, but others are still available to doctors and patients. On the basis of the hypothesis outlined above, in at-risk patients one may infer a mechanism of prostanoid dependent conservation of arterial blood flow due to COX 2 upregulation. Selective COX 2 inhibition, because of its sparing of COX 1 and irreversible binding of COX 2, can be expected to upset this homoeostasis, increasing the risk for cardiovascular events. When prescribing NSAIDs, and especially selective COX 2 inhibitors, doctors should carefully weigh gastrointestinal harm with cardiovascular harm. Patients at risk for cardiovascular events should not be treated with selective COX 2 inhibitors.

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CHAPTER III

Proton-pump inhibitors are associated with a reduced risk for bleeding and perforated gastroduodenal ulcers attributable to non-steroidal anti-inflammatory drugs: a nested case-control study

Harald E Vonkeman, Robert W Fernandes,
Joh van der Palen, Eric N van Roon and Mart AFJ van de Laar

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ABSTRACT

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is hampered by gastrointestinal ulcer complications, such as ulcer bleeding and perforation. The efficacy of proton-pump inhibitors in the primary prevention of ulcer complications arising from the use of NSAIDs remains unproven. Selective cyclooxygenase-2 (COX-2) inhibitors reduce the risk for ulcer complications, but not completely in high-risk patients. This study determines which patients are especially at risk for NSAID ulcer complications and investigates the effectiveness of different preventive strategies in daily clinical practice. With the use of a nested case-control design, a large cohort of NSAID users was followed for 26 months. Cases were patients with NSAID ulcer complications necessitating hospitalisation; matched controls were selected from the remaining cohort of NSAID users who did not have NSAID ulcer complications.

During the observational period, 104 incident cases were identified from a cohort of 51,903 NSAID users with 10,402 patient years of NSAID exposure (incidence 1% per year of NSAID use, age at diagnosis 70.4 ± 16.7 years (mean ± SD), 55.8% women), and 284 matched controls. Cases were characterised by serious, especially cardiovascular, comorbidity. In-hospital mortality associated with NSAID ulcer complications was 10.6% (incidence 21.2 per 100,000 NSAID users). Concomitant proton-pump inhibitors (but not selective COX-2 inhibitors) were associated with a reduced risk for NSAID ulcer complications (the adjusted odds ratio 0.33; 95% confidence interval 0.17 to 0.67; p = 0.002). Especially at risk for NSAID ulcer complications are elderly patients with cardiovascular co-morbidity. Proton-pump inhibitors are associated with a reduced risk for NSAID ulcer complications.

INTRODUCTION

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is known to be complicated by gastrointestinal toxicity. NSAIDs impair prostaglandin-dependent gastric mucosal protective mechanisms. When these defences have been breached, a second wave of injury caused by luminal gastric acid may facilitate deeper ulceration.[1] Prevention of gastroduodenal ulcers attributable to the use of NSAIDs may target the inhibition of gastric acid secretion with histamine-2 receptor antagonists (H2RAs) or proton-pump inhibitors (PPIs). Alternatively, locally depleted endogenous cytoprotective prostaglandins may be replaced by the administration of prostaglandin E_1 analogues, such as misoprostol. Several studies have evaluated and compared these strategies.[2]

High-dose misoprostol is effective in the primary prevention of endoscopic NSAID ulcers and also NSAID ulcer complications, such as bleeding and perforation, but is often poorly tolerated because of diarrhoea and abdominal discomfort.[3] Elevation of the intragastric pH by PPIs and high-dose H2RAs reduces the risk of endoscopic NSAID ulcers.[2] In direct comparison, PPIs show an efficacy comparable to that of misoprostol, but they are better tolerated.[4] Furthermore, PPIs are more effective in the prevention of NSAID ulcers than lowdose H2RAs.[5] However, the efficacy of PPIs and H2RAs in the primary prevention of clinically relevant endpoints, such as bleeding and perforated NSAID ulcers, remains unproven. The discovery of the isoenzymes cyclooxygenase (COX)-1 and COX-2 made it possible to develop highly selective COX-2 inhibitors.[6] The hypothesis is that COX-1 is expressed constitutively and regulates normal physiology, such as the maintenance of gastric mucosal integrity. Conversely, COX-2 is expressed selectively after exposure to inflammatory mediators or trauma, and has a role in inflammation and pain.[7] In randomised controlled clinical trials, selective COX-2 inhibitors have demonstrated a decreased risk for NSAID ulcers and also ulcer complications.[8-11] Furthermore, in elderly patients with a recent history of bleeding NSAID ulcers, secondary prevention (preventing recurrent bleeding) with a selective COX-2 inhibitor seems comparable to combining a non-selective NSAID with a PPI, although in that study the number of cases was small and neither strategy provided adequate protection.[12]

Because of their relatively low incidence, severe gastrointestinal ulcer complications such as bleeding and perforated ulcers can be evaluated most effectively in large observational studies.[13] Randomised controlled clinical trials are designed to evaluate the efficacy of a certain strategy, and despite including thousands of patients they may fail to detect infrequent or long-term complications or side effects. Furthermore, rigorous inclusion and exclusion criteria are maintained, and those at high risk for drug side effects or complications are usually excluded. Conversely, in daily clinical practice, it is especially at-risk patients who are likely to be treated with these new strategies under the assumption of safe, evidence-based pharmacotherapy. Although observational studies are subject to possible bias, they best reflect daily clinical practice and are well suited to study infrequent and long-term complications and side effects. Therefore, to determine the characteristics of patients who are especially at risk for serious NSAID ulcer complications and to compare the effectiveness of different preventive strategies in daily clinical practice, we conducted a large nested case-control study.

MATERIALS AND METHODS

This nested case-control study was performed within the government-initiated healthcare region of the city of Enschede in The Netherlands. On 31 December 2003 the population consisted of 152,989 persons living in a well-defined geographically isolated area largely bordering on Germany. All in-patient healthcare is provided by a single teaching hospital, supplied with all diagnostic and therapeutic facilities. All drug prescriptions are registered in electronic prescription records of 14 local pharmacies. Most drugs, including NSAIDs, are provided by the patient's own pharmacy, directly reimbursed by the healthcare system. A cohort of NSAID users can be identified continuously from the electronic prescription records.

Serious NSAID ulcer complications were defined as ulcerations of the stomach or proximal duodenum causing perforation, obstruction or bleeding that occurred during the use of NSAIDs, necessitating hospitalisation of the patient.

SELECTION OF CASES

During a prospective 26-month observational period (November 2001 to December 2003), we identified all consecutive NSAID users who were hospitalised with serious NSAID ulcer complications. Most patients were identified during endoscopy or abdominal surgery. A few patients were identified on the basis of a clinical presentation of upper gastrointestinal bleeding alone, with haematemesis or melaena, if no further diagnostic procedure was performed because of co-morbidity or advanced age. In some of these patients the diagnosis was confirmed during autopsy. Patients were included in the study if they used NSAIDs (including selective COX-2 inhibitors) at the time of diagnosis of a gastroduodenal ulcer. Aspirin in high dosage (more than 100 mg daily) was considered to be a NSAID. As soon as possible after the diagnosis, patients were given a questionnaire on their sociodemographic characteristics, actual and recent medication, co-morbidity and medical history. The questionnaire contained specific items on the use of NSAIDs, aspirin, anticoagulants, gastroprotective drugs, and steroids, and also on the history of gastroduodenal events. For verification of the questionnaires, we reviewed the medical charts of all cases, as well as reports on endoscopy, surgery and pathology. Medication use before and during hospitalisation, as reported by the patient, was verified by reviewing prescription registrations provided by the in-hospital and community-based pharmacies. Patients were interviewed by one of the authors (HV) if ambiguities were encountered in the questionnaires or during verification. Patients were excluded if they reported not having used NSAIDs, if endoscopy, surgery or autopsy did not reveal gastroduodenal ulcers, if ambiguities remained despite interviewing the patient, if a malignancy of the stomach was diagnosed or if another reason for upper intestinal bleeding (such as esophagogastric varices, arteriovenous malformations, diffuse gastritis or Mallory – Weiss tears) was diagnosed.

SELECTION OF CONTROLS

Matched controls were selected from the remaining cohort of NSAID users. For selecting controls, index dates were defined as the day on which an NSAID ulcer was diagnosed in each of the cases. Controls were frequency-matched on sex and age, and had to be using NSAIDs (including selective COX-2 inhibitors) on the index date. Selected controls were asked to complete the same questionnaire as the cases. Medication use as reported by the controls was verified by reviewing prescription data-

bases. Controls were interviewed if ambiguities were encountered in the questionnaires or during verification. All non-responders were sent a second identical questionnaire. Finally, a random sample of non-responders was telephoned to detect bias in non-responding.

STATISTICAL ANALYSIS

In univariate analyses, potential confounding continuous variables were analysed with Student's t-test and nominal data were analysed with Pearson $\chi 2$ tests or Fisher's exact tests for small numbers. Multivariate analyses were performed by using logistic regression with NSAID ulcers as the dependent variable. A full model consisting of all significant and other likely causational variables was reduced stepwise to a parsimonious model. All p values were two-sided, and $p \leq 0.05$ was regarded as significant. All analyses were performed with SPSS for Windows, version 12.0.1 (SPSS, Chicago, IL, USA).

The study was approved by the Medical Ethics Reviewing Committee of the Medisch Spectrum Twente Hospital. There were no external sources of funding or study sponsors.

RESULTS

Over the 26-month prospective observational period the cohort of NSAID users contained 51,903 NSAID users with 10,402 patient years of NSAID exposure. From this cohort, 104 cases were hospitalised with serious NSAID ulcer complications. Because of the geographically isolated position, referral to other hospitals, especially for acute gastrointestinal events, is extremely rare. Therefore, in this population the incidence of hospitalisation due to serious NSAID ulcer complications can be reliably calculated at 1% per year of NSAID use.

Table 1 shows demographic characteristics and co-morbidities. The typical case is an elderly patient, age at diagnosis 70.4 ± 16.7 years (mean ± SD; range 22 to 98 years), 55.8% were female. Many patients reported concurrent disease or previous medical events suggesting serious, especially cardiovascular, co-morbidity. This self-reported co-morbidity was supported by the concomitant medication used (Table 2). The 104 cases together used 12 different NSAIDs (*Table 2*). The duration of NSAID use before the gastrointestinal event varied; the median was 1.13 months (interquartile range 10 days to 12 months). Most patients did not exceed their prescribed maximum daily dose. However, occasional use of more than one NSAID simultaneously was reported by 12 patients(11.5%).

In most cases (80 patients, 76.9%), serious NSAID ulcer complication was the reason for presentation and hospitalisation. In the remainder a serious NSAID ulcer complication took place during hospitalisation for another reason. Characteristics of the gastrointestinal events are presented in Table 3. No diagnostic procedure was performed in only six (5.8%) patients, because of co-morbidity or advanced age. The mean haemoglobin level at presentation was 6.1 ± 1.9 mmol/l (mean ± SD; range 1.8 to 9.8). In those using coumarin, the international normalized ratio (INR) at presentation was 4.87 ± 1.41(mean ± SD) but the mean haemoglobin level at presentation did not differ from that in patients not taking coumarin, and neither did the number of units of blood administered during hospitalisation.

Tabel 1: Sociodemographic characteristics and co-morbidities for cases and controls

Characteristic	Cases (n = 104)	Controls (n = 284)	OR	95% CI	p
Age at diagnosis (years)	70.4 ± 16.7	67.1 ± 14.3			
Female sex	58 (55.8)	163 (57.4)			
Body mass index (kg/m2)	24.7 ± 4.7	26.7 ± 4.6	-	-	0.001
Smoking	28 (26.9)	51 (18)	1.96	1.15–3.37	0.01
Alcohol (glasses per week)	9.6 ± 33.2	6.2 ± 8.6	-	-	0.12
Coffee (cups per week)	18.9 ± 20.6	22.8 ± 13.8	-	-	0.06
Education low vocational or less	39 (56.5)	176 (64.0)	0.73	0.43–1.25	0.25
Married	42 (46.7)	166 (59.3)	0.60	0.37–0.97	0.04
Medical history					
Hypertension	30 (28.8)	95 (33.5)	0.81	0.49–1.32	0.39
Heart failure	26 (25.0)	32 (11.3)	2.63	1.48–4.67	0.001
COPD	25 (24.0)	57 (20.1)	1.26	0.74–2.15	0.40
Myocardial infarction	20 (19.2)	32 (11.3)	1.88	1.02–3.45	0.04
Stroke	18 (17.3)	28 (9.9)	1.91	1.01–3.63	0.04
Heart rhythm disturbance	18 (17.3)	52 (18.3)	0.93	0.52–1.69	0.82
Diabetes mellitus	16 (15.4)	33 (11.6)	1.38	0.73–2.64	0.32
Anaemia	16 (15.4)	32 (11.3)	1.43	0.75–2.74	0.28
Renal insufficiency	16 (15.4)	15 (5.3)	3.26	1.55–6.86	0.001
Previous gastrointestinal ulcers	16 (15.4)	33 (11.7)	1.37	0.72–2.60	0.34
Malignancy	15 (14.4)	26 (9.2)	1.67	0.85–3.30	0.14
Rheumatoid disease, including OA	42 (40.4)	97 (34.2)	1.31	0.82–2.07	0.26

Scores are means ± SD or number of patients (percentage). OR, unadjusted odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OA, osteoarthritis.

Mortality due to serious NSAID ulcer complications was high: 11 patients (10.6%) died in hospital, and another 4 (3.8%) died within 3 months of the diagnosis. The incidence of in-hospital mortality due to serious NSAID ulcer complications can be calculated at 21.2 per 100,000 NSAID users.

For 104 cases, 757 controls were selected from the remaining cohort of NSAID users. On receiving the first questionnaire 225 controls responded, of whom 203 were included. On receiving a second questionnaire, a further 123 responded, of whom 81 were included. From the 64 excluded responders, 18 questionnaires were returned by someone other than the selected control, 15 denied taking NSAIDs, 17 refused, 1 had been hospitalised in a psychiatric hospital, 1 was a case who had already been included as such, and for 12 controls relatives informed us that the selected person had died. In the group of 20 randomly selected non-responders who were telephoned, no bias for non-responding was found.
In total 284 controls, frequency matched for age and sex, with NSAID use on the index date were included. Demographic characteristics, co-morbidities and current medication use are summarised in Tables 1 and 2. The mean age was slightly lower for the controls than for the cases because insufficientnumbers of controls could be found for some of the extremely elderly cases.

Table 2: NSAIDs and concurrent medication in use at the time of the gastrointestinal event

Medication	Cases (n = 104)	Controls (n = 284)	OR	95% CI	p
Non-selective NSAIDs					
Indometacin	3 (2.9)	4 (1.4)	2.08	0.46–9.45	0.39
Naproxen	10 (9.6)	14 (4.9)	2.05	0.88–4.78	0.09
Diclofenac	44 (42.3)	108 (38.0)	1.20	0.76–1.89	0.44
Diclofenac–misoprostol	8 (7.7)	19 (6.7)	1.16	0.49–2.74	0.73
Other NSAIDs	3 (2.9)	8 (2.8)	1.03	0.27–3.94	1.00
Ibuprofen	16 (15.4)	69 (24.3)	0.57	0.31–1.03	0.06
High-dose aspirin (>100 mg/day)	2 (1.9)	0 (0.0)	-	-	0.07
Selective NSAIDs					
Rofecoxib	16 (15.4)	42 (14.8)	1.05	0.56–1.96	0.88
Celecoxib	1 (1.0)	8 (2.8)	0.34	0.04–2.71	0.46
Meloxicam	1 (1.0)	12 (4.2)	0.22	0.03–1.71	0.20
Gastroprotective drugs					
Proton-pump inhibitors	14 (13.5)	77 (27.1)	0.42	0.23–0.78	0.005
H2RAs	4 (3.8)	9 (3.2)	1.22	0.37–4.06	0.74
Misoprostol	8 (7.7)	20 (7.0)	1.10	0.47–2.58	0.83
Additional risk factors					
High-dose NSAID	11 (10.6)	17 (6.0)	1.86	0.84–4.11	0.12
More than one NSAID	12 (11.5)	54 (19.0)	0.56	0.28–1.09	0.08
Low-dose aspirin (≤ 100 mg/day)	32 (30.8)	69 (24.3)	1.39	0.84–2.28	0.20
Clopidogrel/dipyridamole	5 (4.8)	9 (3.2)	1.54	0.51–4.72	0.54
Coumarin	14 (13.5)	19 (6.7)	2.17	1.05–4.51	0.04
Low-molecular-mass heparin	13 (12.5)	2 (0.7)	20.14	4.46–90.94	<0.001
SSRIs	6 (5.8)	9 (3.2)	1.87	0.65–5.39	0.24
Corticosteroids	14 (13.5)	32 (11.3)	1.23	0.63–2.40	0.55
Analgesics					
Acetaminophen	45 (43.3)	54 (19.0)	3.25	1.99–5.29	<0.001
Tramadol	12 (11.5)	6 (2.1)	6.04	2.21–16.56	<0.001
Morphine	6 (5.8)	2 (0.7)	8.63	1.71–43.48	0.006
Cardiovascular drugs					
Diuretics	34 (32.7)	57 (20.1)	1.93	1.17–3.20	0.009
ACE inhibitors	24 (23.1)	32 (11.3)	2.36	1.32–4.25	0.003
Digoxin	8 (7.8)	11 (3.9)	2.09	0.82–5.35	0.12
Beta-blockers	22 (21.2)	64 (22.5)	0.92	0.53–1.59	0.77
Nitrates	8 (7.7)	26 (9.2)	0.83	0.36–1.89	0.65
Calcium-channel blockers	10 (9.6)	35 (12.3)	0.76	0.36–1.59	0.46
Lipid-lowering drugs	9 (8.7)	38 (13.4)	0.61	0.29–1.32	0.21
Oral glucose-lowering drugs	12 (11.5)	15 (5.3)	2.34	1.06–5.18	0.03
Benzodiazepines	34 (32.7)	65 (22.9)	1.64	0.99–2.68	0.05
Inhalator therapy	22 (21.2)	56 (19.7)	1.09	0.63–1.90	0.76
DMARDs	14 (13.5)	20 (7.0)	2.05	0.99–4.23	0.05

Scores are number of patients (percentage). NSAIDs, non-steroidal anti-inflammatory drugs; OR, unadjusted odds ratio; CI, confidence interval; H2RAs, histamine-2 receptor antagonists; SSRIs, selective serotonin re-uptake inhibitors; ACE, angiotensin-converting enzyme; DMARDs, disease-modifying anti-rheumatic drugs. High-dose NSAID is more than the daily defined dose.

STATISTICAL RESULTS

In univariate analysis, cases and controls differ significantly with regard to body mass index, smoking habits, marital status, medical history of heart failure, myocardial infarction, stroke and renal insufficiency (Table 1). Significant differences in medication use were found for PPIs, coumarin, low-molecular mass heparin, analgesics, diuretics, angiotensin-converting-enzyme inhibitors, oral glucose-lowering drugs, benzodiazepines and disease-modifying anti-rheumatic drugs (*Table 2*).

Concomitant use of PPIs was significantly higher in the controls than in the cases (cases 13.5%; controls 27.1%; p = 0.005). Use of selective COX-2 inhibitors was comparable (cases 16.4%; controls 17.6%; p = 0.77). Use of the preferential COX-2 inhibitor meloxicam differed, but not significantly, and numbers were small (cases 1%; controls 4.2%; p = 0.20).

A full logistic regression model of all significant and other likely causational variables was reduced stepwise to a parsimonious model, finally containing concomitant use of PPIs, low-molecular-mass heparin, acetaminophen, coumarin, and history of heart failure (Table 4). Use of selective COX-2 inhibitors was not associated with a significantly reduced risk for serious NSAID ulcer complications (p = 0.74); neither was the use of preferential COX-2 inhibitors (p = 0.22). Concomitant use of PPIs was associated with a significantly reduced risk for serious NSAID ulcer complications (adjusted odds ratio 0.33; 95% confidence interval 0.17 to 0.67; p = 0.002).

In a post hoc subgroup analysis of selective COX-2 inhibitor users, there were no significant differences in concomitant use of low-dose aspirin (8 cases (47%); 19 controls (38%); p = 0.51), non-selective NSAIDs (3 cases (18%); 10 controls (20%); p = 0.83) or PPIs (3 cases (18%); 17 controls (34%); p = 0.20); neither were there significant differences in concomitant use of coumarin, heparin, steroids or high-dose H2RAs or in ulcer history.

Furthermore, among those taking selective COX-2 inhibitors, cases and controls did not differ significantly with regard to the number of risk factors for NSAID-associated gastropathy, suggesting comparable risk profiles. Similarly, in a post hoc subgroup analysis for those taking either proton-pump inhibitors or high-dose H2RAs, cases and controls again did not differ significantly with regard to the number of risk factors for NSAID-associated gastropathy.

In six patients no diagnostic procedure was performed because of co-morbidity or advanced age. In a post hoc analysis these patients with probable NSAID ulcers were compared with the 98 patients with definite NSAID ulcers. Significant differences between patients with probable or definite NSAID ulcers were age (mean 87.3 and 69.4 years, respectively; p = 0.01), medical history of diabetes mellitus, chronic obstructive pulmonary disease and in-hospital mortality (66.7% and 7.1%, respectively; p = 0.001). Excluding these patients with probable NSAID ulcers from the cases did not significantly change the results of the univariate or multivariate analyses.

In 24 patients, serious NSAID ulcer complications occurred in hospital. These patients were compared

Table 3: Characteristics of the gastrointestinal event attributable to use of non-steroidal anti-inflammatory drugs

Characteristic	Number (percentage)
Clinical presentation	
Melaena	65 (62.5)
Haematemesis	28 (26.9)
Perforation	12 (11.5)
Stomach pain	21 (20.2)
Collapse	16 (15.4)
No previous stomach complaints	57 (54.8)
Ulcer location	
Gastric	53 (51.0)
Duodenal	34 (32.7)
Both gastric and duodenal	11 (10.6)
No diagnostic procedure performed	6 (5.7)
Ulcer perforation	14 (13.5)
Helicobacter pylori	
Positive	21 (20.2)
Negative	45 (43.3)
Not tested	38 (36.5)

The total number of patients was 104.

Table 4: Multivariate analysis of significant variables and other likely causational variables for serious NSAID ulcer complications

Predictor	Adjusted OR	95% CI	p
Proton-pump inhibitors	0.33	0.17–0.67	0.002
Coumarin	2.09	0.93–4.70	0.075
Heart failure	2.44	1.28–4.66	0.007
Acetaminophen	2.80	1.64–4.79	<0.001
Low-molecularmass heparin	17.33	3.71–80.95	<0.001

Serious non-steroidal anti-inflammatory drug (NSAID) ulcer complication was the dependent variable. Only variables from the final parsimonious model are shown. OR, odds ratio; CI, confidence interval.

Table 5: Multivariate analysis after exclusion of patients with inhospital NSAID ulcer complications

Predictor	Adjusted OR	95% CI	p
Proton-pump inhibitors	0.31	0.15–0.66	0.002
Coumarin	2.38	1.03–5.48	0.04
Heart failure	2.10	1.04–4.21	0.04
Acetaminophen	2.47	1.39–4.39	0.002
Low-molecularmass heparin	6.06	0.91–40.6	0 .06

Serious non-steroidal anti-inflammatory drug (NSAID) ulcer complication was the dependent variable. Only variables from the final parsimonious model are shown. OR, odds ratio; CI, confidence interval.

with the 80 patients who presented with NSAID ulcer complications. Significant differences between in-hospital or presenting patients were sex (37.5% and 61.3% female, respectively; p = 0.04), ulcer history (29.2% and 11.3%, respectively; p = 0.03), medical history of a malignancy, diabetes mellitus, use of oral glucoselowering drugs and use of low-molecular-mass heparin (45.5% and 3.8%, respectively; p < 0.001). Exclusion of these in-hospital patients from the cases resulted in a significant change in the univariate analyses for use of oral glucose-lowering drugs (cases 6.3%; controls 5.3%; p = 0.74) and for use of low molecular mass heparin (cases 3.8%; controls 0.7%; p = 0.04). The results of the multivariate analysis also changed (*Table* 5).

DISCUSSION

In this nested case-control study, the concomitant use of proton-pump inhibitors was associated with a two-thirds reduction in the risk for serious NSAID ulcer complications. The efficacy of PPIs in the primary prevention of NSAID-associated gastropathy has so far only been proven for subjective symptoms and surrogate endpoints, such as dyspepsia and endoscopic ulcers, and in the secondary prevention of serious NSAID ulcer complications, PPIs do not seem to prevent recurrence.[12,14,15] Our data suggest that PPIs may be effective in the primary prevention of clinically relevant bleeding and perforated NSAID ulcers, confirming other recent observational studies.[16-18] However, randomised controlled trials powered on these hard endpoints need to be conducted to prove efficacy.

It is noteworthy that in this study the use of selective COX-2 inhibitors was not associated with protection for serious NSAID ulcer complications. Lack of protection from selective COX-2 inhibitors could not be explained by confounders such as concomitant use of aspirin, coumarin, heparin or steroids or by ulcer history. Previous studies demonstrating the efficacy of selective COX-2 inhibitors in the primary prevention of NSAID ulcer complications largely excluded high-risk patients, whereas in high-risk patients selective COX-2 inhibitors may fail to prevent the recurrence of NSAID ulcer bleeding.[12,14,15] Although neither selective COX-2 inhibitors nor concomitant PPIs seem to be entirely effective in preventing the recurrence of ulcer complications, our data suggest that PPIs may be superior to selective COX-2 inhibitors in the primary prevention of NSAID ulcer complications.

Cases used coumarin more often than controls (adjusted odds ratio 2.09; 95% confidence interval 0.93 to 4.70; p = 0.075). Furthermore, in those cases using coumarin, the mean INR at presentation was 4.87 ± 1.41 (mean ± SD) and one-third (5 patients) had an INR greater than 6.5. Although no INR was measured in the controls, it is possible that this elevated INR contributed to these patients developing serious NSAID ulcer bleeding.

Cases used low-molecular-mass heparin significantly more often than controls (adjusted odds ratio 17.33; 95% confidence interval 3.71 to 80.95; p < 0.001). In addition, cases used acetaminophen significantly more often than controls (adjusted odds ratio 2.80; 95% confidence interval 1.64 to 4.79; p < 0.001). It is possible that these differences reflect in-hospital treatment protocols rather than a true elevated risk for serious NSAID ulcer complications. However, an increased risk for NSAID ulcers with concomitant high-dose acetaminophen has been reported previously.[13] Exclusion of patients with in-hospital NSAID ulcer complications truncated the odds ratio for low-molecular-mass heparin (adjusted

odds ratio 6.06; 95% confidence interval 0.91 to 40.60; p = 0.06; Table 5).
Cases reported a history of heart failure significantly more often than controls (adjusted odds ratio 2.44; 95% confidence interval 1.28 to 4.66; p = 0.007). The association between heart failure and risk for NSAID-associated gastropathy has previously been demonstrated, but a credible causational mechanism remains to be identified.[19]

One of the strengths of this study is that it reflects daily clinical practice. The large randomised controlled clinical trials that demonstrated the efficacy and safety of selective COX-2 inhibitors were conducted in relatively young, healthy subjects. Our study suggests that these may not be the patients who areespecially at risk for serious NSAID ulcer complications and confirms another recently conducted large nested case-control study that also found no evidence for enhanced gastrointestinal safety with selective COX-2 inhibitors.[20] Another strength of our study lies in the robustness of the data. Gastrointestinal events in cases and controls were verified, as were data on actual medication used. Other groups have studied populations of up to several thousand patients, but associations were derived by coupling databases and the validity of the data was not always verified.[21,22]

The local infrastructure makes it unlikely that many cases were missed. However, one weakness of this study is that underestimation of the number of events might still have occurred. Another weakness of this study, as in any case-control study, is the possibility of selection bias. Although we have controlled for all known possible confounders, selection by indication or an unknown confounding mechanism cannot be excluded with certainty.

CONCLUSION

Serious NSAID ulcer complications have a significant mortality rate: 10.6% die in hospital and 14.4% within 3 months of the event. At risk are especially elderly patients with cardiovascular co-morbidity. In daily clinical practice, the concomitant use of PPIs is associated with a two-thirds reduction in the risk for serious NSAID ulcer complications.

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CHAPTER IV

Underutilization of gastroprotective drugs in patients with NSAID-related ulcers

H.E. Vonkeman, R.W. Fernandes and M.A.F.J. van de Laar

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Abstract

Objective To determine the proportion of patients with a risk of NSAID gastropathy receiving adequate gastroprotection.

Methods This observational study was performed between November 2001 and December 2003. We selected patients who were hospitalized with perforated and bleeding gastroduodenal ulcers attributable to NSAID use and controls without ulcers. Data were collected on their sociodemographic characteristics, actual and recent medication, co-morbidity and medical history. For each patient and control the number of different risk factors associated with NSAID gastropathy was calculated. A composite risk factor (CRF) was obtained from the sum of all separate risk factors.

