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Short communication

The efficacy and safety of GR38032F in the prophylaxis of ifosfamide-induced nausea and vomiting

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Summary. The novel $5HT_3$ receptor antagonist GR38032F was evaluated in the control of emesis induced by the cyclophosphamide analogue ifosfamide. At a dose of 4 mg q 6 h, GR38032F was given to six patients receiving their first dose of ifosfamide infusion (4–6 g/m^2 over 24 h); over the 42-h study period, major control of retching and vomiting was achieved in five patients. In the second phase of the study six further patients, in whom high-dose metoclopramide had failed to control emesis, were given 8 mg GR38032F q 6 h; major control of emesis was again observed in five patients. Toxicity attributed to GR38032F was minimal. This selective $5HT_3$ antagonist is effective and safe in the control of ifosfamide-induced emesis, even in patients resistant to high-dose metoclopramide.

Introduction

Emesis is a major problem limiting the acceptability of cytotoxic chemotherapy, and the resultant morbidity may lead patients to discontinue potentially curative cancer chemotherapy treatment. With the cytotoxic drug ifosfamide, a cyclophosphamide analogue active against a wide range of tumours, administration by prolonged infusion is required for optimal efficacy, and the nausea and vomiting induced may persist for up to 48 h [2, 10].

Current antiemetic agents are only moderately effective in preventing emesis, and the side effects may in some cases be unacceptable. Severe emesis, such as that induced by cisplatin, can be controlled in up to 50% of cases [1], but drowsiness is frequently seen and extrapyramidal effects have been reported in up to 10% of patients [7].

GR38032F is a selective antagonist at the HT_3 receptor that blocks 5-hydroxytryptamine actions such as neuronal depolarisation and noradrenaline release from sympathetic nerves [3]. It has proved to be a potent antiemetic in animal models [5], and in man has been shown to control emesis induced by agents such as cyclophosphamide and Adriamycin with few side effects [6].

The present study was designed firstly to define the efficacy and safety of GR38032F in the control of the prolonged nausea and vomiting induced by ifosfamide infusion in patients who had not previously received chemotherapy. Secondly, the aim was to define the activity of GR38032F in patients receiving ifosfamide whose emesis had not been controlled by high-dose metoclopramide.

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Patients and methods

A total of 12 patients (Table 1) took part in this study, all of whom gave written informed consent in accordance with the policy of the Wirral District Ethical Committee. Group A (six patients) comprised patients who were receiving their first exposure to ifosfamide, given at a dose of 4–6 g/m^2. Group B consisted of six patients who had experienced more than two emetic episodes while receiving the same dose of ifosfamide together with metoclopramide at a dose of >4 mg/kg over 24 h. In addition, three of these patients had severe extrapyramidal side effects attributed to the metoclopramide. GR38032F was given as a short infusion in normal saline every 6 h for seven consecutive doses, based on the known half-life of 3–6 h in normal patients (Glaxo Group Research, data on file). The doses used were 28 mg in divided doses in group A patients and 56 mg in group B patients, commencing approximately 15 min before the start of the ifosfamide infusion.

The number of vomiting and dry-retching events were charted by the patient under nursing supervision for the study period of 42 h. The response was analysed according to the number of emetic episodes, defined as any vomit productive of liquid or 1–5 retches within a 5-min period. The absence of emesis during the study period was considered a complete response, a major response was defined as 1–2 emetic episodes, a minor response as 3–5 emetic episodes, and failure to respond as >5 emetic episodes. Nausea was assessed by a 10-cm visual analogue scale completed by the patient at 24 and 42 h.

Results

In group A complete control of emesis was accomplished in two of six patients, and three further patients achieved major control (Table 2). In group B complete control was achieved in three patients during the study period. The time of onset of the first emetic episode ranged from 11 to 36 h. Delayed vomiting 2 h after the end of the study period was noted in one patient (group B, patient 3), who had experienced no vomiting episodes and minimal nausea during the preceding 42 h. The maximal number of vomiting episodes recorded was four, and no patient was withdrawn from the study for treatment failure. Nausea appeared to be more severe at 42 h than at 24 h.

