Effect of Aprepitant 40 mg on Cytochrome P-450 2C9 Activity: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study in Healthy Young Adults

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ABSTRACT

This study evaluated effects of the neurokinin-1 receptor antagonis aprepitant on CYP2C9 as measured by the pharmacokinetics of oral tolbutamide, a substrate of CYP2C9. Healthy young adults were randomized to receive either oral aprepitant 40mg or placebo. All subjects received oral tolbutamide 500 mg at baseline (Day -7 to -5), and on Days 2, 4, 8, and 15. The primary variable of interest was the aprepitant/placebo ratio of geometric mean fold-change from baseline in tolbutamide $AUC_{0-\infty}$ on Days 2, 4, 8, and 15. The natural-log-transformed fold-change in AUC was analyzed using a linear mixed-model for repeated measures. Ratios of geometric means for tolbutamide AUC fold-change from baseline on Days 2, 4, 8, and 15 were 0.92, 0.84, 0.85, and 0.90, respectively. Twenty-eight nonserious clinical adverse events were reported. A single 40 mg oral dose of aprepitant, coadministered with tolbutamide 500 mg, has no clinically relevant effect on CYP2C9 activity and is generally well tolerated.

INTRODUCTION

Aprepitant (EMEND®) is a selective neurokinin-1 (NK_1) receptor antagonist used in combination with a 5-HT_3 receptor antagonist and a corticosteroid to prevent chemotherapy-induced nausea and vomiting (CINV), or as monotherapy for the prevention of postoperative nausea and vomiting (PONV).[1] The recommended 3-day

aprepitant regimen for CINV prophylaxis (125 mg p.o. on Day 1 of chemotherapy, followed by 80 mg/day on Days 2 and 3) is known to have a moderate inhibitory effect on Cytochrome P450 (CYP)3A4 activity.[2,3] In addition, a drug interaction study of aprepitant and warfarin[4] suggested that the aprepitant regimen has an inductive effect on CYP2C9, a finding that was confirmed in another study of aprepitant and the CYP2C9 probe drug tolbutamide.[3] In that study of coadministered oral tolbutamide 500 mg and the aprepitant 125/80/80 mg regimen, modest induction of CYP2C9 activity was observed on Days 4 and 8 after dosing, with resolution to near-baseline by Day 15. Few if any intravenous chemotherapy regimens currently in use are believed to be metabolized by CYP2C9; however, cancer patients may receive certain CYP2C9-metabolized drugs with a narrow therapeutic index, such that even modest effects of aprepitant on CYP2C9 may be clinically important. Furthermore, although the 3-day aprepitant regimen used in the CINV setting has been previously studied in terms of its effects on CYP2C9 activity, potential effects of the single 40 mg dose recommended for PONV prophylaxis have not been studied. This dose of aprepitant may be given preoperatively to patients who are taking drugs metabolized by CYP2C9.

In addition to potential effects on CYP2C9 in general, the effects of metabolic inducers on CYP2C9 activity in subjects carrying different CYP2C9 alleles has not been fully characterized. Three polymorphisms of the CYP2C9 gene have been identified (CYP2C9*1 [wild-type], CYP2C9*2, and CYP2C9*3) with allelic frequencies in the Caucasian population of 0.79 to 0.86, 0.08 to 0.125, and 0.03 to 0.085, respectively. The CYP2C9*2 and CYP2C9*3 alleles, which result in decreased enzyme activity, occur at a lower frequency in non-Caucasian populations.[5] In a study using tolbutamide 500 mg as a CYP2C9 probe substrate, healthy subjects were CYP2C9*1 homozygotes, CYP2C9*1*2 heterozygotes, and CYP2C9*1*3 heterozygotes. The cor-

responding values for plasma tolbutamide $AUC_{0-\infty}$ in these subjects were 561, 815, and 1079 μg•hr/mL, respectively.[6]

