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The Use of Analgesics in Patients with Asthma

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Contents

Abstract

Aspirin (acetylsalicylic acid) and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause deterioration in respiratory function in approximately 10% of adults with asthma and a smaller proportion of children with asthma.

We propose evidence-based guidelines for the safe use of NSAIDs in individuals with asthma following systematic review of data from the last 10 years relevant to the use of these drugs in such patients.

We would currently recommend that patients with asthma who are known to be intolerant of NSAIDs or who exhibit any of the high risk clinical features for intolerance to these drugs (severe asthma, nasal polyps or chronic rhinosinusitis) should use NSAIDs only under close medical supervision. In those with high risk features formal aspirin provocation testing would be recommended prior to the therapeutic use of NSAIDs. Those individuals with asthma who regularly use NSAIDs can continue to do so but should be warned that intolerance to NSAIDs

can develop late in life. Lack of relevant experimental evidence precludes the production of evidence-based guidelines for the group of patients with asthma who do not exhibit high risk clinical features and who have never before used NSAIDs. We would currently recommend that this group be treated as potentially intolerant to NSAIDs and use of these drugs can only be recommended under medical supervision but note that further studies and clinical experience could be expected to relax this restriction for many patients.

Recent data have suggested that frequent use of paracetamol (acetaminophen) may contribute to a deterioration of respiratory function in asthma. A small proportion of patients with asthma who are NSAID-intolerant experience short-lived deterioration in respiratory function with the use of high doses of paracetamol but this is uncommon and has not been implicated in life-threatening reactions. Routine warnings about paracetamol use in asthma are, therefore, not warranted. Medical personnel, however, should be aware of the potential for worsening of symptoms in some individuals with asthma using paracetamol and institute formal investigation or withdrawal of the drug if they suspect such a reaction.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to cause worsening symptoms in a small percentage of patients with asthma. Reports of fatalities related to the use of NSAIDs in this patient group mean that, although only a minority of those with asthma are affected, many doctors avoid these potentially useful drugs in all patients with this condition.

Recent work has also raised the possibility that paracetamol (acetaminophen) use may also adversely affect respiratory function in individuals with asthma.[1] This finding has been questioned[2-8] but the very widespread use of paracetamol in this patient group means that this subject merits further consideration.

This article will review the literature relevant to the use of simple analgesics in individuals with asthma and provide guidelines about the safe use of these drugs in this patient group.

Three databases (Medline, EMBASE/Exerpta Medica and Biological Abstracts) were searched using the general search term 'nonsteroidal anti-inflammatory drugs and asthma'. In order to rationalise the search, limits (summarised in table I) were applied.

Each author identified relevant references by reading title and abstract and any points of disagreement were resolved after discussion between the 2 authors. This left a total of 93 references for review. In addition, relevant references lying outside the limits of the database search were identified during preparation of the manuscript and are also included in the review.

1. Aspirin (Acetylsalicylic Acid) Intolerance

In the general population the majority of allergic reactions to aspirin (acetylsalicylic acid) are characterised by urticaria and angioedema.[9] This review is concerned with the minority who react to aspirin with asthmatic symptoms and when either the term aspirin intolerance or aspirin intolerant asthma is used it is referring only to the group who react to the drug in this way.

1.1 Clinical Characteristics of Aspirin Intolerant Asthma

Aspirin intolerance can develop at any age but

Table I. Limits applied to the search 'nonsteroidal anti-inflammatory drugs and asthma'

Search term	Limit applied
Asthma	Chemically induced and drug effects
Nonsteroidal anti-inflammatory drugs	Adverse effects, toxicology, poisoning and contraindications
Whole search	Human
Whole search	1990-2000

Table II. Illustration of the range of definitions of aspirin (acetylsalicylic acid) intolerant asthma used in the papers reviewed

