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A Randomised Double-blind Study of High-dose Intravenous Prochlorperazine versus High-dose Metoclopramide as Antiemetics for Cancer Chemotherapy

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High-dose prochlorperazine 0.8 mg/kg administered intravenously 30 min pre and 7 h 30 min post the initial dose of emetogenic chemotherapy was compared to high-dose metoclopramide 2 mg/kg over 20 min every 2 h for five doses starting 30 min prior to chemotherapy in a randomised, double-blind, parallel subjects design study. On the prochlorperazine arm intravenous dextrose placebos every 2 h maintained blinding. Complete suppression of vomiting occurred in 42% on metoclopramide (53% with non-cisplatin regimens) and 36% on prochlorperazine (52% with non-cisplatin-containing regimens) while major responses (2 or less vomits) occurred in 58% on metochlopramide and 54% on prochlorperazine. In patients who vomited after cisplatin, prochlorperazine achieved a significantly shorter duration of vomiting, a median of 5 h compared to 15 h on metoclopramide ($P = 0.03$). The response rate to prochlorperazine for cisplatin-induced emesis between 12 and 24 h was significantly better than for metoclopramide (prochlorperazine = 0.02). Toxicities were equivalent except for significantly greater sedation and dry mouth on prochlorperazine. Extrapyramidal reactions were recorded equally on both arms but were only severe enough to stop treatment on metoclopramide. The metoclopramide regimen was five times as expensive as prochlorperazine. High-dose prochlorperazine is an active and cost-effective antiemetic.
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WHEN HIGH-DOSE metochlopramide was used as an antiemetic after cytotoxic chemotherapy, it was found to be superior to other single agents, particularly for controlling cisplatin-induced emesis [1–3]. The original schedule of Gralla *et al.* was 2 mg/kg every 2 h although subsequently higher doses with less frequent scheduling (3 mg/kg × two doses) or continuous infusion schedules have been explored [4–7]. It is the agent against which the newer 5-hydroxytryptamine antagonists are being compared [8].

Prochlorperazine is a very frequently used antiemetic and is often the control arm in studies comparing it with new antiemetic agents for use with cytotoxic chemotherapy [1]. Despite this, as with many older drugs, no formal study to establish the maximum tolerated dose had been done until recently.

Studies in a murine gastric distension model of emesis had suggested improved efficacy for higher dose prochlorperazine [9]. In a formal phase I study of prochlorperazine Olver *et al.* established the maximum tolerated dose as a 15 min infusion of 1.2 mg/kg with a recommended dose for further studies of 0.8 mg/kg, which based on the half-life could be repeated every 8 h [10]. Carr *et al.* had demonstrated that higher dose prochlorperazine was superior to conventional doses in a small study, empirically escalating the dose from 10 to 40 mg for patients receiving cytotoxic chemotherapy [11]. In randomised studies of high-dose metoclopramide, 2 mg/kg every 2 h, and low-dose prochlorperazine, 10 mg every 2 h, Gralla *et al.* showed that metoclopramide had greater antiemetic efficacy [1]. Carr *et al.*, however, demonstrated equivalence in the first 3 h between high-dose metoclopramide and conventional dose prochlorperazine with prochlorperazine marginally superior for 3–24 h and greater toxicity with metoclopramide [12].

This study assessed the efficacy of high-dose prochlorperazine 0.8 mg/kg compared with high-dose metoclopramide 2 mg/kg in a randomised double-blind parallel subjects study, for patients receiving cytotoxic chemotherapy.

PATIENTS AND METHODS

Patient eligibility

Adults with malignancy receiving their first ever course of intermittent intravenous chemotherapy containing one or more of the following emetogenic agents: cisplatin or carboplatin, cyclophosphamide, daunorubicin, doxorubicin, actinomycin D, dacarbazine, nitrogen mustard or streptozotocin, were eligible for this study. Patients were required to have a performance status of 60 or more on the Karnofsky scale. Patients were excluded if they were pregnant or breast-feeding or had a serious medical or psychiatric illness, particularly cardiovascular or renal disease or epilepsy. Patients having had previous adverse reactions to phenothiazines were also excluded. The study complied with the ethical guidelines of the National Health and Medical Research Council of Australia and was approved by the Peter MacCallum Cancer Institute Ethics Committee. Written informed consent was obtained from each patient.

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Treatment

Patients were randomly assigned to a treatment arm according to a schedule kept in pharmacy but unknown to patients and investigators.

