

Clozapine and seizures

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.

The Summary of Product Characteristics (SmPC) for Clozaril[®] (clozapine)^{1,2} states that: seizures are a common ($\geq 1/100$ but $< 1/10$) reaction to Clozaril[®]. EEG changes are also listed as an adverse reaction which has a frequency of 'not known'.

Uncontrolled epilepsy is a contraindication to Clozaril[®].

Background

Clozapine lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures.^{1,2}

The overall incidence of seizures during treatment with clozapine has been estimated at 3%.^{3,4} Seizures can occur at any time and with any dose.^{5,6} They have been reported in doses as low as 37.5mg.⁷ The periods of greatest risk are during the initial titration period and at higher doses or plasma levels. Devinsky (1991) reported a 4.4% risk of seizures at doses above 600mg with a risk of 2.7% in patients on 300-600mg and 1% for patients on less than 300mg.³

There is controversy as to how high the clozapine level has to be to put the patient at serious risk of clozapine-induced seizures. A plasma level of between 0.35mg/L and 0.6mg/L has been suggested to optimise response while minimising the risk of side effects such as seizures.^{8,9} Remington (2013) concludes that there is an increased risk of seizures with clozapine doses above 500-600mg but that the relationship between levels and serious side-effects such as seizures is unclear.¹⁰

The most common clozapine-induced seizures are generalized tonic-clonic although other types have been reported.⁵ These include generalized atonic and myoclonic as well as simple and complex partial seizures.⁵

Myoclonus and stuttering

Myoclonus, seen as muscle jerks, orofacial movements or drop attacks, has been reported with clozapine^{11,12,13} and may precede the development of seizures in some patients.¹¹

It is also worth noting that myoclonus, or seizures, may be the first indication of an increased clozapine plasma level. Case reports in the literature document patients who developed myoclonus believed to be secondary to increased clozapine levels due to infection or inflammation.^{14,15} In these cases improvement was seen following clozapine dose reduction or a period of withholding the drug.

Stuttering has been reported in patients on clozapine,^{16,17,18,19} and it has been suggested that this may be an indication of epileptic brain activity.¹⁶ There are cases where stuttering has responded to dose reduction^{17,18} and others where the dose has been increased and seizures have occurred.

EEG changes

EEG changes are common during clozapine therapy, with a reported incidence in the region of 50-65%²⁰⁻²⁴ and do not necessarily relate to the risk of seizure.²³

In a review of clozapine-induced seizures Wong and Delva (2007) conclude that "...EEG findings are of limited value as predictors of clozapine-induced seizures".⁵

Mechanism and risk factors

The mechanism of drug-induced seizures is not fully understood.²⁵ Patients are more likely to have drug-induced seizures if they have other risk factors, including epilepsy or other type of neurological illness, alcohol or drug abuse, or a family history of epilepsy.²⁶

Factors which increase the risk of seizures with clozapine, may include a history of previous seizures, recent electroconvulsive therapy (ECT), concomitant treatment with other drugs which lower the seizure threshold and head trauma with loss of consciousness.³

The risk of seizures may also be increased if drugs that raise the seizure threshold (drugs that protect against seizures), such as benzodiazepines, are discontinued during clozapine treatment.²⁷

Prevention and management of seizures in patients on clozapine

Using the lowest possible dose and avoiding rapid dose increases may reduce the risk of seizures with clozapine.²⁸

Patients on clozapine should be observed for any possible signs of seizure activity such as myoclonic jerks or stuttering. In such cases, reduction of the clozapine dose may prevent the patient from developing seizures. Plasma level monitoring may be useful in some patients.

Patients with epilepsy may be started on clozapine provided that their seizures are well controlled. These patients should be observed closely during clozapine treatment.^{1,2}

If a patient on clozapine suffers a seizure, consideration should be given to dose reduction, EEG and plasma level monitoring and anticonvulsant therapy if indicated.

Clozapine plasma level monitoring may be useful to exclude high levels. Please note, to obtain an accurate plasma level the patient needs to have been on treatment at least a month and to have been on the same dose for at least a week.

Liebermann suggested that if a patient has a seizure whilst on clozapine, the clozapine should be withheld temporarily then restarted, if appropriate, at a lower dose.²⁹ He also recommended that an EEG and a neurological referral should be considered, particularly if it is the patient's first seizure.²⁹

Reducing the dose and retitrating more gradually may prevent further seizures³⁰ although the patient may need to be maintained on a lower dose or started on an anticonvulsant.

The choice of anticonvulsant drug should take into consideration the risk of neutropenia, other side-effects, such as sedation, and the possibility of drug interactions.

Consultation with a neurologist is recommended when selecting a drug and the choice is ultimately a clinical decision.

Carbamazepine and phenytoin are not recommended since they may reduce clozapine levels^{1,2} and carbamazepine may cause bone marrow depression.^{1,2}

Sodium valproate has been used for seizure prophylaxis in patients on high doses of clozapine although it has been suggested that it is not always given at adequate dose.³¹

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where Clozaril was co-administered with valproic acid have been reported.^{1,2} These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.^{1,2}

References

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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