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ORIGINAL ARTICLE

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Continuous infusion prochlorperazine: pharmacokinetics, antiemetic efficacy, and feasibility of high-dose therapy

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Abstract *Purpose*: The purpose of these sequential phase I studies was to evaluate the antiemetic efficacy and pharmacokinetics of high-dose continuous infusion prochlorperazine. *Methods*: A total of 52 patients with advanced cancer were treated in two sequential phase I studies utilizing high-dose prochlorperazine. In study 1, designed to investigate the antiemetic effects of dose-intensive prochlorperazine, various cisplatin-based multiagent chemotherapeutic regimens were administered in combination with escalating doses of prochlorperazine. In study 2, a fixed dose of cisplatin (60 mg/m^2) was administered over 24 h as a continuous intravenous infusion in combination with infusional high-dose prochlorperazine. Antiemetic efficacy in the first trial was assessed in terms of the number of episodes of nausea, retching, and/or emesis during the 24 h following cisplatin administration. The pharmacokinetics of high-dose prochlorperazine were evaluated in eight patients treated in study 2 at the two dose levels below those at which dose-limiting toxicity was noted. *Results*: The maximally tolerated dose of prochlorperazine in combination with cisplatin (60 mg/m^2 administered as a continuous infusion over 24 h) was 24 mg/h. The dose-limiting toxicity was grade 4 agitation and confusion noted in one patient treated at 26 mg/h. This patient died 3 days following cessation of chemotherapy due to the toxicity of the regimen in combination with the debilitating pulmonary effects of the disease. The mean end of infusion prochlorperazine level at the 24 mg/h dose level was 1.1 μM, a concentration previously reported to be consistent with the reversal of the multidrug resistance phenotype. Two partial responses were observed in study 2. *Conclusions*: We conclude that the antiemetic efficacy of high-dose infusional prochlorperazine does not appear to be improved over more convenient bolus administration. However, prochlorperazine levels consistent with those required in vitro for drug resistance reversal are attainable within the dose range having a tolerable toxicity profile.

Key words Prochlorperazine · Continuous infusion

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Introduction

The success rates of modern chemotherapy treatment programs for metastatic solid tumors have improved, but remain modest, due to side-effect profiles that limit the intensity of treatment, or because of the development of acquired drug resistance. Strategies under investigation to improve the efficacy of chemotherapeutic agents include the coadministration of drugs that may increase tumor cell sensitivity [1, 2, 3]. Efforts to decrease the toxicity of chemotherapy include the delivery of newer antiemetic agents [4] and the use of hematopoietic growth factors.

Until the development of $5HT_3$ antagonists, phenothiazines were the mainstay of antiemetic therapy. Their efficacy has been shown to be dose-related when delivered by intermittent i.v. bolus [5]. Recent in vitro studies suggest that in addition to its antiemetic activity, coadministration of prochlorperazine can ameliorate the renal toxicity of the nitrosoureas and platinum analogues [6]. Furthermore, phenothiazines exhibit chemomodulating as well as growth inhibitory effects in cell culture,

perhaps through their activity as calmodulin blockers [7, 8, 9, 10, 11].

The objectives of these sequential phase I studies were: (1) to examine the antiemetic efficacy of high-dose prochlorperazine (study 1), and (2) to evaluate the feasibility and determine the maximally tolerated dose of high-dose prochlorperazine in combination with fixed-dose continuous-infusion cisplatin (study 2). We report the results of these trials.

