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A pharmacokinetic study of granisetron (BRL 43694A), a selective 5-HT_3 receptor antagonist: correlation with anti-emetic response

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Summary. As part of an open dose-ranging study, the pharmacokinetics of granisetron (BRL 43694A), a selective 5-HT_3 receptor antagonist given by the i.v. route, was studied in 18 patients receiving highly emetogenic cytotoxic drugs, predominantly cisplatin, either alone or in combination with other cytostatic agents. All patients received 30-min infusions of granisetron at a dose of 40 μg/kg. Nine showed complete absence of the gastrointestinal side effects normally associated with cisplatin, and in the majority of the remaining patients, the onset and severity of nausea was significantly modified. No acute side effects were observed at this dose and the drug was well tolerated in all cases. Peak plasma concentrations and area under the curve (AUC) values for granisetron showed considerable inter-patient variation. Higher plasma levels of granisetron were observed at 5 h in responding patients compared with those in whom the drug was ineffective in controlling emesis ($P < 0.05$). AUC values were higher in responding patients, but this difference was not statistically significant. There was apparently no defined plasma concentration threshold for the drug's anti-emetic effect in these patients. Granisetron seems to be an effective and safe anti-emetic in patients receiving cytotoxic chemotherapy. Further exploration of its dose scheduling and pharmacokinetic profile is warranted.

Introduction

Clinically, the mechanisms of chemotherapy-induced vomiting remain unclear, although the emetic properties of cisplatin have been attributed to stimulation both at peripheral sites [14] and at the chemoreceptor trigger zone [21]. Metoclopramide is widely used as an anti-emetic and, at conventional doses (10–20 mg), is known to exhibit a variety of pharmacological actions. Those proposed to account for its anti-emetic effects include dopamine receptor blockade (as evidenced by the increase in plasma prolactin) and enhancement of gastric emptying.

However, at high doses, at which it has been shown to be clinically effective [17] against cisplatin-induced vomiting, metoclopramide can produce extra-pyramidal reactions [1] and sedation, side effects attributed to dopamine antagonism. At these doses metoclopramide has recently been shown to exhibit 5-HT_3 receptor antagonism [3, 12, 27], which is thought to account for its anti-emetic activity against cisplatin [23]. This contention is supported by studies demonstrating the potent anti-emetic activity of selective 5-HT_3 receptor antagonists such as MDL 72222, ICS 205-930, BRL 24924, GR 38032F and granisetron (BRL 43694A) in the ferret [2, 7, 8, 24] and in man [19].

Cunningham et al. [10] recently reported on the use of GR 38032F with good effect in patients receiving mildly emetic drugs; however, none of these patients received cisplatin, which is generally considered the most emetogenic of the currently used cytotoxics. In patients receiving high-dose metoclopramide, Meyer et al. [22] have suggested that the optimal therapeutic dose is 850 ng/ml, at which level improved efficacy against cisplatin-induced emesis is observed. At higher doses toxicity has been observed, as reported by Grunberg et al. [13], who showed that levels of > 1,469 ng/ml were associated with an increase in emetic episodes.

Granisetron, *endo-N*-(9-methyl)-9-azabicyclo[3.3.1]-1-non-3-yl-1-methyl-1H-indazole-3-carboxamide monohydrochloride, has been shown to be clinically effective in a sub-group of these patients who received cisplatin [4]. In the current study we report on the pharmacokinetics of granisetron [11] and its relationship to efficacy and tolerance in patients given highly emetogenic anti-cancer drugs, the majority of whom received cisplatin.

Patients and methods

A total of 18 patients receiving chemotherapy as part of an open dose-ranging protocol were entered in this pharmacokinetic study. The clinical results for a sub-group of these patients have previously been reported [4]. Characteristics of the patients are listed in Table 1, and treatment details are shown in Table 2. All patients provided written informed consent prior to participation. Full blood counts, determination of serum urea and electrolytes, liver function tests and blood glucose measurements were carried out immediately before and at 24 h and 3 weeks following treatment. Pulse and blood pressure measurements were taken prior to and immediately following treatment and thereafter, at hourly intervals for 6 h. Cardiac rhythm was recorded using Holter 24-h monitors in all patients.

