Clinical Effect of Norclozapine in a Patient on Intermittent Haemodialysis and the Management Thereof

Veta-Marie Peereboom. Royal North Shore Hospital, Northern Sydney Local Health District, NSW

Objective

Although norclozapine levels are routinely reported with clozapine levels, little is known regarding their interpretation. Clozapine is metabolised to norclozapine primarily through CYP1A2 *(See Figure 1)*[1]. An active metabolite, norclozapine has been shown to have different receptor binding affinity to its parent drug clozapine.[2] It is thought that a high norclozapine:clozapine ratio is an indicator of poor clinical response and increased side-effects[3]. Inter-patient variability of the ratio may be due to inherent P450 enzyme activity, smoking status and other factors.[4]

We report a case of confusion related to high norclozapine levels in a patient with bipolar affective disorder (BPAD) and end stage renal disease (ESRD).

Clinical Features

A 68 year old Caucasian male was admitted to the mental health unit due to mental state deterioration. His medical history included BPAD requiring electroconvulsive therapy (ECT), for which he was a long-term resident at a subacute mental health facility. Other history included ESRD secondary to long-term lithium therapy, requiring haemodialysis. His medications included olanzapine (40mg/day) and lithium (250mg thrice weekly after dialysis). Due to continuing psychotic symptoms olanzapine was changed to clozapine.

Five weeks after clozapine initiation, the patient became increasingly confused and disinhibited – he was disorientated to day/night, unable to recall names or events and asking repetitive questions. Organic causes of delirium including infection were excluded, as well as adverse effects of ECT. Lithium level was 0.5mmol/L pre-dialysis, and 0.2mmol/L post-dialysis (reference range 0.5-0.8mmol/L)[5].

The treating team did not have previous experience with clozapine and dialysis. Renal pharmacology texts available stated 50% of administered dose of clozapine was excreted in urine as metabolites, with dosing recommendations to titrate cautiously to response.[6] With limited information a pre-dialysis clozapine level was taken. This showed a mildly elevated clozapine level [663 microg/L (reference range 300-600microg/L)[5]] and a norclozapine level of 847microg/L. This was compared to post-dialysis levels previously obtained of 437microg/L and 433microg/L, respectively. It was suspected that renal failure caused accumulation of norclozapine and was contributing to acute confusion.

It was also suspected that dialysis was more effective at removing norclozapine than clozapine, leading to the high variability between pre-dialysis and post-dialysis levels. This was further supported when repeat post-dialysis blood levels for clozapine and norclozapine were similar to earlier results, 319 and 387 respectively (*See Figure 2*).

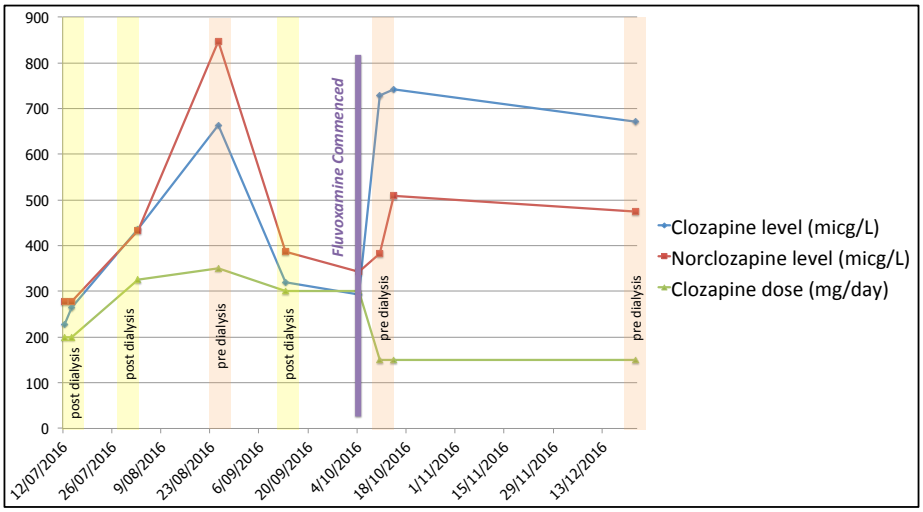

Figure 2. Timeline of clozapine dose with associated clozapine and norclozapine levels

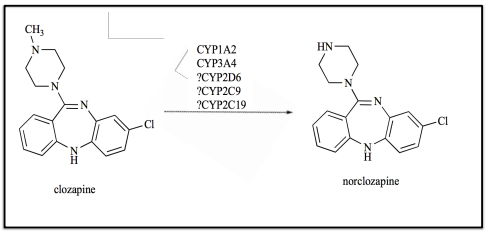

Figure 1. Metabolism of clozapine to norclozapine(1)

Interventions, Case Progress and Outcomes

Following discussions with psychiatry and clinical pharmacy teams, fluvoxamine (50mg daily) was trialled to inhibit cytochrome P450 1A2 and to a lesser extent 3A4[7], thereby reducing the metabolism of clozapine to norclozapine. The clozapine dose was reduced by half, anticipating the increase in clozapine level.

Two weeks later, the patients' confusion and disorientation to time was significantly improved and repeat serum drug levels were obtained. Clozapine level had increased to 703microg/L and norclozapine had reduced to 549microg/L (pre-dialysis).

Conclusion

This case highlights the importance of norclozapine levels in interpreting efficacy and tolerability of clozapine therapy. Clinicians need to be aware of the different pharmacodynamics properties of metabolites compared to parent compounds.

References

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vetamarie.peereboom@health.nsw.gov.au

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