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Review

NSAIDs: take with food or after fasting?

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Abstract

Objective Published and regulatory advice is to take NSAIDs with fluids and/or food irrespective whether NSAIDs are taken over the counter or long-term. The basis for this recommendation is not clear and we sought to establish the reasons for it through a search of published literature and personal files.

Results Results from experimental animals show that fasting increases the gastric side effects of NSAIDs while food increases small bowel damage, but this has not been tested in humans. The possible effects of food in modifying the gastric damage caused by NSAIDs are complex, as food quantity and composition modify the responses substantially. Food usually delays peak levels of NSAIDs (and hence onset of action) without affecting total bioavailability. This may not be important when a steady state is achieved, but rapid onset of action is highly relevant for over-the-counter use of NSAIDs. The safety of over-the-counter use of ibuprofen and naproxen appears to be excellent and comparable with paracetamol.

Conclusion The rapid onset of action of NSAIDs is most important during over-the-counter use, in which case it may be more appropriate to take the drugs on a fasting stomach.

Introduction

Despite the introduction of cyclooxygenase-2 (COX-2) selective agents the use of traditional non-steroidal anti-inflammatory drugs (NSAIDs) has been steadily increasing, attesting to their efficacy and perceived safety. The tendency of these drugs to cause damage throughout the whole of the gastrointestinal tract has nevertheless caused considerable concern.[1] There is a general consensus that there are different risk factors for the development of upper and lower gastrointestinal adverse effects of NSAIDs (inflammation, erosions and ulcers) and the serious outcomes of mucosal damage (bleeding, perforation, strictures and death).[1,2] Furthermore the prevalence and clinical implications of these adverse effects are dose dependent and differ when the drugs are taken in the short and long term.[1–3]

While it is important to inform patients of the risk of developing adverse effects it is equally important that patients have an informed knowledge on the availability of preventative measures that have been tested and proven to minimise adverse outcomes. It follows that such advice should be evidence based.

What is not in doubt is that irrespective of whether NSAIDs are taken over the counter (OTC) or for short or long terms, the published and regulatory advice is to take these drugs with fluids (usually milk) and/or before, during or after food. The purpose of this paper is to examine the evidence for these recommendations, especially when these drugs are taken in the short term or OTC.

Methods

We conducted a search of the published literature (undertaken using PubMed) and personal files.

Results

Current practice – official recommendations

The recommendations to take medicines with liquids are usually made with a view to avoid the rare occurrence of pill-induced oesophagitis. This occurs when there is prolonged contact time between the drug and the oesophageal mucosa. However, to ingest medicines with, before or after intake of food is an equally common with most drugs, as evident in drug or patient information leaflets. However, in the case of NSAIDs these recommendations are widely evident in the published literature. Accordingly, taking NSAIDs with fluids or in conjunction with foods is the advice in most

European countries[4] apart from Romania, where there are no recommendations as to taking NSAIDs with food or fluids. The US Food and Drug Administration patient information leaflet 'Drug Facts' recommends taking NSAIDs 'with food or milk if stomach upset occurs'.[5] Mosby's *Drug Consult* recommends 'If gastrointestinal complaints occur, administer tablets with meals or milk'.[6] *The Australian and New Zealand Nursing Drug Handbook* (2009) states, 'To reduce adverse gastrointestinal reactions, tell the patient to take the drug with meals or milk'.

Hence most regulatory bodies, and the vast majority of OTC package information leaflets, advise taking NSAIDs with food and/or fluids (there are no regulatory requirements on inclusion of package or insert advice on taking ibuprofen, aspirin or naproxen with or without food when sold OTC). There are no specifically claimed benefits from these recommendations and their origins have not been made clear. It can only be presumed that they relate to some supposed protective effects that food may have on the gastric or gastrointestinal effects of the drugs.

The requirement to take NSAIDs in a fasted state or at mealtimes and with food or fluids raises at least two important issues, namely (a) gastrointestinal safety, including ulceration, bleeding, perforation, strictures and death as well as gastrointestinal symptoms (e.g. dyspepsia, nausea, vomiting, heartburn, diarrhoea, constipation etc.) and (b) the effect on the absorption pharmacokinetics and bioavailability of the drug and hence the efficacy of the drug in controlling pain and inflammation.

Hence, it is important to consider the physiological and biochemical effects of fasting and fed states and how this affects the propensity to develop gastrointestinal damage and the pharmacodynamics of the drug.