Patients and methods

Patient selection

A total of 52 patients were treated on sequential, phase I dose escalation protocols. In study 1, 37 patients were treated with escalating doses of continuous infusion prochlorperazine in addition to platinum-containing multiagent chemotherapy regimens (see Table 1). In study 2, 16 patients were treated with high-dose prochlorperazine (escalating doses) combined with a fixed dose of cisplatin (60 mg/m^2) administered as a 24-h continuous infusion. All patients were required to be undergoing a course of emetogenic, platinum-containing chemotherapy and to weigh at least 50 kg, and were required not to have history of phenothiazine hypersensitivity, seizure disorder, psychiatric disturbances requiring medication, active clinical depression, any degenerative central nervous system disorder or brain metastases, and in all patients other antiemetics, tranquilizers, or sedative preparations had to be able to be discontinued for the 24 h of therapy. Pregnant patients or patients with insulin-dependent diabetes were ineligible. Additional eligibility criteria for study 2 included a Karnofsky performance status of 60% or higher, evidence of adequate renal function as shown by a 24-h creatinine clearance of ≥50 ml/min or serum creatinine ≤ 1.5 mg/dl. Adequate bone marrow function for enrollment was defined as a total white count ≥4000/μl with a normal differential count, platelet count ≥150,000/μl, and hemoglobin ≥10 g/dl (patients may have been transfused to meet the hemoglobin requirement). Adequate hepatic function was defined as serum bilirubin ≤ 1.5 mg/dl, and SGOT and SGPT less than twice the institutional upper limit of normal. Patients must have had a normal pretreatment audiogram. All patients voluntarily signed a consent document reviewed and approved by the City of Hope National Medical Center Institutional Review Board.

Pretreatment evaluation

All patients had a complete history and physical examination including documentation of weight, Karnofsky performance status, the presence of measurable or evaluable disease, a complete blood count with platelet count and differential, and an 18-channel blood chemistry analysis. Additional testing for study 2 included a chest radiograph, urinalysis, electrocardiogram, audiogram, and a 24-h creatinine clearance determination. Patients with measurable disease were required to repeat appropriate scans for analysis of measurable disease after every two cycles of chemotherapy.

Table 1 Total number of courses administered. Cisplatin was administered at a dose of 40 mg/m^2 (range 5–100 mg/m^2) in study 1, and at 60 mg/m^2 in study 2

Prochlorperazine dose (mg/h)	Study 1 ($n=36$)	Study 2 ($n=16$)
8	4	
10	5	
12	5	
14	4	
16	4	
18	4	
20	4	
22	4	12
24	2	13
26		5

Treatment plan

This is a report of two sequential phase I studies utilizing escalating doses of prochlorperazine, in study 1 in combination with various cisplatin-containing multiagent chemotherapy regimens, and in study 2 in combination with a fixed dose of single-agent cisplatin delivered as a 24-h continuous i.v. infusion as described below and summarized in Table 1. Standard Southwest Oncology Group response criteria were used in patients having measurable or evaluable disease. The toxicities were measured using version one of the Common Toxicity Criteria of the National Cancer Institute. Because of the potential for neurologic toxicity, the following additional criteria were developed for evaluation of sedation and dyskinesia: *level 1* sleepiness/feelings of restlessness; *level 2* deep lethargy/akathisia; *level 3* obtundation/Parkinsonian movements, any type of dystonia in the presence of diphenhydramine treatment; *level 4* delirium, stupor, coma/tardive dyskinesia, neuroleptic malignant syndrome, opisthotonos.

Prochlorperazine doses in study 1 were begun at 8 mg/h for 24 h and were escalated by 2 mg/h per dose level until a dose level of 24 mg/h was reached. In study 2, cisplatin, 60 mg/m^2 administered as a 24-h continuous infusion, was combined with prochlorperazine doses that began at 22 mg/h (dose level 8), and were escalated by 2 mg/h until the study was closed at the 26 mg/h dose level.

All patients received prochlorperazine, 30 mg, as an i.v. loading dose over 20 min and diphenhydramine 12.5 or 25 mg, as an i.v. bolus beginning 30 min prior to the administration of chemotherapy. Diphenhydramine, 5 mg by i.v. bolus was administered 2, 6, 12, and 18 h after the start of the chemotherapy at prochlorperazine dose levels between 8 and 20 mg/h. At 22–26 mg/h prochlorperazine, diphenhydramine 12.5 mg i.v. was administered 1, 6, 12, and 18 h after the initiation of the prochlorperazine infusion. All patients enrolled in study 2 received mannitol 12.5 mg 8, 16, and 24 h after the initiation of the infusion.

Because of the side effects of sedation and orthostatic hypotension, all patients were advised to remain recumbent during the prochlorperazine infusion. For essential bathroom needs they were accompanied to the bathroom or to the bedside commode.