Study authors	Type of study	Method of defining aspirin intolerance
Hedman et al.[15]	Questionnaire	Have you had hypersensitivity to painkillers? Is the hypersensitivity to painkillers manifested as: shortness of breath, worsening of asthma, eczema, or other?
Settipane et al.[14]	Questionnaire	A history of bronchospasm, urticaria/angioedema, severe rhinorrhoea or shock occurring within 2 hours of aspirin ingestion
Szczeklik et al.[16]	Laboratory oral challenge	Tightness in chest, dyspnoea, wheeze. Fall in peak flow (range from 19 to 68% decrease from baseline)
Settipane et al.[17]	Laboratory oral challenge	20% or greater decline in FEV_1
Estrada Rodriguez et al.[13]	Laboratory oral challenge	Respiratory symptoms and 30% decrease in peak flow from baseline

FEV_1 = forced expiratory volume in 1 second.

most commonly presents during the third decade. Initial symptoms may include chronic nasal congestion, rhinorrhoea and development of nasal polyps with gradual onset of asthma. Acute asthma occurs if the individual ingests aspirin or another NSAID. Patients with asthma who are aspirin intolerant tend to experience relatively severe symptoms, often needing regular inhaled or oral corticosteroids to control symptoms and making up a higher than expected proportion of patients with asthma needing assisted ventilation in intensive care.[10,11] The natural history and clinical features of aspirin intolerant asthma have been described in detail based on the results of a large European survey of the condition.[12]

The clinical characteristics of aspirin intolerance in children differ from those in adults. Aspirin intolerance has been found to be slightly more common in boys and while no association has been found with nasal polyps, a higher rate of sinus abnormalities was noted in aspirin intolerance children than in those who tolerate the drug.[13]

For the purposes of scientific study, aspirin intolerance is defined by 1 of 2 methods. In questionnaire and case note studies descriptive clinical criteria are used,[14,15] whereas in the laboratory, definitions based around the measurement of pulmonary function tests before and after aspirin challenge are used.[16,17] Table II illustrates the range of definitions of aspirin intolerance used in the papers reviewed.

1.2 Prevalence of Aspirin Intolerant Asthma

The prevalence of asthma varies substantially between populations with highest rates observed in urbanised Western countries.[18,19] It is estimated that between 5 and 7% of the adult population and 10% of children in Europe have asthma.[19]

The prevalence of aspirin intolerance in adults with asthma is usually quoted as between 8 and 20% with the wide variation in rates explained, in the main, by methodological differences in data collection.[20]

A 1988 review of the literature on the prevalence of aspirin intolerance in adults with asthma found a rate of aspirin intolerance of about 4% in patients with asthma, rising to 14.2% in those with nasal polyps and to 28% in those with severe atopic asthma.[20] However, the majority of studies reviewed were found to be limited by methodological problems.[20]

A more recent questionnaire based study of the prevalence of aspirin intolerance in the general population found that aspirin provoked worsening of respiratory symptoms in 8.8% of the individuals with asthma questioned compared with 0.8% of the general population.[15]

The dose of aspirin needed to cause respiratory symptoms was not stated in either of the above studies but other laboratory-based work has shown that the majority of patients with aspirin intolerant asthma develop worsening of their asthma at oral doses of less than 75mg of aspirin.[16]

While asthma is more common in children than adults, aspirin intolerant asthma is said to be rare

in this group. No large population based studies of the prevalence of the condition in children were identified but rates of 12% in children with chronic asthma and 28% in atopic children with asthma have been reported from laboratory-based studies inferring that the condition may have a similar prevalence in children as in adults.[13,21] Aspirin was withdrawn from general use in children under 12 years in 1986 because of its association with Reyes syndrome[22] and as a consequence there is unlikely to be any further work on this subject.

1.3 Discussion of Data on the Prevalence of Aspirin Intolerant Asthma

When considering the above data on prevalence, certain problems need to be borne in mind.

There is an undefined population of individuals with asthma who have never before been exposed to NSAIDs because of concerns about adverse reactions. This group will not report any respiratory complications related to NSAID use and their inclusion in questionnaire-based studies will lead to underestimation of the prevalence of aspirin intolerance in the community. In contrast, laboratory-based studies tend to derive their study populations from hospital-based clinics, representing a population with more severe and, therefore, more frequently aspirin intolerant asthma, and thus will overestimate the true prevalence of aspirin intolerant asthma.

