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## MEDICAL INTELLIGENCE



### DRUG THERAPY

JAN KOCH-WESER, M.D., *Editor*

#### Nonsteroidal Antiinflammatory Drugs

(First of Two Parts)

LEE S. SIMON, M.D., AND JOHN A. MILLS, M.D.

THE number of nonsteroidal antiinflammatory drugs (NSAID's) available for use in the United States has tripled since they were last reviewed here in 1974.<sup>1</sup> Although there are several uses for these drugs, the rheumatic diseases remain the most common inflammatory conditions for which they are employed. More than fifty antirheumatic compounds are currently under investigation.<sup>2</sup>

The damage to joints that occurs in the rheumatic diseases is related to the intensity of the inflammatory process. Thus, reduction of inflammation during periods of disease activity should retard the rate at which tissues such as articular cartilage are damaged. Unfortunately, due to the unpredictable course of dis-

ease and the variable response of any given patient to a particular therapy, it has been difficult to prove that proposition. The NSAID's currently in use modify or diminish but do not arrest the inflammatory response. If the disease remains active, damage to joints is likely to continue, though possibly at a slower rate. The exact mode of action of NSAID's remains unknown; however, much information has accumulated in the past few years that helps to explain their anti-inflammatory, antipyretic, and analgesic effects as well as their toxicity.<sup>3,4</sup>

Recent reviews have described the complex response that characterizes inflammation induced by a wide variety of stimuli.<sup>5,6</sup> Most antiinflammatory drugs appear to act on mechanisms that are common to inflammation of many different causes.<sup>3,4</sup> These mechanisms include chemotactic stimuli, phagocytosis, and the lysosomal release of enzymes, as well as activation of the clotting, fibrinolytic, kinin, and complement pathways. Their interactions are illustrated in Figure 1, which also shows some of the points at which NSAID's may act. The initial step shown in the diagram involves a number of different cells and cellular interactions that are still poorly delineated. Some of them may be important sites for the action of NSAID. In different tissues and kinds of inflammation, certain mechanisms may have more important roles than others.

With the discovery that aspirin and other NSAID's inhibit a step in the biosynthesis of prostaglandins, knowledge of the part that these mediators play is rapidly increasing. As shown in Figure 2, prostaglandins are products of several enzymatic reactions beginning with arachidonic acid, which is released from phospholipids through the action of a phospholipase. The released arachidonic acid is rapidly converted to several oxygenated products, one a cyclic

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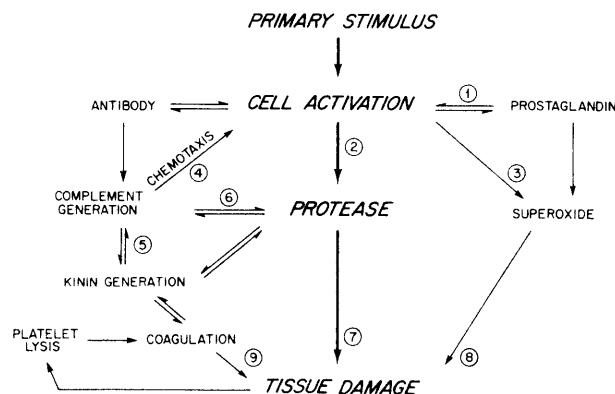


Figure 1. General Scheme of Mechanisms of Inflammation. The primary stimulus may be infection, immune-complex deposition, or trauma, for example. The numbers beside the pathways do not refer to a sequence of steps; rather, they are potential sites for the action of nonsteroidal antiinflammatory agents, and they indicate the following bibliographic references: one: 6-9; two: 8, 10, 11; three: 12; four: 13, 14; five: 15; six: 15, 16; seven: 6, 17, 18; eight: 12; and nine: 19, 20.

endoperoxide whose formation is catalyzed by the enzyme cyclooxygenase (prostaglandin synthetase). The end products of prostaglandin biosynthesis include the prostaglandins, prostacyclins, and thromboxanes. These substances have been shown to be important in platelet physiology<sup>20</sup> and to modulate the response of cells and tissues to many stimuli, including the bacterial products, cytokines, and tissue-fluid components generated in the course of the inflammatory response.<sup>3,6,21</sup> Ferreira and Vane postulate that prostaglandins sensitize blood vessels to the effects of mediators that increase permeability, such as bradykinin and histamine.<sup>3</sup> In addition, they seem to augment pain perception.<sup>3,4</sup>

