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Available online February 2, 2005.
doi:10.1016/j.jaci.2004.12.009

COX-2-selective inhibitor valdecoxib induces severe allergic skin reactions

To the Editor:

Since the 1960s, when the nonsteroidal anti-inflammatory drugs (NSAIDs) were launched into the market, several adverse events have been reported,¹ including skin eruptions mostly caused by nonimmunological rather than allergic mechanisms.^{2,3} NSAIDs exert their analgesic, antipyretic, anti-inflammatory, and antithrombotic effects by inhibiting both COX-1 and COX-2 activities.⁴⁻⁶ However, the primary responsibility for the synthesis of prostanoids involved in acute and chronic inflammatory states has been credited to COX-2, whereas the gastrointestinal adverse effects have been attributed to COX-1 activity.^{1,6} The consequent hypothesis that specific inhibition of this enzyme could have therapeutic effects similar to those of other NSAIDs but without causing gastrointestinal side effects led to the development of COX-2-selective antagonists. Valdecoxib (Bextra, Pfizer, Buckinghamshire, United Kingdom) is one of these new drugs. In the last few years, it has been increasingly prescribed for the treatment of osteoarthritis, rheumatoid arthritis, primary dysmenorrhea, and moderate to severe postoperative pain.⁷

COX-2-specific inhibitors have an alleged safer profile compared with other nonselective NSAIDs.⁴⁻⁶ However, several adverse events caused by selective COX-2 inhibitors have been described.^{8,9} We report here a case of severe hypersensitivity skin reaction caused by valdecoxib.

A 58-year-old man presented with a 2-day history of exanthem, malaise, and fever. For the treatment of arthralgia, the patient had been taking a daily dose of 20 mg valdecoxib for 6 days before the onset of skin lesions. No previous history of skin reactions to other NSAIDs or sulfonamides was reported. On admission, physical examination showed a generalized confluent maculopapular exanthem without mucous membrane involvement (Fig 1, A).

Routine blood examination revealed leukocytosis and increased values of creatinine, lactate dehydrogenase, total bilirubin, C-reactive protein, and eosinophil cationic

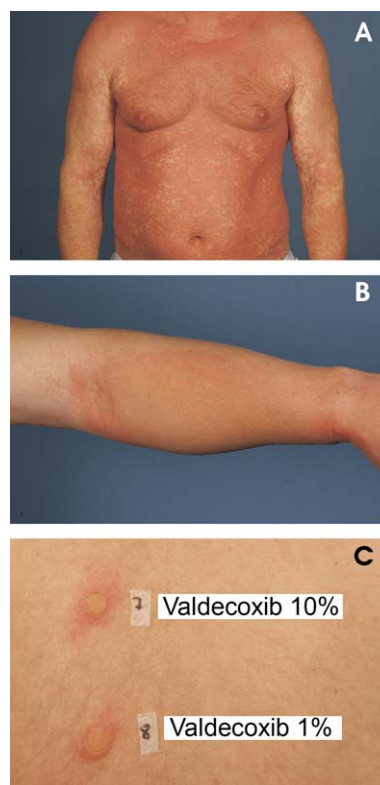


FIG 1. Severe allergic skin reactions to valdecoxib. **A**, A 58-year-old patient with a generalized maculopapular exanthem induced by valdecoxib. **B**, Severe and spreading skin reaction 48 hours after scratch testing with valdecoxib. **C**, Skin reaction (++++) day 2 after epicutaneous patch testing with valdecoxib (at a concentration of 10% in the upper reaction and 1% in the reaction below).

protein. Serological tests for adenovirus, echovirus, coxsackie, measles, and hepatitis virus were negative, and antibodies to rubella and Epstein-Barr virus showed signs of previous infection. Ultrasonography revealed enlargement of lymph nodes caused by local inflammation. After discontinuation of valdecoxib and treatment with systemic glucocorticosteroids, antihistamines, and local glucocorticosteroids, the exanthem disappeared.

Histopathological examination of a skin biopsy revealed slight spongiosis of the epidermis and a perivascular inflammatory infiltrate consisting mostly of lymphocytes, neutrophils, and few eosinophils.

