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ORIGINAL ARTICLE

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Pharmacokinetics of dolasetron with coadministration of cimetidine or rifampin in healthy subjects

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Abstract *Purpose*: Dolasetron is a selective 5-HT_3 receptor antagonist. The purpose of this study was to determine the effect of cimetidine and rifampin on the steady-state pharmacokinetics of orally administered dolasetron and its active reduced metabolite, hydrodolasetron. *Methods*: A group of 18 healthy men (22 to 44 years old) were randomized to receive each of the following three treatments in a three-period crossover design: 200 mg dolasetron daily (treatment A); 200 mg dolasetron daily plus 300 mg cimetidine four times daily (treatment B); or 200 mg dolasetron daily plus 600 mg rifampin daily (treatment C). Each study period was separated by a 14-day washout period. Serial blood samples were collected before the first dose (baseline) on day 1 and at frequent intervals up to 48 h after the morning dose on day 7 for quantification of dolasetron and its metabolites, hydrodolasetron (both isomers), 5′OH hydrodolasetron, and 6′OH hydrodolasetron. Serial urine samples were also collected at baseline and during the periods 0–24 and 24–48 h following the morning dose on day 7, and analyzed for dolasetron and its metabolites. *Results*: Plasma and urine dolasetron concentrations were below quantifiable concentrations for all three treatments. Mean steady-state area under the plasma concentration-time curve ($AUC_{ss(0–24)}$) of hydrodolasetron increased by 24%, mean apparent clearance ($CL_{app,po}$) decreased by 19%, and maximum plasma hydrodolasetron concentration ($C_{max,ss}$) increased by 15% when dolasetron was coadministered with cimetidine. When dolasetron was given with rifampin, mean hydrodolasetron $AUC_{ss(0–24)}$ decreased by 28%, $CL_{app,po}$ increased by 39%, and hydrodolasetron $C_{max,ss}$ decreased by 17%. Small differences were found in mean t_{max} (0.7 to 0.8 h), CL_r (2.0 to 2.6 ml/min per kg), and $t_{1/2}$ (7.4 to 8.8 h) for hydrodolasetron between treatment periods. Approximately 20% and 2% of the dolasetron dose were excreted in urine as the *R*(+) isomer and *S*(−) isomer of hydrodolasetron, respectively, across all three treatments. Dolasetron mesylate was well tolerated in this study during all three treatment periods, with the highest incidence of adverse events reported during the control period when dolasetron mesylate was given alone. *Conclusion*: Based on the small changes in the pharmacokinetic parameters of dolasetron and its active metabolites, as well as the favorable safety results, no dosage adjustments for dolasetron mesylate are recommended with concomitant administration of cimetidine or rifampin.

Key words Dolasetron · Cimetidine · Rifampin · Drug interactions · Pharmacokinetics

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Introduction

Dolasetron is the most recent addition to the class of serotonin antagonists with antiemetic properties. Dolasetron has pharmacological activity that is selective for 5-HT_3 receptors [1, 2]. The safety and efficacy of dolasetron mesylate for the management of chemotherapy-induced emesis and postoperative nausea and vomiting has been well established in controlled clinical trials [3–6].

The pharmacokinetic profile of dolasetron has been previously characterized in healthy men [7–11], healthy women [12], elderly persons [13], anesthetized children [14], and subjects with hepatic impairment [15]. Following oral and intravenous doses of dolasetron mesylate, dolasetron is rapidly eliminated from plasma, with an elimination half-life ($t_{1/2}$) of less than 10 min [7–10]. The primary metabolic pathway for dolasetron is virtually complete reduction of the ketone group by

carbonyl reductases to hydrodolasetron (also referred to as MDL 71, 156 and reduced metabolite). Less than 1% of the dose is excreted as parent drug [8, 11]. Hydrodolasetron is formed rapidly, with a maximum plasma concentration (C_{max}) occurring 0.5 to 1.0 h after the dolasetron dose, and eliminated slowly, with a mean $t_{1/2}$ of 5.9 to 9.7 h [7–10]. The reduction of hydrodolasetron is stereoselective, with preferential formation of the *R*(+) isomer [11, 16, 17].

