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NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

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Rodney Nickander

Department of Immunology and Connective Tissue Research, The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

F. Gilbert McMahon

Department of Medicine, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112

Anthony S. Ridolfo

Clinical Research Division, The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

INTRODUCTION

Nonsteroidal anti-inflammatory agents (NSAIA) have as their major pharmacological effect the reduction of edema, erythema, and resulting tissue damage associated with inflammatory conditions, but many also share the actions of analgesia and antipyresis. This triad of action—anti-inflammatory, analgesic, and antipyretic—describes the classic example and the most widely used NSAIA, aspirin. Aspirin has been commonly used since the turn of the century and today it is still the agent of first choice for mild pain, fever, and arthritis (e.g. osteoarthritis and rheumatoid arthritis).

In this review we initially categorize all nonsteroidal agents used for the treatment of inflammatory conditions, e.g. arthritis, spondylitis, lupus, gout, fever, and pain. These categories include classical NSAIA (e.g. aspirin and indomethacin) as well as immune suppresants, gold compounds, antimalarials, antipyretics, and penicillamine. We confine our discussions primarily to the use and actions of the classical NSAIA. The probable mode of action

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for NSAIA, that of inhibition of prostaglandin synthesis, is presented showing the various mediators in the prostaglandin cascade and discussing their role in inflammation and normal physiological function. In preparation for this review we found approximately 1000 articles on NSAIA published in 1977 and the first 6 months of 1978 including many reviews, books and new book chapters regarding the use of NSAIA in arthritis and rheumatic diseases (1–8). We therefore review this area briefly followed by more detailed discussions of studies involving nonarthritic uses of NSAIA. These subjects included the effect of NSAIA on platelet function and treatment of thrombosis; treatment of dysmenorrhea, pain, and fever; dermal inflammation and treatment with NSAIA; and treatment of premature infants with patent ductus arteriosus. We close with a discussion of the adverse effects of NSAIA on the gastrointestinal tract, kidney, and fetus. In general we reference current reviews rather than cite each original study. It is not our intent to duplicate these reviews but to discuss new experimental observations emphasizing recent nonarthritic uses of NSAIA.

CATEGORIES OF NSAIA

By definition, nonsteroidal agents used for the treatment of inflammatory conditions include a large number of therapeutic agents ranging from the frequently used acetaminophen for treatment of mild pain and fever associated with the common cold or influenza to the less frequently used immunosuppressive compounds cyclophosphamide or azathioprine for the treatment of rheumatoid arthritis. Table 1 lists the NSAIA marketed in the United States and the conditions for which they are prescribed, as well as many of the NSAIA marketed outside the United States or those under clinical investigation. It is our understanding that the Food and Drug Administration (FDA) is presently reviewing some 60 investigational new drug (IND) applications for NSAIA. Our list of drugs under clinical investigation in the United States and abroad is by no means complete. The agents in Table 1 are classified into categories commonly used for antirheumatic drugs (5, 6), but all are nonsteroidal and used to treat various inflammatory conditions. A very complete review of inflammation and the use of most of the anti-inflammatory agents listed in Table 1 was recently published in a book by Arrigoni-Martelli (7). The chemical structures of many of these compounds in Table 1 appear in that book. The Annual Reports in Medicinal Chemistry regularly discuss the chemistry of the NSAIA.

Category A in Table 1 lists agents that are commonly called aspirin-like and that share the anti-inflammatory, analgesic, and antipyretic actions. It is this category that is traditionally called the NSAIA and is the principal

group of agents discussed in this review. A principal mode of action of these agents, that of inhibition of the synthesis or availability of prostaglandins, and other mediators of inflammation, is discussed later.

Category B in Table 1 lists agents that are capable of modifying immune responsiveness and are used for the treatment of rheumatoid arthritis and ankylosing spondylitis. The basis for their use is that diseases such as rheumatoid arthritis may have an underlying immunological abnormality and selective immunosuppression may be beneficial. None of these compounds are approved by the FDA for treatment of rheumatic diseases, but in practice the alkylating agents cyclophosphamide and chlorambucil and the antimetabolites azathioprine and methotrexate have been used to retard the progression of the disease (7). Gold compounds, agents used to treat gout, antimalarials, and penicillamine are not discussed in this review but are tabulated for completeness in the listing of NSAIA. Acetaminophen and mefanamic acid are discussed in a later section on the use of NSAIA for the treatment of pain and fever.

