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A phase I/II study of the 5-HT3 antagonist GR38032F in the anti-emetic prophylaxis of patients receiving high-dose cisplatin chemotherapy

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Summary. A total of 24 patients who were receiving combination chemotherapy (POMB) including cisplatin at a dose of 100 – 120 mg/m^2 were treated with the 5HT3 antagonist GR38032F (GR) as an anti-emetic prophylaxis. GR was given as a 15-min loading infusion followed by a 24-h infusion at three escalating dose levels of 1, 2 and 4 mg/h. In the first 24 h after commencing treatment, six patients had complete control of nausea and vomiting (CR), two had 1 – 2 emetic episodes (MR) and five had 3 – 5 emetic episodes (mR). The major response rate (CR + MR) was thus 35%. Eight responding patients (CR or MR) went on to receive oral GR at 8 or 12 mg t. i. d. for 5 days. In this group there was one CR, one MR, two mRs and four failures (F). There was no evidence of an improved therapeutic effect with increasing dose in either the infusion or the oral section of the study, although numbers were limited in the latter part of the trial. Toxicity was mild, with low-grade headache affecting 25% of patients being the most frequent side effect. Pharmacokinetic data was obtained in six patients at each dose level. There was a progressive rise in clearance with increasing dose, indicating that the kinetics are non-linear. However, there was no evidence of an association between high plasma levels and therapeutic efficacy. GR38032F is well tolerated and has promising single-agent activity in preventing vomiting induced by high-dose cisplatin.

Introduction

High-dose metoclopramide is one of the most effective agents for the prevention of chemotherapy-induced nausea and vomiting [5]. This drug appears to have a number of different mechanisms of action, but there is evidence that blockade of 5HT3 receptors, both centrally and in the gastro-intestinal tract, is one of the most important [2, 7]. This discovery led to the development of specific 5HT3 receptor antagonists that have enhanced anti-emetic activity but lack the dopaminergic side effects of metoclopramide.

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GR38032F is one of the first 5HT3 antagonists to enter clinical trials. Pre-clinical studies have shown this compound to abolish cisplatin-induced vomiting in the ferret model [3] and to have no demonstrable effect on dopamine receptors [1]. In initial studies in human volunteers, the only side effects noted were mild headache and transient elevation of serum hepatic transaminases (Glaxo Inc., data on file). Moreover, early clinical trials suggest that GR38032F is highly effective in preventing nausea and vomiting in patients receiving a variety of chemotherapeutic regimens [4, 6].

The aims of the present study were to assess the effectiveness of GR38032F in a group of patients receiving high-dose cisplatin (100 – 120 mg/m^2) and to determine whether or not a dose-response effect could be demonstrated.

Patients and methods

A total of 24 patients who were receiving POMB (Table 1) chemotherapy were included in the study. 10 of these patients had received prior cisplatin-based chemotherapy and were refractory to anti-emetic prophylaxis involving high-dose metoclopramide + dexamethasone + lorazepam; the remaining 14 patients had received no previous chemotherapy. Patient characteristics are shown in Table 2.

Pre-treatment investigations included a full blood count, biochemical profile, as well as determinations of hepatic transaminases and bilirubin. These tests were repeated at the completion of the GR38032F infusion and again 7 days later. Patients with serious co-existing medical conditions and those with significant hepatic (>2 times the upper limit of normal for bilirubin or transaminases) or renal (EDTA clearance, <50 ml/min) dysfunction were excluded from the trial. The protocol was approved by the local ethical committee and all patients gave written informed consent.

The POMB chemotherapy schedule involves the administration of vincristine, methotrexate and bleomycin on days 1 – 3, followed by a 12-h infusion of cisplatin on day 4. During days 1 – 3, low-dose metoclopramide (10 – 20 mg g. i. d.) was allowed as anti-emetic cover but had to be withdrawn at least 12 h before the start of the cisplatin infusion. GR38032F was given as a loading infusion over 15 min, commencing 30 min prior to the start of the cisplatin infusion and followed by a 24-hour infusion via

