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Research Paper

Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study

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ABSTRACT

Background: Gastrointestinal side effects are particularly common with clozapine and occur with other antipsychotics, ranging from mild constipation to fatal bowel obstruction and/or ischemia. While this adverse-effect spectrum has been attributed to 'gastrointestinal hypomotility', gastrointestinal transit times in antipsychotic-treated patients have not previously been measured, making this mechanism speculative.
Methods: Using standardized radiopaque marker ('Metcalf') methods we established colonic transit times of antipsychotic-treated psychiatric inpatients and compared them with population normative values. We analyzed results by antipsychotic type, antipsychotic dose equivalent, anticholinergic load, duration of treatment, gender, ethnicity, and age.
Outcomes: For patients not prescribed clozapine, median colonic transit time was 23 h. For patients prescribed clozapine, median transit time was 104.5 h, over four times longer than those on other antipsychotics or normative values ($p < 0.0001$). Eighty percent of clozapine-treated patients had colonic hypomotility, compared with none of those prescribed other antipsychotics (olanzapine, risperidone, paliperidone aripiprazole, zuclopenthixol or haloperidol). In the clozapine group, right colon, left colon and rectosigmoid transit times were all markedly abnormal suggesting pan-colonic pathology. Hypomotility occurred irrespective of gender, age, ethnicity, or length of clozapine treatment. Transit times were positively correlated with clozapine plasma level (rho = 0.451, $p = 0.045$), but not with duration of treatment, total antipsychotic load or demographic factors.
Interpretation: Clozapine, unlike the other antipsychotics examined, causes marked gastrointestinal hypomotility, as previously hypothesized. Pre-emptive laxative treatment is recommended when starting clozapine.

1. Background

Gastrointestinal side effects are common with antipsychotics, particularly clozapine, ranging in severity from mild constipation to fatal bowel obstruction and/or ischemia. Constipation is reported in up to 60% of clozapine-treated patients (Hayes and Gibler, 1995) and up to 50% of those receiving other antipsychotics (Ozbilen and Adams, 2009) and is reflected in the high utilization of laxative in clozapine-treated patients (Bailey et al., 2015). The mechanism is considered to be anticholinergic inhibition of gastrointestinal smooth muscle contraction and peristalsis (Ozbilen and Adams, 2009), but serotonin receptor antagonism likely compounds the problem (Palmer et al., 2008), with serotonin playing a crucial role in regulating gastrointestinal motility (Crowell, 2001). Symptoms of slow transit may include low stool frequency, lack of urge to defecate, abdominal distension, bloating, and abdominal discomfort (Foxx-Orenstein et al., 2008).

A systematic search of AMED, BIOSIS, CINAHL, EMBASE, MEDLINE, PsycINFO and PubMed databases with no language restrictions from inception to August 2015 revealed 61 case reports, five large case series and one cohort study on the serious or life-threatening clozapine-induced gastrointestinal effects.[1] For every 1000 patients treated with

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[1] Search terms were: anti-psychotics, keyword search anti-psychotic* or antipsychotic*, 'clozapine' (clozapine.mp OR clozapine/) together with any of the following MESH terms: constipation; intestinal obstruction; gastrointestinal motility; radiopharmaceuticals; digestive system diseases (MEDLINE); digestive system disease (EMBASE); digestive symptoms disorders (psycINFO); and related keywords (e.g. bowel; gastric; intestinal; colon*; digestive; gastrointestinal; or radiopaque and marker*).

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clozapine, between 300 and 600 will develop constipation and four will develop serious gastrointestinal complications (including ileus, bowel obstruction, bowel ischemia and necrosis) from which one will die. Pharmacovigilance data shows that amongst antipsychotics, clozapine has the highest constipation-related mortality. Seventy such deaths were reported in the USA between 1997 and 2009, with a mortality rate three times that of clozapine-induced agranulocytosis (De Hert et al., 2011). A large prospective cohort study showed treatment with clozapine conferred the greatest risk of fatal ileus compared with other psychoactive medication (OR: 6.73; 95% CI 1.55–29.17) (Nielsen and Meyer, 2012).

While these complications have been described as arising from 'gastrointestinal hypomotility' (Palmer et al., 2008; Flanagan and Ball, 2011; Nguyen et al., 2014), gastrointestinal transit times in antipsychotic-treated patients have not been measured previously. There is consensus that clozapine's effect on gastrointestinal function is important, but poorly understood and under-researched.