The present study was performed to evaluate the potential effect of aprepitant 40 mg on CYP2C9 activity and to evaluate the safety and tolerability of coadministration of aprepitant 40 mg and tolbutamide 500 mg. The 40-mg dose of aprepitant was selected because it is the recommended dose for PONV prophylaxis, given within 3 hours prior to induction of anesthesia. Tolbutamide was used as a probe drug specifically to assess the occurrence and time course of any CYP2C9 induction. The 500-mg oral dose of tolbutamide (a commonly used CYP2C9 probe) was selected based on its use in the prior aprepitant study[3] as well as several other studies that have reported it to be well tolerated in healthy volunteers.[7] Genotyping for CYP2C9 was performed at pre-study for each subject who participated in the present study.

METHODS

Subjects

All subjects gave written informed consent to participate in this single-center study (Protocol 140), which was conducted at the Buffalo Clinical Research Center, LLC, Buffalo, NY, and performed in conformance with legal requirements for the ethical conduct of research in human subjects (IntegReview, Inc., Ethical Review Board, Austin, TX). The study enrolled 24 healthy, non-smoking adult subjects (14 males ages 20 to 37 years and 10 females ages 19 to 39 years) who were within 20% of ideal weight (50 100 kg) for gender, age, and height. Birth control measures were required for females of childbearing potential. Subjects were not allowed to consume foods or supplements that could influence CYP3A4 or 2C9 activities, such as St. John's wort or grapefruit juice. No prescription medications were permitted throughout the study, with the exception of acetaminophen at the discretion of the investigator.

Because three distinct polymorphisms of the CYP2C9 gene have been identified,

genotyping for CYP2C9 was performed for all subjects in this study. Analysis of tolbutamide pharmacokinetics was performed regardless of the CYP2C9 genotype for all subjects who completed the study.

Design

In this double-blind, placebo-controlled, parallel-group study, subjects were randomized (12 subjects per group) to one of two treatment groups: Group I received a single dose of aprepitant 40 mg; Group II received matching placebo. In addition, subjects in both groups received open-label CYP2C9-probe drug tolbutamide 500 mg at baseline (Day -7 to -5) and on Days 2, 4, 8, and 15 relative to initiation of aprepitant dosing on Day 1. All study drugs were administered orally (with 240 mL water) in the morning, 30 minutes after a standard breakfast. Capillary blood glucose assays were performed following tolbutamide dosing at 2, 4, 8, and 12 hours postdose at baseline (Day -7 to -5) and on Days 2, 4, 8, and 15. Subjects were given a light snack and orange juice approximately 2 hours after tolbutamide dosing.

Pharmacokinetic Methods

The plasma concentration profile of tolbutamide was measured in all subjects over 0 to 48 hours following oral administration of tolbutamide at baseline (Days -7 to -5) and on Days 2, 4, 8, and 15. Plasma samples collected for tolbutamide assay were analyzed by PPD Development (Richmond, VA) using liquid chromatography/tandem mass spectrometry. The lower limit of quantification (LOQ) for tolbutamide in plasma was 0.1 μg/mL.

The following pharmacokinetic parameters were evaluated for tolbutamide: area under the plasma concentration-time curve from time 0 to time infinity ($AUC_{0-\infty}$), peak plasma concentration (C_{max}), time to maximum concentration (T_{max}), and apparent terminal half-life ($t_{1/2}$). Individual plasma tolbutamide concentrations and nominal sampling times were used to determine the tolbutamide pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max} and $t_{1/2}$) using WinNonlin pharmacokinetic software (Pharsight Corpo-

ration, Mountain View, CA), following the single-dose administration of tolbutamide at baseline and on Days 2, 4, 8, and 15. Plasma tolbutamide concentration values that were less than the LOQ of the bioanalytical assay were assigned a value of zero. The area under the plasma concentration-versus-time curve ($AUC_{0-\infty}$) for tolbutamide was calculated using nominal times by the linear up/log down trapezoidal method. The apparent terminal half-life ($t_{1/2}$) was calculated from the linear portion of the log transformed terminal phase of the concentration-versus-time curve using a uniform weighting scheme. Cmax and Tmax were determined by visual inspection of the plasma tolbutamide concentration-versus-time data.

