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A Dose Finding Study of Prochlorperazine as an Antiemetic for Cancer Chemotherapy

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Abstract—*This phase I study determined the maximum tolerated dose of prochlorperazine when used as an antiemetic prior to cytotoxic chemotherapy. Initially, cohorts of three patients were given prochlorperazine at escalating doses of* 0.2, 0.4, 0.6, 0.8, 1.0 *and* 1.2 mg/kg *as an intravenous infusion over* 20 *min. The maximum tolerated dose was* 1.2 mg/kg. *The dose-limiting toxicity was hypotension which was reversed by a fluid load. The other major toxicities were extrapyramidal reactions which were dose related. All patients at the* 1.2 mg/kg *dose reported restlessness while five of six were restless and two of six at* 1.0 mg/kg *had muscle spasms. Two of seven patients reported restlessness at the* 0.8 mg/kg *level. Sedation and dry mouth were reported at all dose levels but were more common at higher doses. Prochlorperazine in plasma was assayed by high performance liquid chromatography with electrochemical detection and pharmacokinetics were determined for three patients at the* 1.0 mg/kg *dose level. The average terminal elimination half life was* 7.6 ± 0.4 h, *plasma clearance* 27 ± 5 ml/min/kg *and volume of distribution* 17.7 ± 4.5 l/kg. *The dose of prochlorperazine recommended for further studies of antiemetic efficacy is* 0.8 mg/kg *intravenously.*

INTRODUCTION

NAUSEA AND VOMITING associated with anticancer chemotherapy affects a patient's quality of life and may compromise the delivery of optimal chemotherapy doses [1].

The available antiemetics used in 'conventional' doses have proven of limited efficacy in controlling nausea and vomiting since the introduction of highly emetogenic drugs such as *cis*-platinum and the increasing use of combination chemotherapy.

Until new, highly effective agents to control chemotherapy-induced emesis are found, it is very important that 'standard' antiemetics are used optimally as single agents and in antiemetic combinations. For example, metoclopramide was ineffective in controlling the emesis associated with chemotherapy when given as 20 mg three times a day. This dose was originally recommended for diabetic enteropathy [2]. The increased efficacy of high dose metoclopramide against *cis*-platinum-induced emesis in dogs led to a formal phase I study of metoclopramide in patients. Gralla *et al.* found that metoclopramide was safely given at doses of up to 3 mg/kg [3]. Later studies demonstrated the efficacy of high dose metoclopramide against *cis*-platinum-induced emesis [4, 5].

Prochlorperazine is such a commonly used antiemetic that it is often the control arm in phase III studies to test the efficacy of new antiemetics [4, 6–8]. It is superior to a placebo when used with chemotherapy at conventional doses of 5–25 mg orally or 10 mg intramuscularly but rarely achieves complete control of the emesis [9].

A dose–response relationship for prochlorperazine in relieving platinum-induced gastric distension in mice has been demonstrated in a model being developed to test antiemetics pre-clinically [10]. Higher doses have been found to be more effective than conventional doses in relieving *cis*-platinum-induced emesis in patients [11]. Despite this widespread use no formal dose finding study has been reported.

We performed a phase I study with pharmacokinetics to determine the maximum tolerated dose of prochlorperazine when used to control the nausea and vomiting caused by chemotherapy. We aimed to evaluate the toxicity of high dose prochlorperazine and document its efficacy.

METHODS

Patients

To be eligible, patients with a malignancy and a Karnofsky performance status of greater than 60

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had to be receiving their initial course of intravenous bolus chemotherapy containing an agent likely to cause vomiting, i.e. *cis*-platinum, cyclophosphamide, doxorubicin, daunorubicin, actinomycin D, dacarbazine, nitrogen mustard or streptozotocin.

Written informed consent was obtained. Patients with epilepsy or serious medical or psychiatric illnesses, pregnant women, nursing mothers or patients already taking phenothiazines or having had a prior serious adverse reaction to phenothiazines were ineligible.

