Stevens-Johnson Syndrome Associated With Chlordiazepoxide

Journal of Pharmacy Technology
2018, Vol. 34(2) 82–85
© The Author(s) 2018
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122517753595
journals.sagepub.com/home/pmt

Tara Jawaro, PharmD¹, Ayan Kumar³, Oleksandr Pistun, MD²
and Deepali Dixit, PharmD, BCPS, BCCCP^{1,4}

Abstract

Objective: To report a case of chlordiazepoxide-associated Stevens-Johnson syndrome (SJS). **Case Summary:** This case provides insight into a serious adverse drug reaction secondary to a drug not commonly associated with SJS. A 29-year-old female presented with a 4-day history of rash and pruritus. The rash started on her arms and spread all over her body. The patient was started on chlordiazepoxide 3½ weeks ago. On examination, there were multiple, raised, round erythematous lesions in various stages of healing. Skin erosions were noted on her lips and buccal mucosa. However, the rash did not involve the conjunctiva, inner ears, or genitalia. The patient was discharged home with a follow-up appointment with dermatology and instructions to discontinue chlordiazepoxide. Two days after her initial presentation, the patient's rash spread to her eyes and genitalia. A painful, white film developed on her tongue, and she was unable to tolerate oral intake. She was emergently sent back to hospital and transferred to a Burn Unit. The biopsy report revealed full-thickness necrotizing keratinocytes in the epidermis consistent with SJS. **Discussion:** To our knowledge, there is only one other case report of chlordiazepoxide-associated SJS. Chlordiazepoxide is thought to be the cause of this patient's biopsy-confirmed SJS and overall presentation. SJS is a rare but serious condition that is usually a result of drug exposure. **Conclusions:** The close temporal relationship between chlordiazepoxide initiation and onset of SJS provides a convincing theory as to the etiology of SJS in our patient.

Keywords

chlordiazepoxide, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute, but serious cutaneous adverse reactions, associated with exposure to drugs and can result in significant morbidity and mortality. The incidence of SJS ranges from 1.2 to 6 per million per year, with fatality in up to 5% of cases, while TEN affects 0.4 to 1.2 per million per year with mortality in up to 30% of patients.¹⁻³ SJS and TEN are rare variants of severe, adverse cutaneous drug reactions characterized by extensive painful erythematous macules, eventually evolving to epidermal detachment and mucous membrane erosions resulting from massive apoptosis of epithelial cells. Distinguishing features of SJS and TEN from other morbilliform drug rashes is based on the manifestation of skin lesions and the extent of epidermal detachment.^{4,5} SJS/TEN are differentiated by the extent of epidermal detachment. SJS involves <10% body surface area detachment, while TEN is characterized by extensive involvement of >30% body surface area.^{4,5} The exact pathophysiological mechanism has not been fully elucidated, but it is believed to be a delayed hypersensitivity reaction mediated by T1 helper cells. The reaction typically occurs 4 to 28 days

after initiation of the offending drug, although the highest risk of developing SJS and TEN occurs in the first 2 months after exposure to the drug on a continuous basis. Both SJS and TEN may present with prodromal symptoms lasting up to 1 week, such as fever, sore throat, coughing, myalgia, and arthralgia. Following this period, cutaneous manifestations appear as discrete maculopapular rash, similar to a morbilliform rash.^{4,5}

Mucosal involvement is present in nearly all of the patients, whereas ocular and visceral involvement occurs less frequently.^{4,5}

¹Robert Wood Johnson University Hospital, New Brunswick, NJ, USA

²Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

³Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

⁴Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, USA

Corresponding Author:

Deepali Dixit, Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers University, 160 Frelinghuysen Road, Piscataway, NJ 08854, USA.
Email: ddixit@pharmacy.rutgers.edu