Patients were asked to record all episodes of vomiting at 0, 1, 4, 6, 8 and 24 h post-chemotherapy. The severity of nausea was subjectively assessed using two separate methods. A categorical assessment was done using a global

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Table 1. Characteristics of 18 patients receiving granisetron at a dose of 40 μg/kg

Number of patients	18
Sex: Male	12
Female	6
Mean age (range)	51 (25–67)
Mean weight (kg) ± SEM	65.4 ± 7.7
Previous chemotherapy	11
Previous cisplatin (all vomited with previous treatment)	7
Site of malignancy	
Lung	8
Head/neck	2
Other	8

4-point severity score, with the assessments carried out pre-dose and at 4 and 24 h post-infusion. In addition, the severity of nausea was assessed using 10-cm visual analogue scores pre-dose and at 1, 4 and 6 h post-infusion, giving an intensity rating for nausea arbitrarily assessed as follows: 0–0.9 cm, none; 1–4 cm, slight nausea; 4.1–6.9 cm, moderate nausea; and >7 cm, severe nausea. Patients completed simultaneous visual analogue scales for anxiety and sedation. A general systematic enquiry was completed pre-dose and at 4 and 24 h following the granisetron infusion. Statistical analysis of the linear analogue scores for nausea were analysed using a paired Wilcoxon signed-rank test.

Procedure

In patients receiving cisplatin, the drug was given following pre-hydration in 250 ml 0.9% saline over 30 min. Granisetron was given by constant i.v. infusion in 250 ml 0.9% saline over 30 min immediately following the chemotherapy. Chemotherapy regimens are shown in Table 2. Following the completion of chemotherapy and granisetron infusions, patients were hydrated for 24 h.

Blood samples were obtained at the following time points for the measurement of plasma granisetron concentrations: before and after the infusion granisetron, at 30, 60, 90 and 120 min post-infusion, then hourly to 8 h and at 24 and 48 h post-dose. Plasma concentrations of granisetron were measured by high-pressure liquid chromatography (HPLC), a method with lower limits of detection in the region of 0.1 ng/ml [5]. Model-independent pharmacokinetics were used to define the elimination profile.

Table 2. Treatment details of 18 patients receiving granisetron as anti-emetic for control of cytotoxic drug-induced nausea an vomiting

Patient Number	Cisplatin dose (mg/m²)	Cytotoxic drugs	Anti-emetic control
1[a]	40	Adr; HU; Bleo	Complete
2[a]	40	Ifos; VCR	Complete
3[a]	60	Adr; HU; Bleo	Complete
4[a]	75	Nil	Complete
5	75	Nil	Complete
6[a]	75	Mitox	Complete
7	75	Nil	Complete
8[a]	75	Nil	Complete
9	–	Adr; Ifos	Complete
10	50	Nil	Good
11[a]	50	Nil	Good
12[a]	75	Nil	Good
13	100	5-FU	Good
14[a]	60	Adr; HU; Bleo	Poor
15	75	Nil	Poor
16[a]	–	DTIC	Poor
17[a]	–	Adr; Ifos	Poor
18	–	Adr; Ifos	Poor

Mitox, mitoxantrone; Adr, Adriamycin; Ifos, ifosfamide; VCR, vincristine; 5-FU, 5-fluorouracil; HU, hydroxyurea; Bleo, bleomycin

[a] Previous chemotherapy

Results

Treatment details are listed in Table 2, with vomiting prevented in 9 of 18 patients treated. Rescue anti-emetic therapy was necessary in the other patients, although the onset of vomiting was delayed in six of these patients to longer than 12 h. Only two patients vomited or experienced dry retching within the first 6 h post-treatment, and this was limited to two occasions in both. The intensity of nausea experienced by these patients is shown in Table 3, using data derived from 10-cm linear visual analogue scales, with slight nausea experienced by six (33%) patients by 6 h and moderate nausea, by one patient. Four of these subjects complained of slight nausea prior to treatment. Statistical analysis of the linear analogue scores for nausea showed no significant difference at 1, 4 and 6 h compared with pre-dose levels. Table 4 illustrates the degree of nausea and vomiting in these 18 patients as determined by a categorical global rating score, with absence of nausea in 10 patients at 24 h.

