CASE STUDY

Acute Hypersensitivity Syndrome Caused by Valproic Acid: A Review of the Literature and a Case Report

Robert G Bota, MD, MSG
Allein P Ligasan, RN
Tom G Najdowski, LCSW
Andrei Novac, MD

Abstract

Valproic acid (VPA) is an antiepileptic medication used in the treatment of bipolar disorder. Its toxicity profile is characterized by a very rare but well-documented complication—hepatotoxicity. The risk of acute hypersensitivity syndrome (AHS) caused by VPA is less well known. In the vast majority of reported cases of AHS, the syndrome is the result of aromatic anticonvulsants (AAs), such as carbamazepine or phenytoin. These compounds also have in-class cross-reactivity. We present the case of a 25-year-old woman with bipolar disorder who was unable to tolerate aripiprazole, ziprasidone, and lamotrigine. She was given extended-release VPA as a trial and developed AHS with a generalized rash, fever, liver and kidney involvement, and eosinophilia one week after the initiation of treatment. She recovered after one month of treatment, which included ten days of hospitalization. Our review of the literature focuses on AA and non-AA medications causing AHS.

Introduction

Hepatotoxicity is a rare adverse effect of valproic acid (VPA). The severity of hepatotoxicity can range from reversible hepatic dysfunction to irreversible liver failure.[1] In an earlier review, Binek and colleagues[2] reported a risk of 1:5000 to 1:10,000 of liver failure with VPA. Most of the reported cases involved boys younger than 10 years and with mental retardation. Major risk factors were being younger than 2 years and concomitant use of other anticonvulsant medication.[3] Furthermore, 90% of patients developing hepatotoxicity were younger than 20 years.[4] De Wolff et al[5] reported that in 32 children with epilepsy, VPA did not affect γ-glutamyltranspeptidase activity, but it selectively enhanced D-glucaric acid excretion. Demircioğlu and colleagues[6] looked at 38 children with epilepsy, 31 of whom were treated with carbamazepine and 7 of whom were treated with VPA. They reported that although there were no differences between the groups in serum lipid levels and liver-function test results, the total cholesterol levels, low-density lipoprotein levels, and total cholesterol/high-density lipoprotein levels were higher in the carbamazepine group during treatment.

Aromatic anticonvulsants (AAs) such as carbamazepine and phenytoin can induce hypersensitivity syndrome (HS) at a rate of 1:10,000 in new patients and 1:1000 in patients already taking the treatment. Seitz et al[7] suggested that there is a cross-reactivity between AAs and tricyclic antidepressants. Because cross-reactivity can be as high as 75%, they recommended that physicians be taught not to use these agents in such situations, but to instead use VPA, benzodiazepine, lamotrigine, and gabapentin.[8,9] Alldredge et al[10] reported that before the onset of symptoms, physicians for 3 of 4 patients with acute hypersensitivity syndrome (AHS) switched their medications to an anticonvulsant with an aromatic ring in the structure. They also reported that the symptoms subsided after the interruption of the medication and that all patients recovered. Three of these patients required continuation of antiepileptic drugs, and they tolerated VPA well. In an important study, Baba et al[11] described 32 patients with AHS caused by AAs; 22 of them required continuation of anticonvulsive treatment, and they tolerated VPA well.

AHS is a potentially life-threatening condition characterized by the triad of fever, rash (most of the body surface, ranging from mild exanthem to epidermal necrolysis), and multiorgan involvement (50% liver and 11% kidney), usually occurring in the first few weeks after the initiation of anticonvul-

Robert G Bota, MD, MSG, is a Psychiatrist at the Kaiser Permanente Corona Medical Offices in CA and Clinical Assistant Professor at University of Missouri, Kansas City. E-mail: rgbota@yahoo.com.
Allein P Ligasan, RN, is a Nurse at the Kaiser Permanente Corona Medical Offices in CA. E-mail: allein.ligasan@kp.org.
Tom G Najdowski, LCSW, is a Licensed Social Worker at the Kaiser Permanente Corona Medical Offices in CA. E-mail: thomas.g.najdowski@kp.org.
Andrei Novac, MD, is a Professor of Psychiatry at the University of California, Irvine in Orange, CA. E-mail: anovac@uci.edu.