High-dose prochlorperazine was given at a dose of 0.8 mg/kg in 50 ml 5% dextrose infused intravenously over 20 min at 30 min prechemotherapy and 7 h 30 min postchemotherapy. Patients receiving prochlorperazine were given 50 ml of 5% dextrose at 1 h 30 min, 3 h 30 min and 5 h 30 min to maintain blinding in comparison to the metochlopramide arm. The infusion bottle was protected from light by black plastic.

High-dose metoclopramide at 2 mg/kg was given over 20 min in 50 ml of 5% dextrose 30 min prechemotherapy then 1 h 30 min, 3 h 30 min, 5 h 30 min and 7 h 30 min postchemotherapy. If a patient was distressed by severe nausea or vomiting after single agent metoclopramide or prochlorperazine, other agents were used; most commonly phenergan 25 mg orally or lorazepam 0.05 mg/kg orally. Extrapyramidal reactions were treated with benztropine and further doses of the study drug were withheld.

Evaluation

Pretreatment patient characteristics, particularly age, sex and chemotherapy, were recorded. Patients past alcohol consumption, which was not as widely recognised as a prognostic factor when the study commenced, was not recorded.

Both observers and patients assessed pre- and post-treatment nausea and vomiting. The subjective observations such as nausea or side-effects such as sedation were recorded on 4 point ordinal scales (none, mild, moderate or severe). Objective observations which could be quantitated, i.e. the number of vomiting or dry retching episodes were counted and duration recorded. Some toxicities such as rash, dry mouth and extrapyramidal symptoms were simply recorded as present or absent.

If a patient required further antiemetics for uncontrolled vomiting during the 24 h assessment, this was recorded.

Finally, the patients were asked to give an overall assessment of how they tolerated the course of chemotherapy. This was recorded on a 4-point ordinal scale and patients were asked to give reasons for their response, to assess whether any poor tolerance of the therapy was related to uncontrolled vomiting, the toxicity of the antiemetic, or other factors.

Observations were recorded by a nurse every hour and patients completed a questionnaire 24 h after their chemotherapy. This was a study of acute emesis and no recording of delayed nausea and emesis occurred.

Statistical methods

The target sample size of 100 patients randomised to each arm was determined prior to commencement of the study. This enabled clinically important changes in overall complete response rates from 25 to 45% to be detected with a probability (power) of 0.8 using a two-tailed test of significance at significance level (alpha) of 0.05.

Statistical tests were carried out using BMDP software. All P values quoted refer to two-tailed tests of significance. Response rates and incidence rates of toxicities were compared using Fisher's exact test where small numbers were involved or Yates' continuing-corrected chi-square test for contingency tables. The Mantel–Haenszel procedure was used to adjust for prognostic factors (sex, age, cisplatin) in the comparison of response rates where appropriate. All graded data were compared using the chi-square test for trend. Interval data (number of vomiting episodes, duration of vomiting) were compared using Wilcoxon's rank-sum test.

Table 1. Patient characteristics

		Metoclopramide	Prochlorperazine
No. of patients		100	100
Age (years)	Range	23–82	17–80
	Median	61	54%
	< 55	32%	51%
Sex	Male	55%	62%
	Female	45%	38%
Cisplatin chemotherapy		34%	40%
Non-cisplatin chemotherapy		66%	60%

RESULTS

100 patients were randomised to each arm and all were evaluable (Table 1). The two arms were well balanced with respect to the chemotherapy given.

The antiemetics were being tested against chemotherapy regimens likely to cause emesis. The median dose of cisplatin was 100 mg/m^2 (Table 2). A subgroup analysis was performed for patients receiving either high-dose single agent cisplatin or cisplatin in combination. The one significant imbalance between the arms was that there were more younger people (< 55 years) on the prochlorperazine arm (P = 0.01). Most patients had no pretreatment vomiting (93% on metoclopramide and 96% on prochlorperazine).

Control of vomiting

From the data recorded by the observers complete control of vomiting (CR) was achieved in 42% [95% confidence interval (CI) 32–52%] of patients on the metoclopramide arm, 21% with

Table 2. Dose ranges of cytostatic drugs

Drug	No. of patients	Dose range (mg/m^2)*	Median dose (mg/m^2)*
Doxorubicin	61	25–63	50
Daunorubicin	5	47–50	49
Mechlorethamine	9	5–6	6
Cyclophosphamide	69	94–786	729
Dactinomycin	1	200	200
Streptozotocin	1	500	500
Cisplatin	75	19–103	100
Dacarbazine	13	188–800	206
Carboplatin	29	75–375	100
Bleomycin	11	8–18	15
5-Fluorouracil	40	397–1000	1000
Vincristine	38	2 mg	2 mg
Epirubicin	4	47–71	50
Prednisolone	37	50–150 mg	75 mg
Etoposide	38	60–125	109
Procarbazine	11	25–119	50
Teniposide	3	75–100	88
Mitomycin	5	9–10	10
Interferon	12	3 mg	3 mg
Cytarabine	5	100–160	100
Vinblastine	2	1–6	3

*Except where indicated.

