Life-Threatening Clozapine-Induced Gastrointestinal Hypomotility: An Analysis of 102 Cases

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Objective: To raise awareness of potentially lethal clozapine-induced gastrointestinal hypomotility (CIGH) by reviewing cases from the literature and unpublished pharmacovigilance data and to offer strategies aimed at prevention and early treatment.

Method: Databases (PsycINFO, 1967–2007; MEDLINE, 1950–2007; and EMBASE, 1988–2007) were searched using the term *clozapine* together with each of the following: *gastrointestinal*, *dysmotility*, *constipation*, *obstipation*, *fecal impaction*, *fecaloma*, *paralytic ileus*, *adynamic ileus*, *subileus*, *ischemic colitis*, *colon ischemia*, *bowel ischemia*, *gastrointestinal ischemia*, *gut ischemia*, *obstruction*, *necrosis*, *gangrene*, *bowel perforation*, *micro-perforation*, *megacolon*, *toxic megacolon*, *acquired megacolon*, *pseudo-obstruction*, *Ogilvie*, and *Ogilvie's syndrome*. We analyzed the electronic database entries held by the Adverse Drug Reactions Advisory Committee and the New Zealand Intensive Medicines Monitoring Program, which cited suspected clozapine-related gastrointestinal side effects, as well as all relevant published case reports. We reviewed the literature on the treatment of gastrointestinal hypomotility and constipation.

Results: We compiled a database of 102 cases of suspected life-threatening CIGH. There was a mortality rate of 27.5% and considerable morbidity, largely due to bowel resection. Within Australasia, at least 15 patients have died of CIGH. Probable risk factors are identified as recent instigation of clozapine, high clozapine dose or serum level, concomitant anticholinergic use, or intercurrent illness.

Conclusion: The paucity of literature on CIGH suggests that the significance of this uncommon but important and frequently fatal side effect has not been recognized. Clozapine can affect the entire gastrointestinal system, from esophagus to rectum, and may cause bowel obstruction, ischemia, perforation, and aspiration. The mechanism is likely to be anticholinergic and antiserotonergic. Clozapine prescribing should be accompanied by regular physical monitoring, appropriate and timely use of laxatives, and early referral of constipated patients—before life-threatening pathologic processes develop.

(J Clin Psychiatry 2008;69:759–768)

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Acknowledgments appear at the end of this article.

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Clozapine is an atypical antipsychotic commonly prescribed for treatment-resistant schizophrenia. Developed in the 1960s, it was withdrawn in 1975 due to the risk of neutropenia and agranulocytosis (3% and 0.8%, respectively).[1] A pivotal study in 1988[2] demonstrated clozapine's specific effectiveness for patients unresponsive to other treatments, leading to its reintroduction with compulsory hematologic monitoring. This monitoring has effectively ameliorated agranulocytosis-related mortality, with only 1 such death recorded in New Zealand,[3] and 2 in Australia (K. Mackay, Adverse Drug Reactions Unit, written communication, July 2007).

Despite the hematologic risks (which preclude its use as a first-line treatment), clozapine decreases overall mortality in schizophrenia, largely by reducing the suicide rate.[4–6] However, the adverse effect profile is considerable. Alongside agranulocytosis, clozapine is associated with delirium, seizures, cardiomyopathy, myocarditis, venous thromboembolism, sialorrhea, weight gain, metabolic syndrome, sedation, hypotension, and tachycardia. Constipation is a very common complication, occurring in 14% to 60% of patients,[7,8] which is reflected in increased laxative use when commencing clozapine.[9]

Less well recognized is clozapine's potential to impair motility throughout the gastrointestinal system, causing dysphagia, ileus, intestinal obstruction, bowel ischemia, and megacolon. This article focuses on this side-effect spectrum, which we term *clozapine-induced gastrointestinal hypomotility* (CIGH). We hypothesize that due to the many pathologic synonyms and related

terms, CIGH is not as readily distinguishable as hematologic (agranulocytosis) and cardiac (cardiomyopathy and myocarditis) adverse effects, leading to its underrecognition. Consequently, clinicians commonly regard constipation as a vexatious, but mild, complication.

We have collated reports of CIGH from multiple sources to indicate the extent and severity of this adverse event and to postulate risk factors. Although guidelines are available to minimize clozapine's adverse hematologic,[10,11] metabolic,[12] and cardiac effects,[13] existing guidelines do not emphasize the need to monitor for gastrointestinal side effects. We consider paying attention to gastrointestinal adverse effects to be equally important in reducing clozapine-associated mortality and morbidity, and we offer recommendations for managing CIGH and its sequelae.

METHOD

Our CIGH data comprise pharmacovigilance cases reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) and New Zealand's Intensive Medicines Monitoring Program (IMMP) and cases published in the international literature. The methodology for identifying and including cases from each source is described below.