Effects of fasting and food intake on gastrointestinal mucosal responses to NSAIDs

Overnight fasting leads to enhanced development of NSAID-induced gastric lesions in laboratory animals.[7,8] The mechanism is likely to involve an interaction between the low pH of gastric contents (characteristically between 1 and 3 after an overnight fast) and the pKa of the drug, which together determine the degree of the 'topical' damage that these drugs cause. Hence at a neutral pH a weak acidic drug (all conventional NSAIDs are weak acids) will be ionised (proportional to its acidity) and hence unable to partition across the gastric surface epithelium because of its charge. Thus given a postprandial gastric juice pH of 6, a drug such as aspirin with a pKa of 3.5 would be fully ionised while fenbufen, with a pKa of 5.7, would be largely uncharged. The lower the pKa of the NSAID, the greater the effect of an acidic environment for the 'topical' toxicity, which involves a NSAID–phospholipid interaction[9] and the permeation of the drug into the gastric epithelium.[10,11] Once within the gastric cell the NSAID gets trapped within the cell because of ionisation at the intracellular pH near to neutrality (again quantitatively dependent on the pKa of the drug), reaching concentrations that uncouple mitochondrial oxidative phosphorylation.[12–14] The decrease of metabolically important levels of adenosine triphosphate then sets off a sequence of cellular events that interact, with the consequence of COX-1 and 2 inhibition, rendering the mucosa vulnerable to luminal aggressive factors and leading to characteristic NSAID-induced damage.

Despite an extensive search of the literature there do not appear to be any published studies of the gastric damage of NSAIDs in humans when given with or without food. There is, nevertheless, well-established corroborative experimental evidence in humans for the 'irritant' action of NSAIDs on the stomach (topical toxicity). Hence in short-term endoscopy trials (where the relationship between NSAID and food intake has, in general, not been specified) there is a significant correlation between gastric damage and the acidity of the NSAID when given in prescribed doses (which are associated with quantitatively similar inhibition of COX-1 and 2).[15] Non-acidic pro-NSAIDs (such as nabumetone and the so-called nitric-oxide-donating NSAIDs) are associated with significantly less damage than the parent acidic compounds.[16,17] Patients with pernicious anaemia (who are often achlorhydric) are purported to tolerate NSAIDs relatively well[18] and enteric coating reduces the short-term gastric irritancy of aspirin.[18–20] Furthermore, reducing the stomach acidity with proton pump inhibitors (or with high-dose histamine-2 receptor antagonists) markedly reduces the gastric damage of the more acidic NSAIDs such as aspirin.[18,21] These effects are all consistent with the interaction between the pKa of the NSAID and gastric pH, i.e. the ion trapping phenomena.[10,11,15]

Whilst these studies emphasise the contribution of the 'topical' effect in the gastric damage due to NSAIDs, the question of food modifying the effects of NSAIDs is not only lacking, but in principle quite complex.

Food intake and fasting are loose terms. Fasting is defined as the act of abstaining (the time period is not stated) from food and liquid or to 'eat meager' (*Shorter Oxford English Dictionary*, 1964). However, gastric physiological and endoscopy studies used for the investigation of NSAID-related gastrointestinal toxicity require that the act of fasting is at least overnight. These are pre-defined experimental conditions and not those that might be experienced by the average person taking NSAIDs; in fact this might well be a rare occurrence.

Food, of course, alters the gastric pH, but also counteracts some of the local and systemic biochemical and physiologic consequences of fasting. Furthermore, individual components of the diet can vastly influence the development of

injury from NSAIDs in different regions of the gastrointestinal mucosa.[22] Thus, oral glucose, some amino acids and food bulk can reduce mucosal injury in the stomach, but at the same time increase small bowel damage in animals.[8] Studies in humans show that the combination of precursors or intermediates of the tricarboxylic acid cycle reduce gastric damage due to NSAIDs despite an enhanced gastric secretion of acid.[23] Fat, in contrast, can enhance gastric and intestinal damage from NSAIDs.[8]

The type of meals and the consequent changes in patterns of gastric acidity are also not straightforward.[24] Variations in the content of carbohydrate, protein and fat of isocaloric meals do not have marked effects,[24] although there is a small decrease in gastric acidity in response to an isocaloric fat-containing meal compared with that of a balanced diet.[25] In general, following a standardised meal after a fast there is buffering of gastric acid approaching a pH of 6 and a return to below pre-fast levels within 2 h. Thus taking a NSAID before, during and after a meal is likely to have different effects on the gastric mucosa and the composition of the meal is likely to be important. An understanding of the factors responsible for regulating gastric physiology in determining gastric mucosal responses to NSAIDs and the differential influence of different food components on dispersion, dilution, contact time (gastric emptying), blood flow etc. on NSAIDs may thus have a profound impact on what advice patients are given. However, these factors remain experimentally largely unexplored in humans. Given the perceived importance of taking NSAIDs with food this lack of information is curious.