Prostaglandins are also involved in the pyretic response of man and animals. After the injection of pyrogens, there is a rise in prostaglandin in the cere-

brospinal fluid that is prevented by pretreatment with aspirin.<sup>3</sup> It is of interest that acetaminophen, which is antipyretic but not antiinflammatory, blocks brain prostaglandin synthetase in vitro but not that of peripheral tissue such as dog spleen.<sup>3,22</sup>

In the generation of at least some of the endoperoxides by cyclooxygenase, the free radical, superoxide, is formed by the addition of an electron to free oxygen molecules (Fig. 2). The superoxide is converted in turn to the hydroxyl free radical. Both of these strong oxidizing agents appear to have a prominent role in the tissue damage that accompanies inflammation.<sup>12</sup> These free radicals are also byproducts of the respiratory activity of neutrophils and macrophages during phagocytosis, and of their response to chemotactic stimuli.<sup>12</sup> Studies by Simchowicz et al. have shown that superoxide generation is inhibited by a number of NSAID's at concentrations comparable to those achieved therapeutically.<sup>23</sup>

The inhibition of prostaglandin biosynthesis may only partly explain the therapeutic effects of NSAID's.<sup>2,24</sup> Other postulated mechanisms include interactions with the adenylate cyclase system. Indomethacin and some other NSAID's inhibit phosphodiesterase, thereby elevating the intracellular concentration of cyclic AMP.<sup>25</sup> Cyclic AMP has been shown to stabilize membranes, including lysosomal membranes in polymorphonuclear leukocytes, thus preventing the release of enzymes, which appear to play a major role in the inflammatory response. In addition, by decreasing lysosomal activity, cyclic AMP decreases superoxide generation by phagocytes.<sup>26</sup> Most of this work has been accomplished in vitro, and its applicability to natural inflammation is not clear.<sup>27</sup>

The fact that NSAID's are bound to serum proteins may help to explain their effectiveness. Since blood vessels in an inflamed area allow high-molecular-weight proteins to escape, NSAID's that are associated with them may reach greater concentrations in sites of inflammation than are achieved in normal extracellular fluid. Once there and released in the acidic inflammatory environment, free molecules penetrate the lipid membranes of cells. Graf and his co-workers have presented evidence that acidic but not basic derivatives of NSAID's localize in sites of inflammation after parenteral administration to laboratory animals.<sup>28</sup>

Until more is known regarding the response to various phlogistic stimuli and the ways in which such responses differ, antiinflammatory therapy will remain relatively nonspecific. Therefore, this review will discuss the NSAID's primarily with regard to their special properties, actions, and toxicities.

### SALICYLATES

Aspirin remains the most commonly used antiinflammatory drug. Because of its efficacy, low toxicity, and low cost, it is the standard against which all other NSAID's are measured. Its value in the treatment of rheumatoid arthritis was well established by the

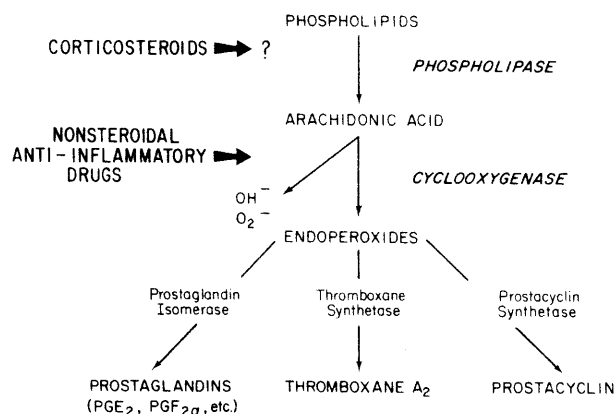


Figure 2. Scheme for Prostaglandin Biosynthesis. The enzyme cyclooxygenase catalyzes the reaction transforming arachidonic acid to the endoperoxide compounds. The formulas  $\text{OH}^-$  and  $\text{O}_2^-$  represent superoxide radicals, which are byproducts of this reaction.

studies of Fremont-Smith and Bayles<sup>29</sup> and those of Boardman and Dudley-Hart.<sup>30</sup> There is less evidence that aspirin has an effect on the extraarticular features of rheumatic disease such as carditis, myositis, or serositis. In systemic lupus erythematosus, aspirin may ameliorate arthritis and serositis, but the vasculitic complications caused by immune-complex deposition are probably not affected.

