A pilot randomised controlled trial of chlorpromazine to prevent postoperative nausea and vomiting

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Citation

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Abstract

PURPOSE: Safety and efficacy of a small dose of chlorpromazine to prevent postoperative nausea and vomiting (PONV) was studied to enable design of a larger trial. Since phenothiazines may prolong the electrocardiogram QT interval and cause dangerous arrhythmias, we focussed on this side effect. METHODS: A double-blind randomised controlled trial was conducted in a tertiary care teaching hospital comparing chlorpromazine 10mg IV at anesthetic induction to saline with primary outcome prevention of PONV (defined as nausea and/or vomiting and/or retching at any time) in laparoscopic surgery, and secondary outcomes cardiac and other side effects. With University Research Ethics Board approval, 120 subjects were recruited. PONV was assessed in the Post-anesthetic Care Unit and 24 hours later.RESULTS: Group demographics were not different. For incidence of PONV, the chlorpromazine group (incidence; ratio; [95%Confidence Interval]: 33/60; 0.55 [0.42 to 0.68]) was not significantly different from placebo (40/60; 0.67 [0.55 to 0.79]. There was no difference in corrected QT or Tp-e intervals. One subject in each group was sleepier than expected; one in the CPZ group had lower blood pressure than expected after anesthesia induction, which was easily corrected.CONCLUSION: Although not statistically significant, PONV occurred more often in the placebo group than the treated group. A larger dose may be efficacious. Chlorpromazine is inexpensive and, at this dose, appears to be safe in the context of anesthesia practice. This study permitted sample size estimation (n = 100/arm) for a definitive study.

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INTRODUCTION

This study was a pilot exploration of safety, efficacy, problems, side effects, and ease of use, of chlorpromazine (CPZ) in the operating room for prevention of postoperative nausea and vomiting (PONV). It was conducted with a view to deciding about the wisdom of, and the design for, a larger dose-ranging study. A conservative dose of 10mg intravenously (IV) was chosen as likely to be safe. Subjects received CPZ or saline placebo intravenously before a standardised anesthetic regimen. PONV during the first 24 hours post-operatively was recorded as emetic episodes (episodes of vomiting or retching) and incidence of nausea.

CPZ, a phenothiazine drug, has a pharmacologic profile that suggests that it might be useful in prevention and treatment of postoperative nausea and vomiting (PONV).[,] Five neurotransmitter receptors are of primary importance in PONV: acetylcholine, dopamine-2, histamine-1, serotonin-3, and neurokinin-1. Of candidate drugs for PONV, CPZ is the only drug that has activity at the first four of these receptors.[,] It is inexpensive (US$1.80 for a 50mg ampoule).[ ] CPZ has been used extensively in cancer chemotherapy to prevent and treat nausea and vomiting.[,] The usual and recommended dose for this purpose is 25 or 50mg orally (PO).[ ] It is used by some anesthesiologists for PONV prophylaxis (personal communication), usually in the dose of 10 to 25mg IV.

Our study focussed on cardiac adverse effects because we felt that significant electrocardiogram (ECG) changes should prohibit further studies. Although the Chlorpromazine CPhA Monograph[8] makes no specific mention of torsade de pointes, phenothiazines may prolong the QT interval.[ ] Recently it has been shown that risk of torsade de points is associated, not with QT prolongation per se, but specifically with increased transmural dispersion of repolarisation across the myocardial wall, often, but not always, found in association with QT prolongation. The time interval between the peak and end of the T wave (Tp-e) is considered a better

measure of risk of transmural repolarisation dispersion and thus of torsade de points than the QT interval.[ ] Therefore, Tp-e was measured.

The ethical question of using placebo control was addressed by giving all subjects midazolam and by proscribing N_2O to help prevent PONV.[ ]

The primary outcome hypothesis was that the incidence of PONV, defined as any report of nausea or vomiting during the first 24 hours after surgery, will be different between subjects given 10mg of CPZ IV and those given saline placebo IV at the onset of anesthesia for laparoscopic surgery. Secondary outcomes were severity of nausea (numerical rating score: NRS) in the Post Anesthesia Care Unit (PACU); length of stay in PACU (min); effects of study drug on QTc and Tp-e intervals; and any reported adverse effects.

