# Can nonsteroidal anti-inflammatory drugs be used in adult patients with asthma?

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## Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) include aspirin, and several other classes of compounds, for example, propionic acid derivatives (e.g. ibuprofen, naproxen, ketoprofen), acetic acid derivatives (e.g. indometacin), enolic acids derivatives (e.g. piroxicam), diaryl substituted pyrazoles (e.g. celecoxib) etc. (1). They act as inhibitors of the enzyme cyclo-oxygenase (COX) which results in the direct inhibition of the synthesis of prostaglandins from arachidonic acid (2).

Aspirin sensitivity that occurs in some asthmatic patients principally manifests as the onset of asthma within one to three hours of ingesting aspirin (3,4). This has been described by a number of terms including ‘aspirin induced asthma (AIA)’, aspirin sensitive asthma, Widal syndrome, Samter triad or ‘aspirin-exacerbated respiratory disease’ (5). Although the terms refer to aspirin only, “patients who are sensitive to aspirin are often cross-sensitive to other NSAIDs as they share a common mechanism of action (2)”.

The main clinical features of patients who have aspirin sensitivity in general include middle-age, female sex, diagnoses of asthma or rhinitis, a personal or family history of atopy, and a history of nasal polyps. The occurrence of aspirin sensitivity in patients with asthma and nasal polyps has been referred to as the ‘aspirin triad' (2). In these patients, nasal symptoms (nasal congestion and rhinorrhoea accompanied by nasal polyps) usually start first in the third or fourth decade of life, followed by the development of asthma and aspirin sensitivity (4,6). Specific clinical features that have been identified to suggest an increased risk of aspirin sensitivity in asthmatics include: a) severe asthma accompanied by chronic nasal congestion and profuse rhinorrhoea; b) frequent development of nasal polyps; c) sudden severe attacks of asthma requiring admission to intensive care unit and d) adult onset, non-allergic asthma (6,7).

In asthmatic patients exhibiting aspirin sensitivity, additional symptoms that accompany the onset of asthma include profuse rhinorrhoea, peri-orbital oedema, conjunctival infection, flushing of head and neck, and on occasions vomiting and diarrhoea (4,7). Patients may have any or all of these symptoms, and the reactions can vary in individuals (7). In some cases, it is likely that aspirin- or NSAID-induced rhinitis and asthma reactions occur in patients who have underlying rhinosinusitis, nasal polyps and asthma but in whom the drug-induced reactions are too mild to be recognised clinically and may go unnoticed (8). Alternatively, bronchoconstriction may be severe and life threatening, requiring hospital admission (8).

The reactions are possibly dose dependent: small doses may not induce a significant reaction, whereas larger and possibly therapeutic doses may provoke severe reactions (8,9). However, some individuals are highly sensitive and develop worsening of their asthma even with low dose aspirin (10).

Data on prevalence of AIA in adult asthmatics are conflicting. It has been stated to occur in approximately 10% of adult asthmatics (4,5,10). However, prevalence has also been quoted to be in the range 2 – 20% (10,11) and up to 44% has also been stated (11). These variations may be explained by the differences in populations studied, methods used for data collection, definitions of outcomes and criteria for defining sensitivity reactions (3).

The symptoms precipitated by aspirin or other NSAIDs in patients with AIA resemble immediate hypersensitivity reactions, however, specific antibodies to aspirin/NSAIDs are rarely shown in these individuals. Additionally, there is cross-reactivity between NSAIDs that do not have similar chemical structures, and the onset of asthma frequently occurs on first exposure to the new NSAID (7,12).

The mechanism of hypersensitivity to aspirin and other NSAIDs in asthmatic patients is therefore not considered to be immunological, but has been attributed to the pharmacological properties of the drugs – inhibition of COX, The two major enzymes in the COX pathway are cyclo-oxygenase 1 and 2 (COX-1 and COX-2 respectively). Most of the evidence suggests that inhibition of COX-1 is related to the pathogenesis of AIA in patients sensitive to aspirin. It is thought that this inhibition causes a deficiency in the protective bronchodilator/anti-inflammatory prostaglandins, and an excess of pro-inflammatory/bronchoconstrictive leukotrienes, specifically cysteinyl-leukotrienes (11,12) Patients with AIA are particularly susceptible to the effects of leukotrienes that manifest as excessive nasoocular and asthmatic reactions. (13)

## Answer

### Asthmatic patients with known Aspirin Induced Asthma (AIA)

**Use of aspirin and NSAIDs**

Aspirin and other NSAIDs are contra-indicated in patients in whom attacks of asthma have been precipitated by aspirin or any other NSAID (14).

