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Efficacy and Tolerability of Nimesulide in Asthmatic Patients Intolerant to Aspirin

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Summary

Inflammation of the airways accompanied by eosinophil infiltration appears to play a fundamental role in the pathogenesis of bronchial asthma. Therefore, anti-inflammatory agents (at present corticosteroids, cromoglycate and nedocromil) are the first-line treatment for this condition. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin (acetylsalicylic acid) and indomethacin, however, have never been used in this setting, mainly for fear of adverse effects (e.g. severe obstructive reactions); these can occur, in a consistent number of patients as a consequence (according to the most widely accepted theory) of inhibition of prostaglandin synthesis. In a double-blind crossover placebo-controlled study involving 20 aspirin-sensitive patients with asthma, we found that oral nimesulide 100mg was well tolerated both clinically and functionally (no significant changes in forced expiratory volume in 1 second and specific airway resistance after drug intake). In a more recent study, we observed a mild obstructive reaction (easily controlled with inhaled bronchodilators) after oral administration of nimesulide 400mg to 3 patients who had previously tolerated a 100mg dose. On the basis of clinical experience, nimesulide (unlike most other NSAIDs) in the recommended doses appears to be well tolerated in aspirin-sensitive asthmatic patients. Furthermore, this distinctive anti-inflammatory agent might provide a novel approach to the treatment of bronchial asthma.

Bronchial asthma is a chronic inflammatory disease of the airways in which proinflammatory cells and mediators of inflammation interact to induce bronchial hyperresponsiveness and bronchospasm. In view of the central pathogenic role of inflammation in asthma (Djukanovic et al. 1990; Laitinen et al. 1985), pharmacological intervention in this disease has principally involved the regular use of anti-inflammatory drugs. On the other hand, bronchodilators should only be used when needed to relieve symptoms.

The most effective anti-inflammatory drugs in

asthma are corticosteroids and, to a lesser extent, sodium cromoglycate and nedocromil. Several other anti-inflammatory agents, including troleandomycin, methotrexate, gold, hydroxychloroquine, dapson and cyclosporin, have been assessed, mainly as steroid-sparing agents; however, their efficacy has not been firmly established, although some are better tolerated than high dose oral corticosteroids (Szeffler 1992; Thomson et al. 1992; Van Bever & Stevens 1992).

Nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclo-oxygenase, such as aspirin (ace-

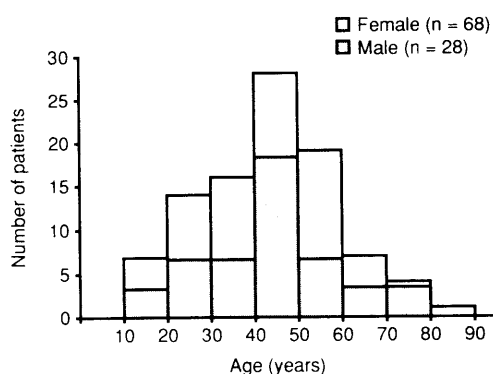


Fig. 1. Age and sex distribution of patients (n = 96) with respiratory intolerance to aspirin (acetylsalicylic acid).

tylsalicylic acid) or indomethacin, have never been seriously considered as a therapy for asthma for 2 principal reasons. First, in several acute and sub-acute studies, performed mainly with indomethacin, no (or only modest) protective effects have been observed against a variety of stimuli, including methacholine, histamine, leukotriene (LT) D₄, exercise, hyperventilation, ultrasonically nebulised water, hypertonic saline, adenosine and allergens (immediate and late reactions) [Bianco et al. 1991a,b]. The second, more important, reason is that aspirin and other NSAIDs can induce severe, sometimes life-threatening obstructive reactions in asthmatic patients (Bianco 1986; Samter & Beers 1968; Szczeklik 1986). This intolerance creates many clinical problems, especially since NSAIDs are used not only as anti-inflammatory agents, but also extensively as antipyretics and analgesics.

1. Aspirin-Intolerant Asthma

1.1 Prevalence and Distribution

The reported prevalence of aspirin intolerance among adult asthmatic patients ranges from < 5% to > 30%. Most realistically, however, the prevalence rate is probably $\approx$ 10% (Bianco 1986). The age and sex distributions of aspirin intolerance among 96 consecutive patients reporting to our clinic are detailed in figure 1. Aspirin-intolerant asthma appears to be an acquired disorder that usually manifests after the age of 10 years, increas-

ing in frequency until 40 to 50 years and then steadily declining with further aging. Aspirin-intolerant asthma is more prevalent in women than in men. Furthermore, in patients affected by this condition, skin tests to common allergens are frequently negative, while the frequency of nasal polyposis (when carefully checked by a rhinologist) is rather high ($\approx$ 60%).