As outlined in Fig. 1, elimination of hydrodolasetron involves both excretion and metabolism [11, 18, 19]. An average of 20 to 31% of the dose is excreted in urine as unchanged hydrodolasetron following an intravenous dose of dolasetron mesylate [8], and 23 to 30% after an oral dose [7]. Hydrodolasetron is metabolized to 5′OH hydrodolasetron, 6′OH hydrodolasetron, hydrodolasetron-*N*-oxide, and glucuronide conjugates [11]. In vitro enzyme-selective inhibition and correlation studies have demonstrated that the cytochrome P450 isoenzyme responsible for the hydroxylation of hydrodolasetron is CYP2D6 [19, 20]. *N*-Oxidation and, to a lesser extent, 6-hydroxylation are CYP3A4-dependent. The 5′OH and 6′OH metabolites are excreted unchanged or further metabolized to glucuronide and/or sulfate conjugates [11].

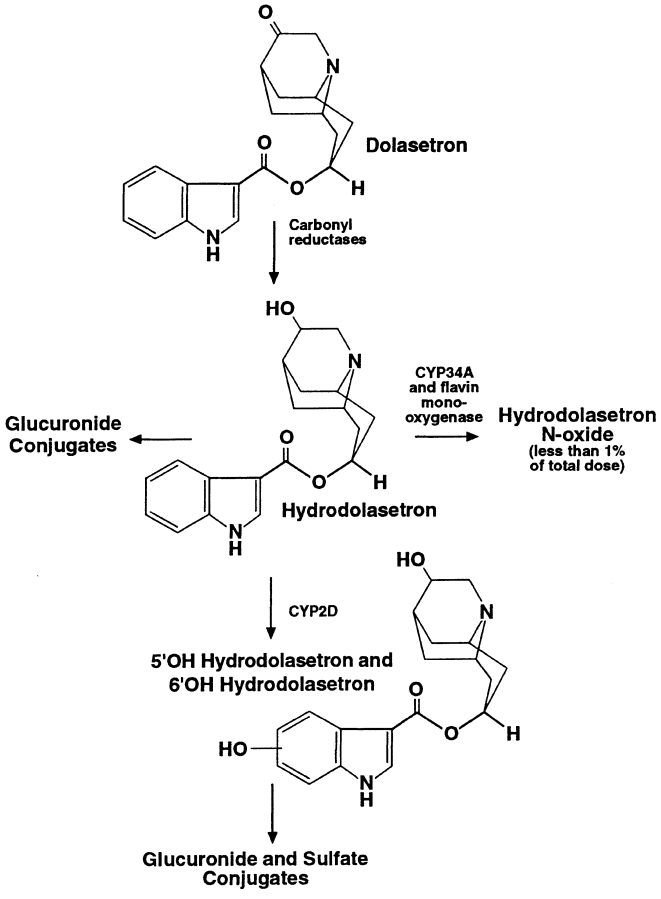

Fig. 1 Proposed metabolic scheme for the biotransformation of dolasetron

Based on in vitro testing, both isomers of hydrodolasetron, as well as the 5′ and 6′ hydroxy metabolites, are selective antagonists at 5-HT_3 receptors [1, 16]. The most active 5-HT_3 receptor antagonist, even exceeding that of parent drug, is *R*(+)-hydrodolasetron. In addition, the *R*(+)-isomer is the predominant metabolite circulating in plasma following an oral or intravenous dose of dolasetron [11, 16, 17]. Therefore, although a cascade of active metabolites is formed following administration of dolasetron, *R*(+)-hydrodolasetron is likely the greatest contributor to the antiemetic effects observed with dolasetron mesylate therapy [10, 11, 15, 17].

Since the elimination of hydrodolasetron includes not only renal excretion but also hydroxylation and *N*-oxidation, the potential for drug-drug interactions exists when dolasetron is administered in conjunction with drugs that affect the CYP450 mixed function oxidase system. Cimetidine has been identified as a potent inhibitor [21, 22] of this enzyme system and rifampin has been identified as a potent inducer [23–25]. The aim of this study was to determine the effect of cimetidine and rifampin on the steady-state pharmacokinetics of dolasetron and its metabolites.