Pharmacovigilance Data

The authors contacted the ADRAC and the IMMP, which receive reports from clinicians of suspected adverse drug reactions in Australia and New Zealand, respectively. We analyzed all clozapine case reports from ADRAC's Gastrointestinal System Organ Class and IMMP's Alimentary System Organ Class to identify cases of serious CIGH. The inclusion criteria were cases recorded in the database as "serious" or "life-threatening" constipation or constipation resulting in hospitalization, surgery, or a fatal outcome; fecal impaction; ileus; bowel obstruction; bowel ischemia; bowel necrosis; bowel perforation; or megacolon. From the ADRAC data, only cases categorized by pharmacovigilance staff on the database as "possible" or "probable" association with clozapine were included. For IMMP data, 2 authors assessed the clinical data for causality, and cases with confounding pathology (e.g., gastrointestinal neoplasms) were excluded from this analysis. Multiple reports of the same (or similar) adverse events for a single patient (identified by demographic data and clinical details) were treated as single cases to eliminate duplications.

Published Case Reports in the Literature

MEDLINE (1950–2007), EMBASE (1988–2007), and PsycINFO (1967–2007) databases were searched using the term *clozapine* together with each of the following: *gastrointestinal*, *dysmotility*, *constipation*, *obstipation*, *fecal impaction, fecaloma, paralytic ileus*, *adynamic ileus*, *subileus, ischemic colitis, colon ischemia, bowel ischemia, gastrointestinal ischemia, gut ischemia, obstruction, necrosis, gangrene, bowel perforation, micro-perforation, megacolon, toxic megacolon, acquired megacolon, pseudo-obstruction, Ogilvie,* and *Ogilvie's syndrome*. The reference lists of articles identified were then handsearched. Relevant foreign language articles were translated into English. Case reports in which a clozapine-treated patient was hospitalized or died from the complications listed above, and in which clozapine was implicated, were included for analysis.

Collated Data Analysis

The cases from the 3 different data sources were pooled. The data were analyzed under the following headings: age, gender, clozapine start date, symptom onset date, time on treatment with clozapine prior to onset of CIGH, clozapine dosage at onset of CIGH, concomitant medications, clinical details of presentation, outcome, and treatment.

All patients receiving clozapine must be entered into a registry. We contacted the operational Australian registries (operated by Hospira Australia Pty Ltd.—previously Mayne Pharma—and by Novartis) and the New Zealand registry (Novartis) to determine the numbers of patients exposed to clozapine in each country. These figures gave us a denominator in order to estimate prevalence.

RESULTS

Twenty-nine published case reports of CIGH were identified[7,14–31] (Table 1). Fifty-seven case reports from the ADRAC data met the criteria, the earliest of which occurred in July 1994. Seventeen reports to the IMMP met the criteria, the earliest of which was reported in January 1999. One case appeared in 2 data sets, giving a total of 102 cases for analysis.

Demographic Data

Sixty-eight patients (66.7%) were male, 31 were female (30.4%), and the gender of 3 patients was unknown. Age was reported for 96 patients, ranging from 17 to 73 years, with a median age of 42 years (SD = 13.2 years) (Figure 1).

Outcome

Twenty-eight patients died (27.5%), 42 recovered (41.2%), and in 32 cases (31.4%) the outcome was unknown or documented as "not yet recovered." Fifteen of the deaths occurred within Australasia, as identified from pharmacovigilance data.

Medications

The dose of clozapine was clear for 92 patients, with a range of 12 to 1000 mg/day, mean = 428 mg/day

Table 1. Published Case Reports of Serious Clozapine-Induced Gastrointestinal Hypomotility

