Clozapine-induced paralytic ileus

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Dear Editor,

Schizophrenia is a psychiatric disorder that affects 1% of the population. Various therapeutic approaches are used, including the pharmacological approach with antipsychotic agents, clozapine being the gold standard for drug treatment.[1,2] Clozapine is a tricyclic dibenzodiazepine classified as an atypical antipsychotic that has a broad receptor profile differing from that of other antipsychotic agents.[3] The side effects of clozapine include hematologic disorders, cardiovascular pathology (myocarditis, QTc prolongation>500 ms), and less studied disorders like gastrointestinal disorders in routine medical practice.[4] An estimated 15% to 60% of patients have intestinal motility problems, most frequently constipation.[1] However, 3 out of every 1000 patients have serious intestinal motility problems, with an estimated mortality of 28%, the primary mechanisms being intestinal obstruction or ileus, aspiration, and secondary infectious complications.[3]

Ileus is a disruption in intestinal transit of sudden onset that can be originated by many factors, notably postoperative, metabolic, endocrine, and pharmacological causes.[5] Among the many causes that can trigger paralytic ileus in a patient with schizophrenia, a pharmacological origin should be ruled out after having considered organic causes. Specifically, clozapine is a risk factor for this condition, with an estimated OR of 6.55 (CI 1.55 – 29.17).[6] The potential pathophysiologic mechanisms include clozapine's anticholinergic action, expressed by its antagonistic effect on muscarinic (M3) and serotonin (mainly 5-HT3) receptors, and its low dopamine antagonism (D2).[3] These effects may be enhanced by other factors associated with abnormal bowel motility, such as surgical procedures[1] or the use of drugs with potential anticholinergic effects, including other antipsychotic agents.

Case

A 58-year-old woman was admitted to our hospital with symptoms of paralytic ileus. Her medical and surgical history included essential arterial hypertension, type II diabetes mellitus, and previous laparoscopic cholecystectomy. Her psychiatric history indicated paranoid schizophrenia since the age of 21 years, which has been followed up on a regular basis. She had experienced several episodes of decompensation that required hospitalization between 2000 and 2009. Her adherence to pharmacological treatment was inconsistent, but since her most recent admission in 2009 she has been treated with clozapine (600 mg/day) and aripiprazole (30 mg/day), and achieved psychopathological stability without new decompensations. She was also taking enalapril and metformin for other medical conditions.

The patient was seen in Emergency Medical Services in May 2014 for diffuse abdominal cramping pain accompanied by nausea and retention vomiting without pathological content. The clinical picture started rapidly and was not preceded by other abnormalities in the days leading up to it. She did not have fever or other related symptoms, or recent changes in her regular treatment. On physical examination, her abdomen was distended, without bowel sounds or signs of peritoneal irritation. On radiological examination, the small bowel loops were dilated (air was present in the rectal ampulla) on plain films, which was confirmed by CT scan without identifying an obstruction or other complications. The laboratory tests showed:

- Elevated acute phase reactants: 25,100 white blood cells/mm^3, 87% neutrophils, fibrinogen 692 mg/dL.
- Mild mixed acidosis with an increased anion gap. Venous blood gases, pH 7.32, pCO2 55 mmHg, bicarbonate 28 mmol/L, and venous lactate 4.60 mmol/L.
- Biochemistry: creatinine 1.5 mg/dL, and normal Na, K, Cl, amylase, transaminases, and lactate dehydrogenase.
- Normal TSH and free T4.

The patient's clinical course during hospitalization was slow, without the return of bowel sounds for a week in which the psychoactive drugs were suspended and supportive measures were used, including no food and prokinetic therapy (metoclopramide and erythromycin). After that period, the patient recovered her bowel function, an oral diet was reintroduced, her biochemical values normalized, and her symptoms disappeared. Given the clinical presentation and context, and the absence of abnormalities in electrolytes or the acid-base balance or of other causes that might explain her condition, the diagnosis of paralytic ileus secondary to clozapine use was made. During admission, she did not experience decompensation of her underlying psychiatric pathology. Consequently, from her previous psychiatric treatment only aripiprazole was resumed at the same dose.

The decision was made to reintroduce clozapine on an outpatient basis.

Ten days after discharge, she was referred to her psychiatrist for assessment for admission for psychotic symptoms (persecutory delusional ideation and auditory pseudohallucinations with great emotional and behavioral impact). She was admitted to the Psychiatric Brief Hospitalization Unit. Clozapine was reintroduced at a rate of 25 mg/day until reaching a dose of 550 mg/day at discharge. The patient was stabilized and her psychotic symptoms disappeared completely. No side effects occurred and the frequency of her bowel movements was adequate. Oral laxative treatment and lifestyle modifications were added to her treatment. The patient's psychopathological condition has remained stable.