Pharmacokinetic evaluation

Pharmacokinetic evaluation was performed in a subset of patients treated in study 2. Plasma samples were drawn immediately prior to treatment, then at 2, 8, 16, and 24 h after initiation of the prochlorperazine infusion, and 6 h following its completion. Plasma prochlorperazine concentrations were determined using a modification of a previously described high-performance liquid chromatographic (HPLC) method [12]. Briefly, following the addition of chlorpromazine as an internal standard, a 0.25-ml aliquot of plasma was alkalinized with sodium hydroxide and extracted with a 4:1 mixture of diethylether/chloroform. The organic layer was evaporated to dryness, the residue reconstituted in 0.5 ml methanol, and 100 μl was injected for analysis. The HPLC system consisted of a Phenomenex (Torrance, Calif.) 150 × 4.6 mm cyano analytical column. Separation was achieved using a mobile phase of 50 m*M* sodium acetate buffer, pH 4, with 40% methanol and 18% acetonitrile (v/v) at a flow rate of 1.2 ml/min. Detection of prochlorperazine and the internal standard was performed by ultraviolet spectrophotometry at a fixed wavelength of 250 nm. Under these HPLC conditions, the plasma prochlorperazine standard curve was linear in the range 50–1000 ng/ml, with inter- and intraday coefficients of variation ≤ 10%.

Statistical analysis

Episodes of nausea (subjective sensation of an impulse to vomit), retching (defined as dry heaves), and emesis were recorded for each patient treated on study 1. Sedation and dystonia levels were analyzed according to the criteria defined above. The maximally tolerated dose of continuous infusion prochlorperazine in combination with infusional fixed-dose cisplatin in study 2 was determined by standard phase I criteria: two episodes of grade 3 or one episode of grade 4 toxicity defined the dose-limiting toxicity. The maximally tolerated dose was defined as one dose level below the dose at which the dose-limiting toxicity was observed. The dose response for number of emeses, nausea, and retching episodes was estimated by Poisson regression, with an adjustment for overdispersion [13].

Results

Patient characteristics

The patient characteristics in studies 1 and 2 were comparable and are summarized in Table 2. In study 1 there were 22 males and 15 females, median age 54 years (range 30–78 years), and in study 2 there were 2 males and 14 females, median age 47 years (range 29–71 years). The primary tumor sites included lung, breast, and gastrointestinal carcinomas, melanoma, and miscellaneous histologies in the two studies in equivalent proportions. The median Karnofsky performance status was 80% and 90% in the two studies (range 60–100%).

Antiemetic efficacy

The mean numbers of episodes of nausea and of emesis and retching by prochlorperazine dose level are illustrated in Fig 1a, b. The cumulative numbers of episodes of nausea, emesis, and retching by prochlorperazine dose level and cisplatin dose level, and as a function of time following cisplatin chemotherapy, are illustrated in Fig. 2a–c. There was no prochlorperazine dose-effect noted, nor was there an apparent difference in the number of episodes of emetic symptoms observed with increasing cisplatin doses. The greatest number of emetic events occurred in the 3–6-h post-cisplatin time period, with the symptoms substantially subsiding after 12 h. In study 2, in which a fixed-dose of cisplatin was administered to all patients in combination with three dose levels of prochlorperazine, varying degrees of nausea and emesis occurred without evidence of a prochlorperazine antiemetic dose-response.

Table 2 Patient characteristics (values are numbers of patients)

	Study 1 ($n=36$)	Study 2 ($n=16$)
Age ranges (years)		
21–40	9	5
41–60	20	6
61–70	6	4
71–80	1	1
Karnofsky performance status (%)		
90–100	12	11
70–80	20	4
60	4	1
Gender		
Male	21	2
Female	15	14
Histology		
Lung	7	4
Breast	2	2
GI	11	2
Melanoma	4	2
Other	12	6
Prior therapy		
Surgery	36	16
Radiation	13	9
Chemotherapy	19	16