PROBABLE MODE OF ACTION OF NSAIA

The most widely accepted mode of action proposed for NSAIA is that of inhibition of prostaglandin synthesis. This mechanism, discovered by Vane and his associates (9–11), was discussed in detail by Ferreira & Vane (12) in the 1974 Review of NSAIA in this series and updated by Vane (13) in 1976. Figure 1 summarizes the present state of knowledge on the enzymatic transformation of arachidonic acid to prostaglandins. It was adapted from recent reports of Vane (14) and Samuelsson (15) and shows the ever-increasing list of substances (mediators) identified with pharmacological actions. Current thinking is that during conditions of inflammation, pain, fever, and platelet aggregation, arachidonic acid is liberated from phospholipid fractions of cell membranes by the action of a phospholipase A_2. Corticosteroids have been demonstrated to inhibit prostaglandin production by apparently limiting substrate or inhibiting the action of phospholipase (16). The end result of the action of corticosteroids would be a total reduction in all proinflammatory mediators (Figure 1). Once arachidonic acid is available, an enzyme complex called prostaglandin synthetase converts it to other products. The first step is an action of cyclooxygenase forming the cyclic endoperoxides (PGG_2 and PGH_2). These intermediates are capable of producing pain and vasoconstriction. This enzymatic step by cyclooxygenase has been identified as the site of inhibition of NSAIA. Virtually all aspirin-like NSAIA reported to inhibit release or synthesis of PGE_2 and $PGF_{2\alpha}$ do so by inhibiting this enzyme. Kuehl and associates (17) have proposed that PGG_2 plays a pivotal role in inducing inflammation in

Table 1 Nonsteroidal anti-inflammatory agents and conditions treated[a]

Class of agents		Condition treated[b]
A. Agents that appear to act by inhibiting the synthesis or availability of prostaglandins		
1. Marketed in the United States		
Aspirin (including other salicylates)—nonprescription		RA, OA, BT, AS, PA, RS, JRA, P, F, G
Fenoprofen		[RA, OA] AS, P, F, G, BT
Ibuprofen		[RA, OA] AS, P, F, G, BT
Indomethacin		[RA, OA, AS, G] F, P
Mefenamic acid		[P] RA, F
Naproxen		[RA] OA, AS, P, F, G, BT
Phenylbutazone and oxyphenbutazone		[RA, OA, AS, BT, PA, G] P
Sulindac		[RA, OA, AS, BT, G]
Tolmetin		[RA] OA, JRA, AS, P, BT
2. Marketed outside the United States and/or under clinical investigation (mode of action less well defined)		
Alclofenac	Flufenamic acid	In general these agents are being investigated for their effect in the same conditions described for Group 1 above, usually beginning with RA, OA, and P.
Amfenac	Flufenisal	
Azapropazone	Flumizole	
Bendazac	Flurbiprofen	
Benorylate	Furobufen	
Benoxaprofen	Indoprofen	
Bucloxic acid	Isoxepac	
Bufexamac	Ketoprofen	
Carprofen	Meclofenamic acid	
Cintazone	Mepirizole	
Clonixin	Nictindole	
Clopirac	Niflumic acid	
Diclofenac	Piroxicam	
Diflunisal	Pirprofen	
Diflumidone	Prenazone	
Diftalone	Proquazone	
Etodolic acid	Sudoxicam	
Fenbufen	Sulindac	
Fenclofenac	Suprofen	
Fenclozic acid	Tianafac	
Fendosal	Triflumidate	
B. Agents that appear to act by modifying immune responsiveness		
1. Marketed in the United States		
Azathioprine		RA, JRS, AS
Chlorambucil		RA, JRA
Cyclophosphamide		RA, AS, JRA
Methotrexate		RA, PA

Table 1 *(continued)*

Class of agents	Condition treated[b]
2. Marketed outside the United States and/or under clinical investigation	
Flazalone	Most of these agents are under investigation for their effect in the conditions described above for Group 1.
Frentizole	
Isoprinosine	
Levamisole	
Tilorone	
WY-13876	
C. Agents that are gold compounds	
1. Marketed in the United States	
Gold sodium thiomalate	[RA] JRA, PA
Aurothioglucose	[RA] JRA, PA
Gold sodium thiosulfate	[RA] [DLE] JRA, PA
2. Marketed outside the United States and/or under clinical investigation	
SKF 36914 (Auranofin)	RA
D. Agents used to treat gout	
1. Marketed in the United States	
Probenecid	[G] US
Sulfinpyrazone	[G] US
Allopurinol	[G]
Colchicine	[G]
Indomethacin	[G] US
Phenylbutazone	[G] US
Oxyphenbutazone	[G] US
Sulindac	[G]
E. Agents that are antimalarial and penicillamine	
1. Marketed in the United States	
Penicillamine	RA, JRA
Chloroquine phosphate	RA
Hydroxychloroquine	[RA, DLE, SLE] JRA
F. Agents that are antipyretic analgesics	
1. Marketed in the United States	
Acetaminophen	P, F, OA
Mefenamic acid	[P] F, RA

[a] AS, ankylosing spondylitis; BT, bursitis, tendonitis; DLE, discord lupus erythematosus; F, fever; G, gout; JRA, juvenile rheumatoid arthritis; OA, osteoarthritis; P, pain; PA, psoriatic arthritis; RA, rheumatoid arthritis; RS, Reiter's syndrome; SLE, systemic lupus erythematosus; US, uricosuric.

[b] Brackets indicate conditions whose treatment by the agent indicated has been approved by the FDA.