Results During the observational period a total of 388 patients using NSAIDs were included in the study, 104 patient cases and 284 matched community-based controls. The mean CRF was significantly higher in patient cases than in controls (cases mean CRF 3.31 (SD 1.67) and controls mean CRF 2.76 (SD 1.45), $p = 0.002$). A total of 148 (38%) patients used an adequate preventative strategy. Significant variables for using a preventative strategy were concomitant use of steroids (corrected odds ratio 4.22, 95% CI 2.11 – 8.47, $p < 0.001$), a history of gastroduodenal ulcers (corrected odds ratio 2.90, 95% CI 1.51 – 5.56, $p = 0.001$) and concomitant use of low dose aspirin (corrected odds ratio 1.96, 95% CI 1.18 – 3.25, $p = 0.01$). Among patients with 4 or more risk factors associated with NSAID gastropathy, 47% still did not use adequate gastroprotection.

Conclusion Gastroprotective drugs are greatly underutilized in patients with a risk of NSAID gastropathy.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are worldwide one of the most frequently prescribed classes of drugs. The most common complication of treatment with NSAIDs is gastrointestinal toxicity. The spectrum of NSAID-related gastrointestinal toxicity may be categorized into 3 groups:

- subjective symptoms like heartburn, dyspepsia, nausea and abdominal pain are most common, occurring in 15 – 40% of NSAID users and causing 10% to change or discontinue their NSAID use.
- superficial gastroduodenal mucosa lesions such as erosions and asymptomatic ulcers occur in 5 – 20% of NSAID users and may heal spontaneously, and
- serious symptomatic gastrointestinal ulcers with life-threatening complications like perforation and bleeding (perforation, ulcer, bleeding, PUB) occur in 1 – 2% of NSIAD users, and for these events mortality is high at 10 – 15%.[1-6]

Several different strategies have been developed to prevent NSAID gastropathy. Concomitant use of high-dose misoprostol has been shown to be effective, but patient compliance is low because misoprostol is often poorly tolerated due to abdominal discomfort and diarrhea.[7] In large randomized controlled clinical trials the use of selective cyclooxygenase-2 (COX-2) inhibitors has been shown to approximately half the risk for NSAID-attributable gastroduodenal ulcers.[1,5,8,9] Concomitant use of histamine-2 receptor antagonists (H2RAs) at standard dosage has been shown to prevent NSAID-associated duodenal ulcers but not gastric ulcers, while high dose H2RAs prevent both.[10] Concomitant use of proton pump inhibitors (PPIs) at standard dosage has been shown to prevent both gastric and duodenal NSAID-attributable ulcers.[10,11,12] In direct comparison PPIs appear to be more effective than H2RAs.[13] Also, in direct comparison, PPIs show comparable efficacy to misoprostol, but are better tolerated.[14] Furthermore, in direct comparison, PPIs show comparable efficacy to selective COX-2 inhibitors in preventing recurrent bleeding in NSAID-taking patients with a recent history of a bleeding gastroduodenal ulcer.[15,16] Several effect modifiers in the relationship between NSAID use and the risk of gastroduodenal ulcers have been identified. These include type, dosage and duration of NSAID use, the patient's age, infection with Helicobacter pylori, comorbid conditions such as diabetes mellitus, heart failure and rheumatoid arthritis, and concomitant use of aspirin, platelet inhibitors, anticoagulants and corticosteroids.[17] Based on these risk factors, several medical societies and scientific associations have issued guidelines for the prevention of NSAID gastropathy.[18] Patients using NSAIDs who have 1 or more additional risk factors for developing NSAID ulcers are advised to either concomitantly use PPIs, high-dose H2RAs, misoprostol or alternatively to switch to selective COX-2 inhibitors.[18] Implementation of these guidelines has risen over the last years, but remains far from complete. Before 2000, in Germany and the Netherlands only 20% of those with additional risk factors used gastroprotective co-therapy.[19,20,21] Despite demonstrating better efficacy than PPIs in preventing NSAID gastropathy, misoprostol is hardly ever prescribed due to poor tolerability, and accounts for only 5% of all gastroprotective co-therapy.[12,22] In 2001, in the Netherlands, the percentage of long-term NSAID users with an adequate gastroprotective strategy had risen to 28%.[23] This was partly due to the availability of selective COX-2 inhibitors form 1999 onwards, which took the market by storm through aggressive marketing, but also because of increased awareness of NSAID gastropathy among physicians and patients, which followed in its wake. Risk factors for NSAID gastropathy appear to be additive.[24] Prescription rates

of adequate gastroprotection also increases with the number of risk factors, but in 2001, almost 40% of the patients with 4 or more risk factors were still not adequately protected.[23]
To date, most information on numbers of patients at risk for NSAID gastropathy and the percentage with adequate gastroprotection originates from a few large drug prescription databases, which may be linked to clinical databases containing hospital discharge diagnoses or primary care information.[21,22,23] However, discrepancies exist between prescribed medication and medication actually being taken by patients, and in prescription databases over-the-counter medication is missed. Furthermore, hospital discharge databases are limited to information on a subset of patients who have been hospitalized, and are incomplete with respect to medical history and comorbidity, and do not contain actual information.
Therefore, to accurately determine the relationship between risk factors for NSAID gastropathy and the likelihood of receiving adequate gastroprotection, we interviewed cases with serious NSAID-attributable gastroduodenal ulcers and NSAID-taking controls without serious gastroduodenal ulcers on their medical history, current medication and comorbid conditions.

METHODS

The population of 153,000 of the city of Enschede in the Netherlands lives in a well-defined area largely bordering upon Germany. All inpatient healthcare is provided by a single large teaching hospital. Medication use of this population is monitored by community-based pharmacies, using electronic medication prescription records. The cohort of NSAID users within this population can be continuously identified. The majority of drugs, including NSAIDs, are provided by the patients own pharmacy, directly reimbursed by the healthcare system. Over-the-counter medication use is infrequent.
During an observational period from November 2001 until December 2003, we identified all NSAID-related ulcer patients. All consecutive patients, hospitalized in the Medisch Spectrum Twente Hospital in Enschede with gastroduodenal ulcers were identified and all patients who used NSAIDs during the development of the gastroduodenal ulcer, were selected. The second group of NSAID users, controls without serious gastroduodenal ulcers, were retrieved from the remaining cohort of NSAID users, from the prescription registration databases of participating community-based pharmacies. Controls were frequency matched on sex, age and ulcer index date. We aimed to attain a 1 – 4 ratio for cases to controls.
Patients and controls were given a questionnaire on their sociodemographic characteristics, actual and recent medication, comorbidity and medical history. The questionnaire contained specific items on the use of NSAIDs, aspirin, anticoagulants, gastroprotective drugs, steroids and also on the history of gastrointestinal events. When applicable for reasons of verification of the questionnaires, we reviewed medical charts, as well as endoscopy-, surgery- and pathology reports. Medication use could be verified by reviewing prescription records from community-based pharmacies and during hospitalization by reviewing prescription records provided by the inhospital pharmacy. Patients and controls were interviewed by one of us (HV) if ambiguities were encountered in the questionnaires or during verification.

RISK FACTORS FOR NSAID GASTROPATHY

Risk factors for NSAID gastropathy were adapted from the Dutch guideline for NSAID use and the prevention of gastropathy.[18] Identified risk factors were: advanced age (over 60 years of age), a history of gastroduodenal ulcers, severe rheumatoid arthritis (requiring the use of disease modifying antirheumatic drugs), heart failure, diabetes mellitus, concurrent use of aspirin, platelet inhibitors (clopidogrel or dipyridamole), anti-coagulants (coumarins), heparin, steroids, selective serotonin reuptake inhibitors, high NSAID dosage (daily average more than the prescribed maximum daily dose), chronic NSAID use (longer than 90 days daily), and the use of more than 1 NSAID simultaneously. Together,[14] different risk factors were identified; 1 known risk factor for NSAID gastropathy which was not included in the present risk set is untreated Helicobacter pylori infection in patients with a history of gastroduodenal ulcers. In concordance with previous studies, risk factors for NSAID gastropathy were considered to be additive.[17,23] For each patient the number of different risk factors for NSAID gastropathy was calculated. Risk factors were not weighed. Since a data-based composite measure is lacking, a simple composed risk factor was defined as the sum of all abovementioned risk factors as a separate variable.[23] This composed risk factor (CRF), therefore, has a range of 0 – 14.

OUTCOME DEFINITION

Serious NSAID-attributable gastroduodenal ulcers were defined as ulcerations of the stomach or proximal duodenum causing pain, perforation, obstruction and/or bleeding during NSAID use, necessitating hospitalization of the patient.

Adequate strategies for the prevention of NSAID-attributable gastroduodenal ulcers were defined as concomitant use of PPIs at standard daily dosage or more, H2RAs at twice standard daily dosage or more, misoprostol at 800 µg daily or more, or the use of the selective COX-2 inhibitors rofecoxib or celecoxib.

ANALYSES

In univariate analyses, continuous variables were analyzed using Student's t-test and nominal data using Pearson's χ^2-tests. Multivariate analyses were performed using logistic regression with use of gastroprotective strategies as the dependent variable. A full model consisting of all significant and also other likely associated variables was reduced to a parsimonious model. For all analyses $p < 0.05$ was considered significant. All analyses were performed with SPSS for Windows, version 12.0.1 (SPSS, Chicago, IL, USA).

The study was approved by the Medical Ethics Reviewing Committee of the Medisch Spectrum Twente Hospital.

RESULTS

During the observational period, 388 NSAID-using patients were included in the study, 104 cases, hospitalized with perforated and bleeding gastroduodenal ulcers and 284 matched community-based controls. All 388 subjects completed the same questionnaire and the results were verified by reviewing medical charts and prescription registration databases. Mean age was 68 years (youngest 22, oldest 98 years), 57% were women. All patients were asked to report their length and weight; the calculated

Table 1. Odds ratio for serious NSAID gastropathy in cases and controls grouped for the composed risk factor

Composed risk factor	Total No. 388	Cases No. 104	Controls No. 284	Odds for serious NSAID gastropathy	p value
0	19 (4.9%)	3 (2.9%)	16 (5.6%)	Reference	Reference
1	53 (13.7%)	15 (14.4%)	38 (13.4%)	1.09 [0.88 – 1.35]	0.77
2	80 (20.6%)	15 (14.4%)	65 (22.9%)		
3	107 (27.6%)	18 (17.3%)	89 (31.3%)	1.16 [0.93 – 1.43]	0.41
4	77 (19.8%)	32 (30.8%)	45 (15.8%)		
5	36 (9.3%)	15 (14.4%)	21 (7.4%)	1.37 [1.01 – 1.84]	0.09
6	11 (2.8%)	3 (2.9%)	8 (2.8%)		
7	1 (0.3%)	1 (1.0%)	0 (0.0%)	2.11 [0.71 – 6.27]	0.08
8	3 (0.8%)	1 (1.0%)	2 (0.7%)		
9	1 (0.3%)	1 (1.0%)	0 (0.0%)		

Composed risk factor = sum of separate risk factors for NSAID gastropathy. Numbers are number of patients (%), Odds [95% confidence interval].

body mass index was 30 or greater in 17% and 20 or less in 6%. For alcohol consumption 48% reported never drinking while 9% reported drinking more than 14 units a week, 9% did not drink coffee while 34% drank more than 21 cups a week, 20% were self reported smokers. For education levels 26% reported no continued education after primary school. Marital status was married for 54% and widowed for 31%. Many Patients reported severe comorbidity, 36% reported rheumatic diseases including osteoarthritis, 21% chronic pulmonary disease, 15% heart failure, 13% diabetes mellitus and 11% a previous or current malignant disease. Self-reported comorbidity was supported by current medication use except for rheumatic diseases, only 9% used disease-modifying antirheumatic drugs. Among the 388 patients, 13 different NSAIDs were used. Most common non-selective NSAIDs were: diclofenac 46%, ibuprofen 22% and naproxen 6%. Selective COX-2 inhibitors were rofecoxib 15% and celecoxib 2%, 24% concomitantly used PPIs and 3% high-dose H2RAs. Misoprostol was used by 28 (7%) patients. All but 1 used misoprostol in a fixed combination with diclofenac, none used misoprostol at the recommended 800 µg or more daily.

The composed risk factor (CRF) ranged from 0 – 9. Most patients (82%) had a CRF between 1 and 4 (*Table 1*). Only 19 (5%) patients had no additional risk factors for NSAID gastropathy (CRF 0). The overall mean CRF was 2.91 (SD 1.53). The mean CRF was significantly higher for cases than controls (cases mean CRF 3.31 (SD 1.67) and controls mean CRF 2.76 (SD 1.45), p = 0.002). The odds ratio for serious NSAID-attributable gastroduodenal ulcers rises with subsequently higher CRF counts. However, due to small numbers of patients, this was not statistically significant, although CRF counts were grouped (*Table 1*).

Overall, 148 (38%) patients used an adequate strategy for the prevention of NSAID attributable gastroduodenal ulcers (Table 2). The odds ratio for using a preventative strategy also rises with subsequently higher CRF counts. In the group at lowest risk for NSAID gastropathy (CRF 0), the prevalence of using a preventive strategy is 21%. In successive groups with higher CRF counts, the percentage of

Table 2. Number of patients using selective COX-2 inhibitors, proton pump inhibitors, high-dose histamine-2 receptor antagonists or any preventive strategy grouped for the composed risk factor

Composed risk factor	Number of patients	Selective COX-2 inhibitors	PPIs or high-dose H2RAs	Any preventive strategy	Odds for using any preventive strategy	p value
0	19	0 (0%)	4 (21%)	4 (21%)	Reference	Reference
1	53	2 (4%)	11 (21%)	13 (25%)	1.14 [0.35 – 3.69]	1.00
2	80	8 (10%)	12 (15%)	18 (22%)		
3	107	22 (21%)	32 (30%)	44 (41%)	2.95 [0.94 – 9.23]	0.09
4	77	19 (25%)	23 (30%)	37 (48%)		
5	36	10 (28%)	14 (39%)	20 (56%)	5.06 [1.46 – 17.6]	0.01
6	11	3 (28%)	5 (46%)	7 (64%)		
7	1	0 (0%)	1 (100%)	1 (100%)	Undefined	Undefined
8	3	2 (67%)	3 (100%)	3 (100%)		
9	1	1 (100%)	1 (100%)	1 (100%)		
Total	388	67 (17%)	106 (27%)	148 (38%)	2.40 [0.78 – 7.38]	0.15

Composed risk factor = sum of separate risk factors for NSAID gastropathy, COX-2 = cyclooxygenase-2, PPIs = proton-pump inhibitors, H2RAs = histamine-2 receptor antagonists, numbers are number of patients (%), Odds [95% confidence interval].

patients using selective COX-2 inhibitors, concomitant PPIs or high-dose H2RAs rises. In the groups with the highest number of risk factors (CRF 7 – 9) all patients use a preventative strategy. However, large numbers of patients at risk for NSAID gastropathy still remain unprotected. Among those with a CRF of 4 or more, 47% did not use a preventative strategy.

In accordance with earlier data, elderly patients over 60 years of age with a history of gastroduodenal ulcers are regarded as having the highest risk for NSAID-attributable gastroduodenal ulcers. In this study, we identified 39 such patients, with a mean age of 73.9 years (SD 7.7). Of these, 10 (26%) used selective COX-2 inhibitors, 22 (56%) used PPIs or high-dose H2RAs, 25 (64%) used either of these strategies and 6 (15%) used both strategies simultaneously. Consequently, 36% of these elderly NSAID-taking patients with a history of gastroduodenal ulcers did not use a gastroprotective strategy.

Controls used significantly more often a preventative strategy (either concomitant PPIs, high-dose H2RAs or a selective COX-2 inhibitor) than cases (controls 117 (41%) and cases 31 (30%), odds ratio 1.65, 95% CI 1.02 – 2.67, p = 0.04). Controls also used more often a combination of preventative strategies, i.e. a selective COX-2 inhibitor and a PPI simultaneously. However, this difference was not significant and the numbers were small (controls 21 (7%), cases 3 (3%), p = 0.10).

In univariate analyses, the use of a preventative strategy was associated with the patient's age, history of gastroduodenal ulcers, concomitant use of steroids, concomitant use of low-dose aspirin, chronic NSAID use, and history of heart failure (Table 3). A full logistic regression model containing all risk factors was reduced stepwise to a parsimonious model. Significant variables for using a preventative strategy were concomitant use of steroids (corrected odds ratio 4.22, 95% CI 2.11 – 8.47, p < 0.001),

Table 3. Odds ratio for using any preventive strategy grouped for individual risk factors for NSAID gastropathy.

Risk factor	Number of patients	Any preventive strategy	Odds ratio for any preventive strategy	p value	Odds ratio for serious NSAID ulcers
Age > 60 years	281	118 (42%)	1.86 [1.15 – 3.01]	0.001	1.28 [0.76 – 2.15]
History of ulcer	49	29 (59%)	2.68 [1.45 – 4.94]	0.002	1.37 [0.72 – 2.60]
Steroids	46	31 (67%)	3.97 [2.06 – 7.66]	0.000	1.23 [0.63 – 2.40]
Low dose aspirin	101	50 (50%)	1.89 [1.19 – 3.00]	0.009	1.39 [0.84 – 2.28]
> 90 days	156	70 (45%)	1.61 [1.06 – 2.44]	0.03	0.78 [0.48 – 1.24]
More than DDD	28	7 (25%)	0.52 [0.21 – 1.25]	0.16	1.86 [0.84 – 4.11]
2nd NSAID	66	28 (42%)	1.24 [0.72 – 2.12]	0.49	0.56 [0.28 – 1.09]
Platelet inhibitors	14	6 (43%)	1.23 [0.42 – 3.60]	0.78	1.54 [0.51 – 4.72]
Coumarins	33	11 (33%)	0.80 [0.37 – 1.69]	0.71	2.17 [1.05 – 4.51]
Heparin	16	3 (19%)	0.36 [0.10 – 1.29]	0.12	20.1 [4.46 – 90.9]
SSRIs	15	6 (40%)	1.09 [0.38 – 3.11]	1.00	1.87 [0.65 – 5.39]
Rheumatic disease	34	13 (38%)	1.00 [0.49 – 2.07]	1.00	1.31 [0.82 – 2.07]
Diabetes mellitus	49	21 (43%)	1.25 [0.68 – 2.30]	0.53	1.38 [0.73 – 2.64]
Heart failure	58	29 (50%)	1.77 [1.01 – 3.11]	0.06	2.63 [1.48 – 4.67]

Numbers are number of patients (%), OR [95% confidence interval]. DDD = daily defined dose, SSRIs = selective serotonin reuptake inhibitors. OR for serious NSAID gastropathy for cases versus controls are presented for individual risk factors as a relative weighting of the risk factors.

a history of gastroduodenal ulcers (corrected odds ratio 2.90, 95% CI 1.51 – 5.56, p = 0.001), and concomitant use of low-dose aspirin (corrected odds ratio 1.96, 95% CI 1.18 – 3.25, p = 0.01).

DISCUSSION

Our data show that a remarkable proportion of patients suffering from NSAID-related gastroduodenal ulcer complications had not been treated with an adequate gastroprotective strategy. In contrast, comparable controls without ulcer complications did more often use gastroprotective drugs, although the number of risk factors in these controls was lower than in their unfortunate littermates. This suggests that still large numbers of patients remain unprotected. Among those at high risk for NSAID gastropathy with 4 or more separate risk factors, 47% did not use a preventative strategy. Also, among elderly NSAID-taking patients with a history of gastroduodenal ulcers, 36% did not use a gastroprotective strategy. Thus, among patients at high risk for NSAID gastropathy, gastroprotective strategies are still greatly underutilized and many are not adequately protected.

In concurrence with previous studies, risk factors for NSAID gastropathy appear to be additive.[17,23] A composed risk factor (CRF) was defined as the sum of 14 separate unweighed risk factors. In this study population the CRF ranged from 0 – 9. The odds ratios for serious NSAID-attributable gastroduodenal ulcers were higher with increasing CRF counts. Also, the mean CRF was significantly higher in

patients with serious NSAID attributable gastroduodenal ulcers compared to NSAID-taking controls.
In daily clinical practice, physicians prescribing NSAIDs appear to recognize and act upon several specific risk factors for NSAID gastropathy. Significant variables for the use of a gastroprotective strategy were concomitant use of steroids, a history of gastroduodenal ulcers and concomitant use of low-dose aspirin. The additive nature of risk factors also appears to be recognized, as the odds ratios for using a gastroprotective strategy rise with increasing CRF counts and those patients with the highest number of risk factors are all prescribed a gastroprotective strategy. Surprisingly, among those with no additional risk factors, 21% still used PPIs. It is possible that subjective symptoms such as dyspepsia or abdominal pain rather than targeted prevention of gastroduodenal ulcers drive these prescription rates.
We demonstrated that the NSAID-taking controls significantly more often used a gastroprotective strategy than the patients who were hospitalized with serious NSAID-attributable gastroduodenal ulcers. However, despite the fact that all of the patients with the highest CRF counts (7 – 9) received the recommended adequate gastroprotection, still 60% (3 out of 5) suffered serious NSAID-attributable gastroduodenal ulcers. Although this number of patients is small, these findings confirm other studies in very high-risk patients.[15] Therefore, in those with a very high additive risk for NSAID gastropathy, the recommended gastroprotective strategies may not be effective in preventing NSAID ulcers.
In daily clinical practice, in prescribing NSAIDs, a simple risk assessment can be performed by counting the number of additional risk factors. In any patient with 1 or more additional risk factors, a preventative strategy should be considered, concomitant use of PPIs, high-dose H2RAs, misoprostol 800 µg or switching to a selective COX-2 inhibitor. However, if many additional risk factors for NSAID gastropathy are present in a patient, NSAID therapy, be it alone, in combination with gastroprotective drugs, or as selective COX-2 inhibitor, cannot be presumed safe.

CONCLUSIONS

Gastroprotective drugs are greatly underutilized in patients at risk of NSAID gastropathy.

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CHAPTER V

Allele variants of the cytochrome P450 2C9 genotype in white subjects from The Netherlands with serious gastroduodenal ulcers attributable to the use of NSAIDs

Harald E. Vonkeman, Mart A.F.J. van de Laar, Job van der Palen, Jacobus R.B.J. Brouwers and Istvan Vermes

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ABSTRACT

Background The most common serious adverse effects (AEs) associated with NSAID therapy are bleeding and perforated gastroduodenal ulcers. These AEs are dose-related, and reduced oral clearance of NSAIDs associated with polymorphisms of cytochrome P450 2C9 (CYP2C9) would, theoretically, increase the risk for AEs.

Objectives The purpose of this study was to determine whether polymorphisms of the CYP2C9 genotype are associated with the development of serious complications of NSAID-related ulcers.

Methods We examined the records of patients with serious complications of NSAID-related ulcers who were hospitalized from November 2001 to December 2003. Diagnosis was confirmed by endoscopy or abdominal surgery, and a group of consecutive patients was identified for genetic analysis. CYP2C9 allele frequencies were determined and compared with those in a matched cohort of subjects receiving stable weekly maintenance doses of oral anticoagulants. Allele frequencies also were compared with those in matched cohorts from earlier studies.

Results All 26 subjects with serious NSAID-related ulcers were white; 15 (58%) were female, and the median age was 74.5 years (range, 32–96 years). All 87 subjects in the reference group were white, 24 (28%) were female, and the median age was 69 years (range, 48–81 years). CYP2C9 genotype frequencies did not differ significantly between subjects with serious complications of NSAID-related ulcers and subjects using oral coumarin anticoagulants. The genotype frequencies in both groups were similar to those reported in previous studies in white subjects.

Conclusion The CYP2C9 genotype was not a significant or clinically relevant risk factor in the development of serious NSAID-related ulcers in this group of subjects.

INTRODUCTION

NSAIDs are among the most frequently prescribed medications in the world, with ~30 million people using them on a daily basis.[1] Bleeding and perforated gastroduodenal ulcers are among the most serious complications of NSAID therapy and may lead to significant morbidity, mortality, and financial costs. Among chronic NSAID users, the annual incidence of serious NSAID-related ulcers requiring treatment and hospitalization is estimated at 1% to 2%, with an associated mortality rate of 10% to 15%.[2–4] In The Netherlands, the annual direct medical costs of the complications of serious NSAID-related ulcers have been estimated to be more than € 42 million.[4]

Several additional risk factors for NSAID-related ulcers have been identified, including advanced age, history of ulceration, and Helicobacter pylori infection.[5,6] The risk of NSAID-related ulcers is influenced by the type of NSAID, dose, and use of >1 NSAID simultaneously.[7–9] Concomitant use of other drugs, such as steroids, anticoagulants, platelet inhibitors, and selective serotonin reuptake inhibitors, may further increase the risk for serious ulcers.[10,11] Coexisting systemic disorders, such as diabetes mellitus and debilitating rheumatic diseases, also have been identified as risk factors.[12] In daily clinical practice, however, serious complications of NSAID-related ulcers also may be seen in subjects who lack obvious risk factors (ie, subjects aged <60 years who are otherwise healthy). It is therefore possible that other unidentified risk factors for NSAID-related ulcers exist.

The cytochrome P450 (CYP) system is a large group of hemoproteins that catalyze the metabolism of many different chemicals. In humans, most drugs are activated and detoxified by 4 CYP families (CYP1, CYP2, CYP3, and CYP4).[13] The CYP2C9 isozyme has been found to catalyze at least part of the metabolism of a number of drugs, including warfarin, tolbutamide, losartan, phenytoin, and at least 16 different NSAIDs, including acetylsalicylic acid, celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, meloxicam, and naproxen.[14] Apart from the wild-type protein, CYP2C9*1, at least 5 CYP2C9 genetic polymorphisms with reduced metabolic activity have been observed.[15,16] Two of these variants, CYP2C9*2 and CYP2C9*3, appear to have significant functional effects and have been found in relatively high frequencies in the white population, although they seem to be much less prevalent in other racial groups.[17–19] In other studies, the CYP2C9*4 variant was to found in Japanese subjects but not in white subjects; the CYP2C9*5 variant was found in black and Hispanic subjects but not in white subjects; and the CYP2C9*6 variant was found in 1 black subject who experienced drug toxicity after receiving normal doses of phenytoin.[19,20]

The normal functioning wild-type of CYP2C9, CYP2C9*1, has been reported to have a population frequency of 65% in white subjects, 87% in black subjects, and 96% in Asian subjects.[17,18,21,22] The CYP2C9*2 allele has a single base substitution at position 144, which results in a change from arginine to cysteine. Subjects with the heterozygous CYP2C9*1/*2 genotype appear to exhibit a minor reduction in catalytic activity of the CYP2C9-encoded enzyme. Studies have reported high population frequencies of this genotype in white (20.4%) and black (8.7%) subjects but not in Asian subjects (0%). A moderate reduction in the functional activity of CYP2C9 has been noted in subjects with the homozygous CYP2C9*2/*2 genotype, but the population frequency of the CYP2C9*2/*2 genotype is much lower (0.9% in white subjects and 0% in black and Asian subjects). The CYP2C9*3 allele has a single base substitution at position 359, which results in an amino acid change from isoleucine to leucine. The catalytic activity of the CYP2C9*3-encoded enzyme appears to be much lower than that of enzymes

encoded by the wild-type, CYP2C9*1. Subjects with the heterozygous CYP2C9*1/*3 genotype and those with the compound heterozygous CYP2C9*2/*3 genotype appear to exhibit a moderate reduction in catalytic activity. The population frequency of the CYP2C9*1/*3 genotype has been reported to be 11.6% in white subjects, 4.3% in black subjects, and 3.5% in Asian subjects, whereas the population frequency of the CYP2C9*2/*3 genotype has been reported to be 1.4% in white subjects and 0% in black and Asian subjects.[17,18,21,22] The homozygous CYP2C9*3 genotype is associated with a very low level of catalytic activity, and the frequency of the CYP2C9*3/*3 variant has been reported to be only 0.4% in white subjects and 0% in black and Asian subjects.[17,18,21,22]

CYP2C9 polymorphisms have been associated with changes in the pharmacokinetics of some frequently used NSAIDs.[17–19,23] Relative to subjects with the homozygous CYP2C9*1 genotype, oral clearance of celecoxib was reduced by 77% in subjects with the homozygous CYP2C9*3 genotype and by 32% in subjects with the heterozygous CYP2C9*3 genotype. Oral clearance of ibuprofen was reduced by 45% in subjects with the homozygous CYP2C9*3 genotype and by 28% in subjects with the heterozygous CYP2C9*3 genotype. Oral clearance of diclofenac was reduced by 14% subjects with the homozygous CYP2C9*3 genotype and by 5% in subjects with the heterozygous CYP2C9*3 genotype. Among homozygous and heterozygous CYP2C9*2 subjects, oral clearance of celecoxib and diclofenac was similar or even greater than the clearance in those with the wild-type CYP2C9*1. However, for ibuprofen, subjects with the homozygous CYP2C9*2 genotype had a 22% reduction in oral clearance, and heterozygous subjects had a 12% reduction.

Serious adverse events associated with to NSAID therapy, such as bleeding and perforated gastroduodenal ulcers, are dose related, which raises the question of whether the reduced NSAID clearance associated with CYP2C9 polymorphisms may increase the risk of serious NSAID-related gastroduodenal ulcers. If so, CYP2C9 allele frequencies would be expected to differ from those in the general population. To test this hypothesis, we examined CYP2C9 allele frequencies in a group of white subjects from The Netherlands with serious NSAID-related ulcers and compared them with frequencies in a group of matched control subjects using oral coumarin anticoagulants and with those reported in white subjects in earlier studies.[17]

SUBJECTS AND METHODS

Subjects

Serious NSAID-related ulcers were defined in this study as ulcerations of the stomach or proximal duodenum causing pain, perforation, obstruction, or bleeding that occurred during the time the subject was taking NSAIDs and resulted in treatment and hospitalization. We identified all consecutive subjects with serious gastroduodenal ulcers who were hospitalized at the Medisch Spectrum Twente Hospital in Enschede, The Netherlands from November 2001 through December 2003. The diagnosis was confirmed by endoscopy or abdominal surgery. If diagnostic procedures were not performed because of comorbidity or advanced age, subjects with gastroduodenal ulcers were identified on the basis of a clinical presentation of upper gastrointestinal bleeding with hematemesis or melena. In a few subjects, the diagnosis was confirmed during autopsy. Subjects were eligible for inclusion if they reported using an NSAID at any time up to the diagnosis of a gastroduodenal ulcer.