**Use of COX-2 selective inhibitors as an alternative to non-selective NSAIDs**

There has been interest in the use of these agents in patients with AIA considering that the pathogenesis of AIA involves mainly inhibition of COX-1.

A systematic review in 2013 identified fourteen placebo-controlled clinical trials evaluating acute exposure to selective NSAID (such as meloxicam) or COX-2 inhibitor (including celexocib, etoricoxib and parecoxib) in patients with AIA. Effect estimates for changes in respiratory function and symptoms were pooled by using fixed-effects meta-analysis (15). There was no significant difference in respiratory symptoms (risk difference, -0.01; 95% CI, -0.03 to 0.01; P =0.57), decrease in FEV1 of 20% or greater (risk difference, 0.00; 95% CI, -0.02 to 0.02; P =0.77), or nasal symptoms (risk difference, -0.01; 95% CI, -0.04 to 0.02; P=0.42) occurred with COX-2 inhibitor exposure. Selective NSAID caused respiratory symptoms in approximately 1 in 13 patients with AIA (risk difference, 0.08; 95% CI, 0.02 to 0.14; P =0.01). Studies included in this meta-analysis predominantly evaluated patients with AIA and stable, mild to moderate asthma. Therefore, results may not be applicable to patients with unstable asthma or those who experienced life-threatening reactions requiring intubation after aspirin or NSAID exposure. Although COX-2 inhibitors are associated with increased cardiovascular risk, authors concluded that their use appears to provide a safe and effective anti-inflammatory and analgesic treatment in asthmatic patients with true AIA or those asthmatic patients unwilling to accept the potential risk from non- selective NSAID exposure when oral challenge tests are unavailable. (15)

Despite the safety data and lack of cross-reactivity for use of COX-2 specific inhibitors in large numbers of patients with AIA, rare case reports of respiratory reactions to them have appeared in the literature. Such reports make it impossible to take the position that they never induce respiratory reactions in patients with AIA (16).

Currently, the manufacturers state in their summary of product characteristics (SPCs), that celecoxib, etoricoxib, parecoxib and meloxicam are contra-indicated in patients who have experienced asthma/bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking aspirin or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors (17-20). Therefore, use of these agents in patients with AIA would be outside the product licence.

Of the other anti-inflammatory agents i.e. nabumetone and etodolac, due to lack of or limited published information regarding their tolerability in patients with AIA, no conclusions can be drawn regarding their use in this setting. The SPCs for both drugs contraindicate their use in patients in whom aspirin or other NSAIDs precipitate asthmatic attacks, urticaria or rhinitis (21, 22).

### Desensitisation as a management option

Desensitisation to aspirin and NSAIDs can be induced in patients with AIA by the gradual introduction of increasing doses of oral aspirin until a dose of about 450 to 600mg daily is tolerated (11). Daily administration of high dose aspirin is required to maintain tolerance (and allow administration of aspirin or other NSAIDs), as tolerance is only maintained for 2-5 days after stopping aspirin in which case patients would need to be desensitised again (7).

Aspirin desensitisation has obvious risks, and should only be carried out by experienced clinicians in a hospital setting with full facilities for cardiopulmonary resuscitation. Further, aspirin may not be tolerated by individuals due to gastrointestinal adverse effects (7,11).

It is also important to note that desensitisation would not necessarily be a viable/realistic option for those individuals who only need NSAIDs on an occasional when–required basis, as they would need to administer high dose aspirin on a regular basis to allow them to do so.

### Leukotriene receptor antagonists in preventing aspirin or other NSAID provoked respiratory symptoms

There has also been interest in the use of leukotriene receptor antagonists in preventing aspirin-provoked respiratory symptoms in patients with AIA, owing to the pathogenesis highlighted above. However, data are limited, and efficacy variable (23, 24). Thus, the role of these agents is yet to be fully established. Montelukast is the only marketed leukotriene receptor antagonists in the UK. It is not licensed for preventing asthmatic or other symptoms following administration of aspirin or other NSAIDs in patients with AIA (25). Furthermore the manufacturer states that “treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs (25)”.

