The Safety of Celecoxib in Patients With Aspirin-Sensitive Asthma

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Objective. To determine whether celecoxib, a selective cyclooxygenase 2 (COX-2) inhibitor, cross-reacts in patients with aspirin-exacerbated respiratory disease (AERD) with asthma.

Methods. Sixty patients with asthma underwent double-blinded, placebo-controlled oral challenges with celecoxib (100 mg, 200 mg, and 2 placebos) over 48 hours in our General Clinical Research Center. The next day, sensitivity to acetylsalicylic acid (ASA) was proven in all patients with the use of single-blinded ASA challenges.

Results. None of the 60 patients experienced any symptoms, changes in nasal examinations, or declines in forced expiratory volume in 1 second during the celecoxib challenges. All 60 patients experienced oculo-nasal and/or asthmatic reactions to ASA, with a mean provoking dose of 69 mg. The exact 1-sided confidence interval for the probability of celecoxib inducing cross-reactions in AERD patients was calculated to be between 0% and 5%.

Conclusion. Cross-reactivity between ASA and celecoxib does not occur in patients with AERD. These results do not preclude the possibility of other types of immune reactions occurring with celecoxib after prior exposure. Our results add to the growing body of evidence that inhibition of cyclooxygenase 1 (COX-1) is a critical initiating event in the precipitation of respiratory reactions in AERD patients following ingestion of nonsteroidal anti-inflammatory drugs.

The treatment of rheumatic conditions is limited in patients with asthma due to concerns of potential nonsteroidal antiinflammatory drug (NSAID)-provoked asthma. Hypersensitivity to aspirin (acetylsalicylic acid; ASA) is present in only ~10% of asthmatic patients, occurring more often in women and rarely in children (1,2). Aspirin-exacerbated respiratory disease (AERD), formerly referred to as aspirin-induced asthma or aspirin-intolerant asthma, is characterized by recalcitrant mucosal inflammation of the upper and lower respiratory tract combined with precipitation of asthma and rhinitis attacks after ingestion of ASA and most NSAIDs (3). It is associated with progressive sinusitis, nasal polyposis, and asthma despite avoidance of ASA and NSAIDs. In sensitive individuals, even small, single doses of ASA may cause rhinorrhea, bronchospasm, and shock symptoms, related to a non–IgE-mediated pharmacologic hypersensitivity reaction. The mechanism of the hypersensitivity reaction appears to be related to inhibition of cyclooxygenase 1 (COX-1) and a resulting imbalance between prostaglandin E2 (PGE2), as an inhibitor of 5-lipoxygenase (5-LO), and overproduction of peptidyl leukotrienes (4,5).

In subjects with AERD, reactions can occur after ingestion of ASA or any of the NSAIDs that inhibit the COX-1 enzyme (6). In contrast, sodium salicylate, salicylamide, choline magnesium trisalicylate, benzylamine, chloroquine, azapropazone, and dextropropoxyphene do not inhibit COX-1 enzymes and do not induce respiratory reactions in subjects with AERD (7). Unfortunately, these drugs are poor analgesics and have fewer antiinflammatory effects than the cross-reacting NSAIDs. Drugs such as acetaminophen (paracetamol) and salsalate, which inhibit COX-1 poorly, can generally be used in subjects with AERD. However, with high doses of these drugs, cross-reactions with ASA can occur in a minority of patients with AERD (8,9). Meloxicam and nimesulide predominantly inhibit COX-2 but also inhibit COX-1 at high doses (10,11). These latter anti-
inflammatory drugs have a low prevalence of cross-reactivity in AERD and only with much higher doses of the drugs.