The i.v. administration of granisetron was well tolerated in all cases. Systematic enquiry at time 0 and at 24 h revealed no unexpected toxicities, with fewer positive responses at 24 h. There were five reports of drowsiness at 24 h post-dose, but this appeared to be related to night se-

Table 3. Evaluation of nausea in 18 patients receiving 40 μg/kg granisetron using a linear visual analogue score (VAS)

Median visual analogue score (cm)[a]				
	Pre-dose	+1 h	+4 h	+6 h
Median VAS, cm (range)	0.2 (0–3.4)	0.25 (0–3.8) (NS)	0.65 (0–5.7) (NS)	0.8 (0–6.8) (NS)
Intensity rating[b]				
	Percentage of patients			
Nausea	Pre-dose	+1 h	+4 h	+6 h
None	78	89	67	61
Slight	22	11	22	34
Moderate	0	0	5	0
Severe	0	0	5	5

[a] Median score in cm (range). Analysis was carried out using a paired Wilcoxon signed-rank test. NS = $p > 0.05$ compared to pre-dose

[b] Intensity rating: None, 0–0.9 cm; Slight, 1–<4 cm; Moderate, 4.1–6.9 cm; Severe, >7 cm

NS, not statistically significant

Table 4. Subjective evaluation of nausea and vomiting in 18 patients receiving 40 μg/kg granisetron using a global rating score

Symptom	Pre-dose	+4 h	+24 h
Nausea:			
Absent	18 (100%)	14 (79%)	10 (56%)
Slight	0	3 (16%)	3 (16%)
Moderate	0	0	5 (28%)
Severe	0	1 (5%)	0
Vomiting:			
Absent	18 (100%)	16 (89%)	9 (50%)
Slight	0	1 (5%)	3 (16%)
Moderate	0	0	5 (28%)
Severe	0	1 (5%)	1 (5%)

dation. Assessment of anxiety and sedation using 10-cm linear visual analogue scores demonstrated no significant changes at 1, 4 or 6 h following granisetron. No significant change in pulse or blood pressure recordings were seen. Asymptomatic cardiac arrhythmias were infrequently observed on 24-h Holter monitoring, but these were not clinically significant and did not exceed the frequency of arrhythmias observed in normal controls [9, 25]. No biochemical changes of clinical significance were observed during this study.

The pharmacokinetic data are shown in Table 5. The decline in plasma concentration was multiphasic and became log linear after several hours, although there was wide variation between patients. Clearance values, terminal half-lives and area under the curve (AUC) values also showed wide inter-individual variation, although volumes of distribution were more similar. Figure 1 shows the pharmacokinetic profile of patients receiving granisetron; patients who achieved complete or good control over nausea and vomiting (Fig. 1 a, b) generally had higher plasma levels than those who were not helped by the drug (Fig. 1 c). However, on an individual basis there was no apparent threshold level for effect.

AUC values were higher for patients who derived benefit from the drug than for those who did not respond (406 vs 193 ng·h/ml), but this did not reach statistical significance. However, analysis of the pharmacokinetic data concerning the plasma level at 5 h, when significant nausea and vomiting would have been expected in poorly controlled patients, revealed a statistically significant difference between the two groups: 16.8 ng/ml in responding patients and 9.1 ng/ml in those with poor control ($P < 0.05$; unpaired Student's t-test). Figure 2 shows comparisons in granisetron plasma levels between patients receiving the same chemotherapy and anti-emetic treatment. Figure 2a shows that the patient whose emesis was not controlled had lower levels of granisetron; however, no such difference is evident in Fig. 2b.