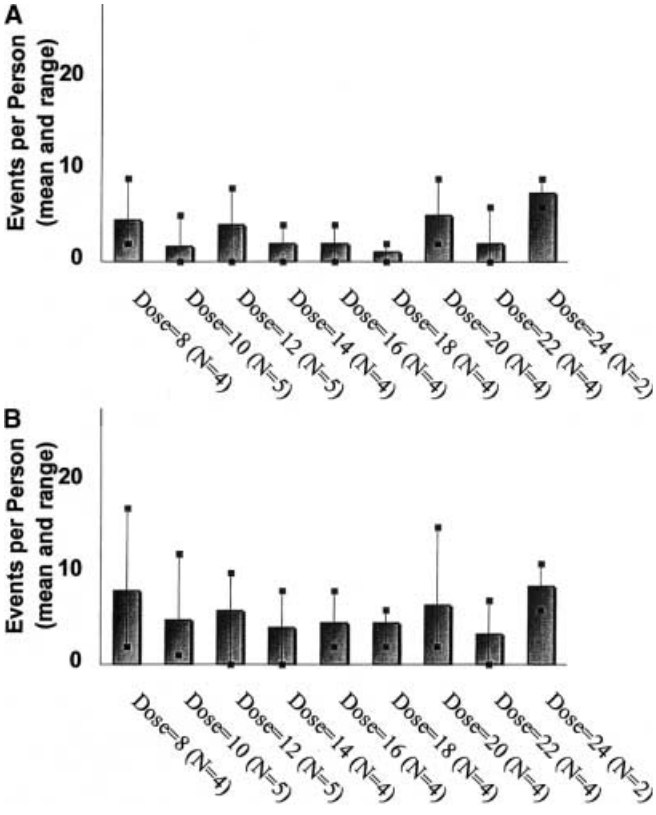

Fig. 1a, b Mean numbers of nausea (**a**) and retching and emesis (**b**) events by prochlorperazine dose (mg/h)

Neurologic toxicity

Essentially all patients experienced sedation at level 1 regardless of the prochlorperazine dose, and 11 experienced varying levels of dyskinesia which were not related to the administered dose of prochlorperazine (see Table 3). The dose-limiting toxicity observed in study 2 was one episode of grade 4 agitation and confusion (delirium).

Pharmacokinetic analysis

Pharmacokinetic analysis was performed on specimens from eight patients treated in study 2, four patients each