Subjects were excluded if written informed consent could not be obtained, if they reported not having

Table I. Characteristics of white subjects with serious NSAID-related ulcers by sex, age, weight, NSAID type, dose, expected effect of CYP2C9 genotypes on NSAID pharmacokinetics, and CYP2C9 genotype.

Subject	Sex	Age,y	Weight, kg	NSAID	Dose*	EXpected Effect of CYP2C9 Genotype†	CYP2C9 Variant
1	M	79	75	Diclofenac/misoprostol	medium	minor	*1/*1 (wild-type)
2	F	89	60	Diclofenac/ misoprostol	medium	minor	*1/*1 (wild- type)
3	F	78	45	Diclofenac	medium	minor	*1/*3 (heterozygous)
4	M	62	77	Diclofenac	low	minor	*1/*1 (wild- type)
5	M	73	103	Diclofenac	medium	minor	*1/*1 (wild- type)
6	F	48	78	Diclofenac	low	minor	*1/*1 (wild- type)
7	M	76	60	Diclofenac	medium	minor	*1/*2 (heterozygous)
8	M	64	77	Diclofenac	high	minor	*1/*2 (heterozygous)
9	M	70	75	Diclofenac	high	minor	*1/*3 (heterozygous)
10	F	86	56	Diclofenac	low	minor	*1/*1 (wild- type)
11	M	32	103	Diclofenac	low	minor	*1/*2 (heterozygous)
12	M	63	100	Diclofenac	medium	minor	*1/*1 (wild- type)
13	F	75	69	Diclofenac	low	minor	*1/*1 (wild- type)
14	F	59	58	Ibuprofen	low	major	*1/*1 (wild- type)
15	M	50	53	Ibuprofen	low	major	*1/*2 (heterozygous)
16	F	93	55	Ibuprofen	high	major	*1/*1 (wild- type)
17	F	36	63	Ibuprofen	low	major	*1/*1 (wild- type)
18	F	89	89	Meloxicam	medium	major	*1/*1 (wild- type)
19	F	80	101	Naproxen	high	minor	*1/*1 (wild- type)
20	M	68	106	Naproxen	high	minor	*1/*1 (wild- type)
21	F	82	59	Naproxen	high	minor	*1/*2 (heterozygous)
22	F	60	56	Naproxen	low	minor	*1/*1 (wild- type)
23	M	74	95	Rofecoxib	high	minor	*1/*1 (wild- type)
24	F	89	61	Rofecoxib	low	minor	*1/*1 (wild- type)
25	F	82	60	Rofecoxib	medium	minor	*1/*2 (heterozygous)
26	F	96	60	Rofecoxib	medium	minor	*1/*2 (heterozygous)

CYP = cytochrome P450; M = male; F = female.
*Medium = maximum daily dose; Low = less than the recommended maximum daily dose; high = more than the recommended daily dose. †Derived from Scordo et al.[21]

used NSAIDs, if endoscopy or surgery did not reveal gastric or duodenal ulcers, if a malignancy of the stomach was found, or if another cause was determined for upper intestinal bleeding (e.g.; diffuse gastritis, esophagogastric varices, arteriovenous malformations, or Mallory-Weiss tears).

CYP2C9 allele frequencies also were also determined in a matched cohort of subjects using oral coumarin anticoagulants at stable weekly maintenance doses under supervision of the Thrombosis Services at the Medisch Spectrum Twente Outpatient Clinic in Oldenzaal, The Netherlands.

Table II. CYP2C9 polymorphisms in white subjects with serious NSAID-related ulcers and subjects using oral coumarin anticoagulants (no. [%] of subjects), and in the historical subjects (no.).

Allelic Variant	Subjects with Serious NSAID-Related Ulcers (n = 26)	Subjects Using Oral Coumarin Anticoagulants (n = 87)	Historical Cohort[17] (N = 100)
CYP2C9*1/*1 (wild-type)	17 (65)	56 (64)	(65)
CYP2C9*1/*2 heterozygous)	7 (27)	12 (14)	(20)
CYP2C9*2/*2 (homozygous)	0 (0)	0 (0)	(1)
CYP2C9*1/*3 heterozygous)	2 (8)	14 (16)	(12)
CYP2C9*2/*3 (compound)	0 (0)	5 (6)	(1)
CYP2C9*3/*3 homozygous)	0 (0)	0 (0)	(0)

CYP = cytochrome P450.

The study was approved by the Medical Ethics Reviewing Committee of the Medisch Spectrum Twente Hospital, Enschede, The Netherlands.

Methods

CYP2C9 genotyping was performed using a standard polymeric chain reaction technique with relevant test controls. This technique has been described in an earlier study of genetic polymorphisms.[24]

CYP2C9 allele frequencies were compared using the Pearson χ^2 test, and, in cases in which the expected values were low, the Fisher exact test was used. All analyses were performed using SPSS for Windows, version 12.0.1 (SPSS Inc., Chicago, Illinois).

Based on previous studies of allele variants,[17-19,23] we assumed that the presence of the variant allele CYP2C9*2 or CYP2C9*3 would increase a subject's risk for serious NSAID-related gastroduodenal ulcers. Based on previously published frequency data for this population, we expected ~35% (30/87) of the subjects in the reference group to have variant alleles. Assuming a ratio of ~3 for the comparison of reference subjects and subjects with serious NSAID-related ulcers, a power of 80%, $\alpha = 0.05$, and an odds ratio of 3, we calculated that it would be necessary to examine CYP2C9 allele frequencies in 35 subjects with serious NSAID-associated gastroduodenal ulcers.

RESULTS

A cohort of 26 consecutive subjects with serious NSAID-related ulcers was selected for CYP2C9 allele analysis. All subjects were white, 15 (58%) were female, and the median age was 74.5 years (range, 32–96). Eleven (42%) of the subjects used diclofenac, 4 (15%) used ibuprofen, 4 (15%) used naproxen, 4 (15%) used rofecoxib, 2 (8%) used diclofenac/misoprostol, and 1 (4%) used meloxicam (*Table I*). Seven (27%) patients used more than the maximum recommended dose of NSAID, and 5 (19%) used >1 NSAID concurrently. Concomitant use of low-dose aspirin was reported by 6 (23%) subjects, coumarin derivatives by 5 (19%), steroids by 4 (15%), low-molecular-weight heparin by 2 (8%), and selective

serotonin reuptake inhibitors by 1 (4%). Five (19%) subjects used either proton-pump inhibitors or high-dose histamine2–receptor antagonists. Only 1 subject had a history of gastroduodenal ulcers. Testing for H.pylori was performed on the biopsy specimens from the gastric mucosa of 20 subjects by histologic examination using hematoxylin and eosin staining and immunohistochemical H pylori antibody staining. The results were positive in 5 (25%) subjects.

A cohort of 87 consecutive subjects using oral anticoagulants also was selected for CYP2C9 allele analysis. All subjects were white, 24 (28%) were female, and the median age was 69 years (range, 48–81) years. The CYP2C9 genotype frequencies for the subjects with serious NSAID-related ulcers, the subjects using oral coumarin anticoagulants, and subjects in previous studies are shown in Table II. CYP2C9 genotype frequencies did not differ significantly between the subjects with serious NSAID-related ulcers and the subjects using oral anticoagulants. The genotype frequencies in both groups were similar to those reported in white subjects in previous studies.[17]

In subjects with serious NSAID-related ulcers, the genotype frequencies were 65% for CYP2C9*1/*1 (Arg_{144}-Ile_{359}, wild-type), 27% for CYP2C9*1/*2 (Cys_{144}-Ile_{359}), and 8% for CYP2C9*1/*3 (Arg_{144}-Leu_{359}). The homozygous CYP2C9*2/*2 genotype and the homozygous CYP2C9*3/*3 genotype were not found in the subjects with serious NSAID-related ulcers or in subjects receiving oral anticoagulants. The compound heterozygous CYP2C9*2/*3 genotype was not found in subjects with serious NSAID-related ulcers, but it occurred at a frequency of 6% in subjects using oral anticoagulants (*Table II*).

DISCUSSION

The results of this study suggest that in these white subjects living in The Netherlands, allele variants of the CYP2C9 genotype were not a clinically relevant risk factor for serious NSAID-related gastroduodenal ulcers.

One possible weakness of this study is that we compared consecutive subjects from 2 different cohorts, the first consisting of subjects with serious NSAID-related gastroduodenal ulcers and the second consisting of subjects using oral anticoagulants. Since it is possible that the 2 groups may not have been comparable in terms of risk for bleeding, we compared the genotype frequencies in these subjects with frequencies reported in previous studies.[17]

Neither the homozygous CYP2C9*2/*2 genotype, the homozygous CYP2C9*3/*3 genotype, nor the compound heterozygous CYP2C9*2/*3 genotype was found in the subjects with serious NSAID-related ulcers. Twice as many subjects with a heterozygous CYP2C9*1/*3 genotype were found among the subjects using oral anticoagulants as in the subjects with serious NSAID-related ulcers. This suggests that, at the population level, the CYP2C9 genotype is not likely to be a clinically relevant risk factor for the development of serious NSAID-related ulcers.

Another possible weakness of this study is that some of the subjects used more than the maximum recommended daily doses of NSAIDs, and others used less than the maximum recommended doses. Also, the CYP2C9 genotype plays only a small role in the overall clearance of some of the NSAIDs used by the subjects.[25] Because the serious adverse effects associated with NSAID therapy, such as bleeding and perforated gastroduodenal ulcers, are dose related, it is possible that the lack of association with CYP2C9 genotypes in this study is related to the types and doses of NSAIDs used by the subjects. The subjects with serious NSAID-related ulcers in this study were representative of the subjects seen

in clinical practice; thus, at population level CYP2C9 genotype is not likely to be clinically relevant risk factor. In an individual subject who is a poor metabolizer, however, high-doses of NSAIDs whose clearance is influenced by CYP2C9 may increase the risk for serious NSAID-related ulcers. Future case–control studies may answer this question by determining CYP2C9 allele frequencies in subjects with and without bleeding gastroduodenal ulcers who use NSAIDs.

Previous studies have examined the role of genotype frequencies in the development of NSAID-related ulcers. In one case–control study in 23 white subjects with previous NSAID gastropathy and 32 asymptomatic control subjects who used NSAIDs, no significant difference in CYP2C9 allele frequencies was found.[26] In a larger Spanish case–control study in 94 subjects with NSAID-attributable gastrointestinal bleeding and 124 asymptomatic control subjects who used NSAIDs, the subjects with serious NSAID-related ulcers were significantly more likely to be carriers of the variant CYP2C9*2 allele ($P < 0.01$), but not of the low-metabolizing CYP2C9*3 allele.[27]

Although CYP2C9 polymorphisms do not appear to play a significant role in the development of NSAID-related ulcers, their effect may be different in subjects who use other drugs concomitantly. Several drugs are known to or can be expected to further increase the risk for NSAID-related ulcers. These include drugs that pharmacodynamically influence blood coagulation, such as platelet inhibitors, low dose aspirin, clopidogrel, and dipyridamole, and drugs whose pharmacokinetics are influenced by the CYP2C9 isozyme either competitively, as in the case of selective serotonin reuptake inhibitors and coumarin anticoagulants, or by inhibition of the CYP2C9 isozyme, as in the case of benzbromarone and amiodarone. Also, the mechanism by which some drugs, such as corticosteroids, increase the risk for NSAID-related ulcers is not completely understood. Subjects who are prescribed combined therapy with NSAIDs and coumarin anticoagulants are at increased risk of bleeding.[28] The CYP2C9 isozyme catalyzes the metabolism of NSAIDs and coumarin anticoagulants, and poor metabolizers who are prescribed this combination may be at particular risk for bleeding. Several studies have found an association between CYP2C9 genotypes and coumarin dose requirements[29,30]; however, studies of the effect of CYP2C9 polymorphisms on the NSAID–coumarin interaction have had conflicting results.[31,32] This conflict may be explained by the difference in study designs (prospective vs retrospective) and the numbers of subjects included in the trials. In our study, only 5 subjects used an NSAID and coumarin concomitantly. Four of these subjects had the CYP2C9*1/*1 variant genotype and 1 subject had the in CYP2C9*1/*2 variant. Future case–control studies may resolve this conflict by comparing CYP2C9 allele frequencies in subjects with bleeding NSAID-related gastroduodenal ulcers who are using NSAIDS and coumarin derivates concomitantly and those in subjects using both drugs without bleeding complications.

CONCLUSION

In this group of white subjects from The Netherlands, allele variants of the CYP2C9 genotype were not a significant or clinically relevant risk factor for serious NSAID-related gastroduodenal ulcers.

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CHAPTER VI

Direct medical costs of serious gastrointestinal ulcers among users of NSAIDs

Harald E. Vonkeman, Rogier M. Klok, Maarten J. Postma, Jacobus R.B.J. Brouwers, and Mart A.F.J. van de Laar

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ABSTRACT

Background The occurrence and prevention of gastrointestinal ulcers during use of NSAIDs has become a major healthcare issue.

Objective To determine the direct medical costs of serious NSAID-related ulcer complications.

Method An observational cost-of-illness study was conducted in a large general hospital serving a population of 152 989 persons. From November 2001 to December 2003 all consecutive patients hospitalised with serious NSAID-related ulcer complications were identified. Serious NSAID-related ulcer complications were defined as ulcerations of the stomach or proximal duodenum causing perforation, obstruction or bleeding that occurred during the use of NSAIDs, necessitating hospitalisation of the patient. Data was retrieved with respect to days hospitalised and the number and type of diagnostic and therapeutic interventions. The main outcome measure was estimated mean direct medical costs of resources used.

Results A total of 104 patients were hospitalised with serious NSAID-related ulcer complications (incidence 31.4 per 100 000 persons per year). Most patients were elderly (mean 70.4 years, SD 16.7). In-hospital mortality was 10.6%. Mean direct medical costs were € 8.375 (95% CI 7.067, 10.393). On the basis of these results, we estimated that approximately 5105 people are hospitalised with serious NSAID-related ulcer complications in The Netherlands each year, of whom 541 die in hospital. The total annual direct medical costs for serious NSAID-related ulcer complications in The Netherlands were estimated to be € 42 754 375 (95% CI 36 077 035, 53 056 265).

Conclusion Serious NSAID-related ulcer complications have a mortality rate of 10.6% in The Netherlands and annual direct medical costs to the country of such complications are approximately € 42 750 000.

BACKGROUND

Cost-of-illness studies provide insight into expenses associated with a particular disease.[1] Treatment of diseases is complicated by adverse effects and strategies may be developed to prevent these complications. The cost effectiveness of preventive strategies depends on the averted costs associated with treatment of these adverse effects and complications.

NSAIDs are one of the most frequently prescribed classes of drugs worldwide. Treatment with NSAIDs is complicated by serious gastrointestinal toxicity, such as perforated and bleeding ulcers. Amongst NSAID users, the annual incidence of serious gastrointestinal ulcer complications necessitating hospital treatment is 1-2%.[2,3] Several strategies have been developed to prevent NSAID-related ulcers.[2,3] In clinical trials, switching to cyclo-oxygenase (COX)-2 selective NSAIDs, or combining classical NSAIDs with proton-pump inhibitors, high dose histamine H_2 receptor antagonists or misoprostol has been shown to decrease the risk for NSAID-related ulcers.[2-4] However, analysis of the cost effectiveness of these preventive strategies has been hampered by a scarcity of cost-of-illness studies for NSAID-related ulcers. Several previous studies have estimated the costs of treating gastrointestinal events.[5-7] However, translation of the results of these studies to NSAID-related ulcers has been difficult because most studied either all causes of peptic ulcers, all abdominal events or specific patient groups.

Cost-of-illness studies identify three types of costs: direct, indirect, and intangible. Most relevant to the discussion of cost effectiveness are direct costs, which are calculated from a societal perspective, i.e. an estimate of the actual resources used in the treatment of a disease, not just from the perspective of an individual or a health-care institution.

The aim of this study was to determine the direct medical costs associated with serious NSAID-related ulcer complications.

METHODS

Patients

From November 2001 until December 2003 all consecutive patients from a cohort of 152 989 inhabitants who were hospitalized with gastric or duodenal ulcer complications were identified. For the purpose of this study, serious NSAID-related ulcer complications were defined as ulcerations of the stomach or proximal duodenum causing perforation, obstruction or bleeding that occurred during the use of NSAIDs, necessitating hospitalisation of the patient. Patients with gastric or duodenal ulcers were identified by means of endoscopy, abdominal surgery or autopsy. In exceptional cases, patients were identified as having a gastrointestinal ulcer on the basis of a clinical diagnosis of upper gastrointestinal bleeding, i.e. haematemesis and melaena, if no further diagnostic procedures were performed because of co-morbidity or advanced age. Patients were included in the study if NSAIDs had been used up to the time the gastrointestinal ulcer was diagnosed. Aspirin (acetylsalicylic acid) in a high dosage (>100mg/day) was considered to be an NSAID. Patients were asked to complete a questionnaire with questions concerning sociodemographic characteristics, intoxications (smoking habits, alcohol and coffee consumption), actual and recent medications, co-morbidities and medical history. To verify data obtained from the questionnaires, the medical charts of all patients were reviewed, as well as endoscopy, surgery, pathology, and microbiology reports. From these charts and reports, additional data wer retrieved on the number of days hospitalised (normal care and intensive care) and on the number and

Table I. Duration of hospitalisation, number of diagnostic and therapeutic procedures, unit prices and median direct medical costs (€, 2003 values) for hospital admission, procedures and resources used

Resource or procedure	Median value [interquartile range] or number of patients (%) [n = 104]	Unit prices	Median costs [interquartile range]
A. Hospital admission (days)			
standard care	9 [6–19.75]	337.00	2864 [2022–6403]
intensive care	0 [0–0]	1684.00	0 [0–0]
B. Emergency department	93 (89.4)	139.00	139 [139–139]
C. Ambulance transportation			
emergency	78 (75)	443.00	443 [110.75–443]
regular	6 (5.8)	212.00	0 [0–0]
none	20 (19.2)	0	0 [0–0]
D. Blood products			
packed cells	2 [0–5]	179.00	358 [0–895]
blood platelets	0 [0–0]	81.00	0 [0–0]
fresh frozen plasma	0 [0–0]	154.00	0 [0–0]
E. Endoscopy	1 [0–2]	369.71	369.71 [369.71–739.42]
F. Surgery			
suture of perforation	16 (15.4)	870.79	0 [0–0]
partial stomach resection	1 (1)	1945.15	0 [0–0]
total stomach resection	1 (1)	3414.66	0 [0–0]
cholecystectomy	1 (1)	944.55	0 [0–0]
abdominal abscess drainage	2 (1.9)	662.00	0 [0–0]
G. (Radio)diagnostic procedures			
plain x-ray	1 [0–2]	134.01	134.01 [0–268.02]
CT scan abdomen	0 [0–0]	198.85	0 [0–0]
CT scan thorax	0 [0–0]	228.85	0 [0–0]
magnetic resonance imaging scan	0 [0–0]	228.85	0 [0–0]
abdominal ultrasound	0 [0–0]	70.30	0 [0–0]
cardiac ultrasound	0 [0–0]	73.01	0 [0–0]
vascular ultrasound	0 [0–0]	58.54	0 [0–0]
radionucleotide imaging of total skeleton	0 [0–0]	151.74	0 [0–0]
radionucleotide imaging of pulmonary embolism	0 [0–0]	359.58	0 [0–0]
radionucleotide imaging of abscess	0 [0–0]	651.84	0 [0–0]
pulmonary function test	0 [0–0]	61.40	0 [0–61.40]
ECG	1 [0–1.25]	34.23	34.23 [0–34.23]
H. Laboratory tests			
standard set of laboratory tests	10 [6–18]	13.85	138.50 [83.10–245.84]
microbiology culture	0 [0–1]	30.97	0 [0–30.97]
pathology testing	0 [0–1]	49.33	0 [0–49.33]
Median total costs			5396.95 [3821.80–9344.39]

type of diagnostic and therapeutic interventions such as endoscopies, surgical procedures, (radio)diagnostic tests and laboratory tests performed and the types and quantities of blood products used. Medication use prior to and during hospitalisation, as reported by the patient, was verified by review of prescription registrations provided by in-hospital and community-based pharmacies. Patients were interviewed by one of the authors (HEV) if ambiguities were encountered in the questionnaires or during data verification.

To verify the study selection procedure, all hospital records of patients discharged within the observational period with an International Classification of Diseases (ICD)[8] code of 531 (gastric ulcer), 532 (duodenal ulcer), 533 (peptic ulcer, site unspecified), 534 (gastrojejunal ulcer) or 578 (gastrointestinal haemorrhage; hematemesis, melena or unspecified) were reviewed.

Patients were excluded if they were not hospitalised, they reported not to have used NSAIDs, no gastric or duodenal ulcers were identified during endoscopy, surgery or autopsy, ambiguities remained despite verification and interviewing the patient, a malignancy of the upper gastroduodenal tract was diagnosed or another cause for upper intestinal bleeding was diagnosed, i.e. diffuse gastritis, esophagogastric varices, ateriovenous malformations or Mallory-Weiss tears. Patients who were transferred from other hospitals in the course of their admission were also excluded. The study was approved by the Medical Ethics Review Committee of the Medisch Spectrum Twente Hospital, Enschede, The Netherlands.

Estimating Direct Medical Costs

Total direct medical costs were calculated as the sum of the costs of utilisation of the following categories: (A) intensive care and standard care hospital in-patient days, (B) emergency department care, (C) ambulance transportation, (D) units of blood products, (E) endoscopies, (F) surgery, (G) (radio)diagnostic procedures and (H) laboratory tests. Direct costs of resources used per patient were estimated by multiplying volumes by costs per unit. Unit costs may vary considerably between hospitals, making extrapolation of outcomes of cost calculations difficult. Therefore, standard unit costs were extracted from Guideline for Cost-of-Illness Study: Methods and Guideline-Rates for Economic Evaluations in Health-Care (Dutch Guidelines for Pharmacoeconomic cost-of-illness studies), the Dutch tariff book for medical specialists and the Dutch tariff list for hospitals (see table I for unit prices).[9-11] All prices were in €, 2003 values. The costs of personnel, materials and equipment used, as well as those of medication, are included in these standard cost prices and were not separately included in the total costs. For those patients who were first seen at the emergency department before subsequent hospitalisation an additional standard cost price for the emergency department was added to the total costs. For those patients who were transported to the hospital by ambulance an additional standard cost price for the ambulance was added to the total costs, differentiated for emergency or regular transportation. For each patient the total number of units of different blood products administered was counted. Unit costs were derived from the 2003 standard cost prices of blood products as determined by the Sanquin Blood Supply Foundation in The Netherlands (see table I for unit prices). The number and types of laboratory tests varied for each patient. Rather than counting each separate laboratory test, we selected a representative standard set of tests, consisting of haemoglobin, hematocrit, blood platelets, leukocytes, creatinine and ALT. We counted the exact number of times blood was taken for laboratory testing and multiplied this by the costs of one standard set. The costs of this standard set comprises a general

charge for the laboratory tests, personnel costs and costs of materials and equipment used (see table I for unit prices). The number and type of (radio)diagnostic and therapeutic procedures utilised per patient was counted. Varying diagnostic and therapeutic procedures were performed in patient management. Some procedures were performed as part of direct management of the gastrointestinal event, such as intervention endoscopy or surgery. Other procedures were performed because of complications that arose during hospitalisation. If these complications were considered to be related to the primary gastrointestinal event, the costs of all procedures that were performed were added to the total costs. However, in some patients, NSAID-related ulcer complications occurred during hospitalisation for another reason. In such cases, we calculated only the duration of hospitalisation following the gastrointestinal event and all subsequent diagnostic and therapeutic procedures that were not obviously related to the primary reason for hospitalisation.

Extrapolation of Incidence and Costs

Within The Netherlands, the city of Enschede forms a unique, geographically isolated system with only one hospital, a large teaching hospital providing all medical specialties to a population of 152 989 inhabitants (population on 31 December 2003).[12] As a result of its isolated position, referral of patients to other hospitals, especially for acute gastrointestinal events, is extremely rare. Therefore, in this population, the incidence of hospitalisation for NSAID-related ulcer complications can be reliably calculated.

The population of the city of Enschede is not expected to differ from that of the rest of The Netherlands in terms of sociodemographic variables, health or medical consumption. Extrapolation of the incidence of hospitalisation for serious NSAID-related ulcer complications and the related direct medical costs is therefore possible. The population of The Netherlands was 16 258 032 on 31 December 2003.[12]

Statistical Analysis

Total direct costs per patient were calculated as the sum of all costs made during hospitalisation and treatment. Means and SDs of the total direct costs were computed. Because data were skewed, a bootstrap procedure of 10 000 replicates was performed. To estimate the 95% confidence intervals (CIs), bias corrected and accelerated intervals were used.[13,14] All bootstrap calculations were performed using the software package S-plus professional version 6.0.

RESULTS

Patients

During the observational period, 170 patients were identified by their physicians as having gastrointestinal ulcer complications potentially associated with the use of NSAIDs and were included in the study. Of these, 66 patients were excluded. Fifty patients were excluded because they had been taking only low-dose aspirin for the purpose of platelet inhibition and not as an anti-inflammatory drug. Six patients were excluded because they were not hospitalised after an NSAID-related ulcer had been diagnosed and, therefore, did not meet the criterion of 'serious' GI ulcer. Five patients were excluded because ambiguities about NSAID use could not be resolved. One patient was excluded because a malignancy of the stomach was diagnosed in biopsies obtained from a supposed NSAID-related ulcer. One patient

Table II. Patient demographic characteristics and self-reported comorbidities

Characteristic or co-morbidity	n = 104[a]
Age (y)	70.4 [16.7]
Female sex	58 (55.8)
Body mass index (kg/m²)	24.7 [4.7]
Smoking[b]	
non-smoker	65 (62.5)
smoker	28 (26.9)
Alcohol (glasses/wk)	9.6 [33.2]
Coffee (cups/wk)	18.9 [20.6]
Medical history	
hypertension	30 (28.8)
heart failure	26 (25)
chronic obstructive pulmonary disease)	25 (24
myocardial infarction	20 (19.2)
stroke	18 (17.3)
eart rhythm disturbance	18 (17.3)
diabetes mellitus	16 (15.4)
anaemia	16 (15.4)
renal insufficiency	16 (15.4)
gastrointestinal ulcer	16 (15.4)
malignancy	15 (14.4)
rheumatoid disease, including osteoarthritis	42 (40.4)

a Scores are mean values [SD] or number of patients (%).

b Data not available for 11 patients

Table III. NSAIDs and concurrent medications used at the time of the gastrointestinal event

Medication	n = 104[a]
Nonselective NSAIDs	
diclofenac	44 (42.3)
ibuprofen	16 (15.4)
naproxen	10 (9.6)
diclofenac/misoprostol	8 (7.7)
indometacin	3 (2.9)
other	3 (2.9)
Selective cyclo-oxygenase-2 inhibitors	
rofecoxib	16 (15.4)
celecoxib	1 (1)
meloxicam	1 (1)
High-dose aspirin (acetylsalicylic acid) [≥100 mg/day]	2 (1.9)
Dosage of NSAID	
≦100% maximum daily dose	40 (38.5)
≥100% maximum daily dose	59 (56.9)
More than one NSAID simultaneously	12 (11.5)
Platelet aggregation inhibitors	
low-dose aspirin (≧100 mg/day)	32 (30.8)
clopidogrel/dipyridamole	5 (4.8)
Coumarin	14 (13.5)
Low-molecular-weight heparin	13 (12.5)
Selective serotonin reuptake inhibitors	6 (5.8)
Corticosteroids	14 (13.5)
Gastroprotective drugs	18 (17.3)
Analgesics	
paracetamol (acetaminophen)	45 (43.3)
tramadol	12 (11.5)
morphine	6 (5.8)
Benzodiazepines	34 (32.7)
Cardiovascular agents	
diuretics	34 (32.7)
ACE inhibitors	24 (23.1)
b-adrenoceptor antagonists	22 (21.2)
calcium channel antagonists	10 (9.6)
lipid-lowering agents	9 (8.7)
digoxin	8 (7.7)
nitrates	8 (7.7)
Oral antihyperglycaemics	12 (11.5)
Inhaler therapy	22 (21.2)
Disease-modifying antirheumatic drugs	14 (13.5)

a Scores are number of patients (%).

was excluded because of transferral from another hospital in the course of his admission. One patient was excluded because of refusal to participate in the study. Two patients could not be traced because of incorrect or missing personal identification data and were therefore excluded because verification of questionnaire data was not possible.

