JPP Journal of Pharmacy and Pharmacology

JPP 2004, 56: 169–175

Received June 20, 2003
Accepted September 26, 2003
DOI 10.1211/0022357022566
ISSN 0022-3573

The effect of repeat dosing with cimetidine on the pharmacokinetics of intravenous granisetron in healthy volunteers

Lawrence Youlten

Abstract

The primary route of elimination of granisetron is by oxidative hepatic metabolism, thus its pharmacokinetic profile may be altered by co-administration of other drugs that inhibit or induce hepatic drug metabolizing enzymes. This open-label study investigated the effect of inhibition of cimetidine, a potent inhibitor of CYP1A2, CYP2D6 and CYP3A4, on the pharmacokinetic profile of intravenous granisetron in healthy male volunteers. Subjects (n = 12; 18–60 years) received granisetron (40 μg kg^{-1}) infused over 3 min, six days before and on the eighth day of dosing with cimetidine (200 mg, four times a day). Blood samples were taken for pharmacokinetic analysis at intervals over 48 h following the administration of each dose of granisetron. Clinical chemistry, haematology and urinalysis were performed before, and 24 h after, each infusion. Electrocardiogram (ECG), resting blood pressure (BP) and pulse were monitored. There were no significant changes in the ECG, lead II trace or ECG time intervals, pulse or blood pressure on each study day. Minor falls in pulse rate and BP (likely to be related to recumbent posture) were seen during both granisetron dosing days, lasting 2 h after each infusion. No significant changes were apparent in the clinical chemistry, haematology or urinalysis measurements following granisetron dosing. No pharmacokinetic parameters measured after cimetidine administration were significantly different from those taken before. Adverse events were mild-to-moderate in severity and were similar to those reported in other studies with granisetron. The pharmacokinetics of granisetron, when administered as a single dose, appeared to be unaltered by cimetidine, an inhibitor of multiple hepatic enzymes (CYP1A2, CYP2D6 and CYP3A4). Granisetron was equally well tolerated before and after repeated dosing with cimetidine.

Clinical Pharmacology Unit, Beecham Pharmaceuticals, Great Burgh, Surrey, UK

Lawrence Youlten

Correspondence: L. Youlten, Periteau House, Winchelsea, East Sussex TN36 4EA, UK.
E-mail: lyoulten@aol.com

Funding and acknowledgements: This study was funded by Beecham Pharmaceuticals. This manuscript was supported by Roche. All analyses described in this study were undertaken in laboratories which comply with the Good Laboratory Practice Regulations of the UK Department of Health and Social Security and those of the US Food and Drug Administration.

Introduction

Granisetron is a potent and selective 5-HT$_3$-receptor antagonist used for the treatment of nausea and vomiting in oncology and post-operative settings (Navari et al 1995; Wilson et al 1996; Spitzer et al 2000). Following oral or intravenous administration of granisetron in man, 10% of the agent is excreted unchanged, while the remainder is metabolized by the cytochrome P450 enzyme system in the liver (Bloomer et al 1994; Clarke et al 1994). 7-Hydroxy and 9′-desmethyl granisetron have been identified as the major metabolites of granisetron with the 7-hydroxy metabolite predominating (Bloomer et al 1994); however, these metabolites circulate primarily as conjugates and they are, therefore, unlikely to contribute to the pharmacological effect of granisetron (Clarke et al 1994). The P450 enzymes involved in the metabolism of granisetron are members of the CYP3A family, with CYP3A3/4 being responsible for the 9′-desmethylation pathway and another enzyme, possibly CYP3A5, for the 7-hydroxylation (Bloomer et al 1994).

Despite the widespread use of 5-HT$_3$-receptor antagonists such as granisetron in the management of nausea and vomiting (Gralla et al 1999), there are few data concerning potential interactions with hepatically metabolized drugs for any of these 5-HT$_3$ agents. Although no serious drug interactions have been reported with granisetron to date, the possibility exists for this agent to interact with chemotherapy agents and/or co-prescribed drugs that affect the CYP3A family.

The histamine$_2$ (H_2)-receptor antagonist, cimetidine, is a potent inhibitor of CYP1A2, 2D6 and 3A enzymes, and can, therefore, decrease the hepatic clearance of co-administered drugs (Gerber et al 1985; Anonymous 2000, Cytochrome P450 website). Cimetidine has been shown in man to impair the elimination of a wide variety of agents such as warfarin, carbamazepine, propranolol and epirubicin, which can lead to clinically significant adverse reactions (Desmond et al 1984; Spina et al 1996; Feely et al 1981; Murray et al 1998). In addition, cimetidine is a commonly prescribed medication for oesophageal reflux disease, and can also be administered as part of the premedication regimen before surgery to inhibit gastric acid production (Wood 1991).