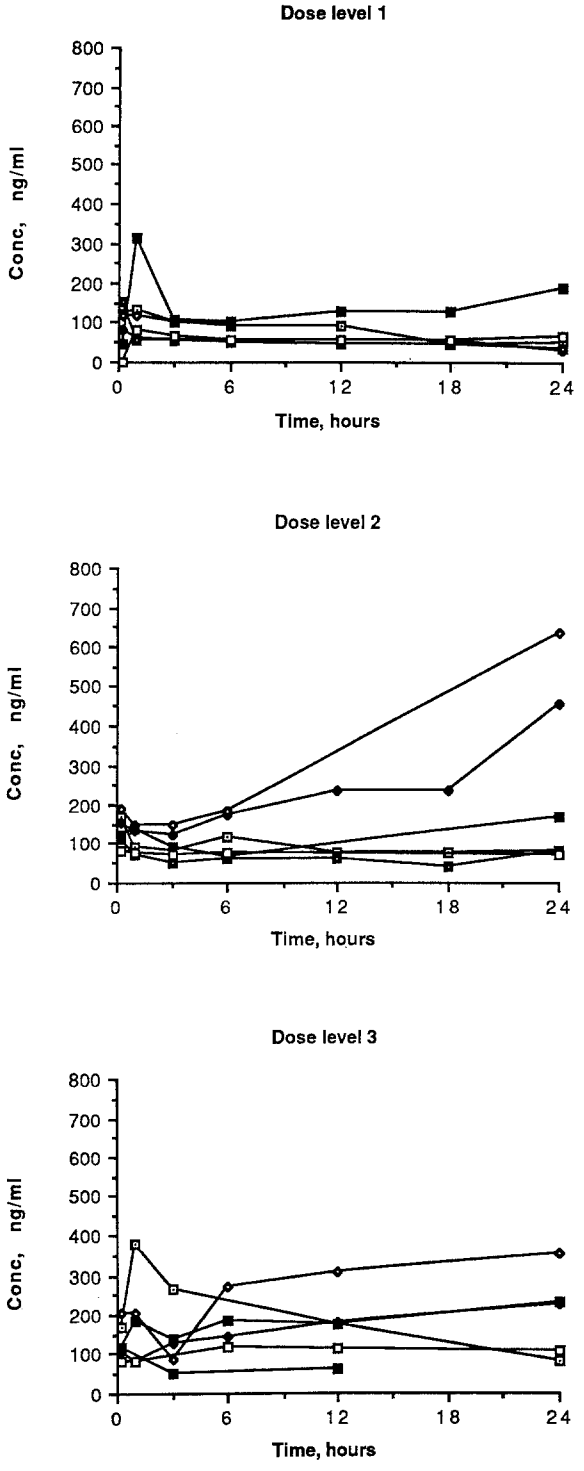

Fig. 1. Serum concentrations of GR38032F at the three dose levels studied

syringe driver that started 15 min before the administration of cisplatin. The following dose levels were studied:

Dose level	15-min infusion	24-h infusion
(1)	8 mg	24 mg (1 mg/h)
(2)	10 mg	48 mg (2 mg/h)
(3)	12 mg	96 mg (4 mg/h)

Table 1. POMB chemotherapy programme

Day 1	1.4 mg/m^2 vincristine (maximum, 2 mg) 300 mg/m^2 methotrexate, 12-h infusion
Days 2–3	30 mg bleomycin (total dose), 48-h infusion 15 mg b. i. d. folinic acid, ×4 doses
Day 4	100 mg/m^2 cisplatin, 12-h infusion (ovary/cervix) or 120 mg/m^2, 12-h infusion (teratoma)

Table 2. Patient characteristics

Total	24
Evaluable	23
Median age (range)	34 years (22–65)
Sex (M : F)	12 : 11
Tumour type:	
Germ cell	12
Ovarian carcinoma	4
Cervical carcinoma	7
Prior chemotherapy	10

Table 3. Anti-emetic activity

Dose level	Patients (n)	CR	MR	mR	F
Day 1:					
1	7	2	0	2	3
2	6	2	1	0	3
3	10	2	1	3	4
Days 2–5:					
8 mg q. d. s.	2	0	0	0	2
12 mg q. d. s.	6	1	1	2	2

This schedule was designed to achieve a high initial serum level of GR38032F in an attempt to provide maximal 5HT3 receptor blockade before the introduction of cisplatin. The concentration of GR38032F would then be maintained for 12 h after the end of the cisplatin infusion to cover the period of rapid clearance of free platinum from the blood.

