## Apropos of a case: relationship of ischemic colitis with clozapine

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Dear Editor

A case report is presented of a female patient with paranoid schizophrenia under treatment with clozapine who developed ischemic colitis secondary to clozapine. She also was receiving treatment with SSRIs, benzodiazepines and proton pump inhibitors. Given their pharmacokinetic profile and metabolization by cytochrome p450 (2D6 and 3A4), these drugs may have influenced the increase in clozapine toxicity, among others reasons, because of their anticholinergic effect. Based on a search in PubMed of relevant articles in the past 10 years on the subject and our clinical case, we have concluded that the gastrointestinal side effects are often underdiagnosed and that different interactions with clozapine must be taken account when we decide on the different patterns of treatment in resistant schizophrenia.

### Introduction

Clozapine was synthesized in 1958 and placed on the market in Europe in 1961. Fifteen years later, a significant number of patients in Finland developed agranulocytosis, which led to the withdrawal of the drug from the market. Later on, in the face of the evidence of its special clinical profile, it was sold in USA in 1989 and was subsequently reintroduced into other European countries in association with hematological monitoring systems. Since then, it has been proposed as the treatment of choice in conventional drug treatment resistant schizophrenia in many clinical guidelines.[1] Its efficacy has been shown to be superior to other antipsychotics in patients at risk of suicide, aggressiveness and dual pathology.[2,3] We currently know the cause and mechanisms of most of the side effects caused by this atypical antipsychotic, due to its extensive receptor profile. Some of these are somnolence, sedation, hypersalivation, weight gain, decrease in seizure threshold, constipation. Other adverse reactions which, although uncommon, are described, such as risk of agranulocytosis, myocarditis, eosinophilic colitis and ischemic colitis, among others. Periodic hematological controls have made it possible to reduce some of its most serious adverse reactions, making clozapine a safe and effective antipsychotic drug in the treatment of resistant schizophrenia.

### A case report

A 67-year old woman diagnosed of long-term paranoid schizophrenia with irregular follow-up by the Mental Health Unit and a history of previous admissions in the Short and Mean Stay Hospitalization Units is presented. The evolution of the picture has been torpid and is characterized by refractoriness with persistence of positive symptoms like delusional ideation of harm in spite of the use of different drug combinations that have included, among others, typical and atypical antipsychotics and depot administration.

She came to the Emergency Service due to a 2-month long picture of abdominal pain and constipation. In recent days, the symptoms had worsened with the appearance of vomiting and fever. She had been receiving the usual treatment with paliperidone 150 mg/month, clozapine 175 mg/day, biperidene 6 mg/day, sertraline 100 mg/day, diazepam 10 mg/day, omeprazole.

The physical examination showed a tight and painful abdomen with abdominal distension. A mass was palpated in the hypogastrium that extended towards the mesogastrium. The digital rectal exam revealed rectal ampulla full of abundant soft stools. The abdominal CT scan showed significant dilation of the upper and sigma rectum with abundant fecal content that conditioned upstream colonic dilatation, of the ileocecal valve and small bowel loops, with evidence of rectosigmodeal segment wall thickening with ischemic involvement. The subsequent colonoscopy showed a 15 cm long section in the descending colon with multiple ulcerations of up to 1 cm, denuded friable mucosa, of which biopsy was obtained. This was evaluated several times by Surgery, proposing the possibility of an intervention. However, the picture disappeared after manual extraction of fecaloma, total diet, serum therapy and antibiotic treatment. During her admission in Internal Medicine, she was evaluated by the Psychiatry Department where clozapine was re-introduced the benzodiazepines decreased and biperidene discontinued.

### Discussion

Appearance of ischemic colitis has been associated with the administration of several drugs, among them antipsychotics. The gastrointestinal side effects associated to clozapine include constipation, bowel obstruction, paralytic ileum, eosinophilic colitis and ischemic colitis, among others.[4-6] Development of gastrointestinal side effects has reached a prevalence of 33% in some studies.[4,7,8]

Among the factors that could contribute to greater toxicity of the clozapine in this case is the association of clozapine with biperidene, both with anticholinergic effect. On the other hand, clozapine is metabolized as a substrate in the pathway of cytochrome p450 1A2, 2D6 and 3A4 in different proportions. The concomitant use of omeprazole, p450 3A4 cytochrome inhibitor drug is described to increase the levels of clozapine 3-4 times,[9] reason why the toxicity of clozapine could have been increased in this case. Sertraline and diazepam, drugs that the patient also took, have an effect of inhibition of cytochrome P450 2D6 and 3A4,[10,11] although less, this inhibition having little clinical significance compared to omeprazole.

The references consulted recommend discontinuing clozapine.[12-14] However, given the refractoriness of the patient's psychotic symptoms and the difficulty to control them, it was decided to continue with the treatment.

In brief, caution is advised in the use of omeprazole and an attempt should be made to avoid prescribing anticholinergics such as biperidene in patients treated with clozapine. In turn, the discontinuation of treatment with clozapine would not be recommendable in case of adverse effects, given its superiority regarding the other antipsychotics in the treatment of resistant patients.[15] There are currently no studies that deal with the possibility of the concomitant use of psychopharmaceutics that do not use the 2D6 or 3A4 pathway (as paliperidone), to potentiate the antipsychotic dose, if dose adjustment is necessary due to side effects. Thus, it would be of interest to study this in future investigations.

Furthermore, following the latest guidelines[16] on physical health in patients with schizophrenia would be beneficial. It is also recommended to provide special attention to the symptoms that initially could give the impression of being non-specific such as constipation and abdominal discomfort in patients under treatment with antipsychotics. Some factors as institutionalization, sedentary life, certain eating habits may make this group of patients a more vulnerable group to this type of complications.[17] More knowledge about pharmacokinetics and the interactions existing between drugs is becoming increasingly more necessary for the carrying out of a good medical praxis.

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