Olanzapine as a cause of neuroleptic malignant syndrome, bibliographic review following a clinical case

Eva M. García-Atienza[1]
José L. Agudo-Mena[2]
Encarnación Cuesta-Vizcaíno[3]
Carmen L. Val-Jiménez[3]
Miguel A. Sáez-Moreno[1]

[1] Department of Integrated Care. Health center area 8. Albacete
[2] Dermatology Service of the University Hospital. Albacete
[3] Emergency Service of the University Hospital. Albacete

Correspondence:
Eva María García Atienza
Centro de Salud Zona VIII
C/ San Juan nº 37
02006 Albacete, Spain
E-mail: evagatienza@gmail.com

Dear Editor,

Neuroleptic malignant syndrome (NMS), which was described in 1960 by Delay and Pichot[1], is characterized by the appearance of muscle rigidity, hyperthermia, altered consciousness and autonomic dysfunction, in addition to certain laboratory alterations such as leukocytosis, and the increase of skeletal creatinine kinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (FA).

It is a disorder of rare occurrence, with an incidence rate in patients treated with neuroleptics which ranges from 0.02% to 3%; this incidence is higher in people of middle age (maximum frequency in ages between 25-50 years) and in males (2: 1)[2]. The most common previous diagnosis in patients suffering from this syndrome is bipolar disorder or schizophrenia[3]. Its pathophysiology is not well understood, but probably the blocking of the dopaminergic hypothalamic and nigrostriatal routes are involved (central dopaminergic systems would intervene in the thermoregulation process and dopamine depletion could play a pathogenic role in this syndrome), as well as the muscle toxicity induced by the neuroleptic acting through the peripheral neuromuscular system (by the excessive release of calcium from the sarcoplasmic reticulum skeletal myocytes). In this way, NMS can be precipitated by either the administration of antidopaminergic drugs or by the withdrawal of dopaminergic agents[2].

Most of dopamine receptor antagonist drugs have been related to NMS. The denominated neuroleptics include: typical antipsychotic drugs (chlorpromazine, haloperidol, fluphenazine), atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine), some blocking dopamine receptors used in the treatment of symptoms such as nausea or gastroparesis (prochlorperazine, promethazine, trimethobenzamide, tiethylperazine, metoclopramide) and amoxapine, which is marketed as an antidepressant[4].

NMS has been classically associated with typical antipsychotic drugs (especially those of high potency such as haloperidol and fluphenazine), although cases with atypical antipsychotics such as olanzapine have been recently described. In fact, it seems that the incidence rate of secondary SNM in the latter is increasing due to their increasing use[5]. Other drugs such as levodopa, cocaine, clozapine and carbamazepine can also induce it[3]. It is important to note the greater frequency of appearance of the syndrome in certain situations: when we combine several neuroleptics in the treatment, when we associate neuroleptics and tricyclic antidepressants or lithium salts in the treatment, when we associate neuroleptics of delayed action with aniparkinsonianos in the treatment, when we administer intravenous neuroleptics, and finally it is more common in patients whit cerebral syndromes of naturalized organic[6].

The main complications of NMS derive first from renal failure, which is secondary to the myoglobinuria produced by rhabdomyolysus; second from respiratory insufficiency which is secondary to aspiration pneumonia due to the commitment of conscience and dysphagia; and third from myocardial infarction which causes heart insufficiency and arrhythmias. There are certain characteristics that predispose to the development of the syndrome, such as prior brain damage or mental retardation. In 91% of the patients in which a NMS appears, the dose of neuroleptics has been recently increased. However, it should not be forgotten that this syndrome can also be precipitated by the withdrawal of drugs, since they cause a sudden interruption of the dopamine availability in the brain[7]. The morbimortality attributed to this syndrome has decreased in recent years thanks to a greater awareness of the condition, to early diagnoses, and to intensive care interventions[8].

CLINICAL CASE

We present the case of a 56-year-old woman, with history of epilepsy during childhood, mental retardation and residual schizophrenia, and which is monitored in the Mental Health Unit, on treatment with olanzapine for more than ten years (she was treated during the first years with doses of 15 mg/day and subsequently her dose was reduced to 5 mg/day) and paliperidone (dose between 3-9 mg/day) for three years. In the context of a progressive reduction of olanzapine fifteen days before the clinic, the patient experiences a progressive worsening of her baseline, with psychomotor slowing, so the treatment with olanzapine 5 mg/24h is restarted. Five days after the reintroduction of the medication, the clinical worsening in the patient continues, and she goes back to the psychiatric emergency department, where the home dose of olanzapine (10 mg/day) is doubled. A day later, in addition to the previous impairment, clonal movements appear along with blank stares, inability to walk and silence, for which she is carried to the emergency room.

