Case Reports and Reviews

Case Report

One case of thrombocytopenia induced by sodium valproate sustained release tablets and literature review

Qiang Xiong[1], and Ying Chan Wang[2*]

[1]Shanghai Songjiang Mental Health Center, No. 209 Ta hui Road, Songjiang District, Shanghai, 201617, China

2Shanghai Mental Health Center, 600 Wan ping South Road, Xuhui District, Shanghai, China

Correspondence

Ying Chan Wang

Shanghai Mental Health Center, 600 Wan ping South Road, Xuhui District, Shanghai, China

E-mail: 13818233341@163.com

- Received Date: 07 Jan 2022
- Accepted Date: 24 Jan 2022
- Publication Date: 03 Feb 2022

Keywords

sodium valproate; platelet count; schizophrenia

Abstract

More than a century ago, American chemist Beverly S. Burton synthesis of sodium valproate (VPA). At present, sodium valproate is widely used in clinic as an effective antiepileptic and emotional stability drug. Its mechanism of anti-epileptic and emotional stability is not fully understood. Studies have shown that VAP is obtained by changing the metabolism of GABA. Recently, several studies have further demonstrated the pharmacodynamic properties of the compound, including direct effects on voltage-gated sodium channels or disruption of the sodium channel membrane environment [2].Sodium valproate sustained-release tablets were used in the treatment of schizophrenia. One case of thrombocytopenia was found. After 6 days of withdrawal, platelet count (PLT) returned to normal. Considering the wide application of sodium valproate and the long-term medication of most patients with chronic diseases, spontaneous bleeding may occur when the platelet count is reduced seriously, and life may be endangered when it is serious, the author reviewed the relevant literature and reported it..

Clinical data

The patient, a 28-year-old female, was aggravated by suspicion for more than a year, and the total course of the disease was unknown. She was sent to the outpatient clinic of our hospital by the staff of the rescue station on December 20, 2020. Outpatient clinic with "schizophrenia?" Admitted to hospital. Psychiatric examination after admission found that patients had obvious victim delusion, absurd content, the object was generalized, and the patient firmly believed it. No obvious abnormalities were found in admission physical examination. The patient denied the history of severe somatic disease, drug allergy and infection. Deny taking any drugs recently. No obvious abnormalities were found in the blood routine examination, liver and kidney function, electrolyte, blood glucose, blood lipid, thyroxine, stool routine, infectious diseases (5 markers of hepatitis B, hepatitis C, syphilis, HIV antibody), electrocardiogram, electroencephalogram, chest CT, abdominal color ultrasound and so on. PANSS score 81. According to ICD-10 diagnostic criteria, schizophrenia was diagnosed after admission, and aripiprazole was given antipsychotic treatment. The initial dose was 10 mg / day, and increased to 20 mg / day after 3 days and maintained until discharge. On January 10,2021, the patient developed impulsive behavior and was treated with sodium valproate sustained-release tablets (VAP) 500 mg / day to stabilize emotion. The effective concentration of drug treatment was 50 – 100μg / mL [3]. During the follow-up of 7 February 2021, the platelet count of the patients was decreased, and the platelet count was 82 x109/L Considering the adverse drug reactions caused by VAP, VAP was stopped immediately on the same day. On February 16,2021, routine blood platelet count showed that it returned to normal. After March 10,2021, the platelet was in the normal range, and further increased compared with February 16. See Table 1.

On April 1, 2021, the father of the patient came to the hospital to receive the patient. At discharge, the PANSS scale score was 40 points. Before and after admission, 75 % > PANSS reduction rate ≥ 50 %, suggesting that the therapeutic effect is remarkable progress.

Discussion

Although the World Health Organization 's definition of sodium valproate-induced thrombocytopenia is a common / very common side effect and has important therapeutic significance, its attractiveness in clinical research is low, and case reports are rare. So far, the mechanism of VAP-induced PLT reduction is not clear and the treatment is not uniform.

Reported sodium valproate sustained release tablets can cause white blood cells, red blood

Citation: Xiong Q, Wang YC. One case of thrombocytopenia induced by sodium valproate sustained release tablets and literature review. Case Rep Rev. 2022;3(1):1-3.