GR38032F was generally well tolerated. Two patients reported side effects, but in only one case was the event (dry mouth and headache) considered to be related to

Table 1. Patient characteristics

	Age	Sex	Tumour	Ifosfamide dose (g)	Other agents given
Group A:					
1	56	M	Lymphoma	9	Etoposide, mitozantrone
2	43	F	Ovarian	6.5	Carboplatin
3	56	F	Ovarian	9	Carboplatin
4	48	F	Ovarian	7.5	Carboplatin
5	57	M	Small-cell lung	9	–
6	55	F	Small-cell lung	7.5	Etoposide
Group B:					
1	32	M	Sarcoma	9	–
2	67	M	Small-cell lung	8.5	Etoposide
3	67	M	Small-cell lung	10	Etoposide
4	46	F	Ovarian	10.5	Carboplatin
5	62	M	Small-cell lung	8.5	Etoposide
6	56	M	Non-small-cell lung	8	Adriamycin, vindesine

Group A, no previous ifosfamide exposure; Group B, failure of high-dose metoclopramide in the previous ifosfamide cycle

Table 2. Response of ifosfamide-related emesis to GR38032F

	Response[a]	Emetic episodes	Time of onset (h)	Nausea (cm)	
				24 h	42 h
Group A:					
1	Complete	0	–	1	1
2	Complete	0	–	1.5	1.5
3	Major	1	11	0.5	1.5
4	Major	2	36	0	2.0
5	Major	2	28	1	0.5
6	Minor	4	22	0	2.5
			Median	0.75	1.5
Group B:					
1	Complete	0	–	0	0
2	Complete	0	–	0	3
3	Complete	0	(44)[b]	0	1
4	Major	2	24	5.3	2.2
5	Major	2	21	2.3	2.3
6	Minor	3	24	2.5	2.5
			Median	1.2	2.3

[a] Complete, no emesis; Major, 1–2 emetic episodes; Minor, 3–5 emetic episodes; Failure, > 5 emetic episodes
[b] After the end of the study period

GR38032F treatment. One patient in group A developed drowsiness and confusion of moderate severity, which was rapidly reversed following the cessation of infusion of both ifosfamide and GR38032F. Minor elevations in liver function tests were observed in seven patients, but in three of these the serum level was elevated before treatment. In no case did the level rise above twice the normal value, and all such events were considered to be disease-related or of no clinical significance.

Discussion

In the first phase of the study, in which GR38032F was given to patients with no previous exposure to ifosfamide, a complete or major response was seen in five patients. In patients whose ifosfamide-induced emesis had not been controlled by high-dose metoclopramide, the decision was taken to use GR38032F at a higher dose of 42 mg in seven divided doses; again, a complete or major response was seen in five patients. This group was expected to be a more resistant population in view of the known conditioning effect of previous emetogenic therapy, although the physiological mechanisms of this component of vomiting may be different from those of the direct chemical effect of the drug [11]. It is interesting that GR38032F could control metoclopramide-resistant vomiting to this extent, as both drugs are thought to exert their antiemetic effects through the $5HT_3$ receptor [3].

The measurement of nausea is by nature subjective, but given the limitations of a visual analogue scale, a qualitative assessment of the data would suggest that nausea was more severe at 42 h than at 24 h. Considerable variation was noticed in the time of onset of the vomiting in both groups of patients, but in six of the seven patients experiencing vomiting episodes, these were first recorded at 21 h or later, which may reflect the time required for the microsomal activation of ifosfamide [4]. The delayed nausea and vomiting, seen in one patient who had a complete response during the study period, is well recognised following cisplatin chemotherapy but is usually associated with the failure of early control. Prolonged maintenance therapy with an oral form of GR38032F, dexamethasone or phenothiazines may be required to control emesis in this phase.

The toxicity observed with GR38032F at the present doses was minimal, and the minor biochemical abnormalities were not considered to be significant. The drowsiness and confusion recorded in one patient in group A was considered to be grade 2 CNS toxicity due to ifosfamide rather than GR38032F [9].

The present study demonstrates that GR38032F can control nausea and vomiting over a 42-h period without significant side effects. Although it may be possible to alter the schedule of administration of cytotoxic drugs to achieve better control with a short antiemetic infusion [8], the resulting effect on the pharmacokinetics of a pro-drug such as ifosfamide may be to alter the effective availability of the activated species. At a dose of 4 mg q 6 h GR38032F appears to reduce vomiting caused by ifosfamide to modest proportions, although a higher dose of 8 mg q 6 h may be more appropriate for patients whose emesis has not previously been controlled with other antiemetic agents.

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