Cutaneous Adverse Reactions to Valdecoxib Distinct From Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Objective: To assess the type of severe skin reactions caused by valdecoxib treatment.

Design: Case registry of severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Setting: All hospitals in Germany that treat patients with severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Patients: Five case notifications of Stevens-Johnson syndrome after the use of valdecoxib were reevaluated following the withdrawal of valdecoxib on April 7, 2005.

Results: A thorough review of all reported cases of severe skin reactions caused by valdecoxib revealed extensive erythematous, targetlike skin eruptions in addition to facial edema and dyspnea. Histologic changes, clinical pattern, and outcome demonstrated a distinct disease entity.

Conclusion: Valdecoxib induces severe skin reactions different from those of Stevens-Johnson syndrome and toxic epidermal necrolysis in clinical and histopathologic findings, course, and outcome.

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STEVENS-JOHNSON SYNDROME (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening skin reactions mainly caused by drugs.1 The consensus definition of these skin reactions is based on the type and distribution of lesions and the extent of blisters and erosions related to the body surface area (BSA).2 The lesions found in severe skin reactions are typical targets, with regular round, well-defined borders with at least 3 different concentric zones: a purpuric central disk with or without a blister, a raised edematous intermediate ring, and an erythematous outer ring. In contrast, raised atypical targets present with only 2 zones and a poorly defined border, while flat atypical targets are characterized by vesicular or bullous lesions in the center, which may be confluent. Targetlike lesions are less clearly demarcated but still have an appearance reminiscent of targets. Manifestations of SJS and TEN include widespread purpuric macules and flat targetlike lesions, mainly on the trunk, preceding epidermal detachment. In contrast, erythema exudativum multiforme majus (also called erythema exudativum multiforme with mucosal involvement) is characterized by typical targetlike lesions mainly on the limbs without confluent exanthema. This is important because erythema exudativum multiforme majus is not induced by drugs but by infection.3 Furthermore, hemorrhagic erosions of at least 1 site of mucous membranes are present. In SJS, skin detachment is limited to less than 10% of the BSA, whereas a diagnosis of TEN requires epidermal detachment of more than 30%. An overlap group of SJS/TEN has been defined with blisters and erosions covering 10% to 30% of the BSA.

Some generalized drug-induced eruptions may be misinterpreted as SJS or TEN because of their extensive targetlike skin lesions. However, severity and course of such drug-induced eruptions and, therefore, prognosis and outcome differ substantially from SJS and TEN.

Because of severe cardiac adverse effects, the use of all cyclooxygenase-2 inhibitors was heavily disputed and the marketing strategies of pharmaceutical companies were questioned.4 In November 2002, the Food and Drug Administration mandated product label changes for valdecoxib based on reports of serious skin reactions such as SJS and TEN. As a con-

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sequence, valdecoxib was withdrawn from the market in April 2005. To elucidate the situation, the database of the registry for severe skin reactions in Germany, the Dokumentationszentrum schwerer Hautreaktionen (dZh), was reevaluated.

Methods

The dZh organizes a permanent communication structure with all hospitals in Germany that treat patients with severe skin reactions. More than 1700 hospitals and departments, including internal medical departments with intensive care facilities, departments of pediatrics, departments of dermatology, and burn units, are included and are routinely checked by quarterly surveillance. Thus, it can be assumed that all hospitalized patients with severe skin reactions are monitored or retrospectively identified during the quarterly surveillance check.5

All cases of severe skin reactions ascertained by the population-based registry in Germany are reviewed by an independent dermatologic expert committee based on clinical information, histopathologic findings, and photographs of the cutaneous and mucosal lesions. The experts are blinded to potential causes of the disease during the clinical review process and classify the cases as “definite,” “probable,” or “possible” SJS, SJS/TEN overlap, or TEN or exclude these diagnoses in favor of another. Erythema exudativum multiforme majus is clearly differentiated from SJS based on the consensus definition for severe skin reactions.2,5,6 For this specific analysis, all potential cases reported in association with the use of valdecoxib were reevaluated using the histopathologic expertise provided by the Department of Dermatology at the University of Jena, Jena, Germany, based on validated criteria.5,6

Report of Cases

Patient 1

A 68-year-old man had received 1 intramuscular injection of 40 mg of parecoxib sodium (Dynastat; Pfizer Inc, New York, NY), a prodrug of valdecoxib, followed by daily oral use of 20 mg of valdecoxib (Bextra; Pfizer Inc) for treatment of lumboischialgia. On the sixth day of treatment, the patient developed generalized skin eruption, facial swelling, and several small erosions on the upper lip as well as restricted hemorrhagic erosions of the oral mucosa and erythema of the glans penis. The next day, mild dyspnea and temperature up to 39.7°C were noted. At clinical examination, almost the entire body was affected with extensive, confluent, targetlike, erythematous-violaceous macules (Figure 1A). Aside from hypertension, treated with metoprolol since May 2001, the patient was otherwise healthy.