1.2 Theories of Pathogenesis

Although the mechanism of aspirin sensitivity still remains elusive, several theories have been proposed to explain its aetiology. Many such theories (e.g. those implicating antigen-antibody reactions, acetylation of body proteins, bradykinin receptor stimulation, complement activation) are of only historical value. At present, the most plausible theory appears to be that implicating cyclooxygenase. According to this hypothesis, inhibition of prostaglandin synthesis by aspirin and aspirin-like drugs triggers a series of biochemical reactions leading to an asthmatic attack (Szczeklik 1986). A central event in this process is considered to be an increased synthesis of LTB₄, LTC₄, and LTE₄, secondary to the removal of the inhibitory control of prostaglandin (PG)E₂/PGI₂ and/or to the overproduction of 12-hydroperoxyeicosatetraenoic acid (HPETE) [Szczeklik 1990].

Because aspirin sensitivity seems to be an acquired disorder, it may arise as a consequence of a latent chronic viral infection and the resultant production of specific cytotoxic lymphocytes (Szczeklik 1990). The activity of these elements is usually suppressed by PGE₂ (possibly produced by lung macrophages); when suppression is removed by NSAIDs, lymphocytes attack and kill virus-infected cells, causing the release of toxic oxygen species, lysosomal enzymes and various inflammatory mediators that provoke asthmatic attacks.

Platelets have also been implicated in the pathogenesis of aspirin-intolerant asthma, since platelets from aspirin-sensitive patients generate cytotoxic molecules when exposed to aspirin and other NSAIDs, unlike those from normal donors and aspirin-tolerant asthmatic patients (Ameisen

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et al. 1985). This finding, however, has not been confirmed by other investigators (Szczeklik 1990).

In conclusion, although the precise mechanism of aspirin-intolerant asthma remains elusive, several observations implicate arachidonic acid metabolites in its aetiology. These observations are summarised as follows:

- 1) The asthmagenic activity of NSAIDs is directly related to their ability to inhibit cyclo-oxygenase activity; analgesics not affecting cyclo-oxygenase do not induce bronchoconstriction in aspirin-intolerant asthmatic patients (Szczeklik 1990).
- 2) The baseline concentrations of LTE₄ in the urine of aspirin-sensitive patients are significantly higher than those of nonsensitive patients. This difference becomes more pronounced after aspirin challenge, although urinary concentrations of thromboxane B₂ are unaffected (Christie et al. 1991b; Kumlin et al. 1992; Smith et al. 1992).
- 3) Aspirin-intolerant asthmatic patients are highly sensitive to inhaled LTE₄ when compared with aspirin-tolerant patients; this difference has not been observed with LTC₄ (Arm et al. 1989; Vaghi et al. 1985).
- 4) Patients desensitised to aspirin by the administration of incremental doses of this drug no longer react to other NSAIDs (Bianco et al. 1977, 1981).
- 5) Sulfidopeptide-leukotriene antagonists prevent aspirin-induced bronchoconstriction (Christie et al. 1991a; Dahlen et al. 1992).
- 6) Inhibitors of thromboxane A₂ synthesis are well tolerated by aspirin-sensitive patients and partially reduce aspirin-induced bronchoconstriction (Rabuschi et al. 1989; Szczeklik et al. 1987).
- 7) Local application of aspirin induces a significant increase in the concentration of peptide-leukotrienes in nasal secretions, with a concomitant decrease in PGE₂ and PGF_{2α} and no change in PGD₂ (Ferreri et al. 1988; Ortolani et al. 1987; Picado et al. 1992).

1.3 Diagnostic Procedures

In most cases, the patient's clinical history alone is sufficient to establish the diagnosis of aspirin-intolerant asthma. However, if any doubt exists,

this may be resolved by challenge with oral aspirin or inhaled lysine-aspirin (Bianco et al. 1977, 1981). The latter method is preferable, since it is safer and less time-consuming; in particular, reactions are confined to the bronchial tree and can easily be controlled with inhaled β_2 -stimulants. Skin challenge tests are diagnostically useless, and the *in vitro* chemiluminescence test with platelets, recently proposed by Ameisen et al. (1985), does not appear sufficiently reliable.