In addition, the prevalence of asthma itself is affected by geographical factors and observed rates of aspirin intolerance may be affected by the location of the population studied.[18]

Overall, there is a problem with the quality of much of the data on aspirin intolerant asthma. Many studies use highly selected populations and, as illustrated by table II, definitions of aspirin intolerance and also of asthma are variable and can be poorly defined.[20] It can therefore be difficult to compare the results of different studies or to apply their finding to the population of people with asthma as a whole.

2. Other Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

While NSAIDs are a chemically diverse group of drugs their pharmacological effect is subserved by the same mechanism. All drugs in the group inhibit cyclo-oxygenase (COX) with a resultant decrease in production of prostaglandins, an action which is thought to be responsible for both beneficial and adverse (gastric mucosal damage, renal impairment) effects of the drug group (see section 4.1).[23] There are reports of adverse reactions to other NSAIDs in patients with aspirin intolerant asthma and it seems likely that this reaction may also be mediated by inhibition of COX.[23] This section looks at evidence for cross intolerance to other NSAIDs in patients with aspirin intolerant asthma.

2.1 Prevalence of NSAID Intolerance in Asthma

The literature search identified no population studies looking at the prevalence of intolerance to NSAIDs other than aspirin in adults or children with asthma.

Lesko and Allen[24] did, however, carry out a large randomised controlled trial looking at the treatment of febrile children with asthma with paracetamol or ibuprofen. They studied 1879 children with asthma of whom 632 received paracetamol 12 mg/kg, 636 received ibuprofen 5 mg/kg and 611 received ibuprofen 10 mg/kg. There was no evidence of increased hospital admissions, physician visits or asthma treatment during the follow up period of 1 month in the ibuprofen-treated children when compared with the paracetamol-treated children. This study found that the ibuprofen-treated children had significantly less need for physician visits for asthma and that this benefit was greatest with the higher dose of ibuprofen. Lesko and Allen[24] concluded that there may be some beneficial anti-inflammatory effect of the ibuprofen in children with asthma and there was no increase in adverse events in the ibuprofen-treated children. This study offers reassurance about the

use of NSAIDs in children with asthma in the community and infers that intolerance to NSAIDs is indeed rare in childhood asthma. It is, however, currently only published in abstract form and needs verification and duplication before its results can be transferred into clinical practice.

2.2 Case Reports of NSAID Intolerance in Asthma

The literature search identified 11 case reports, from the last 10 years, of intolerance to NSAIDs other than aspirin in individuals with asthma.[25-33] Two of the 11 case reports contained insufficient clinical details to allow further analysis and are not discussed further in this section. In addition, 2 reports of fatalities related to the use by individuals with asthma of over-the-counter NSAID medication (ibuprofen) were reviewed because of their obvious importance to this discussion.[34,35]

Of these 11 patients, 4 had no previous history of aspirin intolerance and 5 had no stated history of nasal polyps or chronic sinus congestion. Adverse asthmatic reactions have been reported with oral, topical and ophthalmic preparations of NSAIDs. The outcome was death in 4 patients and admission to the intensive care unit in 4. The clinical details of these 11 patients are summarised in table III.

2.3 Larger Studies on NSAID Intolerance in Asthma

Initial work into cross reactivity between aspirin intolerance and intolerance to other NSAIDs in

Table III. Summary of clinical data from case reports of nonsteroidal anti-inflammatory drug intolerance in patients with asthma identified from a literature search (case reports from 1990 to 2000, plus 2 reports with a fatal outcome from 1987)