Plasma samples collected for possible aprepitant assay and urine samples for possible tolbutamide/metabolite assays were archived by the Department of Drug Metabolism, Merck Research Laboratories (MRL), West Point, PA, as it was determined by the Clinical Pharmacology and Drug Metabolism departments of MRL that it would not be necessary to assay these samples.

Statistical Methods

The sponsor managed the data and performed the analyses. The primary hypothesis concerned the effect of aprepitant on tolbutamide and was assessed by comparing the mean fold change from baseline in tolbutamide $AUC_{0-\infty}$ (aprepitant/placebo) on each of Days 2, 4, 8, and 15 between the two treatment groups (tolbutamide with aprepitant, tolbutamide with placebo). The primary response variable was the $AUC_{0-\infty}$ of tolbutamide on Days 2, 4, 8, and 15. Fold change from baseline was calculated as Day i / Baseline, i = 2, 4, 8, and 15. A linear mixed model appropriate for a repeated measures design was used to analyze the natural log-transformed fold change in AUC. The model included the fixed effects of treatment, day, treatment-by-day interaction, and a random effect of subject within treatment. The two-sided 90% confidence intervals (CI) for the differences (aprepitant - placebo) in mean natural log-transformed fold change $AUC_{0-\infty}$

on Days 2, 4, 8, and 15 were calculated based on this model. These confidence limits were exponentiated to obtain the 90% CI for the ratio (aprepitant/placebo) of true mean AUC values. In addition to $AUC_{0-\infty}$, Cmax was analyzed in similar fashion, and no multiplicity adjustments were made. Summary statistics were provided for T_{max} and $t_{1/2}$.

Given a repeated-measures design with 12 subjects completing the study in each treatment group and a true variance of 0.0385 for log-fold-change in tolbutamide AUC, there was at least 0.99 probability that the 90% CI for the true ratio (aprepitant/placebo) of mean fold change in tolbutamide AUC would fall within the interval (0.70, 1.43) in one single day, given a true ratio of 1. The overall power for all of the CIs to be within (0.70, 1.43) on the four days (Days 2, 4, 8, and 15) was over 96%, assuming independence among the four days.

RESULTS

There were 8 males and 4 females in the aprepitant group (mean age = 27 years, range = 19-37 years; mean weight = 75 kg, range = 57-92 kg). There were 6 males and 6 females in the placebo group (mean age

Table 1. *Pharmacokinetic parameters for plasma tolbutamide, following a single dose of tolbutamide 500 mg in healthy adult subjects who also received a single oral dose of aprepitant 40 mg or placebo on Day 1*

