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Clozapine-associated neutropenia following augmentation with sodium valproate

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Abstract

Clozapine is gold standard for the management of treatment-resistant schizophrenia. It can offer life-changing symptom reduction where other antipsychotics have failed, and for these patients, treatment with clozapine should be maintained, if in any possible way. However, treatment with clozapine comes with a risk of developing potentially fatal adverse reactions, for example, severe neutropenia or agranulocytosis, in which case, treatment must be discontinued. Here, we present a case of clozapine-related neutropenia that commenced after the addition of sodium valproate. A subsequent re-challenge to clozapine resulted in severe neutropenia and led to the permanent cessation of clozapine treatment. The patient had been tolerating clozapine for more than a year before the addition of sodium valproate. The awareness of an interaction between clozapine and sodium valproate could help reduce the risk of clozapine-induced neutropenia and subsequent clozapine discontinuation.

Keywords

Clozapine, valproate, neutropenia, agranulocytosis, adverse reaction, drug interaction

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Introduction

Clozapine is the drug of choice for treatment of otherwise treatment-resistant schizophrenia,[1] and it can offer life-changing symptom reduction where other antipsychotics have failed.[1]

Treatment with clozapine also comes with a risk of developing potentially fatal adverse reactions, for example, myocarditis, ileus, seizures and blood dyscrasias.[2,3] The blood dyscrasias are associated with a rather modest case fatality rate, compared to some of the other potentially fatal adverse reactions, for example, ileus or myocarditis;[4] however, due to a history of fatal clozapine-related hematological reactions, regular hematological monitoring is mandatory for clozapine treatment.[2,4]

The clinically most significant blood dyscrasia is neutropenia.[3]

The term neutropenia refers to an absolute neutrophil count (ANC) less than 1.5×10^9/L[5] and occurs in approximately 3.8% (95% confidence interval (CI): 2.7%–5.2%) of clozapine-treated patients.[5] It can further be dived into mild (ANC = $1.0–1.5 \times 10^9$/L), moderate (ANC = $0.5–1.0 \times 10^9$/L) or severe (ANC $<0.5 \times 10^9$/L) neutropenia. The term "agranulocytosis" is often used interchangeably with "severe neutropenia,"[5,6] and is reported to occur in approximately 0.9% (95% CI: 0.7%–1.1%) of clozapine-treated individuals.[5] The risk of clozapine-induced neutropenia peaks within the first 4 weeks of treatment and accumulates to reach 84% of occurrences within the first 18 weeks of treatment.[5] After 1 year, the risk is unspecific to clozapine.[5]

Development of neutropenia will usually lead to the discontinuation of clozapine treatment,[2,6] although different actions are to be taken, depending on the cause and severity of neutropenia.[2,3,6]

The anticonvulsant sodium valproate is a widely used augmentation to clozapine, due to both its antiepileptic- and mood-stabilizing features.[7] However, bone marrow suppression is a known, although uncommon, adverse reaction to

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valproate as well,[8,9] and it has been reported that the combined use of sodium valproate and clozapine[7] increases the risk of clozapine-associated neutropenia.

The following case reports on a patient who experienced an incidence of clozapine-valproate-associated neutropenia followed by clozapine re-challenge-induced agranulocytosis.

The patient provided written, informed consent prior to pursuing writing of this publication and was considered to have the decisional capacity to provide it.

Case report

A 53-year-old male, Caucasian patient, diagnosed with paranoid schizophrenia, had, since he was diagnosed 5 years earlier, been treated with antipsychotics in the following order: olanzapine, aripiprazole, quetiapine and risperidone. All trials had been without adequate response, and clozapine treatment was initiated. At the time of commencement to clozapine treatment, his total white blood cell (WBC) counts and ANC were within the normal range. Clozapine dose was gradually increased from 12.5 to 550 mg/day in 11 months. Following 13 months of clozapine treatment with stable ANC and WBC counts, valproate was added due to increasing anxiety and negative thinking. Valproate dose was increased from 300 to 900 mg/day over a period of 35 days. Eleven weeks after valproate treatment was initiated, the patient developed a mild neutropenia of 1.5×10^9/L and WBC counts of 3.1×10^9/L. Treatment was continued for 8 weeks, with ANC slowly increasing to 2.1×10^9/L, and the valproate dose was further increased to 1200 mg/day. The ANC then dropped to 1.0×10^9/L but was not recognized until another 4 weeks later when a count of 1.0×10^9/L was repeated. Clozapine was paused for 2 days, after which it was continued at a lower daily dose of 300 mg, due to a new ANC of 1.6×10^9/L. Five days later, the ANC had again decreased to 1.0×10^9/L with a total WBC count of 2.8×10^9/L, leading to the withdrawal of clozapine—19 months into treatment. The clozapine withdrawal showed no beneficial effect on the WBC counts for 6 weeks, and valproate was then paused. Following valproate discontinuation, the ANC increased to 3.6×10^9/L in 2 weeks. Valproate was hence suspected to be the cause of neutropenia and clozapine treatment was re-installed. Treatment was initiated by 25 mg/day and increased up to 400 mg/day in 5 weeks. Twelve weeks after re-challenge, the patient showed for blood sampling and complained about a sore throat. Within hours, the patient presented with fever, stupor, a total WBC count of 0.18×10^9/L and undetectable low neutrophil counts. No WBC counts had been done in 6 weeks prior to the event. However, the ANC and WBC counts were observed within the normal range during the first 6 weeks of re-challenge. The patient was admitted to somatic care for treatment, including bone marrow stimulation with granulocyte colony-stimulating factor (G-CSF). The neutropenic event lasted for 21 days from recognized agranulocytosis.