2. Objectives

This study sought to ascertain:

- How does colonic transit time (CTT) in antipsychotic-treated inpatients, measured by radiopaque markers (ROMs), compare with standardized normative values?
- Does CTT differ significantly between people treated with clozapine and treated with other antipsychotics?
- Are other independent variables (including gender, age, ethnicity, constipation symptoms, antipsychotic load or estimated anticholinergic activity) related to CTT?

3. Research Design and Methods

Methods were pre-specified in the protocol (Every-Palmer et al., 2013 available at http://hdl.handle.net/10523/6070).

3.1. Participants

Participants were inpatients in a New Zealand general and forensic rehabilitation service. They all received similar diets (hospital meals) and had similar lifestyles. Recruitment occurred between April 2014 and April 2015.

A-priori power analysis was not conducted given the absence of earlier investigations.

Eligible participants were adults (over 18) prescribed antipsychotics for at least three months and competent to provide informed consent. Patients prescribed laxatives with a past history of significant gastrointestinal complications (such as fecal impaction) were excluded because withholding laxatives (as required for CTT testing) could expose them to risk.

This study was approved by the New Zealand Health and Disability Ethics Committee (reference 13/CEN/153).

3.2. Measuring Colonic Motility

CTT can be measured using radiopaque markers (ROMs), scintigraphy or wireless motility capsules. These methods are summarized in Table 1.

The conventional, cheapest and most practical way of measuring CTT is with ROMs. This method, used for over 40 years, is the reference standard in clinical practice (Szarka and Camilleri, 2012) and widely employed in research (Rao et al., 2011). Intra- and inter-observer reliability are high (Pomerri et al., 2007), with good correlation ($r = 0.7$, $p < 0.001$) between ROM and wireless motility capsule measurements of CTT in constipated patients (Rao et al., 2009).

Two main ROM methods have developed: a single ROM-bolus technique; and the more sensitive multiple ROM-bolus ('Metcalf') technique used in this study (Kim and Rhee, 2012). This latter technique involves ingesting a capsule containing 24 standardized ROMs on three consecutive days with abdominal X-rays on day four and, if necessary, day seven, quantifying elimination (Metcalf et al., 1987). This method minimizes radiation exposure, is reliable, reproducible (Pomerri et al., 2007; Bouchoucha et al., 1992) and well correlated with stool form in constipated adults (Saad et al., 2010).

Normative data are available for CTT from numerous ROM studies across different countries (see Table 2). Although none are from New Zealand, ethnic differences are not marked. Meta-analysis of relevant international normative data (see Table 1) gives a population mean CTT of 28.79 h with SD of 18.07 h ($n =$ 304 healthy controls). A CTT 2SD above the population mean (i.e. >64.9) was pre-specified as a positive test for colonic hypomotility, as by convention.

Any prescribed laxatives were temporarily withheld from two days prior to ROM testing and during the study. Rescue laxatives were available if participants required them (none did).

On three consecutive days ($t = 0$ h, $t = 24$ h, $t = 48$ h) participants swallowed a dissolvable gelatin capsule (SITZMARKS®, Konsyl Pharmaceuticals Inc.) containing 24 polychlorinated vinyl markers impregnated with 33% barium sulfate (4.5 × 1.0 mm). Each day's capsule contained different shaped markers (Fig. 1).

On day four participants were screened for constipation, firstly by being asked if they considered themselves constipated ('self-reported constipation'), which was intended to mirror normal clinical practice, and secondly by completing a researcher-assisted questionnaire incorporating all Rome III constipation symptoms (Table 3) (Longstreth et al., 2006), available on request from the authors.

At $t = 72$ h, abdominal X-rays determined ROM location and the extent of elimination. If over two-thirds (>48) of ROMs remained, X-rays were repeated at $t = 144$ h. X-rays were read independently on an InteleViewer PACS system by SEP and MN. MN was blinded to independent variables. Vertebral spinous processes demarcated right and left sides of the colon. The rectosigmoid was defined by oblique lines between the fifth lumbar vertebra spinous process and the femoral head. Images were magnified and examined regionally and black-white inversion was applied to increase marker conspicuity.

Table 1
Summary of CTT measurement techniques.

	Radiopaque markers	Scintigraphy	Wireless motility capsule
Radiation exposure	Yes (X-ray) 0.5–0.7 millisieverts (Wall and Hart, 1997)	Yes (radiolabeled meal) 2.67 millisieverts (Graff et al., 2001)	No
Assesses gastric emptying	No	Yes	Yes
Assesses small bowel transit	No	Yes	Yes
Provides segmental colonic transit times	Yes	No	No
Test location	X-ray in local radiology department	Nuclear medicine department	Ambulatory
Cost	Inexpensive (approximately $100)	Moderately expensive (approximately $800)	Expensive (over $1000)