Age, Sex	Medication and Dosage (per day)[a]	Medical and Psychiatric History	Clinical Presentation	Outcome
31, F[14]	Clozapine, 5 wk, 400 mg; heptaminol 2 g	Undifferentiated treatment-resistant schizophrenia	Presented with abdominal pain, severe vomiting + abdominal distension, fecaloma on rectal exam	Died; post mortem: massive colon distension (megacolon), early bowel wall necrosis
29, M[14]	Clozapine, 1 mo, 350 mg; tropatepine 20 mg; chlorazepate 100 mg	Treatment-resistant paranoid schizophrenia (7 y), no medical history	Constipation in 1st week leading to paraffin, lactulose + enemas; 1 mo leading to diarrhea, feculent vomiting; diagnosis: bowel obstruction, fecal impaction	Recovered with conservative therapy
50, M[14]	Clozapine, 6 mo, 600 mg; chlorazepate 150 mg; flunitrazepam 2 mg; mianserin 30 mg; alfuzosin 5 mg	Paranoid schizophrenia (20 y), previous appendectomy	Presented with abdominal pain, severe vomiting + abdominal distension; AXR: colon dilatation; diagnosis: bowel obstruction	Recovered after ileostomy
29, M[7]	Clozapine, 22 d, 400 mg, 36 d total treatment, no other meds	No details given	No details given	Died; aspiration of vomitus due to bowel obstruction of transverse colon
42, M[15]	Clozapine, 2 y, 450 mg; atenolol and ferrous sulphate discontinued prior to surgery; 3 × 1 mg dose of morphine	Hemicolectomy for Dukes c2, adenocarcinoma of cecum	Developed a late and prolonged postoperative ileus (day 6–13)	Recovered on day 13 after conservative treatment
49, M[16]	Clozapine, 2 y, 200 mg increased to 500 mg; salbutamol; beclomethasone; moclobemide; sodium valproate; budenoside	Paranoid schizophrenia, moderately obese	3 wk nausea, indigestion, chest pain, vomiting, constipation, abdominal tenderness; overflow diarrhea; 1 d shortness of breath	Died; post mortem: severe fecal impaction entire colon, pulmonary edema due to inhalation of feculent vomitus
36, M[17]	Clozapine, 4 mo, 600 mg; cisapride 15 mg; psyllium omeprazole 20 mg; docusate sodium 100 mg; benztropine 2 mg	Paranoid schizophrenia, chronic constipation, upper GI complaints	History of abdominal pain, nausea 1 d; collapse; rigid, tender, distended abdomen; hypotension, leukocytosis, acidosis	Died; post mortem: significant dilatation of entire colon and necrotizing colitis
51, M[18]	Clozapine, 2 mo, 275 mg/d at onset of symptoms, had been increased 25–50 mg/wk	Treatment-resistant schizophrenia (33 y), no significant medical history	Constipation, abdominal pain, tenderness, distension, vomiting; hypokalemia (2.8 mmol/L); AXR: bowel obstruction	Recovered with conservative treatment
35, F[18]	Clozapine, 4 mo, 500 mg; propanolol 20 mg	Treatment-resistant schizophrenia, history of peptic ulcer; total gastrectomy 10 y prior	1 wk abdominal pain, constipation; 1 d vomiting; abdomen tender + distended, hypokalemia; bowel sounds increased, empty rectum; AXR: bowel obstruction	Recovered, hospitalized more than a wk
49, M[19]	Clozapine, 6 wk, 400 mg; lorazepam	Paranoid schizophrenia, long history of constipation	Constipation worse with clozapine; acute onset severe abdominal pain; sepsis; diagnosis: colon perforation and fecal peritonitis	Survived; significant morbidity; hemicolectomy and colostomy; perioperative CVA
43, M[20]	Clozapine, 6 y, 750 mg; medroxyprogesterone acetate; sodium valproate 1200 mg; omeprazole 40 mg; psyllium 2 tsp	Paranoid schizophrenia (20 y), history of ulcerative esophagitis, syphilis, aberrant sexual behavior	Complained of vomiting, abdominal pain; omeprazole doubled; after 1 mo, increasing abdominal pain 1 d; feculent vomiting; acute abdomen + hypotension; fecal impaction with peritonitis	Died following colectomy; histology showed severe fecal impaction of entire abdomen, severe ischemic changes, toxic dilation
36, M[21]	Clozapine 500 mg; loperamide 6 mg stat dose	No medical illness	Acute gastroenteritis with abdominal cramps, diarrhea, vomiting; 111 people contacted B cereus/ B licheniformis poisoning; mild in most other cases	Died 16 h after symptoms developed; only patient who died; post mortem showed toxic megacolon
53, M[22]	Clozapine, 2 wk, dose not given (recent change from trifluoperazine and boldolaxine); cyproheptadine; procyclidine	Chronic schizophrenia, history of megacolon and chronic constipation	2 wk abdominal pain, nausea, abdominal distension, constipation; tender abdomen; hypotension, tachycardia; pseudo-obstruction + perforation	Recovered after subtotal colectomy, ileostomy
53, M[23]	Clozapine, 51 d, 500 mg (plasma level 1757 nmol/L); pirenzipine 50 mg; paraffin; biperidine 4 mg; doxepin 30 mg; lorazepam 2.5 mg; flunitrazepam 0.5 mg; bisoprolol; glimepiride	Diabetes mellitus II, gastritis, reflux esophagitis	Complained of constipation 10 d after starting clozapine; at 51 d developed abdominal pain, nausea; distended, soft abdomen; collapsed the next day	Died; Mallory Weiss tear with aspiration; paralytic ileus; massive distension of small and large bowel

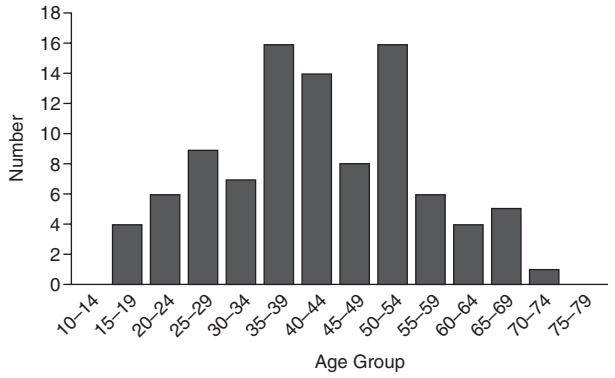
(continued)

Table 1 (continued). Published Case Reports of Serious Clozapine-Induced Gastrointestinal Hypomotility