SJS and TEN lesions are widespread, vary in size, and involve mucous membrane.⁴ The rash begins on the trunk with subsequent generalization, usually sparing the palmo-plantar areas. Macular lesions become purplish, and epidermal detachment occurs, resulting in flaccid blisters that converge and break, resulting in extensive sloughing of necrotic skin.⁵ Nikolsky's sign is positive in perilesional skin.⁵ Nikolsky sign is a dermatological finding in which slight rubbing of the skin results in exfoliation of the outermost layer. Diagnosis of SJS and TEN is clinically evident in most cases, but a skin biopsy is the confirmatory test revealing necrosis of all layers of the epidermis caused by apoptosis of keratinocytes and epidermal detachment.⁵

Various etiologies have been implicated in SJS or TEN including chemicals, infections, systemic diseases, and several drug exposures. Furthermore, individuals with a genetic predisposition may be more susceptible to developing such syndromes. Patient groups primarily at risk include those with cancer, collagen vascular disease, the slow acetylator genotypes, patient groups deficient in enzymes involved in the metabolism of toxic drug metabolites, and individuals with HLA major histocompatibility complex alleles.⁵

Classic drugs with the risk to induce SJS include anti-convulsants, allopurinol, oxycam-type nonsteroidal anti-inflammatory agents, nevirapime, and anti-infective sulfonamides. We describe a case of chlordiazepoxide-associated clinical signs and symptoms of SJS.⁴ This case provides insight into a serious adverse drug reaction secondary to a drug not commonly associated with SJS.⁶

Case Description

A 29-year-old female presents to the emergency department (ED) with a 4-day history of rash and pruritus. According to the patient, the rash started on her arms and spread all over her body. The patient reports returning 6 days prior from a 3-week trip to Florida. Of note, she was prescribed a new medication, chlordiazepoxide 25 mg to be taken as needed for anxiety (quantity 40), 3½ weeks ago. She admitted to taking the medication almost daily instead of as needed; the ED pharmacist conducted a pill count with 11 capsules remaining in the bottle. She denied using any other prescription or over-the-counter medications, illicit substances, or herbal supplements. She also denied having any allergies to food or drugs. Notably, due to concerns of chlordiazepoxide-induced SJS on sun exposure, we inquired on the sun exposure and use of sunscreen while in Florida, and she reported spending a considerable amount of time indoors due to the overcast, rainy weather and wore SPF sunscreen daily for skin protection while out in the sun.

On examination, the patient is alert, awake, and in mild painful distress. Her vital signs are as follows: 98.8°F, heart rate (HR) of 120 beats per minute, respiratory rate (RR) of 16 breaths per minute, blood pressure (BP) of 104/72 mm

Hg, and 100% oxygen saturation on room air (RA). There were multiple, raised round erythematous lesions in various stages of healing in areas including her head, lateral chest, face, ears, arms, abdomen, legs, palms, and soles. Skin erosions were noted on her lips and buccal mucosal. However, the rash did not involve the conjunctiva, inner ears, or genitalia. The primary diagnosis was erythema multiforme with a biopsy taken for confirmation from the right forearm. In addition, mycoplasma antibody titers were sent. The patient was discharged home with cephalexin 500 mg 3 times a day, valacyclovir 500 mg twice a day, topical triamcinolone 0.1%, and mupiricon with a follow-up appointment with dermatology in 3 days. She was instructed to discontinue the chlordiazepoxide; the patient's last dose of chlordiazepoxide was the morning of presenting to the ED.

Two days after her initial presentation, the patient reported that the rash spread to her eyes and genitalia. A painful, white film developed on her tongue, and she was unable to tolerate oral intake. The next day, she presented at her dermatology appointment and was emergently sent back to hospital. Her progressive symptoms were consistent with SJS. At this time her vital signs were as follows: 100.1°F, HR 120 beats per minute, RR 16 breaths per minute, BP 107/63 mm Hg, and 100% oxygen saturation on RA. She was admitted to the intensive care unit (ICU) pending transfer to a burn unit. She was managed with supportive and symptomatic measures: fluid resuscitation, temperature control, and pain control. During her short stay in the ICU, the patient developed new lesions on her arms, bullae on forearms, and sloughing at the axilla. A second biopsy was taken from her right forearm. Both biopsy reports confirmed the clinician's suspicion, revealing full-thickness necrotizing keratinocytes in epidermis consistent with SJS. Our patient was transferred to a burn ICU in the area with complete resolution of SJS associated with chlordiazepoxide.