Prochlorperazine, as a solution of the mesylate salt in 5% dextrose, was given as an intravenous infusion over 20 min, commencing 30 min prior to the chemotherapy. This infusion schedule was chosen because it had been reported by Carr *et al.* that in doses up to 40 mg it did not cause the hypotension associated with more rapid bolus injections. The starting dose was 0.2 mg/kg with subsequent escalations to 0.4, 0.6, 0.8, 1.0 and 1.2 mg/kg. Cohorts of three patients were entered at each dose level. At or around the maximum tolerated dose, six patients were entered to further define the toxicity, so that a dose suitable for further phase II or III testing could be established. A total of 21 patients were entered onto the study.

Each patient had serial full blood examinations, renal and liver function tests and an electrocardiogram.

The assessment of toxicity and efficacy was based on a patient questionnaire at 24 h and observer assessments for 12 h post treatment according to a schema we have previously proposed [12]. Objective parameters such as blood pressure and number of vomits were assessed by an observer. Subjective sensations were recorded by patients, with nausea and sedation graded on four point ordinal scales as none, mild, moderate or severe. Extrapyramidal and autonomic toxicities were recorded as present or absent. Finally, patients were asked to evaluate their overall tolerance of the course of chemotherapy on a four point scale graded from 'very poorly' to 'very well'.

Pharmacokinetics

Blood samples were taken preinfusion of prochlorperazine then at 10, 20, 30 and 45 min and 1, 2, 3, 4, 6, 12, 18 and 24 h. The samples were centrifuged and plasma stored at −70°C.

A method to assay prochlorperazine was developed at the Institute of Drug Technology, Melbourne, Australia using a high performance liquid chromatograph (HPLC) with electrochemical detection (ECD), since prior to ECD it was not possible to assay therapeutic levels of prochlorperazine in plasma [13]. The method used was based on that reported by Fowler *et al.* [14] and employed a Spherisorb 5 μm nitrile column with a mobile phase of 60% 1 M $NH_4H_2PO_4$ and 40% acetonitrile at a flow rate of 2 ml/min with an ECD set at +0.85 V. Using this system, a 2 ng/ml prochlorperazine standard was found to be the limit of detection. Prior to injection into the HPLC system, prochlorperazine was extracted from the plasma at pH 11 into pentane. To validate the method, blank plasma samples spiked with prochlorperazine mesylate were prepared and extracted. These samples were then assayed and compared with the same range of concentrations of prochlorperazine mesylate in mobile phase. Linearity was shown down to 10 ng/ml in plasma with the average percent recovery 49%, coefficient of variation 15.1% and correlation coefficient 0.969.

Pharmacokinetic parameters were calculated with the aid of a computer using standard model-independent equations [15]. The terminal elimination half life ($t_{1/2}\,\beta$) was estimated by regression analysis of the terminal log-linear portion of the plasma concentration vs. time curve. The total area under this curve (AUC) was calculated by the trapezoidal rule. The equation used for plasma clearance was Cl = Total Dose/AUC, while volume of distribution was determined as $V_d = Cl \times t_{1/2}\beta / 0.693$.

RESULTS

Maximum tolerated dose

The maximum tolerated dose of prochlorperazine given as a 20 min intravenous infusion was 1.2 mg/kg (Table 1). The dose-limiting toxicity was hypotension (Table 2). One hour after the start of the infusion one patient at 1.2 mg/kg had a fall in blood pressure of 55 mmHg systolic with an unrecordable diastolic. Although remaining asymptomatic, this patient required a normal saline fluid load to restore the blood pressure. As a result, a further three patients were entered at the previous dose level of 1.0 mg/kg. A patient at this level also recorded a transient fall in blood pressure of 55 mmHg systolic and 15 mmHg diastolic 30 min post infusion, which spontaneously recovered. Neither of these patients had cardiac disease or had received doxorubicin. No other patient at those dose levels or below recorded falls in blood pressure of greater than 15 mmHg.