Table 1. *Drugs and platelet count*

Date	Drug dosage	Platelets Counting x10^9/L
12/20/2020	No medication on the day of admission	180
12/21/2020	Aripiprazole Tablets 10mg / day	172
1/12/2021	Aripiprazole Tablets 10mg / day +Sodium valproate 500 mg / day	183
2/7/2021	Aripiprazole Tablets 20mg / day	82
2/10/2021	Aripiprazole Tablets 20mg / day	85
2/16/2021	Aripiprazole Tablets 20mg / day	116
3/10/2021	Aripiprazole Tablets 20mg / day	162

cells, thrombocytopenia, that is cachexia [4], The mechanism may be: VAP metabolite 2-propyl-2,4-pentadienoic acid destroys hepatocytes and inhibits the synthesis of coagulation factors, and VAP inhibits platelet aggregation by inhibiting the conversion of arachidonic acid to prostaglandin and thromboxane on platelet membrane [5]. Drug-induced thrombocytopenia refers to the fact that some drugs cause platelet count in peripheral blood to be less than 100 × 109 / L. Its clinical manifestations are skin ecchymosis, mucosal bleeding, gastrointestinal bleeding and even intracranial hemorrhage. If not found and treated in time, there is often a high mortality rate. Thrombocytopenia is now known in 5-18 % of patients taking VPA[6,7], 12-18 % of studies with sample size > 150. The prevalence of thrombocytopenia in psychiatric cohorts treated with sodium valproate is about 5 % [8]. More common in women and older subjects [9-11]. In addition, lower baseline platelet count is reported to be an additional risk factor for thrombocytopenia, and VPA dose also affects final platelet count [12-14]. It should also be noted that antiepileptic drugs, including valproates, can also induce hypersensitivity syndrome (DRESS). DRESS is a serious skin adverse drug reaction characterized by systemic acute macular papules with high fever and internal organ involvement. This is a rare but potentially fatal adverse event with mortality rates ranging from 10 to 40 per cent [15]. Chinese scholar Xing Ying et al. believe that thrombocytopenia may be related to 1. the time and cumulative dose of drug use 2. combined medication is more likely to lead to thrombocytopenia [16].

When patients have thrombocytopenia symptoms, there is no unified treatment so far. Buoli M believed that the elderly, women and high doses were high risk factors for thrombocytopenia, so clinicians should be particularly cautious in the use of this compound in elderly women patients, especially when the dose was more than 1 g / day. It should also be remembered that older patients often receive multiple treatments, which may increase the risk of thrombocytopenia or bleeding [17]. Vasudev K believes that elderly, female and low baseline platelet count are independent risk factors for thrombocytopenia. Interestingly, the risk of low platelet count in female subjects increases significantly with the increase of sodium valproate level, while male subjects do not [18]. Xing Ying et al. think that stopping VAP can restore platelet count, but the effect is not good [16]. Looking through the drug instructions of sodium valproate sustained-release tablets, the treatment of this adverse reaction can be reduced according to the control of platelet level and epilepsy disease, and the treatment of asymptomatic thrombocytopenia can usually eliminate thrombocytopenia. Gao Peipei et al. reported 1 case in this way [19]. In this case, VAP was used in a small dose and was not the main drug for treatment. Therefore, no drug reduction scheme was adopted, and the platelet count recovered rapidly after drug withdrawal.

Although thrombocytopenia is described as ' occasional dose-related thrombocytopenia cases ' in the ' adverse reactions ' section of the instruction for sodium valproate sustained release tablets. However, it should be noted that psychiatric patients are different from ordinary patients. VAP is most commonly used in patients with bipolar disorder (BD) and schizophrenia (S) in psychiatric patients. Affected by the disease, most of them have different degrees of cognitive impairment, and often can not take the initiative to provide thrombocytopenia-related discomfort complaints, which is not conducive to early detection of its related adverse reactions. At the same time, it can improve the understanding of the clinical manifestations, diagnosis and treatment of drug-induced thrombocytopenia, so as to achieve the purpose of rational drug use [20]. The purpose of this case report is to alert the majority of psychiatric personnel to use VAP in clinical practice, especially to pay attention to its adverse reactions to thrombocytopenia. At the same time, psychiatric patients may not be able to tell their own history of adverse drug reactions in detail after discharge, which lays a potential safety hazard for the doctors to use similar drugs to again have the same adverse reactions.

