A Case of Stevens-Johnson Syndrome After Exposure to Valproic Acid

Kristen K. Barbour, MD[a]; Christian P. Umfrid, MD[b]; Benjamin A. Brinton, MD[b]; Jonathan D. Avery, MD[b]; and Caitlin E. Snow, MD[b,*]

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening conditions that present with skin erosions and extensive detachment of the epidermis that is typically caused by drug exposure within weeks to months. Although rare conditions, they are potentially lethal even among healthy patients. Among anticonvulsants, phenytoin, lamotrigine, and carbamazepine are most often associated with SJS/TEN,[1–3] while valproic acid is viewed as low risk. However, the risk of valproic acid with regard to SJS/TEN may be underestimated in current clinical practice.

Case Report

A patient was admitted to the inpatient psychiatry unit of an outside hospital for management of bipolar I disorder and prescribed haloperidol, risperidone, valproic acid, and benztropine. Several days after treatment began, the patient developed a blister on lip mucosa, diffuse rash, and dysphagia, which is concerning for possible SJS. Psychiatric medications were held, and the patient was transferred to the medical intensive care unit of a tertiary care center. An intact, diffuse rash involving 75% of body surface area and epidermal detachment of 1%–2% of body surface area was found, which is consistent with SJS. Pathology of a skin biopsy showed necrotic epidermis with epidermolysis and confirmed the diagnosis of SJS/TEN. A 3-day course of intravenous immunoglobulin and tapered pulse methylprednisolone was started. Psychiatric symptoms were managed with olanzapine, lithium, and clonazepam. The Table includes a timeline of the patient's psychiatric medications, reactions, and treatment.

The patient reported 1 prior reaction after receiving valproic acid 500 mg/1,000 mg every 12 hours while admitted to an inpatient psychiatry unit 4 years prior (hair loss and an oral blister), resulting in self-discontinuation of valproic acid and resolution of symptoms. She never continued valproic acid or other psychiatric medications as an outpatient. Using the Algorithm of Drug Causality for Epidermal Necrolysis[4] and given her prior reaction, we determined that valproic acid was a very probable cause of the patient's SJS/TEN, in contrast to haloperidol, risperidone, and benztropine, which were determined very unlikely causes.

Conclusion

Valproic acid is not historically associated with SJS/TEN.[2,5] However, there is growing evidence showing risk of SJS/TEN with valproic acid when used in combination with lamotrigine,[2,3,6] which is thought to be due to valproic acid's slowing the metabolism of lamotrigine by inhibiting glucuronidation.[6] The risk with valproic acid when used in the absence of other anticonvulsants is controversial, although some evidence suggests that valproic acid has independent risk for SJS/TEN.[1,7–10] In a multivariate model, risk of valproic acid remains when controlling for other anticonvulsants.[1] In addition, the current case adds to a growing number of SJS/TEN cases[7–10] reported after exposure to valproic acid in the absence of other anticonvulsants.

Further research is needed to define the risk for SJS/TEN with valproic acid when used in the absence of other anticonvulsants. The risk for SJS/TEN with valproic acid monotherapy may be underestimated in clinical practice. Furthermore, valproic acid and lamotrigine in combination have increased risk for SJS/TEN,[2,3,6] and it is possible that other combinations do as well. Physician knowledge regarding risk can guide clinical decision-making and facilitate early diagnosis and treatment of SJS/TEN.

Lastly, the risk of anticonvulsant-induced SJS/TEN has been associated with genetic and ethnic background. For example, the HLA-B*1502 genotype has a 100% sensitivity and 97% specificity for carbamazepine-induced SJS/TEN in a Han Chinese population.[11] Additional epidemiology and genetic studies are needed. It may be possible to reduce SJS/TEN by avoiding specific anticonvulsants in high-risk ethnic backgrounds or by screening for high-risk genetic variants. Genetic screening has already been successfully implemented in 1 large Taiwanese study,[12] which successfully avoided carbamazepine-induced SJS/TEN in patients with the HLA-B*1502 allele.

[a]Division of Child Neurology, Weill Cornell Medicine, New York, New York
[b]Department of Psychiatry, Weill Cornell Medicine, New York, New York
*Corresponding author: Caitlin E. Snow, MD, Department of Psychiatry, Weill Cornell Medicine, 407 E 61st St, New York, New York 10065 (ces2007@med.cornell.edu).

Prim Care Companion CNS Disord 2019;21(2):18l02374

To cite: Barbour KK, Umfrid CP, Brinton BA, et al. A case of Stevens-Johnson syndrome after exposure to valproic acid. *Prim Care Companion CNS Disord*. 2019;21(2):18l02374.

To share: https://doi.org/10.4088/PCC.18l02374

Potential conflicts of interest: None.
Funding/support: None.