Aspirin inhibits the biosynthesis of prostaglandins by means of an irreversible acetylation and consequent inactivation of cyclooxygenase, in contrast to the action of the newer NSAID's, which are reversible inhibitors.<sup>31,32</sup> Although most cells can synthesize new cyclooxygenase, platelets cannot; thus, the acetylation of their microsomal enzyme lasts for the life of the platelet. The ability of aspirin to acetylate proteins may be one reason for its superiority as an anti-inflammatory agent as compared with other salicylate derivatives. However, acetylsalicylic acid, once absorbed, is rapidly hydrolyzed by serum and hepatic esterases.<sup>33</sup> It is not known how much unhydrolyzed aspirin penetrates sites of inflammation and could thus acetylate enzymes or other proteins involved in the inflammatory response.<sup>34</sup>

It is probable that aspirin, as well as the other NSAID's, inhibits inflammation by other pathways in addition to interrupting prostaglandin biosynthesis.<sup>24</sup> For example, salicylate has been shown to act directly as a scavenger of hydroxyl radicals.<sup>35</sup>

The pharmacokinetics of salicylates have become clearer since the previous review of NSAID's.<sup>1</sup> The metabolic pathways follow first-order and zero-order kinetics.<sup>36,37</sup> At low doses, increments result in proportional increases in serum levels.<sup>38</sup> This response occurs because at low doses most of the drug is converted to salicylurate through conjugation of salicylate with glycine and is subsequently excreted in the urine. Eighty per cent of a dose is metabolized by this major saturable pathway. Therefore, when this pathway is saturated at higher doses, a small increase in dose will result in a relatively large increase in the serum level.

Recent reviews have summarized the differences in metabolism of salicylates between healthy controls and patients with connective-tissue diseases such as rheumatoid arthritis.<sup>37</sup> The volume of distribution of drug appears to be smaller in patients with disease than in normal subjects. This may be due to long-term drug ingestion and variations in total binding of drug in body tissues.

Aspirin toxicity takes many forms. All NSAID's, including acetylsalicylic acid, may induce hypersensitivity reactions, which are of two general types. Both may be related to the inhibition of prostaglandin synthesis.<sup>39</sup> They are the syndrome of asthmatic attacks in patients with vasomotor rhinitis, nasal polyposis, and bronchial asthma, and the syndrome of urticaria and angioedema. The authors of a recent review suggest that all inhibitors of prostaglandin biosynthesis induce these reactions in the appropriate host.<sup>39</sup> It is of interest that sodium salicylate, a weak inhibitor of

prostaglandin biosynthesis, does not precipitate hypersensitivity reactions of this type.<sup>40</sup> Prostaglandin  $E_2$  is a bronchodilator. It stabilizes histamine stores in mastocytes and thus helps to inhibit the inflammatory response.<sup>39</sup> In a susceptible person, the result of the inhibition of prostaglandin biosynthesis may be spontaneous degranulation of mastocytes with release of histamine in the respiratory tract and skin, leading to bronchoconstriction and asthma as well as urticaria.

Direct toxic reactions are of several types. Symptoms of the ear in the form of tinnitus or deafness are usually an early warning of toxicity. Miller reported the Boston Collaborative Drug Surveillance Program's experience with aspirin-induced deafness.<sup>41</sup> Twenty-eight per cent of patients who took coated aspirin and 8 per cent who received plain aspirin tablets had a loss of hearing while taking the drug. All regained their hearing when the dosage was reduced or was discontinued. Because toxic manifestations are related to levels of free drug, which vary inversely with albumin levels, the administration of aspirin to patients with low albumin levels may result in manifestations of toxicity at lower total serum concentrations.

