Neuroleptic malignant syndrome associated with long-acting injection risperidone in a critically ill patient: case report

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ABSTRACT

Neuroleptic malignant syndrome is life-threaning neurological emergency adverse event due to antipsychotic treatment, less common with second-generation antipsychotics. Herein, we report the case of a 47-year-old male patient who was admitted to Intensive Care Unit after suicide attempt by bleach ingest. During the admission, he presented neuroleptic malignant syndrome associated to a first terapeutic dose of long-acting injection risperidone: the clinical presentation, diagnosis and management are described in detail. After receiving supportive care and undergoing pharmacological treatment, the patient recovered without sequelae and was discharged from the hospital after 71 days. Hence, clinicians should closely monitor critically ill patients if antipsychotic treatment is changed in any way.

Keywords: Neuroleptic Malignant Syndrome. Antipsychotic. Long-acting. Dantrolene

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RESUMEN

El síndrome neuroléptico maligno es una emergencia neurológica potencialmente mortal asociada al tratamiento antipsicótico, menos frecuente con los antipsicóticos de segunda generación. Presentamos el caso de un varón de 47 años ingresado en la Unidad de Cuidados Intensivos tras un intento de suicidio por ingestión de lejía. Durante su ingreso, presentó un síndrome neuroléptico maligno asociado a una primera dosis terapéutica de risperidona inyectable de acción prolongada: se describen detalladamente la presentación clínica, el diagnóstico y el tratamiento. Tras recibir cuidados de apoyo y someterse a tratamiento farmacológico, el paciente se recuperó sin secuelas y fue dado de alta del hospital tras 71 días. Por lo tanto, los médicos deben vigilar de cerca a los pacientes críticos si se produce algún cambio en el tratamiento antipsicótico.

Palabras clave: Síndrome Neuroléptico Maligno. Antipsicótico. Acción prolongada. Dantroleno.

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BACKGROUND

Neuroleptic malignant syndrome (NMS) represents a life-threatening neurological emergency, primarily associated with the use of antipsychotic agents (neuroleptics). The underlying mechanism is linked to the excessive blockade of dopaminergic (D2) receptors, which can lead to a tetrad of symptoms: hyperthermia, autonomic dysfunction and neurmouscular abnormalities (rigidity, tremor and dysautonomia), frequently accompanied by altered mental status. Laboratory findings commonly include elevated creatine kinase (related to muscle rigidity), leukocytosis, metabolic acidosis and electrolyte imbalances, which reflect the systemic impact of the syndrome[1,2].

The estimated incidence of NMS in patients receiving antipsychotic medication ranges between 0.01 and 3.23%, with a mortality rate of 10-20%[3]. Several risk factors have been identified, including the co-administration of multiple neuroleptic agents, high doses of a single neuroleptic, concomitant use of tricyclic antidepressants or lithium salts, extended-release formulations, psychoactive substances abuse and organic brain syndromes[4].

General treatment measures involve the immediate withdrawal of the suspected causative drug. Close monitoring is essential to ensure cardiorespiratory stability, maintain euvolemia, and control hyperthermia through physical cooling measures.

Pharmacological treatment is adjunct to supportive care in patients with moderate to severe clinical manifestations. It is usually initiated with benzodiazepines (lorazepam or diazepam) and dantrolene for cases of moderate to severe muscle rigidity with elevated CK; dopamine agonists such as bromocriptine, amantadine, apomorphine or levodopa are also used.

Treatment should be continued for at least 10 days after symptom resolution, ensuring complete elimination of the neuroleptic drug. Patients treated with depot antipsychotics, treatment should be extended for two to three weeks after clinical recovery and then gradually withdraw[1,4].

CASE PRESENTATION

A 47-year-old male patient was admitted to the hospital by emergency medical services for a suicide attempt by bleach ingestion. His medical history included paranoid schizophrenia, which was being adequately managed with risperidone 5 mg/day and lorazepam 5 mg/day. A computed axial tomography and upper gastrointestinal endoscopy were conducted in the emergency department, resulting in a diagnosis of Zargar IIIA caustic oesophagitis. Admission to the Intensive Care Unit (ICU) was clinically indicated.

After evaluation by the Mental Health team and given the difficulty in using the oral route, it was determined to be administered intramuscular prolonged-release risperidone (100mg, equivalence according to the technical data sheet) on day 1 of admission. A few hours later, the patient developed fever and respiratory failure, requiring orotracheal intubation, empirical antibiotic therapy with piperacillin/tazobactam and sedation with propofol 200mg/h and remifentanil 0.2mcg/kg/min to achieve a Richmond Agitation-Sedation Scale (RASS) score of -3. In addition, noradrenaline 0.3mcg/kg/min was initiated for hemodynamic support.