sant treatment. Lymphadenopathy (70%) and eosinophilia (30%) are also frequent.[8] Mortality from this condition has been reported to be up to 10%.[12] Despite being reported to occur with AA treatments, AHS has rarely been reported in patients taking VPA. Roepke and colleagues[13] reported details of a case involving a patient, age 48 years, with schizoaffective disorder whose medications were switched on the third day of hospitalization from haloperidol, fluphenazine, diazepam, clomethiazole, promethazine, biperiden, and vitamins B_1 and B_6 to long-acting VPA, lithium, amisulpride, and vitamins B_1 and B_6. Three weeks later, the patient developed lymphadenopathy, generalized maculopapular rash, and a fever (39.1°C), and his transaminase and creatinine levels were slightly elevated. VPA and vitamins B_1 and B_6 were discontinued, and the patient was instead given olanzapine and prednisolone (initially 80 mg/d). With this treatment, the patient recovered in one week. Another case report described a patient who, after resolution of symptoms caused by carbamazepine-induced AHS, was given VPA and immediately developed life-threatening AHS.[14] In addition, Cogrel and colleagues[15] reported an AHS-like condition with VPA treatment. The patient recovered after the VPA was discontinued. When the patient was again given carbamazepine as a medication challenge, the AHS reappeared and again resolved once the medication was discontinued. In a very recent case report, Dreesman and colleagues[16] described another case of AHS induced by both lamotrigine and VPA. In another case report,[17] two patients, one treated with carbamazepine alone and another treated with a combination of lamotrigine and VPA, developed AHS, which subsided immediately after the interruption of the causative agents and supportive treatment was begun. In a unique report, Chang et al[18] described the case of a woman, age 48 years, with bipolar disorder who was treated with lamotrigine and VPA and then developed AHS because of the lamotrigine. The patient recovered after discontinuation of the anticonvulsant medication and initiation of supportive treatment. Karande et al[19] discussed the case of a boy, age 2 years, treated with VPA and lamotrigine for epilepsy. The child developed AHS because of the lamotrigine, but went on to recover and was given VPA and discharged from the hospital. In addition, Rahman and Haider[20] reported AHS in a patient treated with VPA after the addition of lamotrigine. Conilleau and colleagues[21] described AHS secondary to both VPA and ethosuximide (patch test results were positive with both medications) in a Tunisian, age 6 years. After both medications were stopped and corticosteroid treatment was administered, the patient recovered.

Fatal AHS has also been attributed to VPA. For example, Huang et al[22] discussed a case of fatal AHS caused by VPA: The patient presented to the hospital with nonspecific polymorphous eruptions, fulminant hepatitis, and jaundice. Plantin et al[23] and Picart and colleagues[24] reported a case of AHS caused exclusively by VPA treatment.

Case Report

Ms A was 25 years old when we treated her. Three years earlier, her bipolar II disorder was diagnosed. Initial treatment with quetiapine helped control her symptoms. However, she grew concerned about the significant weight gain (>7% of her initial weight) and increase in total cholesterol level (299 mg/dL), triglyceride level (257 mg/dL), and low-density lipoprotein level (192 mg/dL) that she experienced. As a result, she was willing to explore other options. An initial trial of aripiprazole, at 5 mg/d, caused extrapyramidal symptoms (EPS), and thus the medication was stopped. Lamotrigine was then started at 25 mg/d and increased by 25 mg/wk. She bipolar disorder responded well to this medication. However, after one month, the medication was discontinued because the patient developed a nonspecific rash and had concerns about severe adverse effects. The third medication tried was ziprasidone, which was stopped because of EPS that were very similar to the adverse effects of aripiprazole. While taking ziprasidone, the patient also experienced nausea and vomiting.