Author	Year	Patient gender (age in years)	Severity of asthma	High risk features for aspirin[a] intolerance	History of aspirin intolerance?	Drug ingested (dose)	Outcome
Watts[34]	1987	Woman (65)	NA	NA	NA	Ibuprofen (200mg)	Death
Ayres et al.[35]	1987	Woman (65)	Moderate asthma, regular use of inhaled corticosteroids, occasional use of oral corticosteroids	NA	No	Ibuprofen (400mg)	Death
Bosso et al.[25]	1992	Man (60)	5 previous episodes of acute asthma	Nasal congestion, no nasal polyps	Yes	Flurbiprofen (10mg)	Needed nebuliser
Tanaka et al.[26]	1992	Woman (40)	Previous ICU admission	Sinusitis, nasal polyps	Yes	Topical ketoprofen	ICU
Watanabe et al.[27]	1993	Man (20)	1 year history of asthma	Nasal polyps	Yes	Loxoprofen (10mg)	Death
Chen and Bennett[28]	1993	Woman (25)	Stress induced	Nasal polyps, rhinosinusitis	Yes	Intra-muscular ketorolac	ICU
Antonicelli and Tagliabracci[29]	1995	Woman (40)	Asthma treated with β-agonist only	None	No	Ibuprofen (400mg)	Death
Chan[30]	1995	Woman (66)	Asthma – taking regular inhaled corticosteroids	NA	Yes	Piroxicam (10mg)	ICU
Sitenga et al.[31]	1996	Woman (44)	Chronic asthma	Nasal polyps, rhinosinusitis	No	Ketorolac eye drops	Hospital admission
Sharir[32]	1997	Woman (48)	Mild asthma	Nasal polyps	No	Diclofenac eye drops	Peak flow decreased
Hailmeskel et al.[33]	1997	Woman (53)	Severe asthma, recurrent hospital admissions	NA	Yes	Oxaprozin (600mg)	ICU

a Acetylsalicylic acid.

ICU = intensive care unit; **NA** = not available.

adults was carried out in the 1970s. Szczeklik et al.[16] found that 100% of the individuals with aspirin intolerant asthma studied demonstrated cross sensitivity when challenged with ibuprofen and fenoprofen. They also showed that the dose causing adverse reaction to aspirin was proportional to that causing adverse reaction to the other drugs.

The only available data about the use of other NSAIDs in aspirin intolerant children is the finding that none of 8 aspirin intolerant children were able to tolerate indomethacin.[13]

3. Paracetamol (Acetaminophen)

3.1 Prevalence of Paracetamol Intolerance in Asthma

The search identified no population studies looking at the prevalence of paracetamol intolerance in adults and children with asthma.

Recent epidemiological work suggested that there is an association between severity of asthma and paracetamol use.[1] This paper reported that individuals with asthma were more likely to take paracetamol than those without asthma and that the individuals with the most severe asthma took significantly more paracetamol than those with mild symptom. While this paper was greeted with great interest, its methods and inferences have been criticised[2-8] and it is our opinion that further work into this area is needed before conclusions can be drawn. One criticism of the study is that it did not look at concomitant use of other analgesics such as ibuprofen in the study population.

3.2 Case Reports of Paracetamol Intolerance in Asthma

There are case reports of true paracetamol intolerance in individuals with aspirin intolerant asthma. Henochowicz[36] reported a patient in whom paracetamol intolerance was dose dependent; little ill effect was observed with 325mg of the drug orally but a greater than 50% decrease in forced expiratory volume in 1 second (FEV_1) was demonstrated after 1000mg.[30] The literature search did not identify any fatalities due to paracetamol intolerance in asthma.

3.3 Larger Studies on Paracetamol Intolerance in Asthma

Laboratory based studies have reported rates of paracetamol intolerance in adults with aspirin intolerant asthma of between 0 and 60% depending on the methods and patient group used.[37]

More recently, Settipane et al.[17] studied 50 patients with a history of aspirin intolerance and found that 34% of them developed bronchospasm when challenged with between 1000mg and 1500mg of paracetamol. The mean dose for bronchospastic reaction was 47mg for aspirin and 1227mg for paracetamol and there was correlation between the mean dose for reaction with aspirin and that for paracetamol. The magnitude of decline in FEV_1 for paracetamol was not significantly different from that induced by aspirin but it was shorter lived (mean duration with aspirin was 9.2 hours *vs* 2 hours with paracetamol).

4. Mechanisms of Analgesic Induced Asthma

Although, for therapeutic reasons, asthma is often considered as a homogeneous condition there are many variants that have different pathogenic mechanisms. As stated in section 2, the pathogenesis of aspirin intolerant asthma is thought to be related to the ability of aspirin and other NSAIDs to inhibit COX.