References

1. Kai-da J. Psychological pharmacology. Beijing: People ' s Health Press, 2011.
2. De Berardis D, Campanella D, Matera V, et al. Thrombocytopenia during valproic acid treatment in young patients with new-onset bipolar disorder. J Clin Psychopharmacol. 2003;23(5):451-458.
3. National Pharmacopoeia Commission. Instructions for clinical medication in Chinese Pharmacopoeia (Volumes of Chemicals and Biological Products). Beijing:China Pharmaceutical Science and Technology Press, 2010 : 39
4. Weller EB, Danielyan AK, Weller RA. Somatic treatment of bipolar disorder in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2002;11(3):595-617.
5. Harden CL. Therapeutic safety monitoring: what to look for and when to look for it. Epilepsia. 2000:41(8):S37-S44
6. Kopeikina E, Dukhinova M, Yung AWY, et al. Platelets promote epileptic seizures by modulating brain serotonin level, enhancing neuronal electric activity, and contributing to neuroinflammation and oxidative stress. Prog Neurobiol. 2020;188:101783.
7. Benlachgar N, Doghmi K, Masrar A, Mahtat EM, Harmouche H, Tazi Mezalek Z. Immature platelets: a review of the available evidence. Thromb Res. 2020;195:43-50.
8. Vasudev K, Keown P, Gibb I, McAllister-Williams RH. Hematological effects of valproate in psychiatric patients: what

are the risk factors?. J Clin Psychopharmacol. 2010;30(3):282-285.

9. Orsolini L, Pompili S, Volpe U. The 'collateral side' of mood stabilizers: safety and evidence-based strategies for managing side effects. Expert Opin Drug Saf. 2020;19(11):1461-1495.
10. Ahmad A, Sheikh S, Khan MA, et al. Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder. Bipolar Disord. 2021;23(6):595-603.
11. Buoli M, Gattoni E, Collantoni E, et al. Factors influencing lithium versus valproate prescription preference in the maintenance treatment of bipolar patients: a report from the Italian Early Career Psychiatrists (SOPSI-GG). Int J Psychiatry Clin Pract. 2021;25(1):82-89.
12. Heidemann J, Schmitz B, Kostev K. Association between antiseizure medication use and risk of urinary tract infection: A case-control study. Epilepsy Behav. 2021;115:107502.
13. Capuzzi E, Caldiroli A, Leo S, Buoli M, Clerici M. Initiation of psychotropic medication in hospitalized patients with COVID-19: Association with clinical and biological characteristics. Hum Psychopharmacol. 2021;36(5):e2789.
14. Gatti M, De Ponti F, Pea F. Clinically Significant Drug Interactions Between Psychotropic Agents and Repurposed COVID-19 Therapies. CNS Drugs. 2021;35(4):345-384.
15. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149-153.
16. Ying X, Yuan Y, Jing B, Jian-cun Z. Literature analysis of sodium valproate for adult patients with thrombocytopenia. Chinese pharmacy. 2015;26(03):336–338
17. Buoli M, Serati M, Botturi A, Altamura AC. The Risk of Thrombocytopenia During Valproic Acid Therapy: A Critical Summary of Available Clinical Data. Drugs R D. 2018;18(1):1-5.
18. Vasudev K, Keown P, Gibb I, McAllister-Williams RH. Hematological effects of valproate in psychiatric patients: what are the risk factors?. J Clin Psychopharmacol. 2010;30(3):282-285.
19. Gao P, Hui-ping L, Yahong Z. Thrombocytopenia caused by sodium valproate sustained release tablets in patients with intracranial space-occupying lesions . Medical report. 2018; 37(S1):114-115
20. Dongling L. Pathogenesis, clinical manifestations, prevention and treatment of drug-induced thrombocytopenia. Chinese Medical Guide. 2020;18(01):76-77.