This study was undertaken to assess whether the inhibition of hepatic enzymes by repeat dosing with cimetidine had any effect on the pharmacokinetic profile of an intravenous infusion of granisetron in healthy male volunteers.

Materials and Methods

Patients

Healthy male volunteers aged between 18 and 60 years were enrolled in this 16-day open study if they fulfilled the following criteria: they were within 15% of their ideal body weight; they had a normal medical examination (including electrocardiogram (ECG)); their laboratory values within the normal (95%) range for clinical chemistry, haematology and urinalysis; they had a negative urine drug screen. Subjects were excluded from the study if they had received any other drug therapy during the course of the study period, had participated in any other trial of a systemic drug in the three-month period before this study or had an average daily alcohol intake of greater than six units or a maximum daily intake of 20 units within the previous three months.

Protocol

The study was performed in accordance with the Declaration of Helsinki (1964) and was approved by the Beecham Pharmaceutical Research Division Ethics Committee, which comprised independent medical professionals, including clinical pharmacologists. The written, informed consent of all subjects was obtained before their inclusion in the trial.

Subjects fasted for at least 10 h before commencing the study. On day 1, fasted subjects received granisetron (diluted in 0.9% sodium chloride), 40 $\mu g\,kg^{-1}$, infused at a rate of 5 $mL\,min^{-1}$ over 3 min. During the course of the infusion, and for 4 h after, subjects remained semi-recumbent. Blood pressure (measured via a Critikon Dinamap vital signs monitor) and pulse rate were determined before and immediately after granisetron dosing, and then at 10 min, 30 min, 1, 2, 3, 4, 8, 12 and 24 h after dosing. Blood samples were taken for clinical chemistry and haematology and analysis at the pre-study medical examination, before and 24 h after dosing, and at the post-study medical examination. Urine samples were taken and analysed pre- and post-study. Using a Schiller quantitative ECG monitor, ECG (12 lead) measurements were made at the pre-study medical examination, before and 30 min after dosing, and at the post-study medical examination. A Kontron ECG monitor was used to monitor continuously lead II ECG during and for 4 h after infusion of granisetron. Blood samples were taken for pharmacokinetic analysis before and immediately after dosing, then after a further 2, 5, 10, 15, 20, 30, 45 and 60 min. Additional samples were taken at 1.5, 2, 3, 4, 6, 8, 12, 24, 30 and 48 h after granisetron infusion. Subjects completed a full medical examination within 10 days of the start of the study and between 7 and 14 days after its completion.

Cimetidine dosing commenced on day 7 of the study. Subjects received four doses of oral cimetidine, 200 mg, daily at times corresponding to waking, midday meal, evening meal and before retiring to bed, for a period of eight days (days 7–14 of the study). All volunteers completed a diary card indicating the precise times of each cimetidine dose. On the final day of cimetidine dosing (day 14 of the study), patients received a further infusion of granisetron, 40 $\mu g\,kg^{-1}$, over 3 min and pharmacokinetic parameters were monitored as on day 1. Medications, including over-the-counter remedies, were prohibited from two weeks before the commencement of the study until completion. Subjects refrained from smoking or taking alcohol or caffeine-containing drinks during the study period. Fluid intake was standardized throughout the study. All adverse events experienced during the study were self-reported by the subjects before granisetron dosing, then at 1, 2, 3, 4, 8, 12 and 24 h after dosing, and also at any other time during the study as necessary.

Pharmacokinetic evaluation

Blood samples collected for pharmacokinetic analysis were ejected into EDTA tubes and the plasma separated by centrifugation and transferred into separate tubes. Plasma samples were then frozen at $-20\,^{\circ}C$ until analysed. Concentrations of granisetron in plasma were determined by HPLC with fluorescence detection as described by Clarkson et al (1988). Granisetron and an internal standard (an analogue of granisetron, BRL 43704) were extracted from plasma under alkaline conditions into toluene. Extracts were evaporated to dryness and residues re-dissolved in the HPLC mobile phase. Separation was achieved by reverse-phase HPLC on a 10 μm Apex-CN column eluted with a mobile phase composed of 96% methanol and 4% sodium acetate buffer, at a flow rate of 1 $mL\,min^{-1}$. Detection utilized the native fluorescence at the excitation and emission wavelengths of 305 and 360 nm, respectively. This assay has previously been shown to be specific for granisetron since the relevant chromatographic peak in samples from dosed individuals was found, by mass spectrometry, to contain only granisetron. The assay was linear up to 100 $ng\,mL^{-1}$ and the lower limit of reliable

determination was 0.05 ng mL^{-1}. Assay performance was assessed on the basis of both the statistical characteristics of individual calibration lines and the results of assay of quality control samples stored with the study samples.