Table 1. Patient characteristics at the time of recognized agranulocytosis.

Characteristic	Subject data
Gender	Male
Age	53 years
Smoker	10 cigarettes/day
Diagnoses	Paranoid schizophrenia (ICD-10)
	Opioid abuse (former) (ICD-10)
	Paroxysmal atrial fibrillation
	Myxedema
Medications	Clozapine, 400 mg/day
	Levothyroxine, 150–200 μg/day
	Combined buprenorphine and naloxone, 8 + 2 mg/day
	Metoprolol[a], 50 mg/day

ICD: International Classification of Diseases.
[a]Agranulocytosis has been reported on as a potential adverse reaction to treatment with metoprolol. However, the patient had been treated with metoprolol at a constant dose for more than 3 years prior to commencement of neutropenia and metoprolol was hence not considered related to the event.

Discussion

The commencement of neutropenia in this case was 15 months into treatment with clozapine, and hence constitutes as of late onset. The commencement of neutropenia seems related to the co-administration of valproate, which is substantiated by the unresponsiveness of ANC and WBC counts to clozapine withdrawal and its rapid normalization following valproate withdrawal. The occurrence of agranulocytosis happened 12 weeks after clozapine re-introduction, without the co-administration of valproate, and thus seems related to the clozapine re-challenge.

The rest of the patient's concomitant medications (Table 1) were not considered related to the event.

Despite a low reported incidence of bone marrow suppression with valproate (0.4%),[8] a recent study found that co-administration of sodium valproate and clozapine is a significant risk factor for developing clozapine-associated neutropenia.[7] A number of case reports[10–12] have also described the phenomenon.

Different interactions between clozapine and sodium valproate have been observed in other contexts as well;[13] however, it appears that sodium valproate may act as an inhibitor of clozapine metabolism, perhaps by competitive protein binding.[13] In that case, the interaction could go both ways and bone marrow suppression could be caused by potency of either drug.

Clinicians should know about this interaction and bear it in mind when adding sodium valproate to clozapine treatment. Clozapine treatment is, in clinical practice, often of "last resort" and its discontinuation should therefore be avoided if in any way possible.

If valproate is added and ANC starts to decline, clinicians should consider withdrawing valproate in early stages, to avoid further decline of ANC and the subsequent discontinuation of clozapine.

Published literature indicates that off-label re-challenge could be attempted in some cases of prior neutropenia,[6,14] for

example, when non-clozapine causes have been identified and eliminated,[6] and that re-challenge could be successful in approximately two thirds of such cases.[14,15] However, it has also been reported that neutropenia related to re-challenge tends to be more severe than the initial neutropenia,[15] and that the risk of developing agranulocytosis is 22 times higher when re-challenged with clozapine after neutropenia, than with first introduction.[15] Re-challenge with clozapine after a neutropenic event is in other words not without risks—as this case report clearly states.

The Australian summary of product characteristics (SPC) for sodium valproate[9] already informs that valproate may potentiate clozapine and vice versa, due to competitive protein binding. We are not aware of any other SPCs that inform about the interaction, neither SPCs for sodium valproate nor SPCs for clozapine. Perhaps it is time for this knowledge to be disseminated into clinical practice, thus reducing the risk of clozapine-sodium valproate related adverse events.

Conclusion

Valproate is a widely used augmentation to clozapine treatment. However, the risk of developing clozapine-related neutropenia seems to increase with the concurrent use of sodium valproate—even if sodium valproate is added late in clozapine treatment. Clinical awareness of the interaction is needed to reduce both the risk of drug-related adverse events and unfortunate clozapine discontinuations with uncertain re-challenge potential. This case report highlights such clinical implications of adding sodium valproate to established clozapine treatment, thus making it a valuable tool for the warranted knowledge dissemination into clinical practice.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

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