Pharmacist intervention to detect drug adverse events on admission to the emergency department: Two case reports of neuroleptic malignant syndrome

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Summary

What is known and objective: Neuroleptic malignant syndrome (NMS) is a rare but severe adverse effect of antipsychotic drugs.

Case description: We report two cases of NMS highlighted by clinical pharmacists in an emergency unit during summer. One of them was fatal. Medication reconciliation processes performed at admission identified treatment with loxapine for one of them and with loxapine and clozapine for the other. Interview of the patients highlighted clinical symptoms suggesting NMS, allowing the pharmacists to alert the medical team.

What is new and conclusion: Adverse drug events may be severe and clinical pharmacists in emergency departments can help to detect them.

KEYWORDS

accident and emergency departments, adverse effect, clinical pharmacy, clozapine, loxapine, pharmacist consultation

1 | WHAT IS KNOWN AND OBJECTIVE

Neuroleptic malignant syndrome (NMS) is a rare but severe adverse effect of antipsychotic drugs. NMS is characterized by hyperthermia and muscle rigidity, and at least two of the following symptoms: change in mental status, hypertension, tachycardia, shaking, incontinence, or creatine kinase (CK) increase and/or leukocytosis.[1] Furthermore during heatwave, neuroleptics (NL) may affect the body's thermoregulation.[2] Despite a large use of antipsychotics, this syndrome is rarely notified to health authorities. At the university hospital of Montpellier in France, a pharmaceutical team is present in the Emergency Department (ED) to detect hospital admissions caused by iatrogenic events. After triage and before or during medical examination, the clinical pharmacist questions patients about their clinical history, current treatments and reason for ED presentation, looking for evidence of an iatrogenic event. Iatrogenic events are identified by clinical pharmacists on the basis of collected data using their clinical knowledge and validated databases, such as VIDAL dictionary (French book summarizing the characteristics of all medications, including pharmacology, adverse effects and drug-drug interactions). In case of doubt about an iatrogenic event, the cases are reviewed by an expert committee including emergency physicians, clinical pharmacists and pharmacovigilance physicians.

During July 2015, two patients admitted to the ED of our hospital, presented with NMS in the course of heatwave. We describe these two cases and the role of the clinical pharmacists in their detection.

2 | CASE DESCRIPTION

Patient A was a 49-year-old man with a body mass index (BMI) of 31.1 kg/m^2 and a history of mental disorders (persecution delusions), depression and diabetes. The patient was admitted to the ED in July 2015. He presented a fever over 39.5°C/103.1°F for 7 days. At the ED, clinical examination showed a high blood pressure (163/90 mm Hg), increases in heart rate (139 bpm), a fever around 40.8°C/105.4°F with extrapyramidal reactions, confusion, cogwheel movement and muscle rigidity without infection signs. Cerebral scanner and lumbar

	Patient A	Patient B	Normal values
Blood pressure (mm Hg)	163/90	190/92	120/80
Heart rate (beats per minute)	139	153	60-100
Respiratory rate (respiratory cycle per minute)	18	44	12-18
Physical temperature (°C/°F)	40.8/105.4	41.2/106.2	37.0/98.6
Oxygen saturation (% O_2)	93	99	95-100

TABLE 1 Vital parameters at the time of emergency room admission for patients A and B

	Patient A	Patient B	Normal values
Leucocytes (g/L)	6200	12 800	4000-10 000
Enzymatic creatinine (μmol/L)	84	132	60-110 (for men)
Sodium concentration (mmol/L)	120	131	135-145
Potassium concentration (mmol/L)	3.8	4.3	3.5-5.0
Creatine kinase (UI/L)	419	562	<190
Myoglobin (μg/L)	164.8	275.5	28-72
Lactic acid (mmol/L)	1.2	4.4	0.5-2
C-reactive protein (mg/L)	0.9	2.5	<6
Procalcitonin (ng/mL)	Not informed	0.16	<0.10

TABLE 2 Biological parameters at the time of emergency room admission for patients A and B

puncture were normal. His vital and biological parameters at emergency admission are described in Tables 1 and 2. At admission, a medication reconciliation process was performed by the clinical pharmacist. The patient's treatment included sodium valproate (dose unknown), clozapine 100 mg/d, tropatepine hydrochloride 10 mg/d, loxapine 100 mg/d, duloxetine 60 mg/d, piribedil 50 mg/d and metformin 3000 mg/d. After the patient's consultation, the clinical pharmacist advised the medical team of the possibility of a NMS. The patient's NL treatment was stopped and, due to the absence of severity criterion, there was no indication to initiate muscle relaxant treatment. The symptoms resolved within the following few days, and he was discharged on day 11.

Patient B was a 71-year-old man with a history of schizophrenia (acute mania and symptoms of psychosis), chronic liver failure, vascular dementia and morbid obesity with BMI of 47 kg/m^2. In July 2015, he was admitted to the hospital for confusion with hyperthermia (41.2°C/106.2°F), recent muscle rigidity and clinical signs of dehydration (Table 1). Elevated levels of leukocytosis (12 800 g/L) and CK (562 UI/L) were found at admission (Table 2) and increased rapidly in the first 12 hours (CK 1989 UI/L and leucocyte 22 600 g/L) and 24 hours (CK 6760 UI/L, leucocyte 18 600 g/L and CRP 12.6 mg/L) of hospitalization. The best possible medication history performed by the clinical pharmacist revealed chronic treatment with furosemide 20 mg/d and loxapine 100 mg/d for the past 5 years, suggesting the possibility of NMS after discussion between medical and pharmaceutical teams. Despite antibiotic treatment (ceftriaxone and levofloxacin) for managing a possible lung infection, subsequently not confirmed, the patient's status rapidly worsened with poor conscious state (Glasgow score of 6). He needed artificial ventilation and vasopressive drugs (noradrenaline) for hypotension (80/50 mm Hg) and haemodynamic instability. He was quickly transferred to the intensive care unit before muscle relaxant treatment could be initiated. Then, he developed multiple organ failure with secondary acute renal insufficiency requiring dialysis, metabolic acidosis (blood parameters: pH=7.28; pCO2=41 mm Hg; pO2=84 mm Hg; bicarbonates=17 mmol/L; lactate=5.1 mmol/L), rhabdomyolysis (blood parameters: myoglobin=6760 UI/L; CK=2336 UI/L), nosocomial pneumonia (*Klebsiella pneumonia*) and cardiopulmonary arrest in connection with severe hypoxia requiring cardiopulmonary resuscitation. Cerebral damage was found (flat line on electroencephalogram and extensive bilateral cortical necrotic lesions on brain MRI). The patient died 22 days after the onset of symptoms.

