Clozaril® 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.

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.

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%.

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 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[1-3] 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. Delayed reactions may be seen, including the late occurrence or recurrence of cardiac arrythmias.[4]

Other side effects mentioned in the SmPC of Clozaril® include: 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.[1,2]

Aspiration of ingested food may occur as a consequence of acute overdosage.[1,2]

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, a dose 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.

Hägg *et al* (1999) reported a 2.5g overdose of clozapine in a patient who was also on fluoxetine and buspirone.[8] 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.[9] Following this, they reviewed 3 cases in which prolonged toxicities were seen[10] 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.

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. Gastric lavage and/or administration of activated charcoal may be appropriate within the first 6 hours after the ingestion of the drug. 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.[1,2]

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).

Close medical supervision is necessary for at least 5 days following clozapine overdose due to the possibility of delayed reactions.[1,2]

References

1. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. <http://www.medicines.org.uk/emc/> (Accessed on 08/04/2020).
2. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. <http://www.medicines.ie/> (Accessed on 08/04/2020).
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. Hägg S *et al.* Prolonged Sedation and Slowly Decreasing Clozapine Serum Concentrations After an Overdose. *J Clin Psychopharmacol* 1999; **19**: 282-4.
9. Pollak PT and Shafer SL. Teaching Application of Clinical Pharmacology Skills Using Unusual Observations from Clozapine Overdoses. *J Clin Pharmacol* 2004; **44**: 141-9.
10. Thomas L and Pollak TP. Delayed Recovery Associated with Persistent Serum Concentrations After Clozapine Overdose. *Journal of Emergency Medicine* 2003; **25**: 61-66.

PRESCRIBING INFORMATION
CLOZARIL 25 mg Tablets
CLOZARIL 100 mg Tablets

Please see Summary of Product Characteristics (SmPC) for full information before prescribing Clozaril.
The use of Clozaril is restricted to patients, physicians and nominated pharmacists registered with the Clozaril Patient Monitoring Service (CPMS).
In the UK a white cell count with differential count must be monitored:

- At least weekly for the first 18 weeks of treatment
- At least at 2-week intervals between weeks 18 and 52
- After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals

Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation.
Blood clozapine level monitoring is advised in situations such as a patient ceases smoking or switches to e-cigarettes, when concomitant medicines may interact to increase clozapine blood levels, where poor clozapine metabolism is suspected, when a patient has pneumonia or other serious infection and in the event of onset of symptoms suggestive of toxicity.
Clozaril is associated with an increased risk of myocarditis and cardiomyopathy. If suspected Clozaril must be stopped immediately and the patient referred to a cardiologist and not re-exposed to Clozaril.

Presentations
Clozaril 25 mg Tablets containing 25 mg clozapine. Clozaril 100 mg Tablets containing 100 mg clozapine.

Indications
Treatment-resistant schizophrenic patients and in schizophrenia patients with severe, untreatable neurological adverse reactions to other antipsychotic agents, including an atypical antipsychotic agent prescribed for adequate duration. Psychotic disorders occurring during the course of Parkinson's disease, where standard treatment has failed.

Dosage and Administration
Treatment-resistant schizophrenic patients
12.5 mg once or twice on the first day, followed by 25 mg tablets once or twice on the second day. Increase dose slowly, by increments (see SmPC). In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. If dose does not exceed 200 mg/day, it can be given as a single administration in the evening. Once control is achieved, a lower maintenance dose may be effective. Treatment should be maintained for at least 6 months. Doses up to 900 mg/day can be used but the possibility of increased adverse reactions (especially seizures) occurring at doses over 450 mg/day must be considered.
See SmPC for details on re-starting therapy, ending treatment or switching from another antipsychotic.
Psychotic disorders occurring during the course of Parkinson's disease in cases where standard treatment has failed
The starting dose must not exceed 12.5 mg/day taken in the evening. Increase dose by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, preferably given as a single dose in the evening. The mean effective dose is usually between 25 and 37.5 mg/day.
The maximum dose of 100 mg/day must never be exceeded. Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment. When there has been complete remission of psychotic symptoms for at least two weeks, an increase in anti-parkinsonian medication is possible on the basis of motor status. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.

