Mood Stabilizer Induced Steven Johnson Syndrome: A Case Report

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Abstract

Mood stabilizers are psychiatric medications used to help control mood swings commonly used to treat people with bipolar disorder. Mood stabilizers consist of several drugs, such as lithium, valproate, carbamazepine, clozapine, olanzapine, quetiapine, aripiprazole, risperidone, and lamotrigine. Some anticonvulsants and memantine show some use in the treatment and prophylaxis of bipolar disorder.

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute, life-threatening conditions with clinical symptoms of skin erosion and extensive epidermal detachment, usually caused by drug exposure over weeks to months. Although Stevens-Johnson syndrome is a rare disease, it is potentially fatal even among healthy patients. Among anticonvulsants, phenytoin, lamotrigine, and carbamazepine are most frequently associated with SJS/TEN. Very few cases suggest that clozapine, risperidone, ziprasidone, and aripiprazole can cause Stevens-Johnson syndrome. Meanwhile, valproic acid is considered low risk. However, the risk of valproic acid associated with SJS/TEN cannot be underestimated in current clinical practice.

This case report found that several mood stabilizer drugs had the side effects of Stevens-Johnson Syndrome, where clinical symptoms include blistering, swelling and pain in the skin. The patient is known to have been on medication using risperidone and valproic acid in the last three weeks.

Keywords: Mood stabilizers, Stevens-Johnson Syndrome

Introduction

Mood stabilizers are psychiatric medications used to help control mood swings commonly used to treat people with bipolar disorder. These drugs can prevent the severity experienced and improve the chemical balance in the brain.[1] However, they are not to be used in every phase of bipolar disorder.[2] Mood stabilizers can also be used to treat people with schizoaffective disorder, borderline personality disorder (BPD), and in some cases, depression.[1]

Mood stabilizers are classified into two generations based on the chronology of the psychiatric armamentarium. First-generation mood stabilizers (FGMS), such as lithium, valproate, and carbamazepine, were introduced in the 1960s and 1970s. Mood stabilizers Second-generation mood stabilizers (SGMSs) began in 1995. SGMS include atypical antipsychotics, such as clozapine, olanzapine, quetiapine, aripiprazole, and risperidone, as well as a newer anticonvulsant drug, lamotrigine. Recently, SGMS's new antipsychotic is lurasidone. Several other atypical antipsychotics, anticonvulsants, and memantine show some use in the treatment and prophylaxis of bipolar disorder.[3] Among mood stabilizers, valproic acid treatment appears to carry the highest risk of birth defects. Other specific side effects of clinical importance include lithium toxicity that can cause ataxia, rigidity, cerebral seizures, and shock, decreased bone marrow function caused by carbamazepine treatment, and Stevens-Johnson syndrome and Lyell's syndrome caused by carbamazepine or lamotrigine. Additionally, it is important to be aware of the risks of liver failure and pancreatic damage caused by valproic acid and the weight gain and metabolic disturbances associated with atypical antipsychotics such as olanzapine and quetiapine.[4]

Valproic acid (VPA) is an antiepileptic drug (AED) commonly used in the treatment of seizures, bipolar mood disorder, obsessive-compulsive disorder, and migraines. Valproic acid is a first-line drug indicated for simple and complex seizures as well as complex partial seizures and needs to be given for an extended time. Increased bleeding time, thrombocytopenia, itching, tinnitus, rash, back pain, confusion, catatonia, mood swings, amblyopia, and tremors are known to be severe side effects of Valproic Acid. Erythema multiforme, hyperandrogenism,