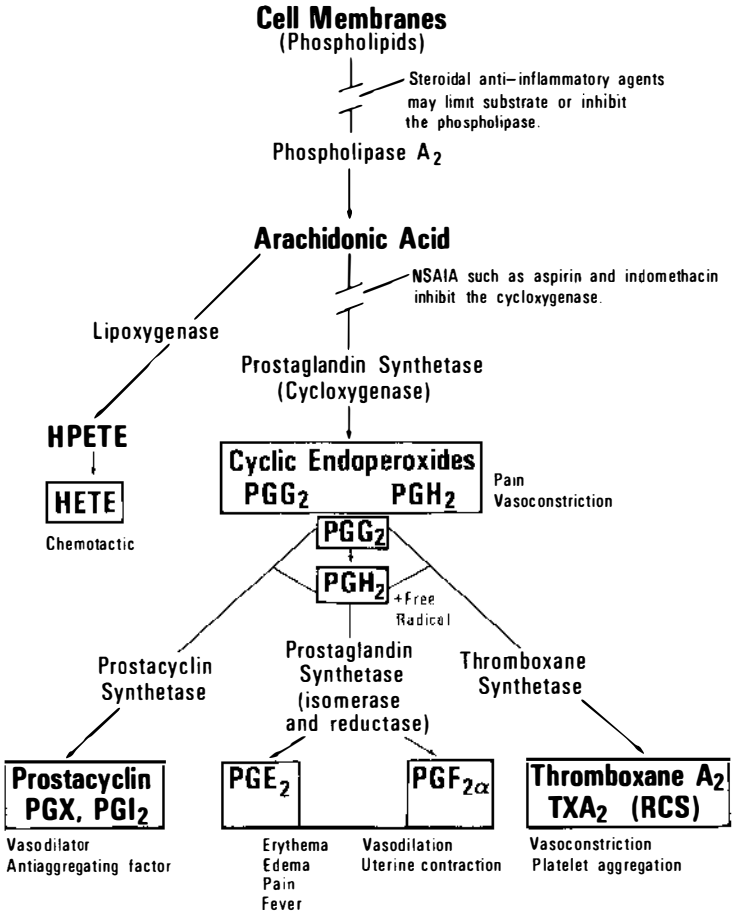

Figure 1 Generation of potential mediators of inflammation by the enzymatic conversion of arachidonic acid.

that they observed that the anti-inflammatory compound MK-447 increased overall PG synthesis by stimulating the conversion of PGG_2 to PGH_2. They further proposed that the free radical liberated upon conversion of PGG_2 to PGH_2 may regulate the formation of proinflammatory mediators. PGH_2 is acted upon by an isomerase and a reductase contained within the prostaglandin synthetase complex producing the widely studied prostaglandins E_2 and $F_{2\alpha}$. The prostaglandins have many biological actions including the ability to produce erythema, edema, pain, fever, vasodilation, and uterine contractions. More recently two other metabolic pathways have been identified originating from either PGG_2 or PGH_2. The

first was the formation of thromboxanes (A_2 and B_2) by an action of thromboxane synthetase. Thromboxane A_2 causes vasoconstriction and platelet aggregation and is now known to be the principal component of RCS (rabbit aortic contracting substance). The most recent pathway identified is that of the formation of prostacyclin (PGX) now called PGI_2. Prostacyclin synthetase acting upon PGG_2 or PGH_2 forms PGI_2 which produces an antiaggregation effect on platelets and vasodilation. These findings suggest a mechanism of control of platelet function whereby TXA_2 and PGI_2 provide a balance of platelet aggregation and arterial constriction. One additional mediator is formed when lipoxygenase acts upon arachidonic acid to form a hydroperoxide (HPETE) and subsequently hydroxyacid (HETE). The latter has been demonstrated to be chemotactic for polymorphonuclear leucocytes.

NSAIA by virtue of inhibition of the cyclooxygenase reduce levels of PGI_2, PGE_2, PGF_{2a}, and TXA_2. Aspirin-like NSAIA are not inhibitors of prostacyclin and thromboxane synthetase. A few inhibitors of these enzymes have been identified, and the subject was recently reviewed by Schaaf (18). Selective inhibitors of these enzymes could well provide desired therapeutic effects with a reduced incidence of side effects. An inhibitor of thromboxane synthetase could inhibit thrombosis without materially altering the levels of PGs. Presently, the cyclooxygenase inhibitors reduce levels of all mediators causing alterations in the physiological function of the intestinal tract, kidney, and uterus. These changes are discussed in the section on adverse effects of NSAIA.

Other possible modes of actions of NSAIA have been recently reviewed by Arrigoni-Martelli (7) and Shen & Winter (8) and include the following: (*a*) inhibition of chemotaxis of cells implicated in the inflammatory process, (*b*) inhibition of lysosomal membrane labilization, (*c*) antagonist effects on mediators other than PGs (e.g. histamine and bradykinin), (*d*) inhibition of the biosynthesis of mucopolysaccharides, (*e*) uncoupling of oxidative phosphorylation, (*f*) fibrinolytic activity, and (*g*) sulfhydryl-disulfide stabilization. Dayer & Krane (19) discussed the possible role of NSAIA in inhibiting collagenase production, and Panush (20) has suggested that suppression of lymphocyte function may be a mechanism of some NSAIA.