Literature Review

Chlordiazepoxide, the original benzodiazepine, was approved in the 1960s for the management of anxiety and alcohol withdrawal symptoms. The product labeling does not mention any serious dermatological reactions.⁷ Classically, chlordiazepoxide has not been strongly associated with SJS or TEN. To date, there has only been one other published report of chlordiazepoxide-associated SJS. This was of a 38-year-old Asian male who ingested 1000 chlordiazepoxide 10 mg tablets in a suicide attempt. He presented 2 days after ingestion with severe oral ulcerations, diffuse macular rash, and multiple bullous lesions on the trunk and extremities.⁶

Other published case reports of benzodiazepine-associated SJS and TEN have been reported, namely, clobazam, flurazepam, and tetrazepam.^{6,8,9} One of the earliest case

reports was that of a 23-year-old female taking clobazam 20 mg for 14 days prior to presenting to an emergency department with a 2-day history of erythematous eruption on sun-exposed areas of her face, thorax, back, and limbs but absent in the areas covered by a swimsuit. She had a positive Nikolsky's sign and biopsy confirmed TEN. The authors concluded that this reaction was photo-induced TEN secondary to clobazam.⁸ In 2013, the US Food and Drug Administration released a Drug Safety Communication warning of serious skin reactions with clobazam resulting in a warning for serious dermatological reactions based on 20 cases of SJS/TEN associated with the use of clobazam.¹⁰ US labeling for clobazam includes an adjunct for intractable epilepsy.

Tetrazepam, a benzodiazepine used for the management of contractures and spasticity in the European Union, has been associated with several published reports of SJS and TEN.¹¹⁻¹³ In 2013, tetrazepam was suspended due to low but increased risk of serious skin reactions compared with another benzodiazepine. A total of 513 cutaneous reactions were identified of which there were 65 cases of SJS and TEN.¹⁴ As a result of tetrazepam suspension across the European Union, Martin-Merino et al evaluated the incidence of SJS and TEN among the general population, new users of benzodiazepines (not including tetrazepam), new users of tetrazepam, and new users of phenytoin in Spain. Interestingly, they found the risk of SJS/TEN to be very rare among tetrazepam users and similar to other benzodiazepines. As a control, they found that incidence in the general population and the use of phenytoin agreed with the literature, suggesting this study accurately estimates the incidence of SJS and TEN in the tetrazepam population.¹⁵

Discussion

Chlordiazepoxide is thought to be the cause of this patient's biopsy-confirmed SJS and overall presentation. Similar to the case described of the 23-year-old female, our patient developed SJS after use of a benzodiazepine.⁸ Our patient reported starting chlordiazepoxide 3½ weeks prior to presentation. The parent drug has a half-life of 28 hours, which is further extended to 95 hours by its metabolites, making it very likely that the drug was present in the body at the time of onset. The close temporal relationship between chlordiazepoxide initiation and onset of SJS provides a convincing theory as to the etiology of SJS in this patient. Moreover, the likelihood of chlordiazepoxide being the causative agent was found to be probable based on 2 pharmacovigilance algorithms, the Naranjo criteria (score of 6) and the Algorithm of Drug Causality for Epidermal Necrosis (ALDEN).^{16,17}

There is no specific treatment for SJS or TEN. Management includes supportive and symptomatic treatment. Optimal management warrants quick recognition, discontinuation of the offending agent, and admission into

the burn ICU. Drugs are the principal cause for SJS or TEN though infections and malignancies can also trigger these syndromes. Commonly used drugs implicated as the cause of SJS or TEN include sulfonamides, antimicrobials, anti-convulsants, allopurinol, and some nonsteroid anti-inflammatory drugs. Chlordiazepoxide and other benzodiazepines have been associated less frequently with SJS or TEN.