The patient was admitted to the Intensive Care Unit (ICU) from the Emergency Department under suspicion of of NMS: clonic movements in the upper extremities, psychomotor slowing and the deterioration of her general condition in the context of a progressive withdrawal of olanzapine and subsequent reintroduction of the drug. At the time of the symptomatology, the patient was being treated with olanzapine 10 mg/24h (second day at that dose) and paliperidone 3 mg/24h.

Upon arrival, the patient presented arterial hypotension (90/60 mmHg), tachycardia (115 bpm), tachypnea (25 rpm) and a temperature of 39,3º. The physical examination highlighted the bad general state, with dry mucous membranes and without additional details of poor perfusion. At the neurological level, bradypsychia was highlighted, with spontaneous opening of the eyes, intelligible language and clonal movements in the upper extremities. In the cardiopulmonary auscultation, a hypoventilation in bases was highlighted, while the remaining exploration by apparatuses was normal. The analytical showed a deterioration in renal function, with creatinine values of 3.63 mg/dL and urea of 98 mg/dL. Other findings were: hypernatremia 168 mmol/l, potassium 3.2 mmol/l, GOT 458 mU/ml, LDH 1226 IU/l, CPK 51638 u/L, leukocytes 14,440, hemoglobin 12.7 mg/dL and prothrombin activity (AP) 61%. Pyuria, bacteriuria and hematuria were observed in the urine sediment. The existence of metabolic acidosis was confirmed in arterial blood gases. Blood cultures and urine cultures were requested and empirical antibiotic therapy with intravenous ceftriaxone was initiated. The X-ray of the chest showed a cardiomegaly, without pulmonary infiltrates. The electroencephalogram (EEG) was compatible with a mild nonspecific encephalopathy with an associated drug component, center-temporal epileptiform anomalies which were predominantly right and of very mild persistence, highlighting the presence of multifocal myoclonus throughout the registry, without correlation in the EEG. The video-EEG also showed a focal slow activity in the right fronto-temporal region, with limited persistence (abnormal but etiologically nonspecific finding), without objectifying activity associated with epilepsy specifically. The rest of the imaging tests did not show interesting findings.

Seizures were treated during the nine days of the stay in the ICU and the psychiatric treatment was discontinued (evaluating risk-benefit), observing a progressive improvement. The therapy with bromocriptine was started, but it was subsequently suspended due to the increase of secondary transaminases. The patient required hemodialysis due to the worsening of kidney function. The urine culture was negative. She presented a single positive blood culture for streptococcus viridans group (contaminant), so that the sepsis diagnosis could not be confirmed. He was treated with trimethoprim-sulfamethoxazole for 7 days.

In this case, the main differential diagnosis was carried out with a systemic infection, but given the background of the patient, her usual treatment, and the results of the complementary tests (negative results from both the urine culture and from one of the blood cultures), she was diagnosed of neuroleptic malignant syndrome, acute renal failure secondary to rhabdomyolysis and seizures.

When all psychopharmacological treatments were initially withdrew, the patient remained calm. Subsequently, during her admission in the ward, the patient began to have a blockage, psychotic distress and listening attitudes. Considering at that moment the benefit-risk, her habitual treatment was gradually reintroduced (olanzapine 5 mg/24h and paliperidone 3 mg/24h). The patient presented a favorable evolution, with disappearance of the psychotic symptoms and with good tolerance to the treatment.

DISCUSSION

The SNM is a reaction of idiosyncratic type, produced by drugs blocking the dopamine receptor[9] (Olanzapine in our case). Ninety percent of the NMS cases occur within the first 30 days of onset or of dose increase of the drug[10]. On this occasion, we can not determine a single trigger, it is likely that both the progressive withdrawal of olanzapine, and its reintroduction and the rapid increase of dose, also influenced by the clinical situation, may have contributed to the development of NMS. The patient underwent a clear improvement after the withdrawal of the atypical antipsychotic and after the prescribed treatment.

According to the new DSM-5 criteria, the diagnosis of NMS requires the identification of rigidity, hyperthermia and exposure to an antagonist dopamine, together with at least two of the following: altered level of consciousness, diaphoresis, dysphagia, tremor, incontinence, tachycardia, mutism, leukocytosis, elevated CPK and lability of blood pressure figures[4]. In the clinical case presented, the previously mentioned criteria are met.

In addition to the identification of the risk factors related to the patient and the treatment that can predict the development of NMS, it is essential to identify the prodromal signs that permit to abort the episodes at an early stage[3]. The catatonic symptoms usually alert of the beginning of the disorder. The most common symptom is hypoactivity and fluctuations of level of consciousness, which can progress to coma, are frequent as well.

