Clozapine-Induced Hepatotoxicity: A Case Report

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Background

Clozapine is an atypical antipsychotic primarily used in treatment-resistant schizophrenia, with an increasing number of reports of its use in other refractory psychotic conditions (for example schizoaffective disorder and psychotic mood disorders)[1]. Whilst it is well known that clozapine is associated with agranulocytosis and cardiomyopathy that mandates strict white cell count and cardiac monitoring, clozapine-induced hepatic impairment has received less attention in the literature. This case report describes a patient with treatment-resistant bipolar affective disorder who developed hepatotoxicity whilst on clozapine.

Clinical Features

A 45 year-old female presented with a relapse of bipolar affective disorder, with symptoms of depression and concurrent psychosis. Psychotropic medication on admission included lithium, sertraline, quetiapine and aripiprazole depot injection. Electroconvulsive therapy was commenced and at the same time a cross-titration from quetiapine to clozapine was undertaken.

Case Progress and Outcomes

Clozapine was initiated at 12.5mg daily and gradually increased in accordance with the standard protocol. Baseline liver function tests (LFTs) were within normal range. On day 26 of clozapine treatment the patient became fatigued, nauseous and had two bouts of vomiting whilst on a daily dose of clozapine 325mg. Repeat LFTs showed elevations greater than three times the upper reference limit (alanine aminotransferase of 295 IU/L, aspartate transaminase of 272 IU/L, alkaline phosphatase of 304 IU/L, gamma-glutamyl transferase of 273 IU/L and lactate dehydrogenase of 309 IU/L). On day 27 clozapine was discontinued, quetiapine and aripiprazole were restarted, and daily LFT monitoring commenced. LFTs peaked two days post discontinuation and the patient experienced additional symptoms of mild pruritus and looser and lighter stools. One week after discontinuation LFTs had reduced (but not yet returned to baseline) and the patient was asymptomatic. The patient however had a relapse of her depressive and psychotic symptoms since stopping clozapine.

The role of the pharmacist in this patient's care included: medication review, literature review of clozapine-induced hepatitis, reporting of the adverse drug reaction, advice on clozapine management and LFT monitoring.

	Reference range	Baseline	Day 26	Clozapine ceased Day 27	Day 28	Day 29	Day 30	Day 32	Day 33	Day 34	Day 35
Alkaline phosphatase (ALP)	30 - 110 U/L	66	304	330	283	418	313	262	227	231	291
Alanine aminotransferase (ALT)	0 - 55 U/L	17	295	333	216	215	122	73	54	46	186
Aspartate aminotransferase (AST)	0 - 45 U/L	13	272	69	29	110	20	24	17	24	177
Gamma-glutamyl Transferase (GGT)	0 - 60 U/L	19	273	297	240	394	247	179	144	137	279
Lactate dehydrogenase (LDH)	120 - 250 U/L	19	309	211	220	383	231	311	244	333	324

TABLE 1: LABORATORY SERIAL REPORT

Literature review

Elevations in liver enzymes are common, occurring in up to two-thirds of patients on clozapine and usually resolve within the first 12 weeks of treatment without dose modification or discontinuation[2]. Whilst elevations in liver enzymes are usually transient and asymptomatic, there are reported cases of clozapine-induced hepatotoxicity, liver damage and fulminant liver failure[2,3]. Rechallenge of clozapine in patients who have developed hepatotoxicity have also been rarely reported with mixed success.

The pathogenesis of clozapine-induced hepatotoxicity is not known. Clozapine is extensively metabolised by the liver, and it has been suggested that the production of a toxic intermediate metabolite may be the cause for the mild elevations in liver enzymes commonly seen[2].

Current guidelines recommend that all patients on clozapine should have baseline LFTs and 6 monthly monitoring thereafter[3].

Conclusion

Clinicians should be aware of other severe adverse effects of clozapine such as hepatotoxicity and constipation, other than the haematological and cardiovascular effects.

References

1. Li X-B, Tang Y-L, Wang C-Y and de Leon J. Clozapine for treatment-resistant bipolar disorder: a systematic review. Bipolar Disorders 2015; 17: 235-247.
2. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Clozapine. [Updated 2017 Oct 16].
3. Taylor D, Barnes T and Young A. The Maudsley Prescribing Guidelines in Psychiatry. 13th Edition. John Wiley & Sons, Incorporated, 2018.

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