Patient Characteristics

During the observational period 104 patients were hospitalized with serious NSAID-related ulcer complications from a cohort of 152 989 inhabitants. Table II shows their demographic characteristics and co-morbidities. Most patients were elderly, with the mean age being 70.4 years (SD 16.7; range 22-98 years). More (55.8%) patients were women. Many patients reported concurrent disease or previous medical events suggesting serious, particularly cardiovascular, co-morbidity. This self reported co-morbidity was supported by the concomitant medication used, as shown in table III. Over 40% of patients reported having a rheumatic condition, including osteoarthritis, and 13.5% were using disease-modifying antirheumatic drugs. Amongst the 104 patients, 12 different NSAIDs were used for a median of 1.13 months (interquartile range (IQR) 10 day to 12 months). Most patients (80.8%) used non-selective NSAIDs, 16.4% used selective COX-2 inhibitors and 1.9% used high-dose aspirin. Concomitant gastroprotective agents (proton-pump inhibitors, high dose H2 receptor antagonists or misoprostol) were used by 17.3%. Other frequently reported drugs were analgesics, cardiovascular drugs, antihyperglycaemic agents and inhaler therapies (table III).

For the majority of patients (76.9%), the gastrointestinal event was the reason for presentation and hospitalisation; in the remainder of the patients, the event occurred during hospitalisation for another reason. In 82.7% of patients the clinical presentation was that of an acute upper gastrointestinal bleed or perforation. In six (5.8%) patients, no diagnostic procedure was performed because of severe co-morbidity or advanced age. In the 94.2% of patients who underwent a diagnostic procedure, a gastric ulcer was found in 54.1%, a duodenal ulcer in 34.7% and both gastric and duodenal ulcers in 11.2%. The ulcer perforated in 13.5% of patients. Helicobacter pylori status was determined in 63.5% of the patients and was found to be positive in 32%. Mortality due to NSAID-related ulcer complications was high; 11 (10.6%) patients died in the hospital, and another four (3.8%) died within 3 months of the diagnosis.

Duration of Hospitalization and Number of Procedures

The duration of hospitalisation due to NSAID-related ulcer complications and the number of diagnostic and therapeutic procedures performed are shown in table I. The median duration of hospitalisation was 9 days (IQR 6-9.75, maximum 87 days). Most patients (92 (88.5%)) did not stay in the intensive care unit (ICU), 11 spent up to 7 days in the ICU, and one patient was in the ICU for 26 days. Most patients (88 (84.8%)) underwent at least one diagnostic endoscopy and 40 (38.6%) patients underwent two or more endoscopies. Endoscopic intervention by means of injecting epinephrine (adrenalin) or clipping a visible vessel was performed in 13 (12.5%) patients. Surgical procedures were performed in 18 (17.3%) patients, with only one patient undergoing more than one operation.

The median number of units of blood given was 2 (IQR 0-5); 31 (30.1%) patients did not receive any packed cells, 61 (59.2%) patients received up to 6 units, one patient received 20 units and one patient

received 39 units). Among those patients that received blood platelets, the median number of units given was 1 (IQR 1-2); 92 (89.3%) patients did not receive any blood platelets and one patient received 7 units. Among those patients that received fresh frozen plasma, the median number of units given was 2 (IQR 2-4); 86 (83.5%) patients did not receive any fresh frozen plasma but one patient received 21 units.
The median number of times blood was taken for laboratory testing was 10 (IQR 6-18). The median number of plain x-rays was 1 (IQR 0-2); 45 (43.7%) patients did not have any x-rays taken and one patient had 17 taken. The median number of ECGs was 1 (IQR 0-1.25). The median number of times a microbiology culture was taken was zero (IQR 0-1); 64 patients had no cultures taken, one patient had 25 cultures taken and one patient had 40 cultures taken. The median number of times pathology testing was performed was zero (IQR 0-1). Five patients underwent a CT-scan (two patients had a CT of both the abdomen and thorax), two patients underwent a magnetic resonance imaging scan, four patients underwent a radionuclide imaging procedure, 21 patients underwent an abdominal ultrasound (two patients twice), three patients underwent a cardiac ultrasound (one patient twice), two patients underwent a vascular ultrasound examination and one patient underwent a pulmonary function test.

Estimation of Costs

The median total direct medical cost of NSAID-related ulcer complications was € 5397 (IQR € 3822-9344) and varied from a minimum of € 1325 to a maximum of € 57 165. Variability was skewed to the right. The maximum of € 57 165 was a clear outlier. For this patient, high costs were mainly due a 26-day stay in the ICU. Using 10 000 bootstrap replicates we calculated a mean total direct cost of € 8375 with a bias corrected and accelerated 95% CI of 7067, 10 393.

Extrapolation of Incidence and Costs

The observational period was 26 months, during which 104 patients were hospitalised from a population of 152 989, making the incidence 31.4 per 100 000 persons per year. On the basis of this finding, we estimated that in The Netherlands approximately 5105 people are hospitalised annually with NSAID-related ulcer complications, resulting in an estimated 541 in-hospital deaths and another 194 deaths within 3 months of the event.
The total Dutch annual direct medical costs associated with serious NSAID-related ulcer complications would thus approximate € 42 754 375 (95% CI 36 077 035, 53 056 265).

DISCUSSION

In this study we estimated the incidence and direct medical costs associated with serious gastrointestinal ulcers among NSAID users. However, observational studies may suffer from under- as well as overestimation. It is possible that patients may have been missed in the selection process. In any study that relies on the attentiveness of those involved in daily clinical patient care, cases may be missed. A further underestimation of direct medical costs might have occurred because of the use of standard cost prices for hospital in-patient days, which may differ from actual charges. When treating bleeding ulcers, expensive procedures and drugs are used that are not regularly prescribed for other indications. In this analysis these costs have not been added to the total costs. In a secondary analysis we calculated costs of treatment with intravenous omeprazole and prothrombin complex concentrate (data not shown). In individual

patients these extra costs amounted to as much as € 1200, but the mean extra cost was only € 174. However, because of the use of standard cost prices, it is possible that total costs were either over- or underestimated. A further underestimation of costs might have occurred because only direct medical costs were calculated. Significant indirect and non-medical costs may also have occurred.

In most patients, NSAID-related ulcer complications were the primary reason for hospitalisation. However, some patients developed NSAID-related ulcer complications while hospitalised for another reason. Subsequent in-hospital days and procedures that were not evidently related to the primary reason for hospitalisation were then calculated. Obviously, it was not possible to determine with certainty whether or not these procedures would have been performed regardless of the NSAID-related ulcer. Furthermore, it remains unclear whether these patients would have remained hospitalised regardless of the ulcer, or even whether they would have been hospitalised for the ulcer in the first place. These uncertainties with respect to causality reflect clinical practice, and although overestimation of costs is a possibility we feel that exclusion of this group of patients would certainly have resulted in an underestimation of costs.

Several studies have previously estimated the medical costs of gastrointestinal ulcers. In a Dutch study on the costs of treating bleeding and perforated peptic ulcers in an academic hospital setting, de Leest et al.[5] used insurance claim prices to determine costs for 53 patients from a third-party payer's perspective. Ulcers were not specifically related to NSAID use. The overall direct medical costs of bleeding and perforated ulcers were estimated at € 15 000 per patient (2002 values). Another Dutch study estimated costs of treating NSAID-associated gastrointestinal events in patients with osteoarthritis and rheumatoid arthritis.[6] Information on resource utilisation was gathered by interviewing physicians. Estimated costs per patient ranged between € 1800 and € 6900 (1999 values). In a third Dutch study, the direct medical costs of treatment of NSAID-attributable gastrointestinal events were estimated using the population attributable risk.[7] The definition of gastrointestinal events was much wider than that used in our study, since it also included ICD[8] codes like 535 (gastritis and duodenitis), 5638 (stomach function disorder) and 5641 (irritable colon/colitis). Total costs included not only hospitalization costs for gastrointestinal events but also the costs of treatment with gastroprotective agents. Total direct costs for The Netherlands were estimated at € 59 255 297 (range € 38 467 133-98 161 013) (1998 values). Our results appear to fall within the range of other study estimates. Our data were collected firstly by observation of the occurrence of serious NSAID-related ulcer complications in a large population, and secondly by simply counting the number of diagnostic and therapeutic procedures performed. Therefore, we consider our data to be a reliable representation of daily clinical practice. However, in extrapolating our results to The Netherlands, both under- as well as overestimation of annual direct medical costs may have occurred because of variability of care among hospitals in The Netherlands.

Sociodemographic variables, self reported co-morbidities and concurrent medication used by the patients suggest that those at risk for serious NSAID-related ulcer complications are particularly elderly patients with significant cardiovascular co-morbidities who use NSAIDs for a prolonged period of time. This type of patient is usually excluded from large randomised, controlled, clinical trials used to establish the effectiveness of strategies aimed at preventing gastrointestinal NSAID-related gastrointestinal toxicity. Notably, in this study, 16.4% of patients with serious NSAID-related ulcer complications

used selective COX-2 inhibitors and 17.3% of such patients used gastroprotective drugs. Whether or not selective COX-2 inhibitors or gastroprotective drugs provide protection against serious NSAID-related ulcer complications in these patients remains to be determined.

CONCLUSION

NSAID-related ulcer complications have an in-hospital mortality rate of 10.6% in The Netherlands. On the basis of the results of this study, the annual direct medical costs to Dutch society of serious NSAID-related ulcer complications were calculated as approximately € 42 750 000. Policy makers should be aware that, to a degree, medical costs are driven by such preventable drug-related complications. In a recent study reported on by Sheldon,[15] van den Bemt et al. demonstrated that in The Netherlands, 5.6% of all acute hospital admissions are drug related, and 46% of these admissions were is potentially preventable. In this light, a recent decision by Dutch policy makers to end reimbursement of paracetamol (acetaminophen), possibly causing patients to switch to reimbursed NSAIDs, may prove erroneous.

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CHAPTER VII

Incremental cost-effectiveness of proton pump inhibitors for the prevention of NSAID ulcers:

A pharmacoeconomic analysis linked to a case-control study

Harald Vonkeman, Louise Braakman-Jansen, Rogier Klok, Maarten Postma, Jacobus Brouwers, Mart van de Laar

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ABSTRACT

Objective To estimate the cost-effectiveness of concomitant proton-pump inhibitors (PPIs) in relation to the occurrence of non-steroidal anti-inflammatory drug (NSAID) ulcer complications.

Methods This study was linked to a nested case-control study. Patients with NSAID ulcer complications were compared with matched controls. Only direct medical costs were reported. For the incremental cost-effectiveness ratio 2 hypothetical scenarios were compared: (1) 1000 patients all using PPIs and (2) 1000 patients not using PPIs. Sensitivity analysis was performed by 'worst case' and 'best case' scenarios in which the 95% CI of the odds ratio (OR) and the 95% CI of the cost estimate of a NSAID ulcer complication were varied. Costs of PPIs was varied separately.

Results 104 Incident cases and 284 matched controls were identified from a cohort of 51.903 NSAID users with 10.402 NSAID exposition years. Use of PPIs was associated with an adjusted OR of 0.33 (95% CI 0.17 to 0.67; p=0.002) for NSAID ulcer complications. In the hypothetical scenarios, the estimated number of NSAID ulcer complications was 13.8 for non-PPI users, and 3.6 for PPI users. The incremental total costs were €50.094 higher for concomitant PPI use. The incremental cost-effectiveness ratio was €4,907 (95% CI €2,813 to €6,290) per NSAID ulcer complication prevented when using the least costly PPI.

Conclusions Concomitant use of PPIs for the prevention of NSAID ulcer complications costs €4,907 per NSAID ulcer complication prevented when using the least costly PPI. The price of PPIs highly influenced the robustness of the results.

INTRODUCTION

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is known to be complicated by serious gastrointestinal toxicity. NSAIDs impair prostaglandin-dependent gastric mucosal protective mechanisms. When these defences have been breached, a second wave of injury caused by luminal gastric acid may facilitate deep ulceration, eventually causing ulcer bleeding and perforation.[1] Several strategies have been developed to prevent NSAID ulcers.[2, 3] In clinical trials different selective COX-2 inhibitors, proton-pump inhibitors (PPIs), high dose histamine-2 receptor antagonists and prostaglandin analogues have been shown to decrease the risk for NSAID ulcers. However, few strategies have been directly compared and for most a formal cost-effectiveness analysis is lacking.

In a previous study, we found that concomitant use of PPIs was associated with a significant reduction of serious NSAID ulcer complications.[4] In a further study, we calculated the direct medical costs of hospitalization for serious NSAID ulcer complications[10]. The objective of the present study was to extend these analyses by performing a pharmacoeconomical evaluation.[5] Such an assessment is relevant to furnish clinical guidelines – for example, on standard concomitant PPI use with NSAIDs – with the appropriate pharmacoeconomic information.

MATERIALS AND METHODS

The pharmacoeconomic evaluation was linked to a 26-month observational study conducted in the Enschede healthcare district of the Netherlands, in which a cohort of 51.903 NSAID users is served by 14 pharmacies and a single large teaching hospital, supplied with all diagnostic and therapeutic facilities.[4] All drug prescriptions for the population are registered in electronic prescription records. The majority of drugs, including NSAIDs, are provided by the patients' own pharmacy, directly reimbursed by the healthcare system. The cohort of NSAID users can continuously be identified using the electronic prescription records.

The study used a nested case-control design. From November 2001 until December 2003 we identified all NSAID users with serious NSAID ulcer complications. Serious NSAID ulcer complications were defined as ulcerations of the stomach or proximal duodenum causing perforation, obstruction or bleeding; during the use of NSAIDs, necessitating hospitalisation of the patient. Patients were identified by endoscopy or abdominal surgery and were included in the study if they used NSAIDs at the time a gastroduodenal ulcer was diagnosed. For each serious NSAID ulcer complication, the patient was invited to complete a questionnaire on his/her sociodemographic characteristics, actual and recent medication, co-morbidity and medical history. When applicable for reasons of verification of the questionnaires, we reviewed medical charts, as well as endoscopy-, surgery-, and pathology reports. Medication use prior to and during hospitalization as reported by the patient, was verified by reviewing prescription records provided by the in-hospital and community based pharmacies.

Controls were retrieved from the remaining cohort of NSAID users, who had not developed serious NSAID ulcer complications at the time of ulcer occurrence in each of the cases. For selecting controls, index dates were defined as the day on which a NSAID ulcer complication was diagnosed in each of the cases. Controls were frequency matched on sex and age, and had to be using an NSAID on the index date. Selected controls were invited to complete the same questionnaire. Medication use as reported by the controls was verified by reviewing prescription records. The study was approved by the Institutional Ethical Review Board.

Omeprazole ≥20mg, pantoprazole ≥20mg, lansoprazole ≥15mg, esomeprazole ≥20mg and rabeprazole ≥20mg were considered proton-pump inhibitors in adequate dosage for the prevention of NSAID ulcers.

Outcome

Because a patient could theoretically have more than one episode with serious NSAID ulcer complications, the preferred unit of analysis was the episode with a serious NSAID ulcer complication rather than the patient. The outcome of interest was the occurrence of a serious ulcer complication during NSAID use.

Costs

The measure of interest was the cost of PPI-treatment and the costs of medical treatment of serious NSAID ulcer complications. Included in the costs of medical treatment were all direct medical costs made during hospitalization.[10] No information was available for costs of general practitioner visits, outpatient treatments by medical specialists or drug therapy. The costs for NSAID therapy and costs related to that therapy were not taken into account as these costs are expected to be similar in both treatment groups. Nonmedical costs (e.g., those related to work absenteeism) were not included.

Hospital service utilization was determined using standard hospital administrative records and included the number of intensive care and standard care in-patient days, emergency department care, ambulance transportation, transfusion of blood products, endoscopies, surgery, (radio)diagnostic procedures, and laboratory tests. Table 1 lists all direct medical costs which were included in the analysis, presenting the method of valuation, the cost price per unit and its source. Unit costs were derived from the Dutch manual for costing[6], the Dutch tariff book for medical specialists[7], the Dutch tariff list for hospitals[8], and Dutch list prices for the various PPIs.[9] All prices were in 2003 Euros. Unit costs for blood products were derived from the 2003 standard cost-prices of blood products as determined by the Sanquin Blood Supply Foundation in The Netherlands[6]. To calculate direct medical costs, health resource use was multiplied by unit-cost estimates.

Statistics

In our previous study, multivariate analysis using logistic regression was performed on the occurrence of serious ulcer complications in patients using NSAIDs.[4] The adjusted odds ratio (OR) was calculated for serious NSAID user complications with concomitant PPIs compared with serious NSAID user complications without PPIs. The estimated OR for the occurrence of a serious NSAID ulcer complication with concomitant PPIs compared with no PPIs can be interpreted as approaching the corresponding relative risk (RR). Exposure times did not differ significantly between cases and controls. The estimated OR would then correspond to the assumption that ~1 – 1/OR of the serious NSAID ulcer complications in NSAIDs users without concomitant PPIs might be averted if these patients had concomitantly used PPIs. Subsequently, we inserted this assumption into the pharmacoeconomic analysis to estimate the proportion of serious ulcer complications in NSAID users that might have been averted by adding a PPI. The mean total direct costs per occurrence of a serious NSAID ulcer complication were calculated and 95% confidence intervals (95%CI) were estimated using a bootstrap procedure.[10]

Table 1. Categories, methods and sources for valuation of unit costs[6,7,8].

Categories costs	Unit of resource	Source of the estimate	Unit cost €
PPI (DDD)			
omeprazole, generic: 20mg	Monthly costs	Pharm.ther. Compass 2007[9]	11.30
lansoprazole (Prezal®): 30mg	Monthly costs	Pharm.ther. Compass 2007[9]	29.71
omeprazole (Losec®): 20mg	Monthly costs	Pharm.ther. Compass 2007[9]	29.85
rabeprazole (Pariet®): 20mg	Monthly costs	Pharm.ther. Compass 2007[9]	31.75
pantaprazole (Pantozol®): 40mg	Monthly costs	Pharm.ther. Compass 2007[9]	36.41
esomeprazole (Nexium®):30mg	Monthly costs	Pharm.ther. Compass 2007[9]	39.37
Hospital admission			
standard care	number of days	cost manual of Oostenbrink[6]	337,00
intensive care	number of days	cost manual of Oostenbrink[6]	1684,00
Emergency department	number of visits	cost manual of Oostenbrink[6]	139,00
Ambulance transportation			
emergency	number of transports	cost manual of Oostenbrink[6]	443,00
regular	number of transports	cost manual of Oostenbrink[6]	212,00
Blood products			
packed cells	number of units	cost manual of Oostenbrink[6]	179,00
blood platelets	number of units	cost manual of Oostenbrink[6]	81,00
fresh frozen plasma	number of units	cost manual of Oostenbrink[6]	154,00
Endoscopy	number of procedures	tarifflist hospitals[8]	369,71
Surgery			
Suture of perforation	number of operations	tarifflist hospitals[8]	870,79
Partial stomach resection	number of operations	tarifflist hospitals[8]	1945,15
total stomach resection	number of operations	tarifflist hospitals[8]	3414,66
cholecystectomy	number of operations	tarifflist hospitals[8]	944,55
abdominal abscess drainage	number of operations	tarifflist hospitals[8]	662,00
(Radio)diagnostic procedures			
plain X-ray	number of procedures	tarifflist hospitals[8]	134,01
CT-scan abdomen	number of procedures	tarifflist hospitals[8]	198,85
CT-scan thorax	number of procedures	tarifflist hospitals[8]	228,85
MRI-scan	number of procedures	tarifflist hospitals[8]	228,85
abdominal ultrasound	number of procedures	tarifflist hospitals[8]	70,30
cardiac ultrasound	number of procedures	tarifflist hospitals[8]	73,01
vascular ultrasound	number of procedures	tarifflist hospitals[8]	58,54
radionucluotide; total skeleton	number of procedures	tarifflist hospitals[8]	151,74
radionucluotide; embolism	number of procedures	tarifflist hospitals[8]	359,58
radionucluotide; abscess	number of procedures	tarifflist hospitals[8]	651,84
pulmonary function test	number of procedures	tarifflist hospitals[8]	61,40
electrocardiogram	number of procedures	tarifflist hospitals[8]	34,23
Laboratory tests			
standard set of laboratory tests	number of procedures	tarifflist hospitals[8]	13,85
microbiology culture	number of procedures	tarifflist hospitals[8]	30,97
pathology testing	number of procedures	tarifflist hospitals[8]	49,33

Table 2. Demographic characteristics, medical history and current medication for cases and controls.

	Cases (n=104)	Controls (n=284)	OR	(95% CI)	p
Demographic characteristics					
Age at diagnosis (years)	70.4 [16.7]	67.1 [14.3]	-	-	0.06
Sex (female)	58 (55.8%)	163 (57.4%)	0.95	0.60-1.47	0.78
Smoking	28 (26.9%)	51 (18%)	1.96	1.15-3.37	0.01
Alcohol (glasses/week)	9.6 [33.2]	6.2 [8.6]	-	-	0.12
Medical history					
Heart failure	26 (25.0%)	32 (11.3%)	2.63	1.48-4.67	0.001
Myocardial infarction	20 (19.2%)	32 (11.3%)	1.88	1.02-3.45	0.04
Stroke	18 (17.3%)	28 (9.9%)	1.91	1.01-3.63	0.04
Diabetes mellitus	16 (15.4%)	33 (11.6%)	1.38	0.73-2.64	0.32
Previous gastrointestinal ulcers	16 (15.4%)	33 (11.7%)	1.37	0.72-2.60	0.34
Rheumatoid disease; including OA	42 (40.4%)	97 (34.2%)	1.31	0.82-2.07	0.26
Medication					
Non selective NSAIDs	86 (82.7%)	222 (78.2%)	1.33	0.75-2.39	0.33
Selective COX-2 inhibitors	17 (16.3%)	50 (17.6%)	0.91	0.50-1.67	0.77
Preferential COX-2 inhibitors	1 (1.0%)	12 (4.2%)	0.22	0.03-1.71	0.20
Proton pump inhibitors	14 (13.5%)	77 (27.1%)	0.42	0.23-0.78	0.005
H2RAs	4 (3.8%)	9 (3.2%)	1.22	0.37-4.06	0.74
Misoprostol	8 (7.7%)	20 (7.0%)	1.10	0.47-2.58	0.83
Low dose aspirin (≤ 100mg/day)	32 (30.8%)	69 (24.3%)	1.39	0.84-2.28	0.20
Coumarin	14 (13.5%)	19 (6.7%)	2.17	1.05-4.51	0.04
SSRIs	6 (5.8%)	9 (3.2%)	1.87	0.65-5.39	0.24
Corticosteroids	14 (13.5%)	32 (11.3%)	1.23	0.63-2.40	0.55

Scores are mean values [SD] or number of patients (%). OR; unadjusted Odds Ratio. CI; confidence interval. COPD; chronic obstructive pulmonary disease. OA; osteoarthritis. NSAIDs; nonsteroidal anti-inflammatory drugs. COX; cyclooxygenase. H2RAs; histamine receptor-2 antagonists. SSRIs; selective serotonin re-uptake inhibitors.

Cost-effectiveness

To calculate the incremental cost-effectiveness ratio (expressed as net costs per serious NSAID ulcer complication prevented) 2 hypothetical scenarios were compared by using a decision tree model: (1) none of the NSAID users concomitantly used PPIs and (2) all NSAID users concomitantly used PPIs. In this model we followed a cohort of 1.000 patients to either receive concomitant PPI therapy or no PPIs for the duration of one year. For effectiveness we used serious NSAID ulcer complications as the main outcome measure. The number of cases was calculated using the risk-estimates of the first part of this study. Costs were calculated by multiplying the number of serious NSAID ulcer complications with the cost of a serious NSAID ulcer complication in combination with the costs of PPI treatment. The incremental cost-effectiveness ratio was calculated by the difference in total direct medical costs

Table 3. Comparison of the number of serious NSAID ulcer complications and associated costs in the two hypothetical scenarios: all using PPIs versus none using PPIs.

	No PPI users (N = 1000)	PPI users (N = 1000)	Difference
Number of complications	13.8	3.60	10.2
(95% CI)	(13.7 – 13.9)	(3.56 – 3.64)	
Costs*	€115,676	€165.770	€50.094
(95% CI)	(114,874 – 116,493)	(160,789 - 173,444)	

*costs of cheapest concomitant PPI (generic omeprazole) was taken into account

divided by the difference in number of serious NSAID ulcer complication for the group using concomitant PPIs and the group not using concomitant PPIs.

To test the robustness of the results two approaches were used. The first one takes the uncertainty of the estimates of risk for serious NSAID ulcer complications into account (95% CI of the OR) as well as the uncertainty for the estimate of the cost of a serious NSAID ulcer complication (95% CI of the cost estimate). To show this uncertainty we used the extreme estimates for both the most positive and the most negative options for concomitant PPI therapy and NSAID use. The second approach was used to show the impact of varying the cost of PPI treatment on the expected incremental cost-effectiveness ratio.

RESULTS

During the 26-month study period 104 incident cases with serious NSAID ulcer complications were observed in a cohort of 51.903 NSAID users with a cumulative 10.402 patient-years of NSAID use (*table 2*).[10] Data for these cases was retrieved from questionnaires and hospital administrative records. The typical case is an elderly patient, mean age at diagnosis 70.4 years [SD 16.7; youngest 22, eldest 98 years], 55.8% were female. In 86 (82.7%) patients the clinical presentation was that of an acute upper gastrointestinal bleeding or perforation. In 53 (51%) patients the ulcer was located in the stomach, 34 (32.7%) had a duodenal ulcer and 11 (10.6%) had both gastric and duodenal ulcers. The ulcer perforated in 14 (13.5%) patients. Mortality due to serious NSAID ulcer complications was high; 11 (10.6%) patients died in hospital, and another 4 (3.8%) died within 3 months of the diagnosis. The median duration of hospitalization was 9.0 days (range 1 to 87 days). Eleven patients spent up to 7 days in the intensive care unit and one patient spent 26 days. Most patients (88; 84.8%) underwent at least one diagnostic endoscopy. A surgical procedure was performed in 18 (17.3%) patients. The estimated mean total direct cost of a serious NSAID ulcer complication was € 8.375 per patient (95% CI 7.067 to 10.393).[10]

From the remaining cohort of NSAID users a total of 284 controls were retrieved, frequency matched on age and sex, with NSAID use on the index date. Demographic characteristics, co-morbidities and current medication use are summarized in table 2. Mean age was slightly lower in the controls than in the cases because insufficient numbers of controls could be found for some of the extreme senior patients. Concomitant use of PPIs was significantly higher in the controls than in the cases (cases 14 (13.5%)

Table 4. Expected monthly costs (based on defined daily dose) and cost-effectiveness for different PPIs at 2007 price levels 9.

Drug	DDD*	Monthly costs (November 2006)	Cost effectiveness (95% CI)**
Generic omeprazole	20mg	€ 11.30	4,907 (2813 – 6290)
Lansoprazole (Prezal®)	30mg	€ 29.71	26,545 (24,327 – 28051)
Omeprazole (Losec®)	20mg	€ 29.85	26,709 (24491 – 28217)
Rabeprazole (Pariet®)	20mg	€ 31.75	28,943 (26,711 – 30,463)
Pantaprazole (Pantozol®)	40mg	€ 36.41	34,420 (32,157 – 35,971)
Esomeprazole (Nexium®)	30mg	€ 39.37	37,899 (35,617 – 39,470)

* The daily dosing schedule on which the cost-effectiveness ratio is based, may not always reflect the actual dosages prescribed in clinical practice

** Cost-effectiveness is expressed as costs (€) per serious NSAID ulcer complication prevented

and controls 77 (27.1%); p=0.005). Use of selective COX-2 inhibitors was comparable (cases 17 (16.4%) and controls 50 (17.6%); p=0.77). Use of the preferential cyclooxygenase-2 inhibitor meloxicam differed, but not significantly, and numbers were small (cases 1 (1%) and controls 12 (4.2%); p=0.20). The adjusted OR for serious NSAID ulcer complications was 0.33 (95% CI 0.17 to 0.67; p=0.002) for concomitant use of PPIs compared with no PPIs.[4] Both groups differed in their risk for developing NSAID ulcer complications. The group using concomitant PPIs significantly more often used chronic NSAID therapy (more than 3 months continuously), concomitant steroids, had a medical history of anemia, and of previous gastroduodenal events.

In the hypothetical scenario in which none of the 1,000 patients used concomitant PPIs, the estimated number of serious NSAID ulcer complications was 13.8 (95%CI 13.7 to 13.8). In the scenario in which all 1,000 patients took concomitant PPIs, the estimated number of serious NSAID ulcer complications was 3.6 (95%CI 3.56 to 3.64). Costs were calculated by multiplying the number of serious NSAID ulcer complications with the cost of a serious NSAID ulcer complication (€ 8.375) in combination with the costs of the cheapest PPI treatment; generic omeprazole, estimated at €135,600 [1,000*€11.30*12 months]. Therefore the total costs associated with serious NSAID ulcer complications was [13.8 * € 8.375] = €115,676 (95%CI 114,874 to 116,493) for the group not using concomitant PPIs and [(3.6* € 8.375) + €135,600] = €165.770 (95%CI €160,789 to €173,444) for the group using concomitant PPIs (*Table 3*). The incremental cost-effectiveness ratio after one year of follow-up was [€ 50,094 / 10.2] = €4.907 (95% CI 2,813 to 6,290) per serious NSAID ulcer complication prevented.