4.1 The Role of Cyclo-Oxygenase Inhibition in Analgesic Intolerant Asthma

It is generally accepted that both the therapeutic and adverse effects of aspirin and other NSAIDs are related to their ability to inhibit COX, the enzyme system involved in the metabolism of arachadonic acid.[23]

There are 2 forms of COX and current belief is that the beneficial effects of NSAIDs are due to COX-2 inhibition whereas the adverse effects are mainly due to COX-1 inhibition. The theory that

the adverse effects of NSAIDs may be related to COX-1 inhibition is based on the finding that the gastrointestinal toxicity of NSAIDs can be correlated with the individual drugs ability to inhibit COX-1.[38] Different analgesics inhibit COX-1 and COX-2 to different extents (see table IV).

It has been proposed that, along with gastrointestinal toxicity, aspirin intolerant asthma may also be related to COX-1 inhibition.[23] This is supported by the finding that the majority of individuals with asthma who are unable to tolerate aspirin and other NSAIDs can tolerate analgesics, such as nimesulide, that preferentially inhibit COX-2.[39] Nimesulide has some residual COX-1 inhibitory effect but the recent development of analgesics such as rofecoxib and celecoxib that have specificity for COX-2 offer exciting opportunity for both clarification of the pathogenesis and treatment of aspirin intolerant asthma. Preliminary work into the use of specific COX-2 inhibitors in aspirin intolerant asthma is encouraging. A recent double-blind, placebo-controlled study showed that all 60 individuals with aspirin intolerant asthma studied were able to tolerate analgesic doses of rofecoxib without significant respiratory symptoms.[40] There is also evidence that COX-2 is up-regulated in the inflamed lungs of individuals with asthma resulting in increased production of bronchoconstrictors such as prostaglandin.[41] It is suggested that the observed benefits in patients with aspirin intolerant asthma who continue taking aspirin after aspirin desensitisation is related to COX-2 inhibition by this drug.[23] This theory may also explain the observed benefit in childhood asthma from treatment with ibuprofen during febrile illness.[24]

Table IV. Cyclo-oxygenase (COX)-2 specificity of different analgesics[23]

Drug	COX selectivity
Ketoprofen, aspirin (acetylsalicylic acid), indomethacin, ibuprofen, fenoprofen	Nonselective COX inhibitors
Piroxicam, diclofenac	<5-fold COX-2 selective
Nimesulide, meloxicam, celecoxib	5-50 fold COX-2 selective
Rofecoxib	>50-fold COX-2 selective

The analgesic action of paracetamol is not exclusively related to COX inhibition. There is evidence that paracetamol is a potent inhibitor of COX in brain[42] but only a weak COX inhibitor in the periphery.[43] While aspirin and other NSAIDs inhibit COX in animal lung, paracetamol does not, making COX inhibition a less likely mechanism for paracetamol intolerance than it is for intolerance to NSAIDs.[37]

There is some support, however, for a hypothesis that COX inhibition is responsible for paracetamol intolerance in patients with asthma. Settipane and Stevenson[37] report on 2 patients with asthma who were intolerant both to aspirin and high dose (1000mg) paracetamol who were able to tolerate both drugs after desensitisation to aspirin. Cross desensitisation between aspirin and paracetamol is analogous to the situation for other NSAIDs (see section 5) and supports a common mechanism for intolerance to both types of drug. In addition, sensitivity to paracetamol tends to occur at high doses and in individuals with aspirin intolerant asthma.[37] This suggests that in a very susceptible minority of aspirin intolerant individuals with asthma, large doses of paracetamol inhibit COX-1 sufficiently to cause bronchospasm.

4.2 The Role of Leukotrienes in the Pathogenesis of Aspirin Intolerant Asthma

A widely accepted hypothesis is that in patients with asthma and aspirin intolerance NSAID-induced COX inhibition results in increased products from the 5-lipoxygenase pathway.[44] The exact mechanism of promotion of this pathway is not clearly understood but its products, leukotrienes (LTs), are both potent bronchoconstrictors and also inducers of mucous hypersecretion and airway oedema. The LTs implicated in aspirin intolerance asthma are cysteinyl-leukotrienes (cys-LTs). It has been suggested that activated mast cells may be an important cellular source of cys-LTs in aspirin intolerant asthma.[41,45]