The maximum observed plasma concentration (C_{max}) was determined by use of a computer program (AUCDAT, version 4.0). The areas under the plasma concentration–time curves between zero and the last point (AUC_L) were calculated using a combined linear-logarithmic trapezoidal method (AUDAT). The area between the last data point and infinity was calculated by dividing the final observed concentration by the rate constant (λ_z), describing the terminal log-linear phase. This rate constant was determined by using unweighted non-linear regression analysis (MODFIT, version 3.0) (Allen 1990) on the concentration–time pairs occurring after the onset of the terminal log-linear phase. The area under the plasma concentration–time curve between zero and infinity (AUC) was estimated by the sum of AUC_L and the area between the last data point and infinity. The terminal phase half-life ($t_{1/2}$) was calculated as the ratio of $\log_e 2$ to the λ_z value determined in each subject. The volume of distribution (Vd) and the total plasma clearance were calculated according to the method described by Gibaldi & Perrier (1982).

Data analysis

Data were analysed by analysis of variance, and a 5% level was considered significant. The following pharmacokinetic parameters were determined from each subject's concentration–time curves: area under the curve (AUC); maximum observed concentration (C_{max}); elimination half-life ($t_{1/2}$); clearance (CL); volume of distribution (Vd). All parameters were logarithmically transformed before analysis and 90% confidence intervals calculated for the difference between after- and before-cimetidine values.

Results

Of the 13 healthy male volunteers who entered the study, 12 completed the trial. One volunteer was withdrawn before receiving the study medication following a vasovagal attack during insertion of an intravenous needle. Subjects had a mean age of 33.9 years (range 21–42 years), a mean height of 1.73 m and a mean weight of 70.4 kg.

Following dosing with granisetron on days 1 and 14, mean pulse rates fell slightly, then remained steady for the following 2 h. Mean pulse rates before and after granisetron administration were slightly higher on day 1 than on day 14. Furthermore, the mean pulse rate (beats min^{-1}) of the 24-h session after administering granisetron on day 1 (before commencing cimetidine dosing) was higher than in the session after granisetron administration on day 14 (on the final day of repeat cimetidine dosing) (64.2 ± 8.0 vs 61.4 ± 5.6 beats min^{-1}, respectively). However, the average difference between the two sessions (2.8 beats min^{-1}) was not statistically significant ($P = 0.22$). Similarly, mean systolic and diastolic blood pressure in the 24-h period after granisetron administration were higher before commencing cimetidine dosing than afterwards (119.9 ± 9.6 vs 116.4 ± 9.1 and 70.2 ± 6.3 vs 68.1 ± 5.6 mmHg, respectively). The difference between sessions was not statistically significant in the case of mean systolic blood pressure ($P = 0.20$), but was significant in the case of mean diastolic blood pressure ($P = 0.009$). No clinically important changes in individual blood pressure or heart rate occurred. Furthermore, computerised analysis of the ECG parameters measured during the study showed no differences between the sessions examined before or after cimetidine dosing.

No formal statistical examination of the haematology and blood chemistry data was performed during the study. However, informal analysis of the mean and standard deviations of these parameters revealed that mean

Table 1 Mean pharmacokinetic parameters of granisetron (40 μg kg^{-1}) infusion in male volunteers measured before and after 8 days treatment with oral cimetidine (200 mg) four times daily.