Materials and methods

Study design

In this open-label, three-period, three-treatment crossover study, 18 healthy male subjects were randomized to receive each of the following treatments on three separate occasions: 200 mg dolasetron daily (treatment A); 200 mg dolasetron daily plus 300 mg cimetidine four times daily (treatment B); or 200 mg dolasetron daily plus 600 mg rifampin daily (treatment C). The dolasetron dose was administered as a 10 mg/ml (20 ml) oral solution at 8:00 a.m. each day, the cimetidine dose was administered as one 300 mg tablet (Tagamet®, SmithKline Beecham) every 6 h starting at 8:00 a.m. each day, and the rifampin dose was administered as two 300 mg capsules (Rifadin®, Hoechst Marion Roussel) at 8:00 a.m. each day. All three treatments were given for 7 complete days. A 14-day drug-free interval separated the three treatment periods.

The protocol was reviewed and approved by the clinic's Institutional Review Board and all subjects signed informed consent prior to participation. Subjects fulfilling the following criteria were eligible for enrollment: between the ages of 19 and 45 years; within 10% of ideal body weight; free from clinically significant organ abnormality or disease based on serum chemistry and hematology testing, urinalysis, electrocardiogram measurements, and physical examination; and negative screens for HIV antigen, hepatitis B surface antigen, and qualitative drug abuse. Any subject who required treatment with either prescription or nonprescription medication within 14 days prior to initiation of the study or who had received any known hepatic or renal clearance-altering drug within 30 days prior to initiation of the study was excluded from participation. During the study, subjects were instructed to refrain from taking any medication.

Study procedures

During each of the three treatment periods, subjects were housed in the clinic starting the day before the first dose of study drug (day 0) and continuing until 48 h after the last dose (day 9). Each 8:00 a.m. dose of study medication was taken after an overnight fast; a

standardized breakfast was served 2 h following ingestion of the dose. Nutritionally balanced meals were provided at specified times throughout the in-house clinic stays. Ingestion of caffeine-containing foods or beverages was not allowed.

Blood samples (9.5 ml) were collected into prechilled Venoject tubes at baseline (immediately before the 8:00 a.m. dose) on day 1, then 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36, and 48 h after the 8:00 a.m. dose of study medication on day 7. Blood samples for determination of trough dolasetron and hydrodolasetron concentrations were also collected before the morning dose on days 5, 6, and 7 of each period. Plasma was immediately separated in the samples by refrigerated centrifugation (0–4 °C at 2000 rpm for 10 min). Aliquots of 1.0 ml were then transferred to prechilled culture tubes containing 50 µl 5 *M* citric acid, frozen on a slant, and stored at −20 °C until analysis. Serial urine samples were collected in plastic containers at baseline on day 1 (total void), then during the periods 0–24 and 24–48 h following the 8 a.m. dose on day 7. During the collection periods, urine was stored in the refrigerator. At the end of the collection period, the urine was mixed, the pH and total volume was recorded, and a 20-ml aliquot was extracted. The aliquot was frozen immediately and stored at −20 °C.

To assess safety during each treatment period, serial heart rate, blood pressure, and 12-lead electrocardiogram measurements were taken prior to the first dose on day 1 (baseline); 2 h after the 8 a.m. dose on days 1, 3, 5, and 6; and 2, 6, 12, and 24 h after the last dose on day 7.

Analytical procedures

Dolasetron and hydrodolasetron were quantitated in plasma using a validated liquid/liquid extraction and reverse-phase HPLC procedure. The assay had a lower limit of quantitation of 0.73 ng/ml for dolasetron and 0.92 ng/ml for hydrodolasetron using 1.0 ml of plasma. Assay validation and analysis of plasma samples were performed at Phoenix International Life Sciences (Saint-Laurent, Quebec, Canada). Validation of the method was accomplished by assaying two replicates of nine calibration standards and a minimum of ten replicates of quality control standards at each of five concentrations on 3 separate days. Over the concentration ranges of 0.73 to 73 ng/ml for dolasetron and 0.92 to 92 ng/ml for hydrodolasetron, the ranges of mean accuracy for quality control samples were 96.1 to 108% and 88.8 to 99.9%, respectively. The respective ranges of precision (coefficient of variation) were 5.3 to 11% and 7.7 to 12%.