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M. M. Amin et al. (eds.), *Proceedings of the 7th International Conference on Neuroscience, Neurology, and Psychiatry Universitas Sumatera Utara (ICONAP 2024)*, Advances in Health Sciences Research 83,
https://doi.org/10.2991/978-94-6463-616-1_6

fingernail and fingernail disorders, Stevens-Johnson syndrome, and toxic epidermal necrolysis are adverse severe drug reactions. Skin reactions associated with antiepileptic drugs are very rare in monotherapy and are generally due to drug-drug interactions when administered with other concomitant medications. Nineteen studies were included, and more cases were reported from India (6), Turkey (5), China (2), Italy (2) and one case each from Pakistan, England, Taiwan, and Cork. Phenytoin, lamotrigine, and carbamazepine are the antiepileptics most frequently associated with reports of SJS or toxic epidermal necrolysis. In several cases of valproic acid, it is suspected that it can cause SJS. As many as seven cases experienced SJS after administering the drug valproic acid, either monotherapy or in combination with other drugs simultaneously.[5]

A systematic review focused on Valproic acid in relation to Stevens-Johnson syndrome. It listed 19 studies (total 98 cases). In most studies, the occurrence of SJS was followed by valproic acid treatment with the use of other anti-seizure drugs, mainly lamotrigine but also carbamazepine and lorazepam. Pharmacovigilance studies have shown that lamotrigine and carbamazepine are associated with Steven Johnson Syndrome in pediatric patients. However, in seven case reports, drug-induced Steven Johnson Syndrome was triggered by valproic acid monotherapy. The duration of valproic acid is <1 month (range 1-3 weeks).[6]

Steven Johnson Syndrome is a rare autoimmune disorder primarily affecting skin and mucous membranes. It is reported that the incidence of SJS is 0.05 to 2 million people per population per year. The reported mortality rate ranges from 3-10%. Steven Johnson Syndrome, or Toxic Epidermal Necrolysis, is a life-threatening, immune complex-mediated hypersensitivity reaction involving the skin and mucous membranes accompanied by systemic symptoms. Steven Johnson Syndrome is generally induced by drugs. Manifestations can include blistering, facial swelling and hyperpigmentation, and pathological changes. The risk of drug-induced hypersensitivity syndrome associated with antiepileptic drugs was found to be greater with lamotrigine, carbamazepine, and phenytoin. The most common drugs that cause SJS are sulfonamides, nonsteroidal anti-inflammatory drugs, imidazole antifungals, cephalosporins, anticonvulsants, allopurinol, broad-spectrum bactericidal agents and highly active anti-radiotherapy regimens. Fluoroquinolones can rarely cause serious skin drug reactions. Among the adverse reactions to drugs is the use of anti-seizure drugs. Most cases of Steven Johnson Syndrome and toxic epidermal necrolysis induced by anti-seizure medications have been reported after puberty and in young adults, with rare cases occurring in infancy or early childhood.[7]

Stevens-Johnson Syndrome/toxic epidermal necrolysis is a spectrum of mucocutaneous reactions that can occur due to reactions to drugs such as antibiotics, antiepileptic and nonsteroidal anti-inflammatory drugs, Mycoplasma pneumonia infection, human immunodeficiency virus (HIV), cancer, and genetics. Stevens-Johnson Syndrome involves less than 10% of the body surface, whereas toxic epidermal necrolysis involves more than 30%. The most common lesions are mucocutaneous surfaces such as the eyes and oral cavity. [4,6] This disease is not only limited to the skin and oral mucosa but involves complications by weakening organ systems, such as the lung, gastrointestinal/liver, otorhinolaryngologic, gynaecological, genitourinary, and kidneys.[5] Stevens-Johnson Syndrome (SJS) is a rare, life-threatening condition with a mortality rate of 30% characterized by severe mucocutaneous epidermal necrolysis and detachment of the epidermis. Stevens-Johnson syndrome causes acute destruction of the skin epithelium and mucous membranes by the immune response.[8,9] Incidence varies by country of origin, age, and associated conditions. In US adults, the incidence of Steven Johnson Syndrome per million individuals ranges from 8.6 to 9.7. The incidence in South Korea ranges from 3.96 to 5 cases per million, with an increase in patients older than 70 years.[8]

