

Randomized Crossover Pharmacokinetic Evaluation of Subcutaneous Versus Intravenous Granisetron in Cancer Patients Treated with Platinum-Based Chemotherapy

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ABSTRACT

Background. 5-HT₃-receptor antagonists are one of the mainstays of antiemetic treatment, and they are administered either i.v. or orally. Nevertheless, sometimes neither administration route is feasible, such as in patients unable to admit oral intake managed in an outpatient setting. Our objective was to evaluate the bioavailability of s.c. granisetron.

Patients and Methods. Patients receiving platinum-based chemotherapy were randomized to receive 3 mg of granisetron either s.c. or i.v. in a crossover manner during two cycles. Blood and urine samples were collected after each cycle. Pharmacokinetic parameters observed with each administration route were compared by analysis of variance.

Results. From May to November 2005, 31 patients were

included and 25 were evaluable. Subcutaneous granisetron resulted in a 27% higher area under the concentration–time curve for 0–12 hours (AUC_{0–12h}) and higher levels at 12 hours, with similar values for AUC_{0–24h}. The maximum concentration was lower with the s.c. than with the i.v. route and was observed 30 minutes following s.c. administration.

Conclusion. Granisetron administered s.c. achieves complete bioavailability. This is the first study that shows that s.c. granisetron might be a valid alternative to i.v. delivery. Further trials to confirm clinical equivalence are warranted. This new route of administration might be especially relevant for outpatient management of emesis in cancer patients. *The Oncologist* 2007;12:1151–1155

INTRODUCTION

Despite major improvements achieved in the management of emesis, it still constitutes one of the most relevant side effects of chemotherapy, and it is often underestimated by physicians [1, 2]. The introduction of 5-hydroxytrypta-

mine-3-receptor antagonists (5-HT₃RAs) has been one major advance to treat and prevent emesis, and they are part of standard antiemetic premedication for moderately and highly emetogenic chemotherapy agents [3, 4]. Granisetron (Kytril[®]; Roche Laboratories, Inc., Nutley, NJ) is a potent

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and highly selective 5-HT₃RA with weak antagonistic action against other 5-HT₃ receptors [5].

Because antiemetic drugs are administered either orally or i.v., outpatient management of emesis remains a challenge when oral intake is limited by vomiting and i.v. administration is not possible as a result of a lack of medical staff and adequate equipment. The s.c. administration of 5-HT₃RAs could be a valid alternative for these patients. Theoretical advantages of the s.c. route over i.v. delivery include its simplicity of use and its lower costs and fewer complications. Although isolated clinical observations have suggested the clinical efficacy of s.c. 5-HT₃RAs, their bioavailability has not been previously evaluated [6].

The aim of this study was to evaluate the bioavailability of s.c. granisetron to assess if this route is a valid alternative for cancer patients. We hypothesized that the bioavailability of s.c. granisetron would not be inferior to that achieved by i.v. delivery. In order to prove this hypothesis, we designed a randomized crossover pharmacokinetic evaluation of s.c. and i.v. granisetron.

PATIENTS AND METHODS

Cancer patients receiving platinum-based chemotherapy were randomized to receive 3 mg of granisetron by either s.c. or i.v. administration during the first cycle and to crossover to the alternative route during the second one. Randomization was performed using random tables generated before study approval. For i.v. treatment, 3 mg of granisetron was diluted in 50 ml of saline and administered over 10 minutes. For s.c. treatment, 3 mg of granisetron was administered s.c. in the upper arm. Chemotherapy was the same in both cycles for each patient. Patients received 20 mg of i.v. dexamethasone and further antiemetic treatment if required, although administration of additional doses of granisetron was not authorized, to avoid pharmacokinetic interference. Additional inclusion criteria were: adequate bone marrow, hepatic, and renal function, respectively defined by: platelets $\geq 100,000/\text{mm}^3$ and absolute neutrophil count $\geq 1,500/\text{mm}^3$; bilirubin, aspartate aminotransferase and alanine aminotransferase $\leq 2 \times$ the upper limit of normal; and creatinine < 1.5 mg/dl. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2 and body mass index of 20–28 kg/m². Patients were not eligible if they were pregnant or had serious concomitant diseases. The main endpoint was bioavailability (F). Although clinical efficacy was not an endpoint in this study, emesis was evaluated using a patient self-assessment questionnaire in which patients recorded the number of emetic episodes per day during the week following chemotherapy and the type and quantity of rescue medication, and they were asked in which cycle they had

better control of emesis. Toxicity was assessed using Common Toxicity Criteria version 3.0 [7].