A few weeks later, Ms A agreed to a trial of extended-release divalproex. The results of liver-function tests at the start of her treatment were normal. The initial dose of divalproex was 500 mg orally at bedtime, which was increased after one week to 500 mg orally twice a day. The plan was to obtain results from new set of laboratory tests on day 10 of therapy. Unfortunately, 6 days later, she reported gastrointestinal symptoms and a low-grade fever. She went to the Emergency Department for evaluation, where her symptoms resulted in a diagnosis of gastroenteritis and she was given 2 antibiotics. Several days later, however, her symptoms had not subsided. Thus, we ordered the laboratory tests earlier than planned. The results were as follows: VPA level, was 60.4 µ/mL;

alanine transaminase, 767 U/L; alkaline phosphatase, 681 U/L; bilirubin total, 10.2 mg/dL. The patient's primary care physician was contacted, and she was admitted to the hospital. During her stay there, she was found to have VPA HS, with generalized rash, fever, liver and kidney involvement, and marked eosinophilia.

Because of the involvement of multiple organs and the multiple possible causes for this clinical presentation, we obtained specialist consults. Possible etiologies for the syndrome at the time of admission included infection (viral or bacterial), medication (lamotrigine or VPA), and autoimmunity. A laboratory work-up for infectious diseases produced negative findings on blood and urine cultures, negative findings on chest radiographs, and negative results for acute hepatitis, Epstein-Barr virus, and human immunodeficiency virus tests. The patient had a monospot test, which produced positive findings for mononucleosis. Results of testing for autoimmune hepatitis, antinuclear antibodies, and antimitochondrial antibody were negative. Test results for serum antitrypsin and ceruloplasmin were also negative, as were tests for alcohol, acetaminophen, and salicylate levels. The gastroenterology consultant provided supportive treatment. The patient was given acetylcysteine (Mucomyst) for its antioxidant property and vitamin K for the coagulopathy that she presented with. The patient's laboratory results improved during her hospital stay.

Ms A also developed an erythematous rash on the body, which initially started on her lower legs and rapidly migrated to her trunk, chest, back, arms, and ultimately to the face and interfered with her ability to open her eyes. The rash did not involve palmar or plantar surfaces or the mucous membranes. Initially the rash was erythematous and slightly raised and patchy but confluent, but over the next few days, it became continuous with significant edema. A dermatologist treated the rash with topical corticosteroids and oral prednisone (Deltasone), starting with 80 mg/d for 10 days and then decreasing the dose by 20 mg every week. After taking 60 mg of prednisone for a week, the patient noticed a gradual exacerbation of her rash, this time including her palms, requiring an increase of the dose to the previous level and then a slower tapering off.

After being discharged from the hospital, Ms A was monitored by the hospital's ambulatory internal medicine service. The results of her liver-function tests improved to normal within the following three weeks. The generalized rash resolved after one month, and corticosteroid treatment was stopped.

At the next few psychiatry visits, Ms A expressed concern at the idea of starting any new medications for her bipolar illness but expressed interest in and commitment to accepting any other interventions.

... even though aromatic anticonvulsant medications have a much lower likelihood of producing Acute Hypersensitivity Syndrome, they do still pose a real, palpable risk for patients.

Discussion

Ms A was treated with lamotrigine one month before the initiation of treatment with VPA. Lamotrigine was stopped because of a rash that developed while she was taking the medication. Thus, we suggest that in patients in whom treatment with lamotrigine is discontinued because of the development of a rash, a more comprehensive review of symptoms should be performed to aid in the diagnosis of AHS. This is particularly important because of the future risk of AHS after initiation of a new antiepileptic medication. Specifically, as one case report described, a patient developed the AHS after the addition of lamotrigine, thus suggesting a possible cross-reactivity[20] between lamotrigine and other antiepileptic medications. However, Krivoy et al[25] suggested that there is no evidence of cross-reactivity between VPA and lamotrigine.

In a recent retrospective study,[26] carbamazepine was identified as the first cause of AHS, with phenytoin as the second cause and lamotrigine as the third. The authors concluded that VPA and benzodiazepine are safe alternatives to use in patients who present with AHS while taking the other medications. However, we identified four published reports of cases in which AHS was caused by VPA[22–24] and another three in which it was caused by VPA and ethosuximide[21] and by VPA and lamotrigene.[16] In addition, most of reported AHS cases have involved patients treated for epilepsy, especially young boys. Apparently, being female and older than 20 years are protective factors against AHS. Cross-reactivity is a serious concern, especially in the AA class of medications.