TREATMENT OF ARTHRITIS AND RHEUMATIC DISEASE

Detailed reviews on the use of NSAIA in arthritis and rheumatic disease have recently appeared by Huskisson (1), Hart (2), Kaye (3), and Ridolfo (4), as well as major treatments in the book of Arrigoni-Martelli (7) and in chapters of Drugs of Choice (6) and AMA Drug Evaluations (5). Although

we refer the reader to these treatments for detailed discussions we would be remiss if we did not briefly discuss their usefulness in this regard.

Since pain and locomotor dysfunction remain among the most common and frustrating afflictions of man, any drug that helps alleviate pain and improve mobility is welcome. Until the introduction of indomethacin, the major drugs available were salicylates, phenylbutazone, steroids, and gold; none of these adequately controlled the patient and all had potential side effects that were not acceptable. More recently fenoprofen, ibuprofen, naproxen, sulindac, and tolmetin have been approved for use in the United States, and many more are used in countries outside the United States. These agents are all helpful in the management of patients with rheumatic disease, when combined with other modalities, such as proper rest, exercise, assistive devices, physical therapy, occupational therapy, and surgery.

The anti-inflammatory and analgesic effects of the NSAIA mitigate the swelling, heat, and effusion accompanying acute inflammation. However, no evidence has been presented to show that the NSAIA modify the proliferative phase of rheumatoid arthritis. More potent remittive drugs are needed to accomplish this, for example, gold, antimalarials, penicillamine, and immunosuppressive agents. During the past few years, enormous experience has been generated with NSAIA in arthritis, and a pattern appears to be emerging. All the presently available agents are useful in treating rheumatoid arthritis or musculoskeletal disorders in which inflammation plays a part, for example, ankylosing spondylitis, acute gout, soft-tissue arthritis, bursitis, tendinitis, and the arthralgias of lupus. They may be used to substitute, one for the other, but generally are not used in combination with each other. All appear to have the same spectrum of side effects (see adverse effect), with some quantitative differences.

When compared to aspirin or to one another in double-blind studies, statistically superior affectiveness is difficult to demonstrate. Some patients do better on one of the NSAIA, and others on another NSAIA. In general, the studies show the new NSAIA to be as effective, but with fewer side effects than aspirin. Some would look at this as a negative statement, but in reality it is not because aspirin is an effective agent when given at therapeutic levels, i.e., greater than 20 mg/100 ml. At this level, however, there is a greater increase in liability for undesirable side effects with aspirin than there is with the other NSAIA.

Since the rapid-acting NSAIA are anti-inflammatory, but not antiproliferative, it is only logical that they have been used in combination with the slower-acting remittive drugs (e.g. steroids and gold) to alleviate pain and inflammation, at least until the therapeutic effects of the remittive drugs are realized.

Studies have been done to show that the combination of aspirin with the NSAIA does not lessen the clinical response to the NSAIA (21), even

though blood levels may be decreased (22). An explanation might be that the added anti-inflammatory effect of aspirin may be great enough to overcome the theoretical decrease in clinical response which should occur as a result of a lower NSAIA blood level.

Osteoarthritis is another area in which the NSAIA have found considerable acceptance. They are more effective than the pure analgesics *d*-propoxyphene or the antipyretic analgesic acetaminophen. This may be due to the fact that the analgesics do not affect the inflammatory component of osteoarthritis, whereas the anti-inflammatory NSAIA should.

A review of many recent clinical studies of new NSAIA in rheumatoid arthritis [alclofenac (23), diclofenac (24), diftalone (25), fenoprofen (26), flurbiprofen (27), indomethacin (24, 29), indoprofen (28), naproxen (28), tolmetin, (23)] and osteoarthritis [diflunisal (29), flurbiprofen (30), indomethacin (30)] indicates a similarity in the type of studies performed, as well as in the results. There is little convincing evidence that one NSAIA is clearly superior in efficacy to another. The reason for this may be that they are all effective anti-inflammatory agents, and larger numbers of patients would be required to show a statistical superiority of one effective agent over another, since the measurements of effectiveness are not very precise.

The usefulness of the NSAIA in rheumatic disorders other than rheumatoid arthritis and osteoarthritis has been demonstrated by studies done in patients with soft-tissue rheumatism and sports injuries (31, 32), gout (33, 34), ankylosing spondylitis (35, 36), and juvenile rheumatoid arthritis (37). In general the newer NSAIA are as effective as the standard treatments of aspirin, phenylbutazone, or indomethacin.

NSAIA EFFECT ON PLATELET FUNCTION AND TREATMENT OF THROMBOEMBOLISM

Many agents can induce platelet aggregation but current evidence strongly suggests that polyoxygenated derivatives of arachidonic acid may play a key role in the aggregation of platelets. Arachidonic acid, endoperoxides PGG_2, and PGH_2 as well as thromboxane A_2 cause platelet aggregation. When examining the effects of various drug substances on platelet aggregation, investigators commonly use collagen as the aggregating agent. Collagen is a natural component of the subendothelium of the vessel wall that appears to release arachidonic acid from the platelet phospholipids presumably by activation of a phospholipase. Indomethacin, aspirin, and numerous other NSAIA have been shown to inhibit collagen-induced platelet aggregation (38, 39).

