Different eicosanoid profile of the hypersensitivity reactions triggered by aspirin and celecoxib in a patient with sinusitis, asthma, and urticaria

To the Editor:

A 30-year-old woman was evaluated at our institution because of asthma and drug hypersensitivity. The patient had been well until 5 years earlier, when she started to experience intermittent lids edema; no relationship to drugs or environmental factors could be detected. Two years later, she developed watery rhinorrhea with nasal blockage which became perennial and was accompanied by itching in eyes, reduced sense of smell, and feeling of stuffiness in the nose. Computed tomography (CT) scan revealed pansinusitis with multiple nasal polyps. Ethmoidectomy was performed, but symptoms of sinusitis recurred within the next 3 months. She then developed dyspnea and wheezing, which was controlled by chronic inhaled corticosteroids and oral prednisone 12 mg/d. Urticaria began to appear sporadically. In June 2005, ingestion of a naproxen tablet led to facial rash, sudden shortness of breath, throat congestion, and abdominal discomfort. Similar symptoms, though less intense, appeared after a tablet of ibuprofen. The personal and family history was irrelevant except that one of her cousins on the maternal side suffered from aspirin-precipitated urticaria/angioedema. Her skin tests to common seasonal and perennial allergens were negative, peripheral blood eosinophil count was $830/\text{mm}^3$, total IgE was 189 IU/mL, and specific IgE was absent. At base, the LT (leukotriene) E_4 urinary excretion, measured on several occasions, was very high (2500–5000 pg/mg creatinine; normal range, below 70 pg/mg creatinine). She was heterozygous for LTC₄ synthase polymorphism -444 AC. The challenge was approved by the University Ethical Committee, and the patient gave informed consent.

For eicosanoid determinations to samples of urine, we added deuterium-labeled LTE₄, 9 α 11 β PGF₂ (urinary metabolite of prostaglandin [PG] D₂), PGE₂-M (urinary metabolite of PGE₂), and 11-dehydro-TXB₂ (urinary metabolite of thromboxane A₂) before further processing, which consisted of thin layer chromatography, derivatization, and gas chromatography–mass spectrometry of prostanooids or immunoaffinity adsorption and HPLC-MS/MS for LTE₄. These measurements permitted discrimination at the biochemical level of the 2 adverse reactions studied.

When challenged with celecoxib 400 mg, the patient developed in 2 hours flushing, dyspnea, and a fall in FEV₁ by 21%; 8 hours later, urticaria on the legs appeared and recurred the next day. Urinary LTE₄ and PGE₂-M excretions remained unchanged (3132 pg/mg creatinine and 7.4 ng/mg creatinine, respectively), and 9 α 11 β PGF₂ rose from 1.3 to 2.6 pg/mg creatinine at 2 hours.

Oral aspirin challenge with cumulative dose of 188 mg precipitated flushing, nasal blockage, throat irritation, and dyspnea with a fall in FEV₁ of 27%. Twenty minutes later,

the patient fell into shock despite administration of subcutaneous adrenaline, salbutamol, and intravenous methylprednisone. Her blood pressure was 60/40 mm Hg, heart rate 128 beats per minute, and oxygen saturation while breathing ambient air 84%. A chest radiograph showed bilateral patchy infiltrates consistent with pulmonary edema. Typical treatment in the intensive care unit led to reversal of the edema and stabilization of the vital signs. Bouts of multiform skin eruptions, covering most of the body, appeared and fluctuated during the next 4 days.

Urinary eicosanoid levels all rose, then peaked 2 to 4 hours after the start of the challenge, at the height of clinical symptoms: LTE₄ from 3448 to 14 310 pg/mg creatinine, 9 α 11 β PGF₂ from 1.85 to 2.73 pg/mg creatinine, PGE₂-M from 14.7 to 56.2 ng/mg creatinine, and 11-dehydro-TXB₂ from 2.01 to 4.61 ng/mg creatinine. No changes in concentration of these metabolites was detected during the preceding placebo challenges.

When seen 2 weeks later in the clinic, the patient complained of nasal blockage and headache; CT scan revealed total opacification of paranasal sinuses. She was prescribed zileutone 600 mg 4 times a day for 6 weeks. Her symptoms resolved, and CT scan showed almost complete disappearance of opacification with some residual mucosal thickening; her urinary LTE₄ decreased gradually from 2800 to 25 pg/mg creatinine. Discontinuation of zileutone for 2 weeks led to recurrence of nasal symptoms and a rise in LTE₄ to 1761 pg/mg creatinine. Zileutone was restarted again, and the symptoms subsided.

