

HETEROGENEITY IN SYSTEMIC AVAILABILITY OF ONDANSETRON AND GRANISETRON FOLLOWING ORAL ADMINISTRATION

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ABSTRACT:

This open-label, randomized, two-way crossover study compared the relative heterogeneity in systemic availability of oral ondansetron and granisetron. It was conducted in 10 healthy male and 10 healthy female subjects aged 18 to 50 years. Following an overnight fast, each subject received 8 mg ondansetron and 1 mg granisetron. Treatments were separated by 7 days. Blood samples for drug assay were collected over a period of 36 h and variability in pharmacokinetic parameter estimates were assessed following standardization by their respective means. Granisetron showed significantly more variability than ondansetron in the three primary endpoints of the area under the curve extrapolated to infinite time, the area under the curve to the last quantifiable time point, and

maximal concentration ($p = .0032, .0037, \text{ and } .0042$, respectively). In one subject, concentrations of granisetron were detectable but below the lower limit of quantitation at any time point. The impact this variability may have on therapeutic efficacy is not clear. An apparent bimodal distribution in granisetron AUC infinite, which appeared to be related to smoking was observed. Because granisetron has been reported to be metabolized primarily by the cytochrome P-450 (CYP) 3A isozyme family in humans, it is possible that cigarette smoke could be an inducer of CYP3A or that CYP1A2, also implicated in the metabolism of granisetron and known to be induced by smoking, is more important in the biotransformation of granisetron than previously thought.

Heterogeneity in drug disposition is well known and can play a major role in the variability observed in therapeutic response to an agent. The CYP3A (cytochrome P-450 3A)¹ subfamily of cytochromes metabolize many drugs and are highly variable in their degree of expression. Of the four known members of the CYP3A subfamily in humans, CYP3A4 and CYP3A5 are found in the digestive tract, in addition to other metabolic sites, and both isozymes display heterogeneity in their expression in different parts of the gut (Lown et al., 1994; Kolars et al., 1994). As a consequence of this, compounds that are metabolized predominantly by CYP3A can show particularly marked variability in oral bioavailability due to intersubject differences in first-pass metabolism in addition to variability in hepatic and other systemic metabolic processes.

Ondansetron (Zofran; Glaxo Wellcome Toronto, Canada) and granisetron and granisetron (Kytrel; SmithKline Beecham, Oakville, Canada) are potent and selective 5-hydroxytryptamine₃ receptor antagonist antiemetics. Both compounds are extensively metabolized, although the range of enzymes responsible for the biotransformation of each is markedly different. Ondansetron is metabolized via a number of CYP450 enzymes, including CYP1A1, CYP1A2,

CYP2D6, and CYP3A4, with no isoform dominating the overall metabolism (Dixon et al., 1995). In contrast, granisetron is largely dependent on the CYP3A family (Bloomer et al., 1994). Given these differences, it was probable that greater heterogeneity in systemic availability would be observed following oral administration of granisetron than ondansetron. Published information supported this view (Pritchard et al., 1992; Cupissol et al., 1993; Allen et al., 1994, 1995), but there were no data generated prospectively under well-controlled conditions to evaluate and quantify any such differences. Hence, the objective of this study was to determine the relative heterogeneity in systemic availability of oral ondansetron (8 mg) to a comparable therapeutic dose of oral granisetron (1 mg) in a normal population of adults.

Materials and Methods

This open-label, randomized, two-way crossover study was conducted in 10 healthy male and 10 healthy female subjects aged 18-50 years. Single oral doses of 8 mg of ondansetron and 1 mg of granisetron, as commercially available tablets, were given in random order with 200 ml of water following an overnight fast. Treatments were separated by a 7-day washout period. Blood samples for serum drug assay were collected pre-dose and at intervals up to 36 h post-dosing for each treatment.

Bioanalysis. Serum samples were analyzed by validated high-performance liquid chromatography with tandem mass spectrometric detection methods with calibration ranges of 1 to 1000 ng/ml for ondansetron and 0.2 to 200 ng/ml for granisetron. Peak area ratios of ondansetron and granisetron versus their respective labeled internal standards were used for quantitation. Linear regression analysis with 1/x weighting was used to derive calibration standard curves. The interday quality control precision for ondansetron was $\leq 10.9\%$, and the accuracy ranged from 88.8 to 101.9% of nominal. The interday quality

¹ Abbreviations used are: CYP, cytochrome P-450; AUC_{∞} , area under the curve extrapolated to infinite time; AUC_{last} , area under the curve to the last quantifiable time point; and C_{max} , maximal concentration; LOQ, limit of quantitation.

