Title of Research Project
Colonic transit studies to measure gastrointestinal motility in antipsychotic treated patients

RESEARCH PROTOCOL

Contact Details of Principal Investigator

Name: Dr Susanna Every-Palmer, consultant forensic psychiatrist
Employer: Capital and Coast District Health Board/ University of Otago
Email: susanna.every-palmer@ccdhb.org.nz

Co-investigators

Professor Pete Ellis, University of Otago
Mike Nowitz, University of Otago
James Stanley, University of Otago
Eve Grant, Capital and Coast District Health Board
Mark Huthwaite, University of Otago
Helen Dunn, Capital and Coast District Health Board

Significance

This is a observational (cross sectional) study investigating gastrointestinal hypomotility caused by antispychotic medication, an important adverse effect spectrum that has caused considerable morbidity and mortality amongst antipsychotic-treated patients.

In New Zealand over the last decade at least 36 patients have developed life threatening gastrointestinal motility problems related to antipsychotics (clozapine), of whom 11 have died (personal correspondence, Janelle Ashton, NZ pharmacovigilance centre). Some of these patients were in their twenties with no other comorbidities.

Although there is a growing body of literature on this topic, the effects of antipsychotics on gastrointestinal motility are speculative, and have not been quantified. This can be done through astrointestinal motility studies using radiopaque markers, which are well tolerated and cost effective.

The development of this research protocol has involved input and support from four different disciplines: psychiatry; radiology; gastroenterology and pharmacology. The research project has been reviewed by the Cnetral Health and Disbility Ethics Committtee and has full ethics approval.

SECTION 1: RESEARCH QUESTION AND BACKGROUND

Research Questions

In antipsychotic-treated psychiatric inpatients, how does gastrointestinal motility (as measured by radiopaque marker (ROM) transit studies (described below) compare with standardised normative values?

Does colonic transit time differ significantly between people treated with clozapine and treated with other antipsychotics?

How are other independent variables such as age, gender, ethnicity, antipsychotic load or estimated anticholinergic activity related to CTT?

Background

Antipsychotic medications are effective agents in the treatment of schizophrenia and other psychotic disorders, but their adverse effect profiles are considerable.

Gastrointestinal hypomotility is one commonly reported and potentially serious adverse effect. The mechanism is usually considered to be anticholinergic inhibition of gastrointestinal smooth muscle contraction and peristalsis (e.g. [1], [2]), but it is likely that antipsychotic medications' antagonism of various serotonin receptor subtypes compounds the problem [3] as serotonin plays a crucial role in gastrointestinal motility [4].

As a result of the pharmacological properties of clozapine and other antipsychotics, it appears gastrointestinal motility is reduced. It has been hypothesised transit time through the gut increases, resulting in the first instance in "slow transit" constipation, associated with accumulation of faeces within the bowel and prolonged time between bowel movements [3]. Symptoms of slow transit constipation include low stool frequency, lack of urge to defecate, abdominal distension, bloating, and abdominal discomfort [5].

The exact mechanisms by which antipsychotics alter colonic anatomy have yet to be elucidated. It is also unknown whether these antipsychotic-induced colonic architectural changes are reversible. Surprisingly, there are no published data on gastrointestinal motility in antipsychotic treated patients.

The earliest manifestation of gastrointestinal hypomotility is usually constipation, which is reported in up to 60% of clozapine-treated patients [6] and in up to 50% of patients treated with other antipsychotics [2].

There appear to be three main mechanisms whereby gastrointestinal hypomotility and colonotoxic changes can progress to life-threatening conditions. These involve the accumulation of faeces within the bowel leading to distension, aspiration or infection [3].

Antipsychotic-treated patients with serious gastrointestinal hypomotility often under-report symptoms, present late and many fatal outcomes have been reported. Progression from

constipation to ileus, intestinal obstruction, bowel ischaemia, megacolon and death is not uncommon in this cohort [3, 7-12].

To date, there is little evidence-based research on the management of gastrointestinal hypomotility in antipsychotic-treated patients. Although guidance exists to minimise antipsychotic medications' 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.

RESEARCH DESIGN AND METHODS

Participants:

Participants will be recruited from inpatients residing in a New Zealand forensic and rehabilitation service (total population of approximately 100 patients). Up to 40 patients will be recruited. Participants will be approached in order determined by a random number generator.

Inclusion criteria:
Male and female adult patients (>18) prescribed antipsychotic medication (any dose), who are able to provide informed consent.

Exclusion criteria
Patients under the age of 18, unable to provide informed consent or who do not understand English will be excluded. We will also exclude patients with established gastrointestinal hypomotility, or those who are taking laxatives which either they, or their treating team, have concerns about withholding for the duration of the ROM test. The rationale for this is to minimise risk to participants.

Recruitment:
Recruitment is planned to commence Monday 3 March 2014 on and continue until 40 participants have been recruited or Friday 1 May 2015, whichever occurs first.

Research methods:

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 is available on request.

The investigator will initially spend approximately half an hour with each potential participant explaining the project and consenting the patient. The investigator will go through the information sheets, which have been designed for low levels of literacy, both reading out the material and providing written material (appended).

The **exposure** is the type and dose of antipsychotic treatment.

The **condition observed** is colonic transit time as measured by ROM (Metcalf technique)

Each participant will participate in the study for 4-7 days. All treatment will continue as usual, apart from bowel motility agents e.g. laxatives, which spuriously increase transit times. These will need to be temporarily paused for two days prior to the ROM study until its conclusion. The researchers will check this is acceptable to the participant and their treating clinician. Rescue laxatives will be available if the participant requires them.

The participant will be asked to swallow a small capsule containing radiopaque markers (ROMs) on three consecutive days. ROMs are a simple, reliable method of measuring gastrointestinal motility (Rao 2005). Using the segmental method, the amount of time that it takes to pass through each section of the intestinal tract can be tracked [17, 18]. On day 1, day 2, and day 3, the participants will swallow one capsule containing the ROMs. We will use standardised ROMS called Sitzmarks. The soft gelatin capsule contain 20 ring-shaped (4.5 x 1.0 mm) radiopaque markers made of polychlorinated vinyl with 33% barium sulphate, are tasteless and are taken by mouth with water. On day four the participant will have an abdominal X-ray to determine the location and extent of elimination of the radiopaque markers. If more than two-thirds of ROMs are retained (n=48), the X-ray will be repeated on day 7. The total number of markers in each segment is 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 are considerably more expensive and not readily available in New Zealand.

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). Any disagreements will be resolved by consensus.

On Day 4 the participant will be asked to complete a bowel motility screen based on the Rome III criteria.

Main Outcome measures:

Primary outcome measure: 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).

Secondary outcome measure: subjective symptoms of constipation from a modified ROME III questionnaire.

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. These will be compared with normative population data. Continuous variables will be analysed using t-tests or ANOVA if data are normally distributed or Kruskall-Wallis chi squared and median tests if not normally distributed.

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

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

Ethics:

Ethical approval for this research has been granted by the HDEC (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. Site approval has been given by Capital and Coast District Heath Board.

Limitations of the research

The initial sample size of 40 participants is small. It is not possible to conduct a pre-study power analysis to determine how many patients are required to demonstrate a significant difference in bowel motility if this exists, as there are no previous studies of this nature from which to extrapolate likely effects. This study may be undepowered, but will be useful to inform future research.

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