In *table 4*, the cost-effectiveness ratio is shown with different monthly costs for the concomitant PPI used. It can be seen that the estimated upper and lower limit for the incremental cost-effectiveness ratio does not differ much from the point estimate, indicating that with the current estimate of the risk of serious NSAID ulcer complications and the estimate of costs associated with those serious NSAID ulcer complications, no large differences in incremental cost-effectiveness should be expected. However, changing the monthly costs of PPI-treatment itself does markedly increase the incremental cost-effec-

tiveness ratio, as is shown in Table 4. When using the most expensive option (on a 2007 DDD level), esomeprazole (Nexium®), the incremental cost-effectiveness ratio is €37,899 per serious gastrointestinal event prevented.

DISCUSSION

In this analysis we found that in NSAID users, concomitant use of PPIs costs €4,907 per serious NSAID ulcer complication prevented, when using the least costly PPI. This pharmacoeconomic analysis extends the findings of our previous clinical study in NSAID users, in which concomitant use of PPIs was associated with a lower incidence of serious NSAID ulcer complications compared with not using PPIs.[4]

The incremental cost analysis was performed from the health care perspective and only direct medical costs made during hospitalization were available. Inclusion of extramural direct medical costs (e.g., general practitioner visits and outpatient treatments), direct non-medical costs (e.g., travel to and from the hospital) and indirect non-medical costs (e.g., those related to work absenteeism) might possibly strengthen the favorable economic profile of concomitant PPI use in NSAID users, compared with not using concomitant PPIs.

For estimation of the effects of using concomitant PPIs, we extrapolated case-control data from a cohort of NSAID users on the occurrence of serious NSAID ulcer complications in patients using concomitant PPIs and in patients not using PPIs. The group using concomitant PPIs however had a significantly higher risk for developing NSAID ulcer complications than the group without PPIs. Therefore the effect size of concomitant use of PPIs may have been underestimated, which would further strengthen the favorable economic profile of concomitant PPI use.

Using the OR as an approximation of the RR may overestimate the favorable economic profile of concomitant PPI use in NSAID users, if the risk of serious NSAID ulcer complications is not very low in the population studied.[12] In the present study the risk of overestimation is negligible as the incidence rate of serious NSAID ulcer complications was approximately 1% per year of NSAID use, which is in concurrence with the current literature.

In this analysis we found that an increase in PPI costs markedly increases the incremental cost-effectiveness ratio. Cost-effectiveness of concomitant use of PPIs in NSAID users may be less favourable if NSAID users switch to more expensive brand name drugs instead of using generic preparations. Due to active legislation it is however probable that the majority of patients will use the cheapest treatment option, generic omeprazole. The incremental cost-effectiveness ratio of concomitant use of PPIs in NSAID users may be raised further by inappropriate use of PPIs (e.g., on demand use during continued NSAID use), or in combination with other gastroprotective strategies (e.g., high dose histamine receptor-2 antagonists or misoprostol). Furthermore, PPI use is sometimes continued indefinitely after its necessity has ended, i.e. after NSAID treatment has stopped.

In the present study, concomitant PPIs were found to cost €4,907 per averted serious NSAID ulcer complication in NSAID users with one or more risk factors for NSAID gastrointestinal toxicity. According to Spiegel et al[13], generic nonselective NSAIDs alone were optimally cost-effective for patients at low risk for NSAID-related gastrointestinal complications. In contrast, another study found selective COX-2 inhibitors to be most cost-effective, while a third study found both strategies to be cost-ef-

fective, dependent on the baseline risk.[14,15] In a comprehensive systematic review with economic modelling, both H_2 receptor antagonists and PPIs were found to be cost-effective for avoiding endoscopic ulcers in patients requiring long-term NSAID therapy. Furthermore, prescribing H_2 receptor antagonists was found to be possibly cost-effective in all patients requiring NSAIDs.[16,17] While these findings from previous studies vary, they all used actual primary clinical data from trials and applied them to an economic model. These data may however not always be generalised outside the controlled environment of the clinical trials. In the present study, we therefore prospectively observed a large cohort of real NSAID users, calculated the actual direct medical costs made by patients with serious NSAID ulcer complications, and conducted a subsequent nested case-control study to evaluate the different gastroprotective strategies used.[4,10] Although observational studies are subject to possible bias, linking pharmacoeconomical analyses to case-control studies may be a valuable addition to the ongoing discussion on cost-effectiveness of preventive pharmacotherapy.

In conclusion, in this pharmacoeconomical analysis in NSAID users, concomitant use of PPIs costs €4,907 to prevent one serious NSAID ulcer complication if generic omeprazole is used. However, using a more expensive PPI will increase the cost of preventing one serious NSAID ulcer complication to more than €25,000.

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CHAPTER VIII

Risk of gastroduodenal ulcers during long-term use of selective NSAIDs in Helicobacter pylori-positive patients

A post hoc analysis on a randomized, double blind, placebo controlled clinical trial in patient with long-term NSAIDs for rheumatic diseases

HE Vonkeman, HTJI de Leest, MAFJ van de Laar, KSS Steen, WF Lems, JWJ Bijlsma, EJ Kuipers, HHML Houben, M Janssen, BAC Dijkmans

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ABSTRACT

Background The gastrointestinal safety of selective NSAIDs (selective cyclooxygenase (COX)-2 inhibitors or COX-2 preferential NSAIDs) has been demonstrated in clinical trials. However, it remains unclear whether this holds true with long-term use or in Helicobacter pylori-positive patients.

Methods We performed a preplanned post hoc analysis of a clinical trial in patients with long-term NSAIDs for rheumatic diseases. H. pylori-positive patients were randomized for H. pylori eradication or placebo. Endoscopy was performed at 13 weeks. Patients with gastroduodenal ulcers were compared to those without ulcers for the use of selective versus non-selective NSAIDs, as well as possible confounders.

Results A total of 301 patients underwent endoscopy, 221 (73%) used non-selective NSAIDs and 80 (27%) selective NSAIDs. Ulcers were diagnosed in 6 (4%) patients in the eradication group and 8 (5%) patients in the placebo group (P=0.65). Long-term use of selective NSAIDs was significantly less common among ulcer patients; 0 (0%) in the ulcer group vs. 80 (28%) in the non-ulcer group (P=0.02). Concomitant use of low dose aspirin was significantly more common among ulcer patients than among non-ulcer patients; 4 (29%) in the ulcer group vs. 27 (9%) in the non-ulcer group (P=0.02).

Conclusion In H. pylori positive patients on long-term NSAID treatment for rheumatic diseases, the use of selective NSAIDs significantly reduces the risk for endoscopic gastroduodenal ulcers. H. pylori eradication therapy does not ameliorate this risk while concomitant use of low dose aspirin significantly increases the risk.

INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed drugs, especially for arthritis and osteoarthritis. Treatment with NSAIDs is complicated by serious gastrointestinal toxicity such as bleeding and perforated ulcers.[1] The annual incidence of serious NSAID ulcer complications is 1 to 2%, and despite improved intervention strategies, the associated mortality rate remains 10% to 15%.[2-6] Therefore, risk assessment and adequate preventive strategies remain of paramount importance. Several strategies have been developed to prevent NSAID ulcer complications[7]. These include concomitant use of proton-pump inhibitors (PPIs), high dose histamine-2 receptor antagonists (H2RAs), high dose prostaglandin analogues, and the use of selective NSAIDs (classical NSAIDs preferentially inhibiting cyclooxygenase (COX)-2 (meloxicam and nabumetone) as well as designed selective COX-2 inhibitors (rofecoxib and celecoxib)).

The gastrointestinal safety of selective COX-2 inhibitors was demonstrated in several large randomised clinical trials.[2,3] However, some issues remain unresolved. Firstly, it is unclear whether selective COX-2 inhibitors retain their gastrointestinal safety during long-term use. In an analysis of data from the gastrointestinal toxicity with celecoxib versus NSAIDs for osteoarthritis and rheumatoid arthritis (CLASS) study, celecoxib was associated with a lower incidence of ulcers compared to non-selective NSAIDs at 6 months, but not at 12 or 16 months of treatment[3,8]. Secondly, the role of Helicobacter pylori infection in the gastrointestinal safety of selective COX-2 inhibitors is unclear. H. pylori plays an important role in gastroduodenal ulcer disease and a possible additive interaction between H. pylori and NSAID use in the development of gastroduodenal ulcers might exist.[9-11] Current understanding of the gastrointestinal safety of selective COX-2 inhibitors in H. pylori positive patients is limited.[12] In an analysis of gastrointestinal risk factors from the Vioxx gastrointestinal outcomes research (VIGOR) study, rofecoxib compared to naproxen did not reduce the risk for duodenal ulcers in H. pylori positive patients[12,13]. Furthermore, in the rofecoxib group, patients with a history of gastrointestinal events who were H. pylori-positive were 3.5 times as likely to have a recurrent event as those who were H. pylori-negative.[12,13] In a study comparing celecoxib to naproxen, among those receiving celecoxib the incidence of endoscopic ulcers was 12.9% in H. pylori-positive patients versus 2.9% in H. pylori-negative patients ($p=0.023$). Conversely, H. pylori status did not influence the ulcer risk in those receiving naproxen.[14] These results suggest that H. pylori infection may (partially) negate the gastrointestinal safety of selective COX-2 inhibitors.

In a recently conducted randomized, double blind, placebo controlled clinical trial we found that eradication of H. pylori did not reduce the incidence of endoscopic gastroduodenal ulcers in H. pylori-positive patients taking long-term NSAIDs for rheumatic diseases[15]. However, in this study some patients did develop NSAID ulcers while others did not, and if H. pylori eradication could not explain this difference, other factors might. We therefore performed a post hoc analysis of the data to determine whether long-term use of selective NSAIDs reduces the incidence of endoscopic gastroduodenal ulcers compared with long-term use of non-selective NSAIDs, to determine whether H. pylori infection influences the gastrointestinal safety of selective NSAIDs, and to determine the role of possible confounders such as concurrent use of low dose aspirin.

Table 1. Characteristics of patients with and without endoscopic ulcers

Characteristics	Ulcer – (N=287)	Ulcer + (N=14)	P-value
Age - years; mean ± SD	59 ± 10	61 ± 10	0.45
Female sex - no. (%)	174 (61)	6 (43)	0.19
Rheumatic disease requiring NSAIDs - no. (%)			
rheumatoid arthritis	176 (61)	9 (64)	0.82
spondylarthropathy	22 (8)	2 (14)	0.37
psoriatic arthritis	23 (8)	0 (0)	0.27
osteoarthritis	25 (9)	1 (7)	0.84
other	41 (14)	2 (14)	1.00
Disease duration - years; median (IQR)	7 (3 to 14)	7 (2 to 14)	0.81
Co-morbidity - no. (%)	193 (67)	6 (43)	0.06
NSAID - no. (%)			
Non-selective NSAIDs	187 (65)	12 (86)	0.11
Diclofenac	61 (21)	4 (29)	0.52
Naproxen	52 (18)	2 (14)	0.72
Ibuprofen	36 (13)	1 (7)	0.55
Indometacine	17 (6)	1 (7)	0.85
Selective NSAIDs	80 (28)	0 (0)	0.02
COX-2 preferential NSAIDs	52 (18)	0 (0)	0.08
Meloxicam	33 (12)	0 (0)	0.18
Nabumetone	19 (7)	0 (0)	0.32
Selective COX-2 inhibitors	28 (10)	0 (0)	0.22
Rofecoxib	23 (8)	0 (0)	0.27
Celecoxib	5 (2)	0 (0)	0.62
Combination drug	20 (7)	2 (14)	0.30
Gastroprotection - no. (%)	139 (48)	7 (50)	0.91
proton pump inhibitor	109 (38)	4 (29)	0.48
histamine-2 receptor antagonist	17 (6)	2 (14)	0.21
prostaglandin analogues	1 (0.3)	0 (0)	0.83
Relative daily dose of NSAID; median (IQR)	1 (0.5 to 1)	1 (0.6 to 1)	0.15
Use of more than one NSAID - no. (%)	4 (1%)	0 (0)	0.66
History of gastroduodenal ulcer - no. (%)	31 (11)	1 (7)	0.67
Current corticosteroid use - no. (%)	27 (9)	0 (0)	0.23
Concurrent use of low dose aspirin - no. (%)	27 (9)	4 (29)	0.02
Concurrent use of coumarin - no. (%)	10 (4)	1 (7)	0.48
Current smoking - no. (%)	71 (32)	3 (30)	0.89
Current alcohol drinking - no. (%)	147 (51)	9 (64)	0.34
Eradication of Helicobacter pylori - no. (%)	144 (50)	8 (57)	0.61

SD: standard deviation; NSAIDs: non-steroidal anti-inflammatory drugs; COX: cyclo-oxygenase; COX-2 preferential NSAIDs: meloxicam, nabumetone; COX-2 selective inhibitors: rofecoxib, celecoxib; Selective NSAIDs: COX-2 preferential NSAIDs or COX-2 selective inhibitors; Combination drug: diclofenac-misoprostol. The relative daily dose of NSAID was calculated by dividing the daily dose by the full therapeutic dose.

METHODS

Patients

The methods of the primary randomized, double blind, placebo controlled clinical trial have been previously described.[15] Briefly; between May 2000 and June 2002, patients were recruited at eight rheumatology outpatient departments throughout The Netherlands. Eligible for inclusion where patients between 40 and 80 years of age with a rheumatic disease requiring long-term NSAID treatment, defined as the use of any selective or non-selective NSAID for at least 3 days a week over the last month. Patients were included in the study if tested positive for H. pylori on serological testing using a commercial enzyme-linked immunosorbent assay for H. pylori IgG-antibodies (Pyloriset® new EIA-G, Orion Diagnostica, Espoo, Finland).

No change in NSAID therapy was permitted during the study, but there was no restraint on other concurrent medication. The study protocol was approved by the institutional review boards of all participating centers and all patients gave written informed consent.

Study design

After stratification on concurrent use of gastroprotective agents, patients were randomly assigned to either H. pylori eradication therapy with omeprazole 20 mg, amoxicillin 1000mg, and clarithromycin 500 mg twice daily for 7 days, or to placebo. Patients with an allergy for amoxicillin were assigned to omeprazole 20 mg, metronidazol 500 mg and clarithromycin 250 mg twice daily for 7 days, or placebo. The study medication was given in a double blind, double dummy manner.

Follow-up visits took place at 2, 13 and 52 weeks. At baseline all patients were interviewed on their sociodemographic characteristics, intoxications, current medication, co-morbidity, and medical history. At 13 weeks all patients underwent gastroduodenal endoscopy, blinded for treatment allocation. The number of erosions and ulcers was recorded for the stomach and duodenum. An ulcer was defined as a break in the mucosa of $\geq$ 5 mm in diameter, penetrating the muscularis mucosae. Smaller or superficial lesions were classified as erosions. After endoscopy, observations continued through week 52.

Statistical methods

The primary endpoint of the study was the proportion of patients with endoscopically proven gastroduodenal ulcers at week 13. Secondary endpoints were the proportions of patients with symptomatic ulcers (defined as gastroduodenal ulcers found after work-up for dyspepsia) or ulcer complication such as bleeding and perforation, occurring at any time during the study and follow-up.

In this pre-planned post hoc analysis we first compared ulcer rates in patients on long-term selective NSAIDs (classical NSAIDs preferentially inhibiting COX-2 (meloxicam and nabumetone) as well as designed selective COX-2 inhibitors (rofecoxib and celecoxib)) with those on long-term non-selective NSAIDs. Secondly, we analyzed the effect of H. pylori eradication in patients on long-term selective NSAIDs. Thirdly, we analyzed possible confounders such as concurrent use of low dose aspirin. All patients who underwent a complete gastroduodenal endoscopy at 3 months were included in the post hoc analysis. To search for possible bias or channelling of risk factors, a sub-analysis was performed comparing risk factors for NSAID-gastropathy in patients using selective NSAIDs inhibitors with those in patients using non-selective NSAIDs.

Continuous variables with a normal distribution were expressed as mean and standard deviation (SD), and continuous variables with a non-normal distribution as median and interquartile range (IQR). Differences between groups were analysed using Students t-test, Mann-Whitney U test and Pearson's Chi-square test or Fisher's Exact test in case of low expected values. For all analyses P <0.05, two sided, was considered significant. All analyses were performed with SPSS for Windows, version 12.0.1 (SPSS, Chicago, IL, USA).

RESULTS

The results of the primary study have been published.[15] Between May 2000 and June 2002, 2761 patients with rheumatic diseases were tested for H. pylori, of whom 1091 (40%) tested positive. Of these, 744 patients refused participation (55%), or met exclusion criteria. The remaining 347 patients were randomized to eradication therapy (172 patients) or placebo (175 patients). Together, 301 patients underwent full gastroduodenal endoscopy at 13 weeks; 149 in the eradication group and 152 in the placebo group. In a further 14 patients endoscopic evaluation was incomplete, either because of technical problems or because the patient would not allow the procedure to be completed.

Baseline characteristics

The treatment groups were comparable in terms of sociodemographic variables, rheumatic diseases and use of drugs.[15] The study population consisted mainly of patients of Dutch Caucasian ethnicity (87%) with predominantly rheumatoid arthritis (61%). Most patients (74%) used non-selective NSAIDs; diclofenac by 100 (29%) patients, naproxen by 63 (18%), ibuprofen by 44 (13%) and indometacine by 21 (6%). Selective NSAIDs were used by 90 (26%) patients; meloxicam by 38 (11%) patients, nabumetone by 22 (6%), rofecoxib by 25 (7%) and celecoxib by 5 (1%). There were no significant differences in NSAID use between the treatment groups.

Gastroduodenal ulcers

At endoscopy, gastroduodenal ulcers were diagnosed in 6 (4%) patients in the eradication group (5 gastric and 1 duodenal ulcer) and 8 (5%) patients in the placebo group (6 gastric and 2 duodenal ulcers) (P=0.65).[15] No patients developed symptomatic ulcers, gastrointestinal bleeding or perforation during the total study period of 52 weeks.

Post hoc analysis

At 13 weeks a full gastroduodenal endoscopy was performed in 301 patients; 14 had gastroduodenal ulcers while 287 did not. Demographic variables, rheumatic diseases, co-morbidity and drug use in those with ulcers vs. those without are shown in table 1.

None of the patients on long-term selective NSAIDs had gastroduodenal ulcers at endoscopy or developed symptomatic ulcers, gastrointestinal bleeding or perforation during the total 52 week study period, thus the use of selective NSAIDs was significantly less common among ulcer patients than among non-ulcer patients; 0 (0%) patients in the ulcer group vs. 80 (28%) patients in the non-ulcer group used selective NSAIDs (P=0.02).

The patients on long-term selective NSAIDs were distributed evenly over both treatment groups by the randomization; 37 (46%) in the eradication group and 43 (54%) in the placebo group. As none

Table 2. Sub-analysis of risk-factors for NSAID-gastropathy in patients using selective NSAIDs and patients using non-selective NSAIDs

Characteristics	s-NSAIDs (N=80)	ns-NSAID (N=221)	P-value
Age - years; mean ± SD	58 ± 11	59 ± 10	0.41
History of gastroduodenal ulcers - no. (%)	11 (14)	21 (10)	0.29
Co-morbidity - no. (%)	56 (70)	143 (65)	0.39
Concomitant use of drugs			
proton pump inhibitors - no. (%)	29 (36)	84 (38)	0.78
histamine-2 receptor antagonist - no. (%)	4 (5)	15 (7)	0.57
low dose aspirin - no. (%)	6 (8)	25 (11)	0.34
coumarins - no. (%)	3 (4)	8 (4)	1.00
corticosteroids - no. (%)	7 (9)	20 (9)	0.94
Eradication of H. pylori - no. (%)	37 (46)	112 (51)	0.50

s-NSAIDs: selective NSAIDs; ns-NSAIDs: non-selective NSAIDs

of these patients developed gastroduodenal ulcers, eradication of H. pylori in patients on long-term selective NSAIDs did not influence the ulcer rate.

Other significant differences between the ulcer- and non-ulcer groups was concurrent use of low dose aspirin; 4 (29%) in the ulcer group vs. 27 (9%) in the non-ulcer group (P=0.02) and borderline significant was co-morbidity; 6 (43%) in the ulcer group vs. 193 (67%) in the non-ulcer group (P=0.06). Concomitant use of gastroprotective drugs, corticosteroids and coumarins did not differ significantly between the groups and neither did history of gastroduodenal ulcers or eradication of H. pylori.

In 14 patients, endoscopic evaluation was incomplete, either because of technical problems during endoscopy or because the patient would not allow the procedure to be completed. In all these patients, the stomach could be evaluated and none of these patients had a gastric ulcer. Adding these patients to those with a full endoscopic evaluation did not change the results.

In a sub-analysis, no significant differences were found in risk factors for NSAID-gastropathy in patients using selective NSAIDs compared with those in patients using non-selective NSAIDs (*table 2*).

DISCUSSION

This study suggests that in Helicobacter pylori-positive patients on long-term NSAID treatment for rheumatic diseases, long-term use of selective NSAIDs significantly reduces the risk for endoscopic gastroduodenal ulcers. Helicobacter pylori eradication therapy does not ameliorate the risk. Moreover, concomitant use of low dose aspirin significantly increases the risk for endoscopic ulcers in patients on long-term NSAID treatment.

Several randomized controlled trials have previously demonstrated a 50% reduction in the risk for gastroduodenal ulcers during short-term use of selective COX-2 inhibitors as compared to non-selective NSAIDs.[2,3] However, it is unclear whether this effect remains during long-term use.[8] In the present study in long-term NSAID users, the reduction in risk for gastroduodenal ulcers might be even larger, as none of the 80 patients using selective NSAIDs developed endoscopic ulcers. However, due to the

zero cases no exact value for the risk reduction could be calculated. A large risk reduction in the present study might be due to several reasons. Firstly, 36% of the patients using selective NSAIDs concomitantly used proton pump inhibitors and 5% concomitantly used histamine-2 receptor antagonists. Although these percentages were slightly lower than in the group of patients using non-selective NSAIDs, a cumulative gastroprotective effect might be expected. Secondly, in previous randomized controlled trials rigorous selection criteria were maintained and those at high risk for NSAID-gastropathy were usually excluded[2,3]. In contrast with these studies, ours was specifically designed to mirror daily clinical practice. We therefore also included long-term NSAID using patients with high risk profiles such as concomitant use of corticosteroids, anticoagulants, low-dose aspirin, and a history of gastroduodenal ulcers. Furthermore, all patients were serologically H. pylori positive. However, at endoscopy the overall incidence of gastroduodenal ulcers was only 4.7%. It is therefore probable that inadvertently patients were pre-selected by time for good NSAID tolerability, leading to very low endoscopic ulcer rates in those on long-term selective NSAIDs.

Previous studies in H. pylori-positive patients suggest that H. pylori infection may negate the gastrointestinal safety of selective COX-2 inhibitors.[12-14] Conversely, in the present study H. pylori eradication therapy did not influence the ulcer risk in those on long-term selective NSAIDs. However, it is possible that a type II error might have occurred due to the low overall incidence of endoscopic NSAID-ulcers and the relatively small number of patients on long-term selective NSAIDs.

In a sub-analysis of risk factors for NSAID-gastropathy, we found no differences between the selective NSAID users and the non-selective NSAID users. Whether or not the gastrointestinal safety of selective NSAIDs is maintained during concomitant use of low dose aspirin remains unclear. In our study, long-term NSAID users who developed an endoscopic ulcer significantly more often used low dose aspirin than those who did not develop ulcers. However, in the group using selective NSAIDs, only 8% of the patients used low dose aspirin, and none of these patients developed an endoscopic ulcer.

CONCLUSIONS

Our data suggests that in H. pylori-positive patients on long-term NSAID treatment for rheumatic diseases, long-term use of selective NSAIDs significantly reduces the risk for endoscopic gastroduodenal ulcers. H. pylori eradication therapy does not modify this risk. Concomitant use of low dose aspirin significantly increases the risk for endoscopic ulcers in patients on long-term NSAID treatment.

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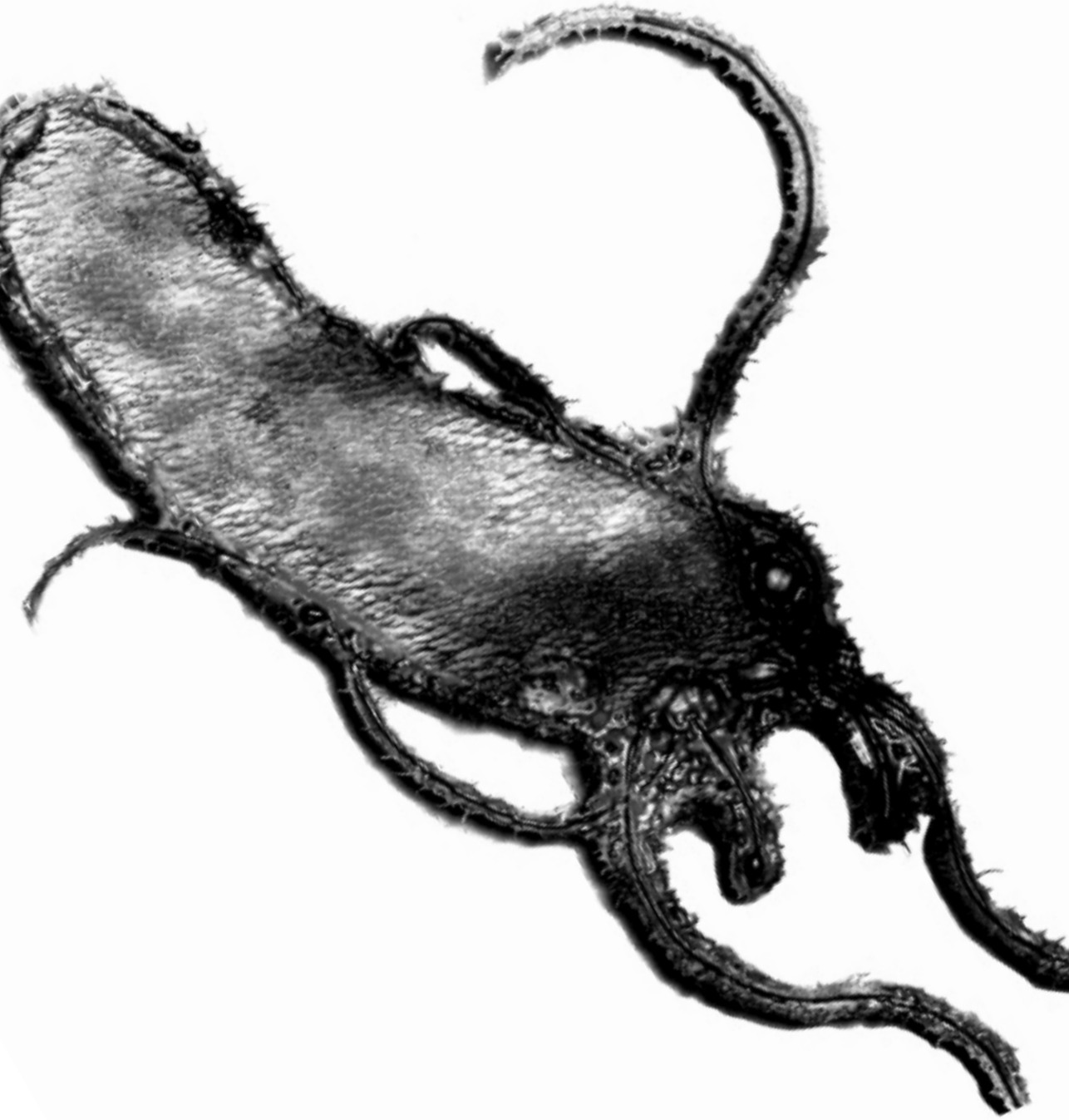

CHAPTER IX

How should we diagnose persistent Helicobacter pylori infection or succesful eradication following triple therapy in NSAID users?

HE Vonkeman, HTJI de Leest, MAFJ van de Laar, J van Baarlen, KSS Steen, WF Lems, JWJ Bijlsma, EJ Kuipers, HHML Houben, M Janssen, BAC Dijkmans

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ABSTRACT

Introduction In a post hoc analysis we compared Helicobacter pylori IgG-antibody titers, hematoxylin and eosin (H&E) stains, immunohistochemical (IHC) stains and H. pylori culture results from a randomized, double blind, placebo controlled clinical trial to determine the sensitivity and specificity of these different detection methods in long-term NSAID taking patients, following H. pylori eradication therapy or placebo. Furthermore, we determined whether adding IHC stains to H&E stains improves the histological identification of H. pylori in these patients.

Methods Sixty-eight long-term NSAID using patients who were H. pylori positive on serological testing were randomized for eradication therapy or placebo. Thirteen weeks after randomization gastric mucosal biopsies and blood samples were taken for H. pylori culture, histological examination and repeated serological testing. The gold standard for H. pylori infection was based on a positive culture or both a positive histological examination and serological test.

Results According to the gold standard criteria, H. pylori eradication therapy was successful in 91.2% of the patients. Serology provided a sensitivity of 100% but overall specificity was 23.7% and 16.1% after eradication. Culture provided an overall sensitivity of 83.3%, and 66.7% after eradication, with a specificity of 100%. Histological examination with either H&E or IHC stains provided sensitivities and specificities between 90% and 100%. Adding IHC to H&E stains did not improve these results.