When platelet aggregation is induced by collagen there is formation and release of PGE_2 and $PGF_{2\alpha}$ but predominantly TXA_2. When TXA_2 formation is inhibited, no aggregation is induced by collagen and there is no

release of ADP and serotonin whereas incubation with PGG_2 restores both actions indicating that prostaglandin endoperoxides and/or thromboxanes may play a role in normal hemostasis (15).

In recent years the prophylactic use of agents that alter platelet function in patients at risk for thromboembolism has received a great deal of attention. Aspirin, with its multiple effects on platelet function (40), is undergoing clinical trials in venous thrombosis (41–44), secondary prevention of myocardial infarction (45–48), and cerebral vascular disease (49, 50). The anti-anginal drug, dipyridamole, and the uricosuric agent, sulfinpyrazone, are currently undergoing extensive prospective placebo-controlled double-blind trials in the secondary prevention of myocardial infarction (51, 52). Preliminary results with these agents appear encouraging although longer follow-up is needed before firm conclusions can be reached.

Venous Thrombosis

Aspirin has been studied at daily doses of 1.2–1.5 g/day alone or with dipyridamole in the prevention of postoperative thrombosis or pulmonary emboli with encouraging but nondefinitive results (41). Part of the problem lies in the variability of the diagnostic method (phlebography is more diagnostic than fibrinogen scanning or purely clinical means). Harris et al (42) in a well-controlled prospective study of elderly patients undergoing total hip replacement, found only four thrombi among 23 men receiving 1.2 g/day of aspirin versus 14 among 25 receiving placebo (p 0.01). Inexplicably, this protection was restricted to males. Other investigators have concluded that aspirin at 1.2–1.5 g/day may reduce postoperative thrombosis or pulmonary embolic complications (43, 44).

Secondary Prevention of Myocardial Infarction

The Boston Collaborative Drug Surveillance Group reported two case-control studies indicating that daily aspirin intake was less often associated with myocardial infarction than among control patients not taking aspirin (45).

In 1971, a Finnish study (46) reported no differences in mortality or morbidity among 430 geriatric patients given either one g/day of aspirin or placebo and followed for one year.

The Medical Research Council of Great Britain reported results after treatment of 1239 men with either 300 mg/day aspirin or identical placebo (47). Although there was a 25% difference in mortality favoring aspirin after 12 months, and a 34% difference after 24 months, these differences did not reach statistical significance.

The Coronary Drug Project Group (48) studied 1529 men in 53 clinics, comparing 324 mg three times a day of aspirin versus placebo. After 28

months treatment, the mortality in the aspirin group was 8.3%, compared with 5.9% in the placebo group (p.n.s.).

The PARIS (Persantin-Aspirin-Re-Infarction) Study (51) involves approximately two thousand men and women. Three treatment groups are being compared: (*a*) 324 mg aspirin with 1 placebo tablet three times daily, (*b*) dipyridamole (75 mg) with aspirin (324 mg), three times daily, and (*c*) two placebo tablets three times daily. Results of this well-controlled study have not yet been reported.

Cerebrovascular Disease

Transient ischemic attacks (TIA) as well as actual embolic cerebrovascular occlusion may be secondary to microembolization of platelet-fibrin thrombi deposited in atherosclerotic lesions of the basilar or internal carotid arteries. Fields et al (49) studied 178 patients with TIA, comparing aspirin 0.6 g twice a day with placebo. After six months, a significant reduction in the frequency of TIA was shown with aspirin, and the data suggested that strokes may be prevented.

The Canadian Cooperative Study Group conducted a randomized trial of aspirin and sulfinpyrazone in threatened stroke (50). The study involved 585 patients followed for an average of 26 months, and 85 subjects went on to stroke and 42 died. Aspirin reduced the continuing ischemic attacks by 19% but more importantly reduced the risk of stroke or death by 31%. It was interesting that the reduction in stroke or death was sex-dependent in that the reduction was 48% for men with a nonsignificant trend among women. Sulfinpyrazone was not effective in this study. They concluded that aspirin was an efficacious drug for men with threatened stroke.

TREATMENT OF DYSMENORRHEA

The use of NSAIA for the treatment of primary dysmenorrhea has been well established. Anderson et al (53) in reporting on the results with mefenamic and flufenamic acids reviewed the rationale for this approach. There are elevated levels of intrauterine prostaglandins in uterine washings and endometrial tissue as well as circulating metabolites of prostaglandins during dysmenorrhea. Also there is a similarity in the symptoms of primary dysmenorrhea and the side effects associated with systemic administration of prostaglandins. Therefore, the lower abdominal pain may be due to PG-induced uterine contractions and the gastrointestinal and other symptoms due to increased levels of circulating PGs. The prostaglandin synthetase inhibitors mefenamic and flufenamic acid were clearly as effective as a dextropropoxyphene/paracetamol combination for relieving symptoms of dysmenorrhea. Kapadia & Elder (54) carried out a double-blind crossover

study in 44 patients with primary spasmodic dysmenorrhea comparing placebo and flufenamic acid (200 mg) taken 3 times a day for 3 months. Flufenamic acid provided significant relief of pain in 82% of the patients, vomiting was relieved in 66%, and diarrhea in 52% of the patients.

