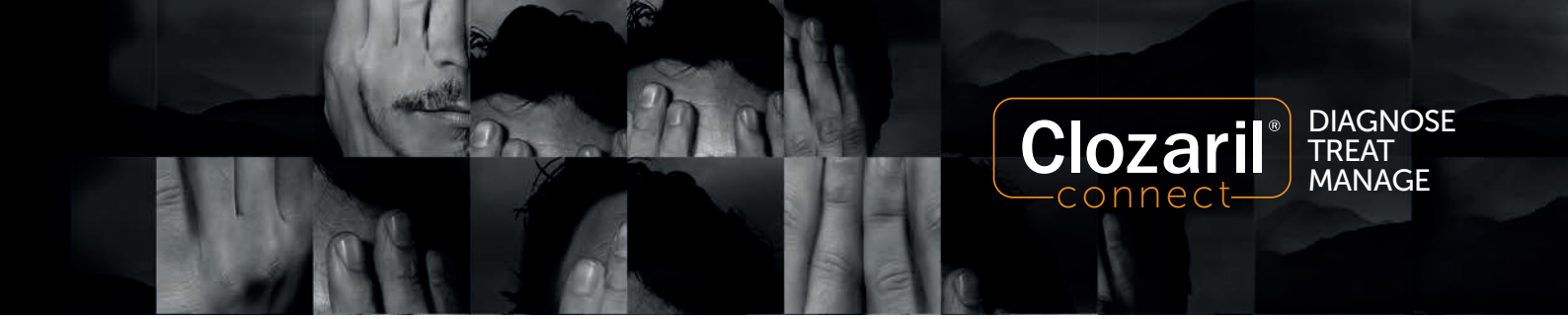


Clozapine overdose

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.

SmPC statement

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine)[1,2] states that:

In cases of acute intentional or accidental Clozaril® overdose for which information on the outcome is available, mortality to date is about 12%.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Aspiration of ingested food may occur as a consequence of acute overdosage.

Treatment

There are no specific antidotes for Clozaril®.

Gastric lavage and/or administration of activated charcoal within the first 6 hours after the ingestion of the drug. Peritoneal dialysis and haemodialysis are unlikely to be effective. Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance.

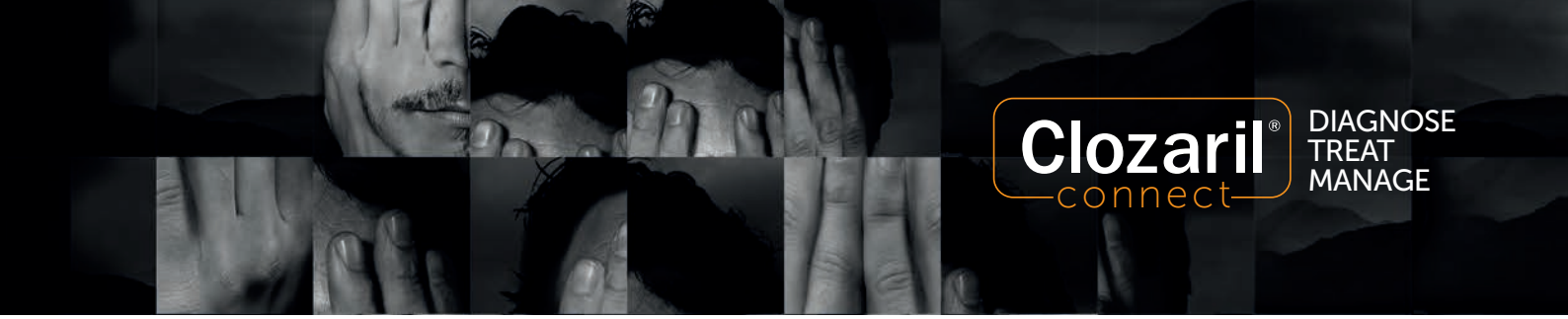
The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

Background

Patients with treatment-resistant schizophrenia have a higher incidence of suicide compared to the general population.[3] Both intentional and accidental overdoses have been reported with clozapine.

