CASE REPORT

Neuroleptic malignant syndrome associated with haloperidol use in critical care setting: should haloperidol still be considered the drug of choice for the management of delirium in the critical care setting?

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SUMMARY

A 48-year-old man was brought to the emergency department because of intoxication. The patient was in respiratory distress, subsequently intubated for airway protection. On hospital day 5, he was diagnosed with delirium. Haloperidol was initiated at 5 mg intravenous every 6 h and titrated up to a dose of 60 mg /day over 5 days. On hospital day 18, his temperature peaked to 107.1°F. Other symptoms included mental status change, muscular rigidity and autonomic dysfunction. Neuroleptic malignant syndrome (NMS) associated with haloperidol was suspected. No other causes for these symptoms were present. Concurrent medications were reviewed and ruled out for possible drug-induced fever. Haloperidol was discontinued and dantrolene and bromocriptine was initiated. The temperature decreased to 102.2°F within 3 h and other symptoms resolved overtime. The temporal relationship between the patient's fever decline with the discontinuation of haloperidol, and improvement with dantrolene and bromocriptine, the diagnosis was believed to be haloperidol-induced NMS.

BACKGROUND

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication associated with the use of neuroleptic agents.¹ The use of neuroleptics including haloperidol is on the rise for the management of intensive care unit (ICU) related delirium, possibly leading to a higher incidence of NMS. All clinicians in the ICU, thus, must increase awareness of this clinical syndrome as it is not widely recognised. Delirium is a well-known complication of an ICU stay, occurs in up to 80% of patients and is manifested by fluctuating disturbance in consciousness and cognition.² NMS is characterised by mental status change, muscle rigidity, hyperthermia and autonomic dysfunction.¹ Recent data suggest an incidence of NMS is approximately 0.01–0.02% in all patients exposed to neuroleptics.^{1 3} The morbidity and mortality from NMS among patients receiving neuroleptics is estimated to be around 10%; however, the mortality, prevalence or the incidence of NMS in the critically ill remains unknown.^{1 3} Although the exact pathophysiology of NMS is not fully understood, drug-induced dopamine receptor blockade in the

brain likely plays a key role in triggering the syndrome, resulting in muscle rigidity and core temperature elevation.¹ Both typical and atypical antipsychotics have been associated with NMS, but high potency typical antipsychotic such as haloperidol is most commonly implicated in NMS attributing to its higher affinity for dopamine D₂ receptors.^{1 3 4} In contrast, the newer atypicals have a lower affinity for dopamine D₂ receptors but higher affinity for receptors such as serotonin and norepinephrine.^{1 3 4} We present a case of a young patient whose hospital course was complicated by NMS related to haloperidol use.

CASE PRESENTATION

A 48-year-old man with a history of alcohol abuse (90 kg; 162 cm) was brought to the emergency department (ED) because of intoxication. The patient had been drinking alcohol all night and was brought by his wife for severe behavioural disturbance. In the ED, the patient was found to be drowsy and in a clear respiratory distress. Vitals included temperature of 100.8°F, blood pressure of 156/88 mm Hg, pulse of 95 bpm, respiratory rate of 56 breaths/min and saturation of 91% at ambient air. Laboratory examination was significant for an alcohol level of 393 mg/dL (normal 0.0–5.0); urine drug screen, comprehensive metabolic panel and haematology were unremarkable. Chest roentgenogram showed enlarged cardiac silhouette without infiltrates. The patient was subsequently intubated because of respiratory distress and broad-spectrum antibiotic therapy with vancomycin and cefepime was started empirically for potential sepsis and fever (100.8°F). In addition, thiamine, folic acid and multivitamin in 1 L dextrose 5% 0.45% normal saline, alcohol withdrawal protocol with lorazepam 4 mg intravenously every 2 h as needed and fentanyl continuous infusion for pain were initiated. He was then admitted to medical intensive care unit. On hospital day 4, an infectious disease consult was obtained for persistent fever of 101.3 °F despite being on antibiotics. Subsequently, the antibiotics were changed to meropenem and linezolid. The initial cultures were negative and all subsequent repeat cultures remained negative. On day 6, all antibiotics were discontinued. However, he continued to have a

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low-grade fever (100.3 °F) through hospital day 8, which was attributed to alcohol withdrawal. On hospital day 5, he was diagnosed with agitated delirium based on the delirium screening tool the Confusion Assessment Method ICU. It is important to note that the patient self-extubated on two different occasions, despite aggressive sedation with continuous infusion fentanyl and lorazepam alcohol withdrawal protocol. Haloperidol was initiated at 5 mg intravenously every 6 h and titrated up to a maximum dose of 60 mg/day over the course of 5 days. On hospital day 18, his body temperature peaked to 107.1°F (figure 1). Physical examination revealed generalised muscular rigidity along with tremors and marked diaphoresis. In view of his altered consciousness, generalised muscular rigidity, hyperthermia, elevated blood pressure (180/100 mm Hg) and tachycardia (138 bpm), NMS associated with haloperidol was suspected by the intensivist and psychiatry specialists. Other concurrent medications were reviewed for possible drug-induced fever. These medications included enoxaparin 40 mg subcutaneously daily, famotidine 20 mg by nasogastric tube (NGT) twice a day, empiric vancomycin 250 mg by NGT every 6 h, fentanyl patch 75 µg every 72 h, multivitamin and haloperidol 6 mg intravenously every 6 h. All involved physicians determined that these medications were highly unlikely to be causative agents.