MATERIALS AND METHODS

Subjects. With approval of the University of Saskatchewan Research Ethics Board

and subjects' written informed consent, 120 adult patients requiring general anesthesia for elective laparoscopic abdominal procedures were studied prospectively in a randomized, double-blinded, placebo-controlled trial.

Included were adult patients (18 years and over) requiring general anesthesia for elective laparoscopic abdominal procedures. Excluded were subjects who were pregnant; had liver or renal dysfunction, vestibular disease, cardiac arrhythmias, prolonged QTc (>440ms), a seizure disorder, Parkinson’s disease, hyperthyroidism, tardif dyskinesia, nausea or vomiting within 24 hr; those who were currently (within 24 hours of admission) receiving antiemetic therapy or chronic steroid therapy or lithium, or drugs for depression; those who were allergic to chlorpromazine or any of the anesthetic or analgesic drugs; were obese (BMI > 35); or had used an investigational drug within 30 days prior to surgery; and those unwilling or unable to give informed consent.

Setting. The study was conducted in teaching hospitals of the University of Saskatchewan. Data was collected from October, 2003, to October, 2006.

Randomisation and blinding. Subjects were randomised with a computer-generated random number table using opaque sealed triple-folded cards containing the study assignment. These were opened in a closed room by a nurse not involved in the subject's clinical care, and with no knowledge of the subject, and only after inclusion of the patient in the study. The nurse prepared the study drug. The study drug was diluted to 10mg/ml and 1ml of study drug or saline was provided. All investigators, the patient, and all personnel involved in patient care were blinded as to treatment, with concealment of allocation. Electrocardiograph (ECG) strips were de-identified and randomised. ECG measurement and data entry was blinded.

Procedures. Patients were randomly assigned to two groups, one group receiving chlorpromazine 10 mg (CPZ group) and the other 0.9% saline as placebo (placebo group) intravenously at induction of anesthesia. The anesthetic regimen was standardized and was commonly used by local practitioners. Routine monitoring included continuous lead II electrocardiogram, non-invasive blood pressure, capnography and pulse oximetry. Anesthesia was induced intravenously with midazolam 2 mg, fentanyl or sufentanyl and propofol, and rocuronium. Anesthesia was maintained using desflurane in oxygen and air (no nitrous oxide). Ventilation was controlled mechanically and adjusted to maintain the end-tidal CO2 between 30 and 35 mm Hg throughout surgery. An orogastric tube was inserted and suction applied to empty the stomach of air and secretions. Additional muscle relaxant, fentanyl, or sufentanyl was administered during the operation at the anesthesiologist's discretion. During surgery, the abdomen was insufflated with carbon dioxide to an intra-abdominal pressure of 10 to 15 mm Hg. All patients received ketorolac 30 mg IV approximately 30 min before the end of surgery. Glycopyrrolate 0.4mg and neostigmine 3 mg were administered for reversal of residual muscle relaxation. Before tracheal extubation, the orogastric tube was suctioned and removed. Esophageal temperature was monitored and maintained at 36–37°C throughout surgery.

Measurements and Data Collection. The patient’s age, gender, weight, height, medications, smoking status, previous surgery with PONV experience, and preoperative vital signs were recorded. Ten-second ECG lead-II recordings were made prior to induction and again in the PACU, using a printer (Hewlett Packard model M116-6B, Hewlett Packard Company, Palo Alto, California, USA.) attached to ECG monitors (Hewlett Packard models M1092A and M1204A). Because the half-life of intravenous CPZ is 11h, Any effects on cardiac conduction could be expected to persist into the PACU.[ ] QT and Tp-e were measured from recording strips with beats free of

interference or baseline wander, using ECG callipers and ruler, and QT correction for heart rate applied, using the formula of Bazett ($QT_c=QT/RR^{1/2}$).[ ] Qt and Tp-e values reported are the means of measurements from three clear ECG beats.