Although celecoxib is generally well tolerated by aspirin-sensitive subjects,^{1,2} occasional reactions because of its intolerance (mainly skin reactions, but also rare cases of anaphylaxis) have been reported.^{3–5} We describe a patient sensitive both to aspirin and celecoxib in whom we managed to measure excretion of the eicosanoids metabolites with a high accuracy. Aspirin precipitated release of both cysteinyl leukotrienes (cys-LTs) and PGD₂. In contrast, celecoxib triggered exclusively release of PGD₂, without affecting cys-LTs production. In the later case, clinical reaction should be attributed predominantly, if not solely, to mast cell activation. Thus, we found a difference with a recently reported⁵ case. In a woman with asthma with extreme sensitivity to paracetamol and aspirin (provocative dose, 10 mg), celecoxib at a dose of 15 mg precipitated bronchospasm and a rise in urinary LTE₄ excretion; PGD₂ was not determined.⁵

Celecoxib belongs to preferential COX-2 inhibitors, with 5-fold to 50-fold selectivity for COX-2 over COX-1.⁶ In contrast, aspirin inhibits both COX isoforms with significantly greater selectivity for COX-1.⁶ It appears that in our patient, a coxib with preferential COX-2 affinity precipitated asthma and urticaria symptoms because of its weak inhibition of COX-1. Aspirin, a nonselective COX inhibitor, triggered severe systemic reaction, in which cys-LTs supervened to asthma/urticaria symptoms

and shock. The provocative dose of aspirin was insufficient to block urinary COX metabolites—PGE₂-M and 11-dehydro-TXB₂. In fact, levels of both these metabolites rose rather than declined. This indicates that a patient with unusually high overproduction of cys-LTs was extremely susceptible to pharmacological inhibition of COXs, at the doses that did not depress any systemic metabolites of these enzymes. Reactions to both drugs were accompanied by an increase in PGD₂, the marker of mast cell activation.⁷ Thus, this cell seemed critical for triggering of an acute episode, progressing to a life-threatening shock when cys-LTs were involved by aspirin.

Our patient produced extreme amounts of cys-LTs, and the severity of the respiratory reactions during aspirin challenge was reported⁸ to be associated with the degree of baseline LTE₄ urinary excretion. We suspect that massive cys-LTs overproduction was related to severe chronic rhinosinusitis⁹ and inheritance of 1 genetic variant of LTC₄ synthase. The remarkable efficacy of the leukotrienes biosynthesis inhibitor, zileutone,¹⁰ which caused a regression of sinusitis concurrently with a return of urinary LTE₄ to the normal range, suggests that the patient's upper airway inflammation was mediated mainly by cys-LTs. Thus, in a patient with severe sinusitis and asthma, pharmacologic inhibition of leukotriene biosynthesis might be a worthy therapeutic option.

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9. Higashi N, Taniguchi M, Mita H, Kawagishi Y, Ishii T, Higashi A, et al. Clinical features of asthmatic patients with increased urinary leukotriene E₄ excretion (hyperleukotrienuria): Involvement of chronic hyperplastic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol* 2004;113:277-83.
10. Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157:1187-94.

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REFERENCES

1. Dahlen B, Szczeklik A, Murray JJ. Celecoxib in patients with asthma and aspirin intolerance. *N Engl J Med* 2001;344:142.
2. Viola M, Quarantino D, Gaeta F, Caringi M, Valluzzi R, Caruso C, et al. Celecoxib tolerability in patients with hypersensitivity (mainly cutaneous reactions) to nonsteroidal anti-inflammatory drugs. *Int Arch Allergy Immunol* 2005;137:145-50.
3. Sanchez Borges M, Capriles-Hulett A, Caballero-Fonseca F, Perez CR. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001;87:201-4.
4. Grimm V, Rakoski J, Ring J. Urticaria and angioedema induced by COX-2 inhibitors. *J Allergy Clin Immunol* 2002;109:370.
5. Baldassarre S, Schandene L, Choufani G, Michils A. Asthma attacks induced by low doses of celecoxib, aspirin, and acetaminophen. *J Allergy Clin Immunol* 2006;117:215-7.
6. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A* 1999;96:7563-8.
7. Dahlen SE, Kumlin M. Monitoring mast cell activation by prostaglandin D₂ in vivo. *Thorax* 2004;59:453-5.
8. Daffern PJ, Muilenburg D, Hugli TE, Stevenson DD. Association of urinary leukotriene E₄ excretion during aspirin challenges with severity of respiratory responses. *J Allergy Clin Immunol* 1999;104:559-64.