RESEARCH PROTOCOL

Comparing gastrointestinal motility in clozapine-treated patients before and after laxative treatment

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Summary

The proposed study is a pre and post treatment study to determine whether commonly used laxative-treatment for clozapine-treated psychiatric inpatients affects gastrointestinal motility (as measured by radiopaque marker (ROM) transit studies). This is a follow up study to the 'Colonic transit studies to measure gastrointestinal motility in antipsychotic-treated patients' study described in a previously published research protocol (Every-Palmer et al 2013, available at: http://hdl.handle.net/10523/6070)

1: RESEARCH QUESTION AND BACKGROUND

Research Questions

The objective is to determine in a naturalistic setting whether commonly used laxative-treatment for clozapine-treated psychiatric inpatients affects gastrointestinal motility when measured objectively by radiopaque marker transit studies.

We will re-measure the gastrointestinal transit times of clozapine-treated participants from our first radiopaque marker transit study after they have received at least two months treatment with docusate & senna and/or macrogol 3350 (prescribed according to the Porirua Protocol, see below) and will compare pre and post laxative transit times.

Background

Clozapine is an effective agent in the treatment of otherwise treatment-resistant schizophrenia, but its adverse effect profile is considerable. Gastrointestinal hypomotility is one commonly reported and potentially serious adverse effect. The exact mechanism by which clozapine alters colonic functioning have yet to be elucidated. This is usually considered to be anticholinergic inhibition of gastrointestinal smooth muscle contraction and peristalsis (e.g. [1], [2]), but it is likely that clozapine's antagonism of various serotonin receptor subtypes compounds the problem [3] as serotonin plays a crucial role in gastrointestinal motility [4].

It has been hypothesised that clozapine use results in increased gastrointestinal transit time – clozapine induced gastrointestinal hypomotility- associated with accumulation of faeces within the bowel and prolonged time between bowel movements [3]. Constipation is reported in up to 60% of clozapine-treated patients [6] and in up to 50% of patients treated with other antipsychotics [2]. Symptoms of slow transit constipation include low stool frequency, lack of urge to defecate, abdominal distension, bloating, and abdominal discomfort [5].

Clozapine-treated patients with serious gastrointestinal hypomotility often under-report symptoms, present late and fatal outcomes have been reported. Progression from constipation to ileus, intestinal obstruction, bowel ischaemia, megacolon and death have occurred in this cohort [3, 7-12]. In New Zealand over the last decade at least 36 patients have developed life threatening gastrointestinal motility problems related to clozapine of whom a number have died. Some of these patients were in their twenties with no other comorbidities.

To date, there is little evidence-based research on the management of gastrointestinal hypomotility in antipsychotic-treated patients. Although guidance exists to minimise clozapine's adverse haematological [13, 14], metabolic [15] and cardiac effects [16], these guidelines do not emphasise the need to monitor (or treat constipation) and its more serious sequelae. It is not known which treatments, if any, are effective in treating clozapine-induced gastrointestinal hypomotility. In the service where this research will occur, the Porirua Protocol for preventing and treating clozapine associated constipation is used. This protocol involves monitoring gastrointestinal function and prescribing docusate and senna in increasing doses up to four tablets daily, augmented by macrogol 3350 where necessary. While anecdotally the results of this intervention are promising, no study has investigated the outcomes with respect to change in transit time, symptoms and serious life threatening sequelae.

RESEARCH DESIGN AND METHODS

Participants:

Participants will be recruited from a cohort residing in New Zealand forensic and rehabilitation inpatient service who have participated in the first ROM gastrointestinal transit time study (currently recruiting) and are prescribed clozapine. None of the participants in the first study will have received laxative treatment at the time their gastrointestinal motility was first measured. Up to 20 patients will be recruited. If more than 20 clozapine treated participants participate in the first study, participants will be approached in order determined by a random number generator in order to randomly select 20 from the original cohort.

Inclusion criteria: Male and female adult patients (>18) prescribed clozapine (any dose), who participated in the first study, and who are able to provide informed consent and who have received laxatives for at least two months.

Exclusion criteria: Patients under the age of 18, unable to provide informed consent or who do not understand English will be excluded.

Only patients competent to provide informed consent will be recruited (capacity will be assessed by the researchers and checked with the treating psychiatrist). The informed consent form and patient information sheets are available from the researchers on request.

Ethical approval:

The research proposal has been reviewed by the Central Health and Disability Ethics Committee and has full ethics approval (reference 13/CEN/153). Consultation with Ngai Tahu has been undertaken through the University of Otago and approval given. Consultation with consumer consultants has occurred. Capital and Coast District Heath Board has granted site approval.

Recruitment:

Recruitment is planned to commence in November 2014 on and continue until all eligible participants from the first study have been approached, or November 2015, whichever occurs first.