Age, Sex	Medication and Dosage (per day)[a]	Medical and Psychiatric History	Clinical Presentation	Outcome
41, F[24]	Clozapine, 14 mo, 600 mg	Not specified	Diagnosis: Ogilvie syndrome (pseudo-obstruction)	Died of ileus and obstruction; no further details provided
19, M[25]	Clozapine, 9 d, 200 mg; laudanam (morphine equiv 64 mg); valpromide 300 mg od	Schizophrenia, disorganized type; delayed puberty, no GI history	Acute abdominal pain, constipation, fever, septic shock, hypotension; fecaloma; increased CK, renal failure, leukocytosis; necrotizing colitis; no viral or bacterial cause	Recovered after hemicolectomy and partial ileectomy
39, F[26]	Clozapine, duration of treatment and dose unknown; topiramate; ranitidine; benztropine; sertraline; oxcarbazepine; frusemide; hydroxyzine; diphenhydramine; trazodone	Paranoid schizophrenia, depression, hypothyroidism, hypertension, chronic constipation	Developed enterotoxigenic C perfingens Type A infection (usually a mild gastroenteritis); acute diarrhea, nausea, vomiting	Died 17 h after developing symptoms; one other patient died (prescribed olanzapine, benztropine, oxybutynin); post mortem: necrotic transverse colon
20, M[27]	Clozapine, 1 y, 900 mg; amisulpiride 800 mg	Treatment-resistant schizophrenia	Constipation 2 d, severe abdominal pain 1 d, collapse	Died before reaching hospital; post mortem: impacted feces, bowel ischemia, infarction
30, M[28]	Clozapine 600 mg (recently increased from 450 mg); sertraline	History of partial small bowel resection for Meckel's 3 mo prior to presentation	1 d abdominal distension with belching, flatus; moderately unwell; no vomiting; Diagnosis: paralytic ileus	Recovered; paralytic ileus resolved with reduction of clozapine to 450 mg
62, M[29]	Clozapine 100 mg; olanzapine 30 mg; clonazepam 1 mg; risperidone 8 mg (37.5 mg depot 4/7 prior to symptoms); theophylline 300 mg; potassium chlorate 1000 mg; frusemide 40 mg; vinpocetine 30 mg; amoxicillin/clavulanate combination 3600 mg	Residual schizophrenia, history of chronic obstructive respiratory disease, hypertonia, erysipelas	Vomiting with marked distension, small bowel obstruction	Recovered after laparotomy; 6 d in ICU, 4 d ventilated
73, F[30]	Clozapine, 15 y, 700 mg; plasma levels 590 µg/L	Paranoid schizophrenia, viral gastroenteritis	Developed gastroenteritis with mild fever; clozapine levels increased; clozapine stopped; days later leading to ileus needing surgery	Died of post operative complications
61, M[30]	Clozapine 500 mg; plasma levels 230 µg/L; lithium carbonate 600 mg; sodium valproate 1500 mg	Bipolar disorder (2 y), Korsakoff syndrome, viral gastroenteritis (acute)	Gastroenteritis, mild pyrexia; WCC normal; clozapine levels increased leading to ileus	Recovered with conservative treatment
47, M[30]	Clozapine, "recent years," 200–350 mg; plasma levels 920 µg/L; clomipramine 100 mg	Paranoid schizophrenia, influenza (acute)	Influenza type illness; clozapine levels increased; fever 39.5°C leading to paralytic ileus	Recovered
67, F[30]	Clozapine, 10 y, 600 mg; plasma levels 646 µg/L	Undifferentiated schizophrenia	High fever (39.9°C), clozapine levels increased; pneumonia; paralytic ileus	Recovered; eventual ileostomy after 10 d conservative treatment failed
55, M[30]	Clozapine, 15 y, 600 mg; plasma levels 495 µg/L; sodium valproate 500 mg	Paranoid schizophrenia (30 y)	1 d history of fever (38°C), hospitalized, severe abdominal pain, pneumonia; paralytic ileus	Recovered; ileus resolved with conservative treatment, then reoccurred 1 wk later; clozapine reduced in dose
35, M[31]	Clozapine, 12 d titration up to 150mg; chlorpromazine X-taper; chlorpromazine stopped 2 days before onset of symptoms	Paranoid schizophrenia (6 y), mild intellectual impairment	Acute onset abdominal cramps, abdominal distension, dyspnoea, drowsiness, tender abdomen, decreased bowel sounds; diagnosis: fecal impaction with aspiration	Recovered; intubated and ventilated for 9 days in intensive care
43, M[31]	Clozapine, > 10 years, increase 400–700 mg 4 mo before death	Disorganized schizophrenia (20 y), no medical history	Food refusal, tender + distended abdomen; diagnosis: bowel obstruction secondary to fecal impaction	Died during surgery; histology showed distended and ischemic colon
23, M[31]	Clozapine started, increased to 400 mg in 1 wk	Schizophrenia, moderate mental retardation	3 wk vomiting and food refusal, 3 d abdominal cramps, constipation, vomiting, peritonitis, increased bowel sounds; AXR: fecal impaction	Died from bowel perforation; no post mortem
56, M[31]	Clozapine, 15 y, 400 mg; phenytoin 300 mg; enalapril 5 mg	Schizophrenia, chronic constipation, hypertension, clozapine-related seizures	Complained of constipation, diarrhea, abdominal pain; AXR: fecal impaction	Died from bowel obstruction; no post mortem, speculation of malignancy

[a]The duration of clozapine treatment prior to the onset of gastrointestinal complications is stated when this information was provided in the case report.
Abbreviations: AXR = abdominal x-ray, CK = creatine kinase, CVA = cerebral vascular accident, GI = gastrointestinal, WCC = white cell count.

