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Constipation, ileus and medication use during clozapine treatment in patients with schizophrenia in Iceland

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Abstract

Purpose of the article

Clozapine is the only evidence based treatment for treatment-resistant schizophrenia. Constipation is a well known side effect of clozapine treatment that can progress to ileus, a potentially lethal outcome. However, ileus has received much less attention than other adverse effects of clozapine, such as agranulocytosis. The aims of this study are to describe the prevalence of constipation and ileus during clozapine treatment of patients with schizophrenia in Iceland and to assess the concomitant use of medication that can cause constipation and laxatives used to treat constipation.

Materials and methods

We identified 188 patients treated with clozapine by searching the electronic health records of Landspítali, the National University Hospital, during the study period 1.1.1998 – 21.11.2014. Cases of constipation and ileus were identified using an electronic search with keywords related to ileus in the patients' electronic health records. Detailed medication use was available for 154 patients that used clozapine for at least one year.

Results

Four out of 188 patients were diagnosed with ileus that resulted in admission to hospital. Two of these required a permanent stoma as a consequence of their ileus. Laxatives were prescribed for 24 out of 154 patients (15.4%) while on clozapine. In total 40.9% of the patients either had laxatives prescribed or had constipation documented in the medical records. Apart from clozapine, other medication known to cause constipation was prescribed by 28 out of 154 patients (18.2%).

Conclusions

Constipation is a common problem in clozapine treatment which can progress to full-blown ileus which can be fatal. Clinicians need to monitor signs of constipation during treatment with clozapine and respond to it with lifestyle advice and laxative treatment.

Keywords: schizophrenia, clozapine, constipation, ileus, laxatives

Running title: Clozapine and risk of constipation and ileus

Background

Approximately 30% of patients with schizophrenia do not respond to conventional antipsychotics and are said to have treatment-resistant schizophrenia (1). Those patients should be treated with clozapine, the only antipsychotic indicated for patients with treatment-resistant schizophrenia (2). Constipation is a very well known side effect of clozapine treatment. A recent meta-analysis estimated the prevalence of clozapine-associated constipation to be 31.2% (3). It is thought that the mechanism whereby clozapine causes constipation is through reduced gastrointestinal motility due to anticholinergic inhibition of gastrointestinal smooth muscle contractions (4). Serotonin antagonism may also compound the constipation problem (5). Many patients with schizophrenia have sedentary lifestyles and low fiber diets which can exacerbate the risk for constipation (6). Clozapine severely slows down the transit time through the gastrointestinal tract. The median colonic transit time for patients clozapine has been shown to increase as much as fourfold, to be as high as 104 hours versus 23 hours in those never on clozapine (7). The risk of constipation has resulted in very high usage of laxatives during clozapine treatment. A UK study on outpatients reported that 35% of outpatients on clozapine used laxatives (8). Constipation can lead to ileus which can be fatal (9-11). Few prevalence studies of ileus during clozapine treatment were identified in the literature. The prevalence of ileus during clozapine treatment was reported to be 0.8% in a Danish study (11) but only 0.1% in a large Chinese sample when studied in 1991 (12). Ileus developing during antipsychotic treatment in Taiwan was, however, reported to have a 3.3% cumulative incidence rate, with patients on clozapine having the highest risk of all (13).

Aims of the study

The aims of the study were to describe the prevalence of constipation and ileus during clozapine treatment in patients with schizophrenia as well as to describe the use of laxatives and, apart from clozapine, other medication that can cause constipation among patients on antipsychotic treatment due to schizophrenia.

