

## NEUROLEPTIC MALIGNANT SYNDROME IN A PATIENT TREATED WITH CLOTIAPINE

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### SUMMARY

**Background:** Neuroleptic malignant syndrome (NMS), which is linked to the use of antipsychotic medication, is a potentially lethal neurological emergency. The interest of our study is that NMS induced by the use of clotiapine has never previously been described.

**Subjects and methods:** We present the case of a 61-year old man whose sleep disorders were treated with clotiapine 40 mg/day. After 7 days of taking 40 mg clotiapine, the patient presented with a deterioration of his general health which had gradually taken hold, with altered consciousness accompanied by generalised muscle rigidity and hypersalivation. Laboratory blood tests revealed elevated levels of Creatine Phosphokinase (CPK) at 812 U/l. The patient was diagnosed with NMS and treated accordingly.

**Results:** The mechanism that underlies the appearance of NMS remains largely unknown. Clotiapine is a second-generation antipsychotic, first released onto the market in the 1970s, and is available in a few countries, including Belgium. NMS is treated as a medical emergency due to the possibility of morbidity and death. The first step in the treatment of NMS consists in withholding the agent suspected of provoking the symptoms.

**Conclusions:** NMS is difficult to diagnose due to a great variability in clinical presentations and the absence of specific tests and laboratory results. The use of clotiapine in treating sleep disorders can provoke NMS as a life-threatening side-effect. To our knowledge, this is the first time a case of clotiapine-induced NMS has been published.

**Key words:** neuroleptic malignant syndrome – clotiapine - sleep disorder

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### INTRODUCTION

Neuroleptic malignant syndrome (NMS), which is linked to the use of antipsychotic medication, is a potentially lethal neurological emergency. The syndrome was first described by Delay et al. in 1960 (Delay et al. 1960). While there is no laboratory verification test, NMS has a distinctive clinical presentation that includes impaired consciousness, muscle rigidity, hyperthermia and symptoms of autonomic nervous system dysfunction, such as tachycardia, high blood pressure or an elevated respiratory rate. Furthermore, anomalies in blood test results are also present; they are characterised mainly by an increase in Creatine Phosphokinase (CPK), leucocytosis, an increase in lactic acid dehydrogenase, an alteration of liver enzymes and of serum electrolyte levels (Levenson 1985). NMS has an incidence of 0.02 to 3% and is difficult to diagnose, with mortality rates estimated at 5.6% (Levenson 1985, Modi et al. 2016, Velamoor 1998). Speedier recognition and diagnosis have probably enabled mortality over the last decades. However, morbidity remains an important factor in a patient's recovery, due to the risk of rhabdomyolysis, deep vein thrombosis and organ failure. NMS is most often associated with the use of first-generation antipsychotics (El-Gaaly et al. 2009, Kantrowitz & Citrome 2008, Pasa et al. 2008, Pope et al. 1986, Strawn et al. 2007, Stubner et al. 2004), but it can also arise with second-generation medication and anti-emetic agents (Breedon et al. 2017).

In this case study, we present the case of NMS in a 61-year old man whose sleep disorders were treated with clotiapine. This patient was hospitalised in the mood disorder department of Centre Hospitalier Universitaire et Psychiatrique de Mons-Borinage (CHUP-MB) and was transferred to the neurology department of CHUP-MB (Mons, Belgium) in June 2017. The interest of this report lies in the fact that we have not found any case of clotiapine-induced NMS described in the literature.

### SUBJECTS AND METHODS

A 61-year old patient was hospitalised in the department specialising in mood disorder at CHUP-MB (Mons, Belgium) for generalised anxiety disorder, benzodiazepine dependency and a major depressive episode. His medication on admission consisted in quetiapine 200 mg/day, prothipendyl 80 mg/day, lorazepam 16 mg/day, mirtazapine 30 mg/day, perindopril 10 mg/day and acetylsalicylic acid 80 mg/day. Weaning off anxiolytics had been initiated. As the patient was reporting sleep disorder due to excessive night time awakenings, medication based on 40 mg clotiapine at bedtime was offered to replace the 80 mg prothipendyl.

After 7 days of daily intake of clotiapine 40 mg, the patient presented with a deterioration of his general condition which took hold progressively, with altered consciousness accompanied by generalised muscle

stiffness and hypersalivation. The patient was transferred to the emergency department of CHUP-MB (Mons, Belgium).

On admission to the emergency department, the clinical examination showed generalised muscle stiffness, extremely slowed limb movements, fine tremors in the extremities, bilateral weakening of osteotendinous reflexes, profuse sweating and sialorrhea. Observations were as follows: peripheral body temperature of 36.9°C; blood pressure of 140/90 mmHg; pulse rate of 108 beat/min; capillary blood glucose level of 145 mg/dl and oxygen saturation of 92%. Blood test results showed elevated levels of CPK at 812 U/l, four times the laboratory norms; other observations were unremarkable. In the light of this, the patient was diagnosed with NMS.

