

Clozapine and liver function

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually.

This information is provided for healthcare professionals and should not be used as a patient information leaflet.

Background

The Summary of Product Characteristics (SmPC) for Clozaril[®] (clozapine)^{1,2} states that: elevation of liver enzymes is a common ($\geq 1/100$ but $< 1/10$) reaction to Clozaril[®], hepatitis and cholestatic jaundice are listed as rare ($\geq 1/10,000$ but $< 1/1,000$) reactions to Clozaril[®] and fulminant hepatic necrosis is a very rare ($< 1/10,000$) reaction to Clozaril[®].

The following hepatic disorders are also listed as adverse events which have a frequency of 'not known': Hepatic steatosis, hepatic necrosis, hepatotoxicity, hepatic fibrosis, hepatic cirrhosis, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant.^{1,2}

Clozaril[®] is contraindicated in patients with active liver disease associated with nausea, anorexia or jaundice. It is also contraindicated in patients with progressive liver disease or hepatic failure.^{1,2}

Patients with stable pre-existing liver disorders may receive Clozaril[®], but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible liver dysfunction, such as nausea, vomiting and/or anorexia, develop during Clozaril[®] therapy. If the elevation of the values is clinically relevant (more than three times the UNL) or if symptoms of jaundice occur, treatment with Clozaril[®] must be discontinued. It may be resumed only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Clozaril[®].^{1,2}

Hepatobiliary disorders

Transient, asymptomatic elevations of liver enzymes and, rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, Clozaril[®] should be discontinued. In rare cases, acute pancreatitis has been reported.^{1,2}

Onset of transient or asymptomatic elevation of liver enzymes generally occurs during the first 3 months of treatment,³ resolving spontaneously within 2-3 months without the need to discontinue clozapine.⁴ There is some evidence that the changes may be dose-related.⁷

Raised liver enzymes are reported to affect between 30% and 50% of patients⁵ although the incidence reported in the literature varies widely depending on the degree of elevation observed, with incidences of up to 78% reported when any values over the upper limit of normal (ULN) were included, but less than half this when only values of at least twice the upper limit of normal were included.³⁻⁶ The incidence does not appear to be affected by age³ however, men may have a greater risk.^{3,4}

Less commonly, more serious enzyme elevations may occur,⁶ and much more rarely, significant liver toxicity (hepatitis, cholestatic jaundice, fulminant hepatic necrosis) has been observed.^{1,2} In addition, there have been isolated case reports of fatal hepatotoxicity in clozapine patients.⁵ Incidences of serious liver toxicity reactions are reported to be 0.06% or less.⁵

Recommencing clozapine

If clozapine has been discontinued, treatment should not be resumed until the liver function has returned to normal. It would be advisable to consult with a hepatologist to discuss the case before recommencing as careful monitoring of the patient's liver function tests (LFTs) may be required.

Recommencing in patients who have had minor elevations of their LFTs is often successful, however recommencing in patients who have previously developed significant LFT elevations may result in rapid re-emergence of abnormalities.⁷

References

1. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. <<http://www.medicines.org.uk/emc/>> (Accessed on 09 May 2018).
2. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. <<http://www.medicines.ie/>> (Accessed on 09 May 2018).
3. Hummer, M *et al.* Hepatotoxicity of Clozapine. *J Clin Psychopharmacol* 1997; **17**: 314-317.
4. Gaertner I *et al.* Relevance of Liver Enzyme Elevations With Four Different Neuroleptics: A Retrospective Review of 7,263 Treatment Courses. *J Clin Psychopharmacol* 2001; **21**: 215-222.
5. Macfarlane, B *et al.* Fatal Acute Fulminant Liver Failure Due to Clozapine: A Case Report and Review of Clozapine-Induced Hepatotoxicity. *Gastroenterology* 1997; **112**: 1707-9.
6. Markowitz J S, Grinberg R, Jackson C. Marked Liver Enzyme Elevations With Clozapine. *J Clin Psychopharmacol* 1997; **17**: 70-71.
7. Marinkovic, D *et al.* The Side Effects of Clozapine: A Four Year Follow-Up Study. *Prog Neuropsychopharmacol Biol Psychiatry* 1994; **18**: 537-544.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

UK: Reporting forms and information can be found at www.mhra.gov.uk/yellowcard

Ireland: HPRa Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie. Adverse events should also be reported to Mylan via cpms@mylan.co.uk