The other major toxicities were extrapyramidal effects. Restlessness or tremulousness was noted by all but one patient at 1.2 and 1.0 mg/kg and two of three patients at 0.8 mg/kg. This required no specific treatment. No severe dystonic reactions, or the common facial dystonias were seen but two patients at the 1.0 mg/kg dose level recorded a sensation of muscle spasms, one lasting only minutes and another for 8 h described as affecting the shoulders. We had planned to use benztropine or valium to

Table 1. *Prochlorperazine efficacy*

Patient No.	Prochlorperazine dose (mg/kg)	Chemotherapy	Observed No. vomits	Overall tolerance (1–4)
1	0.2	BVLD	3	1
2	0.2	A/C	9	2
3	0.2	A/C	3	1
4	0.4	V/A/C	0	1
5	0.4	DDP/VP16	6	2
6	0.4	A	6	1
7	0.6	C/A/V/P	1	1
8	0.6	A/C	0	1
9	0.6	A	0	2
10	0.8	C/A/DDP	3	1
11	0.8	DDP/VP16	4	1
12	0.8	DDP/5FU	2	1
13	1.0	DDP/IFN	1	2
14	1.0	CBDCA/5FU	0	1
15	1.0	DDP/C	2	2
16	1.0	DDP/V16/B	6	2
17	1.0	DDP/V16	9	3
18	1.0	A	18	3
19	1.2	DDP/V16/B	0	2
20	1.2	DDP	4	3
21	1.2	5FU/A/M	0	2

B = bleomycin; V = vincristine; L = lomustine; D = dacarbazine; A = Adriamycin®; C = cyclophosphamide; DDP = *cis*-platinum; VP16 = etoposide; P = prednisolone; 5FU = 5-fluorouracil; IFN = interferon; CBDCA = carboplatin; M = mitomycin C.

Table 2. *Prochlorperazine toxicity*

Toxicity	Dose level (mg/kg) (No. of patients)					
Dose level	0.2	0.4	0.6	0.8	1.0	1.2
Total patients	(3)	(3)	(3)	(3)	(6)	(3)
Restlessness	0	1	0	2	5	3
Muscular spasm	0	1	0	0	2	0
Dry mouth	3	2	1	1	4	3
Observed sedation (Grade 2–3)	2	0	1	2	4	3
Diarrhoea	1	0	0	0	2	1
Greatest change in blood pressure (systolic/dystolic)	1/15	7/20	30/15	30/15	55/15	55/?

treat these effects but no cases required treatment. These effects were dose related as neither muscle spasm nor restlessness were reported below 0.8 mg/kg except for one patient complaining of vague intermittent restlessness at 0.4 mg/kg.

Sedation and dry mouth were experienced by patients at all dose levels. Dry mouth was more common at higher doses with all patients at the 1.2 mg/kg and four of six patients at 1.0 mg/kg reporting this side-effect. Sedation was usually only mild or moderate except in patients who required additional sedatives to control restlessness or muscle spasm.

Minor toxicities included diarrhoea in three patients at the 1.2 mg/kg level while one patient reported blurred vision and another a feeling of 'detachment' in the first 24 h period.

Efficacy

All patients were asked to assess on a four point scale ranked from 'very poorly' to 'very well' how they tolerated the chemotherapy course with prochlorperazine as the only antiemetic. At 0.8 mg/kg and below, all patients reported tolerating the therapy 'well' or 'very well' although the vomiting was better controlled at higher doses. The patients at the 1.2 and 1.0 mg/kg levels who tolerated the treatment poorly did so because of the side-effects of the prochlorperazine. At the 1.2 mg/kg level two patients had no vomiting after *cis*-platinum and

Table 3. Pharmacokinetic parameters calculated from plasma concentrations of prochlorperazine in those patients given 1.0 mg/kg

	Patient No. 1	2	3
Actual dose (mg)	51	78	60
Peak concentration (ng/ml)	314	589	309
Time of peak (min)	10	30	45
$t_{1/2}\beta$ (h)	7.9	7.8	7.1
AUC 0–∞* (ng/ml × h)	522	623	873
Plasma clearance (ml/min/kg)	32	27	22
Volume of distribution (l/kg)	22	18	13

*AUC 0–∞ = area under the plasma concentration time curve from time zero to infinity.