Variable	Day	Geometric mean* (CV%)		Mean fold change from baseline† (day/baseline)			
		Aprepitant 40 mg (N=11)	Placebo (N=11)	Aprepitant 40 mg (N=11)	Placebo (N=11)	Ratio of Geometric Mean Fold-Changes, Aprepitant/Placebo (90% Confidence Interval)	
$AUC_{0-\infty}$ (µg•hr/mL)	Baseline	816.25 (28.1)	794.60 (34.4)	--	--	--	--
	2	715.46 (28.4)	760.30 (38.7)	0.88	0.96	0.92	(0.84, 1.00)
	4	581.06 (37.2)	669.68 (41.6)	0.71	0.84	0.84	(0.78, 0.92)
	8	651.62 (31.4)	745.66 (40.4)	0.80	0.94	0.85	(0.78, 0.93)
	15	720.20 (30.7)	777.28 (36.3)	0.88	0.98	0.90	(0.83, 0.98)
C_{max} (µg/mL)	Baseline	52.14 (13.5)	51.97 (10.6)	--	--	--	--
	2	52.54 (16.3)	51.61 (9.5)	1.01	0.99	1.01	(0.93, 1.10)
	4	50.62 (13.0)	51.08 (15.3)	0.97	0.98	0.99	(0.91, 1.08)
	8	48.47 (12.0)	48.76 (12.5)	0.93	0.94	0.99	(0.91, 1.08)
	15	50.95 (7.6)	48.93 (16.9)	0.98	0.94	1.04	(0.95, 1.13)
$t_{1/2}$ (hours)	Baseline	9.3 (2.5)	8.8 (2.9)				
	2	7.6 (2.0)	8.0 (2.6)				
	4	6.5 (2.1)	7.5 (2.2)				
	8	8.2 (2.4)	9.0 (3.0)				
	15	9.0 (2.2)	8.9 (2.6)				
T_{max} (hours)	Baseline	4.0 (2.0, 6.0)	4.0 (3.0, 6.0)				
	2	4.0 (0.5, 6.0)	4.0 (2.0, 6.0)				
	4	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)				
	8	3.0 (2.0, 6.0)	4.0 (2.0, 6.0)				
	15	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)				

*Geometric mean (coefficient of variation [%]) for AUC and C_{max}; harmonic mean (pseudo SD) for $t_{1/2}$; and median (minimum, maximum) for T_{max}.
† Back-transformed from least-squares mean from the linear mixed model performed on natural log-transformed fold-change on Days 2, 4, 8, and 15.

= 26, range = 19 to 39; mean weight = 75 kg, range = 56 93 kg). Of the 24 subjects enrolled in the study (10 white, 10 black, 2 Asian, and 2 Hispanic), 18 subjects (75%) were homozygous for the wild-type or "normal" CYP2C9 allele (*1), 2 subjects (8%) were heterozygous for the *2 allele, 1 subject (4%) was heterozygous for the *3 allele, and 3 subjects (13%) were compound heterozygous for the *2 and *3 alleles. Twenty-two subjects completed the study; 2 male subjects (1 from each treatment group) withdrew consent and discontinued the study prematurely.

Analyses of tolbutamide pharmacoki-netic data were performed regardless of the CYP2C9 genotype for the entire group of 22 subjects (11 per treatment group) who completed the study. All 24 subjects enrolled in the study were included in the evaluation of safety.

Pharmacokinetics

Figure 1 shows mean plasma concentration profiles of oral tolbutamide at baseline and on Days 2, 4, 8, and 15 for the aprepitant and placebo groups. Table 1 summarizes the effects of aprepitant or placebo on the pharmacokinetic parameters for tolbuta-mide. The single 40-mg aprepitant PONV dose produced induction of CYP2C9, as

