Atypical neuroleptic malignant syndrome with long-term clozapine

Carmela E Corallo and David Ernest

ABSTRACT

Clozapine-induced neuroleptic malignant syndrome (NMS) may present differently from NMS associated with traditional antipsychotic agents, with fewer clinical features, particularly fewer extrapyramidal manifestations. The risk of developing NMS with clozapine does not appear dose-related. In half of cases, it occurs within 2 weeks of beginning clozapine therapy, but it can develop at any stage, especially with long-term use. We describe a patient who presented with atypical NMS after more than 10 years of clozapine treatment, and who was safely re-challenged with the same drug.

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Clinical record

A 50-year-old man presented to our hospital in early 2006 after he was observed by his carers to slump suddenly from a chair, "frothing from the mouth", without other apparent seizure activity. He remained unconscious for 5 minutes and then woke in an agitated and aggressive state. He was given midazolam (total, 16 mg) by attending ambulance officers and transferred to the emergency department.

The patient had a history of chronic paranoid schizophrenia from 1988 and had been hospitalised many times for relapses and major depression. In 1995, he began clozapine therapy, increasing to a final dose of 550 mg daily. He remained well until early 2005, when he was admitted to a psychiatric hospital because of non-compliance and a 2-week history of deteriorating mental state, increasing homicidal and suicidal ideation, self-neglect and failed community treatment. The dose of clozapine was gradually increased over 3 months, from 550 mg to 700 mg, and then to a maintenance dose of 600 mg daily. He had been well under supervised care thereafter.

In the emergency department, the patient was given a further intramuscular dose of midazolam (5 mg) and droperidol (5 mg). An hour after symptom onset, he was noted to have a fever (temperature, 38.6° C) and diaphoresis, tachycardia and a persisting altered conscious state, but normal blood pressure and no focal neurological deficit or rigidity. He was intubated for airway protection and transferred to the intensive care unit.

Laboratory tests at that time revealed hyponatraemia (serum sodium concentration, 121 mmol/L; reference range [RR], 135–145 mmol/L), leukocytosis (white cell count, 12.3×10^9/L; RR, $4.0–11.0 \times 10^9$/L) with neutrophilia (9.58×10^9/L; RR, $1.80–8.00 \times 10^9$/L), and an increased creatine kinase (CK) level (606 IU/L; RR, 30–180 IU/L). Serum concentrations of urea, other electrolytes, glucose, troponin and C-reactive protein, and thyroid function were within normal limits. A urine toxicology screen was negative, and blood alcohol level was < 2 mmol/L. Initial cultures of blood, urine, sputum and cerebrospinal fluid were all sterile, with no abnormal cell counts. Computed tomography of the brain and an electroencephalogram did not reveal any abnormalities. Similarly, appearance on chest x-ray, electrocardiogram and subsequent transthoracic echocardiogram were considered to be within normal limits. Of note, blood clozapine level measured 2 days before symptom onset was 380 ng/mL (therapeutic range, 400–1000 ng/mL).

In the ICU, the patient remained febrile, and empirical treatment for meningitis/encephalitis was begun with ceftriaxone and aciclovir; clozapine was discontinued. Further investigations revealed an increase in CK level to 63 328 IU/L over the subsequent 36 hours, without myoglobinuria or any clinically apparent focus to explain this degree of rhabdomyolysis. Neurological assessment was limited by the use of propofol and midazolam for sedation, although no focal deficits or muscle rigidity became apparent.

In view of the use of the neuroleptic agent, clozapine, together with an unexplained febrile illness associated with altered conscious state and rhabdomyolysis, the possibility of neuroleptic malignant syndrome was considered. Dantrolene (50 mg intravenous 8-hourly) and bromocriptine (2.5 mg 8-hourly) were begun.

By Day 3 after admission, the patient's condition had improved, and serum CK level had halved to 31 183 IU/L; dantrolene and bromocriptine were ceased. On Day 5, clozapine was recommenced at the request of the supervising psychiatrist, at an initial dose of 25 mg daily, doubling every 3 days to a final dose of 275 mg. There was no associated deterioration in the patient's neurological status. Serum CK level gradually decreased to within normal limits after 12 days.

Discussion

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction characterised by hyperthermia, muscle rigidity, altered conscious state and autonomic dysfunction.[1] It may occur with any neuroleptic agent or other dopamine-depletor, such as metoclopramide, or after withdrawal from levodopa, a dopamine precursor.[2] Predisposing factors vary and include changes in neuroleptic dose, dehydration, functional psychoses and organic brain disorders.

In our patient, there was no evidence of infection or neurological, metabolic or endocrine disorder, and no recent history of alcohol intake or use of restraints that could readily explain the clinical and laboratory abnormalities observed. The presenting clinical features, and their resolution after clozapine discontinuation and administration of dantrolene and bromocriptine, were highly suggestive of NMS. An unusual finding was the lack of rigidity, previously noted by other authors,[3] and the long induction period (10 years after starting clozapine). No precipitating factor was identified, and, as the patient was under supervised care, we considered non-compliance with medication was unlikely.