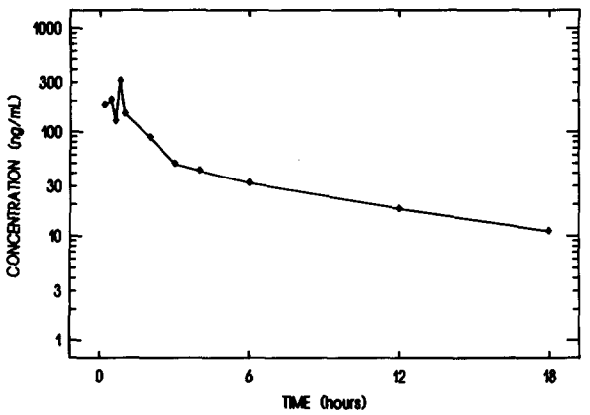

Fig. 1. Semilogarithmic plot of plasma concentration of prochlorperazine vs. time in a representative patient receiving 1.0 mg/kg *as a* 20 *min infusion (total dose =* 60 mg).

doxorubicin respectively while the third had only four vomiting episodes after platinum.

At the 0.8 mg/kg level all patients received regimens containing *cis*-platinum and reported only two, three and four vomiting episodes over 24 h respectively, while tolerating the prochlorperazine well.

On the basis of these results we recommend 0.8 mg/kg as the dose of prochlorperazine for further phase II and III antiemetic studies.

Pharmacokinetics

Pharmacokinetic analysis was done on plasma samples from three patients entered at 1.0 mg/kg (Table 3). The mean values for terminal elimination half-life, plasma clearance, and apparent volume of distribution were 7.6 ± 0.4 h, 27 ± 5 ml/min/kg and 17.7 ± 4.5/l/kg. The plasma concentration vs. time curve for a representative patient (No. 3) demonstrates a biphasic elimination profile (Fig. 1) with a somewhat erratic initial 'distribution' phase followed by a well-defined terminal elimination phase.

DISCUSSION

One of the difficulties in assessing published antiemetic studies is that the drugs are often given in differing doses and schedules [12]. Whereas phase I studies to define optimal doses are performed for newly introduced antiemetics such as the serotonin antagonists, this is not the case for all of the older agents [16]. Re-evaluating older agents such as metoclopramide has led to the finding of increased efficacy at higher doses. Other common drugs such as steroids and prochlorperazine have not been assessed in this way.

In this study we have established the maximum intravenous dose for prochlorperazine in a formal phase I trial. The maximum dose reached of 1.2 mg/kg is six times the conventional dose and antiemetic efficacy was seen at these higher doses. Since major toxicity is unacceptable for an antiemetic, 0.8 mg/kg or four times the conventional dose is recommended as a safe dose for phase II or III trials. This is two dose levels below the MTD and the lack of major toxicity at this level should allow multiple dosing with a dose interval estimated from the pharmacokinetic data of 8 h. Carr *et al.* have already demonstrated a dose response relationship for prochlorperazine when empirically escalated up to 40 mg (between 0.5 and 0.6 mg/kg) for control of *cis*-platinum-induced emesis [19].

Few attempts at assaying prochlorperazine have been reported [13, 14, 17] with consequently little information available on its disposition. Our pharmacokinetic parameters are comparable to those of the only other published pharmacokinetic study, which used doses of 6.25 and 12.5 mg as a bolus intravenous injection in healthy volunteers [18]. This suggests that prochlorperazine elimination is not significantly dose-dependent at therapeutic doses. The drug is hydrophobic, and this may explain its high apparent volume of distribution and rapid plasma clearance since sequestration into adipose and muscle tissue is likely. Uptake into red blood cells might also account for the high plasma clearance. The half life is an indicator of the dosing interval which at high doses should be 8 h or more. This differs markedly from the 4–6 h often advocated at lower doses [9, 19]. This may allow less frequent dosing schedules than are required for metoclopramide [4].

The side-effects of prochlorperazine at the 0.8 mg/kg level are tolerable since severe hypotension or the uncomfortable extrapyramidal effects were not seen until the dose was above this level. Dryness of the mouth was transient, and sedation may be beneficial in the control of emesis, as has been reported in studies which add sedatives to low dose prochlorperazine [20].

The information documented in this study will aid further testing of high dose prochlorperazine for its efficacy as an antiemetic with cancer chemotherapy, or for more general use.