In 1999, 2 new antiarthritis drugs, celecoxib and rofecoxib, were introduced into the US market. Both drugs selectively inhibit COX-2 (12). The original package inserts for both drugs stated that prescribing these drugs to patients with AERD was absolutely contraindicated and urged caution with regard to giving them to any patients with asthma. Based on evidence already available on the relative COX-2 inhibitors, meloxicam and nimesulide, this warning did not entirely make sense because both celecoxib and rofecoxib would be incapable of depleting PGE\textsubscript{2}, a protective prostanoid, generated through constitutive COX-1. Since then, information has begun to emerge suggesting that selective COX-2 inhibitors can be safely ingested by patients with AERD (13–15). We recently published the results of a double-blind, placebo-controlled challenge with rofecoxib in 60 patients with documented AERD (16). During the challenge with rofecoxib, none of the patients experienced any symptoms or changes in forced expiratory volume in 1 second (FEV\textsubscript{1}), as had also been shown in a similar study by Szczeklik et al (17) involving 12 patients with AERD.

The purpose of the present study was to determine whether a large, statistically powerful sample of patients with AERD could tolerate celecoxib without adverse effects.

SUBJECTS AND METHODS

Selection of subjects. Subjects with asthma and a history of asthma attacks induced by ASA and/or NSAID ingestion were admitted to the General Clinical Research Center (GCRC) at Scripps Green Hospital. Efforts were made to enroll subjects at times when their asthma was quiescent. In general, nasal, bronchial, and systemic corticosteroids were continued. Antihistamines, cromolyn sodium, nedocromil sodium, salmeterol, and albuterol and ipratropium bromide were discontinued upon admission, allowing adequate time for washout of the drugs. Leukotriene modifiers and topical or systemic corticosteroids were continued. Celecoxib is a diaryl-substituted pyrazole derivative containing a sulfonamide substituent. Because of this structural component, the manufacturer states that celecoxib is contraindicated for use in patients who have demonstrated allergic reactions to sulfonamides. Subjects with a history of sulfonamide sensitivity were therefore excluded from celecoxib challenges. Pregnant women were also excluded. Women of childbearing potential underwent a screening urine pregnancy test before participating in the oral challenges. No subjects had prior exposure to COX-2 inhibitors. All subjects gave informed consent. Both the Human Subjects Committee and the GCRC advisory committee had approved the study protocol.

Celecoxib challenges. During the first day in the GCRC, a single-blinded placebo oral challenge was conducted to determine whether lung function was stable enough for the subject to participate in the next day’s drug challenge. Nasal examinations were performed, and bronchial airway stability was ascertained. A wedge spirometer with integrated flow/volume output (Koko Spirometry; Pulmonary Data Services Instrumentation, Louisville, CO) was used to monitor pulmonary function. FEV\textsubscript{1} determinations were recorded every hour for a total of 6 hours after dosing.

Based on the results of the single-blinded placebo challenge on day 1, a decision was made with previously established inclusion criteria to begin double-blinded celecoxib challenges on day 2. For a subject to participate in the study, his or her baseline FEV\textsubscript{1} value had to be >70\% of the predicted value, and hourly FEV\textsubscript{1} had to vary <10\% during the placebo challenge on day 1.

On day 2, celecoxib was placed in green gelatin capsules by the nurse coordinator. Identical-appearing placebo capsules were filled with sucrose. A charge nurse prepared 4 envelopes, each with a single green capsule; 1 capsule contained 100 mg celecoxib, 1 capsule contained 200 mg celecoxib, and 2 capsules contained sucrose. At 7:00 AM and noon on the first challenge day, the nurse gave the patient 1 capsule containing either 100 mg celecoxib or placebo and watched the patient ingest it; capsules 3 and 4 were given at 7:00 AM and noon on the second challenge day. For safety reasons, 100 mg celecoxib was given on day 1, and 200 mg celecoxib was given on day 2. However, neither the patient nor the nurse knew the sequence of placebo and active drug challenge. Nasal, ocular, cutaneous, and chest examinations were conducted hourly. The code for the contents of the capsules was broken at the end of the third day upon completion of the 2-day, double-blinded challenges with celecoxib.