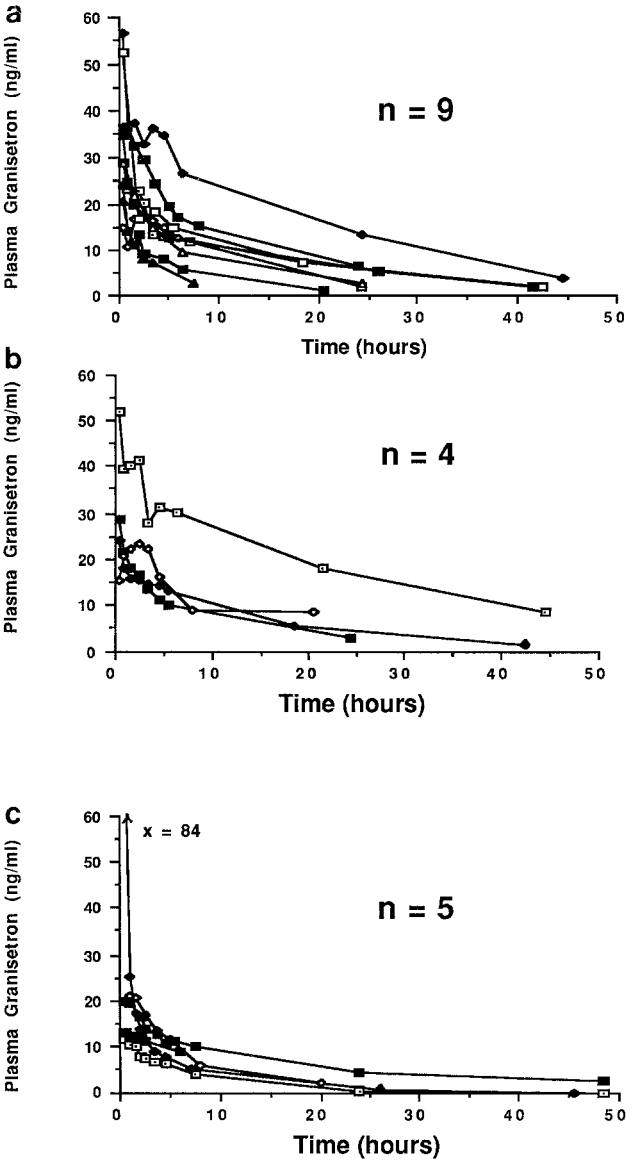

Fig. 1. Pharmacokinetic profile of patients receiving granisetron (40 μg/kg). **a** Profile of patients who had no retching or vomiting. **b** Profile of patients who had 1 or 2 episodes of vomiting or retching. **c** Profile of those who had more than 2 episodes

Discussion

The pharmacokinetics of granisetron, a selective 5-HT_3 receptor antagonist, was studied in 18 patients receiving cy-

Table 5. Pharmacokinetic parameters in 18 patients receiving 40 μg/kg granisetron by constant i.v. infusion over 30 min. Four patients had insufficient data points for full pharmacokinetic analysis

Parameter		Patients (n)	Mean	Range
Terminal half-life	$t_{1/2}$, z (h)	14	10.6	(2.92–21.0)
Total clearance	Cl (l/h per kg)	14	0.213	(0.035–0.602)
Area under the curve	AUC (ng · h/ml)	14	350.0	(66.5–1,127)
Apparent volume of distribution	V_d (l/kg)	14	2.20	(1.06–4.2)
Peak plasma concentration	C_{max} (ng/ml)	18	37.5	(11.3–124)