The pivotal role of cys-LTs in the pathogenesis of aspirin intolerance asthma is supported by the finding that inhalation of aspirin by aspirin intolerant but not aspirin tolerant individuals with asthma produces increased cys-LTs in bronchioalveolar lavage samples.[46] In addition, baseline urinary cys-LT levels are raised (2- to 10-fold higher) in individuals with aspirin intolerant asthma[47] and, on oral aspirin challenge, urinary cys-LT levels increase by up to 4-fold in patients with aspirin intolerant asthma when compared with individuals with aspirin tolerant asthma.[47] It has also been noted that the individuals with aspirin intolerant asthma with the highest baseline urinary cys-LTs levels have the most severe respiratory reactions when challenged with aspirin.[48]

Further support for the LT hypothesis is the finding that LTC4 synthase, the terminal enzyme for cys-LT production, is markedly over expressed in bronchial biopsy specimens from patients with aspirin intolerance asthma.[49]

There have been recent advances in the treatment of asthma involving the use of drugs that either inhibit LT synthesis or block cys-LT receptors. The finding that pretreatment with these drugs allows certain individuals with aspirin intolerant asthma to tolerate aspirin gives some support to the LT hypothesis.[50] A recent review of such studies, however, shows that bronchospastic reaction is completely abolished only in some patients with aspirin intolerant asthma treated whereas in others there is only partial or no attenuation of bronchospasm.[51] The non-uniform response to these drugs in aspirin intolerant asthma infers that either they inhibit LT production only partially in some patients with aspirin intolerant asthma or that LT release is not the only pathogenic mechanism at work in some patients with aspirin intolerant asthma.[51]

5. Desensitisation to Analgesic Related Intolerance

It is possible to produce tolerance to aspirin in intolerant individuals by the gradual introduction of increasing doses of aspirin until a dose of about 600mg is tolerated. Desensitisation is maintained only while this dose is continued and is gradually lost if the patient omits aspirin for 2 to 5 days with full sensitivity returning after 6 to 7 days.[52,53] Tolerance to one NSAID results in tolerance to all drugs in the class and cross desensitisation has also been demonstrated in individuals who are intolerant to both aspirin and paracetamol.[37,54]

This procedure is therapeutic in some patients with aspirin intolerant asthma with 30 to 50% gaining improvement in their asthma after desensitisation[55] and can also be considered for patients with aspirin intolerant asthma who need anti-inflammatory medication for rheumatic conditions or in those who require aspirin for ischaemic heart disease.[55] Aspirin desensitisation, however, has obvious risks and must be carried out where there are full facilities for cardiopulmonary resuscitation. The risk of the procedure along with need for continuing treatment with high doses of aspirin, with the attendant risk of gastrointestinal toxicity, means that this procedure is only warranted in those individuals with aspirin intolerant asthma in whom it is being considered as a therapeutic manoeuvre or who have very concrete medical need for treatment with NSAIDs.

6. Identification of Analgesic Intolerance in Asthma

From the data presented in section 1.2, it is clear that about 90% of individuals with asthma are able to use aspirin and other NSAIDs without adverse reactions. It would be beneficial, therefore, if this group, representing the majority of individuals with asthma, could be identified so they can be offered the widest range of possible analgesia.

Szczeklik and Nizankowska[10] identified clinical features that increase the likelihood of aspirin intolerance in an adult with asthma as:

- severe asthma accompanied by chronic nasal congestion and profuse rhinorrhoea
- frequent development of nasal polyps
- sudden severe attacks of asthma requiring admission to intensive care unit.

Unfortunately, however, severe reactions to aspirin can occur in people who do not exhibit any of

the above clinical features[29] and, therefore, they cannot be used to identify with certainty individuals with asthma that may safely take NSAIDs.

The position is even less clear in children that in adults. The report from Lesko and Allen[24] on ibuprofen use in children with asthma is reassuring but has not been replicated or published in its full form.

