

An extremely unusual case presentation of aspirin-exacerbated respiratory disease (AERD)

Dear Editors:

It was with great interest that we read the Clinical Pearls and Pitfalls in the May–June 2011 issue by Umemoto J. et al.¹: Selective cyclooxygenase-2 inhibitor cross-reactivity in aspirin exacerbated respiratory disease.

The case was extremely unusual as a presentation of aspirin-exacerbated respiratory disease (AERD) and may be more reflective of another as yet undefined sensitivity to COX-2 inhibitors. The case is similar in some aspects to a report by Baldassarre in 2006 in which asthma was triggered by low dose celecoxib as well as by aspirin and acetaminophen in a patient who clearly had AERD.²

In your case, the features that are atypical for AERD include the absence of a description of nasal polyps. This would be most unusual in a patient with AERD. Additionally she is described as experiencing anaphylactic shock from a variety of structurally unrelated antibiotics most of which have only been reported to be associated with anaphylaxis in single drug reactors. Your initial description of exercise-induced anaphylaxis associated with the ingestion of dietary salicylates has to our knowledge not previously been described. Specific food-dependent exercise-provoked anaphylaxis has been described to a number of foods that yielded positive skin tests as well as a few food additives. There is no evidence to suggest that there is significant inhibition of the COX-1 enzyme with dietary salicylates, because the mechanism of aspirin's effect on both COX-1 and COX-2 is acetylation of the enzymes. NSAIDs prevent the function of the COX-1 enzyme through dose-dependent competitive inhibition. The salicylate molecule is too small to block the COX-1 channel. Therefore, there is no mechanism to trigger a COX-1-dependent reaction and even huge amounts of natural salicylates are not adequate to elicit any respiratory reactions in AERD patients.³

It is unusual, in our experience for AERD patients to have supranormal lung function. In addition, it is quite unusual to see any asthmatic patient with above-normal lung function who has such exquisite methacholine and histamine sensitivity.

Furthermore, your described aspirin challenge results are very atypical in that she experienced a severe reaction at 15 mg of aspirin with loss of consciousness. For the more than 1500 patients challenged at our institution with proven

AERD we have not seen such a severe reaction at any dose of aspirin, much less this extremely low dose that you used. It has been our experience that the typical provoking dose for aspirin in patients with AERD is between 60 and 100 mg. To react so severely at 15 mg of aspirin suggest that perhaps another mechanism is occurring. The follow up challenge with 50 mg celecoxib was also atypical. Celecoxib is a potent inhibitor of COX-2 and very weak inhibitor of COX-1 at very high doses. When the selectivity is estimated by the human whole blood assay, celecoxib has a selectivity of 7.6 in favor of COX-2, suggesting that there would be very little, if any, inhibition of COX-1 at the 50 mg dose of celecoxib.⁴ As cited earlier, this may reflect a new reaction process to molecules of celecoxib. Other COX-2 inhibitors were not used in subsequent challenges, and therefore a class effect was not proven.

The authors go on to outline their treatment strategy that included high dose fluticasone, salmeterol, 10 mg prednisolone daily, and montelukast. Given her normal lung function at baseline, it is unclear as to the utility of so many medications, and this in addition to all of the above, calls into question the possibility of paradoxical vocal fold movement disorder or other, nonasthmatic mechanisms to explain the reported severe respiratory reactions at minor doses of aspirin and celecoxib. The authors only report the FEV₁ decreases. Changes in FVC, PEF, FEF_{25–75} would be of interest as would seeing actual flow/volume inspiratory loops.

In summary, this represents an extremely unusual case, which is not suggestive of the typical AERD patient. The experience with the highly selective COX-2 inhibitors, is that they are generally safe. It has always been our recommendation that the first dose of a COX-2 inhibitor be given in the physician's office in view of the few reports in the literature of single drug reactions to specific COX-2 inhibitors.

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R. Simon is a speaker for GSK, Merck, Novartis, and AstraZeneca. The remaining authors have no conflicts to declare pertaining to this letter.

Reply

To the Editor

We thank Dr. Woessner and her colleagues¹ for their interest in our work. They point out that the case we have presented is unusual and is not suggestive of typical aspirin-exacerbated respiratory disease (AERD). Our patient reacted to a very low dose of aspirin (15 mg) with severe aspirin-induced asthma (AIA) and had very severe airway hyperresponsiveness to acetylcholine (PC₂₀-ACh 0.635 mg/mL) or histamine (PC₂₀-Hist 0.375 mg/mL). Bronchial constriction led to a decrease in FEV₁ from 3.13 to 1.88 L and in V₅₀ from 4.08 to 1.44 L/s at a histamine dose of 0.375 mg/mL. Like the FEV₁, the V₅₀ decreased after provocation with aspirin or celecoxib. It was impossible for this to be associated with vocal cord dysfunction. This patient was atopic, with positive IgE RAST results for house dust mite, cedar pollen, ragweed, and *Candida*. Our patient had frequently experienced asthma attacks triggered not only by NSAIDs, but also by food additives, and by upper respiratory tract infections, exposure to house dust mites, and atmospheric depressions in spring. The patient therefore had many triggers for her asthma attacks, the asthma attacks lasted for more than half a week, and she needed treatment with oral prednisolone 10 mg/day, high doses of inhaled fluticasone propionate, montelukast sodium 10 mg, and salmeterol xinafoate. In between asthma attacks the patient had normal lung function at baseline, but during asthma attacks her %PEF decreased by more than 20% from her personal best. Hope et al.² reported that 264 (62.9%) of 420 AIA patients had normal lung function (>80% of baseline FEV₁) and that 30 mg of aspirin (the lowest provocation dose) produced positive challenge results in 9% of patients. We consider it possible that among this 9% of patients there are some that would react positively to <15 mg of aspirin. Akiyama et al.³ mentioned that extremely low doses of aspirin

(as low as 10 mg) can induce a response in oral challenge tests: some extremely reactive patients develop severe silent airway obstruction—in other words, severe obstruction with low continuous rhonchi. This is similar to what occurs in status asthmaticus or IgE-dependent anaphylaxis. Our patient had silent airway obstruction with loss of consciousness in response to aspirin, celecoxib, acetylcholine, or histamine.

We confirmed the presence of sinusitis with mucosal hypertrophy in the sphenoid and maxillary sinuses on computed tomography (CT) scan, but without nasal polyps. However, it is possible that the polyps were absent only because the CT scan was performed after treatment with systemic steroids.

The salicylate molecule is indeed too small to block the COX-1 channel and may therefore not be an influence in most AERD patients. However, there is a report of one patient with AERD who experienced a bronchoconstriction reaction to 30 mg of aspirin and also developed a broncho-obstructive reaction after taking sodium salicylate.⁴ Moreover, a salicylate-free diet for 3 weeks improved the clinical symptoms and lung function in a child with AERD.⁵ The patient that we presented had very severe AERD and IgE-dependent atopic asthma. We consider that when extremely low doses of aspirin are given, the salicylate molecule may be able to block the COX-1 channel.

The authors have nothing to disclose pertaining to the original article or reply.

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