Method of administration
Clozaril is administered orally.
Switching from a previous antipsychotic therapy to Clozaril
It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.
Special populations: Hepatic impairment Patients with hepatic impairment should receive Clozaril with caution along with regular monitoring of liver function tests (see section 4.4 of SmPC).
Paediatric population No paediatric studies have been performed. The safety and efficacy of Clozaril in children and adolescents under the age of 16 years have not yet been established. Clozaril should not be used in this group until further data becomes available.

Patients 60 years of age and older Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day. See SmPC for information on ending therapy.

Contraindications
Hypersensitivity to the active substance or to any of the excipients. Patients unable to undergo regular blood tests. History of toxic or idiosyncratic granulocytopenia /agranulocytosis (with the exception of granulocytopenia /agranulocytosis from previous chemotherapy). History of Clozaril induced agranulocytosis. Concurrent treatment with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is discouraged.
Impaired bone marrow function. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Circulatory collapse and/or CNS depression of any cause. Severe renal or cardiac disorders (e.g. myocarditis). Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure. Paralytic ileus.

Warnings and Precautions
Agranulocytosis: Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. Clozaril can cause agranulocytosis, so is restricted to patients who have initially normal leukocyte findings (White Blood Cell (WBC) count > 3.5x 10^9/l and Absolute Neutrophil Count (ANC) > 2.0x 10^9l), and in whom regular WBC counts and ANC can be performed within 10 days prior to starting Clozaril, weekly for first 18 weeks, thereafter at 4 week intervals throughout treatment and for 4 weeks after complete discontinuation.
Patients with history of cardiac illness or abnormal cardiac findings on physical examination prior to treatment should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.
QT interval prolongation: As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation. As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval.
Cerebrovascular adverse events: Clozapine should be used with caution in patients with risk factors for stroke. Risk of thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered. Metabolic changes: Atypical antipsychotic drugs, including Clozaril, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. Hyperglycaemia: Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Hepatic impairment: 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.

Prior to treatment initiation, physicians must ensure that the patient has not experienced an adverse haematological reaction to clozapine that necessitated discontinuation.
Immediate discontinuation of Clozaril is mandatory if either the WBC count is less than 3.0x10^9 /l or the ANC is less than 1.5x10^9 /l at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Clozaril. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred. **If Clozaril has been withdrawn and either a further drop in the WBC count below 2.0x10^9 /l occurs or the ANC falls below 1.0x10^9 /l the management of this condition must be guided by an experienced haematologist.** The patient should be educated to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.
Low WBC count/ANC: If, during Clozaril therapy, either the WBC count falls to between 3.5x10^9/l and 3.0x10^9/l or the ANC falls to between 2.0x10^9/l and 1.5x10^9/l, haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3.0-3.5x10^9/l and 1.5-2.0x10^9/l respectively, or higher.

Eosinophilia: Discontinuation of Clozaril is recommended if the eosinophil count rises above $3.0x10^9$ /l; therapy should be restarted only after the eosinophil count has fallen below $1.0x10^9$ /l. Discontinuation of Thrombocytopenia: Clozaril therapy is recommended if the platelet count falls below $50x10^9$ /l. Cardiovascular disorders: Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest which is more likely to occur with concurrent use of certain medications (See SPC for more details) and during initial titration with rapid dose escalation. Patients starting Clozaril treatment require close medical supervision. Clozaril is associated with an increased risk of myocarditis, pericarditis/pericardial effusion and cardiomyopathy; and if suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril. In patients who are diagnosed with cardiomyopathy while on Clozaril treatment, there is potential to develop mitral valve incompetence, including mild or moderate mitral regurgitation. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure or symptoms mimicking myocardial infarction. Flu-like symptoms may also be present. Myocardial infarction (MI): There have been post marketing reports of MI which include fatal cases. Epilepsy: Patients with a history of epilepsy should be closely observed during Clozaril therapy since dose related convulsions have been reported. Hepatic impairment: Patients with stable pre-existing liver disorders or liver dysfunction need regular liver function tests. If the LFTs are elevated, discontinue Clozaril and resume only if LFTs return to normal. Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including Clozaril. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.
Anticholinergic effects: Use with care in patients with a history of colonic disease, a history of lower abdominal surgery, glaucoma, narrow angle glaucoma, prostatic enlargement and in patients receiving concomitant medications known to cause constipation, megacolon and intestinal infarction/ischaemia, paralytic ilius. Pyrexia: High temperatures should be evaluated carefully to rule out underlying infection, agranulocytosis or Neuroleptic Malignant Syndrome (NMS). If NMS is confirmed, discontinue Clozaril immediately and administer appropriate medical measures. Patients with rare hereditary problems of galactose intolerance should not take Clozaril. Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. Falls: Clozaril may cause seizures, somnolence and other conditions that could lead to falls. Fall risk assessments should be performed on patients with exacerbating conditions. Risk of thromboembolism: Immobilisation of patients should be avoided due to reports of thromboembolism. Increased mortality in elderly patients with dementia. Caution when prescribing to pregnant women. Mothers receiving Clozaril should not breast-feed. Adequate contraceptive measures must be ensured in women of childbearing potential. Neonates exposed to antipsychotic drugs (including Clozaril), during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Interaction with other medicinal products and other forms of interaction