Postoperatively, the patients were accompanied to the PACU by investigators who reminded PACU nurses about the study in order to assure accurate charting of the occurrence and treatment of PONV. The incidence of PONV (defined as nausea, vomiting, or retching) and an 11-point (0 to 10) numerical rating scale (NRS) of worst nausea during the PACU stay was recorded at the end of the subjects' stay in the PACU. At this time the attending nurse was asked about any side effects, and specifically about excessive sedation and dysphoria. Inpatients were visited by investigators next day; outpatients telephoned, and PACU incidence and nausea NRS of worst nausea recorded. Additional episodes of PONV were identified by review of the medical chart. Emetic episodes were episodes of vomiting and episodes of retching. Narrative descriptions of any adverse effects were sought from anesthesiologists and PACU nurses.

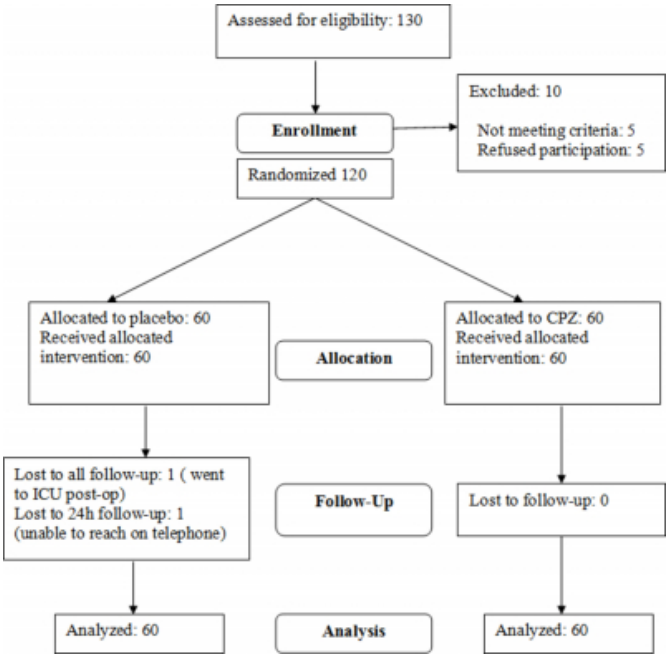
Dimenhydrinate (25-50 mg IV) was given as rescue treatment for PONV as deemed needed by the nurse or requested by the patient. Additional treatment was ordered by the anesthesiologist when needed. Morphine (1-5 mg IV) was given for pain as needed or requested by the patients. Use of antiemetics on the ward was not recorded as part of the study because surgical nurses were in the habit of always giving dimenhydrinate with every dose of opiate.

Statistics. The number of subjects (n) was obtained by a sample-size calculation with alpha = 0.05, and beta = 0.2, assuming a 50% reduction in symptoms as shown in Kvisselgaard's study.[ ] We considered the incidence of PONV from placebo arms of published studies, which showed a total incidence of PONV of 63% for laparoscopic tubal ligation[ ], and 48% for laparoscopic cholecystectomy.[ ] Therefore, we used 50% as a reasonably conservative estimate of incidence. The sample size calculation required 58 subjects in each arm of the study. Sixty subjects per arm were planned for, assuming up to 2 dropouts or technical problems per arm. Dropouts were analysed by intention-to-treat. Continuous variables were compared by t-test, ordinal variables by Mann-Whitney Rank Sum test, counts (total episodes of vomiting) by z-test approximation to a Poisson distribution,[ ] and categorical variables by Chi-squared. Effects of study drug and of general anesthesia on ECG variables were analysed by Two Way Repeated Measures ANOVA (One Factor Repetition). Statistical analysis was performed using SigmaStat for Windows version 3.11 (Jandel Scientific, Div. of Jandel Corp., San Rafeal, CA, USA). Alpha P-value was set at 0.05, beta at 0.2. P-values less than 0.05 were corrected for multiple comparisons, with Bonferroni correction, using the variables of each Table as a family of variables. Ninety-five percent Confidence Intervals (CI) are reported in square brackets.

RESULTS

Figure 1

Figure 1 shows the CONSORT enrolment flow chart. [ ]



Demographic data is presented in Table 1. Sixty subjects were recruited to each group. All but one subject, who had an unplanned admission to the intensive care unit (placebo group) completed the study until leaving PACU, with no protocol violations. One subject in the placebo group could not be contacted subsequently. She had no nausea or vomiting up to discharge from PACU and was analysed in the placebo group as intent-to-treat. Significantly more subjects smoked than expected: 40% of subjects smoked, compared to 20% of adult Canadians in 2004; P = 0.028.