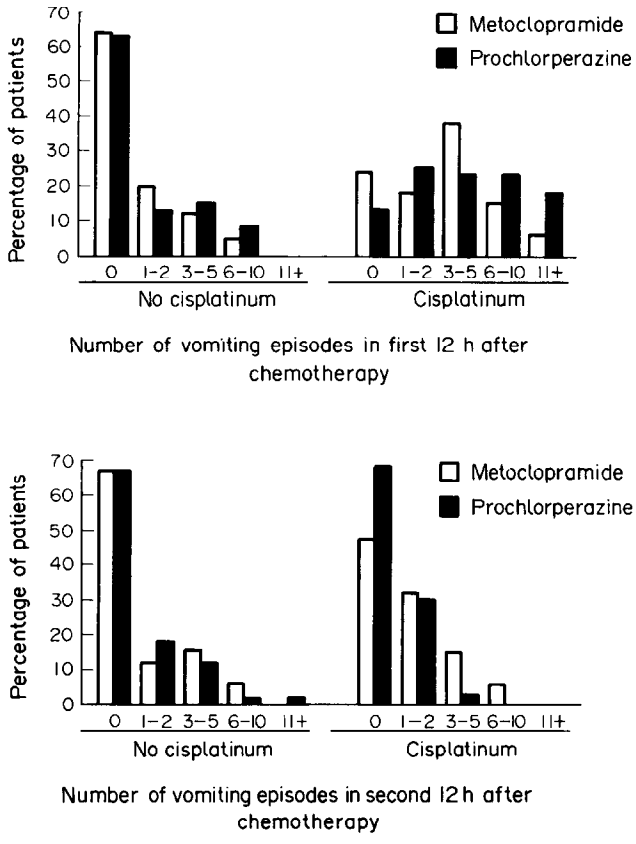

Fig. 1. Percentage of patients by number of vomits. (a) First 12 h after chemotherapy (p = 0.7 if chemotherapy does not include cisplatin, p = 0.11 if chemotherapy includes cisplatin) (b) Second 12 h after chemotherapy (p = 0.8 if chemotherapy does not include cisplatin, p = 0.02 if chemotherapy includes cisplatin).

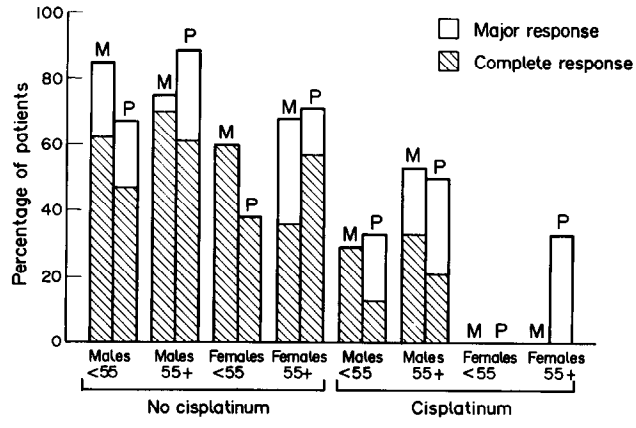

Fig. 2. Percentage of patients with complete response or major response compared by sex, age group (< 55 years, 55 years or more), chemotherapy and randomisation arm. M = Metoclopramide, P = prochlorperazine.

cisplatin regimens and 53% within non-cisplatin regimens while a major response (MR) (0, 1 or 2 vomits) occurred in 58% (95% CI 48–68%). For prochlorperazine the CR rate was 36% (95% CI 27–46%), 13% with cisplatin therapy and 52% with non-cisplatin therapy while a MR occurred in 54% (95% CI 44–64%). There was no statistically significant difference between the arms in any response category.

Only 16% patients on prochlorperazine and 17% on metoclopramide required additional antiemetics because of severe uncontrolled emesis.