Conclusions In long-term NSAID taking patients, following H. pylori eradication therapy or placebo, histological examination of gastric mucosal tissue biopsies provides the best sensitivity and specificity ratios, and is the best method for evaluating success of H. pylori eradication therapy. Adding IHC stains to H&E stains does not improve the results.

INTRODUCTION

Helicobacter pylori (H. pylori) infection is a major cause of peptic ulcer disease and chronic gastritis.[1,2] Accurate diagnosis of H. pylori infection has clinical consequences as H. pylori eradication improves outcome and recurrence of peptic ulcer disease. Several different methods are available for the detection H. pylori infection.[3] These include non-invasive tests such as serological tests based on the detection of antibodies to H. pylori, and invasive tests requiring endoscopically obtained gastric mucosal tissue biopsies, such as tissue culture and examination of histological stains. Serological tests have high sensitivity and are useful in screening for H. pylori infection.[4,5] However, serological tests are unable to discriminate between current or past infection and are not useful in evaluating success of eradication therapy. Culture of H. pylori in biopsy specimens has very high specificity and allows testing for antibiotic susceptibility but has relatively low sensitivity and is labour-intensive.[6] Histological identification of H. pylori in biopsy specimens is considered to be the clinical standard for the diagnosis of H. pylori infection. A high density of H. pylori is readily apparent on routine hematoxylin and eosin (H&E) stains but detection of a lower density of bacteria may require additional staining techniques.[7] H. pylori is more easily visualised with immunohistochemical H. pylori antibody stains than with the standard H&E staining. However, the use of immunohistochemical (IHC) stains adds time and expense to the diagnostic evaluation for H. pylori and is therefore not routinely performed.

The role of H. pylori in the development of NSAID-associated gastric ulcers remains controversial. In a meta-analysis of 16 endoscopic studies in NSAID users from various countries, uncomplicated gastric ulcer disease was twice as common in patients with H. pylori as in patients without.[8] However, the rate of H. pylori infection in NSAID-associated gastric ulcers is significantly lower than that in non-NSAID-associated gastric ulcers.[9]

Furthermore, while eradication of H. pylori in patients who are about to start NSAID-therapy reduces the risk of ulcer development, it does not do so in patients already on NSAID-therapy.[10-12] This was confirmed in a recently conducted randomized, double blind, placebo controlled clinical trial, in which we found that eradication of H. pylori did not reduce the incidence of endoscopic gastroduodenal ulcers in H. pylori seropositive patients taking long-term NSAIDs for rheumatic diseases.[13]

While several previous studies have compared sensitivity, specificity and costs of different methods for the detection of H. pylori, few have studied the effect of preceding H. pylori eradication therapy and none have been conducted in NSAID-using patients.[7, 14-19] We therefore compared H. pylori IgG-antibody titers, H&E stains, IHC stains and H. pylori culture results in follow-up biopsies from H. pylori-positive NSAID-users randomized to eradication treatment or placebo, to determine the sensitivity and specificity of these different methods in long-term NSAID taking patients. Furthermore, we determined whether adding IHC stains to H&E stains improves the histological identification of H. pylori in these patients.

METHODS

Study design

The methods of the primary randomized, double blind, placebo controlled clinical trial have been published in detail.[13] Between May 2000 and June 2002, patients between 40 and 80 years of age with a rheumatic disease requiring long-term NSAID treatment were recruited. Patients were included in

the study if tested positive for H. pylori on serological testing. No change in NSAID-therapy was permitted during the study, but there was no restraint on other concurrent medication. Exclusion criteria were previous H. pylori eradication and severe concomitant disease.
Patients were randomly assigned to either H. pylori eradication therapy or placebo. After three months all patients underwent gastroduodenal endoscopy. During endoscopic examination, four antrum biopsies and four corpus biopsies were taken from each patient for culture and histological examination. Blood samples were taken after endoscopic examination for repeated serological testing. The study protocol was approved by the medical ethics reviewing committee and all patients gave written informed consent. Immunohistochemical staining was only available for patients recruited at the Medisch Spectrum Twente hospital in Enschede, the Netherlands. These patients were therefore included in the present study.

Serology

Serological testing for H. pylori IgG-antibodies was performed by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (Pyloriset® new EIA-G, Orion Diagnostica, Espoo, Finland). Results were considered positive if the antibody titer was ≥250 International Units per mL (IU/mL), according to the manufacturer's guidelines.

Culture

Biopsy specimens of both corpus and antrum taken during endoscopy were inoculated onto Columbia agar (Becton Dickinson, Cockeysville, MD, USA) with 10% lysed horse blood (Bio Trading, Mijdrecht, The Netherlands), and onto Columbia agar with H. pylori selective supplement (Oxoid, Basingstoke, UK). Media were incubated at 37°C under microaerophilic conditions (5% O_2, 10% CO_2 and 85% N_2) for 72 h. The isolated colonies of H. pylori were identified by Gram stain showing spiral-shaped Gram-negative rods, producing urease rapidly, with positive catalase and oxidase tests.

Histology

Biopsy specimens were stained for Hematoxylin and Eosin (H&E) according to the standard procedure. For immunohistochemical (IHC) staining, the slides were heated in an autoclave (Kavoklave, Prestige Medical Ltd, UK) in a citric-acid solution (pH = 6) to 121-126 °C during 30 minutes for antigen retrieval. The slides were then incubated in a Shandon Sequenza Immunostaining Center (Thermo Electron Corporation, the Netherlands) with a polyclonal rabbit IgG anti-Helicobacter pylori antibody (DakoCytomation, Denmark, dilution 1:300), followed by biotinylated goat anti-polyvalent antibody (LabVision Corporation, USA), strepavidin peroxidase (LabVision Corporation, USA) and Liquid DAB + substrate chromogen system (DakoCytomation, Denmark), and counterstained with hematoxylin.
All gastric biopsy specimens were retrospectively examined by a single expert pathologist who was blinded for clinical data, treatment allocation and other test results.

Gold standard definition

A patient was defined as being H. pylori positive on the basis of a positive culture for H. pylori or, in the case of a negative culture, a positive examination of either H&E or IHC stains in combination with H. pylori IgG-antibody titers persistently ≥ 250 IU/mL.

Table 1. Results of H. pylori detection by each test.

Test		Positive (%)	Negative (%)
Serology	Total	59 (86.8)	9 (13.2)
	Eradication	29 (85.3)	5 (14.7)
	Placebo	30 (88.2)	4 (11.8)
Culture	Total	25 (36.8)	43(63.2)
	Eradication	32 (94.1)	2 (5.9)
	Placebo	11 (32.4)	23 (67.6)
H&E stains	Total	28 (41.2)	40 (58.8)
	Eradication	30 (88.2)	4 (11.8)
	Placebo	10 (29.4)	24 (70.6)
IHC stains	Total	32 (47.1)	36 (52.9)
	Eradication	29 (85.3)	5 (14.7)
	Placebo	7 (20.6)	27 (79.4)

H&E: hematoxylin and eosin, IHC: immunohistochemistry. Positive serology was defined as H. pylori IgG-antibody titers at endoscopy ≥ 250 IU/mL.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean and standard deviation (SD), and continuous variables with a non-normal distribution as median and interquartile range (IQR). Differences between groups were analysed using Students t-test, Mann-Whitney U test, Pearson's Chi-square test or Fisher's Exact test in case of low expected values. For all analyses $P<0.05$, two sided, was considered significant. All analyses were performed with SPSS for Windows, version 12.0.1 (SPSS, Chicago, IL, USA).

RESULTS

A total of 68 patients were included in this study; 35 (51%) were male and 33 (49%) were female, with a mean age of 58.8 ± 9.8 years. Patients were equally randomized for H. pylori eradication therapy or placebo.

According to the gold standard criteria, H. pylori eradication therapy was successful in 91.2% of the treated patients. In the total group of 68 patients, the H. pylori status was positive according to the gold standard criteria in 30 (44.1%) and negative in 38 (55.9%) patients. Out of the 34 patients who had been treated with H. pylori eradication therapy, 3 (8.8%) had remained H. pylori positive according to the gold standard criteria and 31 (91.2%) were negative. Out of the 34 patients who had been treated with placebo, 27 (79.4%) had remained H. pylori positive according to the gold standard criteria and 7 (20.6%) were negative (Odds Ratio 0.03, 95% confidence interval 0.01 to 0.11, $P<0.001$).

The results of H. pylori detection by each of the different tests are shown in Table 1. At baseline, there were no significant differences in H. pylori IgG-antibody titers between the groups assigned to H. pylori eradication therapy or to placebo ($P=0.46$). At endoscopy, H. pylori IgG-antibody titers had dropped below the 250 IU/mL threshold for positivity in 9 (13.2%) patients; 5 in the eradication group and

Table 2. Results of H. pylori detection by each test according to the gold standard criteria.

Test	Result	H. pylori positive (No.)	H. pylori negative (No.)
Serology	Positive	30	29
	Negative	0	9
Culture	Positive	25	0
	Negative	5	38
H&E stains	Positive	27	1
	Negative	3	37
IHC stains	Positive	30	2
	Negative	0	36
H&E + IHC stains	Positive	30	3
	Negative	0	35

H&E: hematoxylin and eosin, IHC: immunohistochemistry. Positive serology was defined as H. pylori IgG-antibody titers at endoscopy ≥ 250 IU/mL.

4 in the placebo group (P=1.00). Compared to baseline however, H. pylori IgG-antibody titers were median 56% lower in the eradication group and median 9% lower in the placebo group (P<0.001).
Of the 68 patients, H. pylori culture was positive in 25 (36.8%) and negative in 43 (63.2%) patients. Out of the 34 patients who had been treated with H. pylori eradication therapy, 32 (94.1%) had a negative culture and in 2 (5.9%) it had remained positive. Out of the 34 patients who had been treated with placebo, 11 (32.4%) had a negative culture and in 23 (67.6%) it was positive (P<0.001).
Of the 68 patients, examination with H&E stains was positive in 28 (41.2%) and negative in 40 (58.8%) patients. Out of the 34 patients who had been treated with H. pylori eradication therapy, 30 (88.2%) had a negative H&E stain and in 4 (11.8%) it had remained positive. Out of the 34 patients who had been treated with placebo, 10 (29.4%) had a negative H&E stain and in 24 (70.6%) it had remained positive (P<0.001).
Of the 68 patients, examination with IHC stains was positive in 32 (47.1%) and negative in 36 (52.9%) patients. Out of the 34 patients who had been treated with H. pylori eradication therapy, 29 (85.3%) had a negative IHC stain and in 5 (14.7%) it was positive. Out of the 34 patients who had been treated with placebo, 7 (20.6%) had a negative IHC stain and in 27 (79.4%) it was positive (P<0.001).
According to the gold standard criteria, a patient could be either H. pylori positive or H. pylori negative. Results of H. pylori detection by each of the different tests cross referenced according to the gold standard criteria are shown in table 2. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of each test were calculated for the whole group and also differentiated for preceding H. pylori eradication therapy or placebo, as is shown in table 3. For the combined analysis of H&E and IHC stains, results were positive if either test was positive or results were negative if both tests were negative *(tables 2 and 3)*.

Table 3. Results of the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each test; for the total study group and differentiated for preceding H. pylori eradication therapy or placebo.

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Serology				
Total	100.00	23.68	50.85	100.00
Eradication	100.00	16.13	10.35	100.00
Placebo	100.00	57.14	90.00	100.00
Culture				
Total	83.33	100.00	100.00	88.37
Eradication	66.67	100.00	100.00	96.88
Placebo	85.19	100.00	100.00	63.64
H&E stains				
Total	90.00	97.37	96.43	92.50
Eradication	100.00	96.77	75.00	100.00
Placebo	88.89	100.00	100.00	70.00
IHC stains				
Total	100.00	94.74	93.75	100.00
Eradication	100.00	93.55	60.00	100.00
Placebo	100.00	100.00	100.00	100.00
H&E + IHC				
Total	100.00	92.11	90.91	100.00
Eradication	100.00	90.32	50.00	100.00
Placebo	100.00	100.00	100.00	100.00

H&E: hematoxylin and eosin, IHC: immunohistochemistry. Positive serology was defined as H. pylori IgG-antibody titers at endoscopy ≥ 250 IU/mL.

DISCUSSION

In the present study in long-term NSAID taking patients, following H. pylori eradication therapy or placebo, histological examination of gastric mucosal tissue biopsies provided the best sensitivity and specificity ratios, and is the preferred method for evaluating success of H. pylori eradication therapy. The H&E and IHC staining methods provided comparable high sensitivity and specificity. However, adding IHC stains to H&E stains did not improve these results.

Overall, test results did not differ from those reported in non-NSAID-using patients.[3,20] The choice of a gold standard affects test results of all other tests. A reliable gold standard should consist of at least 2 methods based on different principles for detecting H. pylori infection.[3,21] The gold standard in the present study corresponds to acceptable criteria.

Serological testing for H. pylori IgG-antibodies was found to be highly sensitive (100%) but to have very poor specificity (23.7%), especially following H. pylori eradication therapy (16.1%), and does therefore not appear to be useful for evaluating success of H. pylori eradication therapy. However, these results must be interpreted with caution. All patients were included in the study on the basis of H. pylori IgG-antibody titers ≥250 IU/mL and three months after inclusion, H. pylori IgG-antibody titers had dropped below this threshold in only 9 (13.2%) patients; 5 in the eradication group and 4 in the placebo group.

Culture of H. pylori in gastric biopsy specimens has very high specificity but has relatively low sensitivity [3, 20]. In the present study, culture provided 100% specificity and 83.3% sensitivity. However, after H. pylori eradication therapy sensitivity dropped to 66.7% due to an increasing percentage of false negative cultures. Culture of H. pylori does therefore not appear to be useful for evaluating success of H. pylori eradication therapy.

Histological examination provided the best sensitivity and specificity ratios. Overall, IHC staining was slightly superior to H&E staining. In the total study group, H&E staining provided 1 false positive and 3 false negative test results while IHC staining provided 2 false positive but no false negative test results. In the eradication group, both staining methods provided 100% sensitivity and also very high specificity; H&E staining 96.8% and IHC staining 93.6%. A combined analysis of H&E and IHC stains, in which results were positive if either test was positive or results were negative if both tests were negative, did not improve sensitivity while the number of false positive test results increased. Cost effectiveness of diagnostic tests has become a central issue in modern medical practice. Pathologists will have to balance the added expenses of IHC staining and time saved by quicker screening compared to cheaper H&E staining and longer evaluation, to determine which method is most cost effective in their daily practice.

Histological examination is an invasive test, requiring endoscopically obtained gastric mucosal tissue biopsies. Other accurate, relatively inexpensive non-invasive tests to be considered are urea breath testing, 13C bicarbonate assays and stool antigen tests. These tests were not included in the present study.

In conclusion, in the present study in long-term NSAID taking patients, following H. pylori eradication therapy or placebo, histological examination of gastric mucosal tissue biopsies provided the best sensitivity and specificity ratios, and is the best method for evaluating success of H. pylori eradication therapy. The H&E and IHC staining methods provided comparable high sensitivity and specificity but combining IHC and H&E did not improve results.

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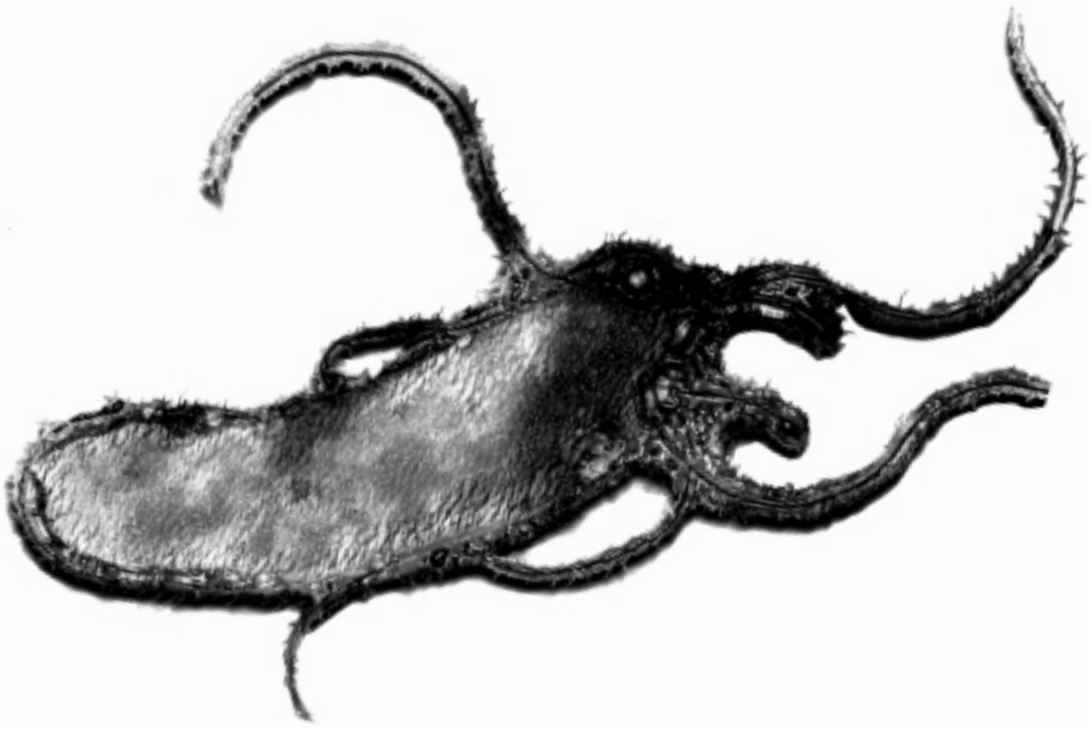

CHAPTER X

Serological assessment of Helicobacter pylori eradication in patients on long-term NSAID treatment

HE Vonkeman, HTJI de Leest, MAFJ van de Laar, J van Baarlen, KSS Steen, WF Lems, JWJ Bijlsma, EJ Kuipers, HHML Houben, M Janssen, BAC Dijkmans

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ABSTRACT

Introduction In a post hoc analysis of a randomized, double blind, placebo controlled, Helicobacter pylori eradication trial, we measured H. pylori IgG-antibody titers to determine the diagnostic value for H. pylori eradication in long-term NSAID users.

Methods Sixty-eight long-term NSAID using patients who were H. pylori positive on serological testing for H. pylori IgG-antibodies were randomized for H. pylori eradication therapy or placebo. Thirteen weeks after randomization gastric mucosal biopsies and blood samples were taken for H. pylori culture, histological examination and repeated serological testing. The gold standard for H. pylori infection was based on a positive culture or both a positive histological examination and serological test. Sensitivity, specificity and receiver operating characteristic (ROC) curves of the serological test results for the successful eradication of H. pylori were analyzed.

Results According to the gold standard criteria, H. pylori eradication therapy was successful in 91.2% of the patients. The ROC curve for percent change in H. pylori IgG-antibody titers had good diagnostic power in identifying H. pylori negative patients, with an area under the ROC curve of 0.86 (95% CI: 0.75 to 0.93, $P<0.0001$). The optimal cut-off point for percent change in H. pylori IgG-antibody titers was -47.3%, corresponding to a sensitivity of 96.7% (95% CI: 82.7 to 99.4%) and specificity of 60.5% (95% CI: 43.4 to 75.9%). Using a cut-off point of 50% decrease in H. pylori IgG-antibody titers provided in the eradication group a sensitivity of 100% and specificity of 71%.

Conclusions In long-term NSAID users, a H. pylori IgG-antibody titer decrease of 50% at 3 months has sufficiently high sensitivity and specificity to be useful in evaluating success of H. pylori eradication therapy.

INTRODUCTION

Helicobacter pylori (H. pylori) infection has been shown to be related to the development of peptic ulcer disease, chronic gastritis, MALT lymphoma and gastric cancer.[1-4] Accurate diagnosis of H. pylori infection has clinical consequences as H. pylori eradication improves outcome and recurrence of peptic ulcer disease. H. pylori infection can be detected using non-invasive tests such as serological tests and the breath urea test, and invasive tests requiring endoscopically obtained gastric mucosal tissue biopsies, such as tissue culture, examination of histological stains and the rapid urease test. Serological tests based on the detection of antibodies to H. pylori have been shown to have high sensitivity and are therefore useful in screening for H. pylori infection.[5-7] However, because serological tests merely detect an immune response, they do not discriminate between current or previous infection. H. pylori infection of the gastric mucosa causes a chronic local inflammatory cell infiltration, which in turn gives rise to a serological response, in which H. pylori specific antibodies are almost always detectable.[8,9] After successful H. pylori eradication therapy, the level of H. pylori specific antibodies decreases progressively over a period of several months, possibly parallel to the slowly healing inflammation of the gastric mucosa.[10] As a result, evaluating success of H. pylori eradication therapy using repeated serological tests has only been shown to be useful if a period of several months is maintained between tests.[11-13]

The interaction between H. pylori infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the development of gastroduodenal ulcers remains unclear. In a meta-analysis of 16 endoscopic studies in NSAID users from various countries, uncomplicated gastric ulcer disease was twice as common in H. pylori positive patients as in H. pylori negative patients.[14] However, the rate of H. pylori infection in patients with NSAID associated gastric ulcers is significantly lower than in those with non-NSAID associated gastric ulcers[15]. Furthermore, while eradication of H. pylori infection in NSAID-naïve patients prior to NSAID therapy reduces the risk of ulcer development, it does not do so in current NSAID users.[16-18] This was also confirmed in our recent randomized, double blind, placebo controlled clinical trial, in which we found that eradication of H. pylori infection did not reduce the incidence of endoscopic gastroduodenal ulcers in H. pylori seropositive patients currently taking NSAIDs for rheumatic diseases.[19]

H. pylori infection has been shown to induce cyclooxygenase (COX)-2 expression in the gastric mucosa, which persists during active H. pylori infection.[20-23] It has been suggested that COX-2 plays an immunosuppressive role in H. pylori gastritis.[24] Conversely, in H. pylori infected mice, NSAID treatment has been shown to significantly decrease the degree of gastric inflammation.[25] It is therefore possible that in patients with H. pylori infection, concurrent NSAID treatment may affect levels of gastric inflammation and may consequently affect the serological response. While several studies have investigated the time course of H. pylori antibody titers after H. pylori eradication therapy, none have been conducted in NSAID users.[9,11-13,26]

This study presents a post hoc investigation into H. pylori IgG-antibody titer changes following H. pylori eradication therapy in long-term NSAID users. In patients participating in the before mentioned H. pylori eradication in NSAID users trial, we measured H. pylori IgG-antibody titers and titer changes in order to diagnose successful H. pylori eradication.[19]

METHODS

Study design

The methods of the primary randomized, double blind, placebo controlled clinical trial have been published in more detail.[19] Between May 2000 and June 2002, patients between the ages of 40 and 80 years with a rheumatic disease requiring long-term NSAID treatment, were recruited and included in the study if tested positive for H. pylori on serological testing. During the study, no change in NSAID-therapy was permitted, but there was no restraint on other medication. Exclusion criteria were previous H. pylori eradication therapy and severe concomitant disease.

Patients were randomly assigned to either H. pylori eradication therapy or placebo. After three months all patients underwent gastroduodenal endoscopy, during which four antrum biopsies and four corpus biopsies were taken for culture and histological examination. At this time, blood samples were taken for repeated serological testing. Immunohistochemical staining was only available for patients recruited at the Medisch Spectrum Twente hospital in Enschede, the Netherlands. These patients were therefore included in the present analysis. The study protocol was approved by the Institutional Ethical Review Board and all patients gave written informed consent.

Serology

Serological testing for H. pylori IgG-antibodies was performed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Pyloriset® new EIA-G, Orion Diagnostica, Espoo, Finland). Results were considered positive if the antibody titers were ≥250 International Units per mL (IU/mL), according to the manufacturer's guidelines.

Culture

Biopsy specimens of corpus and antrum taken during endoscopy were inoculated onto Columbia agar (Becton Dickinson, Cockeysville, MD, USA) with 10% lysed horse blood (Bio Trading, Mijdrecht, The Netherlands), and onto Columbia agar with H. pylori selective supplement (Oxoid, Basingstoke, UK). Media were then incubated for 72 hours at 37°C under microaerophilic conditions (5% O_2, 10% CO_2 and 85% N_2). The isolated colonies of H. pylori were identified by Gram stain showing spiral-shaped Gram-negative rods, producing urease rapidly, with positive catalase and oxidase tests.

Histology

Biopsy specimens were stained for Hematoxylin and Eosin (H&E) according to the standard procedure. For immunohistochemical (IHC) staining, the slides were heated in an autoclave (Kavoklave, Prestige Medical Ltd, UK) in a citric-acid solution (pH = 6) to 121-126 °C during 30 minutes for antigen retrieval. The slides were then incubated in a Shandon Sequenza Immunostaining Center (Thermo Electron Corporation, The Netherlands) with a polyclonal rabbit IgG anti-Helicobacter pylori antibody (DakoCytomation, Denmark, dilution 1:300), followed by biotinylated goat anti-polyvalent antibody (LabVision Corporation, USA), strepavidin peroxidase (LabVision Corporation, USA) and Liquid DAB + substrate chromogen system (DakoCytomation, Denmark), and counterstained with hematoxylin. All stained biopsy specimens of corpus and antrum taken during endoscopy were examined by a single expert pathologist who was blinded for clinical data, treatment allocation and other test results.

Table 1. Results of the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of serological testing; for the total study group and differentiated for preceding H. pylori eradication therapy or placebo.

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Serology < 250 IU/mL				
Total	100.0	23.7	50.9	100.0
Eradication	100.0	16.1	10.4	100.0
Placebo	100.0	57.1	90.0	100.0
Serology ≥ 50% decrease				
Total	96.7	60.5	65.9	95.8
Eradication	100.0	71.0	25.0	100.0
Placebo	96.3	14.3	81.3	50.0

Gold standard definition

As gold standard for H. pylori infection in this study, at 3 months a patient was defined as being H. pylori positive on the basis of a positive culture for H. pylori or, in the case of a negative culture, a positive examination of either H&E or IHC stains in combination with H. pylori IgG-antibody titers persistently ≥ 250 IU/mL.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean with standard deviation (SD), and continuous variables with a non-normal distribution as median with interquartile range (IQR). Differences between groups were analysed using Students t-test, Mann-Whitney U test, Pearson's Chi-square test or Fisher's Exact test in case of low expected values. For all analyses $P<0.05$, two sided, was considered significant. All analyses were performed with SPSS for Windows, version 12.0.1 (SPSS, Chicago, IL, USA).

RESULTS

A total of 68 patients were included in the present study; 35 (51%) were male and 33 (49%) were female, with a mean age of 58.8 ± 9.8 years. Patients were equally randomized for H. pylori eradication therapy or placebo.

According to the gold standard criteria for H. pylori infection, H. pylori eradication therapy was successful in 91.2% of the treated patients. In the total group of 68 patients, the H. pylori status was positive according to the gold standard criteria in 30 (44.1%) and negative in 38 (55.9%) patients. Out of the 34 patients who had been treated with H. pylori eradication therapy, 3 (8.8%) had remained H. pylori positive according to the gold standard criteria and 31 (91.2%) were negative. Out of the 34 patients who had been treated with placebo, 27 (79.4%) had remained H. pylori positive according to the gold standard criteria and 7 (20.6%) were negative (Odds Ratio 0.03, 95% confidence interval 0.01 to 0.11, $P<0.001$, Figure 1).