Materials and methods

The study cohort has been described in a previous article by the authors (14). Patients in the study were recruited from Landspítali University Hospital (LUH) Department of Psychiatry. All 611 patients who were participants in the study had a confirmed diagnosis of schizophrenia according to the “Schedules for Affective Disorder and Schizophrenia-Lifetime version” (SADS-L) and were alive on 1.1.2003 (15). Patients using clozapine were identified using keyword search in the electronic health records for the text “clozapin”, “closapin” and “Leponex”. Medical notes with the clozapine keywords were reviewed to assess whether clozapine had been used and the time frame of use. In addition to electronic health records, paper medical records were reviewed for additional information. In this way we identified 201 patients with schizophrenia who had used clozapine. LUH started using electronic health records in 1998. Of the 201 patients using clozapine there were 188 patients with sufficient medical data available during the study period and a documented use of clozapine after 1.1.1998. The start of the follow up period was defined from 1.1.1998 or the start of clozapine treatment if it occurred later. The end of the follow up period was defined as earliest date of following possible end points: the end of the study (21.11.2014), date of death if the patient had died, end of follow up date in LUH health records or the date of clozapine discontinuation if the patients had discontinued clozapine treatment.

We assessed medication use as the last known medication regime in the medical notes before the end of follow-up or the date that the patient discontinued. The time to maximum improvement achieved in positive symptoms may be as long as 6 months or more on clozapine treatment (16). Dosing adjustments of clozapine can therefore take as long as a year and accordingly patients had to have been on clozapine for at least one year to be included in the study. We had detailed medication information for 154 patients with schizophrenia and 145 out of them had been taking 100 mg or more of clozapine. We looked for three classes of other medication, apart from clozapine, that are known to cause constipation. We defined

anticholinergic as medication in the World Health Organization ATC class N04A***. Opioids were defined as medication in the ATC class N02A*** and paracetamol-codeine combinations. Tricyclic antidepressants (TCA) were defined as amitriptyline, nortriptyline, imipramine, clomipramine and doxepin.

A keyword search in the electronic health records was done to find medical notes that called for further assessments of constipation and ileus. The keywords used were: “hægð”, “hægðatr”, “stíflaður”, “stífluð”, “constip”, “obstip”, “ileus”, “intestinal”, “garnastífla”, “Stoma”, “stoma”, “garnalömun”. All medical notes found in the electronic searches were reviewed and assessed if the patient had, in the electronic health records, been reported to have developed constipation or ileus during clozapine treatment. Ileus was defined as a severe obstruction of the gastrointestinal tract that resulted in an admission to a LUH somatic department and required treatment. Constipation was rated if the patient had a documented complaint of constipation in the electronic health records during clozapine treatment or if he was treated with laxatives in the last known medication regime while on clozapine.

All participants gave written informed consent. The study was reviewed and approved by the Icelandic National Bioethics Committee (FS-02-041(03–030)) and the Data Protection Authority (2009090737þS).

Commented [MJ1]: How could they give consent if it was a record linkage study? In the UK and most countries, consent is not required for such studies as long as personal data are not reported – presumably the same applies in Iceland?

Results

The mean observational period during clozapine treatment for the 188 patients ever on clozapine was 8.9 years and median time was 9.3 years. The mean age at the end of follow up was 50 years. Four patients out of 188 (2.1%) were diagnosed with ileus with no tumor detected. The estimated ileus incidence rate was therefore 2.4 cases per 1000 person years. Two of the four patients developing ileus required ileostomy surgery that resulted in a permanent stoma. The mean time from the onset of clozapine treatment to ileus was 13.7 years (15.3, 8.7, 17.6 and 13.3 respectively). The mean age at the time of ileus was 50.6 years (47.4, 54.4, 66.5 and 34.0). No fatalities were associated with ileus. Three out of these four patients continued on clozapine treatment after being diagnosed with ileus while one patient discontinued clozapine treatment shortly after developing ileus but this patient recommenced the clozapine treatment half a year later.

There were 28 patients out of 154 (18.2%) participants on clozapine that used other medication which are known to reduce bowel movements (anticholinergics, TCA and opioids). Of them **biperiden** was the most common medication, 21 patients using it. Four patients were on amitriptyline, two on tramadol, two on morphine and one on codeine-paracetamol combination. Of the 28 patients on clozapine as well as some other medication associated with constipation only half were receiving laxatives. Of the four patients diagnosed with ileus, three were taking biperiden (an anticholinergic) and two out of four were on laxatives.

