Aspirin sensitive asthma: current concepts

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Introduction

Aspirin or acetylsalicylic acid is one of the most frequently used drugs of all times. Gerhardt discovered aspirin in 1853 but it was Felix Hoffmann, a German chemist who developed aspirin as treatment for his father's arthritis more than a hundred years ago. The annual consumption of aspirin in the United Kingdom is approximately a hundred tons, while in the United States 80 billion tablets are consumed every year. Aspirin possesses analgesic and antipyretic properties and also has anti-platelet activity because of which it is used in the prophylaxis of thromboembolism, the prevention of transient ischaemic attacks and strokes. It is well known to reduce morbidity and mortality in patients with atherosclerotic heart disease (unstable angina and myocardial infarction).

The first examples of its negative effects in the form of asthma were discovered as early as 1911 by Gilbert, and then by Reeds and by Cookes.[1] In 1922, Widal et al described the association of aspirin sensitivity, asthma and nasal polyposis in 19 patients.[2]

Aspirin induced asthma (AIA) refers to a distinct clinical syndrome which is characterised by the development of bronchoconstriction in asthmatic individuals following the ingestion of aspirin. It encompasses classic symptoms of chronic rhinoconjunctivitis, nasal polyps, and bronchial asthma. Patients with AIA have acute exacerbations superimposed on a background of chronic severe asthma. These attacks are precipitated following the ingestion of small amounts of aspirin or other non-steroidal anti-inflammatory drugs. The exact prevalence of AIA is not certain but it affects 10-20% of the adult asthmatics.[3,4] AIA is more common in women. Nasal symptoms are less commonly seen in children afflicted with AIA. In a Finnish study the prevalence of AIA was found to be only 1.2% and the overall aspirin intolerance was 5.7%[5] Life threatening attacks of asthma may be precipitated by a small amount of aspirin. This review discusses the current concepts in our understanding of AIA.

Aspirin and the Arachidonic pathway

Arachidonic acid is mainly found in the phospholipids of cell membranes and is mobilised by the action of phospholipase A. Its metabolic pathways include (see Figure 1)

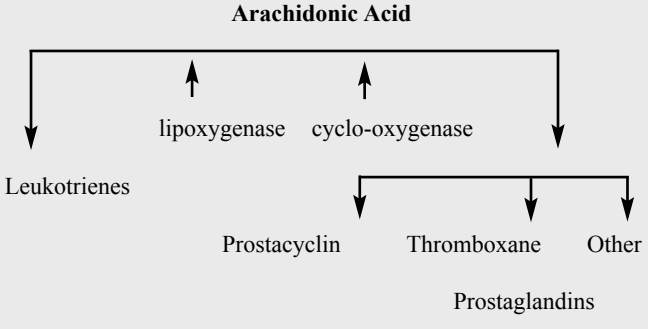
1) Formation of leukotreines (LT) by the action of 5 lipoxygenase (LO pathway). These by-products are pro-inflammatory and lead to bronchoconstriction.
2) Formation of prostaglandins by the action of cyclo-oxygenase prostaglandin synthase (COX pathway).

Aspirin inhibits the COX pathway resulting in diversion of metabolites to the LO pathway causing an increase in the number of cysteinyl leukotreines (LTC4, LTD4 LTE4). This also leads to a decrease level of anti-inflammatory prostaglandin (PGE2)

Aetiopathogenesis of AIA

Asthma is an inflammatory disease of the airways characterised by infiltration with lymphocytes, eosinophils and mast cells, together with epithelial desquamation and thickening and disorganisation of the tissues of the airway wall resulting in intermittent airway obstruction.

Figure 1: Metabolic pathway of arachidonic acid



AIA is characterised by chronic persistent inflammation of airways resulting in eosinophilic infiltration in bronchioles and accumulation in blood, nasal and bronchial secretions. In their study Nasser *et al* subjected 12 patients with AIA to bronchial biopsy and compared them with 8 non-aspirin sensitive controls.[6] They found that bronchial biopsies from patients with AIA revealed significantly greater number of mast cells and eosinophils per square millimetre of tissue in comparison to controls. Aspirin releases cysteine-leukotrienes (cys-LTs) into the airways and precipitates asthma attack. In their study on patients with AIA, Sampson *et al* found that there was over-representation of LTC4 synthase, (the perinuclear membrane enzyme that forms LTC4) in the bronchial biopsies in comparison with controls and aspirin tolerant asthmatics.[7] The gene for LTC4 has been localised to the chromosome 5q35 region.[8] Polymorphism directed to regulation of LTC4 expression could predispose to this highly leukotriene dependent asthma.

Clinical presentation

Samter and Beers in 1968 described a constellation of symptoms consisting of rhinitis, nasal polyps, sinusitis, asthma and aspirin sensitivity.[9] The usual age of presentation is the second decade with peak incidence being noted in the third decade of life. The disorder usually commences after viral infection. An acute asthma attack occurs within 3 hours of ingestion of the offending agent (aspirin or NSAID 'Table 1'). This is accompanied by conjunctival congestion, profuse rhinnorrhea, periorbital puffiness and occasionally flushing of the face and neck. Half the

patients affected with AIA have chronic severe steroid dependent asthma, 30 % have moderate asthma treated with inhaled steroids and the remainder have mild intermittent asthma.[10] An acute attack may be life threatening and may require ventilatory support.
In their study in 50 children with atopic asthma aged 6-18 years, Rachelefsky *et al*[11] found that 28% were intolerant to aspirin.