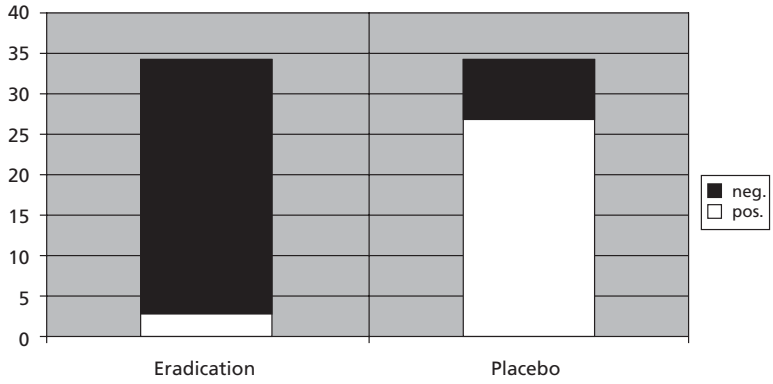

Figure 1. Number of patients positive for H. pylori at endoscopy, according to the gold standard definition, in the eradication and placebo groups

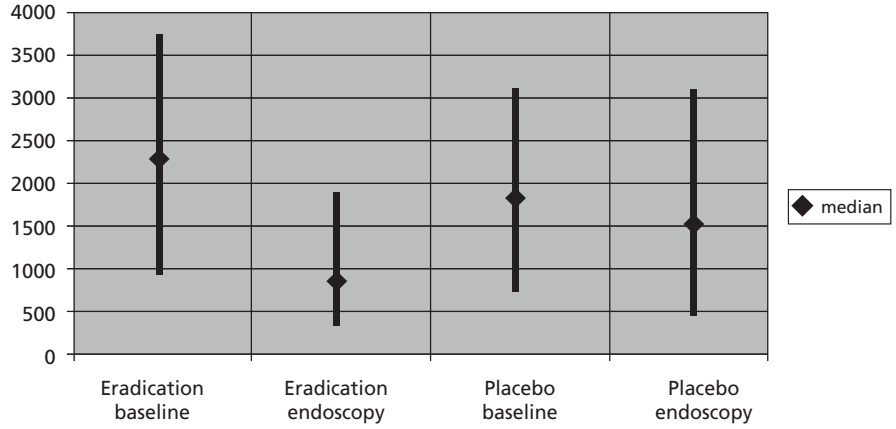

Figure 2. Median and interquartile range of H. pylori IgG-antibody titers (IU/mL) at baseline and endoscopy, in the eradication and placebo groups

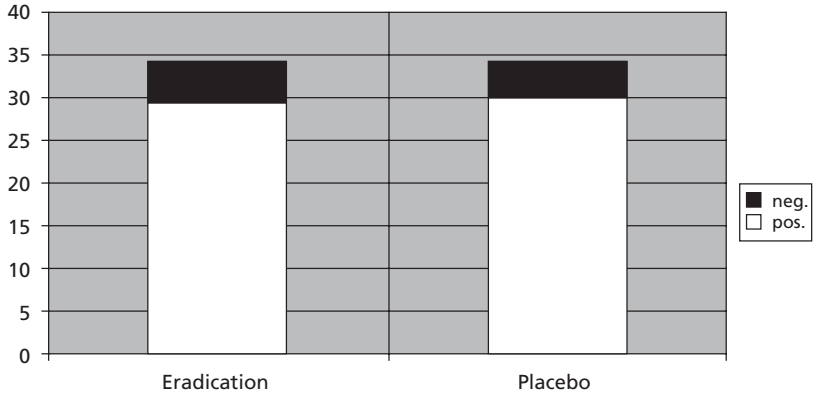

Figure 3. Number of patients positive for H. pylori at endoscopy, according to H. pylori IgG-antibody titers >250 IU/mL, in the eradication and placebo groups

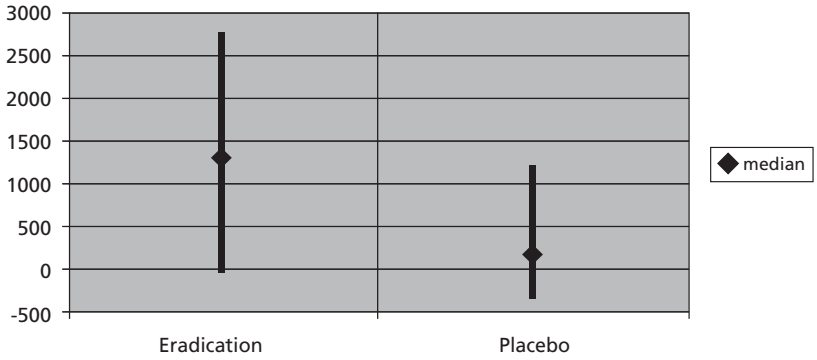

Figure 4. Median and interquartile range of absolute decrease in H. pylori IgG-antibody titers (IU/mL) at endoscopy compared to baseline, in the eradication and placebo groups

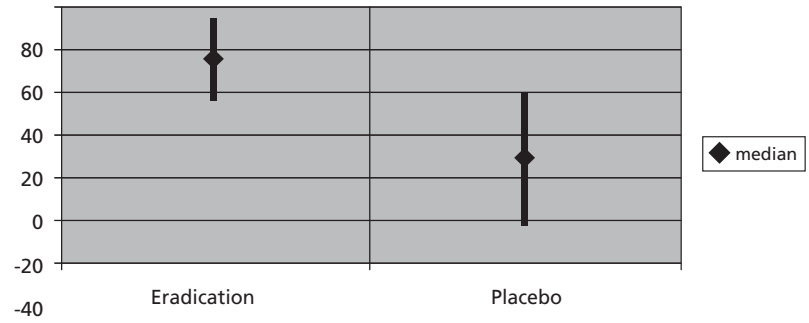

Figure 5. Median and interquartile range of percent decrease in H. pylori IgG-antibody titers (%) at endoscopy compared to baseline, in the eradication and placebo groups

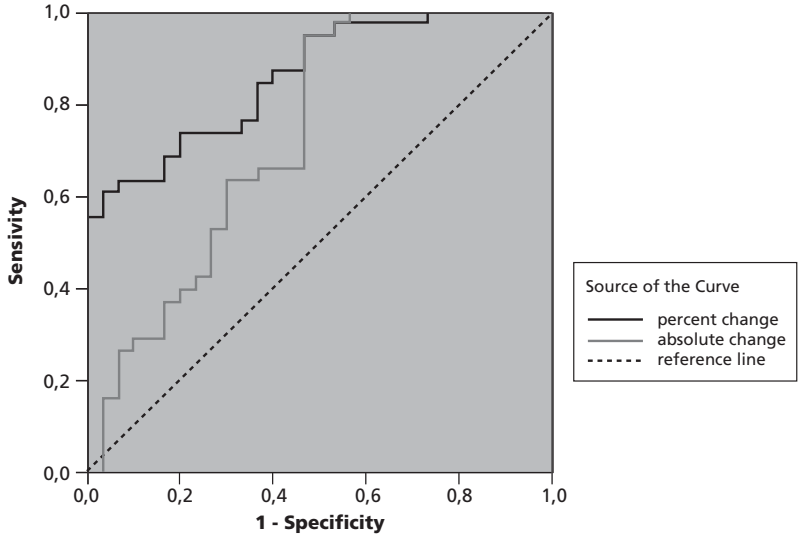

Figure 6. ROC curves for absolute and percent change in H. pylori IgG-antibody titers, associated with a negative result for the gold standard criteria for H. pylori infection

At baseline, H. pylori IgG-antibody titers varied from 253 IU/mL to 19029 IU/mL with a median of 1891 IU/mL (interquartile range (IQR) 795 to 3354 IU/mL). At baseline, there were no significant differences in H. pylori IgG-antibody titers between the groups assigned to H. pylori eradication therapy or to placebo; eradication group median 2214 IU/mL (IQR 925 to 3606 IU/ml) and placebo group median 1785 IU/mL (IQR 702 to 2979 IU/mL) (P=0.46, Figure 2). At endoscopy at 3 months, H. pylori IgG-antibody titers varied from 126 IU/mL to 10283 IU/mL, with a median of 1121 IU/mL (IQR 380 to 2811 IU/mL). Patients who had been treated with H. pylori eradication therapy had lower H. pylori IgG-antibody titers than those treated with placebo; eradication group median 802 IU/mL (IQR 318 to 1787 IU/mL) and placebo group median 1503 IU/mL (IQR 438 to 2981 IU/mL) (P=0.07, Figure 2).

At endoscopy, H. pylori IgG-antibody titers had dropped below the 250 IU/mL threshold for positivity in 9 (13.2%) patients; 5 in the eradication group and 4 in the placebo group (P=1.00, Figure 3).

The change in H. pylori IgG-antibody titers from baseline to endoscopy (titer at baseline minus titer at endoscopy) did differ significantly between the groups; eradication group median 820 IU/mL (IQR 173 to 2576 IU/mL) and placebo group median 128 IU/mL (IQR -295 (elevation of titer) to 617 IU/mL) (P<0.001, Figure 4). Compared to baseline, H. pylori IgG-antibody titers were median 55.7% lower (IQR 29.8% to 73.1% lower) in the eradication group and median 8.8% lower (IQR -22.0% to 39.9% lower) in the placebo group (P<0.001, Figure 5).

According to the gold standard criteria for H. pylori infection, at endoscopy a patient could be either H. pylori positive or H. pylori negative. Using the predefined H. pylori IgG-antibody titer cut-off point of ≥250 IU/mL, serological testing for H. pylori IgG-antibodies was found to be highly sensitive (100%) but with very poor specificity (23.7%), especially following H. pylori eradication therapy (16.1%, Table 1). Arguably, the absolute or percent change in H. pylori IgG-antibody titers from baseline represents a better method for evaluating success of H. pylori eradication. Figure 6 presents the receiver operating characteristic (ROC) curves for absolute and percent change in H. pylori IgG-antibody titers, associated with a negative result for the gold standard criteria for H. pylori infection. Both absolute and percent change scores had good diagnostic power in identifying H. pylori negative patients, with area under the ROC curves (AUCs) of 0.73 (95% CI: 0.61 to 0.83, P=0.0002) and 0.86 (95% CI: 0.75 to 0.93, P<0.0001), respectively. The better overall accuracy of change in H. pylori IgG-antibody titers expressed as a percent change score was represented by a significantly higher AUC for percent change scores (P<0.001). The optimal cut-off point for percent change in H. pylori IgG-antibody titers was -47.3%, corresponding to a sensitivity of 96.7% (95% CI: 82.7 to 99.4%) and specificity of 60.5% (95% CI: 43.4 to 75.9%). Using a more convenient cut-off point of 50% decrease in H. pylori IgG-antibody titers provided an identical overall sensitivity of 96.7% and specificity of 60.5% (Table 1). Using a cut-off point of 50% decrease in H. pylori IgG-antibody titers, in the eradication group sensitivity was 100% and specificity 71%, in the placebo group sensitivity was 96.3% but with a specificity of 14.3% (Table 1). Low specificity was due to a relatively large number of false positive test results. When using 50% decrease in H. pylori IgG-antibody titers as the cut-off point, 16 gold standard negative patients were falsely identified as H. pylori positive; 9 in the eradication group and 6 in the placebo group (Table 2).

Table 2. Results of H. pylori detection using a cut-off point of 50% decrease in H. pylori IgG-antibody titers, according to the gold standard criteria; for the total study group and differentiated for preceding H. pylori eradication therapy or placebo.

Group	Result	Gold standard positive (No.)	Gold standard negative (No.)
Total	Positive	29	16
	Negative	1	22
Eradication	Positive	3	9
	Negative	0	22
Placebo	Positive	26	6
	Negative	1	1

DISCUSSION

The data of this study show that in long-term NSAID users, repeated serological testing using a cut-off point of 50 percent decrease in H. pylori IgG-antibody titers after 3 months has sufficiently high sensitivity and specificity to be useful in evaluating success of H. pylori eradication therapy.

Using a predefined H. pylori IgG-antibody titer cut-off point of 250 IU/mL, repeated serological testing for H. pylori IgG-antibodies was found to have no diagnostic value. At baseline, H. pylori IgG-antibody titers ranged from 253 IU/mL to 19029 IU/mL, and although titers dropped a median 820 IU/mL in the eradication group, still only 5 patients came out below the 250 IU/mL threshold for positivity, resulting in a large number of false positive test results. Using a cut-off point of 50 percent decrease in H. pylori IgG-antibody titers increased diagnostic accuracy, but specificity remained at only 71% in the eradication group. This was due to still a relatively large number of false positive test results. In 9 (26.5%) patients in the eradication group who where H. pylori negative according to the gold standard criteria, the 3 month drop in H. pylori IgG-antibody titers was smaller than 50%. In 3 of these patients, H. pylori IgG-antibody titers remained more or less constant, with a 3% elevation, a 4% drop and a 6% titer drop. In the remaining 6 patients, the H. pylori IgG-antibody titers showed a much larger decrease; median 29.5% (IQR 18.4% to 35.7%). It is therefore possible that the specificity of this test will increase to approximately 90% if a longer in-between test period is maintained. Other groups have found high sensitivity and specificity ratios for percent decrease in H. pylori IgG-antibody titers using cut-off points of 25% at 6 months and 40% at 3 to 6 months.[10,11,27]

The choice of a gold standard affects test results of all other tests. According to the guidelines for clinical trials in H. pylori infection, a reliable gold standard should consist of at least 2 methods based on different principles for detecting H. pylori infection.[5,28] In the present study, a patient was also considered H. pylori positive if culture alone was positive, in view of its absolute specificity. The gold standard in the present study corresponds to acceptable criteria.

Overall, long-term NSAID use did not seem to influence H. pylori eradication rates or serological testing for H. pylori IgG-antibodies. Theoretically, if NSAID treatment decreases the degree of gastric inflammation and subsequently affects the serological response, one would not expect to find many false positive test results. However, an effect cannot be ruled out because in the present study, a relatively strong

decline in H. pylori IgG-antibodies was noted 3 months after H. pylori eradication (median 55.7% decline) compared to other studies. A previous longitudinal analysis of H. pylori IgG-antibody titers following successful H. pylori eradication demonstrated a mean decline of 26% at 3 months, 43% at 6 months, and 55% at nine months follow-up, after which titers appeared to plateau at approximately 50% compared to baseline.[26]

CONCLUSION

In long-term NSAID users, a H. pylori IgG-antibody titer decrease of 50% at 3 months has sufficiently high sensitivity and specificity to be useful in evaluating success of H. pylori eradication therapy.

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CHAPTER XI

Summary and general conclusions

The aim of this thesis is to promote safe pharmacotherapy with nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are among the world's most prescribed drugs, being used on a daily basis by millions of people for effective relief of pain, fever and inflammation. However, NSAID treatment is associated with severe treatment side effects and complications, with significant morbidity, mortality, and costs. Most feared among these complications are bleeding and perforated gastroduodenal ulcers, and serious cardiovascular events such as myocardial infarction and stroke. This thesis addresses these serious NSAID treatment complications, delves into their underlying pathophysiological mechanisms, tries to paint a clearer picture of those at risk, and studies the effectiveness of possible preventive strategies. Over the last decade, different strategies have been developed to help prevent NSAID treatment associated gastroduodenal ulcers. Unfortunately, that which is good for the gastrointestinal risk may be bad for the cardiovascular risk, and vice versa. For physicians the challenge ahead is to learn to balance these risks when prescribing NSAIDs to individual patients.

Chapter I presents a review on the history of aspirin, the development of NSAIDs, and the discovery of prostaglandin synthesis and the cyclooxygenases (COX). The review further discusses the pathogenesis of NSAID associated gastrointestinal, cardiovascular and renal complications and side effects, provides an overview of the literature on the efficacy of different preventive strategies, and finally offers recommendations for balancing gastrointestinal and cardiovascular risks in daily clinical practice.

Chapter II discusses possible pathophysiological mechanisms involved in the elevated risk of cardiovascular events with COX-2 selective and nonselective NSAIDs, and presents an overview of the data on cardiovascular events from clinical trials and observational studies. On the basis of the presumed mechanisms involved we surmised that in clinical syndromes of platelet activation, COX inhibition by any NSAID but especially by COX-2 selective NSAIDs, would be expected to increase the risk of cardiovascular events. While an elevated risk with COX-2 selective NSAIDs was clear from placebo controlled trials, this was much less so in trials with nonselective NSAIDs as the active comparator. However, we assumed the risk of cardiovascular events to be greater with COX-2 selective than with nonselective NSAIDs. Since their publication, these assumptions have been partially revoked. In a meta-analysis of 138 randomized trials by Kearney PM, et al. BMJ 2006;332:1302-8, the incidence of serious vascular events was similar between COX-2 selective NSAIDs and high dose nonselective NSAIDs, with the exception of naproxen. However, the general conclusion of Chapter II remains unchanged. When prescribing NSAIDs and especially COX-2 selective NSAIDs, physicians should carefully weigh gastrointestinal harm with cardiovascular harm. Patients at risk for cardiovascular events should not be treated with COX-2 selective NSAIDs.

Chapter III presents a nested case-control study that describes which patients are especially at risk for serious NSAID ulcer complications and investigates the effectiveness of different preventive strategies in a general population of NSAID users. During an observational period of 26 months, 104 incident cases with serious NSAID ulcer complications were identified from a cohort of 51,903 NSAID users with 10,402 patient years of NSAID exposure (incidence 1% per year of exposition, age at diagnosis 70.4 ± 16.7 years (mean ± standard deviation), 55.8% women), and 284 matched controls from the

same cohort, without serious NSAID ulcer complications. Cases were characterized by serious, especially cardiovascular, co-morbidity. In-hospital mortality associated with serious NSAID ulcer complications was 10.6% (incidence 21.2 per 100,000 NSAID users). Concomitant proton-pump inhibitors (PPIs), but not COX-2 selective NSAIDs, were associated with a reduced risk of serious NSAID ulcer complications (adjusted odds ratio (OR) 0.33; 95% confidence interval (CI) 0.17 to 0.67; p=0.002).
Several different strategies have proven efficacy for the primary prevention of NSIAD ulcers and NSAID ulcer complications, such as ulcer bleeding, obstruction and perforation. Arguably, for the primary prevention of NSAID ulcer complications concomitant use of misoprostol 800 µg is supported by the best evidence. However, in daily clinical practice patient compliance in using high dose misoprostol is low due to associated diarrhea and abdominal discomfort. Both efficacy and side effects of misoprostol are dose dependent. In this study, misoprostol was not associated with a reduced risk for NSAID ulcer complications. Misoprostol was used by 7.7% of the cases and 7.0% of the controls (OR 1.10, 95%CI 0.47 to 2.58, p=0.83). All but one patient used misoprostol in a fixed combination with diclofenac, and all at doses lower than the recommended 800 µg.
The efficacy of COX-2 selective NSAIDs in the primary prevention of NSAID ulcer complications has been proven in many randomised clinical trials. However, these trials largely excluded high-risk patients, whereas in high-risk patients COX-2 selective NSAIDs may fail to adequately prevent the recurrence of NSAID ulcer bleeding. Furthermore, several observational studies have failed to demonstrate the effectiveness of COX-2 selective NSAIDs in preventing NSAID ulcer complications in the general population. Likewise in this study, COX-2 selective NSAIDs were not associated with a reduced risk for NSAID ulcer complications. COX-2 selective NSAIDs were used by 16.3% of the cases and 17.6% of the controls (OR 0.91, 95%CI 0.50 to 1.67, p=0.77).
The efficacy of concomitant PPIs has been proven for the primary prevention of endoscopic NSAID ulcers, and for the secondary prevention of recurrent NSAID ulcer bleeding in high risk patients. The results of the present study may add further evidence for the effectiveness of concomitant PPIs in the primary prevention of NSAID ulcer complications in the general population.

Chapter IV presents an observational study that explores the relationship between risk factors for gastrointestinal events and the likelihood of receiving recommended gastroprotection; concomitant PPIs, high dose histamine H_2-receptor antagonists (H2RAs), misoprostol 800 µg or COX-2 selective NSAIDs. We calculated the number of different risk factors for NSAID-gastropathy in 104 patient cases with serious NSAID ulcer complications and 284 matched controls. A composite risk factor (CRF) was obtained from the sum of all separate risk factors. The mean CRF was 3.31 [SD 1.67] in cases and 2.76 [SD 1.45] in controls (p=0.002). Overall, a recommended preventive strategy was used by 38% of the patients. Significant variables for using a preventive strategy were; concomitant steroid use (corrected OR 4.22, 95%CI 2.11 to 8.47, p<0.001), ulcer history (corrected OR 2.90, 95%CI 1.51 to 5.56, p=0.001), and concomitant low dose aspirin (corrected OR 1.96, 95%CI 1.18 to 3.25, p=0.01). In the population studied, the use of gastroprotective drugs was greatly underutilised. Among patients with 4 or more risk factors 47% did not use recommended gastroprotection.
The effectiveness of gastroprotective strategies in a general population of NSAID users depends to a great extend on their level of implementation in at-risk patients. Physicians prescribing NSAIDs appear

to recognize and act upon several specific risk factors and the odds for using a gastroprotective strategy rise with increasing CRF counts. In the population studied, patients with the highest number of risk factors were all treated with gastroprotective strategies. Amongst those with no additional risk factors 21% still used PPIs, possibly for subjective symptoms such as dyspepsia or abdominal pain rather than as targeted ulcer prevention. Despite being treated with the recommended gastroprotection, 60% of the patients with the highest CRF counts (7 to 9) still suffered serious NSAID ulcer complications. These findings confirm other studies in very high risk patients.

Chapter V presents an observational study that examines frequencies of allele variants of the cytochrome P450 2C9 genotype (CYP2C9) in Caucasian subjects with serious NSAID ulcer complications, and compares them with a matched cohort of subjects using oral coumarin anticoagulants and with those reported in earlier studies in Caucasian subjects. CYP2C9 polymorphisms have been associated with changes in the pharmacokinetics of some frequently used NSAIDs, and slow metabolizing genotypes have been identified. Serious adverse events associated with NSAID therapy, such as bleeding and perforated gastroduodenal ulcers, are dose related, which raises the question of whether the reduced NSAID clearance associated with some CYP2C9 polymorphisms may increase the risk of serious NSAID ulcer complications. If so, CYP2C9 genotype frequencies would be expected to differ from those in the general population. In this study population, CYP2C9 genotype frequencies did not differ significantly between subjects with serious NSAID ulcer complications and subjects using oral coumarin anticoagulants. The genotype frequencies were also similar to those reported in previous studies in Caucasian subjects. Therefore in this population, the CYP2C9 genotype is not a significant or clinically relevant risk factor in the development of serious NSAID ulcer complications.

Chapters VI and **VII** present a cost-of-illness study for serious NSAID ulcer complications and a further pharmacoeconomic analysis to estimate the cost-effectiveness of concomitant PPIs in relation to the occurrence of serious NSAID ulcer complications. For cases hospitalised with serious NSAID ulcer complications, data was retrieved on days hospitalised and on the number and type of diagnostic and therapeutic interventions utilised, to estimate the mean direct medical costs of resources used. Mean direct medical costs were € 8.375 (95%CI € 7.067 to € 10.393). In The Netherlands; annually approximately 5.105 people are hospitalised with NSAID ulcer complications. The total annual Dutch direct medical costs for NSAID ulcer complications are estimated at € 42.754.375 (95%CI € 36.077.035 to € 53.056.265). These cost estimations were linked to the results of the case-control study. For the incremental cost-effectiveness ratio 2 hypothetical scenarios were compared: (1) 1000 patients all using concomitant PPIs and (2) 1000 patients not using PPIs. Sensitivity analysis was performed by 'worst case' and 'best case' scenarios in which the 95%CI of the odds ratio and the 95%CI of the cost estimate of a NSAID ulcer complication were varied. Costs of PPIs was varied separately. In the hypothetical scenarios, the estimated number of NSAID ulcer complications was 13.8 for non-PPI users, and 3.6 for PPI users. The incremental total costs were € 50.094 higher for concomitant PPI use. The incremental cost-effectiveness ratio was € 4.907 (95%CI € 2.813 to € 6.290) per NSAID ulcer complication prevented when using the least costly PPI, but the price of PPIs highly influenced the robustness of the results.

The generalisability of the results of this pharmacoeconomic analysis may be hampered by several factors. Firstly, the incremental cost analysis was performed from the health care perspective and only direct medical costs made during hospitalisation were available. Inclusion of extramural direct medical costs (e.g., general practitioner visits and outpatient treatments), direct non-medical costs (e.g., travel to and from the hospital) and indirect non-medical costs (e.g., those related to work absenteeism) would influence the results and possibly strengthen the favourable economic profile of concomitant PPI use in NSAID users, compared with not using concomitant PPIs. Secondly, direct medical costs may have been underestimated due to the use of standard cost prices for hospital in-patient days, which may differ from actual charges. Further under as well as overestimation of extrapolated annual direct medical costs may have occurred due to variability of care among hospitals in The Netherlands.

Chapter VIII presents a pre-planned post hoc analysis of a randomized clinical trial in Helicobacter pylori positive patients with long-term NSAID use for rheumatic diseases, which investigates whether long-term use of selective NSAIDs is associated with a lower incidence of endoscopic ulcers than long-term use of nonselective NSAIDs. In the clinical trial, patients were randomized for H. pylori eradication or placebo, with endoscopy for ulcers after 13 weeks. Among 301 patients who underwent endoscopy, 80 (27%) used selective NSAIDs and 221 (73%) nonselective NSAIDs. At endoscopy, ulcers were diagnosed in 6 (4%) patients in the eradication group and 8 (5%) patients in the placebo group (p=0.65). In the post hoc analysis, patients with or without endoscopic ulcers were compared for their use of selective and nonselective NSAIDs, as well as for possible confounders for the occurrence of gastroduodenal ulcers. None of the selective NSAID users had ulcers at endoscopy; selective NSAIDs were used by 0 (0%) in the ulcer group and 80 (28%) in the non-ulcer group (p=0.02). Concomitant low dose aspirin was used by 4 (29%) in the ulcer group and 27 (9%) in the non-ulcer group (p=0.02). PPIs were used by 4 (29%) in the ulcer group and 109 (38%) in the non-ulcer group (p=0.48), H2RAs by 2 (14%) in the ulcer group and 17 (6%) in the non-ulcer group (p=0.21), and prostaglandin analogues by 0 (0%) in the ulcer group and 1 (0.3%) in the non-ulcer group (p=0.83).
The efficacy of selective NSAIDs for the prevention of endoscopic ulcers and serious ulcer complications has previously been demonstrated in several large randomised clinical trials. However, it remains unclear whether selective NSAIDs retain their efficacy during long-term use, and in H. pylori positive patients. In this pre-planned post hoc analysis of a randomized clinical trial in H. pylori positive patients on long-term NSAID treatment, long-term use of selective NSAIDs was associated with a significantly reduced risk for endoscopic ulcers. Furthermore, concomitant use of low dose aspirin was associated with a significantly increased risk.
Interestingly, the results of this analysis are largely opposite to those reported for the case-control study in Chapter III. This again illustrates the necessity of interpreting NSAID-study results in the context of their study-populations. Several important differences between the studies in Chapters III and VIII may have attributed to the current discrepancies. Firstly, the case-control study described in Chapter III was conducted in a general population of NSAID users, while the randomized trial was conducted in H. pylori positive patients on long-term NSAID treatment for rheumatic diseases. H. pylori positive long-term NSAID users most likely represent a cohort of NSAID-survivors; i.e. those with an intrinsic risk for gastroduodenal ulcers during NSAID use would have dropped out of this cohort

long before inclusion into the randomized trial, which would also explain the overall low incidence of endoscopic ulcers in the trial. Secondly, most patients in a general population would have had their NSAIDs prescribed by a general physician, while patients with rheumatic diseases would have had their NSAIDs prescribed by a rheumatologist, with regular follow-up at a rheumatology outpatient department. This would lead to differences in risk assessment and in implementation of preventive strategies; i.e. concomitant PPIs were used by 37.5% in the randomized trial versus 23.5% in the case-control study, while COX-2 selective NSAIDs were used by 9% in the randomized trial versus 17% in the case-control study. Also, low dose aspirin was used by 10% in the randomized trial versus 26% in the case-control study. Thirdly, there are important differences in study design; i.e. randomized controlled trial versus case-control study, in study duration; i.e. 3 months versus an open timeframe, and in study endpoints; i.e. endoscopic ulcers versus serious ulcer complications.

Chapter IX presents a post hoc analysis of a randomized clinical trial in Helicobacter pylori positive patients with long-term NSAID use for rheumatic diseases, which investigates how we should diagnose persistent Helicobacter pylori infection or successful eradication following triple therapy in NSAID users. In the clinical trial, patients were diagnosed with H. pylori infection using serological testing for H. pylori IgG-antibodies. H. pylori positive patients were randomized for H. pylori eradication triple therapy or placebo, with follow-up endoscopy after 13 weeks. In the post hoc analysis, we compared repeated H. pylori IgG-antibody titers, and hematoxylin and eosin (H&E) stains, immunohistochemical (IHC) stains, and H. pylori culture results in follow-up biopsies from 68 patients, to determine the sensitivity and specificity of these different detection methods. Furthermore, we determined whether adding IHC stains to H&E stains improves the histological identification of H. pylori in these patients. According to the gold standard criteria of a positive culture or both a positive histological examination and serological test, H. pylori eradication therapy was successful in 91.2% of the patients. Repeated serology provided 100% sensitivity, but overall specificity was 23.7% and 16.1% after eradication. Culture provided 100% specificity, but overall sensitivity was 83.3% and 66.7% after eradication. Histological examination with either H&E or IHC stains provided sensitivities and specificities between 90% and 100%. Adding IHC to H&E stains did not improve these results.

Chapter X presents a post hoc analysis of a randomized clinical trial in Helicobacter pylori positive patients with long-term NSAID use for rheumatic diseases, which investigates the serological assessment of Helicobacter pylori eradication following triple therapy in patients on long-term NSAID treatment. In the clinical trial, patients who were H. pylori positive on serological testing for H. pylori IgG-antibodies were randomized for H. pylori eradication triple therapy or placebo. Thirteen weeks after randomization, gastric mucosal biopsies and blood samples were taken for H. pylori culture, histological examination and repeated serological testing. In the post hoc analysis, we analyzed sensitivity, specificity and receiver operating characteristic (ROC) curves of the repeated serological test results from 68 patients. According to the gold standard criteria of a positive culture or both a positive histological examination and serological test, H. pylori eradication therapy was successful in 91.2% of the patients. The ROC curve for percent change in H. pylori IgG-antibody titers had good diagnostic power in identifying H. pylori negative patients, with an area under the ROC curve of 0.86 (95%CI 0.75 to 0.93, $p<0.0001$). The

optimal cut-off point for percent change in H. pylori IgG-antibody titers was -47.3%, corresponding to a sensitivity of 96.7% (95%CI 82.7 to 99.4%) and specificity of 60.5% (95%CI 43.4 to 75.9%). Using a cut-off point of 50% decrease in H. pylori IgG-antibody titers at 3 months provided a sensitivity of 100% and specificity of 71% for determining success of H. pylori eradication therapy.

GENERAL CONCLUSIONS

A 3500 year history of discovery has led to the development of non steroidal anti-inflammatory drugs (NSAIDs) that are effective for relief of pain, fever and inflammation. However, over the last decades it has become increasingly clear that NSAID treatment is associated with severe treatment side effects and complications. NSAIDs may cause gastrointestinal ulcers, which may be complicated by ulcer bleeding, perforation and obstruction, and also serious cardiovascular events, such as myocardial infarction and stroke. For physicians the challenge ahead is to learn to balance these risks when prescribing NSAIDs to individual patients.

