HETEROGENEITY IN SYSTEMIC AVAILABILITY OF ONDANSETRON AND GRANISETRON FOLLOWING ORAL ADMINISTRATION

B. W. CORRIGAN, B. NICHOLLS, B. THAKRAR, R. LAM C. GROSSE, J. ALIANTI, AND J. L. PALMER

Clinical Pharmacology, Glaxo Wellcome, Mississauga, Ontario, Canada (B.W.C., B.N., R.L.); Department of Drug Metabolism, Glaxo Wellcome, Research Triangle Park, North Carolina, United States of America (C.G., J.A.); and Clinical Pharmacology Division, Glaxo Wellcome, Greenford, Middlesex, United Kingdom (B.T., J.L.P.)

(Received January 16, 1998; accepted June 18, 1998)

This paper is available online at http://www.dmd.org

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, 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 bio-transformation 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) 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 isoforms 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 (Kytril; 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 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 predose and at intervals up to 36 h postdosing 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 ±10.9%, and the accuracy ranged from 88.8 to 101.9% of nominal. The interday quality...
control precision for granisetron was ≤9.5%, and the accuracy range was 97.4 to 105.6% of nominal.

**Pharmacokinetic and Statistical Analysis.** Maximal concentration ($C_{\text{max}}$) was the highest observed concentration. The elimination rate constant ($\lambda_z$) 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 $C_{\text{max}}$ and log trapezoidal thereafter. AUC from the last measured concentration to infinite time was calculated by dividing the last measured concentration by $\lambda_z$. 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, $AUC_{\text{last}}$, and $C_{\text{max}}$. 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 $AUC_{\text{inf}}$ 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 $AUC_{\text{inf}}$ 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 $AUC_{\text{inf}}$ 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 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Standardized Mean</th>
<th>Standardized Minimum</th>
<th>Standardized Maximum</th>
<th>S.D.</th>
<th>CV (%)</th>
<th>Ratio of variance</th>
<th>95% confidence interval</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{\text{inf}}$</td>
<td>226</td>
<td>62</td>
<td>445</td>
<td>1.0</td>
<td>0.27</td>
<td>1.97</td>
<td>44.5</td>
<td>4.5</td>
<td>3.39</td>
<td>1.55, 7.42</td>
<td>0.0032</td>
</tr>
<tr>
<td>$AUC_{\text{last}}$</td>
<td>37.1</td>
<td>1.9</td>
<td>77.3</td>
<td>1.0</td>
<td>0.07</td>
<td>2.09</td>
<td>82.0</td>
<td>8.2</td>
<td>3.19</td>
<td>1.50, 6.78</td>
<td>0.0037</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>210</td>
<td>54</td>
<td>410</td>
<td>1.0</td>
<td>0.26</td>
<td>1.96</td>
<td>45.4</td>
<td>4.5</td>
<td>3.52</td>
<td>1.52, 8.15</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

* Granisetron data exclude one subject in whom all concentrations below the LOQ.
not established. These data may only be considered preliminary ob-
servations, because the study was not designed to detect bimodality and, hence, the subject numbers are insufficient to perform a mean-
gingful 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 re-

sults of this study could be interpreted as supporting this view, the
apparent bimodality in $AUC_{\text{in}}$ distribution, if real, suggests otherwise.
Many drugs (e.g., rifampicin, phenobarbital, carbamazepine, and
dexamethasone) and even dietary salt (Durbaret 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 contrib-
uting only a minor role in the 7-hydroxylation of granisetron
(Bloomer et al., 1994), may be more important in granisetron bio-
transformation than previously suspected, particularly in individuals
who smoke.

The impact that variability in systemic exposure of the 5-hydroxy-
tryptamine3 receptor antagonists may have on the therapeutic out-
come in a clinical setting remains unclear, because there are conflict-

ing 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 con-
sistent 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.

References
Allen A, Asgill CC, Pierce DM, Upward J and Zussman BD (1994) Pharmacokinetics and
tolerance of ascending intravenous doses of granisetron, a novel 5-HT3 antagonist, in healthy

(1995) The pharmacokinetics of granisetron, a 5-HT3 antagonist in young and elderly volun-

Bloomer JC, Baldwin SJ, Smith GJ, Ayton AD, Clarke SE and Chenery RJ (1994) Characteri-
sation of the cytochrome P450 enzymes involved in the in vitro metabolism of granisetron.


Carmichael J, Cantwell BMJ, Edwards CM, Zussman BD, Thompson S, Rapeport WG and
Harris AL (1989) A pharmacokinetic study of granisetron (BRL36944A), a selective 5-HT3
receptor antagonist: Correlation with anti-emetic response. Cancer Chemother Pharmacol
24:45–49.

D (1993) Evaluation of the bioequivalence of tablet and capsule formulations of granisetron in
1284.


Dixon CM, Colthup PV, Sarabjit-Singh CJ, Kerr BM, Boehlert CC, Park GR and Tarbit MH
(1995) Multiple forms of cytochrome P-450 are involved in the metabolism of ondansetron in

on the pharmacokinetics and pharmacodynamics of alprazolam. Abstracts of the 37th Inter-


modeling of single dose and multiple dose data for an immediate release (IR) and a controlled


heterogeneity in expression of CYP3A4 and CYP3A5 in small bowel. Lack of prediction by

Labiker KL and Goo KL (1991) Granisetron: A review of its pharmacological properties and

effects on ondansetron pharmacokinetics: Evaluation of healthy aged volunteers. Clin Phar-
macol Ther 51:51–55.


in man: Identification of a major metabolite, and effects of smoking and rifampicin pretreat-