A separate issue is whether NSAIDs alter gastric acid secretion, as gastric parietal cells have receptors for prostaglandin E_2 that inhibit acid secretion. It appears that synthetic prostaglandins have only a modest inhibitory effect on gastric acid secretion[26,27] and there are only a few studies in humans on the effects of NSAIDs on gastric acid secretion.[28] This review concluded that most studies showed that indomethacin does not affect basal acid secretion, but some showed that it increased histamine-stimulated secretion.[28] Subsequent studies seem to support these conclusions.[29,30] Thus, it might appear that NSAIDs have some, albeit relatively minor, effects on gastric acidity in humans.

Effects of food and fasting on the effect on the absorption pharmacokinetics and bioavailability of NSAIDs

It is well established that intake of foods or the fasting state can markedly affect the bioavailability of analgesics and anti-inflammatory drugs.[31–33] The mechanisms underlying these food–drug interactions vary with individual drugs and there are no simple rules governing them. Single-dose studies are usually used to assess bioequivalence. Bioequivalence food-effect studies aim to demonstrate comparable bioavailabilities between test and reference products when co-administered with meals. In the case of NSAIDs several studies have highlighted the delay of absorption of NSAIDs in the presence of food (the type and amount of food in these studies has not been standardised) as a consequence of delay in gastric emptying.[32–36] The drug-delivery systems have varied markedly, with substantial quantitative differences between sustained release, enteric-coated, immediate-release and 'solubilised' (e.g. liquigel, arginine salts, lysine or other formulations) formulations.[37,38] Although peak levels are delayed (about 20–30%) and lower with food, the total bioavailability (as measured by the area under the serum concentration versus time curve) remains the same as that during fasting.[39,40] The effect of taking the drugs before, during or after meals therefore predominantly determines the rapidity of onset of action. Onset of action may not be an important issue when NSAIDs are taken regularly long term after a steady state has been reached. However, onset of action is highly relevant for OTC use, where indeed this is a therapeutic issue and a 'selling' point for the drugs.[41] Hence the patient's expectation may be that the analgesic effect of OTC NSAIDs is next to immediate. When this is not the case, due to taking the drug with food, the patient may ingest another dose immediately. Furthermore the patient may be tempted to double the dose the next time that the anti-inflammatory analgesic is required, in the belief that this leads to more rapid onset of action. Either of these may increase the risk of gastrointestinal adverse events.

Safety and onset of action

What are the safety issues with OTC NSAIDs (e.g. ibuprofen ($\leq$1200 mg/day) and naproxen ($\leq$600 mg/day)) for ten days or less?

From endoscopy trials it is clear[15,42–45] that gastric bleeding is exceedingly rare when NSAIDs are taken at prescription doses for 7–10 days, irrespective of the uncertainty of the relationship between drug and food intake. A direct comparison between haemoglobin levels in patients with osteoarthritis taking paracetamol (3 g/day) or ibuprofen (1200 mg/day) for 13 weeks showed no significant difference between the two drugs.[46] In other studies OTC ibuprofen is reported to be equal to, or safer than, paracetamol.[44,47–49] Indeed, it is clear from a large body of data[42–45] that the occurrence of severe ulcer complications (ulceration, bleeding) is rare at OTC dosages for both ibuprofen or naproxen.[50,51] Symptomatic events (e.g. heartburn, dyspepsia) occur with OTC ibuprofen, but the data to date suggest that this is equivalent to that of paracetamol.[44,52–55]

Summary

Most drugs carry with them instructions to take the medicines with fluid and/or before, during or after meals.

These recommendations would ordinarily be based on considerations of efficacy and safety. In the case of NSAIDs the recommendation for taking the drugs with food is particularly widespread. This review provides very little experimental evidence to justify these recommendations considering that (1) the effect of food on gastrointestinal physiology and biochemistry and hence the side effects of NSAIDs varies according to the type of food ingested, (2) food may have differential effects on the damage caused by NSAIDs in the stomach and small bowel, and (3) the studies that have been performed are sometimes far removed from real-life events.

The paucity of human data on the safety and tolerability of NSAIDs when taken with food or after fasting is somewhat surprising. Apart from providing unsubstantiated 'safety' information by advocating food intake with NSAIDs it may be more appropriate to advocate OTC NSAIDs be taken on a fasting stomach in order to achieve a rapid onset of action and hence avoid an 'extra' dose of the drug because the rapidity of pain relief did not meet the patient's expectations.

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