Conclusion

This case report emphasizes the fact that severe hypersensitivity reactions occur with chlordiazepoxide, which can be potentially serious and life threatening. It is hence important for the clinicians to be alert to such severe hypersensitivity reactions even with drugs that are considered to be potentially safe such as chlordiazepoxide.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Bulisani ACP, Sanches GD, Guimarães HP, Lopes RD, Vendrame LS, Lopes AC. Síndrome de Stevens-Johnson e necrólise epidérmica tóxica em medicina intensiva. *Rev Bras Ter Intensiva*. 2006;18:292-297.
2. Dodiuk-Gad RP, Laws PM, Shear NH. Epidemiology of severe drug hypersensitivity. *Semin Cutan Med Surg*. 2014;33(1):2-9.
3. Naldi L, Crotti S. Epidemiology of cutaneous drug-induced reactions. *G Ital Dermatol Venereol*. 2014;149:207-218.
4. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. *J Am Acad Dermatol*. 2013;69:173.e1-e13. DOI:10.1016/j.jaad.2013.05.003.
5. Oliveira A, Sanches M, Selores M. Stevens-Johnson syndrome and toxic epidermal necrolysis [in Portuguese]. *Acta Med Port*. 2011;24(suppl 4):995-1002.
6. Huang P, Tsai W. Chlordiazepoxide-induced Stevens Johnson syndrome. *J Chin Med Assoc*. 2005;68:276-278. doi:10.1016/S1726-4901(09)70150-9.
7. Chlordiazepoxide [package insert]. Sellerville, PA: Teva Pharmaceuticals; 2012.
8. Redondo P, Vincente J, Espana A, Subira ML, De Filipe I, Quintanilla E. Photo-induced epidermal necrolysis caused by clobazam. *Br J Dermatol*. 1996;135:999-1002.
9. Loncar C, Franić T, Bilusić M. Toxic epidermal necrolysis caused by flurazepam? *Psychiatr Danub*. 2005;17:236-239.
10. US Food and Drug Administration. FDA drug safety communication: FDA warns of serious skin reactions with the anti-seizure

- drug Onfi (clobazam) and has approved label changes. <https://www.fda.gov/Drugs/DrugSafety/ucm377204.htm>. Updated January 15, 2016. Accessed May 24, 2017.
11. Sánchez I, García-Abujeta JL, Fernández L, et al. Stevens-Johnson syndrome from tetrazepam. *Allergol Immunopathol*. 1998;26:55-57.
 12. Lagnaoui R, Ramanampamonjy R, Julliac B, Haramburu F, Ticolat R. Fatal toxic epidermal necrolysis associated with tetrazepam. *Therapie*. 2001;56:187-188.
 13. Delesalle F, Carpentier O, Guatier S, Delaporte E. Toxic epidermal necrolysis caused by tetrazepam. *Int J Dermatol*. 2006;45:480. doi:10.1111/j.1365-4632.2006.02654.x.
 14. European Medicines Agency. Tetrazepam-containing medications. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Tetrazepam_containing_medicinal_products/human_referral_prac_000015.jsp&mid=WC0b01ac05805c516f. Accessed May 24, 2017.
 15. Martín-Merino E, de Abajo FJ, Gil M. Risk of toxic epidermal necrolysis and Stevens-Johnson syndrome associated with benzodiazepines: a population-based cohort study. *Eur J Clin Pharmacol*. 2015;71:759-766. doi:10.1007/s00228-015-1850-y.
 16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.
 17. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther*. 2010;88:60-68. doi:10.1038/clpt.2009.252.