Urinary LTE4 levels have been suggested as a way of identifying the individuals with asthma who are most likely to react to aspirin and other NSAIDs.[48] There is, however, significant overlap in urinary LTE4 levels between patients with aspirin intolerant and aspirin tolerant asthma and this marker alone is unlikely to be a reliable marker of susceptibility in an individual.[56] Genetic studies offer some marker of susceptibility but again lack the specificity to be useful in clinical practice.[57]

Currently, the only certain method of establishing or excluding a diagnosis of aspirin intolerance is aspirin provocation testing.[10] There are 4 methods of administering aspirin during a provocation test: oral, nasal, bronchial and intravenous.[10] The most sensitive method is oral challenge with aspirin.[58,59] but this procedure has obvious risks and the need for the presence of full facilities for cardiopulmonary resuscitation means it is not an option for the majority of individuals with asthma. A safer method using nasal instillation of lysine-aspirin has been developed for the diagnosis of aspirin intolerance[60] This method is very specific but lacks the sensitivity to conclusively exclude the possibility of aspirin intolerance in an individual.[58]

7. Conclusions

Intolerance to aspirin occurs in about 10% of all adults with asthma. People with more severe asthma and those who have nasal polyps or chronic rhinosinusitis are more likely to be aspirin intolerant than those who do not exhibit these features. The majority of patients with aspirin intolerant asthma develop worsening of their asthma with oral doses of aspirin of less than 75mg. Low dose aspirin for the prevention of ischaemic heart disease, therefore, should be used with the same caution in individuals with asthma with analgesic doses. The prevalence of the condition in childhood asthma may be less than in adults but based on current knowledge must be considered a possibility in all age groups.

Extrapolation from limited laboratory data infers that an individual with asthma who is known to be intolerant to aspirin is likely to be intolerant of all other COX-1 inhibiting NSAIDs and should therefore avoid all drugs in this group. This position is supported by understanding of the pathogenesis of aspirin intolerant asthma along with the mechanism of action of NSAIDs. If an individual with asthma regularly uses COX-1 inhibiting NSAIDs without worsening of respiratory symptoms they can continue to use these drugs freely. This group should, however, be warned that aspirin intolerance can develop in those who have previously tolerated aspirin and other related drugs and any deterioration in respiratory function in this group after taking NSAIDs should prompt medical attention.

Individuals with asthma who have never been exposed to NSAIDs but exhibit the high risk features identified by Szezklik and Nizankowska[10] are very likely to be aspirin intolerant (up to 28%) and use of NSAIDs should only be started under close medical supervision with consideration of formal aspirin challenge prior to institution of the drug.

It is difficult to produce recommendations for the group of individuals with asthma without high risk features who have never been exposed to NSAIDs. Is not clear from current data how likely such an individual with asthma is to have a significant reaction to aspirin or a related drug and information is not available about whether NSAID use is common in this group or generally avoided because of fears of adverse reactions. Shaheen et al.[1] found that 39% of the patients with asthma had used aspirin in the past, which was not significantly different to control individuals without asthma. Use of other over the counter analgesics, notably ibuprofen, was not assessed but it is likely that use of this drug was equal or greater in this group than use of aspirin. Unfortunately, the study was not designed to elicit whether there was a temporal relation-

ship between onset of asthmatic symptoms and use of analgesics so it is difficult to draw any conclusions about the relationship between the relatively widespread use of aspirin and worsening of asthmatic symptoms.

Clinical indicators and laboratory measures (urinary cys-LTs) can identify those who are likely to be aspirin intolerant but these markers are not specific enough to represent a 'test' to exclude the possibility of aspirin intolerance. As it is currently not possible to effectively exclude aspirin intolerance in this group, they should be considered potentially aspirin intolerance and use of these drugs should only be considered under medical supervision. In childhood asthma, those who fall into the unknown group should currently be subject to the same recommendations as for adults. If the work of Lesko and Allen[24] is replicated these guidelines may be able to be relaxed in the future.

Weak COX-1 inhibitors (paracetamol, nimesulide) may produce short-lived bronchospasm at high doses in very susceptible patients with aspirin intolerant asthma. Reaction to paracetamol is uncommon and has not been implicated in severe reactions and does not, therefore, warrant routine warnings. Medical personnel should, however, be aware of the potential for worsening of symptoms in some individuals with asthma using paracetamol and institute formal investigation or withdrawal of the drug if they suspect such a reaction.