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REFERENCES

1. Coates A, Abraham S, Kaye SB *et al.* On the receiving end—patient perception of the side effects of cancer chemotherapy. *Br J Cancer Clin Oncol* 1983, **19**, 203–208.
2. Moertel CG, Reitemeier RJ. Controlled clinical studies of orally administered antiemetic drugs. *Gastroenterology* 1969, **57**, 262–268.
3. Gralla RJ, Braun TJ, Squillante A *et al.* Metoclopramide: initial clinical studies of high dosage regimens in cisplatin induced emesis. In: Poster D, Penta J, Bruno S, eds. *Treatment of Cancer Chemotherapy Induced Nausea and Vomiting*. New York, Masson, 1981, 167–175.
4. Gralla RJ, Itri LM, Pisko SE *et al.* Antiemetic efficacy of high dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy induced nausea and vomiting. *N Engl J Med* 1981, **305**, 905–909.
5. Meyer BR, Lewin M, Drayer DE *et al.* Optimizing metoclopramide control of *cis*-platinum induced emesis. *Ann Intern Med* 1984, **100**, 393–395.
6. Markman M, Sheidler V, Ettinger DS *et al.* Antiemetic efficacy of dexamethasone: randomized, double-blind, crossover study with prochlorperazine in patients receiving cancer chemotherapy. *N Engl J Med* 1984, **311**, 549–552.
7. Johansson R, Kilkku P, Groenvoos M. A double blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. *Cancer Treat Rev* 1982, **9**, 25–33.
8. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 1980, **302**, 135–138.
9. Wampler G. The pharmacology and clinical effectiveness of phenothiazines and related drugs for managing chemotherapy induced emesis. *Drug* 1983, **25** (suppl 1), 33–51.
10. Olver IN, Roos IA, Thomas K, Hillcoat BL. The effect of escalating doses of prochlorperazine on *cis*-platinum (DDP) induced gastric distension in mice. *Proc Am Assoc Cancer Res* 1987, **28**, 1703.
11. Carr BI, Blayney DW, Goldberg DA, Braly P, Metter GE, Doroshow JH. High doses of prochlorperazine for *cis*-platinum induced emesis: a prospective, random dose response study. *Cancer* 1987, **60**, 2165–2169.
12. Olver IN, Simon RM, Aisner J. Antiemetic studies: a methodological discussion. *Cancer Treat Rep* 1986, **70**, 555–563.
13. Sankey MG, Holt JE, Kaye CM. A simple and sensitive HPLC method for the assay of prochlorperazine in plasma. *Br J Clin Pharmac* 1982, **13**, 578–580.
14. Fowler A, Taylor W, Bateman DN. Plasma prochlorperazine assay by high performance liquid chromatography—electrochemistry. *J Chromatogr* 1986, **380**, 202–205.
15. Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd edn. New York, Marcel Dekker, 1982.
16. Kris MG, Gralla RJ, Clark RA, Tyson LB. Dose-ranging evaluation of the serotonin antagonist GR-C507/75 (GR 38032F) when used as an antiemetic in patients receiving anticancer chemotherapy. *J Clin Oncol* 1988, **6**, 659–669.
17. Midha KK, Harves EM, Raauw G *et al.* Radioimmunoassay for prochlorperazine in human plasma. *Ther Drug Monitor* 1983, **5**, 117–121.
18. Taylor WB, Bateman DN. Preliminary studies of the pharmacokinetics and pharmacodynamics of prochlorperazine in healthy volunteers. *Br J Clin Pharmac* 1987, **23**, 137–142.
19. Carr BI, Bertrand M, Browning S *et al.* A comparison of the antiemetic efficacy of prochlorperazine and metoclopramide for the treatment of cisplatin-induced emesis: a prospective, randomized double-blind study. *J Clin Oncol* 1985, **3**, 1127–1132.
20. Bishop J, Olver IN, Wolf MM *et al.* Lorazepam: a double blind, crossover study of a new antiemetic in patients receiving cytotoxic chemotherapy and prochlorperazine. *J Clin Oncol* 1984, **2**, 691–695.