

## Severe Bronchospasm after Parenteral Parecoxib: Cyclooxygenase-2 Inhibitors: Not the Answer Yet

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IN a subset of patients with asthma, nonsteroidal antiinflammatory drugs (NSAIDs) that inhibit both cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) can precipitate dangerous asthmatic attacks. It has been proposed that in these patients, the attacks are triggered by inhibition of COX-1 and not COX-2, and that the use of highly selective COX-2 inhibitors may be safe in asthmatic patients, even those with sensitivity to NSAIDs.<sup>1</sup> We describe two cases of acute, life-threatening bronchospasm after administration of parecoxib, a parenteral COX-2 inhibitor, in patients with a history of asthma but no previous history of aspirin or other NSAID sensitivity.

### Case 1

A 26-yr-old woman was admitted for arthroscopy of her left knee. She reported a history of mild asthma, which was well controlled with inhaled salbutamol and beclomethasone. She had no known drug allergies. Anesthesia was induced with fentanyl and propofol, and a laryngeal mask airway was inserted. Anesthesia was maintained with sevoflurane in oxygen and nitrous oxide. Surgery proceeded uneventfully, and toward the end of the case, 40 mg parecoxib sodium was administered intravenously. Within 10 min after administration, the patient began to desaturate, and her peak airway pressures increased acutely to the extent that she became extremely difficult to ventilate. The laryngeal mask airway was removed on suspicion that it had become displaced. However, the patient continued to desaturate despite the application of positive end-expiratory pressure *via* a facemask. The patient underwent immediate intubation with a clear view of the endotracheal tube going through the glottic opening. After intubation, the patient continued to desaturate, and there was minimal chest movement with hand ventilation. No end-tidal carbon dioxide was detected, and there was no air entry heard on auscultation. The patient became bradycardic and required one dose of 0.6 mg atropine and a brief period of chest compressions. During this time, salbutamol was administered *via* a metered dose inhaler through the endotracheal tube. An end-tidal carbon dioxide trace appeared on the monitor, and the chest began to move more easily with hand ventilation. On auscultation, there was diffuse bilateral wheezing. The patient's saturations recovered to 98%,

and after a short period of ventilation in the operating room, she was allowed to wake up and was extubated. She was transferred to the postanesthesia care unit, where she received nebulized ipratropium bromide and salbutamol, and her bronchospasm resolved within 30 min. A chest x-ray film showed normal lung fields with no evidence of pneumothorax. Arterial blood gas measurement was normal. The patient was returned to the ward after a few hours in the postanesthesia care unit, with no lasting adverse effects. Her case was reviewed by the respiratory physicians, who commenced her on a short course of oral steroids. She was discharged home the next day.

### Case 2

A 70-yr-old man presented for urgent laparotomy for large bowel obstruction. He had a history of ischemic heart disease and had undergone coronary artery bypass grafting 10 yr previously; he had atrial fibrillation for which he was anticoagulated with warfarin, non-insulin-dependent diabetes mellitus, and chronic obstructive airway disease. He used inhaled ipratropium bromide four times a day. He had no known drug allergies. On examination, he had mild bilateral wheezing.

A rapid sequence induction was performed, and anesthesia was maintained with sevoflurane in oxygen and nitrous oxide. Muscle relaxation was achieved with vecuronium, and morphine was given for analgesia. The patient was ventilated for a few hours in the intensive care unit postoperatively. He underwent extubation the next morning and was later transferred to the ward on a morphine patient-controlled analgesia pump.

The next day, the patient was allowed to sit out of bed and continued his preoperative ipratropium bromide regimen. He received routine chest physiotherapy and was noted to have a moderately effective cough with little sputum and no wheezing on auscultation. He later reported breakthrough pain and was given an intramuscular injection of 40 mg parecoxib sodium. During the next 2 h, the patient became increasingly dyspneic, wheezy, and hypoxic. He required reintubation and transfer back to the intensive care unit, where he was treated with nebulized bronchodilators and intravenous steroids. He underwent extubation 3 days later and was discharged back to the ward, where he made a full recovery.

## Discussion

Nonsteroidal antiinflammatory drugs are now widely used for the management of postoperative pain. However, these drugs are associated with a number of adverse effects, including gastrointestinal damage, deterioration in renal function, impaired platelet aggregation, and bronchospasm. In some asthmatic individuals, aspirin and other NSAIDs exacerbate the condition. This may sometimes take the form of a distinct clinical syndrome called *aspirin-induced asthma* or *aspirin-sensitive respiratory disease* and is characterized by an eosinophilic rhinosinusitis, nasal polyposis, aspirin sensitivity, and asthma. The incidence of NSAID sensitivity in asthmatic adults is thought to be 3-5% based on patients' histories alone but may be as high as 15%

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when adult asthmatic patients are prospectively challenged with an NSAID.<sup>2</sup> However, because asthmatic patients may deliberately avoid NSAIDs or may not recognize mild NSAID-induced reactions, aspirin-sensitive respiratory disease remains widely underdiagnosed in this particular population. The asthmatic attacks that ensue are often severe and, in many cases, may be life threatening, requiring emergency mechanical ventilation.<sup>3</sup>

The clinical presentation of an NSAID-related attack is usually that of an acute asthma attack developing within 3 h after ingestion of the drug. This can be accompanied by profuse rhinorrhea, conjunctival injection, sometimes a scarlet flushing of the head and neck, and occasionally periorbital edema, abdominal pain, and minor degrees of urticaria. Definitive diagnosis can be established only by provocation tests using increasing doses of aspirin. More recently, provocation tests have been accompanied by measurement of urinary leukotriene E<sub>4</sub>, which increases proportionally with the increasing severity of the respiratory reaction.<sup>4</sup>

