The importance of COX-2 inhibition for aspirin induced asthma

Alan Bennett

There have been recent reviews of aspirin induced asthma (AIA), the use of the COX-2 preferential inhibitor nimesulide in asthmatic patients intolerant to non-steroidal anti-inflammatory drugs (NSAIDs), and of nimesulide in general. This paper discusses the importance of inhibiting prostaglandin E2 (PGE2) synthesis in AIA, and the relative safety of NSAIDs that preferentially inhibit COX-2.

Aspirin and other NSAIDs cause bronchoconstriction in about 10% of asthmatic subjects but NSAIDs relieve asthma in about 0.3%. This variability helps to show the complexity of the problem. Prostaglandins in human lung are formed by various tissues and cells, including bronchial muscle, epithelium, and inflammatory cells, so the inhibition of prostaglandin formation can have numerous effects. In addition, the prostanooids (prostaglandins and thromboxanes) formed have different, and sometimes opposite, effects on the lungs. Furthermore, NSAIDs may alter the synthesis of various prostaglandins differently in patients with AIA—for example, aspirin reduces the synthesis of PGE2 but not of the bronchoconstrictors PGD2 and PGF2α. Inhibition of PGE2 synthesis seems to be particularly important in AIA for several reasons: PGE2 can relax bronchial muscle, inhibit the formation or release of various bronchoconstrictor agents, such as leukotrienes and histamine (levels of which are raised in AIA), and PGE2 administered as an aerosol inhibits aspirin induced bronchoconstriction.

Since PGE2, and other prostanooids are formed by both constitutive COX-1 and induced COX-2, the effect on the lung may partly reflect the relative activities of each NSAID on the enzymes. Generally, in various tissues and organs such as the gastrointestinal mucosa and kidney, COX-1 produces prostaglandins that have physiological protective roles, whereas COX-2 induced at sites of inflammation forms prostaglandins that contribute to the disease. It is generally agreed that blocking COX-1 can damage the stomach and kidneys, at least when other factors are involved, and perhaps this applies to the lungs.

**COX-2/COX-1 inhibition in relation to AIA**

Examination of the relative importance of COX enzymes in AIA can be partly assessed from studies using preferential COX-2 inhibitors. The term “preferential” is used here to denote activity that is somewhat greater against COX-2 than against COX-1, whereas the term “specific” is used here to denote that the activity is (usually) much greater against COX-2 than against COX-1. Two drugs with a “preferential” status are nimesulide and celecoxib, whereas two drugs that probably deserve the title “specific” are rofecoxib and celecoxib.

Nimesulide (4-nitro-2-phenoxymethanesulphonanilide) is particularly important in AIA because several studies have shown that it is tolerated by most patients with the disorder to about the same extent as paracetamol. This sulphonamide NSAID, which is effective in treating a wide spectrum of inflammatory and painful conditions, was first marketed in 1985 and 10 years later it was found to be a preferential inhibitor of COX-2. Because it is not marketed in the USA, Japan, or the UK, nimesulide is not well known in some parts of the world. Nevertheless, in the 50 countries where it is now sold, nimesulide is often the first or second NSAID in the local market, and it is fifth worldwide despite being absent from the largest markets.

In every study of COX selectivity nimesulide was more potent against COX-2 than COX-1. However, as with all NSAIDs, its COX-1/COX-2 ratio varies in different reports (from about 4.5 to 2500 in favour of COX-2). Factors influencing the ratio include the enzyme source, cell type, substrate concentration, and incubation time.

Our own investigations were on COX-1 and COX-2 sheep pure enzymes, and human gastric mucosa (constitutive COX-1) and leucocytes (induced COX-2). We found that COX-1 from sheep seminal vesicles was not inhibited by nimesulide, in contrast to the concentration-related inhibition by indomethacin, naproxen, piroxicam, ibuprofen, tolmetin, and diclofenac. COX-2 from sheep placenta was blocked by all the NSAIDs. In our human in vitro studies nimesulide blocked COX-2 in leucocytes, but only weakly inhibited COX-1 in isolated gastric mucosa. Similarly, with human subjects nimesulide inhibited leucocyte COX-2 to a considerable extent but had little effect on COX-1 in the gastric mucosa and platelets.