For those patients who vomited following cisplatin, the median duration of vomiting if treated with prochlorperazine was 5 h as compared to 15 h on metoclopramide (P = 0.03). Vomiting commenced 3 h after chemotherapy on both regimens. The control of cisplatin-induced vomiting by prochlorperazine was significantly better than by metoclopramide between 12 and 24 h (P = 0.02), whereas both drugs achieved similar control in the first 12 h after chemotherapy (Fig. 1).

Control of nausea

The control of nausea paralleled the results with vomiting. The severity of nausea was equal in both arms with 30% experiencing no nausea. Where patients experienced nausea there was a significantly shorter duration of nausea in patients receiving high-dose prochlorperazine (median 7 h) compared to metoclopramide (median 15 h, P = 0.02). Again, there was a highly statistically significant reduction of nausea between 12 and 24 h for patients receiving prochlorperazine as compared to metochlopramide (P = 0.009 for all patients and P = 0.006 for those treated with cisplatin), whereas the severity of nausea was the same for both arms in the first 12 h.

Prognostic factors

The impact of the factors known to affect emesis i.e., age, sex and platinum chemotherapy, on response rates in each arm was tested (Table 3, Fig. 2). The impact of other factors which may affect outcome, but are unknown or known factors such as alcohol intake which were not recorded, is reduced by randomising large numbers to make it more likely that these factors are equally distributed between the arms. The CR rates of females receiving metoclopramide were significantly less than for males (P = 0.024 unstratified for cisplatin or P = 0.0057 stratified for cisplatin, Mantel–Haenszel procedure) while this difference was not significant for prochlorperazine (P = 0.8 unstratified for cisplatin and P = 0.4 stratified for cisplatin). The major response rates were less for females than for males on both arms of the study.

Major response rates were significantly lower for younger patients (aged < 55) than older patients (aged 55+) receiving prochlorperazine (P = 0.016 stratified for sex and cisplatin) but not for those receiving metoclopramide (P = 0.25). There were no significant differences between CR rates for younger and older patients (P = 0.42 stratified by arm, sex and cisplatin).

Table 3. Percentage response rates

		Complete response		Major response	
		M(%)	P(%)	M(%)	P(%)
No cisplatin	Male	68	55	79	79
	Female	39	48	67	56
Age	< 55	61	43	78	54
	≥ 55	50	59	71	81
Cisplatin	Male	32	17	45	41
	Female	0	0	0	9
Age	< 55	14	9	14	22
	≥ 55	25	18	40	47

M = Metoclopramide, P = prochlorperazine.

Table 4. Incidence of antiemetic toxicities as recorded by nurses

Toxicity	All patients Metoclopramide (%)	Prochlorperazine (%)
Sedation*		
None	4	3
Mild	39	22
Moderate	46	52
Severe	11	23
Dry mouth†	48	75
Restlessness	53	53
Muscle spasms	17	13
Blurred vision	11	8
Rash	2	1

*$P = 0.004$.
†$P = 0.0002$.

The differences in response rates for the major subgroups studied did not affect the overall comparison of prochlorperazine and metoclopramide [$P = 0.6$ for comparison of CR rates and $P = 1.0$ for comparison of MR rates stratifying by age, sex and cisplatin (Fig. 2)].

Toxicities of antiemetics

The major toxicities were the extrapyramidal side-effects, restlessness or muscle spasms, and the autonomic side-effects, particularly dry mouth and finally, sedation (Table 4).

There was no significant difference in the incidence of extrapyramidal side-effects, but these side-effects were severe enough to discontinue the antiemetic for 5 patients on metoclopramide.

Also, younger patients have extrapyramidal effects more frequently with metoclopramide yet the age imbalance had more younger patients in the prochlorperazine arm. Such side-effects are often difficult to evaluate and report because of their subjectivity. We used categorical scales. Visual analogue scales theoretically provide a greater range for expression of severity allowing for a continuous variable but many patients can only report their experience in broad categories.

There was no severe postural hypotension in the patients receiving prochlorperazine at the dose established from the phase I study. However, the patients were receiving in-patient chemotherapy and most remained in bed.

The only significant differences occurred in clinically minor toxicities. Prochlorperazine caused significantly more sedation then metoclopramide in the first 12 h ($P = 0.0004$). A dry mouth occurred in 75% of patients on prochlorperazine and 48% on metoclopramide ($P = 0.0002$) which persisted throughout the 24 h.

Nurse vs. patient assessments

The results presented above were based on the data collected by the nurses. When the data recorded by observers and patients were compared, similar results for the differences between prochlorperazine and metoclopramide were obtained.