A validated liquid/liquid extraction and reverse-phase HPLC procedure was also used to quantify dolasetron, hydrodolasetron (total, *R*(+) isomer, and *S*(−) isomer) and the 5′ and 6′ hydroxy metabolites of hydrodolasetron in urine. Parallel chiral and achiral columns were used to separate the enantiomers in urine samples. Assay validation and analysis of urine samples was performed at Hoechst Marion Roussel (Kansas City, Mo). The assay had a lower limit of quantitation of 25 ng/ml for each analyte using 1.0 ml of urine. Validation of the assay was conducted over the concentration range of 25 to 5000 ng/ml for 5′OH hydrodolasetron, 6′OH hydrodolasetron, and dolasetron using an achiral column. Hydrodolasetron, although resolved, was not quantified on this column. A validation range of 25 to 2500 ng/ml was also used for *R*(+)-hydrodolasetron and *S*(−)-hydrodolasetron. Validation of the achiral system was accomplished by assaying two replicates of seven calibration standards and a minimum of ten replicates of quality control standards at each of four concentrations on 3 separate days. The chiral system validation involved analysis of two replicates of six calibration standards and a minimum of ten replicates of quality control standards at each of three concentrations on 3 separate days. The ranges of mean accuracy for quality control samples of dolasetron, 5′OH hydrodolasetron, 6′OH hydrodolasetron, *R*(+)-hydrodolasetron, and *S*(−)-hydrodolasetron were 88.3 to 92.2%, 99.0 to 105%, 100 to 106%, 95.8 to 99.9%, and 99.4 to 103%. The respective ranges of precision were 4.0 to 7.4%, 3.2 to 7.1%, 5.0 to 7.7%, 4.7 to 7.4%, and 5.9 to 10.1%.

Data analysis

Steady-state pharmacokinetic parameters for each analyte were calculated from the plasma and urine concentration data by model-independent methods. Since dolasetron was administered as a methane sulfonate salt, dose correction was made based on the appropriate molecular weights for the calculation of pharmacokinetic parameters involving dose. The calculated dose correction factors for dolasetron, hydrodolasetron, and 5′OH hydrodolasetron and 6′OH hydrodolasetron were 0.740, 0.744, and 0.781, respectively. Because dolasetron is reduced so rapidly to hydrodolasetron, pharmacokinetic evaluation of the parent compound was not conducted.

The following pharmacokinetic parameters were computed for hydrodolasetron and the 5′ and 6′ hydroxy metabolites: area under the plasma concentration-time curve ($AUC_{ss(0–24)}$), apparent oral clearance ($CL_{app,po}$), renal clearance (CL_r), percent of dose excreted in the urine, and apparent half-life ($t_{1/2}$). The AUC values for the dosing interval were calculated by the trapezoidal rule, $CL_{app,po}$ was calculated by dividing the dose corrected for molecular weight by $AUC_{ss(0–24)}$ and normalizing to body weight, CL_r was calculated by dividing total amount of drug excreted in urine for 0–24 h on day 7 by $AUC_{ss(0–24)}$ and normalizing to body weight, and $t_{1/2}$ was calculated by dividing 0.693 by the terminal elimination rate constant. The terminal elimination rate constant was estimated by linear least squares regression of log plasma concentration-time data during the terminal elimination phase. Time to maximum plasma concentration (t_{max}), maximum plasma concentration ($C_{max,ss}$), and minimum plasma concentration ($C_{min,ss}$) were derived directly from the raw data.