Figure 1. Age of Patients With Clozapine-Induced Gastrointestinal Hypomotility



(SD = 208 mg/day). Doses were higher among those who died (range, 250–900 mg/day; mean = 535 mg/day; SD = 179 mg/day). Eighty cases (78.4%) reported the duration of clozapine treatment until onset of symptoms, with varying specificity (days, months, or years). The pre-onset treatment duration ranged from 3 days to 15 years. Twenty percent of patients developed serious CIGH within the first month of treatment, 36.3% within the first 4 months, and just over 50% of cases occurred within the first year of treatment.

Forty patients (39.2%) received clozapine alone. Twenty-one patients (20.6%) were prescribed concomitant anticholinergic medication (anticholinergics such as benztropine, or other medication with clinically significant anticholinergic adverse effects, such as chlorpromazine or oxybutynin). Of the remainder, 14 patients were prescribed other medications that can cause constipation. Only 12 patients were prescribed laxatives: the osmotic laxative, lactulose, in 8 cases; bulking agents in 4 cases; and a stimulant laxative (senna) in 1 case. Sodium valproate was the most frequently co-prescribed medication (18 instances), followed by omeprazole (10 instances).

Presenting Symptoms

Twenty-two of the 29 case reports included a comprehensive account of the clinical presentation. The frequency of presenting signs and symptoms in these cases is shown in Table 2. The onset of symptoms occurred between 4 weeks and 6 hours before development of CIGH complications.

Estimate of Prevalence

Between 1988 and February 2007, a total of 5216 people were exposed to clozapine in New Zealand (A. E. C. Cutten, Ph.D., Novartis New Zealand Ltd., written communication, June 2007). Our data suggest that at least 17 of these patients developed CIGH. From January 1992 to June 2007, a total of 20,167 Australian patients were exposed to clozapine, with 17,322 starting Clozaril (A. E. C. Cutten, Ph.D., Novartis New Zealand Ltd. following communication with Novartis Pharmaceuticals Ltd. Australia, written communication, June 2007) and 2845 starting Clopine (S. A. Wright, B.Sc., Clopine Services, Hospira Australia Pty. Ltd., written communication, July 2007). Our data suggest that at least 57 developed CIGH. Although there are limitations in such estimates (see Discussion), these data suggest a prevalence of potentially life-threatening CIGH in Australia and New Zealand at around 3 cases per 1000 patients exposed to clozapine.

Table 2. Frequency of Clinical Findings Reported in 22 Cases With Comprehensive Medical Histories

Clinical Finding	No. of Cases	Frequency, %
Abdominal pain	16	73
Abdominal distension	12	55
Vomiting	12	55
Constipation	10	45
Diarrhea	7	32
Nausea	5	23
Septic shock (tachycardia, hypotension)	7	32

DISCUSSION

In this article we have documented the largest case series to date of serious gastrointestinal hypomotility events reported with clozapine. The diversity in age, sex, dose, and duration of treatment in the 102 patients suggests that clozapine-prescribed patients may be at risk of CIGH, regardless of these factors. The age and sex distribution probably reflects the demographics of the treatment population. Approximately two thirds of Australian clozapine-treated patients are male with a median age of 37 years. [32]

Possible Risk Factors

The results suggest that higher doses of clozapine may pose a greater risk, with mean clozapine doses of 428 mg/day overall in this series and 535 mg/day in fatal cases, exceeding a mean population dose of 369 mg/day in a large New Zealand epidemiologic study[33] ($p > .01$ and $p > .0001$, respectively).

The risk of constipation with clozapine is dose dependent,[34] but clozapine plasma levels may reflect serum antimuscarinic activity more accurately than the dose does.[35] Co-prescription of other anticholinergic medication is likely to increase the risk. Concomitant medical illness and fever may inhibit metabolism of clozapine, increasing the serum level and risk of adverse effects. Kok et al.[30] describe 5 cases of illness and pyrexia with acutely increased clozapine plasma levels and subsequent paralytic ileus. Concomitant administration of cytochrome P450 enzyme inhibitors may also increase clozapine plasma levels. Ferslew et al.[36] report a fatal drug interaction with treatment doses of clozapine (500 mg) and

fluoxetine (40 mg). The autopsy showed paralytic ileus and visceral and pulmonary edema, with a plasma clozapine concentration of 4900 μg/L.

The first 4 months of treatment may be a particularly vulnerable time, with 36.3% of cases occurring in this period.

We speculate that illness and clozapine-related factors, such as obesity, low fiber diets, poor bowel habit and dehydration from reduced fluid intake, hypersalivation, and diaphoresis, may predispose patients to constipation and its more severe sequelae. It has been suggested that long-term treatment with high-dose antipsychotics may predispose a patient to CIGH.[7] Other possible risk factors include a history of bowel surgery, constipation, or gastrointestinal pathology. An increased risk of postoperative ileus in patients with schizophrenia is noted in the anesthetic literature.[37,38]

Mortality

In this case series there were 28 fatal outcomes. The high mortality rate is almost certainly a reporting artifact, as clinicians will be more inclined to report deaths than nonfatal outcomes. The large number of deaths may also indicate difficult or delayed diagnosis or rapid decompensation. Late presentation may relate to the reduced pain sensitivity purported in patients with schizophrenia,[39–42] difficulty in expressing pain,[43] or the co-prescription of medications such as antidepressants or other neuroleptics and anticonvulsants, which may have sedative and pain modulating effects.[31] Clozapine's antiserotonergic properties may result in reduced intestinal nociception (see Pharmacologic Mechanisms below) contributing to a disparity between physical symptoms and severity of illness, and thus diagnostic delay.