Figure 1. *Mean plasma concentration-time profiles of tolbutamide in healthy young adults subjects following a 500-mg oral dose given prior to (baseline) or following (Days 2, 4, 8, and 15) administration of oral aprepitant 40 mg (top; n = 11) or placebo (bottom; n = 11) on Day 1.*
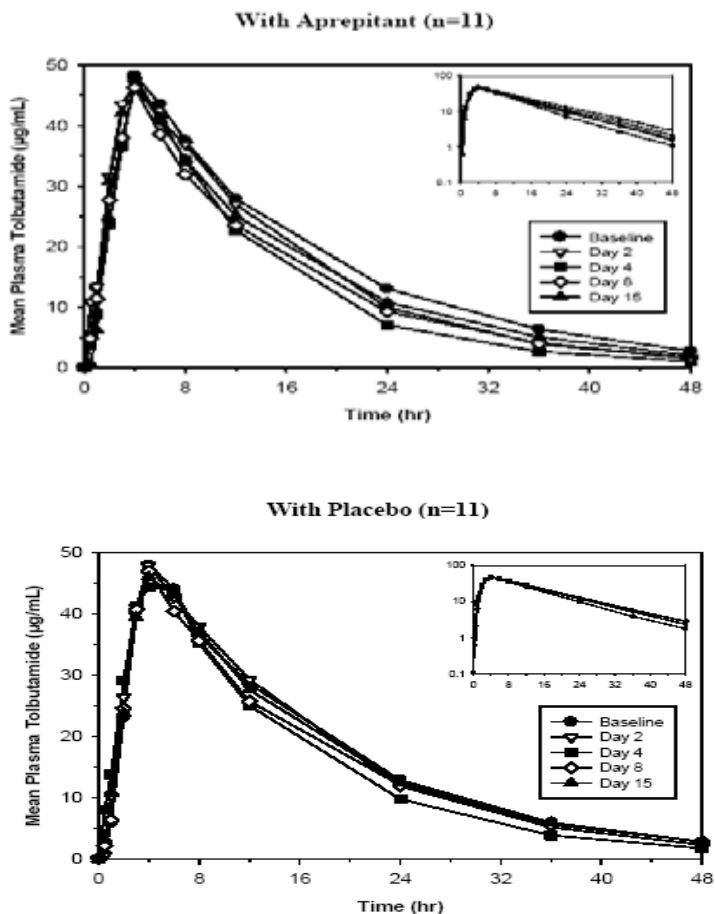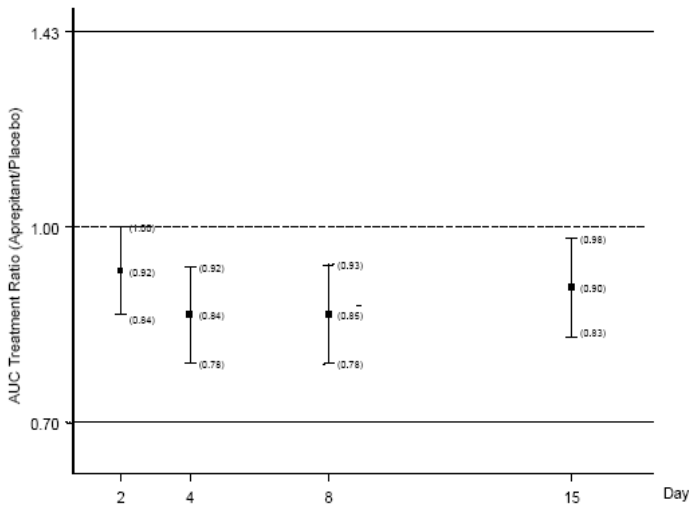
Figure 2. *Tolbutamide $AUC_{0-\infty}$ ratio (aprepitant/placebo) of geometric mean fold-change from baseline and 90% CI by study day (n=11 for each treatment arm. Solid lines represent the hypothesized bounds of (0.70, 1.43).*

observed by mean percentage decreases in plasma tolbutamide $AUC_{0-\infty}$ fold-change from baseline of 8% on Day 2, 16% on Day 4, 15% on Day 8, and 10% on Day 15, after the single 40-mg oral dose of aprepitant was coadministered with 500 mg tolbutamide on Day 1. As shown in Figure 2, the ratios (aprepitant/placebo) of geometric means for tolbutamide AUC fold-change from baseline on Days 2, 4, 8, and 15 were 0.92 (90% CI= 0.84, 1.00), 0.84 (90% CI = 0.78, 0.92), 0.85 (90% CI = 0.78, 0.93), and 0.90 (90% CI = 0.83, 0.98).