Our patient received a single dose of droperidol at the time of initial resuscitation, and such single doses have been associated with the development of NMS.[4,5] However, as his altered conscious state and other clinical features suggestive of NMS were present before he received droperidol, we considered clozapine to be a more likely contributor to the development of NMS.

According to the criteria of the *Diagnostic and statistical manual of mental disorders* (4th edition, text revision), the essential feature of NMS is the development of severe muscle rigidity and elevated temperature (ranging from mild to marked hyperthermia) in an individual using a neuroleptic medication.[3] This is accompanied by two or more of the following: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (eg, elevated serum CK level), where these features are not due to other factors. They may be accompanied by agitation or acute dystonic reactions.

However, the presentation of NMS associated with clozapine may differ from that of NMS associated with classic neuroleptic agents. Waiting for rigidity or fever may delay or prevent the diagnosis of NMS in patients taking clozapine. While it was once thought that serum CK level increases more slowly in clozapine-induced NMS, more recent data suggest clozapine is associated with more frequent and higher CK elevations than other neuroleptics.[6] In patients taking clozapine, physicians may more appropriately diagnose NMS with Levenson's original diagnostic criteria: the presence of three major criteria (fever, rigidity and elevated serum CK level), or any two major criteria plus four minor criteria (tachycardia, diaphoresis, leukocytosis, altered consciousness, tachypnoea and abnormal blood pressure).[1]

The rigidity associated with NMS is thought to be due to D_2-receptor blockade in the nigrostriatal pathway. However, the lack of rigidity observed in some cases of clozapine-induced NMS suggests that other pathways may be involved. This conclusion is further supported by the observation that clozapine causes virtually no extrapyramidal symptoms.[7] The atypical NMS picture seen with clozapine is postulated to include imbalances in noradrenaline, serotonin, acetylcholine and γ-aminobutyric acid, disordered calcium regulation and state-dependent changes in receptor sensitivity.[8]

Although the incidence of NMS following exposure to neuroleptics is low (0.02% to 2.4% with conventional agents), the associated morbidity and mortality are quite high, with a mortality rate between 4% and 25%.[2,9] The reported mortality rate is lower in NMS associated with atypical antipsychotics than in NMS associated with conventional agents,[10] but the mortality rate may simply reflect physicians' awareness and ensuing early treatment.[7] Risk factors for the development of NMS include extremes in age, concomitant use of neuroleptics and lithium or anticholinergic medications, high potency, rapid dose increases and intramuscular neuroleptics, dehydration, male sex, and mood disorders with agitation.[2] Furthermore, addition of a selective serotonin reuptake inhibitor to an atypical antipsychotic may increase the risk of NMS, and has been reported with combined use of clozapine and paroxetine.[8]

According to the product information, NMS has been reported in patients receiving clozapine, often in combination with lithium or other agents active in the central nervous system in fewer than 0.1% of patients.[11] However, clozapine is the most commonly reported cause of NMS to the Australian Adverse Drug Reactions Advisory Committee (ADRAC). Up to February 2006, there were 78 reports of NMS associated with clozapine; in 52 cases, clozapine was the sole agent responsible. In comparison there were 42 cases involving olanzapine, and 20 cases involving risperidone (ADRAC, personal communication, Feb 2006).

Clozapine-induced NMS usually occurs during initiation of treatment, but is possible any time from a few hours to years after starting treatment. In a review of 25 cases, Karagianis et al reported that the longest delay to onset was over 3 years,[7] whereas in the reports submitted to ADRAC the longest delay was 5.5 years. Huang described a 34-year-old woman who developed NMS after 7 years of clozapine monotherapy (250 mg per day).[12] The only precipitating factor in that case was dehydration. The patient was

successfully re-challenged with clozapine, increasing the dose to 250 mg over 18 days. The author described another four cases of NMS with long-term clozapine and successful re-challenge. In contrast, Franzen et al reported a case of NMS which occurred after 30 years of clozapine treatment.[13] In that patient, re-challenge with clozapine caused an acute recurrence of symptoms.

Clozapine-induced NMS is usually not fatal if the medication is stopped quickly, and supportive measures are implemented.[11] NMS has occurred after re-challenge with clozapine, but there are case reports of successful re-challenge,[7] and our case suggests that the risk of re-challenge in a supervised setting is acceptable. It is important to be aware of this, to avoid unnecessary changes to stable antipsychotic medication for a patient who may require reintroduction of clozapine therapy.

Author details

Carmela E Corallo, Deputy Director, Pharmacy Department
David Ernest, Director of Intensive Care
Box Hill Hospital, Box Hill, VIC.
Correspondence: david.ernest@easternhealth.org.au

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