As noted in the SmPC, mortality associated with Clozaril® overdose is about 12%.[1,2] Most of the fatalities reported were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000mg.[1,2] Fatalities have also been reported in patients following ingestion of only 1000mg of clozapine[4] or with post-overdose plasma levels of approximately 2mg/L.[5] A few adults, especially those not previously exposed to clozapine, have suffered life-threatening comatose conditions with doses as low as 300-400mg and, in one case, to death.[1,2,3]



Seizures have been reported to occur in patients with plasma clozapine levels greater than 1mg/L following overdose.[6] Conversely, there are reports of patients recovering from overdoses in excess of 10,000mg[3] or following plasma levels greater than 9mg/L (optimum therapeutic range 0.35-0.6mg/L).[7]

Signs and symptoms of clozapine overdose

All of the side-effects associated with clozapine at therapeutic dose may be seen following overdose except those seen with long-term therapy only, for example; constipation, weight gain and agranulocytosis.[4] In addition, altered respiratory function and aspiration may be observed and these are seldom seen at therapeutic doses. Pulmonary oedema is not a recognised side-effect but has occurred following overdose.[4]

The central nervous, cardiovascular and respiratory systems are most commonly affected following acute overdose. The signs and symptoms listed in the SmPC are stated above.

Delayed reactions may be seen, including the late occurrence or recurrence of cardiac arrythmias.[4]

Literature reports of clozapine overdose

Le Blaye *et al* (1992) reviewed 150 cases of acute overdose with clozapine.[4] Overdose was considered to be an initial starting dose of more than 50mg or, in patients already treated with clozapine, an increase of more than 100mg or any non-therapeutic ingestion in children. The doses ingested ranged from 50mg to 25g although in some cases the doses were uncertain or unknown.

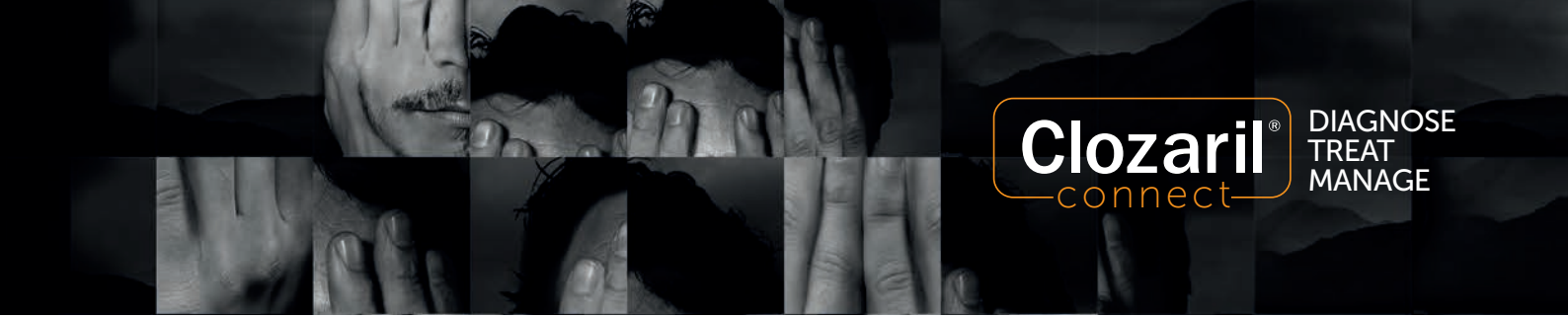
The most frequent symptoms were impaired vigilance ranging from coma to somnolence and tachycardia. The major complications seen were aspiration pneumonia associated with coma, electrocardiographic (ECG) changes including severe arrhythmia, hypotension leading to renal failure and seizure.

97 patients were hospitalised, 124 patients recovered fully and 15 patients died. Of the patients that died 2 had taken 1g or less. Causes of death included cardiac failure (3 patients), aspiration pneumonia (3), renal failure (1) with the cause of death unstated for 4 patients and another 4 patients were found dead. They conclude that, for patients not previously treated, 400mg may be life-threatening and that coma may result from an overdose of 300mg in a previously treated patient.

Browne and Larkin (1997) reported an accidental ingestion of 100mg clozapine in a neuroleptic naïve woman.[8] She was admitted to a general hospital with profound sedation, tachycardia and hypotension. She recovered slowly over the next 2 days and was discharged on the third day following ingestion of the clozapine.