### Biologics

Both omalizumab (an anti-immunoglobulin E [IgE] monoclonal antibody) and mepolizumab have been assessed as a treatment of AIA. A small trial (26) suggested that omalizumab might be useful in patients with nasal polyps. Twenty-four patients with chronic rhinosinusitis, nasal polyposis and concomitant bronchial asthma, roughly half of whom had AIA, received 4–8 subcutaneous doses of omalizumab (n = 16) or a placebo (n = 8), in line with omalizumab dosing recommendations for bronchial asthma (according to serum IgE level and the body mass). Omalizumab treatment was associated with improved airway symptoms and quality of life, and with a significant decrease in total endoscopic nasal polyposis scores after 16 weeks compared with placebo. Changes in polyposis scores were confirmed by means of sinus computed tomography (CT) scoring (Lund-Mackay score) and were independent of the presence of allergy. However, in the subset of patients with AIA, improvement was **not** clearly observed on CT. Thus, it is unclear whether this effect is specific to AIA. (27)

Case reports describe clinical improvement in asthma and loss of aspirin sensitivity to aspirin challenge were observed when patients with AIA and severe asthma were given omalizumab in case reports (28-31).

In a small randomised trial, patients with severe nasal polyposis refractory to glucocorticoid therapy were randomised to receive two doses of intravenous mepolizumab (28 days apart) or placebo. (32) The primary outcome was total polyp score as evaluated by nasal endoscopy at two months. Five of 20 patients in the mepolizumab arm were aspirin intolerant and 10 had asthma. After two months of treatment, 12 of 20 patients in the mepolizumab arm had a significant reduction in total polyp score, compared with one in the placebo arm. Despite limitations in this study (a high overall dropout rate and an unclear number of patients with confirmed AIA), the results suggest the potential of eosinophil-specific therapies in the treatment of eosinophilic nasal polyposis that is common in AIA. (26)

It should be noted that omalizumab and mepolizumab are not licensed for preventing asthmatic or other symptoms following administration of aspirin or other NSAIDs in patients with AIA. Large randomised control trials are needed to confirm their places in the management of AIA.

### Asthmatic patients who have not been exposed to aspirin or other NSAIDs

Aspirin and other NSAIDs should be used with caution in patients with a history of asthma (2). However, based on prevalence data, a large proportion of adult asthmatic patients will be able to tolerate aspirin and NSAIDs. The clinical features that suggest an increased risk of AIA in these individuals are outlined above.

### Asthmatic patients who are tolerant of aspirin and other NSAIDs (i.e. known exposure)

Based on prevalence data, a large proportion of adult asthmatic patients will be able to tolerate aspirin and other NSAIDs. It has been suggested however, that these individuals should be warned about the potential development of AIA late in life (11).

## Summary

NSAIDs are contra-indicated in patients in whom attacks of asthma have been precipitated by aspirin or any other NSAID. Further studies are required to confirm the safety and tolerability of COX-2 selective inhibitors as “safe” alternatives to non-selective NSAIDs in patients with AIA. At present, their use in patients with AIA would be outside the product licence.

For adult asthmatic patients who have not been exposed to aspirin or other NSAIDs, it is not possible to provide a definitive answer. However, in making the clinical decision as to whether aspirin/NSAIDs should be used in this patient group, the following should be considered:

* Prevalence of aspirin induced asthma (AIA) in adult asthmatics is approximately 10%, and patients who are sensitive to aspirin will often exhibit cross-sensitivity to other NSAIDs.
* Clinical features that suggest an increased risk of sensitivity to aspirin/NSAIDs in asthmatics include female sex, middle age, severe asthma accompanied by chronic nasal congestion and profuse rhinorrhoea, and a history of nasal polyps. Aspirin/NSAIDs can induce asthma/bronchoconstriction and a range of other symptoms in susceptible patients. These can range from mild reactions which may not be recognised clinically to severe and life threatening asthma.
* Based on prevalence data, approximately 80-90% of adult asthmatics will be able to tolerate aspirin and other NSAIDs, but may need to be warned of the potential for development of AIA, particularly late in life.

Limitations

This review has NOT included the following:

* A detailed and comprehensive review of the literature available regarding aspirin desensitisation and its regimes**.**
* Aspirin provocation tests (i.e. challenge tests) that may need to be employed to confirm the diagnosis of aspirin sensitivity.
* Any Information that may be available for asthmatic children who are sensitive to NSAIDs.

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### Search strategy 2020

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**Low quality studies were removed since the last update and replaced by a recent meta-analysis.**

### Search strategy Oct 2012

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* Embase 2008 to date: ((Nonsteroid-antiinflammatory-agent.DE.) AND (Asthma.W.DE.) AND (Drug-hypersensitivity.DE.) AND (Human=yes))
* Medline 2008 to date: 1) ((Anti-inflammatory-agents-non-steroidal.DE.) AND (Asthma.W..DE.) AND (Drug-hypersensitivity.DE.) AND (Human=yes)) 2) (( Anti-inflammatory-agents-non-steroidal-AE.DE. OR Anti-inflammatory-agents-non-steroidal -CT.DE. )) and ( Asthma-CI.DE. ) and (Human=yes"))
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