There are several studies on the treatment of dysmenorrhea with naproxen. Henzl et al (55) reported on two independent double-blind trials, and in both studies naproxen was superior to placebo in the relief of pain of menstrual cramping. Earlier Csapo et al (56) in an open trial had observed that naproxen not only reduced menstrual pain but also reduced the pressure and frequency of cyclic uterine activity in dysmenorrheic patients. Massey et al (57) observed that naproxen reduced the pain and discomfort following the insertion of an intrauterine device, again suggesting that unwanted uterine myometrial activity can be suppressed by NSAIA.

Another uterine pain commonly employed for establishing efficacy of new analgesics is postpartum pain. Using the same rationale as that for dysmenorrhea, it was expected that NSAIA would relieve postpartum pain. Bloomfield et al (58) observed in a parallel double-blind trial that single oral doses of naproxen and aspirin were equally efficacious in relieving postpartum pain and in that study were superior to codeine.

The use of aspirin-like drugs (NSAIA) for the relief of menstrual pain is not a new observation as the proprietary medicines for this purpose attest but there are now an increasing number of controlled clinical trials and an understanding or rationale for their use.

TREATMENT OF PAIN

Van Winzum & Rodda (59) reported on the efficacy of diflunisal in postoperative pain, pointing out that many doctors and nurses fearing opiate-type drug-induced addictions have accepted pain as an inevitable consequence of surgery and not given full consideration to the oral NSAIA as analgesics. The study involved 740 patients with pain after oral or orthopedic surgery or episiotomy and compared either single doses of diflunisal (125, 250, or 500 mg) and aspirin (600 mg) or repeat doses of diflunisal (375 or 500 mg). Diflunisal proved effective as an analgesic in 75–85% of the patients suffering from postoperative pain.

Mahler et al (60) in a Veterans Administration Cooperative Analgesic Study explored the efficacy of naproxen in postoperative pain. In a double-blind assay, 200 mg and 400 mg of naproxen were compared with 600 and 1200 mg of aspirin and with placebo. Both agents provided a significant analgesic effect.

Sechzer (61) evaluated the effect of fenoprofen as a postoperative analgesic. Patients with moderate to severe postpartum or postoperative

pain were given single oral doses of placebo, aspirin (975 mg), or fenoprofen calcium (600 mg). Fenoprofen provided significantly more analgesia than did placebo.

Winter et al (62) examined the analgesic activity of ibuprofen in postoperative oral surgical pain. In a double-blind study of 510 patients experiencing pain subsequent to extractions, alveolectomy, or impactions, single oral doses of ibuprofen (400 or 800 mg), aspirin (650 mg), dextropropoxyphene HCl (65 mg), or placebo were compared. Both doses of ibuprofen and 650 mg of aspirin were effective analgesics with pain relief scores greater than placebo or dextropropoxyphene HCl.

Mefenamic acid was examined by Stableforth (63) for its effectiveness in the relief of acute post-injury pain. A double-blind prospective study compared mefenamic acid (250 mg) with dextropropoxyphene HCl (32.5 mg) plus paracetamol (325 mg). Patients with soft-tissue injuries arriving at the hospital accident and emergency department were instructed to take up to 6 capsules daily as necessary. Both preparations controlled pain adequately.

Sacchetti et al (64) examined the analgesic effects of the indoprofen using biliary colic as the model for assessing analgesic activity in man. The study was a double-blind comparison with the centrally acting opiate-type agent pentazocine and both were given intravenously. The pain-relieving effects of indoprofen at 400 mg and pentazocine at 30 mg were significantly higher than that of placebo, and whereas pentazocine caused drowsiness in 3 of 10 cases and slight confusion in 2 of 10 cases, indoprofen had no side effects. This study not only suggests that NSAIA can provide analgesia in conditions of severe pain but may have some obvious advantages over narcotic-type analgesics. In an earlier double-blind study Fuccella et al (65) found that indoprofen in single oral doses of 100 and 200 mg was effective as an analgesic in patients with primary and metastatic cancer and with neuralgia. Ventafridda et al (66) compared indoprofen (100 and 200 mg) with aspirin (600 and 1000 mg) in patients with pain due to malignant tumors. Both doses of indoprofen and 1000 mg of aspirin provided significant pain relief when compared to placebo. The effect of both drugs was maintained for at least 4 hr with 200 mg of indoprofen reaching the level of almost complete relief. Indoprofen was also examined in a double-blind placebo-controlled trial in women with pain due to episiotomy (67). A single dose of 100 mg produced significantly more analgesia than placebo and was devoid of any side effects.