Extrapyramidal symptoms include akinesia, rigidity, tremor, chorea and oculogyric crisis. It can cause dysphagia and dysarthria by the change in muscle tone of the oropharynx muscles. The most important autonomic symptom is hyperpyrexia, which usually appears at a later stage.

The main differential diagnosis of NMS should be considered with syndromes that present encephalopathy, fever and hypertonia: malignant hyperthermia (produced during anesthesia), malignant catatonia (proposed by some authors as the NMS prodrome, without previous exposure to neuroleptic drugs), Parkinsonian hyperthermia syndrome after the abrupt suppression of dopamine agonists (absence of fever, leukocytosis and autonomic alterations), central nervous system (CNS) infections (alterations in the cerebrospinal fluid), drug toxicity (cholinergic drugs - absence of rigidity and low CPK- , lithium - absence of fever, low CPK- ...), and systemic infections (which can clinically simulate a NMS)[4].

The treatment consists of the immediate suspension of the drugs involved, together with the introduction of general support measures (hydration, antipyretics, avoiding broncoaspiration, etc.)[11]. The optimal pharmacological treatment has not been standardized yet, as the drugs typically used for this syndrome (bromocriptine and dantrolene) are given for the symptomatic treatment of its complications and not for the treatment of the syndrome itself[8]. Upon the resolution of the NMS, it is recommended a period of more than two weeks to reintroduce the neuroleptic, which should preferably belong to the atypical low-potency antipsychotics group [8]. It is estimated a risk of relapse of 15% after the onset of psychotropic drugs.

The consumption of drugs that can motivate the clinical profile is currently very widespread, and we must be alert in these patients. Despite the low incidence of NMS, its mortality rate remains high. Cases like the one presented here show the importance of always maintaining an expectant behavior, even with low-potency extrapyramidal neuroleptics[4].

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Use of perampanel in treatment-resistant insomnia

[1]Jorge Gómez-Arnau
[2]Paula Artieda-Urrutia
[3]Daniel Hernández-Huerta

[1]Centro de Salud Mental de Coslada, Madrid
[2]Centro de Salud Mental de Ciudad Lineal, Madrid
[3]Hospital Universitario Ramón y Cajal, Madrid

Correspondence:
Jorge Gómez-Arnau
Servicio de Psiquiatría. Hospital Universitario del Henares
Avenida de Marie Curie s/n. 28822 Coslada, Madrid
Correo eléctronico: jorge.gomezarnau@salud.madrid.org

Dear Editor,

Roughly 10% of the general population could suffer from chronic insomnia. Of these, half have other psychiatric problems, especially anxiety and depressive disorders[1]. Sleep disturbances are often not only present during the course of the disorder but persist as residual symptoms, even when the disorder is in remission[2,3]. These sleep problems may worsen the course of the underlying psychiatric disorder and affect functionality and quality of life[4,5].

Among the pharmacological approaches to insomnia, benzodiazepines and their analogs (zolpidem, zopiclone, etc.) stand out with specific indication. The use of off-label drugs for the treatment of insomnia is widespread. For example, some antidepressants with sedative action such as trazodone are often more prescribed than benzodiazepines[6]. On the other hand, cognitive-behavioral therapy (CBT) focused on insomnia has shown efficacy in cases of resistance to pharmacological treatment[7].

To date, however, the approach to chronic insomnia in psychiatry is still complicated. Many of the drugs are used off-label, without a solid body of scientific evidence to support their use. In addition, pharmacological regimens restricted to a few weeks, as recommended by clinical guidelines, or CBT are often unsuccessful[1].

Perampanel is a selective non-competitive antagonist of the glutamatergic AMPA receptor. It has efficacy for both partial seizures and generalized epilepsy and is marketed in Europe with these indications[8]. We present three cases in which it was tested in insomnia resistant to other therapies.

CLINICAL CASES

Case 1

44-year-old woman in psychiatric follow-up since ten months ago. Twelve years before, she had undergone a nephrectomy secondary to chronic pyelonephritis. She has no other medical history of note. As a result of a job conflict she presents with low mood, hyporexia and insomnia and has withdrawn from social life. She is diagnosed with adjustment disorder with prolonged depressive reaction (ICD-10: F43.21). In the following months, the symptoms improve with venlafaxine (225 mg/day) and CBT. However, she still suffers from severe difficulties in initiating sleep, with a reduction in the number of sleep hours, and she does not feel rested. These problems are reluctant to CBT, as well as to treatment with usual doses of hypnotics (zolpidem, lormetazepam), antidepressants (mirtazapine, trazodone) and benzodiazepines with longer half-lives (clonazepam). Snoring, apnea/hypopnea or abnormal movements that may suggest a parasomnia are not detected in the anamnesis. She scores 17 on the Pittsburgh Sleep Quality Index (PSQI).