Parameter	Granisetron, no cimetidine (day 1)		Granisetron + cimetidine (day 14)		Geometric mean ratio* (90% CI)
	Mean	CV (%)	Mean	CV (%)	
C_{max} (ng mL^{-1})	49.5	65	47.4	71	0.91 (0.63, 1.31)
AUC (ng h mL^{-1})	82.9	55	71.4	55	0.85 (0.67, 1.08)
Vd (L)	235	42	260	33	1.12 (0.87, 1.45)
(L kg^{-1})	3.39	46	3.66	27	
CL (L h^{-1})	42.7	47	51.7	53	1.18 (0.93, 1.51)
([L h^{-1}] kg^{-1})	0.62	49	0.74	52	
λ_z (h^{-1})	0.1991	46	0.2052	45	
$t_{1/2}$ (h)	4.75	69	4.39	64	0.94 (0.75, 1.18)

C_{max}, maximum observed plasma concentration; AUC, area under the plasma concentration–time curve to infinity; Vd, volume of distribution (terminal phase; CL/λ_z); CL, total clearance (dose/AUC); λ_z, terminal phase rate constant; $t_{1/2}$, elimination half-life; CV, coefficient of variation; CI, confidence interval. *Geometric mean ratios were calculated by comparing values measured after granisetron administration plus cimetidine (day 14) with those after granisetron administration alone (day 1).

Table 2 Mean blood chemistry and haematology parameters measured before and after (+24 h) granisetron, 40 $\mu g\,kg^{-1}$, infusion in male volunteers on day 1 (before cimetidine treatment) and day 14 (after 8 days treatment with oral cimetidine, 200 mg four times daily).

Parameter	Granisetron, no cimetidine (day 1), mean (s.d.)		Granisetron + cimetidine (day 14), mean (s.d.)	
	Pre-infusion	Post-infusion	Pre-infusion	Post-infusion
Creatinine ($mmol\,L^{-1}$)	91.9 (11.1)	91.6 (10.3)	103.2 (10.6)	102.3 (15.5)
Alkaline phosphatase ($U\,L^{-1}$)	114.5 (24.5)	109.6 (21.5)	104.6 (25.5)	108.4 (21.1)
Total bilirubin ($\mu mol\,L^{-1}$)	11.8 (3.8)	9.5 (3.5)	10.3 (4.0)	9.5 (2.7)
Total protein ($mmol\,L^{-1}$)	69.2 (2.8)	68.3 (2.0)	68.7 (5.1)	69.0 (3.5)
Creatine kinase ($IU\,L^{-1}$)	79.0 (32.6)	57.3 (24.2)	73.6 (24.0)	59.2 (17.3)
Haemoglobin ($g\,L^{-1}$)	149.7 (7.0)	149.2 (7.9)	146.2 (9.3)	146.7 (8.4)
Red blood cells ($\times 10^{12}\,L^{-1}$)	4.70 (0.25)	4.71 (0.33)	4.58 (0.37)	4.62 (0.31)
Platelets ($\times 10^{9}\,L^{-1}$)	241.6 (46.6)	244.2 (35.2)	257.6 (58.2)	251.4 (43.80)
Neutrophils ($\times 10^{9}\,L^{-1}$)	3.44 (1.49)	3.59 (1.44)	2.70 (0.43)	2.94 (0.53)
Lymphocytes ($\times 10^{9}\,L^{-1}$)	2.02 (0.35)	2.13 (0.48)	2.20 (0.45)	2.29 (0.50)

plasma creatinine was higher in the session on the final day of cimetidine dosing than in the session before cimetidine: mean creatinine values before granisetron infusion for the two sessions were 91.9 and 103.2 $mmol\,L^{-1}$, respectively (Table 2). As these values were measured in the pre-infusion period, they cannot be related to granisetron administration but are more likely to be due to an inhibitory effect of cimetidine on tubular creatinine secretion, indicating that subjects' compliance with the cimetidine treatment was good. Furthermore, the values had returned to pre-study levels by the post-study follow-up examination (96.3 $mmol\,L^{-1}$). Mean total bilirubin levels showed a small decrease following granisetron administration on days 1 and 14: on day 1, values fell from 11.8 $\mu mol\,L^{-1}$ before infusion to 9.5 $\mu mol\,L^{-1}$ 24 h after infusion, whilst on day 14 (on the final day of cimetidine dosing), values fell from 10.3 to 9.5 $\mu mol\,L^{-1}$. A similar decrease was seen in mean creatine kinase after granisetron infusion. Mean creatine kinase values on day 1 fell from 79.0 $IU\,L^{-1}$ before infusion to 73.6 $IU\,L^{-1}$ 24 h after infusion, whereas on day 14 mean values fell from 73.6 to 59.2 $IU\,L^{-1}$ after infusion. However, the changes in total bilirubin and creatine kinase were not associated with changes in other parameters and were not considered to be of clinical significance. There were no notable changes in any other clinical chemistry or haematology parameters measured after granisetron infusion, either before or after cimetidine dosing (Table 2). Similarly, there were no notable changes in the mean values observed for the urinalysis parameters between pre- and post-study examinations (urine creatinine, potassium and sodium, creatinine clearance, potassium, sodium and urine output).