Literature Review

The association between clozapine and gastrointestinal hypomotility has been recognized by other authors. In 1999, the United Kingdom Medicines and Healthcare products Regulatory Agency noted 17 cases of suspected clozapine-related gastrointestinal obstruction[44] reported in 1997/1998, three of which had fatal outcomes. The large Arzneimittelsicherheit in der Psychiatrie drug safety program found gastrointestinal side effects were more common for clozapine than all other antipsychotics combined. Of the 21 patients prescribed antipsychotics who developed subileus or ileus, 12 were taking clozapine.[23] In a French study of 170 patients prescribed clozapine, treatment was stopped in 2.4% because of severe constipation, and in a further 2.4% because of subileus.[24] One patient died from intestinal obstruction. In 7921 Chinese patients prescribed clozapine,[45] 8 developed paralytic intestinal obstruction. Another Chinese article documented 10 cases of antipsychotic related intestinal obstruction, with clozapine implicated in 9 cases and perphenazine in 1 case.[46]

Prevalence

The New Zealand clozapine data sheet[47] lists intestinal obstruction/ileus/fecal impaction as a "very rare" side effect, which equates to a rate of less than 1 per 10,000 patients or "isolated case reports." This study suggests a prevalence of around 3 cases per 1000 patients exposed to clozapine.

A limitation of this article is that prevalence is estimated using pharmacovigilance data. Such data rely on voluntary reporting, and demonstrate association, but cannot prove causation. Pharmacovigilance data do not capture all cases. Kok et al.[30] note that none of the 4 patients they identified retrospectively with clozapine-related paralytic ileus had been reported as having a suspected drug reaction. There is at least 1 relevant death in Australia that does not appear in the ADRAC database.[48]

Prevalence calculations from pharmacoepidemiologic data are compromised by difficulties in determining accurate numerators and denominators. In this article the denominator comprises the total number of patients exposed to clozapine since it became available on the market (in 1992 in Australia and 1988 in New Zealand). However, cases of CIGH do not appear in the databases until 1994 and 1999, respectively, and it may be that cases were not reported prior to these dates, understating the prevalence. Nonetheless, our estimate of around 3 per 1000 patients suggests that serious CIGH is significantly more common than reported in the data sheet. We are not aware of any study that accurately estimates the incidence of CIGH.

Pharmacologic Mechanism of Clozapine-Induced Gastrointestinal Hypomotility

The pharmacology of clozapine differs from other antipsychotics in its relatively high affinity for dopamine D_1 and D_4 versus D_2 receptors alongside a powerful degree of serotonin type 2 (5-HT_2) antagonism. It also antagonizes a variety of muscarinic, histaminic, and α-adrenergic (α_1 and α_2) receptors and acts at other 5-HT sites.

The anticholinergic hypothesis of CIGH. Gastrointestinal hypomotility caused by antipsychotics is generally considered to be a consequence of their anticholinergic activity.[49,50] This view is supported by reports of gastrointestinal hypomotility with other psychotropic medications with anticholinergic properties.[49–54] Acetylcholine is the primary excitatory neurotransmitter in the enteric nervous system. It stimulates muscarinic receptors on intestinal smooth muscle cells and adjacent Cajal cells, a fundamental component of the pacemaker apparatus of the gastrointestinal tract.[55] Clozapine is sufficiently anticholinergic to induce an atropine-like poisoning on overdose.[56] By antagonizing acetylcholine, clozapine may disrupt autonomic mediation of the intestine and inhibit intestinal smooth muscle contraction, delay intestinal transit, and cause functional bowel obstruction. However, this effect alone does not account for the higher prevalence of

gastrointestinal hypomotility with clozapine than with other equally anticholinergic agents. In one study, clozapine induced constipation 3 times as frequently as chlorpromazine,[57] while in a large European study, clozapine was associated with more cases of ileus than all other antipsychotics combined.[58]

An antiserotonergic component. Clozapine's greater potential for gastrointestinal adverse effects compared with other anticholinergic agents may reflect its potent antiserotonergic properties. Serotonin plays a complex and crucial role in the normal motor and secretory function of the gut. Clozapine antagonizes 5-HT_2, 5-HT_3, 5-HT_6, and 5-HT_7 receptors.[59] There has been increasing interest in the role of 5-HT_2 in modulating visceral sensation,[60] while 5-HT_7 receptors are involved in mediating relaxation in gastrointestinal smooth muscle.[61] Clozapine's potent 5-HT_3 antagonism may be particularly relevant, with gastrointestinal effects of 5-HT_3 receptor antagonism including slower colon transit, reduced gastrocolic reflexes, increased colonic compliance,[62,63] and possibly reduced intestinal sensitivity to distension.[64–66] Parallels may be drawn between clozapine and 5-HT_3 antagonists, such as alosetron and cilansetron, which are prescribed to reduce gastrointestinal motility in diarrhea-predominant irritable bowel syndrome. Twenty-five to thirty percent of alosetron-prescribed patients develop constipation,[67] and obstruction, perforation, impaction, toxic megacolon, ischemia, and death have also been reported.[68] Safety concerns (ischemic colitis affecting between 1/700 and 1/1000 patients receiving the drug)[69] prompted the voluntary withdrawal of alosetron from the market in November 2000, but it was reintroduced in 2002 with stringent safety regulations.[70] Ironically, although alosetron has been investigated for antipsychotic properties,[71] the gastrointestinal implications of 5-HT_3 antagonism by clozapine have not yet been explored.

