Clozapine-induced neutropenia reversed by lithium

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Clozapine is effective in treating refractory cases of schizophrenia and schizoaffective disorder, however, it can induce the serious side-effect of neutropenia. There is an evolving evidence base in which lithium is used to increase the neutrophil and white cell count in patients who develop neutropenia from clozapine treatment, thus allowing clozapine treatment to continue. Dr Yadav *et al.* describe such a case.

In refractory cases of schizoaffective disorder, treatment with clozapine has been found to be efficacious and safe.[1-3] However, clozapine carries a risk of neutropenia and agranulocytosis. It is estimated that around 2.7% of patients treated with clozapine develop neutropenia and around 0.8% of clozapine-treated patients develop agranulocytosis.[4]

Lithium increases the white cell count (WBC) and neutrophil count, both acutely[5] and chronically.[6] This tendency of lithium to increase the WBC (leucocytosis) is harnessed in successfully treating neutropenia resulting from carbamazepine therapy and during cancer chemotherapy.[7]

The mechanism by which lithium increases the neutrophil count and total WBC is not completely understood and the effect is poorly quantified.[7] However, various suggestions have been put forward: stimulation of GM-CSF (granulocyte-macrophage colony stimulating factor);[8] demargination;[2] direct stem cell stimulation; stimulation of cytokines, and increased cortisol production have been suggested.

A case report is now described in which lithium was used to reverse clozapine-induced neutropenia.

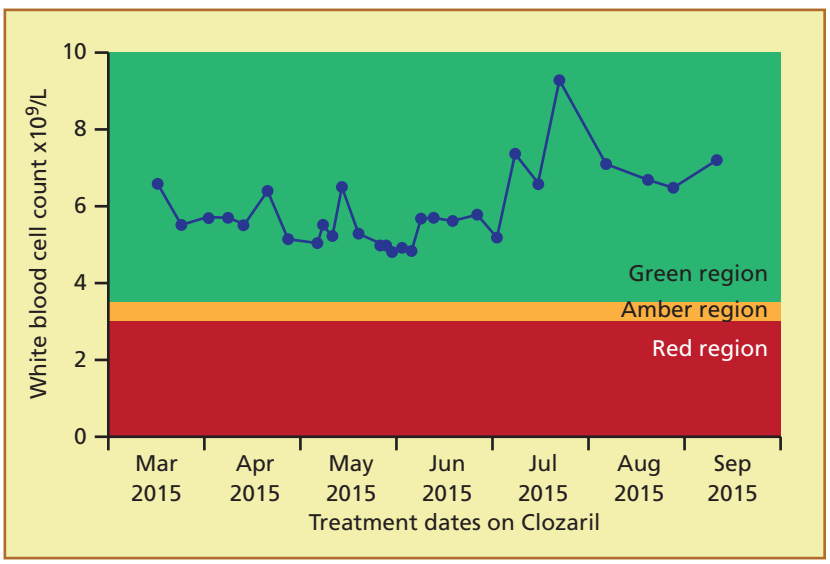

Figure 1. White blood cell count during clozapine treatment

Presentation

Miss A, a 31-year-old caucasian female first presented to psychiatric services at the age of 18 years with depression. Subsequently, from the age of 18 years to 29 years, she had multiple hospital admissions and received various combinations of psychotropic medications. She presented with features of mania and psychosis and she was eventually diagnosed with schizoaffective psychosis, which unfortunately was treatment resistant.

She was admitted in March 2015 to our low secure inpatient unit, following a relapse and also because of the risks she posed to others. Her risks were predominantly threats of violence towards her ex-partner, impulsivity, risks of absconding from the inpatient unit and risk of self-neglect. She presented with irritability, delusions of erotomania, auditory hallucinations (responding to unseen stimuli, hearing voices of screaming babies), and delusions of persecution. She was on olanzapine 15mg *nocte* and sodium valproate 500mg BD at the time of the admission and had been prescribed this combination of medications since December 2014.

During her inpatient stay on the unit a decision was made by the MDT to increase the dose of olanzapine and sodium valproate. However, this was not effective and a decision was made to start her on clozapine. Olanzapine 20mg was gradually tapered and stopped; sodium valproate was continued at 1g BD.

In order to initiate clozapine, patients must have a baseline WBC count of 4.0×10^9/L and a neutrophil count of 2.5×10^9/L. If the patient has a 'red' result, *ie* leucopenia (WBC $<3\times10^9$/L) or neutropenia (neutrophils $<1.5\times10^9$/L), clozapine should not be given.

Total WBC on the 17.03.15 was 6.6×10^9/L, the neutrophil count was 3.3×10^9/L – both within normal limits.

The dose of clozapine was gradually increased to 50mg a week later, and later to 75mg on 02.04.15 and gradually built up to 275mg. Total WBC in March and April ranged from 4.8×10^9/L to 6.4×10^9/L (see Figure 1) and the neutrophil count ranged from 2.2×10^9/L to 3.5×10^9/L (see Figure 2). Serum clozapine and norclozapine levels at 275mg on 27.04.15 were 0.33mg/L and 0.20mg/L, respectively.

