Six Cases of Perforated Appendicitis During Clozapine Treatment

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In a forensic-psychiatric hospital in Germany, we observed 6 cases of appendicitis within 14 years, all of them perforated. All patients were diagnosed with schizophrenia and were treated with clozapine. They were Caucasian males, their mean age was 34.4 years, and the mean duration of treatment with clozapine at the time of the appendicitis was 26 months (range, 6–46 months).

In the 14-year period, we observed 220 person-years with exposure to clozapine, compared to 642 years with other antipsychotics. No case of appendicitis was observed during treatment with other antipsychotics. The observed incidence was calculated as 2,726/100,000 years during treatment with clozapine compared to 130/100,000 for the general population in males of the same age group,[1] more than 20-fold.

A PubMed search with the terms *clozapine* and *appendicitis*, with no language or date limits, revealed only 1 similar case that was classified as stercoral colitis mimicking appendicitis.[2] In our cases, histologic examination did not provide evidence for mechanisms other than bacterial inflammation. In addition to the epidemiologic estimation, pathophysiologic considerations add to the possibility of a side effect attributable to clozapine. Clozapine has the strongest anticholinergic properties among all antipsychotics. Gastrointestinal hypomobility in varying degrees, up to ileus, is a well-known side effect of clozapine. According to self-reports, it affects up to 30% of those treated.[3] However, objective examination using colonic transit tests yields considerably higher percentages,[4] showing that the prevalence of clozapine-induced gastrointestinal hypomobility is probably widely underestimated. Three of our patients received laxatives due to chronic constipation. Constipation has been well established as a risk factor for appendicitis, probably via vascular compression, necrosis, and subsequent bacterial infection.[5] In 2 of our 6 patients, subileus was found during the diagnostic procedures.

In addition, there is evidence that clozapine causes an increase of proinflammatory cytokines, which has been discussed as a reason for the occurrence of pneumonia, abacterial pericarditis, and polyserositis.[6] The described effects of clozapine are at least partially dose-dependent, and the inflammation itself, as well as smoking cessation during intestinal inflammation and administered antibiotics, especially fluoroquinolones via inhibition of the cytochrome P450 1A2 enzyme, can lead to a considerable increase in serum clozapine levels. A self-enhancing circle of toxic inflammation could thereby result. Although dosages exceeded 500 mg daily in only 1 case among our patients, serum levels exceeded 750 µg/L in 3 and 1,200 µg/L in 2 cases during the course of appendicitis, compared to values below 750 µg/L determined within the last 4 weeks before the beginning of the appendicitis in all cases. Three patients had been treated with fluoroquinolones.

With regard to perforation, which was observed in all of our cases but occurs in only about 20% of appendicitis cases in the general population,[5] constipation could also be a substantial causal factor. The other reason could be genuinely psychiatric: Patients with schizophrenia typically suffer from negative symptoms with affective flattening and poverty of speech, such that patients may not report gastrointestinal symptoms. Furthermore, some patients suffer from cenesthesia or somatic delusions, and physical symptoms may be misinterpreted as psychiatric symptoms. This phenomenon of "diagnostic overshadowing"[7] applied to at least 4 patients in our case series. An altered threshold for pain conception has also been discussed.[8] There is evidence that risk of perforated appendicitis is about 5-fold higher among patients with schizophrenia than in the general population.[8] In our case series, all 6 patients eventually recovered.

As a clinical consequence of the association, appendicitis should be considered as a possible adverse event of clozapine. Dosage should be decreased rapidly in cases of acute intestinal inflammation, interactions with antibiotics should be taken into account, and serum levels of clozapine should be determined daily. Clinicians should monitor closely for constipation, and comedication with other anticholinergic agents should be avoided.

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