Case 2

34-year-old man who began psychiatric follow-up three years before for an obsessive-compulsive disorder with mixed obsessional thoughts and acts (ICD-10: F42.2). As a medical background, he had consulted for recurrent nephrolithiasis. He has had a poor tolerance to several serotonergic antidepressants (sertraline, fluoxetine, escitalopram) due to digestive side effects, so during the last year he has only been treated with CBT. As a result, mild, not disabling compulsive checking persisted. During the last 6 months, with no apparent trigger, he has fragmented sleep and difficulties in falling asleep. He complains of restlessness when in bed and express catastrophic cognitions. Sleeping difficulties persist despite completely restricting stimulants. The patient reports poor efficacy with usual doses of zolpidem, lormetazepam, diazepam and agomelatine, and low tolerance, due to an excessive daytime somnolence, with low doses of trazodone, mirtazapine and quetiapine. There are no signs of a sleep-related respiratory or neurological disorder. His PSQI score is 13.

Case 3

49-year-old male in psychiatric follow-up since three years ago, with a diagnosis of dysthymia (ICD-10: F34.1). He has no medical history of note. In the last year, he has had a sustained stable mood, with adequate functionality and no relevant anxious symptoms, in treatment with duloxetine (120 mg/day) and pregabalin (300 mg/day). Previously, he had been treated with other antidepressants, with lower efficacy (paroxetine, sertraline, bupropion). He reports, however, significant sleep fragmentation with frequent and recurrent nightmares and a subjective feeling of not resting, which are resistant to CBT, medium doses of mianserin, lormetazepam, clonazepam and melatonin, and low doses of trazodone and quetiapine. The patient prefers to carry on treatment with duloxetine, given its efficacy in depressive symptoms, despite being warned of its possible influence on his sleep pattern. There is no data for sleep-related neurological or respiratory disorder. His score on the PSQI is 14.

In all three cases it was decided to introduce perampanel at a dose of 4 mg at bedtime, titrating from 2 mg, prior informed consent. The three patients describe a significant improvement in their sleep pattern within a few days of the start of treatment. They agree that their sleep is more refreshing, with fewer night awakenings. None of them describes daytime somnolence. Case 3 also reports a decrease in the frequency of nightmares. In all three cases, an improvement in PSQI was observed after one month of treatment (scores of 8, 8 and 7, respectively). In cases 2 and 3, the improvement persisted after three months of follow-up, without significant side effects. In case 1, two weeks after the start of treatment, a substantial increase in irritability was observed, with greater verbal hostility, which is confirmed by her partner. Although these symptoms improve after decreasing the dose of perampanel to 2 mg, her sleep pattern worsens again after the reduction, so it is finally decided to withdraw the drug.

DISCUSSION

In recent years, several antiepileptic drugs have emerged in psychiatric practice, in some cases even despite a lack of controlled studies supporting their use. Thus, gabapentin, oxcarbazepine, topiramate or zonisamide have been used off-label in several psychiatric disorders[9]. With regard to sleep disorders, gabapentin has shown efficacy in residual insomnia after a depression[10]. Likewise, other antiepileptic drugs such as pregabalin[11,12] or tiagabine[13] may also improve the quality of sleep in psychiatric patients.

In the case of perampanel, some authors have argued that it could improve the quality of sleep in epileptic patients[14]. In a recent study that included 44 epileptic patients treated with perampanel as an adjuvant, a significant improvement in sleep quality was observed at three months of treatment, with an average decrease of about 1.5 points in the PSQI[15]. This effect apparently does not lead to an increase in daytime sleepiness[15,16]. Although data have recent-

ly been published on the use of perampanel in non-epileptic patients, for example in restless legs syndrome[17], there is no evidence from clinical trials to support its use in the psychiatric population.

In one of the cases, perampanel was withdrawn due to the emergence of irritability. In the pivotal trials of perampanel, although the most frequent side effects were dizziness and drowsiness, irritability appeared in 3.9-11.8% of cases, with a trend to dose-dependence[18]. Subsequent studies have confirmed these findings. For example, in an observational study conducted in 281 epileptic patients, the most frequent side effects with the taking of perampanel were somnolence and dizziness. The incidence of irritability and aggressiveness was between 2 and 3%[19]. More recently, in a one-year follow-up of 464 patients, Villanueva et al. found an incidence of irritability of 17.9%, which was even higher in patients with prior psychiatric history[20]. Thus, special attention should be paid to psychiatric patients, who may be more vulnerable to the onset of irritability, as well as to the emergence of suicidal ideation, depressive or psychotic symptoms (although the latter seem less common)[18,20,21].

Perampanel could be an option to consider in cases of resistant insomnia. The absence of scientific evidence to support its use in this indication and its side effect profile demand great caution.

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