Aromaa & Asp compared the analgesic effects of naproxen, indomethacin, and aspirin in pain after varicose vein surgery (68). In their opinion the soft tissue trauma associated with radical varicose vein surgery could best be treated by an agent with both analgesic and anti-inflammatory effect, and they had routinely used indomethacin (69). A total of 120 female patients

participated in the double-blind study and were randomly assigned to either naproxen 500 mg or 750 mg, indomethacin 75 mg, or aspirin 1500 mg in daily oral doses taken for six days postoperatively. In the combined naproxen groups, 98% of the patients reported adequate analgesia. The 750 mg dose of naproxen was equal to 75 mg indomethacin and both were clearly superior to 1500 mg of aspirin.

When pain is secondary to prostaglandin-induced smooth muscle contractions, NSAIA may be superior to centrally acting analgesics in that the cause of pain is reduced or removed.

TREATMENT OF FEVER

The antipyretic effect of aspirin and other NSAIA is widely known, and the use of aspirin for fever associated with colds and influenza is widespread. Prostaglandin E_1 is a potent pyretic agent (13), and NSAIA appear to act as antipyretics by reducing the production of prostaglandins (13, 70). None of the newer NSAIA are approved by the FDA for the treatment of fever but there are numerous studies demonstrating that effect in man. Simila and associates (71) reported that mefenamic acid reduced fever in children at 3–5 mg/kg comparable to aspirin (10 mg/kg) and paracetamol (10 mg/kg). Gruber and associates (72–74) found that single oral doses of 400 mg of fenoprofen produced a significant decrease in fever in patients with influenza and various medical-surgical diseases and 400 mg every 6 hr suppressed the febrile state of patients with chronic disease. Marcolongo reviewed 10 years of experience with the use of indomethacin in febrile states (75).

DERMAL INFLAMMATION, PROSTAGLANDINS, AND TREATMENT WITH NSAIA

Histamine, a mediator of inflammation and pruritus, is released from mast cells. The resulting pruritus from histamine is potentiated by prostaglandins (76). NSAIA not only reduced the available prostaglandins, but Lewis & Whittle (77) found that they also inhibit the release of histamine from rat peritoneal mast cells suggesting that two of the mediators of inflammation and pruritus will be reduced by NSAIA.

Williams (78) demonstrated that PGE_2, unlike histamine, did not cause a direct increase in vascular permeability in rabbit skin but acted as a vasodilator. PGE_2 in combination with histamine, as is likely to occur in dermal inflammatory lesions, potentiated the plasma exudation produced by histamine. Their results supported the proposal that NSAIA suppress dermal inflammatory swelling by inhibiting vasodilatation.

Concentrations of prostaglandins and their metabolites are increased in exudate from human skin irradiated with "sunburn" (290–320 nm) ultraviolet in vivo (79), suggesting that these vasoactive substances mediate sunburn erythema. Black et al (80) confirmed that irradiation of human skin with ultraviolet B (290–320 nm) significantly increased arachidonic acid, PGE_2, and $PGF_{2\alpha}$ in inflammatory exudate and found that both topical and oral indomethacin reduced the PG levels but only partially suppressed the resulting UV-induced erythema. Kaidbey & Kurban (81) also found that topical indomethacin suppressed sunburn erythema in human skin and was more effective than a topical corticosteroid. Sunburn damage to epidermal cells was not altered by these drugs. Synyder & Eaglestein (82) demonstrated that a single application of a 2.5% solution of indomethacin will decrease the redness, warmth, and tenderness of sunburned human skin for 24 hr or longer and was more effective than a corticosteroid cream.

In oxazolone-sensitized Swiss Webster mice, Lowe et al (83) demonstrated that topical application of indomethacin and triamcinolone acetonide reduced the erythema and ear weight gain from inflammation induced by experimental contact allergic eczema. The inflammation was also reduced by a phenyl phosphonate derivative, N0164, recently shown to exhibit in vitro and in vivo antagonism to the actions of PGE_2 and $PGF_{2\alpha}$.

Bufexamac is a NSAIA available as a topical cream for the treatment of various dermatological conditions. A double-blind comparison of the effect of bufexamac, β-methasone, and fluocinolone creams on eczema, contact dermatitis, and allergic dermatitis revealed that after 4 weeks of therapy bufexamac yielded the same degree of proportional improvement as β-methasone and only slightly less than flucinolone (84). All three preparations were well tolerated. The therapeutic efficacy of bufexamac in inflammatory dermatoses was reviewed by Brogden et al (85) and as a 5% cream it was indistinguishable from that of commonly used topical fluorinated corticosteroids in eczema and various other inflammatory dermatoses. More recently, Christiansen et al (86) in a multicenter trial was unable to confirm the efficacy of bufexamac as compared to triamcinolone acetonide and hydrocortisone.

Topical NSAIA, which are comparable in effectiveness to corticosteroids, would have wide application if the problems or hazards of skin atrophy, and promotion of viral, bacterial, and mycotic infections associated with long-term topical use of steroids (87–89) could be avoided.

TREATMENT OF PREMATURE INFANTS WITH PATENT DUCTUS ARTERIOSUS

The management of premature infants with patent ductus arteriosus (PDA) was recently reviewed by Merritt et al (90) with the major finding that

inhibition of prostaglandin synthesis by a single intravenous dose of 0.01 mg/kg of indomethacin caused significant constriction of the PDA. This pharmacological approach to constriction and closure of the PDA had been previously reported by Friedman et al (91) and Heymann et al (92) and provided a new development in the use of NSAIA.