7.1 Guidelines for the Use of Analgesics in Individuals with Asthma

From our analysis of the data we have prepared evidence-based guidelines for the use of simple analgesia in individuals with asthma. The recommendations for the last group in table V (those who have never before used NSAIDs and have no high risk features for aspirin intolerance) are likely to be over-cautious for the majority of individuals with asthma but are based on the safest possible practice given the lack of current evidence. In this respect, we note that in Australia and New Zealand an algorithm on management of asthma intolerance for

Table V. Guidelines for the use of analgesics in individuals with asthma

Patient characteristics	Drug type		
	potent inhibitors of COX-1[a]	weak peripheral inhibitors of COX-1 and COX-2[b]	specific COX-2 inhibitors[c]
Aspirin intolerant (adult or child)	Avoid Consider aspirin desensitisation if use of these drugs is necessary	Can use If suspicion of exacerbation of asthma with use then for formal investigation	Currently not known
Aspirin tolerant (adult or child)	Can use Warnings about potential for the development of aspirin intolerance should be given	Can use	Can use Warnings about the potential for the development of aspirin intolerance should be given
No known exposure to NSAIDs and high risk features[d] (adult or child)	Avoid if possible Use only under medical supervision Consider diagnostic aspirin challenge prior to use	Can use If suspicion of exacerbation of asthma with use then for formal investigation	Can use If suspicion of exacerbation of asthma with use then for formal investigation
No known exposure to NSAIDs and no high risk features[d] (adult or child)	Current recommendations are for use under medical supervision only but ongoing surveillance suggests possibility for relaxation of guidance	Can use	Can use Warnings about the potential for the development of aspirin intolerance should be given

a For example, ketoprofen, aspirin (acetylsalicylic acid), indomethacin, ibuprofen and fenoprofen.

b For example, paracetamol (acetaminophen).

c For example, rofecoxib and celecoxib.

d Severe asthma accompanied by chronic nasal congestion and profuse rhinorrhoea, frequent development of nasal polyps, sudden severe attacks of asthma requiring admission to intensive care.

NSAID = nonsteroidal anti-inflammatory drugs.

healthcare professionals has be produced/developed by a pharmaceutical company in collaboration with the Australian National Asthma Campaign in which people with asthma with no high risk features for asthma intolerance are offered a full range of options for analgesia (A. Steans, personal communication). No specific adverse drug reaction monitoring system has been introduced for this project but there has been no identified increase in reports of asthma intolerance through normal channels during the first year of operation. The same algorithm is now being introduced in the UK and we would encourage the development of surveillance in order to ensure that this relaxation of the guidelines is supported by continuing evidence of safety.[61]

7.2 Further Recommendations

The literature review has allowed the preparation of evidence-based guidelines for the use of simple analgesia in different groups of individuals with asthma. However, it is currently not possible to produce evidence-based guidelines for the use of NSAIDs in the group of individuals with asthma who have never used these drugs in the past and who do not have any high risk features for aspirin intolerance. Further epidemiological studies are needed into the use of prescribed and over-the-counter NSAIDs in individuals with asthma in the community. If significant worsening of asthmatic symptoms is associated with use of NSAIDs by this group, then it would support the cautious recommendations for first time use of these drugs in this population. If no such association is found then relaxation of the guidelines for the use of NSAIDs in low risk individuals with asthma may be possible.

The use of COX-2 inhibitors in patients with aspirin intolerant asthma is an exciting new area for investigation and these drugs may offer a therapeutic alternative for those individuals with asthma that are unable to tolerate traditional analgesia. Initial laboratory work into the use of these drugs in aspirin intolerant asthma is very encouraging. However, preliminary analysis of UK 'yellow card' reports of adverse reactions to the Medicines Control Agency (ADROIT drug analysis printout from launch to August 2001) lists reports of asthma and bronchospasm in 70 cases (23 for celecoxib and 47 for robecoxib). In 19 of these cases the reports suggest exacerbation of known disease but in the remaining 51 the implication is that the respiratory symptoms represent a new problem. Thorough investigation of the use of specific COX-2 inhibitors in individuals with asthma is therefore needed before they can be considered for use in all such patients.

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