Patients with both a low cardiovascular and a low gastrointestinal risk may be treated with a nonselective NSAID. Patients with a low cardiovascular and a moderate gastrointestinal risk (one or two gastrointestinal risk factors) may be treated with a nonselective NSAID plus a PPI or misoprostol 800 µg, or with a COX-2 selective NSAID. Patients with a low cardiovascular and a high gastrointestinal risk (more than two gastrointestinal risk factors or previous ulcer complications) may be treated with a COX-2 selective NSAID plus a PPI.

Patients with a high cardiovascular risk should receive prophylactic low dose aspirin. Patients with a high cardiovascular and a low to moderate gastrointestinal risk may be treated with naproxen plus a PPI or misoprostol 800 µg. Patients with both a high cardiovascular and a high gastrointestinal risk should avoid NSAID therapy.

CHAPTER XII

Samenvatting en conclusies

Dit proefschrift heeft als doel het bevorderen van veilige farmacotherapie met niet-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs). NSAIDs behoren tot de meest voorgeschreven geneesmiddelen en worden wereldwijd dagelijks door miljoenen mensen gebruikt voor de effectieve verlichting van pijn, koorts en ontsteking. Behandeling met NSAIDs is echter geassocieerd met het optreden van ernstige bijwerkingen en complicaties, met significante bijbehorende morbiditeit, mortaliteit en kosten. Het meest gevreesd onder deze complicaties zijn de bloedende en geperforeerde maagzweren en de ernstige cardiovasculaire complicaties zoals hartinfarcten en hersenbloedingen. Dit proefschrift behandelt deze ernstige NSAID gerelateerde complicaties, gaat in op de onderliggende pathofysiologische mechanismen, tracht een duidelijker beeld te schetsen van welke patiënten hiervoor risico lopen en bestudeerd de effectiviteit van mogelijke preventieve strategieën. Gedurende de laatste tien jaar zijn er verschillende strategieën ontwikkeld om NSAID geassocieerde maagzweren te helpen voorkomen. Helaas is dat wat goed is voor het gastrointestinale risico soms slecht voor het cardiovasculaire risico, en vice versa. Voor artsen is nu de uitdaging om te leren deze risico's in balans te houden bij het voorschrijven van NSAIDs aan individuele patiënten.

Hoofdstuk I beschrijft de geschiedenis van aspirine, de ontwikkeling van de NSAIDs en de ontdekking van prostaglandine synthese en de cyclooxygenases (COX). Het overzicht bespreekt verder de pathogenese van NSAID geassocieerde gastrointestinale, cardiovasculaire en renale complicaties en bijwerkingen, geeft een overzicht van de literatuur over de effectiviteit van verschillende preventieve strategieën, om te besluiten met aanbevelingen voor het in balans houden van gastrointestinale en cardiovasculaire risico's in de dagelijkse klinische praktijk.

Hoofdstuk II bespreekt de mogelijke pathofysiologische mechanismen die betrokken zijn bij het verhoogde risico op cardiovasculaire complicaties tijdens het gebruik van COX-2 selectieve en niet selectieve NSAIDs en geeft een overzicht van de gegevens over cardiovasculaire complicaties uit klinische en observationele studies. Op grond van de veronderstelde onderliggende mechanismen vermoedden wij dat in klinische syndromen van bloedplaatjes activatie, COX remming door elk NSAID maar vooral door COX-2 selectieve NSAIDs zal leiden tot verhoging van de kans op cardiovasculaire complicaties. Hoewel het verhoogde risico met COX-2 selectieve NSAIDs duidelijk naar voren kwam in placebo gecontroleerde studies, was dit veel minder duidelijk in studies met niet selectieve NSAIDs als de actieve vergelijker. Wij namen echter aan dat het risico op cardiovasculaire complicaties groter was met COX-2 selectieve dan met niet selectieve NSAIDs. Sinds hun publicatie zijn deze aannames gedeeltelijk herroepen. Uit een meta-analyse van 138 gerandomiseerde studies door Kearney PM, et al. BMJ 2006;332:1302-8, blijkt de incidentie van ernstige vasculaire complicaties vergelijkbaar te zijn tussen COX-2 selectieve NSAIDs en hoog gedoseerde niet selectieve NSAIDs, met uitzondering van naproxen. De algemene conclusie van hoofdstuk II blijft echter onveranderd. Bij het voorschrijven van NSAIDs en vooral van COX-2 selectieve NSAIDs moeten artsen zorgvuldig de gastrointestinale risico's wegen met de cardiovasculaire risico's. Patiënten met een verhoogd risico voor cardiovasculaire complicaties moeten niet met COX-2 selectieve NSAIDs worden behandeld.

Hoofdstuk III presenteert een patiënt-controle onderzoek dat beschrijft welke patiënten een risico

lopen voor gecompliceerde NSAID gerelateerde maagzweren en dat de effectiviteit van de verschillende preventieve strategieën bestudeerd in een algemene populatie van NSAID gebruikers. Gedurende een observationele periode van 26 maanden werden er 104 incidente gevallen van gecompliceerde NSAID gerelateerde maagzweren geïdentificeerd uit een cohort van 51,903 NSAID gebruikers met 10,402 patiëntjaren van NSAID blootstelling (incidentie 1% per jaar blootstelling, leeftijd ten tijde van de diagnose 70.4 ± 16.7 jaar (gemiddelde ± standaarddeviatie), 55.8% vrouwen), en 284 gepaste controles uit hetzelfde cohort, zonder gecompliceerde NSAID gerelateerde maagzweren. De patiënten werden gekarakteriseerd door ernstige, vooral cardiovasculaire, co-morbiditeit. De gecompliceerde NSAID gerelateerde maagzweren geassocieerde ziekenhuissterfte was 10.6% (incidentie 21.2 per 100.000 NSAID gebruikers). Concomitant gebruik van proton pomp remmers (PPIs), maar niet van COX-2 selectieve NSAIDs, was geassocieerd met een verminderd risico op gecompliceerde NSAID gerelateerde maagzweren (adjusted odds ratio (OR) 0.33; 95% betrouwbaarheidsinterval (BI) 0.17 tot 0.67; p=0.002).
Verschillende strategieën zijn bewezen effectief voor de primaire preventie van NSAID gerelateerde maagzweren en hun complicaties, zoals bloeding, obstructie en perforatie. Mogelijkerwijs geldt nog het beste bewijs voor de primaire preventie van gecompliceerde NSAID gerelateerde maagzweren voor het concomitante gebruik van misoprostol 800 µg. In de dagelijkse praktijk is de therapietrouw van hoge dosis misoprostol echter laag door de hiermee geassocieerde buikklachten en diarree. Zowel de effectiviteit als de bijwerkingen van misoprostol zijn dosis gerelateerd. In de huidige studie was het gebruik van misoprostol niet geassocieerd met een verminderd risico op gecompliceerde NSAID gerelateerde maagzweren. Misoprostol werd gebruikt door 7.7% van de patiënten en 7.0% van de controles (OR 1.10, 95%BI 0.47 tot 2.58, p=0.83). Allen behalve één patiënt gebruikten misoprostol in een vaste combinatie met diclofenac, en in alle gevallen in doses lager dan de aangeraden 800 µg.
De effectiviteit van COX-2 selectieve NSAIDs voor de primaire preventie van gecompliceerde NSAID gerelateerde maagzweren werd in meerdere gerandomiseerde klinische studies aangetoond. In deze studies werden hoogrisico patiënten echter veelal geëxcludeerd, terwijl juist bij hoogrisico patiënten COX-2 selectieve NSAIDs mogelijk recidief maagbloedingen niet kunnen voorkomen. Ook hebben verschillende observationele studies niet kunnen aantonen dat COX-2 selectieve NSAIDs effectief zijn voor de preventie van gecompliceerde NSAID gerelateerde maagzweren in de algemene populatie. In de huidige studie was het gebruik van COX-2 selectieve NSAIDs eveneens niet geassocieerd met een verminderd risico voor gecompliceerde NSAID gerelateerde maagzweren. COX-2 selectieve NSAIDs werden gebruikt door 16.3% van de patiënten en 17.6% van de controles (OR 0.91, 95%BI 0.50 tot 1.67, p=0.77).
Concomitant gebruik van PPIs bij NSAID gebruik is bewezen effectief voor de primaire preventie van endoscopische maagzweren, en voor de secundaire preventie van recidief maagbloedingen in hoogrisico patiënten. De uitkomst van de huidige studie levert aanvullend bewijs voor de effectiviteit van concomitant gebruik van PPIs voor de primaire preventie van gecompliceerde NSAID gerelateerde maagzweren in de algemene populatie.

Hoofdstuk IV presenteert een observationele studie die de relatie onderzoekt tussen het hebben van risicofactoren voor gastrointestinale complicaties tijdens NSAID gebruik en de waarschijnlijkheid van het krijgen van de aanbevolen maagbescherming; concomitante PPIs, hoge doses histamine H_2-receptor

antagonisten (H2RAs), misoprostol 800 µg of COX-2 selectieve NSAIDs. We berekenden het aantal verschillende risicofactoren voor NSAID gastropathie in 104 patiënten met gecompliceerde NSAID gerelateerde maagzweren en in 284 gepaste controles. Een samengestelde risicofactor (CRF) werd verkregen uit de som van alle verschillende risicofactoren. De gemiddelde CRF was 3.31 [SD 1.67] in de patiënten en 2.76 [SD 1.45] in de controles (p=0.002). Algemeen gebruikte 38% van de patiënten een aanbevolen preventieve strategie. Significante variabelen voor het gebruik van een preventieve strategie waren; concomitant gebruik van steroïden (gecorrigeerde OR 4.22, 95%BI 2.11 tot 8.47, p<0.001), voorgeschiedenis van maagzweren (gecorrigeerde OR 2.90, 95%BI 1.51 tot 5.56, p=0.001), en concomitant gebruik van lage dosis aspirine (gecorrigeerde OR 1.96, 95%BI 1.18 tot 3.25, p=0.01). In deze studiepopulatie bleven gastroprotectieve middelen sterk onderbenut. Door 47% van de patiënten die 4 of meer risicofactoren hadden werd geen aanbevolen vorm van maagbescherming gebruikt. De effectiviteit van gastroprotectieve strategieën in een algemene populatie van NSAID gebruikers hangt voor een groot deel af van hun implementatie niveau in hoogrisico patiënten. Artsen die NSAIDs voorschrijven lijken verschillende specifieke risicofactoren te herkennen en de kans op het gebruik van een preventieve strategie stijgt met het toenemen van de CRF. In deze studiepopulatie werden de patiënten met de hoogste CRFs allemaal behandeld met een gastroprotectieve strategie. Onder degenen zonder additionele risicofactoren gebruikte 21% toch een PPI, mogelijk ter bestrijding van subjectieve symptomen zoals dyspepsie of buikpijn in plaats van als doelgerichte maagzweer preventie. Ondanks de behandeling met de aanbevolen maagbescherming kreeg 60% van de patiënten met de hoogste CRFs (7 tot 9) toch een gecompliceerde NSAID gerelateerde maagzweer. Deze bevindingen bevestigen andere studies onder zeer hoogrisico patiënten.

Hoofdstuk V presenteert een observationele studie die de frequentie van allel variaties van het cytochroom P450 2C9 genotype (CYP2C9) onderzoekt in Caucasische patiënten met gecompliceerde NSAID gerelateerde maagzweren en deze vergelijkt met die in een cohort van orale antistolling gebruikers en met frequenties zoals gerapporteerd in eerdere studies in Caucasische populaties. Verschillende CYP2C9 polymorphismen zijn geassocieerd met veranderingen in de farmacokinetiek van enkele veelgebruikte NSAIDs, waarbij ook genotypen met een traag metabolisme zijn geïdentificeerd. Ernstige NSAID geassocieerde bijwerkingen, zoals bloedende en geperforeerde maagzweren, zijn dosis gerelateerd, wat de vraag doet rijzen of een CYP2C9 geassocieerde verminderde NSAID klaring het risico op gecompliceerde NSAID gerelateerde maagzweren doet toenemen. Als dat zo is, dan zullen de in deze groep waargenomen CYP2C9 frequenties verschillen van die in de algemene populatie.
In de huidige studie waren er geen significante verschillen in CYP2C9 genotype frequenties tussen patiënten met gecompliceerde NSAID gerelateerde maagzweren en controles met oraal antistolling gebruik. De waargenomen frequenties verschilden ook niet van eerder gerapporteerde frequenties in de literatuur. In deze studiepopulatie is het CYP2C9 genotype daarom geen significante of klinisch relevante risicofactor voor het ontwikkelen van gecompliceerde NSAID gerelateerde maagzweren.

Hoofdstukken VI en **VII** presenteren een kostenconsequentie studie voor gecompliceerde NSAID gerelateerde maagzweren en een verdere farmaco-economische analyse voor het schatten van de kosteneffectiviteit van concomitant PPI gebruik in relatie tot het optreden van gecompliceerde NSAID

gerelateerde maagzweren. Van patiënten die in het ziekenhuis waren opgenomen met gecompliceerde NSAID gerelateerde maagzweren werden gegevens verzameld over het aantal opnamedagen en over het aantal en soort gebruikte diagnostische en therapeutische interventies, om een schatting te maken van de gemiddelde directe medische kosten van de gebruikte middelen. De gemiddelde directe medische kosten waren € 8.375 (95%BI € 7.067 tot € 10.393). In Nederland worden jaarlijks ongeveer 5.105 mensen opgenomen met gecompliceerde NSAID gerelateerde maagzweren. De totale jaarlijkse Nederlandse directe medische kosten voor gecompliceerde NSAID gerelateerde maagzweren werd geschat op € 42.754.375 (95%BI € 36.077.035 tot € 53.056.265). Deze kostenschattingen werden gekoppeld aan de uitkomsten van het patiënt-controle onderzoek. Voor de incrementele kosteneffectiviteitratio werden 2 hypothetische scenario's vergeleken: (1) 1000 patiënten die allemaal concomitant PPIs gebruikten en (2) 1000 patiënten die geen PPIs gebruikten. Gevoeligheidsanalyses werden uitgevoerd met 'beste geval' en 'slechtste geval' scenario's waarin het 95%BI van de OR en het 95%BI van de kostenschatting van een gecompliceerde NSAID gerelateerde maagzweer werden gevarieerd. De kosten van de PPIs werden apart gevarieerd. In de hypothetische scenario's was het geschatte aantal gecompliceerde NSAID gerelateerde maagzweren 13.8 onder de niet-PPI gebruikers en 3.6 onder de PPI gebruikers. De incrementele totale kosten waren € 50.094 hoger voor concomitant PPI gebruik. De incrementele kosteneffectiviteitratio was € 4.907 (95%BI € 2.813 tot € 6.290) per gecompliceerde NSAID gerelateerde maagzweer die voorkomen werd met het gebruik van het goedkoopste PPI, echter de robuustheid van de uitkomsten werd sterk beïnvloed door de prijs van de PPIs.
De generaliseerbaarheid van de resultaten van deze farmaco-economische analyse wordt mogelijk beperkt door een aantal factoren. Ten eerste werd de incrementele kostenanalyse verricht vanuit het gezondheidzorg perspectief en waren alleen de directe medische kosten die gemaakt waren tijdens de ziekenhuisopnames beschikbaar. Inclusie van extramurale directe medische kosten (zoals huisartsbezoek en poliklinische behandeling), directe niet-medische kosten (zoals vervoer van en naar het ziekenhuis) en indirecte niet-medische kosten (zoals ziekteverzuim) zou de uitkomsten beïnvloeden en mogelijk het gunstige economische profiel van concomitant PPI gebruik versterken, vergeleken met het niet gebruiken van concomitante PPIs door NSAID gebruikers. Ten tweede is het mogelijk dat de directe medische kosten zijn onderschat door het gebruik van standaard kostprijzen voor ziekenhuis opnamedagen, welke kunnen verschillen van de daadwerkelijke lasten. Verdere onder- maar ook overschatting van de geëxtrapoleerde jaarlijkse directe medische kosten kunnen het gevolg zijn van verschillen in patiëntenzorg tussen de diverse ziekenhuizen in Nederland.

Hoofdstuk VIII presenteert een vooraf geplande post hoc analyse van een gerandomiseerde klinische studie onder Helicobacter pylori positieve patiënten met langdurig NSAID gebruik voor reumatische ziekten, dat onderzoekt of langdurig gebruik van selectieve NSAIDs geassocieerd is met een lagere incidentie van endoscopische maagzweren dan langdurig gebruik van niet selectieve NSAIDs. In de klinische studie werden patiënten gerandomiseerd voor H. pylori eradicatie therapie of placebo, met endoscopische analyse na 13 weken. Onder de 301 patiënten die endoscopie ondergingen, gebruikten 80 (27%) patiënten selectieve NSAIDs en 221 (73%) niet selectieve NSAIDs. Tijdens endoscopie werd bij 6 (4%) patiënten in de eradicatie groep en 8 (5%) patiënten in de placebo groep maagzweren gediagnosticeerd (p=0.65). In de post hoc analyse werden patiënten met en zonder maagzweren

vergeleken voor het gebruik van selectieve en niet selectieve NSAIDs en voor mogelijke confounders voor het optreden van maagzweren. Geen van de selectieve NSAID gebruikers had maagzweren tijdens endoscopie; selectieve NSAIDs werden gebruikt door 0 (0%) patiënten in de maagzweren groep en door 80 (28%) patiënten in de niet-maagzweren groep (p=0.02). Een concomitante lage dosis aspirine werd gebruikt door 4 (29%) patiënten in de maagzweren groep en 27 (9%) patiënten in de niet-maagzweren groep (p=0.02). PPIs werden gebruikt door 4 (29%) patiënten in de maagzweren groep en 109 (38%) patiënten in de niet-maagzweren groep (p=0.48), H2RAs door 2 (14%) in de maagzweren groep en 17 (6%) in de niet-maagzweren groep (p=0.21) en prostaglandine analogen door 0 (0%) in de maagzweren groep en 1 (0.3%) in de niet-maagzweren groep (p=0.83).

De effectiviteit van het gebruik van selectieve NSAIDs voor de preventie van endoscopische en van gecompliceerde maagzweren werd eerder aangetoond in meerdere grote gerandomiseerde klinische studies. Het blijft echter onduidelijk of selectieve NSAIDs hun effectiviteit behouden tijdens langdurig gebruik of bij H. pylori positieve patiënten. In deze vooraf geplande post hoc analyse van een gerandomiseerde klinische studie onder H. pylori positieve patiënten met langdurig NSAID gebruik, was het langdurig gebruik van selectieve NSAIDs geassocieerd met een significant lager risico voor endoscopische maagzweren. Daarnaast was het concomitante gebruik van lage dosis aspirine geassocieerd met een significant verhoogd risico.

Opvallend is dat de resultaten van deze analyse voor een groot deel tegenovergesteld zijn aan die van het patiënt-controle onderzoek uit hoofdstuk III. Deze discrepantie illustreert de noodzaak om resultaten van NSAID onderzoek te interpreteren in de context van de betreffende studiepopulaties. Meerdere belangrijke verschillen tussen de studies uit hoofdstukken III en VIII kunnen hebben bijgedragen aan de verschillende uitkomsten. Ten eerste werd het in hoofdstuk III beschreven patiënt-controle onderzoek uitgevoerd in een algemene populatie van NSAID gebruikers, terwijl de gerandomiseerde studie werd uitgevoerd in een groep H. pylori positieve patiënten die langdurig NSAIDs gebruikten voor reumatische ziekten. H. pylori positieve patiënten die langdurig NSAIDs gebruiken vertegenwoordigen hoogst waarschijnlijk een cohort van NSAID overlevers; dat wil zeggen, patiënten met een intrinsiek risico voor maagzweren tijdens NSAID gebruik zullen lang voor inclusie in de gerandomiseerde studie al uit dit cohort verdwenen zijn, wat tevens de algeheel lage incidentie van endoscopische maagzweren in deze studie zou kunnen verklaren. Ten tweede zullen de meeste patiënten in een algemene populatie van NSAID gebruikers hun NSAID voorgeschreven hebben gekregen door een huisarts, terwijl de meeste reumatische patiënten hun NSAID voorgeschreven zullen hebben gekregen door een reumatoloog, met regelmatige controleafspraken op een reumatologische polikliniek. Dit zou kunnen leiden tot verschillende risico inschattingen en verschillende implementatie van preventieve strategieën; d.w.z, in de gerandomiseerde studie gebruikte 37.5% concomitante PPIs versus 23.5% in het patiënt-controle onderzoek, terwijl in de gerandomiseerde studie 9% COX-2 selectieve NSAIDs gebruikten versus 17% in het patiënt-controle onderzoek. Ook was het gebruik van lage dosis aspirine verschillend; 10% in de gerandomiseerde studie versus 26% in het patiënt-controle onderzoek. Ten slotte zijn er belangrijke verschillen in de studie opzet; d.w.z. gerandomiseerde gecontroleerde studie versus patiënt-controle onderzoek, in studie duur; d.w.z. 3 maanden versus een open kalender, en in studie eindpunten; d.w.z. endoscopische zweren versus gecompliceerde maagzweren.

Hoofdstuk IX presenteert een post hoc analyse van een gerandomiseerde klinische studie onder Helicobacter pylori positieve patiënten met langdurig NSAID gebruik voor reumatische ziekten, dat onderzoekt hoe we het beste persisterende Helicobacter pylori infectie dan wel succesvolle eradicatie na tripel therapie kunnen diagnostiseren. In de klinische studie werd H. pylori infectie bij patiënten vastgesteld door middel van serologisch onderzoek naar H. pylori IgG-antilichamen. H. pylori positieve patiënten werden gerandomiseerd voor H. pylori eradicatie tripel therapie of placebo, met controle endoscopie na 13 weken. In de post hoc analyse vergeleken we herhaalde H. pylori IgG-antilichaam titers, hematoxyline en eosine (H&E) kleuringen, immunohistochemische (IHC) kleuringen en H. pylori kweek resultaten in follow-up biopsieën van 68 patiënten, om de sensitiviteit en specificiteit van deze verschillende detectie methoden vast te stellen. Verder bepaalden we of toevoeging van IHC kleuringen aan H&E kleuringen de histologische detectie van H. pylori in deze patiënten verbeterd. Overeenstemmend met de gouden standaard criteria van of een positieve kweek of zowel een positief histologisch onderzoek als een positieve serologische test, was H. pylori eradicatie therapie succesvol bij 91.2% van de patiënten. Herhaalde serologie leverde 100% sensitiviteit, maar de overal specificiteit was 23.7% en 16.1% na eradicatie. Kweken leverde 100% specificiteit, maar de overal sensitiviteit was 83.3% en 66.7 na eradicatie. Histologisch onderzoek met of H&E of IHC kleuringen leverde een sensitiviteit en specificiteit tussen de 90% en 100%. Toevoeging van IHC aan H&E kleuringen verbeterde de resultaten niet.

Hoofdstuk X presenteert een post hoc analyse van een gerandomiseerde klinische studie onder Helicobacter pylori positieve patiënten met langdurig NSAID gebruik voor reumatische ziekten, dat de serologische evaluatie van Helicobacter pylori eradicatie na tripel therapie onderzoekt in patiënten met langdurig NSAID gebruik. In de klinische studie werden patiënten die H. pylori positief waren bij serologische testen voor H. pylori IgG-antilichamen gerandomiseerd voor H. pylori eradicatie tripel therapie of placebo. Dertien weken na randomisatie werden maagmucosa biopsieën en bloedmonsters afgenomen voor H. pylori kweken, histologisch onderzoek en herhaald serologisch onderzoek. In de post hoc analyse analyseerden we de sensitiviteit, specificiteit en receiver operating characteristic (ROC) curves van de herhaalde serologische testresultaten van 68 patiënten. Overeenstemmend met de gouden standaard criteria van of een positieve kweek of van zowel een positief histologisch onderzoek als een positieve serologische test, was H. pylori eradicatie therapie succesvol bij 91.2% van de patiënten. De ROC curve voor percentuele verandering in H. pylori IgG-antilichaam titers had een goede diagnostische power voor het identificeren van H. pylori negatieve patiënten, met een oppervlakte onder de ROC curve van 0.86 (95%BI 0.75 tot 0.93, $p<0.0001$). Het optimale afkappunt voor percentuele verandering in H. pylori IgG-antilichaam titers was 47.3% wat correspondeerde met een sensitiviteit van 96.7% (95%BI 82.7 tot 99.4%) en een specificiteit van 60.5% (95%BI 43.4 tot 75.9%). Het gebruik van een afkappunt van 50% daling in H. pylori antilichaam titers na 3 maanden leverde een sensitiviteit van 100% en een specificiteit van 71% voor het vaststellen van het succes van de H. pylori eradicatie therapie.

CONCLUSIES

Een 3500 jaar durende geschiedenis van ontdekking heeft geleid tot de ontwikkeling van niet-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs) die effectief zijn voor de verlichting van pijn,

koorts en ontsteking. Over de laatste decennia is het echter in toenemende mate duidelijk geworden dat behandeling met NSAIDs geassocieerd is met ernstige bijwerkingen en complicaties. NSAIDs kunnen maagzweren veroorzaken, welke gecompliceerd kunnen worden door bloeding, perforatie en obstructie, en ook ernstige cardiovasculaire complicaties, zoals hartaanvallen en hersenbloedingen. Voor artsen is de voorliggende uitdaging om deze risico's te leren balanceren bij het voorschrijven van NSAIDs aan individuele patiënten.

Patiënten met zowel een laag cardiovasculair als een laag gastrointestinaal risico kunnen worden behandeld met een niet-selectief NSAID. Patiënten met een laag cardiovasculair en een matig gastrointestinaal risico (een of twee gastrointestinale risico factoren) kunnen worden behandeld met een niet-selectief NSAID plus een PPI of misoprostol 800 µg, of met een COX-2 selectief NSAID. Patiënten met een laag cardiovasculair en een hoog gastrointestinaal risico (meer dan twee gastrointestinale risico factoren of eerdere gecompliceerde zweren) kunnen worden behandeld met een COX-2 selectief NSAID plus een PPI.

Patiënten met een hoog cardiovasculair risico zouden profylactisch lage dosis aspirine moeten gebruiken. Patiënten met een hoog cardiovasculair en een laag gastrointestinaal risico kunnen worden behandeld met naproxen plus een PPI of misoprostol 800 µg. Patiënten met zowel een hoog cardiovasculair als een hoog gastrointestinaal risico zouden NSAIDs moeten vermijden.

CHAPTER XIII

Dankwoord

Veel mensen hebben een bijdrage geleverd aan het tot stand komen van dit proefschrift. In de hoop niemand te vergeten, wil ik de volgende mensen speciaal noemen.

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CHAPTER XIV

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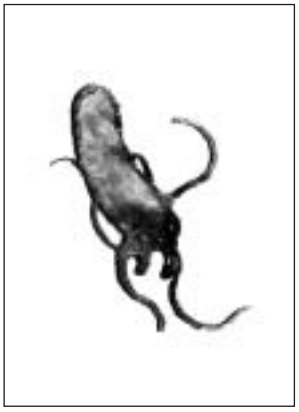
CHAPTER XV

Curriculum vitae

Harald Erwin Vonkeman werd op 6 januari 1969 geboren te Maassluis. In 1988 behaalde hij het VWO diploma aan de scholengemeenschap Westland-Zuid te Vlaardingen. Hij studeerde geneeskunde aan de Vrije Universiteit te Amsterdam en behaalde in 1994 het doctoraalexamen.
Tijdens de doctoraalfase deed hij onderzoek onder leiding van dr. P. Voorn in het Research Institute of Neurosciences, van de afdeling Anatomie en Embryologie aan de Vrije Universiteit te Amsterdam, en onder leiding van dr. E.K. Richfield in het Department of Neurology and Pharmacology aan de Universiteit van Rochester te Rochester, New York.
Tijdens een keuze co-schap reumatologie in het Jan van Breemen Instituut en het Slotervaartziekenhuis te Amsterdam onder begeleiding van Prof.dr. B.A.C. Dijkmans en dr. W.F. Lems werd zijn belangstelling voor de reumatologie gewekt.
Na het behalen van het artsexamen in 1997 werkte hij enkele maanden als arts in het Antoni van Leeuwenhoek Ziekenhuis te Amsterdam, waarna hij in 1998 begon met de vooropleiding Interne Geneeskunde in het Medisch Spectrum Twente te Enschede (opleiders Prof.dr. D. Richel en dr. B. Hylkema).
Van 2001 tot 2005 volgde de opleiding tot reumatoloog in het Medisch Spectrum Twente te Enschede (opleider Prof.dr. M.A.F.J. van de Laar). In deze periode werd ook gestart met het onderzoek zoals beschreven in dit proefschrift.
Sinds 2005 werkt hij als reumatoloog in het Medisch Spectrum Twente en als onderzoeker aan de Universiteit Twente.
Harald woont samen met Daniëlle en is vader van Erik.

Cover, chapter II-VII: rofecoxib, recrystallised and photographed under the microscope. This thesis is all about close scrutiny of non steroidal anti-inflammatory drugs, but there are many ways of looking, and from an unusual perspective one may see unexpected scenes.

Chapter I: Salix alba, the white willow, the bark of which is an original source of aspirin-like compounds.



Chapter VIII-X: Helicobacter pylori, photographed under the microscope.