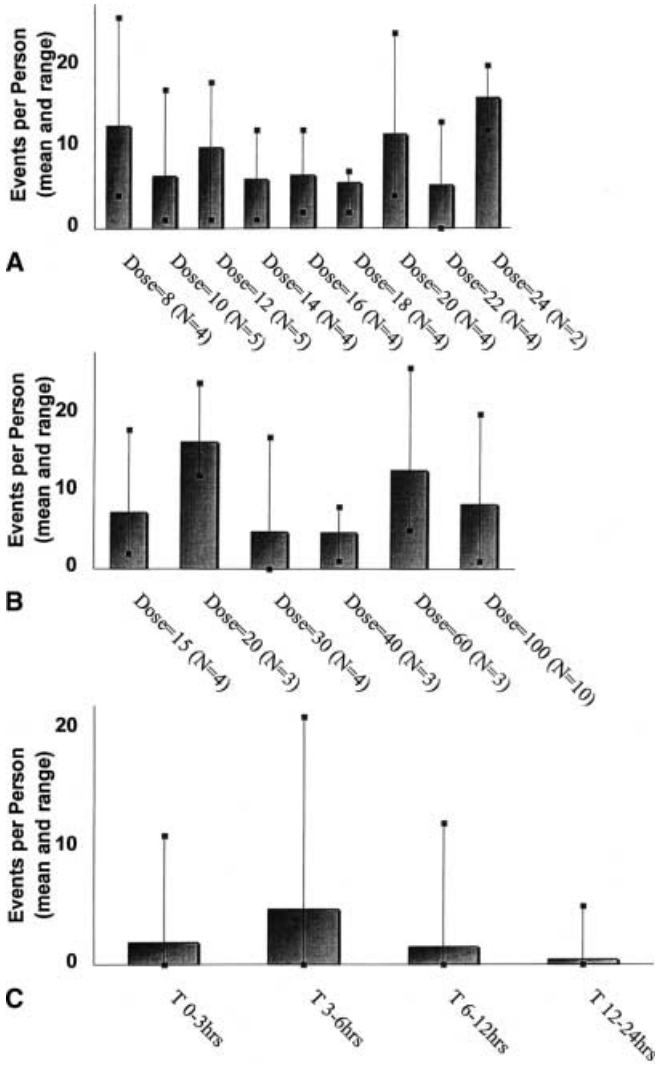

Fig. 2a–c Nausea, emesis, and retching events by (**a**) prochlorperazine dose, (**b**) cisplatin dose, and (**c**) with time following cisplatin administration. Neither a prochlorperazine dose-effect nor a difference in episodes of emetic symptoms was noted with increasing cisplatin doses. The majority of emetic events occurred in the 3–6-h post-cisplatin time period

Table 3 Number of episodes of sedation and dystonia by dose level according to the scheme outlined in the Treatment plan

Prochlorperazine dose (mg/h)	No. of patients experiencing grade 1 sedation	Maximum dystonia level (no. of patients)
8	4	
10	5	3 (2), 1 (1)
12	3	2 (1)
14	4	3 (1)
16	4	3 (1)
18	4	2 (1)
20	4	2 (1), 1 (1)
22	4	1 (1)
24	4	3 (1)
26	2	4 (1)

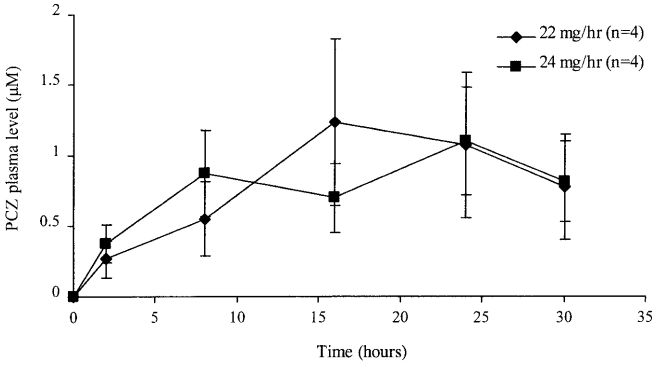

Fig. 3 Plasma prochlorperazine (*PCZ*) concentrations by dose level administered, with the median concentration and range shown

at the 22 mg/h and 24 mg/h dose levels. The results are shown in Fig. 3. The mean plasma levels of prochlorperazine at 2, 8, 16, 24 and 30 h were 0.37, 0.87, 0.70, 1.10 and 0.82 μ*M* at 22 mg/h, and 0.55, 0.94, 0.98, 1.07 and 0.78 μ*M* at 24 mg/h. The mean peak plasma concentration of the patients analyzed at the two dose levels at the end of the infusion was 1.1 ± 0.35 μ*M*.

Other toxicities

With the exception of neurologic toxicity, the observed toxicities were attributable to the platinum-containing chemotherapeutic regimens. One initial patient treated in study 2 received cisplatin 100 mg/m^2 and experienced grade 4 thrombocytopenia and granulocytopenia; the dose of infusional cisplatin was subsequently reduced to 60 mg/m^2. Mild (grade 2) anemia was noted in two patients, and one patient experienced grade 3 anemia. Neither grade 3 or 4 leucopenia nor thrombocytopenia were observed in any other patient or cycle. One patient in study 2 was withdrawn due to a decrease in 24-h creatinine clearance from 51 to 39 ml/min following the initial cycle of treatment. One patient with lung carcinoma died 3 days following treatment on this study after experiencing agitation and confusion (delirium). This was considered the dose-limiting toxicity and the protocol was closed following this episode.