ASA challenges. At 7:00 AM on the morning of the fourth day, single-blinded oral ASA challenges were begun. Identical green capsules containing varying doses of ASA were used. The first dose of ASA was 30 mg. Three hours later, if no reaction had occurred, the dose was increased to 45 or 60 mg of ASA (at the discretion of the physician on the basis of the severity of the historical reaction to ASA or NSAIDs). If there was no reaction to the 45- or 60-mg dose of ASA after 3 hours, the next highest dose of 60 or 100 mg of ASA was given. Escalating doses of ASA (100, 150, 325, and 650 mg) were given every 3 hours during the day until a reaction occurred or the patient reached a dose of 650 mg without having a reaction. Reactions to ASA were observed and documented as previously described (18). ASA respiratory sensitivity was defined as a decline of 15% or more in FEV\textsubscript{1} values and oculonasal reactions within 3 hours of incremental oral ASA challenges. Alternatively, a 20\% decline in FEV\textsubscript{1} without associated oculonasal reaction was accepted as a respiratory reaction.

Oculonasal reactions. Signs and symptoms of reactions in the upper airways were simultaneously recorded through use of a standard scoring system (19). A positive response consisted of rhinorrhea accompanied by any of the following: ocular chemosis, injection, and periorbital swelling; swelling and congestion of the nasal turbinates; and paranasal sinus pain. The scores were recorded as follows: 0 = absence of any
reaction; 1+ = rhinorrhea, nasal congestion; 2+ = rhinorrhea, nasal congestion with conjunctival injection; 3+ = complete nasal obstruction with conjunctival injection and paranasal sinus headache; and 4+ = severe reactions with periorbital edema in addition to manifestations of all oculonasal signs and symptoms. All patients continued with ASA to complete ASA desensitization.

Statistical analysis. Mean, SEM, and Wilcoxon’s signed rank test results for challenge data at baseline were compared with challenge results by means of StatView 4.01 for Windows (Abacus Concepts, Berkeley, CA). The method of calculation of exact 1-sided confidence intervals (CIs) for binomial probabilities was based on the following parameters: in the situation of no successes in the number (n) of independent trials with underlying probability (P) of successes at each trial, the calculation of the 1-sided \( (1 - P) n = \alpha \) (20).

**RESULTS**

Demographics. Eighty-two patients with asthma who believed they were ASA/NSAID-sensitive volunteered to enter this study. Four subjects were excluded because of a history of sulfonamide allergy. An additional 9 were excluded because their asthma was unstable on the first day of placebo challenges or their FEV\(_1\) values were <70% of the predicted values. Nine subjects completed the 2-day, double-blinded, placebo-controlled oral challenge with celecoxib without adverse effects but then failed to react to ASA on day 4 or 5. There were no exclusions because of pregnancy. Sixty patients with asthma who met all criteria for entry completed the 2-day celecoxib challenges (days 2 and 3) and then experienced respiratory reactions to ASA on day 4 or 5 (Figure 1). Table 1 presents the clinically relevant information about the 60 patients who completed the study. Their average age was 45 years; 34 women and 26 men were included.

The number of patients who were taking significant controller medications (systemic corticosteroids and leukotriene modifiers) during this inpatient study is shown in Table 2. Both systemic corticosteroids and leukotriene modifiers interfere with ASA-induced bronchospasm in some AERD patients but rarely block oculonasal reactions in patients with AERD (13,19,21). These drugs are frequently essential in maintaining stable bronchial airways, particularly in the asthma population participating in this study. Antihistamines, which can block the oculonasal reaction induced by ASA, were discontinued at the time of admission (22).

