Clozapine and neuroleptic malignant syndrome

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) states that Neuroleptic Malignant Syndrome (NMS) is an uncommon (>1/1,000 but <1/100) side effect.1,2

NMS is a serious and potentially fatal symptom complex that has been reported in association with antipsychotic drugs. The incidence of NMS reported with antipsychotics is in the region of 1% and the mortality rate for untreated NMS is in the region of 20%.3,5 The incidence of NMS reported in patients on clozapine is similar, or (due to its lower D2 affinity) possibly slightly less, than that seen with other antipsychotics.4-7 Cases have been reported in patients using clozapine either as monotherapy or more commonly, in combination with lithium or other central nervous system (CNS) agents, e.g., other neuroleptics.4,5,8

Risk factors

NMS can occur at any time during therapy,9 although it is most often seen early in treatment4,6 and it has also been reported following abrupt discontinuation of neuroleptics.9 In one review of NMS, it was reported that 90% of cases of NMS occurred within the first 10 days.3 There appears to be an association with dose, with an increased risk reported in patients who are started on high doses or who undergo rapid dose titration, or in patients who have had a significant dose alteration.3,4,11 Males appear to have twice the risk compared to females.3,11 The median age reported in the literature is between 20-50, which may correlate with peak neuroleptic use.3,4,11

Other risk factors/precipitating factors for NMS include:3,4,10,11

- History of NMS
- History of organic brain disease or alcoholism
- History of Parkinson’s disease/ Huntingdon’s Chorea
- Hyperthyroidism
- Catatonia
- Dehydration
- Agitation
- Elevated temperature
- Rechallenge with suspect medication
- Abrupt cessation of anticholinergics
- Concomitant use of predisposing drugs (e.g., lithium)
- Low serum iron concentrations
- High potency neuroleptics
- Depots/IM neuroleptic injections
- Extrapyramidal side-effect/tardive dyskinesia
**Diagnosis**

Diagnostic evaluation of patients with NMS is complicated and is based on the history, clinical presentation and laboratory findings. It is important to exclude other drug-induced, systemic or neuropsychiatric illness, but the diagnosis must be considered in any patient presenting with the clinical features of NMS, including those with high fever.

Clinical manifestations may include:

- Hyperthermia/fever
- Muscular rigidity (lead-pipe)
- Altered mental status: confusion, agitation, or altered consciousness
- Evidence of autonomic instability: tachycardia, fluctuating blood pressure with hypertension or hypotension, diaphoresis (sweating, which may be profuse), or tachypnoea
- Laboratory findings can include leucocytosis, metabolic acidosis, increased creatine phosphokinase (CPK) or increased urinary myoglobin

Due to clozapine’s different pharmacologic profile NMS may present atypically in clozapine-treated patients. There may be fewer motor abnormalities and a milder fever.

As mentioned above, diagnosis of NMS can be difficult, especially as clozapine-induced NMS may not present with all the classical features. Many of the symptoms, signs and laboratory findings seen in NMS are known adverse reactions to clozapine (e.g., fever, rigidity, confusion, agitation, tachycardia, hypertension, hypotension, disturbances in sweating, hypersalivation, incontinence, tremor, leucocytosis and increased CPK) and occur in the absence of NMS. Marked increases of CPK (mostly asymptomatic or less commonly associated with myopathy or rhabdomyolysis) which were not associated with NMS have been reported in patients on clozapine.

**Differential diagnosis**

A number of other differential diagnoses need to be considered, including CNS infections; lethal catatonia; malignant hyperthermia; heat stroke; Serotonin Syndrome; or other drug reactions (e.g., lithium toxicity) or drug withdrawal syndromes.

It is important to review the complete clinical picture of any patient who presents with features of NMS or in whom a diagnosis of NMS is suspected.
Management

If NMS is suspected, clozapine and any other antipsychotics should be withdrawn immediately and the patient referred for urgent hospitalisation. Specialist care will be needed. The patient should be given general supportive medical care as an in-patient. Particular attention should be paid to cooling the patient (antipyretics, cooling blanket), adequate rehydration with intravenous fluids and correction of electrolyte abnormalities.11 There is no proven effective treatment for NMS but brief guidelines are given in the British National Formulary (BNF) which mentions that cooling, and treatment with dantrolene or dopamine agonists such as bromocriptine have been used (unlicensed indications).15 Most patients recover from NMS in 2-14 days without any cognitive impairment11 although mortality from untreated NMS has been reported to be as high as 20%.3

Clozapine rechallenge following NMS

Rechallenge of patients with a history of antipsychotic-induced NMS (including clozapine-induced NMS) is not contraindicated with clozapine. However, the decision to rechallenge must be made following a careful risk-benefit assessment of each individual case.

Clozapine has been used in patients with a history of NMS secondary to typical antipsychotics and, due to its different pharmacological structure, is the recommended choice of some authors.11 However, there are reports of patients with a history of NMS due to other antipsychotics who developed a further episode of NMS following treatment with clozapine.5,6,14 Successful rechallenge after clozapine-induced NMS has also been reported.5,7,8,14,16 Rechallenge should only be considered after full recovery from the NMS. Low dose restart and slow titration must be used while monitoring the patient carefully for side-effects.

References

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, Earlistown 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)

CLZ-2018-0132 Date of preparation: June 2018