Aspirin, as well as other NSAID's, causes a transient decrease in renal function.<sup>42,43</sup> This effect may occur more often in patients with underlying renal disease.<sup>44,45</sup> The postulated mechanism is the inhibition of the renal synthesis of prostaglandin, which may be important in the autoregulation of renal blood flow.<sup>46,47</sup> Aspirin can also block the diuretic effect of spironolactone by inhibiting its binding to the tubular-cell receptor.<sup>48</sup>

A voluminous literature has accumulated to explain gastrointestinal intolerance to aspirin and the other NSAID's.<sup>49,50</sup> Prostaglandins appear to have important effects on gastric physiology. They can inhibit gastric acid secretion<sup>51</sup> and may have an independent cytoprotective role.<sup>52,53</sup> The administration of an analogue of prostaglandin  $E_2$  orally with aspirin has been shown to reduce the severity of gastric ulceration.<sup>53</sup> This protective effect is not entirely related to the inhibition of acid secretion, because it is also found when additional acid is given at the same time.<sup>54</sup> Kauffman and Grossman postulate that the cytoprotective role may be mediated by prostaglandin stimulation of the adenylate cyclase system, which inhibits gastric acid secretion.<sup>55</sup>

Blood flow in the gastric mucosa is reduced by inhibitors of prostaglandin synthesis, and damage may occur in relatively ischemic areas where the dissipation of aspirin is slowed.<sup>50,56</sup> Although the natural role of prostaglandins in gastric physiology is still the subject of speculation, their inhibition by NSAID's may be a cause of gastric irritation. It is important to note that the parenteral administration of salicylate may also cause gastric erosions.<sup>57</sup> Nonacetylated products, such as choline salicylate, choline magnesium salicylate, and condensation products of acetyl-

salicylic acid and acetaminophen or two salicylate molecules (salsalate), produce less gastric irritation but are considerably more expensive and no more effective than buffered aspirin.<sup>58,59</sup> Choline magnesium trisalicylate taken twice daily provides adequate anti-inflammatory serum levels and is without aspirin's effect on platelet cyclooxygenase.<sup>60</sup> It appears to cause less occult gastrointestinal blood loss than aspirin. The frequency of dosage may enhance compliance by patients; however, individual variations in absorption may demand closer follow-up of serum salicylate levels. Mielants et al.<sup>57</sup> compared the amount of gastrointestinal blood loss in patients with osteoarthritis given buffered aspirin, parenteral aspirin, or coated aspirin. They found that of these, buffered aspirin taken by mouth caused the greatest gastrointestinal blood loss. However, the other two types of salicylate caused greater gastrointestinal blood loss than during control periods when those patients were not receiving salicylate.

The use of cimetidine with aspirin has been shown to reduce the incidence of gastric erosions in animals and man.<sup>55,61</sup> Cimetidine does not affect serum salicylate levels. However, some as yet unanticipated toxicity might ensue from cimetidine during prolonged therapy, which is required by patients with rheumatoid arthritis. Furthermore, the additional medication may increase problems with compliance. Aspirin and the other NSAID's have relatively little effect on the lower gastrointestinal tract in normal human beings. They may be helpful in the control of diarrhea induced by radiation.<sup>62</sup>

Aspirin is clearly hepatotoxic in certain situations. Early reports suggested that patients treated with aspirin for rheumatic fever, juvenile rheumatoid arthritis,<sup>63</sup> systemic lupus erythematosus,<sup>64</sup> or Reiter's syndrome<sup>65</sup> all had a higher incidence of abnormal results of liver-function tests than did patients with these diseases not treated with aspirin. Later, case reports described two patients without inflammatory diseases in whom liver-enzyme abnormalities developed during salicylate treatment.<sup>66</sup> Initially, the dose of aspirin was thought to be important. However, O'Gorman and Koff<sup>67</sup> described hepatotoxicity in patients whose serum levels of salicylate were less than 25 mg per 100 ml. Furst et al. reported in a letter that of 28 normal volunteers given intravenous sodium salicylate, 40 mg per kilogram of body weight, and later, in a second study, buffered aspirin by mouth, none had liver-enzyme abnormalities.<sup>68</sup> Seaman and Plotz<sup>64</sup> followed 20 patients with rheumatoid arthritis, 16 with systemic lupus erythematosus, and three normal persons, all given aspirin to produce morning salicylate levels between 25 to 30 mg per 100 ml. In four patients with rheumatoid arthritis, seven with systemic lupus, and one normal volunteer of the total of 49 patients, liver-function tests gave abnormal results. It appeared that the seven patients with systemic lupus had a more rapid onset of enzyme elevation. Biopsies showed mild toxic hepatitis. In all

cases, either with reduction or cessation of the dose, the enzymes returned to normal. Biopsies when repeated revealed more normal histology.