Other Possible Clinical Uses

Shen & Winter (8) in their extensive review of the biological studies on indomethacin cite studies that indicate a number of possible therapeutic applications for NSAIA including treatment of ocular inflammation, acute and chronic glomerulonephritis, pericardial effusion, pleurisy, hypercalcemia, peridontal disease, and sunburn. The treatment of Bartter's syndrome with prostaglandin synthetase inhibitors (NSAIA) has been quite successful (93).

ADVERSE EFFECTS OF NSAIA

Aspirin, phenylbutazone, and indocin are known to cause some degree of gastrointestinal and renal toxicity. These two effects are shared by most if not all NSAIA. The relative differences in margin of safety between the many NSAIA can only come from careful observation of the efficacy versus adverse effects in man. There is a growing opinion that this difference is very much dependent on individual patient differences resulting in populations that respond more favorably to one agent than to another (1).

In general, NSAIA share the same potential side effects, with gastrointestinal problems and skin rash being the most common. However, there are occasional reports of more serious problems such as aplastic anemia (94, 95), hepatoxicity (96, 97), acute anaphylactic reactions (98), sialadenitis (99), edema (100), and goiter (101). Considering the widespread use of these agents, however, the benefit-to-risk ratio continues to be better than that of the steroids, immunosuppressants, and penicillamine. In addition, cross-sensitivity with aspirin, producing acute asthmatic attacks, has been reported when patients sensitive to aspirin have taken another NSAIA (102).

Gastrointestinal Effects

Arrigoni-Martelli (7) reviewed the toxic effects of NSAIA on the gastrointestinal (GI) tract, emphasizing that GI complaints were not only the most commonly reported side effect but toxicity related to the GI tract was the most common reason for rejecting new NSAIA from further clinical consideration. The possible causes of gastric damage by NSAIA include denaturation or sloughing of the surface mucosal cells, changes in permeability of the gastric mucosa, reduction in acid output or an increase in production

of histamine or pentagastrin (7). Shriver and associates (103, 104) developed profiles of gastrointestinal toxicity of several new NSAIA in rats. These studies emphasized that these agents differ somewhat in the site and degree of gastrointestinal damage and that both effects could be dependent on the dosage schedule.

The most common method for assessing relative GI effects of NSAIA in man is to measure GI blood loss as evidenced by the amount of radioactive labeled red blood cells in stool samples (105); however, gastroscopic methods recently have been employed (106). In the 1978 meeting of the American Rheumatism Association, Lang and associates reported on the gastroscopic evaluation of the effects of ibuprofen, indomethacin, naproxen, and tolmetin on the gastric mucosa of normal volunteers. Gastroscopic photographs confirmed that severe gastric mucosal hemorrhagic and ulcerative changes could occur in subjects using antirheumatic doses of NSAIA. This method provided an excellent tool for defining the extent and degree of damage. The use of cimetidine has been demonstrated to reduce aspirin-induced gastrointestinal ulcerations and bleeding (107). The concomitant use of cimetidine may also expand the usefulness of other NSAIA.

Renal Effects

One of the most common toxicities reported in animals after prolonged administration of NSAIA is that of renal papillary necrosis (7). Although the mechanism of this action is not clear, prostaglandins act as intrarenal hormones regulating renal blood flow (108); therefore, alterations in PG synthesis may well modify renal function to the extent of pathology. In man renal function is not normally altered during antiarthritic therapy with NSAIA but instances of renal abnormalities have been reported (109, 110).

Fetal Effects

The desired action of NSAIA in constricting the PDA of premature infants could well cause detrimental effects to a fetus. Levin et al (111) found morphological alterations in the pulmonary vascular bed of two infants, one exposed to salicylates and the other to indomethacin in utero. They as well as others (112) postulate that NSAIA may alter the fetal pulmonary vasculature by causing constriction of the ductus arteriosus or directly stimulating pulmonary arterial smooth muscle. Csaba et al (113) stated that of 10 mothers treated with indomethacin for preventing premature delivery, 5 babies were born having symptoms of disturbed cardiopulmonary adaptation and two died on the first day of life. In this same regard Turner & Collins (114) reported that babies of 144 mothers who took salicylates regularly in pregnancy had reduced birth weight and that perinatal mortality was increased. The observations of Turner and Collins could well relate

to the effect of NSAIA on uterine motility and function (115). Maternal treatment with NSAIA especially near term could be a potential hazard.

CONCLUSIONS

In recent years the number of nonsteroidal anti-inflammatory agents available for therapy has significantly increased. In the United States they are approved for the treatment of arthritis, but like aspirin they have found use in the treatment of pain and fever. The approval of more NSAIA is pending but more importantly the extension of their use to condition of gout, thrombosis, dermal inflammation, fever, and other inflammatory conditions will be likely. NSAIA as a class share many of the adverse effects of aspirin, phenylbutazone, and indocin but the margin of safety with some of these new agents will hopefully be greater.

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