CASE REPORT

THROMBOCYTOPENIA WITH VALPROATE AND CLOZAPINE COMBINATION THERAPY

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Abstract

Objective: The occurrence of thrombocytopenia with valproate and clozapine combination therapy has not been noted in the literature. This case report highlights thrombocytopenia as a potential outcome of drug-drug interaction between valproate and clozapine, and serves to remind practitioners that regular monitoring of platelet counts is necessary in such combination therapy. *Method:* We report on a patient on valproate therapy who developed thrombocytopenia when clozapine was added to her treatment regime. *Results:* Thrombocytopenia resolved 1 week after valproate was tailed off and the patient was placed on clozapine monotherapy. *Conclusions:* A precise pathophysiologic understanding of valproate and clozapine-induced thrombocytopenia is lacking, and further studies are required. ***ASEAN Journal of Psychiatry, Vol.12(1), Jan – June 2011: XX XX***

Keywords: Thrombocytopenia; Valproate; Clozapine

Introduction

Valproate is commonly used in the treatment of bipolar disorder and schizoaffective disorder, or as augmentation to antipsychotics in schizophrenia. A range of blood dyscrasias can occur with valproate including thrombocytopenia, macrocytic anemia and leucopenia. Clozapine is an atypical antipsychotic agent with superior efficacy for the management of treatment resistant schizophrenia. Common hematological adverse effects include agranulocytosis, neutropenia, leukocytosis, and eosinophilia. Thrombocytopenia as a complication of clozapine therapy is seldom reported.

We present the case of a 29-year-old lady on valproate therapy who developed thrombocytopenia when clozapine was added to her treatment regime. The occurrence of thrombocytopenia with valproate and clozapine combination therapy has not been noted in the literature. We discuss the possible mechanisms for this drug-drug interaction.

Case Report

The patient, Miss N, is a Malay lady who suffered from schizophrenia and first presented in 2003 at the age of 22. Throughout the years, Miss N was treated with various antipsychotic medications at therapeutic doses and adequate durations, and received both oral and depot formulations. Antipsychotics prescribed included haloperidol, chlorpromazine,

risperidone, olanzapine, flupenthixol, and zuclopenthixol.

During an admission in 2008, Miss N had affective features such as elevated mood, increased irritability, and aggressiveness. Valproate was added and titrated to 800 mg per day. Her baseline full blood count (FBC) yielded normal results: Hemoglobin (Hb) 11.2 g/dL; white blood cell (WBC) count 9.88 x 10^9/L; platelet count 353 x 10^9/L; absolute neutrophil count (ANC) 6.32 x 10^9/L. In September 2009, Miss N suffered a relapse of her schizophrenia illness. During this admission, valproate was titrated to 1500 mg per day, and her antipsychotic was switched to clozapine. Physical examination and laboratory investigations then were normal. Hematological indices were: WBC count 7.9 x 10^9/L; platelet count 341 x 10^9/L; ANC 4.7 x 10^9/L. Her clozapine dose was gradually titrated over 1 week to 150 mg per day. A week after starting clozapine, a repeat FBC showed a drop in platelet count to 99 x 10^9/L. WBC count and ANC were normal at 8.4 x 10^9/L, and 5.7 x 10^9/L respectively. FBC repeated 2 days later showed falling platelet count to 88 x 10^9/L; WBC count 10.1 x 10^9/L; ANC 7.2 x 10^9/L.

Miss N's mental state had improved significantly with clozapine. Thus a decision was made to decrease and tail off valproate, but titrate the dose of clozapine to 250 mg per day. FBC done 3 days after reducing valproate yielded these results: platelet count 92 x 10^9/L; WBC count 6.7 x 10^9/L; ANC 3.9 x 10^9/L. One week after the patient was taken off valproate and placed on clozapine monotherapy, her platelet count had normalized to 346 x 10^9/L; WBC count 8.7 x 10^9/L; ANC 4.8 x 10^9/L. The patient's mental state continued to improve on clozapine 250 mg per day monotherapy and she was eventually discharged with outpatient follow-up.

Discussion

Thrombocytopenia is one of the commonest side effects associated with valproate therapy. However, the exact mechanism of valproate-associated thrombocytopenia is unclear. Kishi et al have shown that a high serum concentration of valproate is associated with bone marrow suppression [1]. On the other hand, supporting an immune-mediated hypothesis, Barr et al demonstrated that 82% of cases of thrombocytopenia was associated with an increased platelet-associated immunoglobulin (Ig) G level, and that the platelet count was inversely correlated to the level of platelet-associated IgG [2].

Clozapine-associated agranulocytosis has been reported extensively, but how clozapine affects hematopoiesis is still unknown. The existence of a peripheral immune-mediated mechanism is supported by the common side effect of eosinophilia, and the fact that antibodies to IgM attenuate the cytotoxic activity observed in the serum of patients with agranulocytosis [3]. However, a direct toxic effect on hematopoiesis seems more likely, and a number of clinical observations support this: firstly, the agranulocytosis has a delayed onset, is not dose-dependent, and has a rapid course even if the drug is discontinued; secondly, bone marrow examination reveals an absence of myeloid precursors. Furthermore, in vitro culture experiments indicate that clozapine and its metabolite N-desmethylclozapine have toxic effects on bone marrow progenitor cells [4]. The relationship between clozapine and thrombocytopenia is even more of an enigma. Occurrences of thrombocytopenia both with and without agranulocytosis have been reported, suggesting the independent

nature of clozapine-induced platelet abnormality.

In this patient, there was a temporal relationship between valproate and clozapine combination therapy, and the development of thrombocytopenia. Prior to starting clozapine, the patient was prescribed approximately 2 months of valproate therapy without any decrease in platelet count. One week after clozapine was added to the treatment regime, the platelet count had dropped drastically from 341 x 10^9/L to 99 x 10^9/L. Immediately after cessation of valproate, there was a rapid return of the platelet count to normal levels despite being on clozapine monotherapy.

Pharmacokinetically, clozapine has minimal interactions with valproate. A study on the effects of co-treatment of valproate and clozapine showed only a minor increase in serum concentration of total clozapine metabolites [5]. Therefore, it is unlikely that thrombocytopenia is a consequence of clozapine increasing serum valproate levels and hence toxicity.

A possible explanation would be the synergistic effects of both drugs on bone marrow suppression. However, the white and red blood cell lines were not affected in our patient, suggesting that other mechanisms may have been involved in rendering the platelet cell lineage more vulnerable to valproate and clozapine toxicity.

Given the rapid onset and resolution of thrombocytopenia with the introduction of clozapine and discontinuation of valproate respectively, a more likely postulation would be that of an immune-mediated mechanism. Clozapine may have enhanced the immune-mediated peripheral platelet destruction effect of valproate, leading to the development of thrombocytopenia in a patient who is able to tolerate both drugs independently.

A precise pathophysiologic understanding of valproate and clozapine-induced thrombocytopenia is lacking, and further studies are required. Nevertheless, this case report highlights thrombocytopenia as a potential outcome of drug-drug interaction between valproate and clozapine combination therapy, and serves to remind practitioners that regular monitoring of platelet counts is warranted, particularly for patients who require two or more agents with thrombocytopenic potential.

References

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