Skin prick tests with seasonal and perennial airborne allergens as well as standard food allergens were uniformly negative. Scratch tests performed with nonspecific NSAIDs (acetylsalicylic acid, metamizol, paracetamol, diclofenac, indometacin, ibuprofen) as well as the COX-2-selective inhibitors celecoxib and valdecoxib showed no skin reactions after 20 minutes. However, 24 hours later, a severe erythematous and edematous skin lesion occurred, spreading over the forearm where scratch tests had been performed (Fig 1, B). Notably, subsequent scratch tests with acetylsalicylic acid, metamizol, paracetamol, diclofenac, indometacin, ibuprofen, and celecoxib, but without valdecoxib, were uniformly negative at 20

minutes as well as 24 hours after exposure. In epicutaneous patch testing with standard allergens and Bextra, the tests with benzalkonium chloride and cetalkonium chloride were + (according to the International Contact Dermatitis Research Group criteria),¹⁰ and in the test with Bextra, a +++ delayed-type skin reaction with a peak response on day 3 developed. In addition, patch testing with single components of Bextra revealed +++ skin reactions to the pure active substance valdecoxib (1% and 10% in aqua) with peak responses on days 2 and 3 (Fig 1, C). To exclude valdecoxib-induced irritant responses, healthy individuals (n = 4) were patch-tested with valdecoxib (1%, 10%) and demonstrated no skin reactions.

Nonimmunological hypersensitivity reaction to non-specific NSAIDs is a well-known and frequent cause of skin reactions. An increasing number of studies suggest that the COX-2-selective antagonists can be safely taken by patients who develop cutaneous reactions caused by nonselective NSAIDs.^{3,4,6} However, here we report that the COX-2-selective inhibitor valdecoxib may induce severe allergic skin reactions.

Because valdecoxib and celecoxib have an analogous chemical structure,^{7,8} one could expect a cross-reaction between these 2 drugs. However, in previous reports showing allergic skin reactions to celecoxib, tests with other specific COX-2 inhibitors were either negative⁸ or not mentioned.⁵ A scratch test with celecoxib demonstrated no reaction in our patient. Although these findings suggest that a cross-reaction is unlikely, further studies are necessary to confirm this.

To the best of our knowledge, this is the first report of valdecoxib-induced skin allergy confirmed by a positive patch test. The presented case shows that the COX-2-selective inhibitors valdecoxib may cause severe allergic cutaneous reactions, adding a new aspect to the side effect profile of this drug.

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doi:10.1016/j.jaci.2004.12.1135

Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases

To the Editor:

Eosinophilic esophagitis (EE) is a chronic, IL-5-driven inflammatory disorder of the esophagus.¹ It is characterized clinically by acute and recurrent dysphagia to solid food, occasionally leading to food impaction, vomiting, and abdominal pain, as well as typical endoscopic features and histopathologic findings.¹

Previous observations revealing (1) that more than 70% of adult and 80% of pediatric patients with EE have allergic disorders,^{2,3} (2) that the pattern of inflammatory cells and cytokine expression in EE¹ is similar to the findings in allergic diseases of the airways⁴ or the skin,⁵ (3) that the medication effective in asthma also works in EE,⁶ and (4) that allergen challenge of the upper airways leads to eosinophilia in the esophagus in a mouse model of EE⁷ raise the question of whether EE can be considered an additional manifestation of atopy. This study was designed to investigate whether EE in adults is connected to airway or food allergies. Therefore we investigated the frequency and onset of concomitant atopic diseases and systematically analyzed the allergen sensitization pattern.

We prospectively examined 31 patients (6 female and 25 male patients; age range, 18-66 years; mean age, 37 ± 2.3 years) with previously diagnosed EE.¹ The mean duration of EE was 12 ± 1.7 years (range, 1-40 years). Specific serum IgG levels were determined to exclude *Anisakis simplex* infections as a cause of EE, but all patients had completely negative results. A detailed history of all patients, including current or previous physician-diagnosed atopic diseases, was obtained by means of a questionnaire. Written informed consent was obtained from all patients. The study was approved by the Medical Ethics Committee of Kantonsspital Olten. Total IgE and specific IgE levels to the aeroallergens grass pollen, birch pollen, mugwort pollen, cat dander, and house dust mites and the food allergens cow's milk, egg white, wheat flour, rye flour, and gluten were determined by using the UniCAP system (Pharmacia Diagnostics, Dübendorf, Switzerland). For skin prick tests (SPTs), a standard protocol of 14 aeroallergens and 14 food allergens was applied with allergen extracts (ALK, Horsholm, Denmark), as well as with 3 native probes of