Pathophysiology Steven Johnson Syndrome is not fully understood but is identified by widespread keratinocyte apoptosis. Several mediators are thought to be involved in these cell-mediated cytotoxic reactions, with T lymphocytes and natural killer cells (NK cells) possibly being the primary causes of the induction of apoptosis. Other mediators include cytotoxic proteins such as Fas-Fas ligand, tumour necrosis factor-alpha, and perforin-granzyme B. Still, recent research suggests that granulysin may be the key mediator of keratinocyte reaction destruction.[8]

Early signs of Steven Johnson Syndrome are difficult to diagnose, often leading to misdiagnosis and delays in treatment. Many patients experience nonspecific prodromal symptoms that occur 1 to 3 weeks after taking the drug.[6] The skin rash is often preceded by malaise, fever, and upper respiratory symptoms (flu-like). Mucosal lesions often appear first, including the oral, respiratory, conjunctival, and genitourinary areas. The involvement of multiple organs can cause complications and sequelae. Skin infections, pneumonia, hepatitis and sepsis are frequently reported complications of Steven Johnson Syndrome / toxic epidermal necrolysis, which can cause death.9 Diagnosis can be made by skin biopsy with findings of full-thickness dermal necrosis. The acute phase of

SJS usually lasts between 8-12 days. It can cause significant, painful areas of bald skin that will begin to re-epithelialize about one week after the onset of symptoms and can take up to 3 weeks.[6]

Psychological problems, including anxiety, depression, and post-traumatic stress disorder, may be present in people with Stevens-Johnson Syndrome. According to a study, physical and psychological sequelaeSteven Johnson Syndrome/toxic epidermal necrolysis causes a lack of ability to work in 28.2% of patients, and 68.1% and 30.0% of patients fear or avoid taking medication.[10] Although Steven Johnson Syndrome/toxic epidermal necrolysis is a severe disease, there is no standard treatment for SJS / toxic epidermal necrolysis. Supportive care for patients with Steven Johnson Syndrome / toxic epidermal necrolysis is similar to the management of patients with severe burns.[8] Suspected drugs should be discontinued, and treatment should be started immediately with specific therapies such as wound care and medication topical, immunosuppressive therapy (especially corticosteroids, which decrease immune response and inflammation), and other medications such as antihistamines, antibiotics, supportive therapy measures, fluid maintenance/electrolytes, nutritional support, analgesia, and other symptomatic management.[5]

Case Report

A 23-year-old woman came to the psychiatric clinic brought by her father. According to her father, during the past month, the patient often laughed and talked to herself, threatened people around her with a knife, and liked to spend more than 1 million rupiah on a spree. The patient admitted that he saw people who often bullied him as a child, so he frequently got angry and was easily offended. Then, treatment was carried out by giving oral therapy of risperidone 1 x 1 mg and valproic acid 1 x 250 mg and evaluated every week. One week later, the patient came for control treatment and was given risperidone 1 x 2 mg and valproic acid 1 x 500 mg. In the second week during the treatment phase, the patient returned for control treatment and was found to have improved symptoms. According to the patient's father, her anger had decreased, but the hallucinations became clearer. Then, she was given an increase in the dose of risperidone from 2 mg to 3 mg. The medicines included risperidone 1 x 3 mg and valproic acid 1 x 500 mg. Three days later, after consuming the medicine and the final control, the patient came to the emergency room, where she complained that the skin and mucous membranes around her mouth were blistering and peeling, the patient complained that his body was hot and her whole body felt painful, the patient complained of fever and pain throughout the body, so the patient was referred and treated at the referral center hospital and was treated by a dermatologist. After an evaluation, it was discovered that the patient had Stevens-Johnson Syndrome and the doctor immediately stopped the psychiatric medication, providing treatment according to the patient's complaints. After treatment and wound care, the patient's condition improved and improved. Still, the delusions and hallucinations reappeared, so it was recommended that she be referred to a referral center hospital for psychiatric treatment options to continue treatment according to the patient's complaints, and it was discovered that the patient was given oral medication in the form of aripiprazole and alprazolam, and continued with the medication without experiencing any side effects.