Pathophysiology

Clozapine can affect the entire digestive system, causing esophageal to rectal hypomotility. Clozapine-related dysphagia,[72] delayed gastric emptying, and gastric outlet obstruction,[73] as well as small and large bowel pathology, have been reported.

There appear to be 3 main mechanisms whereby CIGH can have a fatal outcome:

1. Untreated bowel obstruction/pseudo-obstruction leading to distension, necrosis, perforation, or sepsis. A large impacted stool bolus can cause increased intraluminal pressure proximal to the impaction, reducing perfusion and causing ischemia.[74] The viability of colonic mucosal tissue is particularly vulnerable to intraluminal distension.[75] Colonic distension may result in perforation, especially if the bowel diameter exceeds 12 cm. The mortality rate for pseudo-obstruction may be as high as 50% if it progresses to ischemic necrosis and perforation.[76]
2. Aspiration from inhalation of feculent vomitus or dysphagia.
3. Fecal stasis leading to infection. CIGH with dilatation may render the bowel more susceptible to microbacterial proliferation,[17] leading to serosal invasion by pathogens such as Clostridium perfringens. Fecal impaction may prevent expulsion of enterotoxins via the normal protective mechanism of diarrhea, prolonging exposure and causing tissue damage.[26] This could account for fatal outcomes in clozapine-treated patients with gastroenteritis, while in others the course was benign.[21,25,26]

There have also been cases of pseudomembranous colitis,[77] eosinophilic colitis,[78,79] and cytomegalovirus[80] in clozapine-prescribed patients.

RECOMMENDATIONS FOR THE PREVENTION AND MANAGEMENT OF CIGH-RELATED CONSTIPATION

No clinical studies have been published examining the treatment of CIGH. Hayes and Gibler[7] reported preliminary positive findings from the instigation of a bowel protocol at the Atascadero State Hospital in California. There is a clear need for further research in this area.

After review of the literature and in lieu of specific evidence relating to the treatment of CIGH, the following preliminary pragmatic recommendations have been formulated pending empirical studies.

Prevention

A gastrointestinal history and abdominal examination is recommended in all patients prior to starting clozapine. If there is preexisting constipation, it should be adequately treated before starting clozapine. Patients should be warned about the risks of constipation and provided with information regarding diet, fluid intake, and exercise. Input from a dietician may be useful. A meta-analysis showed that increasing dietary fiber to approximately 20 g per day increased stool weight and decreased gut transit time[81]; however, a high fiber diet may be ineffective in patients with gastrointestinal hypomotility.[82] If fiber intake is increased, adequate fluid intake (1–2 liters/day) is essential to avoid intestinal obstruction. Bulk laxatives and high fiber diets are contraindicated in patients with obstructive symptoms, megacolon, or megarectum.

When possible, clinicians should avoid prescribing concomitant constipating medications (e.g., opiates), particularly medication with anticholinergic properties (e.g., anticholinergics such as benztropine, tricyclic

antidepressants, mydriatics, antispasmodics, and antihistamines). Although anticholinergics are frequently prescribed to combat clozapine-induced hypersalivation, there are few randomized control trials to support this practice,[83] and the risks may outweigh the benefits.

Screening

Regular enquiry into bowel habit is indicated. Weekly screening may be warranted during the first 4 months of treatment as this seems to be a higher-risk period. It is difficult to define normal bowel habit, which varies considerably among individuals, and antipsychotic-prescribed patients may have longstanding dysmotility problems, but particular attention should be paid to a change in habit. Adapting questions from the Rome criteria,[84] used to assist in diagnosing chronic constipation, may be useful:

Does the patient experience
1. Fewer than 3 bowel motions a week?
2. At least 1 of the following:
   - Straining at defecation at least 25% of the time?
   - Lumpy and/or hard stools at least 25% of the time?
   - A sensation of incomplete bowel evacuation at least 25% of the time?

Colorectal cancer should be excluded in all patients older than 45 years who report a change in bowel habit.

Particular caution should be taken when the patient develops a febrile illness, as this seems to be a risk for increased clozapine levels and gastrointestinal dysmotility.[30]

Management

If a patient acknowledges constipation, abdominal examination and timely treatment is warranted. A plain abdominal x-ray may help. Early liaison with gastroenterology is recommended.

Selecting a laxative. Good quality evidence regarding the effectiveness of laxatives in the general population is limited.[85] In the treatment of another pharmacologically related hypomotility disorder, opioid-induced constipation, some experts believe that both a stimulant and stool softener are required, for example, senna and docusate.[86] Fiber is not recommended in opioid-induced constipation.