Challenge study results. Table 3 shows the results of the double-blinded challenges with 2 placebos and 100 mg and 200 mg celecoxib. During the celecoxib challenge, there were no symptoms with either dose of the drug. One patient experienced a 2+ reaction (nasal congestion and ocular injection and redness) on day 1 with no associated decline in FEV\(_1\). When the code was broken, the oculonasal event was determined to have occurred with the placebo dose. The patient was having

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Table 1. History of reactions and clinical characteristics of the 60 patients

<table>
<thead>
<tr>
<th>Observation or reactions</th>
<th>No. (%) of patients</th>
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<tbody>
<tr>
<td>Prior asthmatic reactions to ASA</td>
<td>48 (80)</td>
</tr>
<tr>
<td>Two or more prior reactions to ASA</td>
<td>24 (40)</td>
</tr>
<tr>
<td>Prior asthmatic reactions to other NSAIDs</td>
<td>30 (50)</td>
</tr>
<tr>
<td>Previously reacted to both ASA and NSAIDs</td>
<td>21 (35)</td>
</tr>
<tr>
<td>ASA/NSAID-induced asthma treated in ER</td>
<td>35 (58)</td>
</tr>
<tr>
<td>ASA/NSAID-induced asthma required hospitalization</td>
<td>23 (38)</td>
</tr>
<tr>
<td>Diagnosed at some time as having nasal polyps</td>
<td>60 (100)</td>
</tr>
<tr>
<td>Diagnosed by computed tomography scan or radiography as having sinusitis</td>
<td>60 (100)</td>
</tr>
<tr>
<td>Reported complete anosmia at the time of study</td>
<td>46 (77)</td>
</tr>
<tr>
<td>Reported partial anosmia at the time of study</td>
<td>14 (23)</td>
</tr>
</tbody>
</table>

* ASA = acetylsalicylic acid; NSAIDs = nonsteroidal antiinflammatory drugs; ER = emergency room.
irritation of her eyes from contact lens solution and was asked to wear her glasses for the remainder of the study. On day 2, after receiving 200 mg celecoxib, she exhibited no oculonosal symptoms or physical findings and only a 7% decline in FEV1. During the ASA challenge, the same patient experienced a 3+ oculonosal reaction and a 16% decline in FEV1 with audible wheezing after 60 mg of ASA. No statistically significant differences between the mean oculonosal scores or changes in FEV1 values were seen when the placebo was compared with either dose of celecoxib.

Table 3 also presents data collected during the single-blinded oral ASA challenges. The mean provoking dose of ASA was only 69 mg, and there were statistically significant differences between the ASA reactions and those recorded for placebo and celecoxib. Of the 60 patients, the reactions to the ASA challenge included 4 patients with oculonosal scores of 2+, 34 patients with scores of 3+, and 22 patients with scores of 4+. Changes in FEV1 during ASA challenges were as follows: 35 patients had pure upper airway reactions (FEV1 declined by <15%), 10 patients’ FEV1 declined 15–20%, and in 15 patients FEV1 values declined by >20%. At the same time that respiratory reactions were occurring, the following extrapulmonary reactions were recorded: laryngeal spasm (3 patients), generalized urticaria (3 patients), generalized pruritis (3 patients), gastrointestinal pain or cramping diarrhea (8 patients), and generalized flush (4 patients). A total of 15 patients experienced 1 extrapulmonary reaction, whereas only 6 experienced 2 extrapulmonary reactions.

In summary, there were no reactions to celecoxib after ingestion of either a 100-mg or 200-mg dose of celecoxib, but significant reactions to ASA occurred in all patients. The 1-sided 95% CI for the underlying probability of celecoxib-inducing respiratory cross-reactions in patients with AERD was calculated to be between 0 and 0.05, or 0–5%.

**DISCUSSION**

AERD is characterized by asthma, often recalcitrant, chronic sinusitis, nasal polyps, and sensitivity to ASA and other NSAIDs. It may occur in up to 10–20% of the general asthmatic population. Severe asthma attacks may be provoked by very small doses of ASA and other NSAIDs, which inhibit COX-2. The results of this study demonstrate that celecoxib, in recommended therapeutic doses of either 100 or 200 mg, was safely tolerated by 60 asthmatic subjects with proven AERD. Because NSAIDs that inhibit COX-1 cross-react with ASA 100% of the time in patients with AERD, one would have expected a significant number of reactions to occur with celecoxib in this study if celecoxib was a cross-reacting NSAID. No such reactions occurred. In contrast to the dose-response reactions seen with relative COX-2 selective NSAIDs such as nimesulide and meloxicam, no reactions to celecoxib (either oculonosal or drops in FEV1 values) were seen as the dose was increased from 100 mg to 200 mg. It could be argued