In the second phase of the study, GR38032F was given orally for the 5 days following cisplatin infusion. The oral GR38032F was commenced 2 h before the end of the 24-h infusion and two dose levels were studied, 8 and 12 mg t. i. d.

The incidence of vomiting and retching during the first 24 h after the start of cisplatin was recorded hourly by trained nursing staff, and the patients completed diary cards over the following 5 days. These cards recorded the number of episodes of vomiting and retching in each 24-h period, the degree of nausea on visual analogue and numerical scales, an assessment of appetite and the occurrence of any new symptoms. For the purposes of this study, a vomit was defined as an emetic episode producing liquid and a retch, as a "vomit" not producing liquid. A

Table 4. Pharmacokinetic data

Total Dose		C_{max} (ng/ml)	C_{ss} (ng/ml)	AUC ($ng \cdot ml \cdot h^{-1}$)	Clearance (l/h)	Response
32 mg	1	133	73	1,777.2	13.69	F
	2	57.5	56	1,262.3	17.85	mR
	3	81.1	45	1,128.4	22.22	CR
	4	156	48	1,188.5	20.83	F
	5	192	125	2,806.7	8.00	F
	6	81.5	60	1,411.1	16.60	mR
Mean		116.8	67.8	1,595.9	16.53	
SEM		21.2	12.12	260.0	2.10	
58 mg	1	167	80	2,226.5	25.00	mR
	2	457	210	5,373.1	9.52	MR
	3	111	61	1,333.8	32.70	F
	4	190	150	3,696.8	13.30	CR
	5	167	120	2,653.1	16.66	F
	6	81	75	1,764.6	26.66	CR
Mean		195.5	116	2,841.3	20.63	
SEM		54.8	23.1	605.1	3.62	
108 mg	1	205	200	4,441.5	20.00	F
	2	117	112	2,645.1	35.70	mR
	3	377	175	5,455.8	22.80	CR
	4	228	163	3,879.3	24.50	MR
	5	120	54	1,418.4	74.07	MR
	6	356	320	7,330.2	12.50	F
Mean		233.8	170	4,195.1	31.59	
SEM		45.7	36.6	850.2	9.03	

single emetic episode was further defined as either one vomit or 1–5 retches in any 5-min period.

Response to therapy was graded in the following manner: a complete response (CR) involved no emetic episodes; a major response (MR) comprised <3 emetic episodes; a minor response (mR) consisted of 3–5 emetic episodes; and failure (F) involved >5 emetic episodes. Patients who failed were immediately treated with rescue medication usually comprising a combination of dexamethasone, prochlorperazine and lorazepam.

Pharmacokinetic study. Blood samples were taken for the measurement of GR38032F at time zero before commencing treatment and thereafter at 0.25, 1.0, 3, 6, 18 and 24 h. Serum was separated immediately and then stored at −20°C prior to assay using a specific reverse-phase HPLC method (Glaxo Inc., data on file). The AUC for the first 24 h was calculated using the trapezoidal rule and an estimate of the clearance in the first 24 h, by the expression:

Clearance = Infusion rate/steady-state plasma concentration.

Results

Anti-emetic activity

The anti-emetic activity of GR38032F in this study is summarised in Table 3. Eight patients were treated at the first dose level, of whom one was unevaluable due to vomiting in the 12 h prior to starting GR38032F. There were two CRs, two mRs and three Fs in this group. The two complete responders went on to receive oral GR38032F at 8 mg t. d. s.; both experienced six emetic episodes during this period of the study and were thus classified as Fs.

Eight new patients were entered at the second dose level, two of whom were unevaluable: one, due to vomiting in the 12 h prior to treatment; the other because the GR38032F infusion was discontinued after 6 h due to syringe pump failure. Of the remaining six patients there were two CRs, one MR and three Fs. The three responders received oral GR38032F at 12 mg t. i. d. for 5 days; one experienced a single emetic episode, one had four episodes and one underwent more than ten episodes during this time. In addition, three patients who failed at the first dose level were re-treated at the second dose level. None of these experienced improved control of emesis at the increased GR38032F dose.

Ten patients were treated at the third dose level. There were two CRs, one MR, three mRs and four Fs. The three patients achieving a CR or MR went on to receive oral GR38032F at 12 mg t. i. d.; one had no emetic episodes, one experienced five episodes and one underwent more than five episodes during the 5-day treatment period.

