

Selective cyclooxygenase-2 inhibitor cross-reactivity in aspirin-exacerbated respiratory disease

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ABSTRACT

Aspirin-induced asthma (AIA) is a severe and difficult-to-treat allergic disease in which acute asthma attacks are induced by nonsteroidal anti-inflammatory drugs. Patients with AIA rarely experience asthma attacks when taking celecoxib, a specific inhibitor of cyclooxygenase (COX) 2. A 33-year-old woman had a severe asthma attack with hypoxia and lost consciousness after oral provocation testing with 15 mg of aspirin and also with 50 mg of celecoxib. After 2 months of treatment with 10 mg/day of oral prednisolone, 1600 µg/day of inhaled fluticasone propionate, montelukast as a leukotriene receptor antagonist (LTRA), and long-term beta-agonist, we again challenged her with a provocation test with up to 200 mg of celecoxib; this time there were neither allergic symptoms nor decrease in forced expiratory volume in 1 second. Patients with severe or poorly controlled asthma may experience asthma attacks even if using selective COX-2 inhibitors. However, treatment with steroids and an LTRAs may inhibit asthma attacks induced by celecoxib.

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Question:

What additional clinical findings in patients with aspirin-exacerbated respiratory disease (AERD) would be helpful in arriving at a diagnosis?

- A. Fungal sensitization
- B. Eosinophilic gastroenteritis
- C. Complicated nasal polyps
- D. Necrotizing vasculitis

AERD, formerly referred to as aspirin-induced asthma (AIA) or aspirin-intolerant asthma, is characterized by recalcitrant mucosal inflammation of the upper and lower respiratory tract combined with precipitation of asthma, rhinitis, and eosinophilic sinusitis attacks after ingestion of acetylsalicylic acid and most nonsteroidal anti-inflammatory drugs (NSAIDs) that preferentially inhibit cyclooxy-

genase (COX) 1.¹ The prevalence of AIA is reported to be 4.3–11% in adult patients with asthma.² AERD is an acquired disease with an onset of symptoms starting between the teenage years and age 60 years; it is more prevalent among women than men.¹ The original chronic rhinitis progresses to chronic hyperplastic eosinophilic sinusitis with nasal polyposis as a characteristic sign of this disease. The prevalence of AIA is 30–42% in patients with both asthma and nasal polyps or abnormal sinusitis as diagnosed by x rays or computed tomography.¹ AIA is a severe and difficult-to-treat allergic disease, and patients are twice as likely to die from their disease as are patients with non-aspirin-sensitive asthma. Patients with AIA have lower postbronchodilator percent forced expiratory volume in 1 second (FEV₁) and greater frequency of intubation, emergency visits, and systemic corticosteroid bursts than patients with non-AIA.³ Patients with AIA rarely experience asthma attacks in response to ingestion of celecoxib, a specific inhibitor of COX-2.⁴ We present the case of a patient with severe AIA who experienced a bronchial asthma attack after taking celecoxib.

CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

A 33-year-old Japanese woman presented with a history of chronic sinusitis since the age of 12 years.

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The authors have nothing to declare pertaining to this article

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Subsequently, she had experienced urticaria, dyspnea, and abdominal pain after taking NSAIDs.

She had bronchial asthma attacks every early spring for the last 5 years, and for the last 3 years she had a history of episodes of exercise-induced anaphylaxis after the consumption of foods containing salicylic acid. For the last 2 years her asthma had taken a turn for the worse and she experienced bronchial asthma attacks with hypoxia and lost consciousness after taking NSAIDs. She also had a history of anaphylactic shock induced by other drugs, including cefaclor, cefcapene pivoxil hydrochloride, erythromycin, minocycline hydrochloride, levofloxacin, and ciprofloxacin hydrochloride. The patient was atopic, with positive IgE radioallergosorbent test results for house-dust mites, cedar pollen, ragweed, and *Candida*. The patient had normal lung function when not experiencing asthma attacks, including vital capacity of 3.45 L, percent vital capacity of 120%, FEV₁ of 3.05 L, percent FEV₁ of 113%, maximum expiratory flow rate at 50% of forced vital capacity (V50) of 3.75 L, and percent V50 of 92%. She underwent bronchial provocation testing with acetylcholine (ACh) and histamine (Hist). Bronchial sensitivity was expressed as provocative concentration (PC₂₀), defined as the PC of agonist in the inhaled aerosol (ACh at up to ≤20 mg/mL or Hist at up to 10 mg/mL) leading to a 20% decrease in FEV₁. The results were positive: PC₂₀-ACh was 0.635 mg/mL and PC₂₀-Hist was 0.375 mg/mL.

The patient also underwent an oral provocation test with 15 mg of aspirin. After 30 minutes, she had clinical symptoms such as a plugged nose, urticaria, dyspnea, stomach ache, and a decrease in FEV₁ from 2.97 to 0.82 L, with silent airway obstruction but with loss of consciousness. She had anosmia complicated by sinusitis with mucosal hypertrophy in the sphenoidal and maxillary sinuses on computed tomography scan. Because patients with AIA rarely experience asthma attacks when taking celecoxib,⁴ we gave the patient an oral provocation test with 50 mg of celecoxib. After 30 minutes, she had clinical symptoms such as a plugged nose, urticaria, dyspnea, and a decrease in the FEV₁ from 2.84 to 0.81 L (Fig. 1).