Statistical analysis

Between-treatment comparisons were evaluated with three analyses, one on the original data, one on the log-transformed data, and one a nonparametric analysis. First, a three-way analysis of variance (ANOVA), with terms for subject, period, and treatment, was done for each analysis. For the nonparametric analysis, treatments were ranked within each subject before the ANOVA was done. For the original and log-transformed analysis, the model assumption of variance homogeneity among treatments was tested with Levene's test on the residuals from the ANOVA, and the model assumption of normality was tested with Shapiro-Wilk tests on each treatment group's residuals from the ANOVA. Adjusted treatment means, treatment differences, and variances of the differences were estimated from the ANOVA, and the 90% confidence intervals for treatment differences were calculated. For the nonparametric analysis, point estimates of treatment means and treatment differences were found using Hodges-Lehmanm estimator associated with the one sample signed rank statistic. The large sample approximation was used to compute 90% confidence intervals for treatment differences. In all analyses, treatment differences were converted to percent differences.

The primary analysis was chosen using the following criteria. If the original data met all model assumptions, (i.e. all *P*-values from the Levene's and Shapiro-Wilk tests were >0.05), then the primary analysis was the analysis of the original data. If model assumptions for original data were not met but all model assumptions for log-transformed data were met, then the primary analysis was the analysis of the log-transformed data. If neither the original nor the log-transformed data met all model assumptions, the primary analysis was the analysis of the rank-transformed data.

Descriptive statistics (means and standard deviation) alone were provided for safety data.

Results

Of the 18 subjects enrolled in the study, 17 completed all procedures. One subject was withdrawn after completing

two treatment periods due to a nondrug-related illness (cellulitis). Therefore, the data analysis includes data from 18 subjects for treatments A and B, and 17 subjects for treatment C. Nine of the men were Caucasian and nine were Hispanic; their ages ranged from 22 to 44 years.

Pharmacokinetic results

Plasma and urine dolasetron concentrations were below the assay quantitation limit for all three treatments. In contrast, plasma concentrations of hydrodolasetron were quantifiable for up to 48 h after the last dose in all three treatment periods. Similar trough hydrodolasetron plasma concentrations were found on days 5, 6, and 7, which indicates that steady-state conditions were achieved for hydrodolasetron by day 5 of multiple daily dolasetron dosing.

Figure 2 presents the mean hydrodolasetron plasma concentration-time plots for all three treatment periods. Mean hydrodolasetron pharmacokinetic parameters with statistical analysis for differences between treatments are presented in Table 1. Mean $AUC_{ss(0-24)}$ of hydrodolasetron increased by 24% (CI_{90} 17.3, 30.7), $CL_{app,po}$ decreased by 19% (CI_{90} −23.5, −14.8), and hydrodolasetron $C_{max,ss}$ increased by 15% (CI_{90} 4.9, 25.0) when dolasetron was coadministered with cimetidine. When dolasetron was given with rifampin, mean hydrodolasetron $AUC_{ss(0-24)}$ decreased by 28% (CI_{90} −30.7, −23.7), $CL_{app,po}$ increased by 39% (CI_{90} 31.0, 46.4), and hydrodolasetron $C_{max,ss}$ decreased by 17% (CI_{90} −27.2, −6.7). Mean t_{max} for hydrodolasetron ranged from 0.7 to 0.8 h between treatments, mean CL_r ranged from 2.0 to 2.6 ml/min per kg, and mean $t_{1/2}$ ranged from 7.4 to 8.8 h. Renal clearance was greater than average glomerular filtration rate (1.73 ml/min per kg), which suggests that hydrodolasetron undergoes active tubular secretion in the kidney.