In children with rheumatoid arthritis who are given antiinflammatory doses of salicylate, abnormal results of liver-function tests may occur with an incidence that approaches 40 per cent.<sup>69</sup> There are several reports of acute hepatic necrosis in children who were receiving usual therapeutic doses of aspirin. This event is usually associated with severe encephalopathy and mimics Reye's syndrome.<sup>70</sup> In many cases, but not all, serum salicylate levels were in the toxic range. In some instances, an additional cause of hepatic necrosis may have been involved. Salicylate remains the mainstay of therapy for juvenile rheumatoid arthritis, but it must be given under close observation.

When administered during pregnancy salicylates may reach substantial levels in the fetus. Birth defects have not been proved to occur more commonly in women who used aspirin habitually during pregnancy as compared with occasional users.<sup>71,72</sup> However, babies born to habitual users were smaller. No substantial experience has been reported regarding the use during pregnancy of full therapeutic doses of aspirin for rheumatoid arthritis. There is experimental evidence in monkeys that high doses of aspirin may be teratogenic.<sup>73</sup> Aspirin taken at term may delay the onset of labor for three to 10 days,<sup>71</sup> and it has been associated with increased bruising of the newborn child, particularly when instrumentation was necessary. The administration of aspirin or indomethacin at term to delay the onset of labor has been reported to cause serious pulmonary vascular disease in the newborn infant.<sup>74</sup>

In summary, although salicylates remain among the most effective of the NSAID's, overt toxicity or poor tolerance may prevent their use by a substantial number of patients. These problems have stimulated an intense effort to develop other antiinflammatory agents.

#### INDOMETHACIN

Although phenylbutazone is one of the more effective NSAID's,<sup>75,76</sup> its potential hematologic toxicity has limited its use.<sup>77</sup> As a result, indomethacin (Fig. 3) has gradually replaced phenylbutazone in the treatment of acute musculoskeletal disorders such as tendinitis and bursitis, trauma, and other inflammatory arthropathies such as ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, and the arthritis associated with enteropathic diseases.<sup>78</sup>

In addition to inhibiting prostaglandin biosynthesis, indomethacin has been shown to exert antiinflammatory effects in other ways. In rats, indomethacin interferes with the migration of leukocytes into inflammatory sites.<sup>3,79</sup> In vitro, it is a potent inhibitor of phosphodiesterase and thus increases intracellular concentrations of cyclic AMP.<sup>25</sup>

Minkes et al.<sup>80</sup> have postulated that cyclic AMP

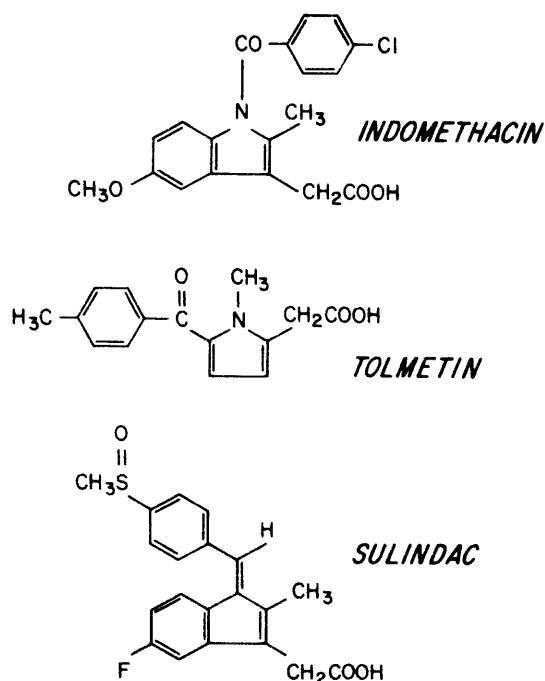


Figure 3. The Indoleacetic Acids.

Tolmetin, not an indoleacetic acid, nevertheless resembles these compounds.

inhibits the phospholipase-mediated conversion of platelet phospholipid to arachidonate, thus suppressing the formation of prostaglandins, prostacyclins, and thromboxanes. Cyclic AMP has also been shown to stabilize lysosomal membranes in polymorphonuclear leukocytes and macrophages.<sup>27</sup> Both of these actions should decrease the generation of superoxide and hydroxyl radicals.