Discussion

Constipation is a frequent phenomenon in people with mental illness (especially schizophrenia), who have a prevalence twice as high as that of the general population (about 34%).[7] If not properly managed, serious complications like paralytic ileus can occur.[7-9] Among the etiological factors that lead to constipation in this population are low-fiber diet, sedentary lifestyle, inadequate hydration, elevation of the pain threshold, difficulty expressing feelings, and treatment with psychotropic agents.[3,6,7,9] Of all the antipsychotic agents, clozapine is the one most often associated with constipation,[6] having a prevalence of 15% to 60%.[8,10,11] Aripiprazole, ziprasidone, and amisulpride are the antipsychotic agents less often associated with constipation.[6,10] The concomitant use of anticholinergic agents increases the risk of constipation.[6,10]

Clozapine has a receptor profile and mechanism of action that favor the occurrence of intestinal hypomotility through anticholinergic activity at the muscarinic receptors (particularly M3),[3, 6,10,11] antagonism of 5HT3 and 5HT4 receptors[3,6] (and, to a lesser extent, 5HT2, 5HT6, and 5HT7),[3] and mild antagonism of the D2 receptors.[11.] In addition, H1 receptor antagonism increases sedation and, secondarily, sedentarism.[6]

Most cases of paralytic ileus associated with antipsychotic agents are secondary to the use of clozapine[6] or polypharmacy. Paralytic ileus secondary to clozapine is a rare side effect with high morbidity and mortality,[3,6] generally due to delayed diagnosis and treatment.[3,9] It occurs most often in women with high doses and/or levels of clozapine,[3,6] usually after four years of treatment.[6] The mortality secondary to clozapine-induced ileus is three times greater than the mortality secondary to hematologic disorders.[6] It is noteworthy that, despite the seriousness of the condition, it has not been given due attention in clinical practice and the literature.[3,6,10]

If clozapine-induced ileus is suspected, treatment should be discontinued, although it can be resumed after the condition resolves.[4] Fifty percent of patients experience psychotic decompensation soon after drug withdrawal.[4] Although there is no evidence supporting it, the logical choice would seem to be to use an antipsychotic without notable gastrointestinal side effects (aripiprazole, ziprasidone, and amisulpride).

Monitoring of constipation should be added to the follow-up of clozapine use to prevent the development of this serious adverse event.[2] In some studies authors recommend obtaining the patient's gastrointestinal history (abdominal illness or surgery, intestinal habit), performing an abdominal examination if constipation is present before clozapine is started, and implementing hygiene and dietary measures.[3] During treatment with clozapine, avoid using other astringent drugs (e.g., anticholinergic agents), question the patient about the occurrence of constipation, and treat it (initially with osmotic laxatives) after ruling out the warning symptoms of colorectal carcinoma.[3,5] If constipation persists, the patient should be referred to a primary care physician or gastroenterologist.[3]

The studies indicate the need to create a protocol for following up of this common side effect.[3,6, 8,9].

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Feasibility of an integrated mindfulness and Mediterranean lifestyle program

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Dear Editor,

Full attention or mindfulness programs are being increasingly used as a way to reduce stress in persons seeking to improve their emotional well-being. They have also been used as a therapeutic approach in persons with anxious or depressive mental disorders. However, because their efficacy is only moderate, several programs have been developed that seek to increase their efficacy, standing out among them those combined with cognitive psychotherapy.[1]

Physical exercise and the Mediterranean diet are two fundamental mainstays of the Mediterranean lifestyle programs. Furthermore, and they are also being evaluated as a complementary treatment in physical and mental disorders, such as diabetes or depression. The results are encouraging, although, of course, there is room for improvement.[2-4]

Mindfulness is considered to be a proposal for overall change in lifestyle in which attention to the body is of critical importance. Thus, dedicating time within the program to improve diet and level of physical activity fits in very well.[5] In fact, some experiences have already been published in this sense, based on the hypothesis that these interventions have a synergic action in healthy individuals.[6] In our group, we have combined the classical Mindfulness-Based Stress Reduction program (8 sessions in consecutive weeks with an additional session of 8 hours), this program dedicating 50% of its time to working on characteristic aspects of a Mediterranean lifestyle program. Thus, we have included the encouragement of daily physical exercise, promotion of the Mediterranean diet pattern, exposure to environmental light with the due precautions, sleep hygiene measures and promotion of the social network of support. This program aims to advance in the knowledge of whether the interventions used are supported in practice. Our intention is to test this in depressive patients. However, prior to this, we have completed the implementation of the complete program in two groups to evaluate its feasibility in volunteers interested in improving their stress-management skills. A total of 32 subjects began the program, 24 of whom completed it (25% drop-outs, most of which were attributed to lack of time to spend in the program). The impact of the intervention was evaluated with the MAAS mindfulness scale, the IPAQ physical activity questionnaire, the SF-12 questionnaire on the health condition and scale of adherence to the PREDIMED Mediterranean diet. Mean age of the participants was 51.1±13.1 years and 25 (78.12%) were women. Eighteen subjects (56.25%) were regular collaborators of the non-governmental organization (NGO) where it was held (Palma Center of Hope Telephone). This circumstance could have favored the acceptability of the intervention, given the special motivation of these persons. The scores for all the scales changed when comparing pre- and post-intervention, but this change was only statistically significant in the MAAS scale (47.0±12.9 *vs* 37.7±10.4; t=2.828; p=0.022). Satisfaction level with the program was high, even though it was considered as demanding due to the time needed and the participants very positively evaluated the possibility of simultaneously practicing mindfulness and the health lifestyle. An example of this is that a large part of the program was dedicated to instruction and practice of walking at a good rhythm, endeavoring to spend as much time as possible paying full attention to breathing and to the bodily and sensory sensations.

In summary, this pilot study reveals that the integrated program of mindfulness and Mediterranean lifestyle is viable in healthy volunteers and has an acceptable rate of drop-outs, so that we plan to test it in patients with depression. The fact that both the interventions on lifestyle and mindfulness have shown complementary efficacy individually in some studies on depression gives us hope that a program combining both interventions will have even more conclusive results. However the doubt remains about whether depressive patients will be capable of carrying it out without resulting in a sharp increase in the number of drop-outs. In any event, this intervention is not proposed as an alternative to others considered to be of first choice in depression, such as psychotherapy or pharmacotherapy, since what it intends to study is its usefulness as a coadjutant.

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