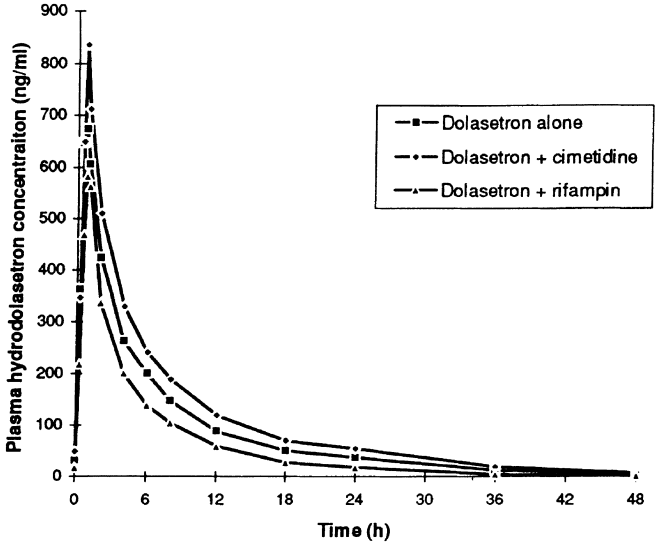

Fig. 2 Mean hydrodolasetron plasma concentration versus time plots following multiple daily oral doses of dolasetron mesylate alone (treatment A; $n = 18$), dolasetron mesylate plus cimetidine (treatment B, $n = 18$); and dolasetron mesylate plus rifampin (treatment C, $n = 17$)

Table 2 summarizes the percent of the dolasetron dose excreted as hydrodolasetron (both enantiomers), and 5′OH and 6′OH hydrodolasetron in urine at steady-state over the 24-h dosing period. Approximately 20% and 2% of the dolasetron dose, respectively, were excreted in urine as the $R(+)$ isomer and $S(-)$ isomer of hydrodolasetron across all three treatments. Similar to the findings of previous investigations [11, 15], $R(+)$-hydrodolasetron accounted for the majority ($>89\%$) of hydrodolasetron excreted in urine. Approximately 1% and 5% of the dolasetron dose was excreted in the urine as 5′OH hydrodolasetron and 6′OH metabolites, respectively, following all three treatments. A significantly greater percent dose was excreted as 6′OH hydrodolasetron with concomitant rifampin administration compared to dolasetron alone, but the difference was only 16%.

Safety results

Of the 18 subjects who participated in the study, 13 (72%) experienced at least one adverse event during the course of the study. The overall incidence rate was higher with dolasetron alone (11/18 subjects, 61%) compared with dolasetron plus cimetidine (16/18 subjects, 33%) or dolasetron plus rifampin (6/17, 35%). Most of the adverse events were mild; none required withdrawal from the study. The most frequent adverse event was sinus bradycardia (8/18 subjects, 44%), defined as a heart rate < 50 beats/min. The average heart rate observed in these subjects was considered normal for a population of healthy young men [26]. Other adverse events reported by more than one subject were abdominal cramps, nausea, and dizziness (each occurring in 2/18 subjects, 11%). Headache, which is commonly reported with 5-HT_3 receptor antagonists, was only reported by one subject [27, 28]. Small and asymptomatic ECG changes were recorded in seven subjects, with no apparent relationship to treatment period. This type of ECG change has been previously reported with dolasetron [9, 29–31], as well as with the other 5-HT_3 receptor antagonists ondansetron [31, 32] and granisetron [33], in healthy volunteers and cancer patients.

Discussion

The potential for clinically significant pharmacokinetic drug-drug interactions to occur with dolasetron was predicted to be minimal based on its pharmacokinetic characteristics. First, dolasetron is completely reduced to hydrodolasetron by carbonyl reductases. This group

Table 1 Mean hydrodolasetron steady-state pharmacokinetic parameters and statistical comparisons following multiple daily oral doses of dolasetron mesylate alone (treatment A; $n = 18$), dolasetron mesylate plus cimetidine (treatment B, $n = 18$); and dolasetron mesylate plus rifampin (treatment C, $n = 17$) (*CI* confidence interval for treatment differences, *CV* coefficient of variation)

