Quetiapine-induced ischemic colitis. A case report

Colite ischémique secondaire à l’usage de quétiapine. À propos d’un cas

Ischemic colitis (IC) encompasses three subtypes depending on the severity of the necrotic lesions. When the necrosis affects the mucosa, the colitis is called "non-gangrenous" (70% of the cases). When it affects the muscularis propria, the colitis can cause colonic stenosis (15-20%). The last stage is a transmural "gangrenous" necrosis (15-20%), which worsens the prognosis (50% of death due to septic shock) [1,2] and requires surgery. The very high mortality rate is linked to diagnosis delay and fast evolution of the disease. However, in most cases, with an appropriate treatment, ischemic colitis heals within two weeks [3].

Despite the lack of pathognomonic clinical feature, the combination of abdominal pain, diarrhoea and hematochaezia is found in 40% of the cases. Mild fever, tachycardia, anorexia, intestinal meteorism with localized guarding [2] and occlusive syndrome can occur. Diagnosis of IC is confirmed by colonoscopy showing lesions due to circulatory anoxia. No treatment has been found to be effective for intestinal reperfusion. Recurrence of ischemic colitis seems to be rare [4].

Accountability of psychotropic drugs in colitis genesis has been suggested since the 1960s [5-7] with a prevalence of one case in every 2000 patients [8]. Most of the cases of drug induced-colitis are reported with phenothiazines [9,10] and clozapine [11,12]. Ischemic colitis induced by quetiapine has been highlighted in pharmacovigilance reports [13]. Pseudo-inflammatory bowel disease induced by quetiapine has also been described [14].

Case report

A 66-year-old woman was diagnosed with a severe bipolar disorder and hospitalized in a psychiatric unit for a depressive episode. She had been treated in the past with lithium, which was stopped because of an induced nephropathy (baseline creatinine = 100 μmol/L). Anticonvulsive drugs were ineffective.

Her daily treatment included amlodipine 10 mg, levothyroxine 150 μg, zolpidem 10 mg, hydroxyzine 100 mg and clorazepate 20 mg. Quetiapine was introduced at a dose of 300 mg. On January 2012, 20 days after quetiapine initiation, the patient exhibited acute-onset abdominal pain resistant to acetaminophen and antispasmodic treatment. She then presented three episodes of faecal vomiting, profuse diarrhoea and minor hematochaezia. She had previously been constipated for five days. The physical examination at this point showed no fever, no hemodynamic shock, no abdominal guarding but bowel sounds were reduced. Biological exams found functional renal failure (creatinine = 200 μmol/L) due to dehydration and mild hyperleukocytosis. The patient was transferred to a medical care unit for paraclinical tests and support. When she arrived in the emergency department, the blood pressure was 80/60 and the temperature was 38 °C.

The abdominal CT-scan (figures 1 et 2) didn’t show any occlusive syndrome but a wall thickening of the left colon (a) and of the pelvic colon, a net infiltration of the mesocolons (b), a pelvic peritoneal effusion and a small intestine distension suggestive of a left ischemic colitis. The CT-scan was not injected due to renal failure.

Colonoscopy was performed seven days after the symptoms began. It showed lesions such as erythematous mucosa, ulcers and erosions, 40 centimeters from the anus onwards. The superior pole of the colitis could not be observed. These lesions were quite evocative of an ischemic colitis. The pathology of the left colon samples (figure 3) demonstrated atrophic changes of mucosal glands (a) which were quite typical of an ischemic mechanism [15], acute inflammatory infiltrates (b) and mucosal infraction (c).

Clinical and paraclinical features were fully consistent with a diagnosis of ischemic colitis. On the advice of gastroenterologists, the patient underwent a treatment by aspirin, metronidazole and ofloxacin. Quetiapine was stopped.

Figure 1
Abdominal CT scan, transverse plane, showing a wall thickening of the left colon (a) and of the pelvic colon, and a net infiltration of the mesocolons (b)
Common obstructive or non-obstructive processes for ischemic colitis were excluded by the paraclinical check-up. The abdominal ultrasound exam was perfectly normal; in particular, there was no occlusion of the mesenteric or mesocolic vessels. The patient recovered fully and no recurrence was observed. Afterwards, the patient was treated by olanzapine.