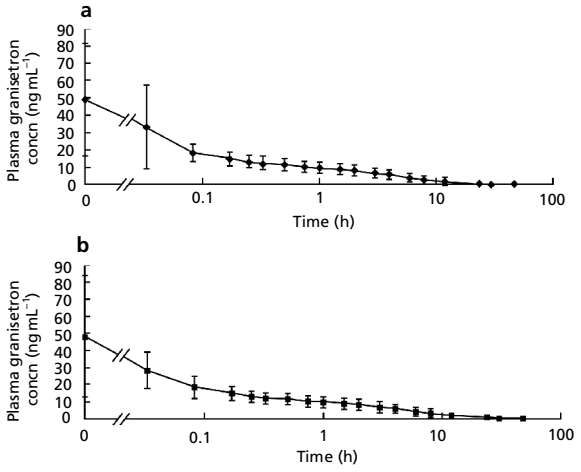

Figure 1 Plasma granisetron concentrations over 48 h following intravenous infusion of granisetron 40 $\mu g\,kg^{-1}$. a. Day 1 before commencement of cimetidine dosing. b. Day 14, the eighth day of dosing with cimetidine 200 mg, four times daily.

Pharmacokinetic parameters (C_{max}, AUC, Vd, CL, $t_{1/2}$) measured after granisetron infusion, before (day 1) and on the final day (day 14) of cimetidine administration were not significantly different (Table 1). Maximum plasma concentrations of granisetron were observed at, or around the end of, the infusion period and, in most cases, had fallen below the limit of reliable detection by 24 h post-infusion. The mean plasma granisetron concentration–time profiles were similar on both granisetron study days (Figure 1).

The symptom most frequently reported after granisetron infusion was headache, which was reported by five of the 12 volunteers during day 1, and by four subjects during day 15; the headache experienced was mild in severity in all cases bar one in which it was moderate. Constipation was the next most common adverse event, reported by 5/12 volunteers on day 1 and 6/12 on day 15. The constipation generally lasted between one and four days, though one subject experienced severe constipation for 12 days. Three volunteers received concomitant medication in the form of laxatives to relieve constipation. One subject reported feeling nauseous on the third day of cimetidine dosing, though this was unlikely to be related to the administration of granisetron. Other symptoms reported were sporadic and not clearly related to drug administra-

tion. All adverse events experienced (apart from the case of severe constipation mentioned above) were mild-to-moderate in severity and had resolved by the post-study medical examination. There were no withdrawals due to serious adverse events.

Discussion

Although 5-HT_3-receptor antagonist anti-emetics such as granisetron are among the most widely used medications in oncology, and are frequently used in the post-operative setting, little information is available on the potential interactions of such agents with drugs which are commonly co-prescribed with them. However, such information is of vital importance to physicians, since polypharmacy has become commonplace in recent years, and oncology patients in particular are likely to be receiving multiple medications to treat their cancer and other conditions (e.g. pain, cardiovascular disease, ulcers, arthritis, psychiatric illness) over long periods of time. Furthermore, many such patients are elderly and their drug metabolism may, therefore, already be compromised by hepatic or renal impairment.

This open study, conducted in 12 healthy male volunteers, was designed to assess the influence of the H_2-receptor antagonist and CYP enzyme inhibitor, cimetidine, on the pharmacokinetics of granisetron. Analysis of the parameters C_{max}, AUC, Vd, CL, $t_{1/2}$, measured after granisetron infusion, indicated that the pharmacokinetics of intravenous granisetron, 40 $\mu g\,kg^{-1}$, appeared to be unaltered by repeated dosing with cimetidine, 200 mg, orally four times daily. There were no significant differences in any of the pharmacokinetic parameters measured after granisetron infusion following cimetidine treatment compared with those measured before cimetidine treatment. This finding was reflected by the range of geometric mean ratios for these parameters (0.85–1.18), which were all close to unity.

ECG monitoring following granisetron infusion revealed no significant study-related changes, either before or after cimetidine dosing. This was consistent with other studies that have shown no ECG changes with granisetron either in healthy adults (Gray et al 1996) or cancer patients (Jantunen et al 1996). Similarly, there were no notable effects of cimetidine on blood pressure, pulse, blood haematological or biochemical factors or urinalysis. Analysis of subjects' vital signs measured during the study revealed minor falls in pulse rate and blood pressure, lasting approximately 2 h, on both granisetron dosing days. These reductions were most likely to be related to the recumbent posture of the volunteers during this period. Although the subjects' mean pulse rates and blood pressure observed on the second granisetron dosing day (on the last day of repeat dosing with cimetidine) were consistently, though not significantly, lower than those measured on the first granisetron dosing day, these differences were likely to be an order effect, possibly related to the stress of an unfamiliar procedure on the first day, and are not thought to be related to cimetidine.