The protocol was approved by the appropriate ethics committee and by the Spanish Agency for Medicines and Healthcare Products. The Eudract number was 2004-003877-10. All patients signed written informed consent before treatment.

Pharmacokinetic Study

Blood samples (5 ml) were drawn before dosing and at 10, 15, 30, 45, and 60 minutes and 1.5, 2, 3, 4, 6, 8, 12, and 24 hours following granisetron administration. Ten-minute and 24-hour samples were not collected in all patients. Ten-minute samples were obtained once it had been confirmed in the first patients that 15-minute samples were elevated enough to make them informative. Twenty-four-hour samples were collected when it was possible, because as a result of logistic reasons, patients were not always available at this time. Blood was drawn in heparin tubes, centrifuged (4°C, 3,000 r.p.m., 10 minutes) and frozen at -80°C until analysis. Urine was collected for 12 hours after treatment. An aliquot of urine was frozen at -80°C until assay. Granisetron levels were determined by high performance liquid chromatography with fluorescence detection after liquid/liquid extraction of acidified plasma samples. The quantitation limit was 0.5 ng/ml. Calibration curves were prepared at a concentration range of 0.5–100 ng/ml. Plasma concentrations were analyzed by a Good Laboratory Practices–certified laboratory.

Maximum concentration (C_{max}) and time to maximum concentration (t_{max}) were obtained from experimental data. Area under the concentration–time curve for 0–12 hours ($\text{AUC}_{0-12\text{h}}$) and $\text{AUC}_{0-24\text{h}}$ were calculated by the trapezoidal rule. Half-life ($t_{1/2}$) and terminal phase rate constant (k_e) were determined by unweighted nonlinear regression analysis of the terminal slope of the log plasma concentration–time curve. Total plasma clearance (Cl) was calculated as the ratio between dose and $\text{AUC}_{0-24\text{h}}$, and volume of distribution (V) as the ratio between Cl and k_e .

Statistical Analysis

Twenty-five patients were required to have a power of 0.80 to conclude bioequivalence at a significance level of 0.05 in total bioavailability of s.c. administration in relation to i.v. administration.

Pharmacokinetic parameters were compared by analysis of variance (ANOVA) including the factors sequence, period, formulation, and study participant to the log-transformed parameters log(AUC) and log(concentration); the relative bioavailability and the 90% confidence intervals

Table 1. Pharmacokinetic characteristics of s.c. and i.v. granisetron, compared by Student's *t*-test for paired samples and Wilcoxon test

	i.v. (mean ± SD)	n i.v.	s.c. (mean ± SD)	n s.c.	p-value
AUC _{0-12h} (μg × hours/l)	101.7 ± 56.7	21	128.4 ± 69.5	22	.029
AUC _{0-24h} (μg × hours/l)	179.4 ± 100.3	10	185.5 ± 113.2	10	NS
C _{max} (μg/l)	72.4 ± 35.8	27	43.7 ± 33.2	28	<.001
t _{max} (hours)	NA	NA	0.456 ± 0.26	28	NA
k _e (1/hour)	0.169 ± 0.285	25	0.137 ± 0.095	26	NS ^a
t _{1/2} (hours)	11.3 ± 10.6	25	7.9 ± 5.6	26	NS ^a
V (l)	274.1 ± 193.5	27	218.9 ± 140.2	28	NS
Cl (l/hour)	34.2 ± 49.7	27	35.1 ± 68.7	28	NS ^a
C _{12h} (μg/l)	4 ± 3.1	21	5.4 ± 3.4	22	.031 ^a
C _{24h} (μg/l)	3.5 ± 2.7	10	3.6 ± 2.4	11	.028
A _{e12h} (mg)	0.902 ± 0.594	23	0.954 ± 0.698	23	NS ^a

^aWilcoxon's test.