Figure 2

Table 1 - Demographics

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	Placebo	CPZ
Age (years; mean ± S.D.)	37 ± 13	39 ± 13
Gender (M/F)	5/54	10/59
Height (cm)	165 ± 9	165 ± 9
Weight (kg)	71 ± 15	72 ± 14
Smokers	25 (42%)	21 (35%)
Previous PONV/surgery	26/50	20/53
Surgery: (c/g/o)*	8/49/2	14/40/6

*(cholecystectomy/gynecology/other)

Efficacy. Comparisons between drug and placebo are presented in Table 2. Taking incidence (number of subjects) at any time in the study with any of nausea, vomiting, or retching as "PONV incidence", PONV was not significantly different between the two groups (P = 0.26). The power of the performed test (0.188) is not sufficient to declare equivalence. Emetic episodes (total counts of vomiting and retching), were not significantly different (P = 0.28) although the counts for the placebo group were 46% higher than for the CPZ group. The overall incidence of PONV in the placebo group (incidence (fraction)[95%CI]: 40/60 (0.67) [0.55 to 0.79]) was not significantly different from the subjects' own previous experience: (26/50(0.52) [0.38 to 0.66]; P = 0.34).

Figure 3

Table 2 – Treatment comparisons

	Placebo	CPZ	P-value
NRS nausea scores	5.5 ± 5.2 [4.8 to 7.1]	3.9± 4.4 [4.6 to 5.9]	0.21
PONV (nausea, vomiting or retching at any time)*	40/60(0.67) [0.55 to 0.79]	33/60(0.55) [0.42 to 0.68]	0.26
Emetic episodes†	38 [26 to 50]	26 [16 to 36]	0.28
PACU rescue medication* incidence	20/60(0.33) [0.21 to 0.45]	11/60(0.18) [0.09 to 0.28]	0.09
Stay in PACU (min)**	69 ± 30 [61 to 76]	67 ± 24 [61 to 73]	0.72
Emesis in PACU	2	1	
Excessive sedation (PACU)	1	1	
Hypotension (intra-op)	0	1	

* proportion in brackets; 95% Confidence Intervals in square brackets
† total counts of vomiting or retching at any time; 95% CI in square brackets
** mean ± standard deviation; 95%CI in square brackets

Safety. Corrected QTc and Tp-e intervals were not different at baseline between placebo and CPZ groups. Two way repeated measures ANOVA (one factor repetition) comparing the QTc intervals of all subjects pre- and post-operatively (see Table 3) showed a significant effect from surgery/anesthesia (P < 0.0001), but not from CPZ (P = 0.28). Tp-e showed no effect from either factor. One subject in each group was sleepier than expected by the PACU nurse, and one CPZ-group subject had lower blood pressure than expected by the anesthesiologist immediately after anesthesia induction, which was easily corrected. No subject appeared to have, or complained about, dysphoria, and no other adverse effects were reported.

Figure 4

Table 3 – Effects on ECG intervals (means, with 95%CI in square brackets; ms)

Drug effect*	placebo	CPZ	Change	P-value
QTc	441 [433 to 448]	435 [427 to 442]	-6	0.28
Tp-e	78.8 [75 to 82]	79 [75 to 83]	+0.2	0.93
Anesthetic effect*	**Before GA**	**After GA**		
QTc	429 [424 to 434]	448 [443 to 453]	+19	0.0001
Tp-e	80 [77 to 83]	77.9 [75 to 81]	-2.1	0.35

*effect of CPZ compared to placebo independent of anesthesia, and effect of anesthesia independent of study drug as calculated using two-way ANOVA with one factor repetition.