**Table 2.** Medications taken by the patients before and during the study

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. (%) of patients</th>
</tr>
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<tbody>
<tr>
<td>Topical nasal corticosteroids</td>
<td>47 (78)</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>49 (82)</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Burst</td>
<td>30 (50)</td>
</tr>
<tr>
<td>No systemic corticosteroids</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>40 (67)</td>
</tr>
<tr>
<td>Montelukast sodium</td>
<td>28 (47)</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Zileuton</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

**Table 3.** Results of challenges with placebos, celecoxib, and ASA in 60 patients*

<table>
<thead>
<tr>
<th>Oral challenge substance</th>
<th>Nasal score, mean ± SEM (range)</th>
<th>% change in FEV1, mean ± SEM (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 1</td>
<td>0.03 ± 0.03 (0–2)</td>
<td>−2.67 ± 0.78 (+10 to −10)</td>
</tr>
<tr>
<td>Placebo 2</td>
<td>0.00 ± 0.00 (0)</td>
<td>−1.13 ± 0.91 (+10 to −10)</td>
</tr>
<tr>
<td>Celecoxib, 100 mg</td>
<td>0.00 ± 0.00 (0)†</td>
<td>−2.92 ± 0.69 (+10 to −10)†</td>
</tr>
<tr>
<td>Celecoxib, 200 mg</td>
<td>0.00 ± 0.00 (0)†</td>
<td>−2.09 ± 0.72 (+10 to −10)†</td>
</tr>
<tr>
<td>ASA</td>
<td>3.30 ± 0.08 (2–4)‡</td>
<td>−15.40 ± 1.39 (0 to −50)‡</td>
</tr>
</tbody>
</table>

*The mean provoking dose of acetylsalicylic acid (ASA) was 69 mg (range 30–150 mg). The mean elapsed time from ASA ingestion to onset of reaction was 1.69 hours, and the time of reaction was 3.2 hours.
† P not significant versus either placebo and versus other celecoxib dose for nasal scores and changes in forced expiratory volume in 1 second (FEV1), by Wilcoxon’s signed rank test.
‡ P < 0.0001 versus both placebos and both doses of celecoxib for nasal scores and changes in FEV1, by Wilcoxon’s signed rank test.
that the first dose of celecoxib resulted in a “silent desensitization.” Following an ASA/NSAID reaction or silent desensitization, a refractory period occurred that lasted between 48 hours and 7 days. During this refractory period, ASA and NSAIDs could be taken without consequence in ASA-sensitive individuals (18). In this study, however, celecoxib ingestion could not have silently desensitized the participants, because all 60 patients reacted to ASA 24 hours after having received 200 mg of celecoxib.

A critical component of this study was confirming aspirin sensitivity in all the participants. In subjects with AERD, life-threatening asthma exacerbations can occur with therapeutic doses of ASA and NSAIDs. Thirty-eight percent of the patients had previously been hospitalized following ingestion of ASA or NSAIDs. Because ASA-induced respiratory reactions are dose-dependent, we used single-blinded oral ASA challenges to induce measurable respiratory reactions without provoking severe asthma. The mean provoking dose of ASA was 69 mg in this study.

A confounding factor in designing a challenge protocol for subjects with AERD is the issue of controller medication use. In most subjects with AERD, controller medications are critical components of their asthma control. If systemic corticosteroids or leukotriene modifiers are discontinued during challenge studies, spontaneous bronchospasm tends to reappear, confounding the results. Such a situation will produce drops in FEV1 values, which may be wrongly attributed to the challenge substance. Discontinuing controller medicine may place the AERD patient at great risk for a very serious reaction to ASA. If, on the other hand, controller medications are continued, they can modify or even block bronchospastic reactions (19,21,23). Interestingly, systemic corticosteroids and leukotriene modifiers do not block ocular reactions (19,21,23). We were therefore able to continue the controller medications and still identify ASA sensitivity. Antihistamines, which can efficiently block the ocular reactions induced by ASA, were withheld in this study (22). This study addressed only the cross-reacting respiratory reactions that can occur in patients with AERD.