TREATMENT

Haloperidol was discontinued and the patient was initiated on dantrolene sodium 90 mg intravenously single dose followed by 90 mg intravenously every 6 h and bromocriptine 5 mg NGT twice a day along with cooled normal saline, a cooling blanket and aggressive hydration. The patient's temperature decreased to 102.2° F within 3 h of the first dose of dantrolene and subsequently his symptoms began to resolve gradually; by day 7 of the diagnosis, his fever as well as muscle rigidity had markedly abated. As a result of the temporal relationship between the patient's fever decline with the discontinuation of haloperidol, and improvement with dantrolene and bromocriptine, the diagnosis was believed to be haloperidol-induced NMS.

OUTCOME AND FOLLOW-UP

The patient was subsequently discharged to a rehabilitation facility on day 32 of his admission.

DISCUSSION

The Society of Critical Care of Medicine sedation guidelines recommend haloperidol as the preferred agent for the management of delirium in the critically ill (grade C recommendation).² This recommendation is extrapolated from observational studies and case series in general patient population.² As a result, the optimal dose, regimen, efficacy and safety of haloperidol have not been well defined for the management of ICU delirium.² Delirium is a well-known complication of an ICU stay and is associated with poor outcomes including increased morbidity, mortality, increased hospital length of stay and long-term cognitive impairment.² The use of neuroleptics including haloperidol is thus on the rise potentially leading to a higher incidence of NMS.

During our literature review, we found limited published case reports of haloperidol-induced NMS in critical care units. Majority of the cases reported were in burn, traumatic brain injury or perioperative setting.^{5–10} All neuroleptics have been implicated in the genesis of NMS, although, high-potency agents like haloperidol is reported most often with NMS.^{11–12} NMS is an idiosyncratic reaction independent of the dose and may occur at any time during treatment. Predisposing risk factors include dehydration, agitation, restraints, substance abuse, parenteral administration, high doses or rapid upward titration of neuroleptics.^{1–11–13} NMS is characterised by the development of hyperthermia, muscle rigidity, change in mental status and autonomic dysfunction. Approximately 16% of cases of NMS develop within 24 h after initiation of antipsychotic therapy, 66% within the first week and nearly all cases within 30 days.¹ NMS usually lasts for 7–10 days; however, duration may be longer when depot injections of the drug is implicated.^{3–14}

The predisposing factors that probably led to the development of NMS in our patient included high dose, rapid titration of initial haloperidol dose of 5 mg intravenous every 6 h up to 15 mg intravenous every 6 h over 5 days and agitation. Our patient exhibited classic symptoms of NMS with development of hyperthermia and muscular rigidity. Notably, this patient's creatine kinase (CPK) level was not elevated; a likely explanation was the timely recognition and management of NMS. In addition, the use of serum CPK level as a major criterion for the diagnosis of NMS has been questioned due to lack of specificity.^{4–6} Time of onset of symptoms after initiation of haloperidol was 18 days and the recovery time after haloperidol discontinuation was 7 days. Of note, the prolonged duration of delirium our patient experienced was a consequence of extended

Figure 1 Relationship between escalating haloperidol dose and temperature measurements.

exposure of high-dose lorazepam for the management of alcohol withdrawal syndrome. Lorazepam has been identified as a risk factor for ICU delirium in a study conducted by Pandharipande *et al*¹⁵ which reported that lorazepam was an independent risk factor for daily transition to delirium.

Our patient had no other source of fever as the septic workup was repeatedly negative; moreover, the patient's fever persisted despite being on broad spectrum antibiotics.

The dramatic response to dantrolene with improvement in temperature was consistent with the diagnosis of NMS. The patient made a remarkable recovery from NMS and was discharged to a rehabilitation centre.

As demonstrated by our case, high dose and quick up-titration of the haloperidol dose can lead to the development of NMS. Although the cumulative dose administered was 60 mg/day, a dose relatively on the lower end in comparison with higher doses of haloperidol (400 mg/day) reported.² Owing to considerable variability between patients in their clinical response to regimens, some patients may require high doses but most usually do not. Further studies are needed to establish the optimum dosage, efficacy and safety of haloperidol for ICU delirium. In the meantime, lowest effective dose should be used with gradual dose escalation and for the shortest time needed to achieve the desired outcome. Alternatively, newer atypical antipsychotics may be helpful in the treatment of ICU delirium as pilot data suggest equal efficacy as haloperidol with safety advantages.^{16 17} The application of the Naranjo scale¹⁸ indicated a possible adverse effect reaction secondary to haloperidol.

Learning points

- ▶ Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication associated with the use of neuroleptic agents.
- ▶ NMS may be increasingly relevant to intensive care unit clinicians, given the frequent administration of neuroleptics to critically ill patients for agitated delirium as demonstrated in our case report.
- ▶ Our patient exhibited the classic symptoms of NMS with development of altered mental status hyperthermia, muscular rigidity and autonomic dysfunction.
- ▶ Predisposing risk factor for NMS in our patient case possibly included high doses of haloperidol and rapid rates of dose escalation.
- ▶ Early recognition, discontinuation of the haloperidol and supportive care ensued improvement in symptom resolution and successful recovery.

Competing interests None.

Patient consent Obtained.

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