DISCUSSION

Efficacy. CPZ at this dose is not efficacious for prevention of PONV. Comparisons with the subjects' previous surgical experience suggest that the study results are representative of PONV occurrence in this population undergoing laparoscopic surgery. This is a pilot study to determine sample size for a definitive trial. Using the lower 95% CIs of proportions in sample-size calculations (0.55 for placebo and 0.42 for CPZ), with alpha = 0.05 and beta = 0.2, 231 subjects per arm are needed if the experiment is repeated unaltered (most conservative estimate). If smokers are excluded, the incidence of PONV is increased by approximately 20%.[ ] Then the corresponding sample size is 135 subjects per arm. A larger dose would mean that the expected change in incidence with treatment would approach the 50% change reported by Kvisselgaard, giving the required sample size of 41 per arm. Thus, as a suitable compromise, Apfel's suggestion of n = 100 per arm would be appropriate.[ ]

Safety. The anesthetic and operation, but not the study drug, resulted in an increase in the QTc interval, but no change in Tp-e. This increase is likely due to the effects of desflurane.[,] CPZ had no effect on these intervals compared to placebo.

It has long been stated that phenothiazines prolong the QTc interval, with no distinction made among different phenothiazines.[,] It was concerning therefore that CPZ might induce torsade de pointes, a potentially fatal arrhythmia. Our study shows no effect at the small dose of

CPZ used, but how safe would it be to study larger doses? Other phenothiazines (promethazine, perphenazine and prochlorperazine) are recommended for PONV prophylaxis and treatment. [18] Is the risk of arrhythmias from CPZ and other phenothiazines different?

A literature search reveals only three case reports of torsade de pointes associated with CPZ, and seven reports of other ventricular arrhythmias.[,] Torsades occurred with chronic use of 100, 900, and 1600mg per day of CPZ given over more than a year. The three patients had low potassium, calcium, or both. On the one hand, torsade de pointes associated with CPZ is likely to be under-reported. On the other hand, CPZ has been used for more than fifty years by millions of psychiatric and oncology patients.[ ] Thus, if torsade de pointes occurs in significant numbers of CPZ users, more than three reports would be expected.

Further evidence that CPZ is unlike other phenothiazines with respect to risk of torsade de pointes emerges from two observational studies. First, in a study of patients with drug overdoses, 171 patients with CPZ overdose did not have QTc prolongation, while 65 patients with thioridazine overdose had prolongation, and had a correlation of QTc with dose.[ ] Second, a study of 495 psychiatric patients and 101 healthy reference individuals found that thioridazine, droperidol, and tricyclic antidepressants resulted in QTc prolongation, but CPZ did not.[ ] Thus, it seems reasonably safe to study CPZ for PONV prophylaxis in larger doses.

Previous studies. CPZ has not been formally studied for PONV for more than 40 years. [13,] In these early trials, a fixed dose of 25 or 50 mg was administered by the intramuscular (IM) route. Both studies found that CPZ was associated with hypotension., a recognised pharmacologic effect now known to be caused by CPZ-induced alpha-adrenergic blockade.[ ] Kvisselgaard's study found that CPZ 25 mg IM was efficacious, decreasing vomiting by half (incidence of no vomiting: CPZ: 56/94; placebo: 28/90 $P < 0.0001$). Dundee's study was stopped after 29 subjects because of hypotension. The hypotension can be attributed to two circumstances of Dundee's study: first, the dose of 50 mg may be excessive; second, at the time of the study, IV fluid was not routinely used for most surgery. Pre-medication was given IM on the ward, and thiopental was administered directly into a vein without a running IV. A recent trial of IV chlorpromazine for migraine found 0.1mg/kg to be safe and effective.[ ]

Weaknesses of the study. First, the sample size is not sufficient to declare difference or equivalence between groups. However, it is sufficient for the purpose of the study, which was to enable sample size estimation for a definitive study. Second, and more importantly, we can conclude only that CPZ appears to be safe at the small dose studied. We have no direct evidence for its safety in anesthesia practice at the larger doses that might be necessary for efficacy.

Summary. CPZ in a low dose of 10mg intravenously to prevent PONV was not efficacious in this pilot study, but was safe and easy to use, with minimal side effects. It is inexpensive, and may be safer than droperidol with respect to QT-related arrhythmias.[28] This pilot study suggests that a dose-ranging study, possibly excluding smokers, with larger numbers, and a range of doses greater than 10mg, is warranted. Future studies should measure Tp-e rather than QTc ECG intervals.

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