None of the participants had previously ingested celecoxib. Therefore, there was no possibility of type I or IgE-mediated reactions or hypersensitivity immune reactions with ingestion of celecoxib in this study. As is true with any medication, drug-specific reactions have been reported for celecoxib, including gastric intolerance, hives, angioedema, renal impairment, and anaphylaxis (24). A case of anaphylaxis following the third dose of celecoxib has also been reported, consistent with a classic IgE-mediated immune response (25). A case of an anaphylactoid reaction to rofecoxib 40 minutes after what was suggested to be the first exposure to the medication, in an individual with a known sensitivity to diclofenac, was reported recently (26).

Unlike NSAIDs, which inhibit COX-1, celecoxib appears to be an acceptable alternative in patients with AERD. This is particularly important given the fact that many patients with asthma do not know whether they are sensitive to ASA or NSAIDs. In contrast to IgE-mediated reactions that require prior drug exposure, ASA- and NSAID-induced respiratory reactions can occur on first exposure in sensitive individuals. Because of this potential for a severe reaction, patients with asthma are usually consistently warned to avoid ASA and NSAIDs, by physicians, package inserts, the Internet, nurses, pharmacists, and the press. As a result, many patients are not receiving adequate antiinflammatory therapy for a variety of conditions because of the potential for a serious reaction. Our data suggest that with the availability of celecoxib, this medication can be safely given to any asthmatic individual without concern that first exposure might induce an asthma attack.

This study also provides further elucidation of the pathways involved in AERD. A change in arachidonic acid metabolites occurs during the ASA reaction, with a decrease in prostaglandins and an increase in cysteinyl leukotrienes. A critical component is the COX pathway, or PGH synthases. The COX pathway converts arachidonic acid to prostaglandins, prostacyclin, and thromboxane A2 (12,27,28). There are 2 isoforms of COX, COX-1 and COX-2 (28). COX-1 is constitutively expressed in most tissues, including respiratory epithelial and endothelial cells. Prostaglandins derived from COX-1 are involved in cellular housekeeping functions, are produced by most cells, and serve a cytoprotective role (29). Because of the sheer number of cells synthesizing prostaglandins, COX-1 is the main source of PGE2 in all organ systems (30). PGE2 is an essential protective prostanooid for the airways, reducing leukotriene synthesis by inhibiting 5-LO, particularly in subjects with AERD (31,32). COX-2 is induced during inflammation and synthesizes inflammatory prostanooids, which participate in inflammatory diseases, including asthma and arthritis.

By inhibiting the COX pathway, ASA and NSAIDs divert arachidonic acid metabolites to the LO pathway. As PGE2 levels decline, the inhibitory effect on mast cells and eosinophils is lost, allowing the release of preformed mediators such as histamine and tryptase as...
as synthesis of cysteinyl leukotrienes (33). This ultimately leads to bronchoconstriction as well as the histamine-mediated upper respiratory reactions. It appears that inhibition of COX-1 results in this dramatic shift in prostanoids and is critical in initiating the severe asthma response to low doses of potent COX-1 NSAIDs seen in sensitive individuals.

In conclusion, the results of this study further support the notion that COX-1 inhibition plays a role in precipitation of severe asthma attacks in AERD and demonstrate the safety of the COX-2 selective inhibitor celecoxib in asthmatic individuals. We have now challenged more than 120 patients with proven ASA sensitivity with the selective COX-2 inhibitors celecoxib and rofecoxib, and have not seen cross-reactions (13).

REFERENCES