Our patient, Ms A, expressed serious concerns regarding starting a new medication to treat her bipolar disorder. In addition, AA medications, such as carbamazepine, are associated with a higher risk of AHS than non-AAs are. We could not identify any reports regarding patients who developed AHS in response to lamotrigine or VPA who subsequently were able to tolerate antiepileptic medications with an AA ring. Thus, it is logical to question whether this is a potential consideration. Our patient was unable to tolerate aripiprazole and ziprasidone because of EPS despite

preventive treatment with hydroxyzine and lorazepam. The alternative of using other antipsychotic medications can be considered, but the risk of adverse effects is quite significant. Our patient will view any new intervention through the lens of her own recent challenging experiences. Not only was she hospitalized for ten days but also during that period, there were discussions about the possibility of liver transplantation, heightening our patient's anxiety. In addition, Ms A's concern about her own well-being was further intensified by the recent death of a family member. She wanted reassurance that any new medication regimen would be 100% effective and complication free. Unfortunately, no physician can make such a promise. Therefore, for now, any further treatment with anticonvulsants has been deferred. Thanks to her above-average intelligence, good self-insight, and a stable support system, she was more than willing to stay involved in psychiatric treatment, which consisted of monthly psychiatric follow-up visits and cognitive behavioral therapy and supportive psychotherapy. She also remained open to alternative treatment methods such as electroconvulsive therapy and hospitalization if needed. The patient was aware of the warning signs of depressive and manic relapses and had a history of reporting her symptoms at the earliest of times. After further discussions, she agreed to occasional benzodiazepine use for sleep and overt anxiety, as an additional preventive measure against further relapses.

Conclusions

Since the 1980s, it has been known that VPA can cause hepatotoxicity and liver failure,[1,2] but only three cases of AHS had been reported before our report here. Overall, the previous reports showed that AAs induce AHS and that there is cross-reactivity between compounds of that class. Non-AA antiepileptic medications were presumed safe.[7] Our case suggested that even though AA medications have a much lower likelihood of producing AHS, they do still pose a real, palpable risk for patients. In addition, medical professionals must remain alert regarding the potential of cross-reactivity between AA and non-AA medications. Additional studies and pharmacologic insight are needed to shed more light on this subject. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

We thank Daniela Alexandru, MD, and Bonita Jaros, PhD, for scientific review and critical suggestions. Dr Bota also thanks Carla Hix, PsyD, Linda DeSoucy, RN, and Soncerie Villegas, RN, for support.

Katharine O'Moore-Klopf, ELS, of KOK Edit provided editorial assistance.

References

1. Cotariu D, Zaidman JL. Valproic acid and the liver. Clin Chem 1988 May;34(5):890–7.
2. Binek J, Hany A, Egloff B, Heer M. [Acute fatal liver insufficiency due to valproic acid therapy]. [Article in German]. Schweiz Med Wochenschr 1991 Feb 16;121(7):228–33.
3. Bell EA, Shaefer MS, Markin RS, et al. Treatment of valproic acid-associated hepatic failure with orthotopic liver transplantation. Ann Pharmacother 1992 Jan;26(1):18–21.
4. Fisher RL, Sanuik JT, Nau H, Gandolfi AJ, Brendel K. Comparative toxicity of valproic acid and its metabolites in liver slices from adult rats, weanling rats and humans. Toxicol In Vitro 1994 Jun;8(3):371–9.
5. de Wolff FA, Peters AC, van Kempen GM. The effects of valproic acid on liver function. Arch Toxicol Suppl 1983;6:369–73.
6. Demircioğlu S, Soylu A, Dirik E. Carbamazepine and valproic acid: effects on the serum lipids and liver functions in children. Pediatr Neurol 2000 Aug;23(2):142–6.
7. Seitz CS, Pfeuffer P, Raith P, Bröcker EB, Trautmann A. Anticonvulsant hypersensitivity syndrome: cross-reactivity with tricyclic antidepressant agents. Ann Allergy Asthma Immunol 2006 Nov;97(5):698–702.
8. Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. Drug Saf 1999 Dec;21(6):489–501.
9. Bohan KH, Mansuri TF, Wilson NM. Anticonvulsant hypersensitivity syndrome: implications for pharmaceutical care. Pharmacotherapy 2007 Oct;27(10):1425–39.
10. Alldredge BK, Knutsen AP, Ferriero D. Antiepileptic drug hypersensitivity syndrome: in vitro and clinical observations. Pediatr Neurol 1994 Mar;10(2):169–71.
11. Baba M, Karakaş M, Aksungur VL, et al. The anticonvulsant hypersensitivity syndrome. J Eur Acad Dermatol Venereol 2003 Jul;17(4):399–401.
12. Papp Z, Török L. [Anticonvulsant hypersensitivity syndrome]. [Article in Hungarian]. Orv Hetil 2004 Aug 8;145(32):1665–8.
13. Roepke S, Treudler R, Anghelescu I, Orfanos CE, Tebbe B. Valproic acid and hypersensitivity syndrome. Am J Psychiatry 2004 Mar;161(3):579.
14. Arévalo-Lorido JC, Carretero-Gómez J, Bureo-Dacal JC, Montero-Leal C, Bureo-Dacal P. Antiepileptic drug hypersensitivity syndrome in a patient treated with valproate. Br J Clin Pharmacol 2003 Apr;55(4):415–6.
15. Cogrel O, Beylot-Barry M, Vergier B, et al. Sodium valproate-induced cutaneous pseudolymphoma followed by recurrence with carbamazepine. Br J Dermatol 2001 Jun;144(6):1235–8.
16. Dreesman A, Hoorens A, Hachimi-Idrissi S. Multiple organ dysfunction syndrome: infection or hypersensitivity reaction? Eur J Emerg Med 2010 Aug;17(4):228–9.
17. Bin-Nakhi HA, Sadeq S, Pinto RG, Habeeb Y. Anticonvulsant hypersen-