Discussion

Stevens-Johnson syndrome and toxic epidermal necrolysis are rarely reported side effects of valproate.[11] Nineteen studies were included, and more cases were reported from India, Turkey, China, and Italy, with one case each from Pakistan, England, Taiwan, and Cork. Phenytoin, lamotrigine, and carbamazepine are the antiepileptics most frequently associated with reported cases of Steven Johnson syndrome. There is no definite mechanism for the drug-induced Steven Johnson syndrome of valproic acid. Still, a highly reactive intermediate metabolite can trigger this type of reaction with drug intake and is believed to be a type 4 hypersensitivity reaction. In general, it is found that the anticonvulsant arene-oxide metabolite accumulates and binds to cellular molecules, causing toxicity and manifesting Steven Johnson syndrome reactions. The combination of valproic acid and lamotrigine may inhibit lamotrigine liver enzymes and prolong the half-life of lamotrigine from 30 to 60 hours.

The mechanism of anticonvulsant-induced Stevens-Johnson Syndrome describes that these agents can be converted to arene-oxides by hepatic cytochrome P-450, and functional and/or structural effects in epoxide hydrolases inhibit the excretion of areneoxide metabolites formed during anticonvulsant metabolism. These accumulated metabolites bind to cellular macromolecules, resulting in a toxic role or hapten in type 4

hypersensitivity reactions. Toxic reactions by areneoxide metabolites in this anticonvulsant hypersensitivity syndrome result in skin lesions and can extend from a mild morbilliform rash to Stevens-Johnson Syndrome and toxic epidermal necrolysis. [6] In most studies, SJS was caused by valproate when used in combination with other drugs.[11] Previous findings reported that some antipsychotic drugs can trigger Stevens-Johnson Syndrome. Only 1 case was first reported to be induced by the drug risperidone, that Desarkar reported risperidone induced minor erythema multiforme.[13]

In this case, the patient had received risperidone and valproic acid drug therapy for three weeks to overcome the patient's complaints such as frequently laughing and talking to himself, threatening people around him with a knife, spending more than 1 million on a spree, and seeing visual hallucinations. After treatment, and increased dose of therapy, complaints arose in the form of the skin and mucous membranes around the mouth blistered and peeled. The patient complained that his body was hot and his whole body felt painful, which indicated that the patient was experiencing signs of Stevens-Johnson Syndrome.[12] Then, the drugs risperidone and valproic acid, which were suspected of causing SJS, were immediately stopped and repaired.[13,14] Valproate administration can cause SJS in some cases, when given together with other drugs, whereas SJS due to valproate monotherapy is rarely reported.[15,16] The patient was immediately referred to a skin specialist for immediate treatment.[17] After the patient's complaints improved, he was re-evaluated, and it was found that the delusions and hallucinations reappeared because the mood stabilizer in the previous treatment was stopped. The patient was consulted again to a psychiatric doctor at referral center hospital and given oral medication, namely aripiprazole and alprazolam, which were known to be different from the mood stabilizer medication previously given. Aripiprazole is generally considered to have a lower risk and rarely causes Stevens-Johnson syndrome (SJS) compared to other antipsychotics. Although aripiprazole can cause skin reactions may occur, such severe reactions are generally not associated with this drug.[18, 19]

Conclusion

Valproic acid can cause Stevens-Johnson Syndrome, which is a skin hypersensitivity reaction that can be fatal and life-threatening. The mortality rate seen with severe cutaneous adverse drug reactions can be reduced by immediate withdrawal of the opposing drug, providing symptomatic relief, but there is no standard treatment for SJS/toxic epidermal necrolysis, but supportive care can be undertaken. Health professionals must be aware of the impacts or risks that will arise before starting therapy, and it is necessary to monitor patients carefully if signs of Stevens-Johnson Syndrome / toxic epidermal necrolysis appear; although the incidence is low, it is dangerous for the patient. Risperidone itself has also been reported to cause the side effect of erythema multiforme minor. In this case, it is still a matter of debate whether the patient's condition diagnosed with Steven Johnson was caused by valproate or risperidone.