Laxatives were prescribed by 24 patients out of 154 (15.6%). Five patients were prescribed more than one laxative while on clozapine. The laxatives used were sorbitol (n = 9), senna glycosides (n = 7), magnesium hydroxide (n = 6), sodium picosulfate (n = 5), **Semen psyllii** (n = 3) and bisacodyl (n = 2). Of the 154 patients, more than one in three, 55 (35.7%), had constipation documented in their health records. When defining constipation as being present for those patients that either had a documented constipation problem in the health records or were prescribed laxatives then 63 patients out of 154 (40.9%) had constipation. The mean clozapine

Commented [MJ2]: I am not familiar with that name. Either we do not have it or we call it by a different name. Is that the trade name or a generic name?

Commented [MJ3]: Another one i haven't heard of – I've heard of semen but not as a laxative!

dose for patients with constipation defined in this way was 328 mg versus 284 mg for patients that did not have constipation but the difference fell just short of statistical significance ($p = 0.06$).

Conclusion

The observed prevalence of ileus in the cohort was 2.1% which is higher than previously reported in Denmark (0.8%) (11) and much higher than in China (0.1%), the latter difference may be partially explained of course by differences in diet and lifestyle (12). The higher incidence we observed compared to the Danish study might be explained with a longer observation period but ileus can occur anytime during clozapine treatment as was evident in our sample where the mean time to ileus was 13.7 years versus 4.2 years in Denmark (11). The incidence rate was 2.4 cases per 1000 person years which was though lower than in Taiwan where it was observed to be 4.4 in patients with schizophrenia on any antipsychotic, the association being though strongest with clozapine (13). This continuous risk of ileus is different than with agranulocytosis where around 80% of the overall risk is present during the first half year of treatment but only 20% remain as the cumulative risk in due course during long-term treatment (17, 18). The prevalence of ileus in this study is higher than the prevalence of agranulocytosis in Iceland and in other larger studies where the prevalence has been reported to be 0.7% (17-19). The case fatality in ileus has been reported be in the range from 7.3% - 27.5% (9-11) versus 3% in agranulocytosis (20, 21) so physicians should be at least as vigilant with regard to constipation and the development of ileus as they are with neutropenia and the possible development of agranulocytosis. The use of laxatives was low in our sample with only 15.6% of patients using laxatives compared to 35% in a UK sample (8). This suggests that laxatives may be underused in Iceland for these patients. There were up to six different laxatives prescribed in the cohort for constipated patients on clozapine. This may reflect lack of evidence as to which laxative have most efficacy in the treatment of constipation during clozapine treatment (22).

There are some limitations in our dataset. The prevalence of constipation may be underestimated if some patients raised their complaints about constipation only in primary care but not at LUH since we did not have access to the primary care records to do an electronic health

record search. It is also possible that some patients may have received off-label laxatives not recorded in the medical prescription charts.

Physicians must pay close attention to signs of constipation in these patients and respond promptly both with lifestyle advice, including dietary advice, and treat it with laxatives as well. Laxatives appear to be under-prescribed for patients on clozapine treatment in Iceland. Given the high prevalence rates of constipation during clozapine treatment it may be beneficial to start all patients on clozapine on preventive measures, even laxatives, especially those who are also receiving other medication that are associated with constipation.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Biographical note

Oddur Ingimarsson is a consultant psychiatrist working at Landspítali University Hospital specialized inpatient rehabilitation unit at Kleppur where most patients have schizophrenia, substance abuse disorders and are involuntarily committed. Oddur submitted his Phd thesis in November 2017. His research in the thesis focuses on the descriptive epidemiology of clozapine use in schizophrenia in Iceland and serious adverse-drug reactions to clozapine, including agranulocytosis and type 2 diabetes.

Engilbert Sigurðsson is a consultant psychiatrist and professor of psychiatry and Landspítali and the University of Iceland where he currently serves as the Dean of the Faculty of Medicine.

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