Intravenous granisetron was well tolerated on both infusion days and there were no apparent differences in the adverse events experienced before or after cimetidine dosing. The adverse events observed were similar to those reported in other studies, with headache being the most common symptom experienced, followed by constipation (Dilly 1994).

The results indicated that granisetron could be safely administered with cimetidine and required no dose adjustment. The lack of effect of cimetidine on the pharmacokinetics of granisetron was notable, as cimetidine is a known inhibitor of CYP3A enzymes, including CYP3A4/5 (Martinez et al 1999), though the agent is also an inhibitor of CYP1A2 and CYP2D6. Granisetron is metabolized by members of the CYP3A family, with CYP3A3/4 being responsible for the 9′-desmethylation of the agent and possibly CYP3A5 in the 7-hydroxylation pathway (Bloomer et al 1994). Granisetron has been found to have no inhibitory effect on any P450 enzyme studied (CYP1A2, CYP2A6, CYP2B6, CYP2C9/8, CYP2C19, CYP2D6, CYP2E1, CYP3A and CYP4A) at concentrations up to 250 $\mu mol\,L^{-1}$ (Bloomer et al 1994). Although cimetidine is a known inhibitor of CYP3A subfamily enzymes, the precise effect of this agent on individual CYP3A enzymes, and in particular CYP3A3, is unclear. Therefore, it is possible that cimetidine administration may have resulted in complete inhibition of some of the CYP3A enzymes responsible for the hepatic metabolism of granisetron but not others. This may explain why co-administration of cimetidine had no effect on the metabolism of granisetron in this study. However, cimetidine is a known inhibitor of the metabolism of many drugs and further studies are required to clarify why cimetidine did not affect the metabolism of granisetron. A further possibility may be that inhibition of hepatic enzymes resulted in non-hepatic metabolism of granisetron, as the agent can also be eliminated via renal excretion and it is possible that this route predominated during the study period.

Cimetidine has been shown to have no effect on the pharmacokinetics of mexiletine after either oral or intravenous administration, despite the fact that mexiletine, like granisetron, is primarily metabolized in the liver with 10% of the agent being eliminated by renal excretion (Brockmeyer et al 1989). Nevertheless, cimetidine has been shown to impair the metabolism and elimination of many drugs given intravenously which are eliminated by hepatic metabolism (e.g. phenytoin, propranolol and theophylline), and has been reported to reduce hepatic blood flow (Feely et al 1981; Frigo et al 1983; Powell et al 1984). Such effects can be clinically important and may result in an increase in drug concentration and effect, as well as potentially serious adverse events. Although repeat dosing with cimetidine was found to have no effect on the pharmacokinetics of granisetron in this study, it should be noted that the sample size was small, as reflected in the range of 90% confidence intervals of the geometric mean ratios for all the pharmacokinetic parameters (0.63 to 1.51). This was not surprising, as previously it had been reported that

the inter-individual variability of granisetron pharmacokinetics was large (Allen et al 1994). Indeed, granisetron AUC was relatively stable before and after repeated administration of cimetidine (± 30%), but in two individuals it varied by −51% and +67%.

Only intravenous administration of granisetron was investigated as the study was performed before oral granisetron was widely available. Thus a larger, well-controlled study investigating the effect of cimetidine on both intravenous and oral granisetron is required to verify the result. This study only included healthy males and caution should be used when extrapolating the data to female patients or cancer patients, many of whom have comorbid illnesses.

Conclusions

Granisetron is a medication commonly used to control the nausea and vomiting associated with cytotoxic therapy, radiation therapy or following surgery. In each case, patients are likely to receive a number of therapeutic agents in the course of their treatment. It has been estimated that during the average hospital stay, patients will receive ten different medications. When fewer than six drugs are administered, the probability of a drug interaction is approximately 5%, but this probability increases to over 40% if over 15 agents are administered (Jick et al 1970; Miller 1973). Thus, it is important to recognise the potential of medications for drug interactions with co-prescribed drugs so that this phenomenon can be avoided or minimized. No serious or clinically significant drug interactions have been reported with granisetron to date, and the results of this study further support the safety of this agent.

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