References

1. Seven Z. What are Mood Stabilizers? Medically reviewed. April 03, 2022
2. Gfesser J, Schneider SK Guidelines on mood stabilizers. Neuropsychopharmacology. pp. 1639-1686. June 11 2020
3. Rybakowski J, Mood Stabilizers of First and Second Generation. Neuropsychopharmacology in Mood Disorders 13(5)10.3390/brainsci13050741.(2023)
4. Riederer P, Laux G, Nagatsu T, et al. 2022, Mood Stabilizers: Side Effects, Contraindications, and Interactions. NeuroPsychopharmacotherapy, pp 1447-1467. November 05 2022
5. Yang Wei Jain, Chen Zhen, Zheng Yi Nan. Valproic acid induced aplastic crisis and Stevens-Johnson syndrome in a single pediatric patient.10.1016/j.heliyon.2022.e12461. 2023.
6. Rashid Muhammed, Pharm B, Pharm M. Kashyap A, et al. Review of Valproic acid and Stevens-Jonhson syndrome: a systematic review of descriptive studies. International Journal of Dermatology. Doi: 10.1111/ijd.14411.2019
7. Miya Riyaz, Malpani AK, Keri Sangamesh, et al. Drug-Induced Steven-Johnson Syndrome (SJS), Journal of Pharmacy Practice. June 2019

8. Edinoff A, Nguyen LH, Gerald MJ, et al. Lamotrigine and Stevens-Johnson Syndrome Prevention. 2021 Mar 16; 51(2); 96-114.
9. Dutt J, Sapra A, Sheth-Dutt P, et al. Steven-Johnson Syndrome: A Perplexing Diagnosis. Published online 2020 Mar;12(3);e7374. Doi:10.7759/cureus.7374
10. Chang Hua C, Wang Tsung-J. Lin Ming H, et al. A Review of the Systematic Treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.10.3390/biomedicines10092105. 2022, 10(9), 2105
11. Nveen KN, Arunkumar JS, Hanumanthayya and Pai VV. Stevens-Johnson syndrome induced by sodium valproate monotherapy. 10.4103%2F2229-5151.94904. Jan-Apr;2(1):44-45. 2012
12. Marks ME, Botta RK, Abe R, et al. Updates in SJS/TEN: collaboration, innovation, and community. Vol 10-2023. Doi: https://doi.org/10.3389/fmed.2023.1213889
13. Desarkar P, Nizamie SH. Risperidone-induced erythema multiforme minor. Br J Clin Pharmacol. 2006 Jun;62(4):504-505. Doi: https://doi.org/10.1111/j.1365-2125.2006.02708.x
14. Barbour KK, Umfrid CP, Brinton BA, et al. A Case of Stevens-Johnson Syndrome after exposure to valproic acid. Prim Care Companion SSP Disord. 2019; 21(2):18l02374
15. Naveen KN, Arunkumar JS, Hanumanthayya. Stevens-Johnson Syndrome Induced by Sodium Valproate monoteraphy. International Journal of Critical illness & Injury Science. 2012 Jan-Apr;2(1):44–45. Doi: 10.4103/2229-5151.94904
16. Kavitha, anbuchelvan T, Mahalakshmi V, et al. Stevens-Johnson Syndrome Induced by a Combination of Lamotrigine and Valproic Acid. Journal of Pharmacy and Bioallied Sciences 7(Suppl 2):p S756-S758, August 2015. | Doi: 10.4103/0975-7406.163545
17. Gupta LK, Martin AM, Agarwal N, et al. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis: an Indian perspective. Therapeutic Guidelines – IADVL, 2016:82:6;603-625. Doi: 10.4103/0378-6323.191134
18. Coulson CJ, Daghman MY. Aripiprazole-Induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Case Study. Jun 2023. Doi: 10.1097/WNF.0000000000000560
19. Santanu N, Rehman, Sajjadur, et al. Aripiprazole-induced skin rash: Case Report. Industrial Psychiatry Journal 25(2):p 225-227, Jul–Dec 2016. | Doi: 10.4103/0972-6748.207862

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