**Nimesulide**

Since nimesulide was initially thought to act mainly by non-prostaglandin mechanisms (before it was realised that tissue containing COX-1 was used to measure inhibition of prostaglandin synthesis), nimesulide was tested in patients who could not tolerate other NSAIDs. The studies summarised in table 1 show that nimesulide can be tolerated by most patients with AIA. It can usually
the possibility that inhibition of COX-1 is the (main) cause of AIA, the drug is found in larger studies to be relatively safe in AIA. The picture should be clarified in due course by examination of the selective COX-2 inhibitors rofecoxib and celecoxib. It remains to be seen how much COX-1 activity is needed to allow production of prostaglandins for physiological functions, and whether a small inhibition of COX-1 added to a stronger effect on COX-2 might be beneficial in relieving inflammatory processes that contribute to asthma and other diseases.

Table 1 Tolerance data on nimesulide in AIA

<table>
<thead>
<tr>
<th>Nimesulide dose (mg)</th>
<th>Patients tolerating nimesulide (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>20/20 (100%)</td>
<td>12</td>
</tr>
<tr>
<td>100</td>
<td>20/20 (100%)</td>
<td>12</td>
</tr>
<tr>
<td>400</td>
<td>18/20 (90%)</td>
<td>13</td>
</tr>
<tr>
<td>200</td>
<td>46/50 (92%)</td>
<td>14</td>
</tr>
<tr>
<td>100</td>
<td>7/12 (58%)</td>
<td>15</td>
</tr>
</tbody>
</table>

Nimesulide was started at a low dose and then increased to the amount shown. The usual anti-inflammatory dose is 100 mg twice daily. In the study by Bianco et al. 20 the 20 patients were the same in the 100 mg and 400 mg groups.

Table 2 Tolerance data on nimesulide in patients with other symptoms of NSAID intolerance

<table>
<thead>
<tr>
<th>Nimesulide dose (mg)</th>
<th>Patients tolerating nimesulide (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 (over 84 h)</td>
<td>86/92 (93%)</td>
<td>16</td>
</tr>
<tr>
<td>200</td>
<td>39/42 (93%)</td>
<td>17</td>
</tr>
<tr>
<td>100</td>
<td>270/284 (95%)</td>
<td>18</td>
</tr>
<tr>
<td>200</td>
<td>83/87 (95%)</td>
<td>19</td>
</tr>
<tr>
<td>200</td>
<td>415/429 (97%)</td>
<td>20</td>
</tr>
<tr>
<td>175</td>
<td>14/15 (93%)</td>
<td>21</td>
</tr>
<tr>
<td>100</td>
<td>7/8 (88%)</td>
<td>15</td>
</tr>
</tbody>
</table>

Nimesulide was started at a low dose and then increased to the amount shown. The usual anti-inflammatory dose is 100 mg twice daily. Symptoms in the few patients showing some intolerance to nimesulide were often mild.

Meloxicam

Only one small study has been reported on the use of meloxicam in patients with AIA. In five NSAID intolerant patients dyspnoea occurred in two with aspirin and two with ketoprofen, but three of these four had no dyspnoea with 11 mg meloxicam (therapeutic dose 7.5–15 mg daily). 21

Celecoxib and rofecoxib

These new selective COX-2 inhibitors have not yet been examined in AIA and are currently contraindicated in such patients. If inhibition of COX-1 is the (main) cause of AIA, the selective COX-2 inhibitors may well be safe in patients who cannot tolerate other NSAIDs. Studies with these new drugs would help to elucidate the mechanism(s) of AIA.

Analysis of the current evidence that absence of COX-1 inhibition would avoid intolerance to NSAIDs

The findings discussed above, and the clinical evidence mainly with nimesulide, are consistent with the possibility that inhibition of COX-1 is an important cause of AIA. However, nimesulide is not just a COX-2 inhibitor, as discovered partly before COX-2 was known. Other effects that occur with therapeutically relevant amounts of nimesulide include (a) inhibition of the formation of superoxide anions by neutrophils, 21 (b) inhibition of histamine action and release, 14 21 (c) TNF-α hyperalgesia, 26 and (d) synthesis of stromelysin and collagenase (which degrade proteoglycan and collagen). 27

Thus, the usual lack of bronchial problems with nimesulide in patients with AIA might result partly from these other pharmacological actions. Meloxicam has also been reported to have non-prostaglandin activity and this might become relevant to the present discussion if the drug is found in larger studies to be relatively safe in AIA. The picture should be clarified in due course by examination of the selective COX-2 inhibitors rofecoxib and celecoxib. It remains to be seen how much COX-1 activity is needed to allow production of prostaglandins for physiological functions, and whether a small inhibition of COX-1 added to a stronger effect on COX-2 might be beneficial in relieving inflammatory processes that contribute to asthma and other diseases.
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