The mechanism of this extreme sensitivity to NSAIDs remains unclear. We know that cyclooxygenase enzymes exist in at least two isoforms, which are encoded by distinct genes. Both isoforms constitute the central core of a coenzyme called *prostaglandin H<sub>2</sub> synthase*, which in turn is responsible for the formation of oxygen radicals, prostacyclin, prostaglandin F<sub>2α</sub>, and prostaglandin E<sub>2</sub> from arachidonic acid. COX-1 is the constitutive form and is found in most cells in the body. It is the main source of prostaglandin E<sub>2</sub> in all organ systems. COX-2 is induced during inflammation and enhances the synthesis of inflammatory prostanoids. Much evidence suggests that prostaglandin E<sub>2</sub> may have an important part to play in maintaining bronchial patency.<sup>5</sup> Prostaglandin E<sub>2</sub> partially inhibits 5-lipoxygenase, which is involved in the production of leukotrienes. These provoke constriction of smooth muscle and stimulation of airway mucus production, a hallmark of allergic and inflammatory reactions. Prostaglandin E<sub>2</sub> also has a role in stabilizing mast cells, thus preventing discharge of preformed mediators, histamine and tryptase. The reduction of prostaglandin E<sub>2</sub> by COX-1 inhibitors seems to contribute to the pathogenesis of NSAID-induced respiratory reactions. When concentrations of prostaglandin E<sub>2</sub> decrease, their inhibitory effect on mast cells and eosinophils declines and then disappears. 5-Lipoxygenase activity remains unchecked and hastens the synthesis of new leukotrienes. At the same time, mast cells discharge their contents. The upper respiratory reaction is thought to be predominantly caused by histamine.<sup>6</sup> It has been found that in patients with NSAID-induced asthma, bronchial prostaglandin E<sub>2</sub> is already deficient, thus making them more susceptible to cyclooxygenase inhibition.<sup>7</sup>

Recent clinical studies indicate that it is the inhibition of COX-1 and not COX-2 that precipitates asthmatic attacks, and there is a growing body of evidence indicating that the new, highly specific COX-2 inhibitors,

known as *coxibs*, are well tolerated and can be safely used in these patients.<sup>1,8-11</sup>

These highly selective inhibitors of COX-2, namely celecoxib, rofecoxib, and parecoxib, theoretically should not cause airway mucosal inflammation because of the preservation of constitutive prostaglandin E<sub>2</sub>. Therefore, it is thought that selective COX-2 inhibitors should be safe in patients with NSAID sensitivity.

*Parecoxib sodium* is an injectable prodrug of valdecoxib, which is a potent and selective inhibitor of COX-2. It is the first parenteral COX-2-selective inhibitor to be developed for the management of pain. Various studies have demonstrated the tolerance of selective COX-2 inhibitors in patients with NSAID-sensitive respiratory disease. Martin-Garcia *et al.*<sup>8</sup> showed that all 40 of their study patients, who had previously experienced asthma induced by at least two different NSAIDs, tolerated a 25-mg dosage of rofecoxib well, without any signs of immediate or delayed reactions, and concluded that rofecoxib is a suitable NSAID for treatment of patients with aspirin- and other NSAID-induced asthma. Similarly, the same investigators showed that celecoxib at a dose of 200 mg was well tolerated by all 33 participants in a study of patients with the same condition.<sup>9</sup> Stevenson and Simon<sup>1</sup> showed that none of 60 patients with aspirin-induced asthma reacted to rofecoxib after oral ingestion and concluded that cross-reactivity between aspirin and rofecoxib does not occur in these patients. Dahlen *et al.*<sup>10</sup> examined 27 patients with aspirin intolerance for bronchospasm after the administration of celecoxib and found that it did not induce any adverse reaction. In a recent double-blind, randomized, crossover, increasing-dose challenge study with placebo or celecoxib, investigators looked for biochemical and clinical evidence that COX-2 inhibitors are well tolerated in aspirin-intolerant asthmatic patients, and the study showed no significant differences in pulmonary function, nasal symptom scores, extrapulmonary responses (such as dermal flush, urticaria, and gastrointestinal symptoms) or urinary leukotriene E<sub>4</sub> concentrations after oral celecoxib in 33 subjects with aspirin-intolerant asthma.<sup>11</sup> However, all of these studies involved limited numbers of patients, and the patients were desensitized by receiving progressively larger oral doses of the COX-2 inhibitor for a few days before receiving a therapeutic dose.

In both of our cases, severe, life-threatening bronchospasm occurred within a short period after administration of parenteral parecoxib. On questioning after the event, the patient in case 1 confirmed that she had taken oral COX-2 inhibitors infrequently in the past without noticing any ill effects. The patient in case 2 had avoided NSAIDs because he was taking warfarin. All of the studies in the literature to date involved gradually exposing subjects to therapeutic doses of oral COX-2 inhibitors over a period of days. Both of our patients received the recommended dosage of parecoxib (40 mg) by the par-

enteral route without any previous desensitization. Furthermore, because NSAID-induced respiratory reactions are dose dependent, the comparatively rapid uptake of a parenteral COX-2 inhibitor as opposed to an oral one may be a factor in the severity of the bronchospasm experienced by our patients.

We therefore propose that, although oral COX-2 inhibitors may be found to be safe in NSAID-sensitive patients, parenteral COX-2 inhibitors should be used with extreme caution in patients with any history of bronchospasm who have not previously been desensitized to their bronchoconstrictor effects. We also suggest that further studies with parenteral doses of COX-2 inhibitors in larger numbers of patients with NSAID-sensitive respiratory disease would be necessary to verify the safety of these drugs in this particular patient population.

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