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TABLE 1

Pharmacokinetic parameter estimates and mean standardized pharmacokinetic parameter estimates following oral administration of 8 mg of ondansetron (Ond) and 1 mg of granisetron (Gran)

| | Ond | Gran ^a | Ond | Gran ^a | Ond | Gran ^a |
|-------------------------|----------------|-----------------------------------|--------------|-----------------------------------|-----------|-------------------|
| | AUC_{∞} | $(ng \cdot h^{-1} \cdot ml^{-1})$ | AUC_{last} | $(ng \cdot h^{-1} \cdot ml^{-1})$ | C_{max} | (ng/ml) |
| Mean | 226 | 37.1 | 210 | 32.8 | 31 | 3.8 |
| Minimum | 62 | 1.9 | 54 | 1.4 | 16 | 0.6 |
| Maximum | 445 | 77.3 | 410 | 66.8 | 48 | 6.4 |
| Standardized mean | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Standardized minimum | 0.27 | 0.07 | 0.26 | 0.06 | 0.51 | 0.30 |
| Standardized maximum | 1.97 | 2.09 | 1.96 | 2.04 | 1.53 | 1.70 |
| S.D. | 0.45 | 0.82 | 0.45 | 0.81 | 0.29 | 0.55 |
| CV (%) | 44.5 | 82.0 | 45.4 | 81.0 | 29.1 | 54.6 |
| Ratio of variance | | 3.39 | | 3.19 | | 3.52 |
| 95% confidence interval | | 1.55, 7.42 | | 1.50, 6.78 | | 1.52, 8.15 |
| <i>p</i> | | 0.0032 | | 0.0037 | | 0.0042 |

^a Granisetron data exclude one subject in whom all concentrations below the LOQ.

control precision for granisetron was $\leq 9.5\%$, and the accuracy range was 97.4 to 105.6% of nominal.

Pharmacokinetic and Statistical Analysis. Maximal concentration (C_{max}) was the highest observed concentration. The elimination rate constant (λ_z) was calculated by linear least-squares regression of the terminal elimination phase of the log serum concentration versus time plot. The area under the curve (AUC) was calculated by the linear trapezoidal method before C_{max} and log trapezoidal thereafter. AUC from the last measured concentration to infinite time was calculated by dividing the last measured concentration by λ_z . The data were standardized by dividing individual values for each treatment by the corresponding mean. The primary analyses compared ratios of standardized variances for the two treatments on AUC_{∞} , AUC_{last} , and C_{max} . The null hypothesis of equal variance was evaluated by testing whether the linear correlation between individual sums (ondansetron + granisetron) and differences (ondansetron - granisetron) was zero. The strength of any evidence against the null hypothesis was assessed by the corresponding *p* value ascertained for testing that the correlation coefficient was zero. All statistical tests were carried out at the two-sided 5% level of significance.

Results and Discussion

All subjects received the study treatment and had blood drawn during both dosing periods of the study. In one male subject serum granisetron concentrations were below the 0.2 ng/ml limit of quantitation (LOQ) at all time points. Clinical staff verified that the subject took the dose, and evidence of granisetron below the quantifiable limit was observed in the chromatograms. Serum ondansetron concentrations in the same subject were quantifiable. Parameter values for ondansetron and granisetron before and following mean standardization are shown in Table 1 along with the estimated ratios (granisetron/ondansetron) of variances, associated 95% confidence intervals, and *p* values. For all parameters, the variance associated with granisetron was significantly greater than that associated with ondansetron. For both compounds, the range of AUC_{∞} values (ondansetron, 7-fold; granisetron, 41-fold) was similar to that reported following i.v. administration (Allen et al., 1994; Roila and Del Favero, 1995). However, the 41-fold range for granisetron AUC_{∞} excludes the subject in whom granisetron concentrations were below the LOQ at all time points. If an assay with a sufficiently low LOQ were available, inclusion of this value would have resulted in a substantially greater range for all granisetron parameters.

The normalized granisetron AUC_{∞} values displayed an apparent bimodal distribution, whereas the ondansetron values in the same subjects appeared to be more normally distributed (Figure 1). The demographic data collected during the study revealed that the granisetron bimodality appeared to be related to the smoking history of the subjects, with nonsmokers having higher normalized AUC values than