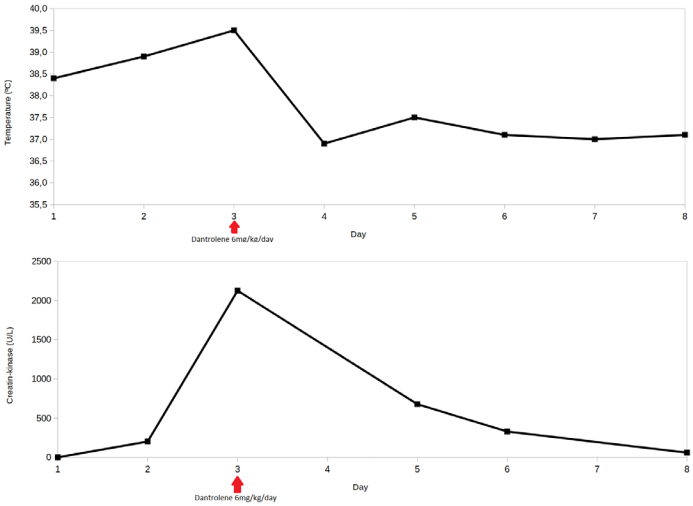
On day 3 of admission, despite broad-spectrum antibiotic therapy, the patient continued to present persistent hyperthermia (up to 39,5ºC), along with tremor, cogwheel rigidity, and an inability to communicate and collaborate. Laboratory tests demonstrated elevated levels of procalcitonin (14.96 ng/mL), C-reactive protein (206.1 mg/L), and leukocytes (13,600/µL), with a predominant neutrophil count (78.9%). Additionally, creatine-kinase levels were elevated (2,126 U/L).

Given the persistence of symptoms, the Mental Health team was consulted. A 2 mg bolus of clonazepam was administered, and the patient continued treatment with diazepam (5mg/12h) and biperidene (2mg/12h). Despite the absence of clinical improvement and taking into account the administration of risperidone depot upon admission, NMS was suspected based on DSM-V criteria. Consequently, intravenous dantrolene was inititated at 100mg/6h (6mg/kg/day) associated to diazepam 5mg/12h. Following this administration, there was an improvement in muscle rigidity, but neurological function remained unchanged (Figure 1).

The frequency of dantrolene administration was adjusted (from every 6 hours to every 12 hours). On the 10th day of admission, bromocriptine (2.5 mg/6h) was introduced after nasogastric tube placement to facilitate administration.

Following the improvement in the patient's general symptoms and laboratory parameters, sedoanalgesia was gradually reduced to allow neurological assessment and dantrolene was discontinued after 12 days of treatment. However, within hours of dantrolene withdrawal, the patient developed a hyperthermia

Figure 1. Temperature (ºC) and Creatine-kinase (U/L) evolution after dantrolene administration.



peak, raising suspicion of an infection with no clear focus: cultures were taken and empirical antibiotherapy was started. Over the next 48 hours, despite the abscence of microbiological isolation and a decrease in acute phase reactants, the patient presented poor clinical evolution with hyperthermia, diaphoresis, tremor, rigidity and sialorrhoea.

Considering this findings, and taking into account the 28-day duration of risperidone depot, NMS recurrence was suspected, prompting the reinitiation of intravenous dantrolene which resulted in improved symptom control.

Finally, considering the unfavorable progression, it was decided to continue treatment, maintaining dantrolene and bromocriptine for a total of 38 and 40 days respectively. The patient was discharged from the ICU 44 days after admission, being transferred to a Mental Health hospitalisation facility where antipsychotic and antidepressant treatment was reinitiated: clozapine and vortioxetine. Notable clinical response with complete remission permitted subsequent discharge one month later with a total hospital stay of 71 days.

DISCUSSION

NMS is most commonly associated with the use of first-generation antipsychotic agents such as fluphenazine, although cases of NMS related to second-generation long-acting injections (SG-LAI) have also been reported. According to guidelines, risperidone long-acting injection (LAI) is recommended for patients who have been stabilised on oral antipsychotics (OA) and have not experienced any adverse events (AE) related to these medications. Nonetheless, the inability to discontinue treatment if an AE occurs, like NMS, is a key argument against the use of LAI[2].

Despite the availability of pharmacological treatment options for NMS, two similar case reports described different pharmacological management approaches: one using supportive treatment alone and the other one without dopaminergic agonist[5,6]. This variability reflects the heterogeneous clinical presentation of NMS, which necessitates individualized management based on illness severity and patient characteristics.

In a systematic review, different outcomes were compared in NMS caused by LAI or OA. The review identified 662 cases, of which 122 were associated with LAI and 540 cases were linked to OA. Among the 122 LAI-associated cases, only 10 (1.5%) involved SG-LAI, indicating that SG-LAI is an uncommon causant agent. The median duration of NMS due to SG-LAI was of 1.6 weeks with a median hospital stay of 2.7 weeks. No patients experienced sequelae due to NMS[7].

This case report details the appropiate management of NMS caused by SG-LAI in a young adult patient with schizophrenia. The duration of NMS ranged from 1.7 to 3.4 weeks, -in accordance guidelines recommending-, discontinuation of both dantrolene and bromocriptine should be considered after 10-14 days of NMS resolution[2]. The total treatment duration in this patient was 5.4 weeks, with a hospital stay of 10.2 weeks and no subsequent sequelae. Since the patient was initially admitted due to suicide attempt, medication adjustments rather than hospitalization was required. This case is consistent with the abscense of sequelae but it does not align with other outcomes reported of the systematic review mentioned above.

In conclusion, this report represents the first documented case of NMS and its management in relation to a single therapeutic dose of SG-LAI, administered without concomitant antipsychotic medication. This case contributes valuable information to the existing literature as no recent evidence with similar characteristics has been identified. Therefore, this case represents the first instance of appropriate management in this context, contibuting to the clarification of evidence in such scenarios, as suggested in other studies[7].

INFORMED CONSENT

The patient has provided signed informed consent form for writing and publication.

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