sitivity syndrome: report of 2 cases from Kuwait. Med Princ Pract 2003 Jul–Sep;12(3):197–9.

18. Chang CC, Shiah IS, Yeh CB, Wang TS, Chang HA. Lamotrigine-associated anticonvulsant hypersensitivity syndrome in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2006 Jun;30(4):741–4.
19. Karande S, Gogtay NJ, Kanchan S, Kshirsagar NA. Anticonvulsant hypersensitivity syndrome to lamotrigine confirmed by lymphocyte stimulation in vitro. Indian J Med Sci 2006 Feb;60(2):59–63.
20. Rahman M, Haider N. Anticonvulsant hypersensitivity syndrome from addition of lamotrigine to divalproex. Am J Psychiatry 2005 May;162(5):1021.
21. Conilleau V, Dompmartin A, Verneuil L, Michel M, Leroy D. Hypersensitivity syndrome due to 2 anticonvulsant drugs. Contact Dermatitis 1999 Sep;41(3):141–4.
22. Huang YL, Hong HS, Wang ZW, Kuo TT. Fatal sodium valproate-induced hypersensitivity syndrome with lichenoid dermatitis and fulminant hepatitis. J Am Acad Dermatol 2003 Aug;49(2):316–9.
23. Plantin P, Cartier H, Le Bihan G, Clouard P, Lellouche F, Leroy JP. [Drug hypersensitivity syndrome during treatment with valproic acid]. [Article in French]. Presse Med 1995 Nov 11;24(34):1624.
24. Picart N, Périole B, Mazereeuw J, Bonafé JL. [Drug hypersensitivity syndrome to valproic acid]. [Article in French]. Presse Med 2000 Apr 1;29(12):648–50.
25. Krivoy N, Taer M, Neuman MG. Antiepileptic drug-induced hypersensitivity syndrome reactions. Curr Drug Saf 2006 Aug;1(3):289–99.
26. Mansur AT, Pekcan Yaşar S, Göktay F. Anticonvulsant hypersensitivity syndrome: clinical and laboratory features. Int J Dermatol 2008 Nov;47(11):1184–9.

The Effect of Drugs on the Body

Following chlorpromazine, a veritable cornucopia of antipsychotic, antimanic, and antidepressant drugs poured forth, changing psychiatry from a branch of social work to a field that called for the most precise knowledge of pharmacology, the effect of drugs on the body.

— A History of Psychiatry: From the Era of the Asylum to the Age of Prozac, *Edward Shorter, social historian of medicine, Hannah Professor in the history of medicine and Professor of Psychiatry at the University of Toronto*