Indomethacin is rapidly absorbed from the upper gastrointestinal tract and may be assimilated even more quickly when given as a rectal suppository.<sup>81</sup> It is highly bound to albumin. Metabolism involves demethylation and deacetylation in the liver with subsequent excretion of inactive metabolites and unchanged drug in the bile and urine.<sup>82</sup> Because its toxicity may be increased, indomethacin should be given cautiously to patients with liver disease. Probenecid may inhibit the renal excretion of unchanged indomethacin, thereby increasing serum levels.<sup>83</sup>

Indomethacin seems to have a more prolonged activity than its serum half-life of two hours would indicate.<sup>76</sup> This effect may be partly explained by the presence of two "pools" of the drug. Degradation and excretion take place from the plasma pool, and tissue stores return indomethacin to the plasma as the circulating drug is metabolized.<sup>84</sup>

Despite initial reports to the contrary,<sup>85</sup> indomethacin appears to be effective in patients who have rheumatoid arthritis.<sup>86</sup> However, the doses that produce benefits equal to aspirin's in rheumatoid arthritis are large and frequently produce comparable side effects. To relieve morning stiffness in patients with rheuma-

toid arthritis, Huskisson recommends the use of indomethacin at night together with other daytime therapy.<sup>59</sup> This use of indomethacin with salicylate appears to be successful, but conflicting data indicate that concomitant aspirin therapy may interfere with the absorption or antiinflammatory activity of indomethacin.<sup>87</sup> Indomethacin is equal to phenylbutazone and more effective than aspirin in patients who have ankylosing spondylitis.<sup>75</sup>

Indomethacin in doses of 100 to 200 mg per day for several days is the treatment of choice for acute gouty arthritis, particularly during the first 18 to 24 hours after the beginning of an attack.<sup>88</sup> In low doses, 25 mg twice daily, it can be used as prophylaxis against gout if colchicine is not tolerated.

The effect of indomethacin in primary osteoarthritis of the hip is remarkable and remains unexplained. Osteoarthritis in other joints does not appear to be as responsive, and other NSAID's do not provide as much benefit.<sup>89</sup> Although pain may be relieved over prolonged periods while the patient is taking indomethacin, the anatomic progression of the disease is not slowed.<sup>90</sup>

Indomethacin is useful in the control of fever in patients with lymphoma, the symptoms associated with postcardiomyotomy syndrome, and other non-specific inflammatory reactions.<sup>91</sup> Recently, indomethacin, as well as other NSAID's, has been used in experiments in vitro to inhibit mucosal prostaglandin biosynthesis, which may contribute to the pathogenesis of diarrhea in ulcerative colitis.<sup>92</sup>

Gastritis and gastric ulceration are the major complications of indomethacin therapy.<sup>93</sup> Boardman and Dudley-Hart found that in 10 per cent of 228 patients given indomethacin, indigestion, nausea, or epigastric pain developed within the first few weeks after the start of therapy.<sup>94</sup> Several cases of toxic hepatitis associated with indomethacin administration have been reported.<sup>59</sup>

Headache occurs in 50 per cent of patients when the total dose exceeds 100 mg per day. Other central-nervous-system manifestations are dizziness, confusion, depression, drowsiness, hallucinations, depersonalization reactions, seizures, and syncope.<sup>94</sup> In susceptible persons these symptoms may occur after ingestion of a single 25-mg capsule. Corneal deposits have been reported.<sup>95</sup>

Indomethacin has a number of effects on renal function. It causes a transient rise in blood urea nitrogen and creatinine, possibly due to inhibition of prostaglandin synthesis in the kidney, but in patients with diminished glomerular filtration from congestive heart failure, severe azotemia may result.<sup>45</sup> Hyporeninemia and consequent hypoaldosteronism may develop in patients treated with indomethacin, and the renin response to furosemide administration is inhibited.<sup>96,97</sup> As a result, indomethacin has been used, with some success, to treat Bartter's syndrome.<sup>98</sup> Unfortunately, this use has been complicated in some patients by the occurrence of pseudotumor cerebri.<sup>99</sup> The mechanism

responsible for the condition is not known. Lee et al. reported a case of severe hypertension in a patient who took indomethacin concomitantly with phenylpropanolamine.<sup>100</sup>

The use of indomethacin in children was curtailed in 1967 on the basis of a report that it might impair responses to infections, with serious consequences.<sup>101</sup> Such findings have not been reported since. Indomethacin has assumed a prominent place in the therapy of various inflammatory conditions and osteoarthritis.

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