Parameter	Treatment	Mean (%CV)	Pairwise difference (%)[a]	*P*-value for pairwise difference[a]	90% CI for pairwise difference[a]
$AUC_{ss(0-24)}$ (ng · h/ml)[b]	A	3654 (31)			
	B	4551 (33)	B-A, 23.8	< 0.01	17.3, 30.7
	C	2682 (31)	C-A, −27.8	< 0.01	−31.7, −23.7
$C_{max,ss}$ (ng/ml)	A	732.7 (24)			
	B	842.2 (31)	B-A, 14.9	0.02	4.9, 25.0
	C	614.3 (23)	C-A, −16.9	< 0.01	−27.2, −6.7
t_{max} (h)	A	0.67 (29)			
	B	0.78 (10)	B-A, 16.7	0.01	6.5, 26.9
	C	0.82 (18)	C-A, 23.6	< 0.01	13.1, 34.0
$Cl_{app,po}$[b] (ml/min/kg)	A	10.5 (29)			
	B	8.4 (28)	B-A, = 19.2	< 0.01	−23.5, −14.8
	C	14.4 (30)	C-A, 38.5	< 0.01	31.0, 46.4
$t_{1/2}$ (h)[c]	A	8.8 (19)			
	B	8.4 (18)	B-A, −4.2	0.28	−12.6, 4.1
	C	7.4 (20)	C-A, −15.3	< 0.01	−21.5, −9.5
CL_r (ml/min/kg)	A	2.15 (48)			
	B	2.00 (33)	B-A, −6.9	0.57	−27.2, 13.4
	C	2.58 (38)	C-A, 21.6	0.09	0.8, 42.3

[a] Pairwise difference (%), *P*-value, and 90% confidence interval for the pairwise difference (%) were done using adjusted means from ANOVA
[b] Statistical analysis done using log-transformed data
[c] Statistical analysis done using rank-transformed data

of enzymes is present in virtually all tissues including blood, has a high metabolic capacity, and variation in activity among individuals is small [34]. Second, hydrodolasetron, the active metabolite formed by reduction of dolasetron, is eliminated by multiple routes, including renal excretion and metabolism by hydroxylation, glucuronide conjugation, and *N*-oxidation. Renal excretion of unchanged hydrodolasetron, which involves active tubular secretion, accounts for the largest percentage of a dolasetron dose (about 20–30%) [7, 8, 11, 15]. The metabolites formed through oxidative hydroxylation represent less than 10% of all circulating species. The *N*-oxidation of hydrodolasetron is a very minor elimination pathway (< 0.5% of the dose) compared with other elimination routes.

In the present study, the magnitude of potential dolasetron pharmacokinetic drug-drug interactions was evaluated using a nonspecific CYP450 enzyme inhibitor, cimetidine [21, 22, 35], and a classic CYP450 enzyme inducer, rifampin [23–25]. Similar to the findings of

Table 2 Mean percent of dolasetron dose excreted in urine during the 24-h period following the last dose of dolasetron mesylate on day 7. *Treatment A* dolasetron mesylate 200 mg/day alone ($n = 18$); *treatment B* dolasetron mesylate 200 mg/day plus cimetidine 300 mg four times daily ($n = 18$); and *treatment C* dolasetron mesylate 200 mg/day plus rifampin 600 mg/day ($n = 17$) (*CI* confidence interval for percent difference between treatments, *CV* coeficient of variation)

Analyte	Treatment	Mean (%CV)	Pairwise difference (%)[a]	*P*-value for pairwise difference[a]	90% CI for pairwise difference[a]
R(+)-hydrodolasetron	A	19.3 (49)			
	B	22.6 (39)	B-A, 16.9	0.11	−0.4, 34.2
	C	17.6 (52)	C-A, −9.1	0.39	−26.8, 8.5
S(−)-hydrodolasetron[b]	A	2.4 (43)			
	B	2.6 (95)	B-A, −11.1	0.50	−27.9, 10.7
	C	2.2 (62)	C-A, −12.0	0.31	−33.0, 10.2
Total hydrodolasetron[b]	A	21.7 (47)			
	B	25.2 (37)	B-A, 17.3	0.17	0.0, 32.9
	C	19.8 (52)	C-A, −11.6	0.24	−35.4, 10.0
5′OH hydrodolasetron[b]	A	1.4 (61)			
	B	1.2 (54)	B-A, −18.4	0.22	−45.6, 6.9
	C	1.3 (60)	C-A, −2.8	0.61	−24.1, 22.1
6′OH hydrodolasetron[b]	A	4.2 (59)			
	B	4.6 (61)	B-A, −5.9	0.85	−28.6, 24.6
	C	5.0 (51)	C-A, 27.4	< 0.01	3.2, 45.0

