# Chlordiazepoxide-induced Stevens-Johnson Syndrome

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The causes of Stevens-Johnson syndrome (SJS) can be categorized as iatrogenic, infectious or idiopathic. Drug-induced SJS is associated with various antibiotics, anticonvulsants, and other drugs. However, no previous reports have mentioned an association between chlordiazepoxide, a benzodiazepine sedative, and SJS. Here, we present a case of SJS induced by chlordiazepoxide overdose. This case reminds us that SJS may be an adverse effect of chlordiazepoxide. Further, overdosage with benzodiazepine sedatives should be added to the list of potential causes of SJS. [*J Chin Med Assoc* 2005;68(6):276–278]

**Key Words:** benzodiazepines, chlordiazepoxide, Stevens-Johnson syndrome

## Introduction

Stevens-Johnson syndrome (SJS) is a relatively rare but severe disease characterized by exfoliative dermatitis, and accompanied by fever, inflammation of the gastrointestinal mucosa, and severe purulent conjunctivitis. It is often associated with high morbidity and mortality, depending on patient age and the underlying condition. The causes of SJS may be iatrogenic, infectious or idiopathic. The most common causes of drug-induced SJS are antibiotics (cephalosporins, erythromycin, penicillins, sulfonamides, and tetracycline) and anticonvulsants (carbamazepine, phenobarbital, and phenytoin).[1–3] Chlordiazepoxide (Librium®; Roche Laboratories, Nutley, NJ, USA), a benzodiazepine sedative used extensively in the treatment of anxiety states, insomnia, and alcohol withdrawal, has not previously been associated with SJS. Here, we describe a case of SJS induced by chlordiazepoxide overdose.

## Case Report

A 38-year-old, single, Asian male, previously in good health, was admitted with the chief complaints of sore throat, malaise and fever. He had taken 1,000 chlordiazepoxide 10 mg tablets in a suicide attempt, after a conflict with his girlfriend. He had slept at home for 2 days, and then awoke with a severe sore throat. He visited our outpatient department for help, and was admitted because of his poor general condition.

The patient denied taking any other drugs before, or during, this event. No previous history of asthma, or skin or drug allergy, was claimed. The patient looked very ill, but had clear consciousness. Vital signs were as follows: temperature, 40°C; pulse rate, 104 beats/minute; respiratory rate, 22 breaths/minute; blood pressure, 144/90 mmHg. Physical examination revealed severe oral ulceration, and a diffuse macular rash and multiple bullous lesions on the trunk and extremities, but no genital ulceration was found. An eye examination revealed teariness, congestion, and subconjunctival hemorrhage.

Laboratory tests showed a white blood cell count of $12.3 \times 10^9$/L, hemoglobin of 15.6 g/dL, and platelet count of 288,000/mm.[3] The differential counts of segmented neutrophils, lymphocytes, monocytes, and eosinophils were 71.4%, 18.3%, 8.5%, and 1.0%, respectively. Electrolytes, liver enzymes, and renal function tests were within normal limits. The level of C-reactive protein (CRP) was 15.5 mg/dL (normal,

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< 0.5 mg/dL). Drug screen tests of urine and serum for opiates, phencyclidine, cocaine, paraquat, barbiturates, phenytoin, acetaminophen, cannabinoids, and methaqualone, were negative. Total immunoglobulin (Ig) E and total eosinophil counts were 2,263 kU/L (normal, < 300 kU/L) and 200/$mm^3$ (normal, < 200/$mm^3$), respectively. Antinuclear antibody was not detected. Chest X-ray was normal, without signs of infiltration. Tests for herpes simplex virus IgM, and an enzyme-linked immunosorbent assay for anti-HIV antibodies, were negative. *Mycoplasma pneumoniae* particle agglutination and cold agglutinin tests were also negative.