Sample size:

No similar studies have been conducted, making power calculations speculative. At alpha=0.05 and beta=0.8, a sample size of 20 is adequately powered to detect a difference between two dependent means (pre and post treatment transit times) of >10 hours (SD=15). It is possible this study may be underpowered to detect a true difference, but it will serve to inform future studies.

Process:

The methodology is pre –specified in detail in the Investigators' Handbook. A researcher will initially spend approximately half an hour with each potential participant explaining the project and consenting the patient. The investigator will provide information sheets, which are also suitable for low levels of literacy, reading out the material, answering any questions and leaving a copy with the potential participant. Participants will be familiar with the methodology, as they will be recruited from a cohort who participated in the earlier study.

If the participant provides informed consent they will be recruited into the study, with gastrointestinal motility testing occurring the following week. Each participant will participate in the study for 4-7 days. All treatment will continue as usual.

The participant will be asked to swallow a small capsule containing ROMs on three consecutive days. ROMs are a simple, reliable method of measuring gastrointestinal motility [17]. Using the 'Metcalf' segmental method, the amount of time that the ROMs take to pass through each section of the intestinal tract can be tracked [17, 18]. The methodology will be identical to that pre-laxative gastrointestinal motility test. At the same time on day 1, day 2, and day 3, the participants will swallow a soft gelatin capsule contain 24 ring-shaped (4.5 x 1.0 mm) radiopaque markers made of polychlorinated vinyl with 33% barium sulphate (sitzmarks). These are tasteless and are

taken by mouth with water. On day four (t= 72 hours), participants will undergo radiological imaging to determine the location and extent of elimination of the ROMs. If more than two-thirds of ROMs are retained (n=48), abdominal X-ray will be repeated on day 7. The total number of markers in each segment will be used to determine transit time. Transit times will be compared with population normative values (from meta-analysis of data from healthy controls).

The researchers have chosen to use ROM method for studying gastrointestinal motility despite some limitations and drawbacks including radiation exposure (abdominal X-ray). The alternatives are scintigraphy (also involving radiation) and a newer technique using a wireless motility capsule both of which are considerably more expensive and not currently readily available or logistically possible for our population of interest.

For consistency all the X-rays will be read independently by SEP then by senior radiologist MN (who will be blinded to clinical and demographic factors). The rectosigmoid will be defined by oblique lines between the fifth lumbar vertebra spinous process and the femoral head. Any disagreements will be resolved by consensus.

Numbers of ROMs in each segment will be used to determine total and segmental CTT using the formula:

$$\Delta t = \frac{T}{N} \sum_{i=1}^{j} n_i$$

where Δt = mean transit time, T = time interval between X-rays, N = number of ingested markers, j = number of X-rays taken, and ni = total number of markers present on a given film sector.

On day four participants will be screened for constipation, firstly by being asked if they consider themselves constipated ('self-reported constipation'), which is intended to mirror normal clinical practice, and secondly by completing a researcher-assisted questionnaire incorporating all Rome III constipation symptoms, available on request from the authors.

Demographic and clinical data will be collected on all participants including age, gender, ethnicity, diagnoses, smoking status, height and weight and over-the-counter and prescribed medication.

Main Outcome measures:

We will compare pre and post laxative treatment colonic transit times.

Primary outcome measure: changes in colonic motility times, including segmental transit times (right colon, left colon and rectosigmoid transit times) as measured by ROMs (Metcalf technique)

Continuous and categorical outcomes will be reported (i.e. both transit time in hours, and the proportion of patients diagnosed with gastrointestinal hypomotility.) Cut-off points for 'abnormal' motility tests are derived from meta-analysis of normative data in healthy controls and set at 2SD above the population mean (i.e. colonic transit time of 65 hours or more). Transit times 4SD above the population mean will be considered severe colonic hypomotility.

Secondary outcome measure: subjective symptoms of constipation including self reported constipation and a modified ROME III questionnaire. Adverse effect data will also be collected.

Data Analysis:

A biostatistician (JS) is consulting on the statistical analysis for this project.

Descriptive statistics (frequencies with confidence intervals, means with standard deviations) will provide data summaries for bowel transit times.

We will use survival analysis to compare continuous outcomes (colonic transit times) and McNemar's test to compare categorical outcomes (proportion of patients with gastrointestinal motility and severe gastrointestinal hypomotility.)

Linear and logistic regression methods will then be used to examine which factors are associated with the different transit times (age, sex, laxative type and dose).

For hypothesis tests, differences will be considered statistically significant when $P<0.05$.

Funding:

This research is supported by a Capital and Coast District Heath Board small research grant. The District Health Board is the statutory entity that owns and funds the public hospital in which this research will take place.

Dissemination of scientific findings:

Data will be analysed and a paper reporting the results will be submitted to a high quality peer-reviewed journal within a year of the completion of data collection.

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