Abbreviations: A_e, amount of granisetron eliminated by urine; AUC, area under the concentration–time curve; C, concentration; Cl, clearance; C_{max}, maximum concentration; k_e, elimination constant; NA, not applicable; NS, not statistically significant; t_{1/2}, half-life; t_{max}, time to maximum concentration; V, distribution volume.

(CIs) were estimated using the residual variance of the ANOVA [8].

Other pharmacokinetic parameters were analyzed by paired Student's *t*-test or Wilcoxon test. Statistical analyses were performed using SPSS 11.0 (SPSS Inc., Chicago, IL) and WinNonlin® Pro 4.1 (Pharsight Corporation, Mountain View, CA).

RESULTS

From May to November 2005, 31 patients were included and 25 of them were evaluable. Six patients were not evaluable because of an incorrect dose of granisetron (one patient), volunteer decision to leave the study (three patients), and treatment discontinuation because of disease progression (two patients). Patient characteristics were: 20 men/5 women; mean age, 56 years (standard deviation [SD], 9.3); and mean body mass index, 25.6 kg/m² (SD, 4.1). All patients were diagnosed with non-small cell lung cancer. From 23 patients evaluable for antiemetic symptoms, 15 reported no differences between the two cycles, six had less emesis with s.c. granisetron, and two presented better control with the i.v. route. No adverse events related to granisetron were observed. s.c. granisetron did not produce local skin reactions.

Pharmacokinetic parameters are presented in Table 1. Following i.v. administration, C_{max} was observed at the end of the infusion. However, after s.c. administration, C_{max} was reached after 30 minutes. As expected, the C_{max} value was 48%–68% lower with s.c. than with i.v. administration. Mean plasma concentrations of granisetron are shown in

Figure 1. The s.c. administration of granisetron produced a 27% higher AUC_{0-12h} (90% CI, 7%–74%) than with i.v. delivery and higher concentrations at 12 and 24 hours. No statistically significant differences were seen in AUC_{0-24h} or urinary elimination between the two routes, indicating similar bioavailability with a relative F of 1.0339 (103%). Other pharmacokinetic parameters (t_{1/2}, Cl, V) were not statistically different.

DISCUSSION

The availability of oral 5-HT₃RA has facilitated outpatient management of emesis. Oral granisetron has adequate bioavailability and shows comparable efficacy and tolerability with i.v. 5-HT₃RA [9–11]. However, the use of oral antiemetics is impaired when heavy vomiting precludes their intake, and often, i.v. administration is not possible in an outpatient setting. We have shown that the s.c. administration of granisetron has similar bioavailability to that of i.v. delivery, achieving an even higher AUC_{0-12h}, and seems, therefore, to be a valid alternative route to administer this drug.

The use of higher granisetron doses has not been proven to be superior to doses of 1 mg [12–14]. We used a 3-mg dose to improve our ability to detect adequate plasma levels, and therefore to achieve valid conclusions, because granisetron pharmacokinetics appear to be independent of dose in the range of 1–24 mg [15].

C_{max} values of 13.8–39.8 ng/ml have been previously observed following i.v. administration of 3 mg of granisetron for a 0.5- to 1-hour infusion [16]. By the oral route, 1