1.4 NSAIDs that Cross-React with Aspirin

A list of NSAIDs that can cross-react with aspirin and induce respiratory symptoms in patients with aspirin-intolerant asthma is reported in table I. The listed compounds are all cyclo-oxygenase inhibitors and there is direct but tentative correlation between their ability to inhibit cyclo-oxygenase and their ability to induce asthma. In general, acetylated salicylates, indole- and indene-acetic acids, and arylpropionic acids appear to possess the greatest capacity for inducing asthma. Fenamates, oxicams and pyrazolone derivatives (pyrazolones, pyrazolidinediones) are better tolerated. For a given spe-

Table I. Nonsteroidal anti-inflammatory drugs (NSAIDs) that cross-react with aspirin (acetylsalicylic acid)

Salicylates	L-aspirin, diflunisal, benorilate, salsalate
Indole- and indene-acetic acids	Indomethacin, oxametacin, proglumetacin, glucametacin, sulindac, zomepirac
Arylacetic acids	Diclofenac, fenclofenac, fentiazac
Arylpropionic acids	Ibuprofen, ketoprofen, fehoprofen, naproxen, flurbiprofen, indoprofen, tiaprofenic acid, carprofen, fenbufen
Fenamates	Mefenamic, flufenamic, cyclofenamic, meclofenamic and niflumic acids
Pyrazolone derivatives	Propyphenazone, aminophenazone, dipyrone
Pyrazolidinediones	Phenylbutazone, oxyphenbutazone, azapropazone, bumadizone, pyrazanone, feprazone
Oxicams	Piroxicam, isoxicam, tenoxicam

cific sensitivity to NSAIDs, the greater the non-specific bronchial reactivity (as is seen in poorly controlled asthma), the stronger the asthmatic response to NSAIDs.

Nonacetylated salicylates such as sodium salicylate, salicylamide and choline magnesium trisalicylate are well tolerated. Other well tolerated compounds include dextropropoxyphene, benzydamine, chloroquine and imidazole-hydroxybenzoate.

Fenbufen can induce late obstructive reactions in aspirin-sensitive patients. These usually begin 3 to 4 hours after drug intake and last for several hours (Bianco 1986). Interestingly, fenbufen (3-4 biphenylcarbonyl propionic acid) is a prodrug that is devoid of anticyclo-oxygenase activity, although such activity is possessed by its principal active metabolite, *p*-biphenylacetic acid. It is likely that the reaction starts when a sufficient concentration of this active metabolite is reached in the bronchi. The identity of the mechanism underlying the 2 types of reactions is further confirmed by the demonstration that patients desensitised to fenbufen no longer react to aspirin and vice versa (our unpublished observations).

Paracetamol is relatively safe, causing asthmatic reactions in only about 5% of aspirin-sensitive patients.

1.5 Nimesulide

Another anilide derivative, nimesulide (4'-nitro-2-phenoxy methane sulfonanilide), is even safer than paracetamol (4'-hydroxy acetanilide). *In vitro*, nimesulide exhibits a rather weak anticyclo-oxygenase activity, but, because of its remarkable antioxidant, antianaphylactic and antihistaminic properties (Berti et al. 1991; Magni 1991), this compound can produce potent anti-inflammatory effects.

In a double-blind crossover study that recruited 20 adult asthmatic patients with respiratory intolerance to NSAIDs, the tolerability of nimesulide was compared with that of placebo. A single dose of nimesulide 100mg was well tolerated by all recipients and no effects on ventilatory function were

observed that could be attributed to the anti-inflammatory agent (fig. 2) [Bianco et al. 1991a].

In a more recent study, we observed a mild (easily controlled with inhaled bronchodilators) asthmatic reaction in 3 aspirin-sensitive patients after oral administration of nimesulide 400mg (4 times greater than the recommended dose). The results of the various challenge tests in 1 of these patients are reported in figure 3. It is worthy of note that this female with intrinsic asthma clearly reacted more strongly (in terms of therapeutically equipotent doses) to paracetamol and dipyrone than to nimesulide.

In conclusion, even if the tolerability of nimesulide in patients with respiratory intolerance to NSAIDs is not absolute, this drug may be considered the safest among the most effective NSAIDs.