Overall tolerance

Patients were asked to record overall tolerance of the chemotherapy since this assessment takes into account both the efficacy and toxicity of the antiemetic. There was no difference between the two arms with 74% of patients on metoclopramide reporting tolerating their therapy "well" or "very well" as compared to 83% on prochlorperazine.

DISCUSSION

The most striking result is that high-dose prochlorperazine and high-dose metoclopramide achieve equivalent response rates for postchemotherapy nausea and vomiting for both platinum and non-platinum-containing chemotherapy regimens, but that the duration of prochlorperazine's effect is longer in the schedules compared.

Since high-dose metoclopramide has been shown to be a superior antiemetic compared to low conventional doses of prochlorperazine, this result underlines the value of giving higher doses of prochlorperazine, as a preliminary study had suggested [10]. It is also worth emphasising that the equivalence of high-dose prochloroperazine to high-dose metoclopramide extends to cisplatin-treated patients since this was the group of patients which was said to have benefited most from the introduction of high-dose metoclopramide [1, 13]. The longer duration of action of the prochlorperazine may be particularly important in these patients since the prolonged and delayed emesis seen in the cisplatin-treated patients is less frequent if the acute control of emesis is better [7].

The reason for the prolonged duration of action of prochlorperazine may relate to its longer half-life which we have established at between 7 and 8 h [10]. The half-life of high-dose metoclopramide is approximately 6 h [14]. It is interesting to note that the half-life of some of the new 5-hydroxytryptamine 3 receptor antagonist antiemetics is short. For example, ondasetron has a half-life of 3 h, so similar comparisons of the duration of action may be important in the applications of this antiemetic [15].

Prochlorperazine is less expensive than metoclopramide at the doses being compared. On current Australian costs, *each* dose of high-dose metoclopramide (2 mg/kg) is twice as expensive as prochlorperazine (0.8 mg/kg), therefore the five doses of metoclopramide were five times as expensive as the two doses of prochlorperazine, and for equivalent duration of effect even further doses of metoclopramide may have been required.

A sex difference in response has previously been reported for metoclopramide [16–18]. The reason for the inferior result in females is unknown but in analysing antiemetic studies this factor cannot be assessed in isolation, as we have demonstrated by the strong interaction in emetic outcome between having cisplatin-containing chemotherapy and being female. Neither metoclopramide nor prochlorperazine resulted in control of emesis in this group which also shows itself to be more refactory to serotonin antagonists [19].

Age has been reported as a prognostic factor for the severity of emesis, with younger patients not responding as well to metoclopramide as older patients; the dividing line being 50 or 55 years [17, 18, 20, 21]. The current study confirms this for the whole study population but it is more pronounced in the prochlorperazine arm.

The value of combination antiemetic therapy to improve efficacy and decrease toxicity has been increasingly recognised and has been the thrust of many recent studies, which show the value of adding drugs such as sedatives and steroids to other antiemetics [22–26]. It is therefore important to highlight the fact that in our study using the high-dose single agent therapy, only a small percentage of patients (17% for metoclopramide and 16% for prochlorperazine) needed additional antiemetics because of distress caused by emesis.

A major finding in this trial was not only equivalent activity for prochlorperazine and metoclopramide but similar toxicity profiles. Extrapyramidal reactions, always identified as the major toxicity of these drugs, were identified in 50% of patients but were only serious enough to cause discontinuation of metoclopramide in 5 patients.

Prochlorperazine was associated with significantly more sedation than metoclopramide, but rather than being looked upon as an adverse effect, this may be helpful in its antiemetic efficacy.

Certainly we have previously demonstrated that adding a sedative (lorazepam) to antiemetic therapy improved the patient tolerance of the chemotherapy [24].

In evaluating the success of an antiemetic regimen, an assessment of the patient's overall tolerance of chemotherapy balances the antiemetic efficacy with toxicity. In other reported randomised studies, superiority of an antiemetic regimen in controlling emesis has not always translated into patient preference for that regimen. For example, Cunningham *et al.* [27] reported that metoclopramide and dexamethasone in combination were more effective than nabilone with prochlorperazine, yet patients preferred the second antiemetic regimen because it could be given orally rather than intravenously. Patients' tolerance of their therapy after prochlorperazine is as good as after metoclopramide suggesting that the increased sedation and dry mouth seen with prochlorperazine are not serious adverse effects. Therefore, high-dose prochlorperazine is a cost-effective antiemetic for use with cancer chemotherapy with a prolonged duration of action, which requires further evaluation in combination and for indications other than with anticancer chemotherapy.

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