[a] Pairwise difference (%), *P*-value, and 90% confidence interval for the pairwise difference (%) were done using adjusted means from ANOVA
[b] Statistical analysis done using rank-transformed data

previous oral pharmacokinetic studies [7, 12–15], dolasetron was not detected in either plasma or urine during any of the three treatment periods, supporting the prediction that elimination of dolasetron (or formation of hydrodolasetron) is not affected by the concomitant administration of rifampin or cimetidine. The mean steady-state plasma AUC and $C_{max,ss}$ of hydrodolasetron increased by 24% and 15%, respectively, when dolasetron was coadministered with cimetidine, and decreased by 28% and 17%, respectively, when dolasetron was given with rifampin. The increase in $AUC_{ss(0–24)}$ and $C_{max,ss}$ of hydrodolasetron with concomitant cimetidine was most likely a result of decreased metabolism of hydrodolasetron due to inhibition of CYP450 enzymes by cimetidine. This explanation is supported by the increased urinary excretion of unchanged hydrodolasetron (by 17%) after coadministration of cimetidine. In turn, the decrease in $AUC_{ss(0–24)}$ and $C_{max,ss}$ of hydrodolasetron with rifampin coadministration was most likely the result of increased metabolism of hydrodolasetron as a result of enzyme induction. Again, this is supported by the decreased urinary excretion of unchanged hydrodolasetron (by 12%) after coadministration of rifampin.

Compared with dolasetron alone, changes in plasma AUC_{ss} and $C_{max,ss}$ of hydrodolasetron found with concomitant cimetidine or rifampin administration were small and not likely to affect the efficacy or safety of dolasetron mesylate. The oral dosage regimens of dolasetron demonstrated to be effective in the management of chemotherapy-induced emesis and postoperative nausea and vomiting are 200 mg and 25 mg of dolasetron, respectively, administered as a single, one-time dose [3–6]. In healthy volunteers, single oral doses of dolasetron mesylate up to 400 mg are well tolerated [29].

Identification of the CYP450 isoenzyme responsible for the biotransformation of a drug and its metabolite is key for predicting potential metabolic drug interactions. The hydroxylation of hydrodolasetron is primarily mediated by the isoenzyme, CYP2D6; *N*-oxidation is mediated by both CYP3A4 and flavin monooxygenase [19, 20]. The isoenzymes, CYP2D6 and CYP3A4, also play key roles in the metabolism of other indole-containing 5-HT_3 receptor antagonists. In in vitro enzyme inhibition and correlation studies, the hydroxylation of both hydrodolasetron and tropisetron has been found to be CYP2D6-dependent, whereas that of ondansetron is dependent on both CYP2D6 and CYP2E1 [20, 36, 37]. The involvement of CYP3A4 [37, 38] and CYP1A2 [38] in the metabolism of ondansetron has also been suggested in enzyme inhibition studies. The enzymes primarily involved in granisetron metabolism are CYP3A4/5 [39].

Because the primary route of elimination of ondansetron [36, 40, 41] and granisetron [42] is by hepatic phase I metabolism, pharmacokinetic interactions with drugs that are hepatic enzyme inducers or inhibitors are possible. Published data with these drugs are lacking, however. The only information regarding a potential pharmacokinetic drug-drug interaction involving the elimination of either granisetron or ondansetron appears in the ritonavir (Norvir®, Abbott Laboratories, 1997) product labeling. No specific data are provided, but the label indicates that coadministered ritonavir may produce large (more than three times) increases in ondansetron AUC.

The oral 200 mg daily dose of dolasetron mesylate was well tolerated in this study during all three treatment periods. The adverse events observed in these subjects were similar to those reported in the literature for healthy volunteers receiving 5-HT_3 receptor antagonists [7–10, 29]. The highest incidence of adverse events actually occurred during the control treatment period when dolasetron mesylate was given alone. Therefore, the small changes in metabolism of dolasetron caused by cimetidine or rifampin appear to have no impact on its safety profile. Based on these safety findings, as well as the small changes in the pharmacokinetic parameters of hydrodolasetron, no dosage adjustments for dolasetron mesylate are recommended with concomitant administration of cimetidine or rifampin.

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