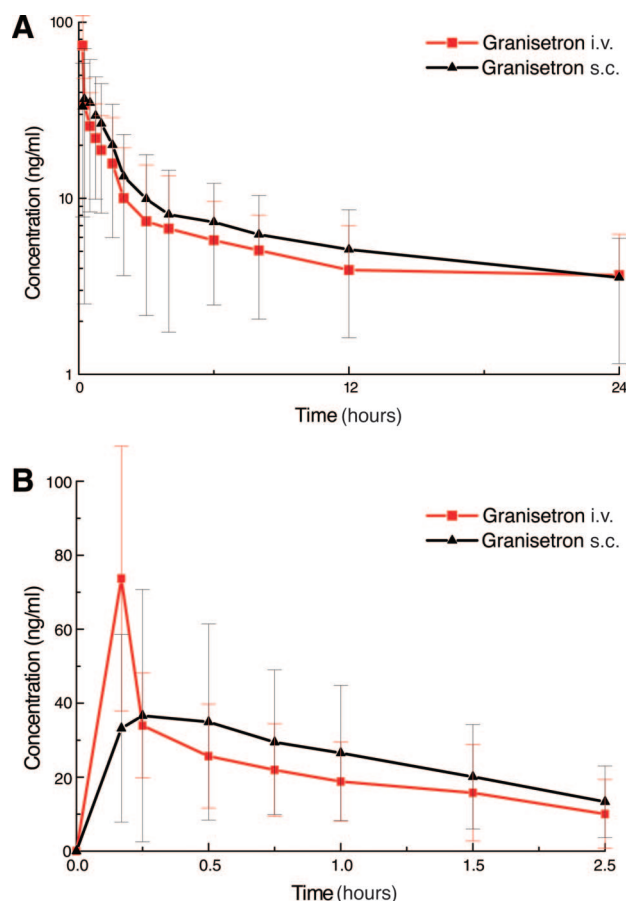


Figure 1. Granisetron mean plasma levels (\pm standard deviation) following a single 3-mg dose i.v. or s.c. (A): First 24 hours, semilogarithmic graph. (B): First 2 hours.

mg of granisetron achieved C_{\max} values of 7.42 and 8.8 ng/ml [17]. A rapid i.v. infusion of 3 mg of granisetron over 30 seconds produced a concentration of 233 ng/ml [18]. We observed a granisetron level of 43.7 ng/ml following s.c. administration, which is consistent with the values reported in these studies, considering differences in dose and infusion rate. Moreover, the elimination $t_{1/2}$ values observed in our study for the s.c. and i.v. routes were, respectively, 7.9 hours and 11.3 hours, also in the range of previously reported results, 1.63–11.7 hours [19, 20]. The differences observed in C_{\max} between the two administration routes are unlikely to affect clinical efficacy, because they were only observed over a short time period of around 5 minutes. In addition, as mentioned above, higher doses of granisetron have not been proven to have greater clinical efficacy than lower doses. As for differences in t_{\max} , it is also unlikely that they may affect clinical efficacy in the setting of prevention, because antiemetics are given several minutes before chemotherapy. Nonetheless, this difference may be

relevant for treatment of emesis that is already ongoing, because t_{\max} is achieved faster with i.v. administration.

Subcutaneous granisetron showed complete bioavailability, similar to i.v. treatment, as confirmed by the fact that the AUC_{0-24h} of the former was 102.1% of the latter (90% CI, 100.6%–131.1%). This was confirmed by the urinary clearance, which was not statistically different between the two routes. As expected, no differences were observed in $t_{1/2}$, V, or CI, because the drug administered was the same. Intravenous administration achieved a higher C_{\max} than s.c. delivery as a result of the zero-order absorption process. The C_{\max} was observed 30 minutes (range, 10–60 minutes) after s.c. administration. In comparison, t_{\max} occurred 180 minutes after oral administration [19]. Granisetron concentrations at 12 hours were 40% higher after s.c. than after i.v. administration. The difference in AUC_{0-12h} is probably related to the slow s.c. absorption. Chaturvedula et al. [21] observed a subdermal depot formation of granisetron following application of iontophoretic cutaneous patches. This depot was responsible for prolonged absorption and for the high plasma concentrations observed. Another report showed that one elimination route of granisetron is back diffusion into the bloodstream from a peripheral compartment [16]. If so, a slow and continuous infusion of granisetron would retard its disappearance from the blood and increase AUC values in patients when granisetron is administered s.c. Nonetheless, the observed differences in AUC between the two administration routes would be likely to disappear, or even to favor i.v. delivery, if the pharmacokinetic assessment had been performed over a more prolonged time period.

SUMMARY

The s.c. administration of granisetron has similar bioavailability to i.v. delivery, achieving an even higher AUC_{0-12h} . This is the first study that shows that s.c. granisetron might be a valid alternative to its i.v. use. This new route of administration might be especially relevant for outpatient management of emesis in cancer patients. Further studies are warranted to confirm the clinical efficacy of s.c. granisetron.

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