The patient was given 100 mg/d of prednisolone systemically, with subsequent dose reduction during 3 weeks. In addition, intravenous fluid substitution, antioxidants, proton pump inhibitors, and low-dose heparin were given. The lesions regressed and fever resolved. The patient was discharged from the hospital in good condition after 2 weeks.

Histopathologic analysis of a skin biopsy specimen showed a normal epidermis. In the superficial dermis, there was a sparse perivascular and interstitial lymphocytic infiltrate in the superficial dermis and a few lymphocytes in the epidermis (hematoxylin-eosin, original magnification ×40).
cystic infiltrate. A few lymphocytes were found in the epidermis (Figure 1B). Typical histologic features of SJS or TEN, such as necrotic keratinocytes, could not be proved.

PATIENT 2

A 70-year-old woman was administered valdecoxib (Bextra) to treat lumboischialgia. On the fourth day of treatment, facial swelling developed, which was followed by generalized pruritus. Two days later, a measlelike eruption that progressed to erythroderma, on which focally tense blisters occurred, led to hospitalization. The extent of erythema was almost 80%, but blisters covered only approximately 4% of the BSA. Skin symptoms were accompanied by vomiting, diarrhea, hypotension (70/30 mm Hg), temporary tachycardia, and temperature up to 38.8°C. Mucosal involvement was present with a few hemorrhagic areas on the lips. The patient had no com- medication with drugs initiated within 1 month before the onset of the adverse reaction despite taking oral magnesium, intravenous mepivacaine hydrochloride with glucose, and lidocaine hydrochloride.

The patient was treated with a low dose of systemic steroids. Resolution of the skin lesions was accompanied by improvement in her general clinical condition, and the patient was discharged from the hospital after 2 weeks. A skin biopsy specimen was obtained from an older skin lesion and showed only superficial necrosis and an infiltrate of neutrophilic granulocytes. Therefore, a definite histopathologic judgment was impossible.

PATIENT 5

A 46-year-old man received 20 mg of valdecoxib (Bextra) for 8 consecutive days. On the first and second days, the patient had taken 1 tablet of novaminsulfone. On the last day of valdecoxib use, the patient developed generalized exanthema along with pruritus, shivering, mild dyspnea, and facial swelling. Within the next 3 days, skin lesions progressed and the patient was hospitalized. Clinical examination revealed generalized erythematos-violaceous, maculopapular exanthema. The primary lesions had a targetlike appearance (Figure 2A). Mucous membranes were not involved. The patient was treated systemically with prednisolone at an initial dose of 200 mg/d with rapid dose reduction. The skin lesions regressed quickly and, after 5 days, the patient was discharged from the hospital taking an oral dose of 40 mg of prednisolone during the next few days.

A biopsy specimen revealed a normal epidermis along with a superficial perivascular and interstitial lymphocytic infiltrate that consisted of a few eosinophilic granulocytes (Figure 2B). Histopathologic analysis demonstrated features compatible with a drug reaction, but changes of SJS or TEN could not be proved.

ADDITIONAL PATIENT DATA

Patient data and specific findings are given in Table 1 and Table 2, respectively. In addition, the following laboratory findings were abnormal: C-reactive protein concentration was elevated in all 5 patients, serum urea concentration was elevated in patient 1, both serum urea and serum creatinine concentrations were slightly elevated in patient 4, and the percentage of eosinophils was increased in patients 1 (8%), 3 (6%), and 4 (10%). Lung function tests were not performed. Chest x-ray films demonstrated perihilar and basal infiltrates in patient 2.

Valdecoxib (Bextra) became available on the pharmaceutical market in March 2002. Based on reports of serious skin reactions including SJS and TEN, the Food and Drug Administration informed health care professionals in November 2002 about the new warnings. Finally, on April 7, 2005, valdecoxib was withdrawn from the market. Since 1990, the dZh has organized a permanent com-
munication network with all hospitals in Germany that are likely to treat patients with severe skin reactions such as SJS and TEN. After withdrawal of valdecoxib, 5 case notifications of SJS were reevaluated following the use of this drug. All patients developed extensive skin eruptions 5 to 11 days after daily intake of valdecoxib (Table 1). Clinically, generalized erythema developed initially, followed by a maculopapular exanthema, and targetlike lesions appeared in 4 of the 5 patients. In addition, all 5 patients had facial edema, 4 patients had temperatures up to 39.7°C, and 3 patients each had mild dyspnea and pruritus (Table 2). These skin reactions and systemic symptoms do not fit the consensus definition of severe skin reactions. Moreover, only 2 of our patients developed small blisters locally (1%-4% of the BSA). Extensive hemorrhagic erosions of at least 1 site of mucous membranes is another important criterion for the diagnosis of SJS and TEN, but our patients showed none or only mild mucosal involvement, with erythema, minor hemorrhage, and small erosions. In particular, our patients consistently displayed symptoms like facial edema and dyspnea.