DIAGNOSIS

We diagnosed the patient with severe AIA and it became clear by other provocation tests that she had also had asthma attacks induced by other NSAIDs, including etodolac, meloxicam, and tiaramide hydrochloride.

MANAGEMENT

The patient had frequently experienced asthma attack triggered by consuming foods containing salicylic acid or exercise; these attacks caused hypoxia that had required her to use a noninvasive positive-pressure-

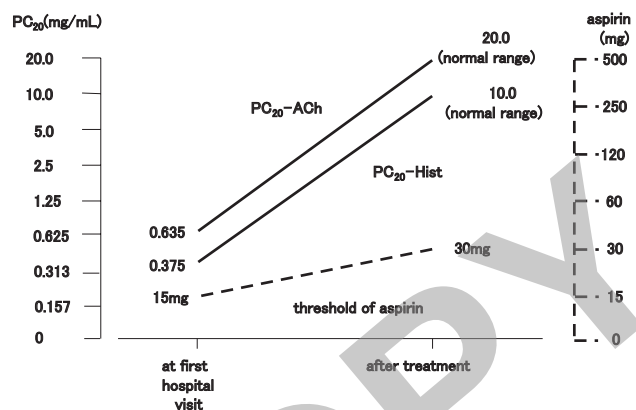


Figure 1. Bronchial sensitivity to acetylcholine (ACh), histamine (Hist), and aspirin at first visit to the hospital and after 2 months of treatment.

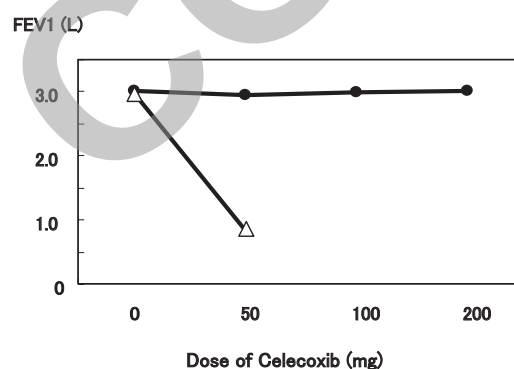


Figure 2. Change in the forced expiratory volume in 1 second (FEV₁) after provocation with 50 mg of celecoxib before treatment (open triangle) and with 50, 100, and 200 mg after treatment (closed circle).

assist device to breathe overnight. To check whether these same reactions would be caused by placebo, after recovery we provided a placebo-controlled oral challenge with lactose; the patient showed no positive reactions to the placebo.

We diagnosed the patient with severe asthma and prescribed treatment with 10 mg/day of oral prednisolone; 1600 µg/day of inhaled fluticasone propionate; 10 mg of montelukast sodium, which is a leukotriene receptor antagonist; and salmeterol xinafoate, which is long-acting β-agonists. After 2 months of treatment, her PC₂₀-Hist had improved from 0.375 to 10 mg/mL (normal range) and her PC₂₀-ACh had improved from 0.635 to 20 mg/mL (also normal range) (Fig. 1). We again challenged her with the oral provocation tests with 50, 100, and 200 mg of celecoxib; the antiasthma medications (prednisolone, fluticasone, montelukast, and salmeterol xinafoate) were withheld for 12 hours before the provocation test: there were neither allergic symptoms nor a decrease in FEV₁ (Fig. 2). However, the aspirin threshold in the airway hyper-sensitivity test did not change almost from 15 to 30 mg

after treatment (Fig. 1). The frequency of asthma attacks with loss of consciousness decreased, and the patient could eat some foods containing salicylic acid without suffering an asthma attack.

Answer B

Pearls

- Patients with severe or poorly controlled asthma may experience asthma attacks triggered by selective COX-2 inhibitors. The aspirin dose (15 mg) at which this patient was sensitive was extremely low, in contrast to the average aspirin provocation dose of 60 mg (range, 30–100 mg) in typical AIA patients (this range is characteristic of a large number of patients with AIA undergoing oral aspirin challenges).⁵ Our patient was diagnosed with severe asthma because her asthma attacks were induced by a low dose of aspirin (15 mg) and she had higher bronchial hyperresponsiveness to ACh or Hist than most patients with AIA or non-AIA.
- After treatment with corticosteroids and leukotriene receptor antagonist, nonspecific bronchial hyperresponsiveness in this patient improved to the normal ranges for ACh and Hist, but not for aspirin.

Pitfalls

- Cross-reaction of selective COX-2 inhibitors with the COX-1 receptors targeted by aspirin or similar NSAIDs almost never occurs in patients with AIA.⁴ However, despite all the safety data and lack of cross-reactivity in the use of selective COX-2 inhib-

itors in large numbers of patients with AIA, rare case reports show that celecoxib can induce clinical symptoms such as urticaria, angioedema, rhinorrhea, conjunctive erythema, bronchospasm, and dyspnea when given to patients with severe or active AIA.^{6,7} There have been similar case reports for other selective COX-2 inhibitors: rofecoxib⁵ and etoricoxib⁸ have induced asthma attacks, and etoricoxib⁹ has caused urticaria or angioedema.

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