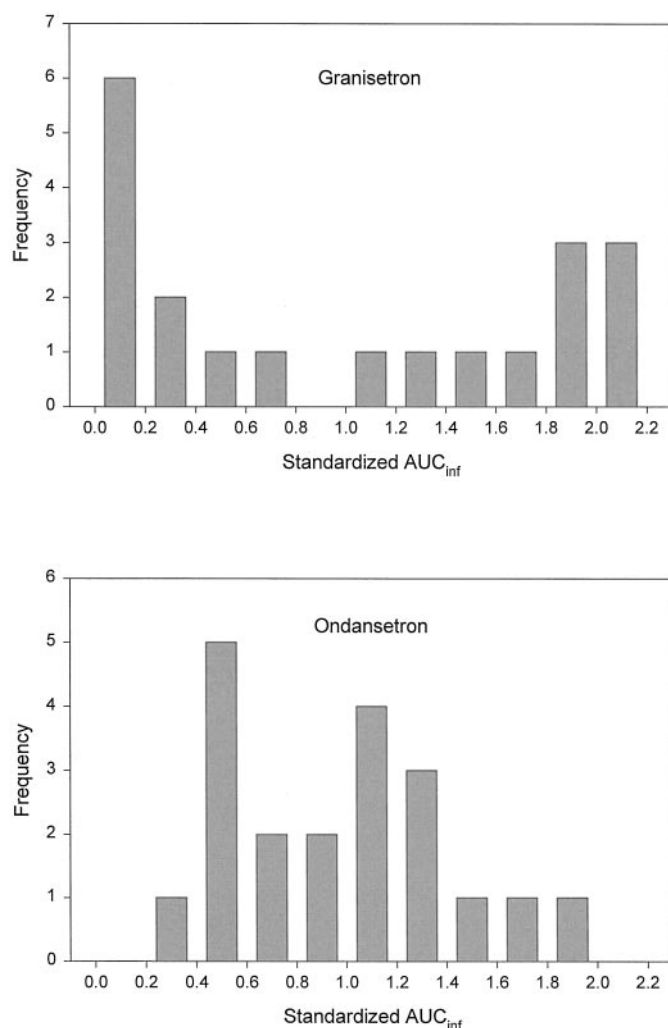


Fig. 1. Distribution of mean standardized AUC_{∞} values following oral administration of 8 mg of ondansetron (upper panel) and 1 mg of granisetron (lower panel).

current smokers with median (and range) values of 1.82 (0.53–2.09) and 0.18 (0.07–1.01), respectively. This trend was not apparent for ondansetron for which the median and range normalized AUC values were 1.15 (0.59–1.97) and 0.91 (0.54–1.46) in nonsmokers and smokers, respectively. These values exclude three subjects who were recorded as “former” smokers, because the time since cessation was

not established. These data may only be considered preliminary observations, because the study was not designed to detect bimodality and, hence, the subject numbers are insufficient to perform a meaningful statistical analysis. However, if real, these observations may be relevant to the interpretation of the existing *in vitro* metabolism data for granisetron. The variability in granisetron pharmacokinetics *in vivo* has been linked to the *in vitro* variability of rate of human liver 7-hydroxylation of granisetron (Bloomer et al., 1994), suggesting that the majority of the variability in the metabolism of granisetron could be explained by heterogeneity in CYP3A activity. Although the results of this study could be interpreted as supporting this view, the apparent bimodality in AUC_{∞} distribution, if real, suggests otherwise. Many drugs (e.g., rifampicin, phenobarbital, carbamazepine, and dexamethasone) and even dietary salt (Darbareh et al., 1997) are known to induce CYP3A. CYP3A is not, however, generally accepted to be inducible by cigarette smoking, although there is emerging data that may suggest otherwise (Wanwimolruk et al., 1995; Hossain et al., 1997; Frye et al., 1997). Alternatively CYP1A2, reported as contributing only a minor role in the 7-hydroxylation of granisetron (Bloomer et al., 1994), may be more important in granisetron biotransformation than previously suspected, particularly in individuals who smoke.

The impact that variability in systemic exposure of the 5-hydroxytryptamine₃ receptor antagonists may have on the therapeutic outcome in a clinical setting remains unclear, because there are conflicting reports regarding the correlation, or lack of correlation, between systemic concentration or exposure and effect. In part, this may be due to the heterogeneous nature of the patient population, particularly with regard to age, gender, and other environmental factors such as alcohol consumption, which are known to affect response to emetogenic stimuli. However, there are also reports of relationships between concentration (Carmichael et al., 1989; Pritchard et al., 1995) or total exposure (Haberer and Palmer, 1995) and effect for this class of antiemetic agents, and reliability in systemic drug delivery following oral administration could therefore be advantageous in ensuring consistent clinical results. It has also been proposed that the local action of granisetron in the proximal gut mucosa could explain the apparent lack of a pharmacokinetic–pharmacodynamic relationship (Blower, 1995). This would now appear unlikely because, before reaching the afferent neurones in the proximal gut mucosa, an orally administered

drug would be subject to gut wall metabolism, which this study has demonstrated is a significant factor in determining the variability in systemic exposure for granisetron.

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