The time of symptoms relative to the ingestion of chlordiazepoxide led to a diagnosis of chlordiazepoxide-induced SJS. Subsequently, empirical antibiotic therapy with pefloxacin and clindamycin was prescribed for high fever and severe oral ulceration. However, bacterial cultures of blood, sputum and urine samples were negative during hospitalization. Fever subsided after antibiotic therapy. On the third day after admission, methylprednisolone (40 mg every 8 hours) was prescribed. Although oral ulceration reduced slowly, the patient's generalized skin lesions improved gradually within 3 weeks, without scar formation. Therefore, 3 weeks after admission, the methylprednisolone dosage was tapered gradually. Total IgE and CRP levels measured 3 weeks later were 455 kU/L and 0.34 mg/dL, respectively. The patient was discharged in a stable condition and advised against the future use of benzodiazepine-related sedatives.

## Discussion

SJS, first described in 1922,[4] is a rare but life-threatening disease. It presents as a bullous form of erythema multiforme, with extensive mucocutaneous reactions. The incidence of SJS is estimated at 1–6 cases per million person-years and, although rare, may contribute to severe complications and death.[5] The mortality rate associated with SJS varies widely from 5% to 30%, depending on patient age and the underlying condition.[6]

Drug-induced SJS has been associated with various medications, the most notorious of which are antibiotics (cephalosporins, erythromycin, penicillins, sulfonamides, and tetracycline) and anticonvulsants (carbamazepine, phenobarbital, and phenytoin).[1–3] Other drugs suspected of contributing to SJS include chlorpropamide,[2] allopurinol, nonsteroidal anti-inflammatory agents,[7] aspirin, and phenolphthalein-containing laxatives.[8] However, the mechanisms, which may involve hypersensitivity reactions to drugs and their metabolites, are not yet known.[2] The most popular concept, although not universally accepted, is that SJS is an immunologic disease. Non-drug causes of SJS include infections (*M. pneumoniae*, herpes simplex virus) and idiopathic factors.[2]

Benzodiazepines are used extensively in the treatment of anxiety, insomnia, and alcohol withdrawal syndrome. Although bullae have been reported after overdosage with oxazepam,[9] a MEDLINE search using the key terms "Stevens-Johnson syndrome" and "benzodiazepines" revealed no direct evidence of benzodiazepine-induced SJS. SJS usually presents with prodromal symptoms of fever, sore throat, malaise, dysphagia, and conjunctivitis. Some of the most characteristic findings in SJS that differentiate the condition from erythema multiforme are severe inflammation and erosion of the mucosal membranes of the oropharyngeal cavity, as well as genitourinary involvement. Considering the time of symptoms and the drug history, we concluded that our patient had chlordiazepoxide-induced SJS. However, a dose-related response has not been clearly identified in previous reports and now warrants further study.

The effective management of drug-induced SJS requires prompt recognition of the condition, withdrawal of the causative drugs as soon as possible, and initiation of appropriate supportive therapy. If there is a strong suspicion of SJS or toxic epidermal necrolysis, prompt withdrawal of drug treatment will reduce the risk of death by about 30% per day.[10] It remains controversial as to whether corticosteroids are beneficial in treating patients with SJS. Several case reports and short studies advocate the use of high-dose corticosteroids, based on the rationale that mucocutaneous lesions are a hypersensitivity response,[11–13] and systemic corticosteroids may cause faster resolution of fever, malaise and skin lesions than would otherwise be the case. Conversely, several reports suggest that corticosteroid use in patients with SJS increases morbidity and mortality from infectious complications.[14] Thus, well-controlled, prospective, double-blind studies are needed to verify the effects of corticosteroids in patients with SJS.

In conclusion, we present the case of a patient with chlordiazepoxide-induced SJS who was treated successfully with supportive measures and corticosteroid therapy. We did not rechallenge the patient with benzodiazepines because of the high risk of SJS complications. In summary, extremely high doses of benzodiazepines can cause severe drug reactions such as, in this case, SJS.

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