Reasons for discontinuation of treatment and therapeutic efficacy

Of the 16 patients entered into study 2, 2 showed a partial response and 3 had stable disease. Nine patients progressed, four following one cycle of treatment and five following two cycles of treatment. The final patient treated in study 2 was inevaluable for response as she died 3 days following treatment due to respiratory failure. The patients experiencing partial responses included the one patient with lung carcinoma who was withdrawn from treatment after one cycle due to a decreased creatinine clearance; this patient died 11 months following

treatment. One patient with metastatic squamous cell carcinoma of unknown primary received four cycles of treatment prior to disease progression. Of the three patients with stable disease, one patient with ovarian carcinoma refused further treatment following two cycles, and one patient with laryngeal cancer was withdrawn from treatment following one cycle of therapy due to an abnormal audiogram. She was treated with a second cycle of cisplatin alone but subsequently developed an elevated serum creatinine level after two cycles, when platinum-containing treatment was discontinued. The third patient had lung cancer and received five cycles of treatment and then progressed.

Discussion

Phenothiazines have been used as the mainstay of antiemetic therapy for many years. More recently, increased understanding of mechanisms of resistance to chemotherapeutic agents has resulted in efforts to administer chemomodulating agents designed to reverse acquired cellular resistance. Calmodulin inhibitors, such as the phenothiazines, have been shown to exhibit such activity in vitro, probably by altering cellular signaling pathways [3, 7, 9, 10, 14]. Enhanced DNA damage and cytotoxicity has been reported in vitro for combinations of calmodulin antagonists and a variety of chemotherapeutic agents including streptozotocin, dacarbazine, actinomycin D, mitoxantrone, methotrexate, 5-fluorodeoxyuridine, doxorubicin, and cisplatin [14].

To be effective clinically, it must be possible to administer dosages of the chemomodulator in vivo that approach that necessary for drug-resistance reversal in vitro. In these studies, we demonstrated that sustained administration of high-dose prochlorperazine is tolerable when delivered as a 24-h continuous infusion. Plasma levels were achieved which have been shown to reverse acquired cisplatin or anthracycline resistance in vitro [14, 15].

The toxicity of the phenothiazines includes sedation and the appearance of dyskinesias. More rarely, a severe ''neuroleptic malignant syndrome'', characterized by fever, rigidity, tremulousness, autonomic instability and obtundation, has been reported, which may exhibit mortality rates of up to 20% [16]. To assess these possible neurologic side effects of high-dose prochlorperazine, we utilized specific sedation and dyskinesia criteria outlined above. Sedation was universal at all doses. Interestingly, dystonic reactions were noted in only a few patients and were reversible with diphenhydramine. Several patients suffered from mild dystonic reactions many hours after discontinuation of the prochlorperazine infusion. We hypothesize that this may have been due to the release of the drug from fat stores for prolonged periods following the end of infusion. Sedation was reversible within 12–24 h following the discontinuation of prochlorperazine. With the exception of the symptoms that occurred in the patient who experienced dose-limiting confusion and agitation, all other neurologic effects of the infusion were tolerable. There were no instances of neuroleptic malignant syndrome noted in either of these two studies.

Several studies have shown that the antiemetic effect of the phenothiazines is dose-related, with higher doses exhibiting increased antiemetic efficacy. Carr et al. [5] treated 71 patients receiving cisplatin chemotherapy in a randomized trial of four different doses of prochlorperazine administered as intermittent boluses ranging from 10 to 40 mg every 3 h for three doses. A significant relationship was observed between the administered dose of prochlorperazine and the antiemetic effect. The observation in our trial that episodes of nausea or emesis with increasing cisplatin doses were unchanged suggests the possibility of a modest antiemetic effect of the high plasma levels of prochlorperazine. This level of efficacy appears to be comparable to the more convenient and less toxic bolus administration. More effective combination or single-agent antiemetic regimens including $5HT_3$ antagonists, glucocorticoids, and benzodiazepines are necessary to significantly relieve cisplatin-induced nausea.

We have shown that concurrent administration of high doses of infusional prochlorperazine in combination with platinum-based chemotherapy is tolerable and feasible at doses up to 24 mg/h for 24 h. The major toxicity experienced was sedation and dystonia. Antiemetic efficacy of continuous infusion high-dose prochlorperazine appears to be equivalent to the more easily administered bolus-dosing schedule. We are currently attempting to assess efficacy by utilizing infusional prochlorperazine in a subsequent phase I trial to evaluate combinalism.

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