Clozaril must not be used concomitantly with substances having a well-known potential to suppress bone marrow function. (See Section 4.3 of the SmPC, Contraindications).
Long-acting depot antipsychotics (with myelosuppressive potential) must not be used with Clozaril because these cannot be removed from the body in situations where they may be required e.g. neutropenia. Alcohol should not be used with Clozaril due to possible potentiation of sedation.

Caution is advised if Clozaril is used concomitantly with other CNS active agents such as, MAOIs, perazine, SSRIs especially fluvoxamine, caffeine, CNS depressants including narcotics, antihistamines and benzodiazepines, Caution is advised if Clozaril is used concomitantly with antihypertensive agents, highly protein bound drugs (e.g. warfarin and digoxin), phenytoin, lithium, rifampicin, valproic acid, noradrenaline [norepinephrine], adrenaline [epinephrine] or omeprazole. Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated. Hormonal contraceptives (including combinations of estrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore initiation or discontinuation of hormonal contraceptives, may require dose adjustment of clozapine according to the individual medical need. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects. See SPC for more details.

Fertility, Pregnancy and Lactation

Pregnancy: Caution should be exercised when prescribing to pregnant women. Neonates exposed to antipsychotics (including Clozaril) during the third trimester are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Lactation: Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving Clozaril should not breast-feed.
Fertility: Limited data available on the effects of clozapine on human fertility are inconclusive.
Women of child-bearing potential: A return to normal menstruation may occur as a result of switching from other antipsychotics to Clozaril. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Ability to Drive and Operate Machinery

Owing to the ability of Clozaril to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Undesirable effects

Adverse reactions are ranked under headings of frequency. Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.
The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever.

Very common: Drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation.
Common: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, weight gain, blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures, convulsions, myoclonic jerks, ECG changes, hypertension, postural hypotension, syncope, nausea, vomiting, anorexia, dry mouth, elevated liver enzymes, urinary incontinence, urinary retention, fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation, dysarthria.
Uncommon: Agranulocytosis, neuroleptic malignant syndrome, dysphemia, falls.
For details of rare, very rare and not known undesirable effects please refer to SmPC."

Package Quantities and basic NHS price

28 x 25 mg tablets : £2.95 ; 84 x 25 mg tablets : £6.30; 100 x 25 mg tablets : £7.50
28 x 100 mg tablets : £11.76 ; 84 x 100 mg tablets : £25.21 ; 100 x 100 mg tablets : £30.01
Supply of Clozaril is restricted to hospital pharmacies registered with the CLOZARIL Patient Monitoring Service.

Marketing Authorisation Holder

Mylan Products Limited, 20 Station Close, Potters Bar, Herts, EN6 1TL, UK.

Product Authorisation Numbers

25 mg tablets: PL 46302/0054
100 mg tablets: PL 46302/0057

Legal Category: POM

Further information is available in the UK from: BGP Products Ltd., Building Q1, Quantum House, 60 Norden Road, Maidenhead, Berkshire, SL6 4AY, UK.

Date of last revision: May 2020

Clozaril is a registered Trademark

Reporting of adverse reactions:
Please continue to report suspected adverse drug reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme.
It is easiest and quickest to report adverse drug reactions online via the Yellow Card website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, you can report via some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) or by calling the Commission on Human Medicines (CHM) free phone line: 0800-731-6789. Adverse reactions/events should also be reported to Viatris via cpms@viatris.com

uk-pi-clozaril-May20-v5

Clozaril® (clozapine)

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

CLZ-2020-0074 Date of preparation: January 2021

VIATRIS