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Olanzapine-associated neuroleptic malignant syndrome. A case report and favorable response to risperidone

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Malignant neuroleptic syndrome (MNS) is an uncommon and potentially fatal entity[1], whose diagnosis is based on clinical criteria (DSM-IV), laboratory data and exclusion of other alternative causes. The existence of a dopaminergic block (D2) has been hypothesized in its pathophysiology, it also having been observed in patients with Parkinson's disease after sudden suppression of the dopaminergic drugs used in this condition[2].

The association of MNS with potency in the D2 block contributed to the fact that this idiosyncratic reaction to drugs was initially attributed to classical, high potency neuroleptics (NL) such as haloperidol. However, the appearance of cases associated to low potency NL such as chlorpromazine and atypical NL such as clozapine, risperidone and olanzapine[3-6] suggest the presence of other factors involved in the pathophysiology of this syndrome.

Olanzapine is a thienobenzodiazepine related with clozapine that acts on dopaminergic, serotoninergic, histaminergic and muscarinic receptors, with a favorable profile of adverse effects. Mild-moderate sedation, dizziness and weight increase, and more rarely adverse effects associated to MNS, stand out.

In the following, we present the clinical case of a patient diagnosed of MNS secondary to olanzapine. We describe the response to the readministration of a new neuroleptic and discuss the preventive measures to avoid recurrences.

This is a 26-year-old woman under treatment with alprazolam (1 mg/24 h) due to anxiety disorder without any other background of interest and with a family background of a schizophrenic father. She came to the Emergency Service because of having sensorial-perceptive disorders and visual distortion and was diagnosed of acute self-referential psychotic and paranoid episode. On admission, alprazolam was discontinued, initiating treatment with chlorazepate dipotassium (10 mg/24 h) and olanzapine at a dose of 10 mg/24 h that was increased over three days to 30 mg/24 h due to persistence of these symptoms. After one week with a maximum dose, the patient began with a fever of 41°C, muscular stiffness, stupor and coma, and it was decided to admit her to the Intensive Medicine Unit (IMU). The following stood out in the laboratory analyses: leukocytosis, 23,430/µl; urea, 56.2 mg/dl; creatinine, 1.42 mg/dl; AST, 96 IU/l, and CK 3,315 IU/l, the remaining parameters being normal. Seriated blood cultures, and cranial CT scan, EEG and CSF showed no pathological findings. Once treatment with olanzapine and chlorazepate potassium was discontinued, the patient required mechanical ventilation and was treated with dantrolene, bromocriptine and carbamazepine, remaining asymptomatic at 2 weeks. After discharge from the IMU and four weeks after the complete resolution of the picture, the patient had to begin NL treatment again. Resperidone was prescribed at a dose of 1 mg/8 h with increases in the dose for 10 days until reaching 2 mg/8 h with good tolerance. After 25 days of treatment with the maximum dose, the drug was withdrawn due to absence of psychotic symptoms without presenting signs of relapse in a 9-month follow-up period.

We can establish causality of a case of MNS secondary to olanzapine in a young woman who had not been treated previously with antipsychotic drugs. This was based on the DSM-IV diagnostic criteria and excluding other alternative causes with complementary tests.

As described in the literature, the clinical picture appeared after one week of treatment with olanzapine. Increase in the drug dose to the maximum one due to bad clinical control stands out as a precipitating factor.

After a first episode of MNS occurs, the following question often arises: can the patient receive another antipsychotic drug from the same therapeutic group again? Given the seriousness, recurrence (35%-75%) and potential deadliness of the clinical picture, it seems wise to avoid typical NLs in those patients who have developed MNS. Thus, the

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use of low potency atypical NLs at the minimum possible dose, initiated when at least two weeks have passed since the complete resolution of the MNS, is recommended.

Selection of risperidone, in spite of it having been associated to cases with MNS[7], was based on structural differences and on the action mechanism in regards to olanzapine.

In conclusion, high suspicion of MNS should be maintained in patients who receive treatment with atypical NLs, and specifically with olanzapine. Identification of possible precipitating factors and early recognition of the symptoms, immediate withdrawal of the responsible drug, and early treatment in the IMU are determining factors in reduction of MNS morbidity-mortality.

Considering that this is an uncommon syndrome, with certain diagnostic difficulty, that may be potentially fatal, we consider it is appropriate to create a case registry that would allow us to achieve greater diagnostic certainty and to collect biological samples to identify genetic and acquired factors involved in the pathophysiology of the condition.

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