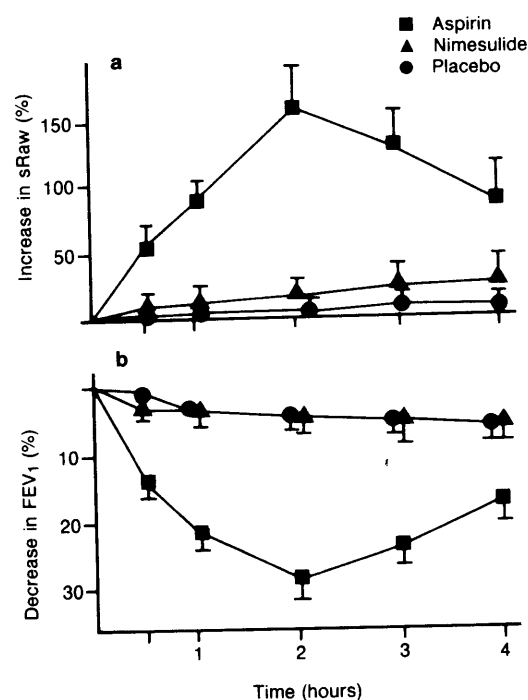
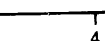
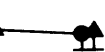


Fig. 2. Mean ($\pm$ SEM) changes in specific airway resistance (sRaw) [a] and forced expiratory volume in 1 second (FEV₁) [b] after challenge with placebo (saline) or aspirin (acetylsalicylic acid) by inhalation (nebulised solution of lysine-aspirin), and after oral intake of placebo or nimesulide 100mg in 20 aspirin-sensitive patients (after Bianco et al. 1991a).

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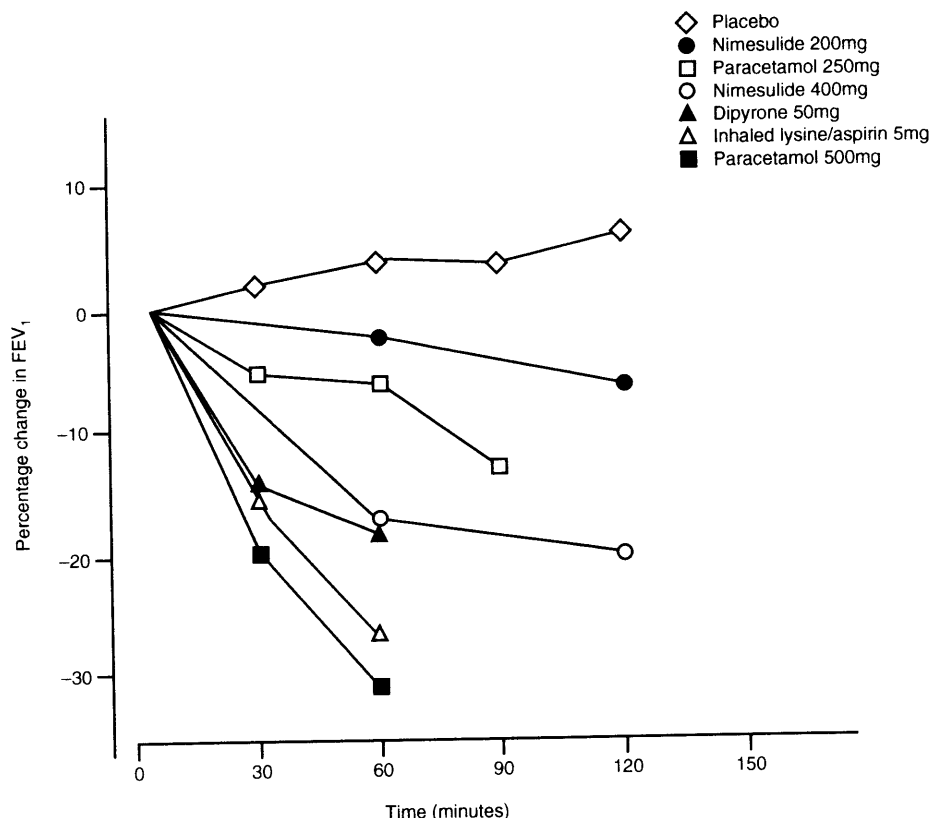


Fig. 3. Changes in forced expiratory volume in 1 second (FEV₁) in a female patient aged 30 years after oral administration of placebo, nimesulide 200 or 400mg, paracetamol 250 or 500mg, dipyrrone 50mg or after inhalation of lysine-aspirin 5mg. Challenges were performed at least 4 days apart.

Indeed, in recommended doses, nimesulide is practically devoid of respiratory adverse effects in such patients and might provide a novel approach to the treatment of bronchial asthma.

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