Overall, 8/23 (35%) patients treated had <3 emetic episodes during the first 24 h of the study and 2/8 (25%) experienced <3 episodes during the next 5 days. Of the eight patients with <3 emetic episodes in the first 24 h, four had received prior chemotherapy and four had not; thus, there was no correlation between response to

GR38032F and the presence or absence of previous treatment.

Patients who failed GR38032F were treated with rescue anti-emetics usually comprising 8 mg dexamethasone t. i. d., 25-mg prochlorperazine suppositories t. i. d. and 1–2 mg lorazepam b. i. d. In no case was vomiting completely abolished immediately, but all patients showed a slow response over the following 1–3 days.

Toxicity

Few side effects were noted during the study. Five patients (22%) experienced mild headache and one complained of drowsiness and ataxia and muscular pains. These symptoms all resolved within 12 h of the completion of treatment. No haematological or biochemical abnormalities attributable to GR38032F were documented during the study.

Pharmacokinetic study

Pharmacokinetic data were obtained in six patients at each dose level. The data are presented in Table 4 and Fig. 1. The results indicate that the method of administration was successful in achieving and maintaining a steady-state serum level of GR38032F during the 24-h infusion. There was no consistent evidence of drug accumulation (Fig. 1) and no evidence that higher serum levels correlated with improved anti-emetic control.

The mean AUCs at the three dose levels were 1,595.5, 2,841.3 and 4,195.1 ng·ml h^{-1}, and the corresponding clearance values were 16.53, 20.63 and 31.59 l/h. These results indicate that the kinetics of GR38032F are non-linear.

Discussion

Early clinical experience with GR38032F has shown the drug to be highly effective in the prophylaxis of non-cisplatin and single-agent cisplatin chemotherapy-induced emesis (Glaxo Inc., data on file). These studies have included rather heterogeneous groups of patients receiving a variety of different drugs at a range of doses. The present study set out to test the activity of GR38032F against high-dose cisplatin in a group of patients receiving a standard chemotherapy regimen.

On our current anti-emetic combination regimen (high-dose metoclopramide + dexamethasone + lorazepam) it is rare for patients to be entirely free of nausea and vomiting. Moreover, the nausea of <50% of patients will be reasonably controlled (<5 emetic episodes). In the present trial, GR38032F as a single agent completely controlled nausea and vomiting in 6/23 (26%) of patients and in all 8/23 (35%) had <3 emetic episodes. These results are considerably better than might be expected from any other anti-emetic agent used alone [5] and are similar to those reported by Kris et al. (<3 emetic episodes in 12/21 patients) in a group of patients receiving single-agent cisplatin at a dose of 120 mg/m^2 [6]. Moreover, GR38032F appears to be largely free of side effects, with mild headache in some 25% of patients being the most common complaint.

The pharmacokinetic data indicate that although it was possible to achieve steady-state plasma levels during the 24-h infusion, there was no evidence that increasing the dose above 32 mg in 24 h resulted in an improved therapeutic effect. In addition, there was no clear correlation between individual serum levels and response (Table 4). Animal studies have shown that GR38032F is extensively metabolised with <1% being excreted unchanged in the urine (Glaxo Inc., data on file). Thus, the non-linear kinetics with rising clearance as the dose is increased may be due to induction of the enzyme systems responsible for metabolism. Further studies on patients with hepatic dysfunction may provide interesting data in this regard.

A 24-h infusion was chosen for this study to maintain constant serum levels of GR38032F with the aim of achieving maximal 5HT3 receptor blockade. The results show that it was possible to maintain relatively steady serum concentrations using such a schedule, but clearly either the 5HT3 receptors were not fully blocked or some other mechanism was interacting with the vomiting centre in the patients who failed. Given the oral bioavailability of GR38032F of 60% and the serum half-life of 4 h, it is likely that oral GR38032F may be effective in the majority of patients. However, for high-dose cisplatin regimens we currently recommend that GR38032F be used at a loading dose of 8 mg over 15 min, followed by a 24-h infusion at a rate of 1 mg/h.

GR38032F is clearly an effective agent for the prophylaxis of cisplatin-induced emesis but is not the complete answer to this problem. Where high-dose cisplatin is being used, it is likely that 5HT3 antagonists in combination with other anti-emetics will provide optimal anti-emetic cover.

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