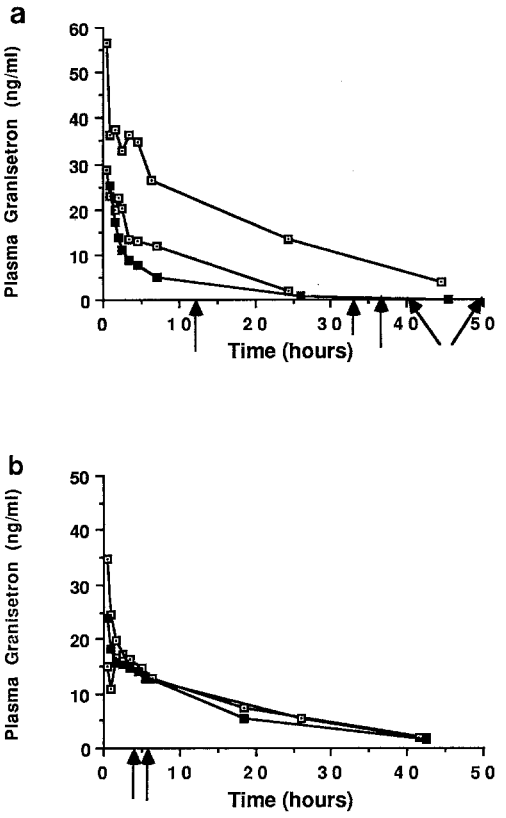

Fig. 2. Pharmacokinetic profiles of patients receiving the same chemotherapeutic drugs and granisetron (40 μg/kg). **a** Profile of 3 patients who received chemotherapy for small-cell lung cancer, with cisplatin, hydroxyurea and bleomycin. **b** Profile of 3 patients who received 75 mg/m^2 cisplatin as a single agent. The *open symbols* represent patients who achieved complete control over emesis, and the *closed symbols* represent those with poor control, with vomiting episodes in the poorly controlled patients indicated by *arrows*

totoxic chemotherapy. Pharmacokinetic profiles on these patients showed wide inter-individual variation. Similar profiles and inter-individual variation have previously been reported in a normal, healthy population [28]. The profiles were analysed in an attempt to define a plasma concentration-effect relationship. Higher plasma levels were seen in patients whose chemotherapy-induced gastrointestinal toxicity was well controlled compared with those in poorly controlled patients, as is illustrated in Fig. 1 and 2. However, on an individual basis a threshold plasma level was not defined, which is not surprising in view of the many potential mechanisms involved in chemically induced emesis [15]. The clearance of granisetron is thought to be predominantly metabolic, and in this study creatinine clearance values bore no relationship to clearance. Interestingly, the pharmacodynamic action of granisetron in reducing the 5-HT$_3$ dermal axon-reflex flare size [6] persists for 24 h, and this test may prove to be a valuable indicator of peripheral 5-HT$_3$ receptor blockade. The prolonged action of granisetron as an anti-emetic (for up to 24 h) may be correlated with the peripheral inhibition of 5-HT$_3$ receptors, as evidenced by dermal axon flare inhibition.

Of the 18 patients receiving granisetron (40 μg/kg), 9 experienced no nausea or vomiting, and in 6 of the remaining patients the onset of nausea and vomiting was delayed to beyond 12 h. This prolongation is significant compared with the early onset of emesis (3 h) commonly encountered following chemotherapy, particularly that involving cisplatin [20], with five of seven patients who received 75 mg/m^2 cisplatin experiencing no vomiting following 40 μg/kg granisetron. Similarly, nausea was controlled in many of these patients, particularly over the first 6 h, with the majority of patients expressing a preference for granisetron rather than dexamethasone and domperidone, which they had received on previous or subsequent courses of cytotoxic chemotherapy.

The drug was extremely well tolerated; in particular, the absence of a sedative effect enables a possible out-patient application. Serious cardiac arrhythmias, which have previously been described with the use of the dopamine antagonist domperidone [26], were not observed in this study. Occasional supraventricular and ventricular ectopics were observed, but their incidence did not exceed that in a normal population [9, 25]. No clinically relevant changes in biochemical profiles or blood counts were observed in these patients. Systematic enquiry did not reveal any unexpected side effects, although headache lasting 36 h was reported by one patient; however, this symptom was not reported in a previous study, in which healthy subjects received 2.5–40 μg/kg granisetron in an incremental tolerance and pharmacokinetic study [28].

The use of selective 5-HT$_3$ receptor antagonists would appear to play a major role in the control of emesis due to the administration of a wide range of cytotoxic drugs, including cisplatin. Granisetron given at a dose of 40 μg/kg as a single 30-min infusion was shown to ameliorate nausea and vomiting significantly in patients receiving highly emetogenic chemotherapy; at this dose the drug was remarkably free of side effects. Further studies are under way to examine the activity and safety of larger doses of granisetron given as single 30-min infusions and in split doses.

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