The patient was then hospitalised in the neurology department for monitoring. Antipsychotic medication was discontinued. The patient was given a bolus of 1 litre of saline solution in 1 hour, followed by a maintenance perfusion of a mixed solution of 2.5 l/24 hours for the first 24 hours. The treatment consisted in intravenous injections of dantrolene 80 mg/day for 8 days, as well as scopolamine 0.25 mg/day for 3 days. The patient's clinical condition gradually improved. On the 7<sup>th</sup> day after the NMS diagnosis, the patient presented with a pain in the right leg. A Doppler ultrasound revealed a deep vein thrombosis, requiring the introduction of enoxaparin 120 mg/day for 10 days, followed by acenocoumarol. From then on, the patient's evolution was favourable.

## RESULTS

The mechanism underlying the development of NMS remains largely unknown and poorly understood. The blocking of dopamine receptors may be the cause (Mann et al. 2000). First-generation antipsychotics seem to present a higher risk of NMS than second-generation antipsychotics (El-Gaaly et al. 2009, Kantrowitz & Citrome 2008, Pasa et al. 2008, Pope et al. 1986, Strawn et al. 2007, Stubner et al. 2004). Furthermore, NMS has also been described in patients taking medication that interacted with dopamine receptors, such as the antiemetic agent metoclopramide (Breedon et al. 2017).

Clotiapine is a second-generation antipsychotic that has been on the market since the 1970s, and is available in a few countries, including Belgium. This molecule belongs to the dibenzothiazepine family of antipsychotics, and has a chemical structure close to that of clozapine.

There is no consensus in the literature about the potential risk factors for the development of NMS. The symptoms generally appear within one week, almost all cases manifest within 30 days of initiation of antipsychotic treatment (Caroff & Mann 1988). The majority of patients initially present with altered mental state, then muscle stiffness, followed by hyperthermia and

impairment of the autonomous nervous system (Vela-moor 1994). Hyperthermia may be a symptom that is less present in NMS associated with second-generation antipsychotics (Picard et al. 2008, Sakar & Gupta 2017). There is great variability in way NMS can present, making diagnosis sometimes difficult. Blood test result anomalies are frequent, with elevated CPK, typically above 1000 U/l, or four times higher than laboratory norms (Gurrera et al. 2011, Levenson 1985). The elevation in CPK is a factor in the severity and prognosis of NMS (Levenson 1985). Other anomalies in blood test results are frequent, but non-specific, such as leucocytosis, a moderate elevation of lactates, alkaline phosphatases and liver transaminases, electrolyte anomalies, signs of kidney insufficiency that could be the result of rhabdomyolysis (Levenson 1985). Thus, clinical presentation and laboratory results can lead to a diagnosis of NMS, but other pathologies need to be excluded, such as meningitis, non-convulsive status epilepticus, malignant hyperthermia and serotonin syndrome (Strawn 2007).

The treatment of NMS is considered as a medical emergency due to possible morbidity and mortality. The first step in the treatment of NMS consists in discontinuing the agent suspected of provoking the symptoms. When clinical manifestations are severe, care in an intensive care unit may be necessary. In order to avoid complications, supportive care must be put in place. This consists in hydration to prevent kidney lesions due to elevated CPK levels, as well as reducing body temperature using cooling techniques. If blood pressure is too high, antihypertensive drugs may be administered. Dantrolene, a skeletal muscle relaxant, is a medicine that can be used in the treatment of NMS. Dantrolene is administered in a dose of 1 to 2.5 mg per kilogramme of body weight (Strawn et al. 2007). The literature is currently divided as to the effectiveness of dantrolene (Reulbach et al. 2007, Rosenberg & Green 1989). Whilst the literature may be contradictory, dantrolene is used in the absence of other treatment options. Other treatment options include bromocriptine, a dopamine agonist, and amantadine, which have a dopaminergic activity (Strawn et al. 2007). Once NMS is suspected in a patient, antipsychotic medicines are to be avoided to prevent a relapse. However, for some patients, treatment with antipsychotics remains necessary. The recommendation then is to wait at least two weeks before recommencing taking an antipsychotic drug.

## CONCLUSION

NMS is difficult to diagnose due to a great variability in the clinical presentations and in the absence of specific laboratory tests and results. Patients suffering from NMS generally present with muscle stiffness, an impairment of the autonomous nervous system, elevated body temperature and altered consciousness. When NMS is suspected, antipsychotics must be suspended and the patient needs to be monitored. Treatment for

NMS consists in supportive care and dandrolene may be administered. Psychiatric patients often need antipsychotic drugs as part of their medical treatment, and it is possible to reintroduce antipsychotics in a patient suffering NMS. The use of clotiapine in sleep disorders can provoke NMS, a side-effect that is potentially life-threatening. To our knowledge, this is the first time that a case of NMS induced by clotiapine has been published.

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