Both cases were reviewed by the expert committee and were reported to the regional pharmacovigilance centre.

3 | WHAT IS NEW AND CONCLUSION

NMS is described by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* as occurrence of muscle rigidity and elevated temperature during treatment with a NL medication, and the presence of at least two other symptoms among tachycardia, hypotension or hypertension, change in mental status with alteration in consciousness, profuse sweats, incontinence, CK increase and leukocytosis.[3] Usually, NMS occurs in the first 4 weeks after neuroleptic treatment onset. In two-thirds of the cases, it appears during the first week of treatment.[4] However, NMS can occur after several months with an unchanged treatment, as in our two patients. NMS risk factors include high dose of NL, type of

NL (intramuscular NL, long acting NL, older NL like haloperidol), male gender, previous history of NMS, organic brain syndrome, dehydration, surrounding heat environment, poor general status and physical exhaustion.[2,5,6] Thus, second-generation antipsychotics (SGA) such as clozapine and loxapine were initially described to be less at risk of NMS because of their pharmacodynamic profile.[7] However, as in our two cases, NMS induced by SGA, at high but also low dosages, have been reported notably with clozapine[7] and in a very few case with loxapine.[8,9] Moreover, other drugs with dopamine-blocking properties have been associated with neuroleptic malignant-like syndrome, such as metoclopramide, tricyclic antidrepressants or selective serotonin reuptake inhibitors.[10,11] In both cases, the best possible medication history performed by the clinical pharmacist did not reveal this type of treatment. The diagnosis of NMS is unclear and very uncertain.[2,11] NMS is an adverse drug reaction that is uncommon, challenging to diagnose and therefore is based on clinical and biological criteria,[12] and often becomes a diagnosis of exclusion.[13,14] According to studies, major criteria were hyperthermia, rigidity and/or extrapyramidal symptoms, and minor criteria were altered consciousness, tachycardia, hypertension, tachypnoea, diaphoresis and leukocytosis.[15,16] For some studies, elevated CPK was a major[15] or a minor[16] criteria for NMS diagnosis. Furthermore, the level of CPK in the NMS diagnosis is not clearly established[16-18] and differs between studies.[15,19] A large number of cases published did not mention the criteria used to diagnose NMS.[13] Our two cases presented two major (hyperthermia and rigidity) and three minor (altered consciousness, hypertension and tachycardia) criteria of NMS. In addition, our two cases had increased CK and myoglobin levels. Moreover, these results and the absence of a differential diagnosis allowed us to establish the diagnosis of NMS. In addition, we observed that patient B, who presented with more severe criteria for NMS compared with patient A, also showed a greater clinical severity resulting in the death of the patient. One hypothesis may be that patient A was at the beginning of the NMS and presented less risk factors. However, NMS has a low incidence (0.02%-2.4% of the patients treated by antipsychotics) but may have a fatal outcome (10%-50%).[5] The health authorities have established a list of dangerous drugs during heatwaves, which can alter body adjustment to hot temperatures.[20,21] Different drugs are involved, such as antipsychotics which inhibit sweating by anticholinergic activity and cause hyperthermia and furosemide which produces dehydration. NMS affects different areas of the brain: basal ganglia, limbic system and hypothalamus, and causes damage to thermoregulation by dopaminergic activity.[22] The toxic effect on skeletal muscle is probably caused by abnormal calcium availability in muscle cells and generates muscle rigidity with possible rhabdomyolysis and hyperthermia.[4]

According to various studies, there is a link between heatwaves and the occurrence of NMS of malignant hyperthermia (MH).[23,24]. Due to heat stroke, MH occurs spontaneously in vulnerable or sensitive patients (obese, elderly patient, psychiatric disease, etc.) without excessive agitation or exercise. A study concluded that antipsychotic medications are a risk factor of heat-related hospitalization for hyperthermia during heatwave.[25]

During July 2015, in the Herault region (South of France), record-breaking temperatures were registered with high peak temperatures at 36.2°C/96.8°F and 34.3°C/93.2°F on the days of hospitalization of patient A and patient B respectively. These cases of NMS occurred in patients suffering from severe dehydration associated with risk factors during a heatwave.

4 | CONCLUSION

In the ED, clinical pharmacists have an important role. They can implement activities such as medication history, medication reconciliation or research of iatrogenic events, facilitating rapid and appropriate medical care and raising awareness of medical teams about iatrogenic events.[13]

To conclude, medical and pharmaceutical teams must keep in mind that NMS is a rare pathological state but a potentially fatal adverse effect of NL drugs. It is not easily distinguishable from malignant hyperthermia during high heat. At-risk subjects must be identified, and their treatment must be evaluated and monitored to maintain a benefit-risk balance. Symptoms suggesting NMS must be rapidly identified, in particular during heatwave periods.

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