The temporal association between the introduction of quetiapine and the onset of symptoms supports a drug-induced etiology. Quetiapine or the combination of quetiapine and hydroxyzine are strongly suspected to be the causative agents, likely secondary to their anticholinergic properties. We reported the suspected adverse drug reaction to our regional pharmacovigilance center.

**Discussion**

Neuroleptics may cause severe constipation through the antagonism of muscarinic receptors, especially when used in conjunction with other psychiatric drugs or anticholinergic compounds. Most of the cases of drug-induced colitis are reported with phenothiazines such as chlorpromazine, trifluoperazine, levomepromazine [5,6,9,10,16] and clozapine. Clozapine-induced necrotizing colitis has been reported recently in the literature [11,12]. More recently, olanzapine has also been incriminated [17]. Concomitant intake of anti-muscarinic compounds or psychotropic drugs are found in most of the cases [18] and may promote the illness [19]. There is a significant correlation between the number of prescribed neuroleptics at the onset of the colitis and its severity [20].

Quetiapine is an atypical antipsychotic from the dibenzothiazepine family. It is approved by the FDA for the treatment of schizophrenia (2007), bipolar disorder (2008) and as an add-on to treat depression (2008). In France, it has been approved for similar use in 2010. Quetiapine and its active metabolite norquetiapine bind mainly to serotonin and dopamine receptors, leading to an antagonism of the neurotransmitters signal. According to the summary of product characteristics, quetiapine's affinity for muscarinic receptor should be negligible, so it is theoretically supposed to have very few anticholinergic properties. Nevertheless, it has been shown that therapeutic doses of quetiapine are associated with clinically relevant anticholinergic activity [21].

Antipsychotics-induced ischemic colitis is mainly due to their anticholinergic properties, which reduce intestinal motility and cause a colonic ileus followed by colonic dilation [22]. This may be aggravated by a severe state of faecal retention that will bring gas and bacterial proliferation in the affected segment, ultimately leading to necrosis and systemic sepsis. Other mechanisms have been suggested such as dopaminergic antagonism through DA1 mesenteric receptors, which may block mesenteric reflex vasodilatation [20], and serotoninergic antagonism that may reduce intestinal peristalsis [23].

Pinzani et al. (2014) reviewed eight cases of quetiapine-induced ischemic colitis or gastrointestinal necrosis [13]. The mean age was 34 years and the mean delay of ischemic colitis was 30 days. In most of the cases, quetiapine was associated with other antipsychotics or antiparkinsonic agents. Colon resection occurred in half of the cases and among them, two patients died.

Clinicians must be aware of the anticholinergic properties of neuroleptics, tricyclic antidepressants, antihistamines (alimemazine, hydroxyzine), anti-Parkinson drugs used for muscle stiffness, scopolamine, atropine, urinary incontinence drugs, antispasmodics. All these drugs can cause constipation, as
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can morphine painkillers, statins, blood pressure medications, antiepileptic drugs (pregabalin, carbamazepine), clopidogrel, proton pump inhibitor, antidiabetic agents, anticancer drugs and methadone.

One limitation of our case is that the iatrogenic process can only be suggested. In fact, most of the colonic adverse drug reactions are under-reported or only published in case reports [24]. Moreover, the multiplicity of treatments makes the accountability of a drug difficult to establish.

Other iatrogenic causes of ischemic colitis involve non-steroidal anti-inflammatory drugs [25], antibiotics, laxatives, chemotherapeutics, immunosuppressive agents, contraceptive steroids and cardiovascular drugs [26].

Constipation, although a common gastrointestinal side effect often observed in psychiatry, must be treated with an index of suspicion, especially when it is prolonged or associated with abdominal pain, diarrhea, fecal vomiting or hematochaezia. Physicians should remember the possibility of more serious types of intestinal motility disorders and fatal outcomes.

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References


Julie Vernay
Centre hospitalier Guillaume-Régnier, 108, avenue du Général Leclerc, 35000 Rennes, France
julie9175@hotmail.fr

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