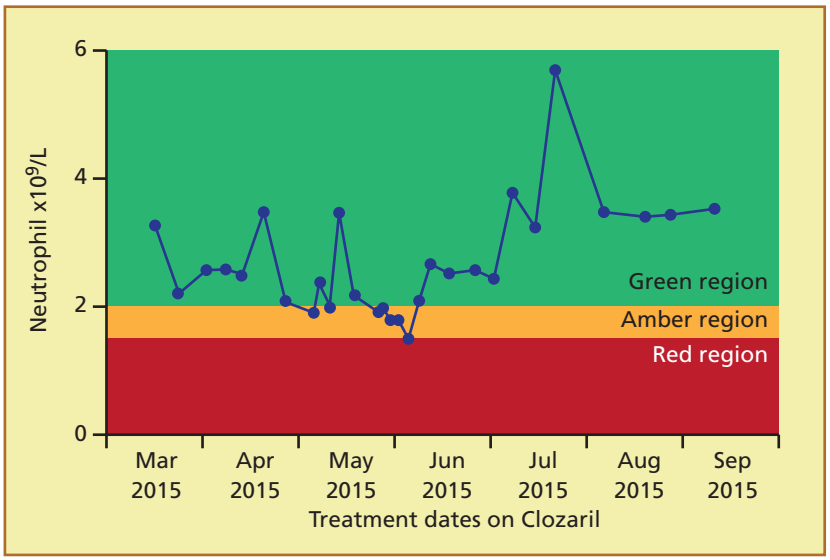

Figure 2. Neutrophil count during clozapine treatment

Diagnosis and treatment

The neutrophil count unfortunately started to decrease from the 06.05.15. The neutrophil count on 06.05.15 and 26.05.15 was 1.9×10^9/L and the clozapine and norclozapine levels at 275mg on the 27.05.15 were 0.25mg/L and 0.14mg/L respectively.

Twice weekly WBC was being done to safeguard the patient, and other potential causes of decreased neutrophils were ruled out by the medical team. She had no signs of infection or inflammation. Neutropenia can arise because of factors unrelated or indirectly related to clozapine treatment. These include benign ethnic neutropenia, concomitant drug therapy, co-existing medical conditions and drug interactions.

The neutrophil count was 1.8×10^9/L on 30.05.15 and 02.06.15. A decision was made by the multidisciplinary team (MDT) to start the patient on lithium instead of sodium valproate. Lithium would not only help with the affective component of the disorder, but would hopefully also increase the WBC levels. This plan was discussed with the patient and a written consent was obtained.

Prior to starting lithium, the MDT suggested decreasing the dose of clozapine to see if this increased the neutrophil levels: clozapine was gradually reduced to 225mg on 30.05.15. The neutrophil count was 1.8×10^9/L on 30.05.15. However, this was not effective and lithium was thus started on 02.06.15 by cross tapering with the sodium valproate, which was eventually stopped.

The neutrophil count decreased to 1.5×10^9/L on 05.06.15. The dose of clozapine was further reduced to 150mg on 06.06.15 and the daily dosage of lithium carbonate was gradually built up to 750mg in divided doses (250mg *mane* and 500mg *nocte*). Gradually the neutrophil crept up to 2.1×10^9/L on the 08.06.15 and reached 2.6×10^9/L on the 26.06.15.

The WBC ranged from 5.8×10^9/L to 7.22×10^9/L and the neutrophil count ranged from 2.45×10^9/L to 5.69×10^9/L from June to September 2015 and were within normal limits.

The serum lithium level was 0.5mmol/L on the 13.08.15 on 750mg of lithium carbonate in divided doses. The serum clozapine and norclozapine on 150mg of clozapine was 0.27mg/L and 0.19mg/L respectively on the 18.08.15.

The patient did respond favourably to the combination of lithium and clozapine. Her delusions of erotomania had decreased considerably and also her delusions of paranoia and persecution had also decreased in intensity. She was less irritable. The improvement in her clinical response and a decrease in her level of risks led to her moving on in her care pathway. She was transferred from our low secure hospital to a locked rehabilitation unit in October 2015.

Discussion

Olanzapine, and rarely sodium valproate, can potentially cause a low neutrophil count. However, the patient was on olanzapine and sodium valproate combination since December 2014, so it looks unlikely that these medications caused neutropenia.

It is well documented that clozapine can potentially cause blood dyscrasias. There are reports that clozapine can potentially cause an increase in WBC (leucocytosis).[9,10] However, this does not apply in the above case.

In the above case, only when clozapine was introduced, a decrease

in neutrophil count (neutropenia) was noted on full blood count (FBC). A reduction in the clozapine dose was not effective in increasing the neutrophil count. In hindsight, it was felt that the clinical decision to decrease the dose of clozapine was not evidence based. The risk of clozapine-induced neutropenia is not dose related and it may differ between individuals and also between milder and severe forms of marrow suppression. The mechanism of clozapine-induced neutropenia is unclear and it is possible that a direct cytotoxic effect and immune-mediated mechanism may play a role.[11,12] The clozapine-induced neutropenia only improved when lithium was added.

The combination of clozapine and lithium is beneficial in some cases. However, the combination warrants close haematological, biochemistry, serological and clinical monitoring, as lithium does not protect against agranulocytosis and can lead to an increased side- effect burden. Clinicians need to be mindful of lithium toxicity and also neurological side-effects.

There is an evolving evidence base in which lithium is used to increase neutrophil and white cell count. The mechanism by which lithium increases the neutrophil count and total WBC is not completely understood and the effect is poorly quantified.[7]

Neutrophilia does not seem to be dose related although a minimum serum level of 0.4mmol/L may be required.[14]

Also, because lithium is not licensed for use to increase the white cell count, psychiatrists and prescribers should be aware of the medico-legal implications of prescribing lithium off-label.[7]

The above case report adds to a growing body of evidence (mostly case reports and case series), in which lithium is used to increase neutrophil and white cell count in patients who developed neutropenia from clozapine treatment, thus allowing clozapine treatment to continue.[13-16]

Conclusion

Lithium can be used successfully to treat clozapine-induced neutropenia. This requires close clinical monitoring of patients. Also discussing with the patient and their close relatives and obtaining their informed written consent before initiating an off-label prescription of lithium is paramount in order to safeguard the prescriber and prevent any medico-legal issues.

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Declaration of interests

No conflicts of interest were declared.

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