Table 1. Patient Data

<table>
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<tr>
<th>Variable</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
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<tbody>
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<td>Dose</td>
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<td>Day 2-7: valdecoxib (Bextra), 20 mg/d</td>
<td>Valdecoxib (Bextra), 20 mg/d</td>
<td>Valdecoxib (Bextra), 20 mg/d</td>
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<td>Indication</td>
<td>Lumboischialgia</td>
<td>Lumboischialgia</td>
<td>Rheumatoid arthritis</td>
<td>Fibromyalgia</td>
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<td>Comedication*</td>
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<td>Tetrazepam and flupirtin</td>
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<td>Mepivacaine hydrochloride with glucose, and lidocaine hydrochloride IV</td>
<td>Novamine sulfone for 1-2 d</td>
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<td>Infection†</td>
<td>None</td>
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Abbreviations: IM, intramuscularly; IV, intravenously.
*With suspected drugs initiated within 1 month before the onset of the adverse reaction.
†Within 1 month before the onset of the adverse reaction.
In addition to these 5 cases, the dZh validated 1 case of SJS (final expert review in clinical terms, “definite case of SJS”) after long-term use of several medications including valdecoxib. Causality assessment by the expert committee could not identify any particular “culprit” drug, and all drugs used by this 61-year-old woman were considered doubtful as causes of the adverse event. During the same period when valdecoxib was available in Germany and when the 6 cases described were reported, 240 cases of severe skin reactions were validated by the dZh. Almost 70% of SJS-TEN cases could be attributed to at least 1 of the following drugs known to induce severe skin reactions: allopurinol, antibacterial sulfonamides, various antiepileptic agents, nevirapine, and oxicam nonsteroidal anti-inflammatory drugs.

It seems that the pattern of the reactions described after the intake of cyclooxygenase-2 inhibitors is a widespread, erythematous, to some extent targetlike, or purpuric skin eruption. Our data are supported by the earlier observations of a Canadian group that reported similar skin reactions associated with valdecoxib in 2 patients. To date, to our knowledge only 1 case report of TEN after the intake of valdecoxib (Bextra) has been published; the patient had a known allergy to sulfa drugs. However, the mechanism of SJS and TEN is not yet clearly understood. They are considered to be T-cell–mediated reactions, which might also be true of the targetlike skin eruptions described after the use of valdecoxib.

Considering other published case reports, we must be aware of the possibility that cyclooxygenase-2 inhibitors are able to induce widespread erythematous targetlike skin reactions with certain additional symptoms, especially dyspnea and facial edema, and often also dermal edema as a histopathological characteristic. Similar reactions have been noted in other patients; however, those cases have not been registered because criteria for SJS or TEN were not fulfilled. Therefore, the incidence of the described valdecoxib-induced drug reactions cannot be calculated. However, the dZh continues to register all patients hospitalized with SJS or TEN. To date, no lethal case of SJS or TEN associated with the use of valdecoxib has been identified in Germany, where sales rates of Bextra were high.

Our results demonstrate that, despite the unquestionable value of spontaneous reports for raising alerts, thorough expert evaluation of systematically ascertained cases of severe skin reactions is important for further decisions about drugs thought to be responsible for severe cutaneous adverse effects. Governments should provide financial resources for monitoring networks of adverse drug events to enable reliable risk estimation for specific drugs or drug groups and certain types of adverse reactions.

Identification and criticism of questionable marketing and education practices of pharmaceutical manufacturers may be appropriate but does not solve the problem. Regulatory agencies and pharmacovigilance institutions are required to address drug safety issues as soon as possible in a professional manner. However, independent, often university-based, research institutions could provide important information if funded appropriately.

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Author Contributions: Dr Ziemer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ziemer and Wiesend contributed equally to this work. Study concept and design: Ziemer and Mockenhaupt. Acquisition of data: Wiesend, Vetter, Weiss, Blaschke, and Mockenhaupt. Analysis and interpretation of data: Ziemer, Wiesend, Vetter, Blaschke, Norgauer, and Mockenhaupt. Drafting of the manuscript: Ziemer, Wiesend, Weiss, and Blaschke. Critical revision of the manuscript for important intellectual content: Ziemer, Wiesend, Vetter, Blaschke, Norgauer, and Mockenhaupt. Obtained funding: Mockenhaupt. Administrative, technical, and material support: Ziemer, Wiesend, Weiss, Norgauer, and Mockenhaupt. Study supervision: Blaschke and Mockenhaupt.

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<table>
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<th>Patient No.</th>
<th>Targetlike Lesions</th>
<th>Facial Edema</th>
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<th>Fever</th>
<th>Pruritus</th>
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</table>

Abbreviations: +, present; −, absent.
REFERENCES


Correction

Incorrect Trial Registration Identifier. In the article titled “A Randomized, Double-blind, Placebo-Controlled Trial of Pentoxifylline for the Treatment of Recurrent Aphthous Stomatitis” by Thornhill et al, published in the April issue of the *Archives* (2007;143:463-470), the trial registration identifier at the end of the “Abstract” on page 463, right-hand column, should have read as follows: NCT00315679. Online versions of this article on the *Archives of Dermatology* Web site were corrected on April 16, 2007.