The prokinetic agent tegaserod is a 5-HT_4 receptor agonist sometimes used for the treatment of chronic constipation. It could potentially have a role in CIGH. There is good evidence for polyethylene glycol and tegaserod in the treatment of constipation.[87]

Recommendation. A stimulant and softening laxative, such as senna with docusate, 2 to 4 tablets per day titrated to need, may be most helpful as a first-line treatment in CIGH, with regular review for side effects. Consideration of a cholinergic agent such as bethanecol or donepezil has been suggested,[7] although there is no specific evidence as to effectiveness. Stimulants should be avoided if intestinal obstruction has already developed, which necessitates immediate medical referral (see Life-Threatening CIGH below).

Life-threatening CIGH. In the cases reviewed in this article, the most consistently reported signs and symptoms heralding serious pathology were moderate to severe abdominal pain, abdominal distension, and vomiting. Other signs and symptoms included constipation; paradoxical "overflow" diarrhea, whereby liquid stool leaks around impacted feces; reduced appetite; nausea; and septic shock. Emergence of these symptoms in a clozapine-treated patient warrants urgent medical referral and treatment.

Clozapine treatment should be withheld, at least temporarily. Physicians may consider using acetylcholinesterase inhibitors that accelerate gastrointestinal transit time by enhancing the contractile effects of acetylcholine at synaptic and neuromuscular junctions. Neostigmine and physostigmine have been used off-label with good results for some gastrointestinal disorders, especially those associated with acute colonic pseudo-obstruction.[88,89] If the underlying pathology is fecal impaction/bowel obstruction, then enemas (such as saline, mineral oil, or diatrizoate) or digital disimpaction may be considered. Massively dilated bowel, impending perforation, and/or ischemia are indications for surgical intervention.

CONCLUSION

Gastrointestinal hypomotility is a serious side effect of clozapine that may result in bowel obstruction, ischemia and necrosis, perforation, or aspiration pneumonia. The paucity of literature on CIGH suggests that the significance of this uncommon but important and frequently fatal side effect has not been recognized, and currently there is significant morbidity and mortality. Vigilance is needed to prevent, recognize, and treat this life-threatening side effect.

The mechanism is likely to be anticholinergic and antiserotonergic. High clozapine doses and/or concomitant treatment with anticholinergic or other constipating medications may contribute. Clozapine should be used with care, with minimization of polypharmacy, regular physical monitoring, regular laxatives, and early referral of constipated patients—before abdominal signs and symptoms develop.

There is a clear need for further research into this area, particularly with regard to the prevalence, mechanism, and treatment of CIGH. We encourage reporting of clozapine-induced gastrointestinal hypomotility to national pharmacovigilance centers to increase the limited knowledge base.

Drug names: alfuzosin (Uroxatral), alosetron (Lotronex), amoxicillin/clavulanate combination (Augmentin), atenolol (Tenormin and others), beclomethasone (Qvar and Beconase), benztropine (Cogentin and others), bisoprolol (Zebeta and others), chlorpromazine (Thorazine, Sonazine, and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), diatrizoate (Reno, Cystografin, and others), diphenhydramine (Benadryl and others), donepezil (Aricept), doxepin (Sinequan, Zonalon, and others), enalapril (Vasotec and others), fluoxetine (Prozac and others), glimepiride (Amaryl and others), hydroxyzine (Vistaril and others), lactulose (Constilac, Laxilose, and others), lithium (Eskalith, Lithobid, and others), loperamide (Imodium and others), lorazepam (Ativan and others), medroxyprogesterone (Provera and others), morphine (Kadian, Avinza, and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), oxcarbazepine (Trileptal and others), oxybutynin (Oxytrol, Ditropan, and others), phenytoin (Dilantin, Phenytek, and others), polyethylene glycol (Glycolax and others), procyclidine (Kemadrin), ranitidine (Zantac and others), risperidone (Risperdal), sertraline (Zoloft and others), theophylline (Theochron, Uniphyl, and others), topiramate (Topamax), trifluoperazine (Stelazine and others), valproate sodium (Depacon and others).

Acknowledgments: The authors are grateful to the Adverse Drug Reactions Advisory Committee and to the Intensive Medicines Monitoring Programme for their services in pharmacovigilance and for supplying some of the raw data. Thanks also to Jeremy Skipworth, M.B.Ch.B., M.Med.Sci. (Hon.), F.R.A.N.Z.C.P., New Zealand Deputy Director of Mental Health, for his helpful comments in the preparation of the manuscript; to Sam Islam, M.B.B.S., F.R.A.C.P., Senior Lecturer of Medicine and Consultant Gastroenterologist, Wellington Hospital, for his specialist contribution; and to René de Monchy, M.D., F.R.A.N.Z.C.P., Consultant Psychiatrist, Lower Hutt, for assistance with translation. Thank you also to David W. J. Clark, Ph.D., F.P.S., Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago, Dunedin, for providing pharmacologic expertise in the preparation of this article. Drs. Skipworth, Islam, de Monchy, and Clark report no financial affiliations or other relationships relevant to the subject of this article.

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