According to a study by Marquette *et al* in 1992, up to 25 % of hospital admissions for asthma requiring mechanical ventilation may be precipitated by NSAIDs ingestion.[12] They also found that AIA was not by itself related to a poorer prognosis.

AIA can be subdivided into 3 types[13]
1) Type A (asthma and/ or rhinitis)
2) Type B (urticaria/ angiooedema)
3) Type C (combination of Type A and B)

Patients with AIA may be more sensitive to other related chemicals such as tartrazine and benzoates[14]

Diagnosis
The diagnosis is generally straightforward in most cases with majority of the patients having moderate to severe persistent asthma. It has been noted that if patients with asthma have healthy sinuses both on plain radiographs or CT scan, then the likelihood of having AIA is low. Where the diagnosis is doubtful, controlled challenge testing can be done in a hospital with full resuscitation facilities. Nasal provocation test using lysine aspirin has been found to be safe and easy to perform.[15]

Treatment
The general strategy for managing patients with AIA is similar to the management of asthma patients. Aspirin and similar derivatives should be avoided. Patients requiring pain relief can safely take the analgesics presented in table 2. These drugs are either devoid of anti-COX activity or act as weak COX-2 inhibitors and hence do not exacerbate symptoms. There have been sporadic cases of AIA cross-reacting with hydrocortisone hemisuccinate provoking acute attacks of bronchoconstriction.[16]

The new group of drugs acting against the leukotriene system is being used in managing patients with AIA.

The two classes of these drugs are
1) 5 LO inhibitor zileuton: - Dahlén *et al* in 1998 concluded that adding 'Zileuton' to conventional therapy led to an acute and chronic improvement in pulmonary function in patients with AIA.[17] They also showed that zileuton inhibited urinary excretion of LTE4 but did not change airway reactivity to inhaled LTD4, suggesting that zileuton specifically inhibits leukotriene biosynthesis.
2) Cysteinyl leukotriene receptor antagonists (zafirlukast, montelukast, pranlukast)
In their study Obase Y et *al*[18] concluded that pranlukast was of use in AIA as it inhibited both leukotriene production and eosinophilic inflammation in the airway.

Table 1: NSAIDs that can cause asthma attacks

Propionic acid derivatives	Ibuprofen, fenoprofen, ketoprofen, flubiprofen, naproxen, naproxen sodium
Fenamic acid derivatives	Mefenamic acid
Pyrazolone derivatives	Phenylbutazone, oxyphenbutazone,
Acetic acid derivatives	Indomethacin, sulindac, diclofenac, tolmetin, etodolac, ketorolac
Oxicam derivatives	Piroxicam

Table 2 Anti-inflammatory drugs (AID) which are relatively safe in AIA

AID not known to cause asthma attack	Acetaminophen, sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, dextropropoxyphene
AID which can cause asthma attacks in high doses	Nimesulide, meloxicam (Relative inhibitors of COX 2)

Szczeklik *et al* have shown that salmeterol, a long acting ß2-agonist is effective in patients with AIA.[19]

Aspirin desensitisation
Desensitisation to aspirin is possible but should be carried out with caution in selected patients[20]
Desensitisation to aspirin will also result in desensitisation to NSAID. This is of importance to patients with AIA with coexistent thromboembolic diseases (myocardial infarction, cerebrovascular disease, peripheral vascular disease) and arthritis.
Generally desensitisation is done with oral preparations but intrabronchial and inhalational preparations have also been tried.
Oral desensitisation requires ingestion of small incremental doses of aspirin over a few days until a dose of 500mg to 650mg is tolerated. There is a refractory period of 2-5 days after each dose of aspirin during which aspirin and other NSAID's can be taken. It is possible to maintain the tolerance state for a long time as long as aspirin is taken regularly.[21] Upto 20% of patients may experience gastritis during desensitisation. Other side effects observed are skin manifestations.

Stevenson *et al* have used endonasal preparations of lysine-ASA for desensitisation.[22] Nasal polyps induced by aspirin have been shown to regress following endonasal desensitisation thus avoiding surgical removal.[23]

The exact mechanism of desensitisation remains unclear. However Juergens *et al* have shown a significant decline in the peripheral monocyte synthesis of LTB4 in patients with AIA after aspirin densitization[24] It has been shown that in patients

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Date Submitted:03/08/01
Date Accepted:31/01/02

Prim Care Respir J. 2002: **11**(4); 125-127

undergoing aspirin desensitisation the effectiveness of leukotrienes is reduced with down regulation of cysteinyl leukotriene receptors.[25] In patients developing urticaria, mast cell degranulation did not occur following desensitisation.[26]

Conclusion

Upto 20% of asthmatic patients are hypersensitive to aspirin and other NSAIDs. This is believed to be due to the diversion of metabolites from the COX pathway to the LO pathway resulting in an increase in leukotriene (LT) production causing bronchconstriction. At the same time there is a decrease in PGE2, which normally exerts an anti-inflammatory effect. LT-modifying drugs are effective in the management of AIA. Densitization is another alternative in patients where there is a strong indication for initiating or maintaining aspirin treatment. ■

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