Hägg *et al* (1999) reported a 2.5g overdose of clozapine in a patient who was also on fluoxetine and buspirone.[9] The patient was comatose for the first 24 hours and drowsy, partially disorientated and confined to bed for the following 4 days, with complete recovery after 9 days.

Pollak and Shafer (2004) report a case of a clozapine overdose of 2000mg where the patient deteriorated physically 72 hours after admission.[10] Following this, they reviewed 3 cases in which prolonged toxicities were seen[11] and suggested that continued effects were the result of delayed absorption due to the anticholinergic properties of clozapine reducing gastrointestinal motility. This may be exacerbated by other medications with anticholinergic effects or medical conditions, such as hypothyroidism, which affect gastrointestinal motility.



Clozaril® connect

DIAGNOSE
TREAT
MANAGE

Management

Any patient who has taken a clozapine overdose, or is suspected to have done so, should be sent to the nearest Accident and Emergency unit immediately or transferred to a general medical ward with facilities for cardiac monitoring.

There are no specific antidotes for clozapine.[1,2] Gastric lavage and/or administration of activated charcoal may be appropriate within the first 6 hours after the ingestion of the drug.[1,2] Activated charcoal may reduce absorption by binding to poisons in the gastrointestinal system and is more effective if it is given soon after ingestion of the overdose.

Peritoneal dialysis and haemodialysis are unlikely to be effective following Clozaril® overdose.[1,2]

Patients should be given symptomatic treatment under continuous cardiac monitoring with surveillance of respiration, monitoring of electrolytes and acid-base balance.[1,2] For hypotension, the use of epinephrine should be avoided due to the possibility of a 'reverse epinephrine' effect[1,2] (patients treated with Clozaril® may paradoxically experience hypotension when administered epinephrine).

The anticholinesterase drugs pyridostigmine and physostigmine (not routinely available in the UK) have been used to treat the anticholinergic symptoms following clozapine overdose.[4,5,12] Benzodiazepines may be used to control seizures.[4]

Close medical supervision is necessary for 5 days following clozapine overdose due to the possibility of delayed reactions.

NB: Extra monitoring of white blood cells is not necessary since neutropenia/agranulocytosis is not dose-related.

References

1. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. <http://www.medicines.org.uk/emc/> (Accessed on 09/05/2018).
2. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. <http://www.medicines.ie/> (Accessed on 09/05/2018).
3. Dev VJ, Krupp P. Adverse Event Profile and Safety of Clozapine. *Rev Contemp Pharmacother* 1995; **6**: 197-208.
4. Le Blaye I *et al.* Acute Overdosage with Clozapine: a Review of the Available Clinical Experience. *Pharm Med* 1992; **6**: 169-78.
5. Broich K and Heinrich AM. Acute Clozapine Overdose: Plasma Concentration and Outcome. *Pharmacopsychiatry* 1998; **31**: 149-151.
6. Taylor D and Duncan D. The Use of Clozapine Plasma Levels in Optimising therapy. *Psych Bulletin* 1995; **19**: 753-5.
7. Ines S *et al.* Intoxication with Clozapine: Plasma Levels above 9000ng/ml. Typical Clinical Picture – Diagnostic Confusion. *Neuropsychopharmacology* 1994; **10**: 1225.
8. Browne R and Larkin C. Clozapine: An Accidental Overdose. *European Psychiatry* 1997; **12**: 266-267.
9. Hägg S *et al.* Prolonged Sedation and Slowly Decreasing Clozapine Serum Concentrations After an Overdose. *J Clin Psychopharmacol* 1999; **19**: 282-4.
10. Pollak PT and Shafer SL. Teaching Application of Clinical Pharmacology Skills Using Unusual Observations from Clozapine Overdoses. *J Clin Pharmacol* 2004; **44**: 141-9.
11. Thomas L and Pollak TP. Delayed Recovery Associated with Persistent Serum Concentrations After Clozapine Overdose. *Journal of Emergency Medicine* 2003; **25**: 61-66.
12. Sartorius A *et al.* High-Dose Clozapine Intoxication. *J Clin Psychopharmacol* 2002; **22**: 91-2.

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

Clozaril® (clozapine)

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

CLZ-2018-0126 Date of preparation: June 2018

Mylan
Better Health for a Better World