Table. Timeline of the Patient's Psychiatric Medications, Reactions, and Treatment[a]

Day	Psychiatric Medications	Signs and Symptoms	Treatment
4 years prior	Valproic acid 500 mg/1,000 mg q12h	Patient reported oral mouth lesion and hair loss.	Medication discontinued by patient.
Day 1	**Psychiatric medications started:** • Valproic acid 250 mg q8h • Risperidone 1 mg q12h (increased to 2 mg q12h on day 2) • Haloperidol 5 mg as needed for agitation (1 tablet on day 1 and 1 tablet on day 2) • Clonazepam 1 mg q12h as needed for anxiety	**Patient admitted to inpatient psychiatry unit.**	
Day 3		• Blister on lip developed. • **Patient treated empirically for HSV lesion.**	• Valacyclovir 2,000 mg daily for 2 days
Day 7		• Pruritic painful red rash developed involving chest, back, arms, face, neck, and palms with fever. • **Patient treated for rash for potentially allergic reaction to medication.**	• Diphenhydramine 50 mg daily • Hydrocortisone 1% topical ointment
Day 8	**Psychiatric medications were discontinued.**	**Patient transferred to general medicine for management of rash concerning for SJS/TEN.**	• Prednisone 60 mg once, then prednisone 40 mg daily
Day 10		• Painful red rash extended with involvement of chest, back, arms, legs, face, neck, and palms. Large bullae on neck and positive Nikolsky sign on face. Mucosal lesion on palate. Conjunctival injection and pain in both eyes. • **Patient transferred to ICU at tertiary care center for further management.**	• Dexamethasone 4 mg IV once
Day 11		**Dermatology consulted and total body surface exam showed:** • Dusky red to violaceous tender patches and plaques involving about 75% of BSA including face, neck, trunk, all 4 extremities, palms, and soles. Flaccid bullae on anterior neck and vesiculation involving nose, cheeks, chin. Denudation on left periorbital region and left forearm. Ulcerations involving oral and genital mucosa. Erythema of scalp diffusely.	• IVIG 65 mg pulsed dose per day for 3 days • Methylprednisone 1,000 mg IV for 2 days, then 500 mg IV for 1 day
Day 12	• Olanzapine started at 2.5 mg daily. • Over 12 days, olanzapine was titrated up to 10 mg/15 mg q12h where it remained for 5 more days and then was reduced to 10 mg q12h. • Olanzapine 5 mg q12h was given as needed for agitation.	Interval improvement in intensity of erythema.	
Day 15		Interval improvement, now with rash involving 60% BSA including face, neck, trunk, all 4 extremities, palms, and soles. Slightly more areas of denudation.	
Day 23		• Rash continues to improve; erythema and pain significantly improved. • **Transferred from ICU to inpatient psychiatry unit.**	
Day 29	• Lithium was started at 300 mg q8h. • Over 7 days, lithium was titrated up to 600 mg extended release q12h.		
Day 38	**Discharge medications:** • Olanzapine 10 mg q12h • Lithium 600 mg extended release q12h	**Patient discharged from inpatient psychiatry unit.**	

[a]Boldface indicates key points in care.
Abbreviations: BSA = body surface area, HSV = herpes simplex virus, ICU = intensive care unit, IV = intravenous, IVIG = intravenous immunoglobulin, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, q8h = every 8 hours, q12h = every 12 hours.

Additional information: Information has been de-identified to protect anonymity.

Published online: March 28, 2019.

REFERENCES

1. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333(24):1600–1607.
2. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol*. 2008;128(1):35–44.
3. Ordoñez L, Salgueiro E, Jimeno FJ, et al. Spontaneous reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with antiepileptic drugs. *Eur Rev Med Pharmacol Sci*. 2015;19(14):2732–2737.
4. 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(1):60–68.
5. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology*. 1997;49(2):542–546.
6. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. *BMJ*. 2014;348:g254.
7. Misra BN, Mohapatra PK, Roy D. Stevens-Johnson syndrome during treatment with lithium and valproate in mood disorder: a report of two cases. *Indian J Psychiatry*. 2002;44(3):301–302.
8. Naveen K, Arunkumar J, Hanumanthayya K, et al. Stevens-Johnson syndrome induced by sodium valproate monotherapy. *Int J Crit Illn Inj Sci*. 2012;2(1):44–45.
9. Kumar PN, Kumar SK. Stevens-Johnson syndrome induced by sodium valproate. *Indian J Psychiatry*. 2004;46(3):269–270.
10. Saaiq M, Iqbal T. Report: fatal toxic epidermal necrolysis induced by sodium valproate. *Pak J Pharm Sci*. 2013;26(3):637–639.
11. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature*. 2004;428(6982):486.
12. Chen P, Lin JJ, Lu CS, et al; Taiwan SJS Consortium. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N Engl J Med*. 2011;364(12):1126–1133.