The ratios (aprepitant/placebo) of geometric means for tolbutamide Cmax fold-change from baseline with 90% CIs were 1.01 (0.93, 1.10), 0.99 (0.91, 1.08), 0.99 (0.91, 1.08), and 1.04 (0.95, 1.13) on Days 2, 4, 8, and 15, respectively. Of the 24 subjects enrolled in the study, 18 subjects were homozygous for the wild or "normal" allele (genotype *1/*1; absence of either *2 or 3 alleles), based on which they would be expected to have "normal" CYP2C9 activity and would be considered extensive metabolizers. By contrast, the *2 and *3 alleles both show decreased CYP2C9 activity compared with that of the *1 allele. Thus the two subjects with a single copy of the CYP2C9*2

allele (genotype *1/*2) could be extensive metabolizers with a normal rate of 2C9-substrate metabolism. The one subject with a single copy of the CYP2C9*3 allele (genotype *1/*3) could be a poor metabolizer with decreased rate of 2C9 substrate metabolism. Lastly, three subjects were found to be compound heterozygous for the CYP2C9*2 and CYP2C9*3 alleles (genotype *2/*3) and would be expected to be poor metabolizers because both the *2 and *3 alleles have a decreased capacity for metabolism of 2C9 substrates compared with the *1 allele.

Tolerability

All 24 subjects were included in the assessment of safety and tolerability. There were no reports of serious adverse events, laboratory or any other significant adverse events, or deaths during the study. No consistent treatment-related changes were observed in laboratory findings, physical examination, vital signs, or ECG safety parameters. A total of 28 non-serious clinical adverse events (11 in the aprepitant group and 17 in the placebo group) were reported among 15 (63%) of the 24 subjects (7 subjects in the aprepitant group and 8 subjects in the placebo group). The most commonly reported adverse event was headache. Three events of

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headache were considered by the investigator as possibly related to study drug, and the remaining 25 nonserious clinical adverse events were not drug-related. Capillary blood glucose was performed following tolbutamide dosing at 2, 4, 8, and 12 hours postdose at baseline (Day -7 to -5) and on Days 2, 4, 8, and 15. One subject (27-year-old Caucasian male) experienced a mild hypoglycemic symptom ("shakiness") following the Day 2 administration of 500 mg tolbutamide, which resolved after the subject was given a glass of orange juice and a light snack at approximately 2 hours after dosing. All clinical adverse events resolved by the end of the study.

DISCUSSION

In addition to the known mild to moderate inhibitory effect of the aprepitant CINV prophylactic regimen (125 mg on Day 1 and 80 mg on Days 2 and 3) on CYP3A4,[2,3] a mild inductive effect on CYP2C9 has also been documented for this 3-day regimen. The present study was performed to investigate the potential effect on CYP2C9 of the aprepitant single oral 40-mg dose, which is used clinically for PONV prophylaxis and which may be given to patients taking known CYP2C9-metabolized drugs. Tolbutamide 500 mg was used as a probe drug to measure CYP2C9 activity.

To compare the results of the present study with the results of tolbutamide interaction following the aprepitant 3-day CINV regimen,[3] the timing of the tolbutamide doses (Baseline [Day -7 to -5] and Study Days 2, 4, 8, and 15) was designed to match the procedures used in the previous study. The earlier aprepitant drug interaction study with tolbutamide[3] did not have tolbutamide dosing on Day 2, but the Day 4 dose was 1 day after the last dose of aprepitant (given on Day 3). In similar fashion, the Day 2 tolbutamide dose in the present study was given 1 day after the single dose of aprepitant 40 mg (given on Day 1), as a strategy to assess possible early inductive effects of aprepitant. The Day 4 to Day 8 assessment of oral tolbutamide pharmacokinetics was

considered to represent the likely period of maximum induction.

In prior research with aprepitant, the 40-mg dose administered in a fasted state resulted in an AUC of 7751 ng•hr/mL and Cmax of 675 ng/mL. Although prior studies have found little to no effect of food with the 40-mg aprepitant dose given under fed and fasted conditions, and the prescribing information indicates that aprepitant may be administered without regard to food, aprepitant/placebo and tolbutamide were given in the morning within 30 minutes following a standard light breakfast. This was in order to simulate procedures in the earlier aprepitant drug interaction study with tolbutamide[3], and to preclude hypoglycemic events given the known glucose-lowering effect of tolbutamide.

The single 40-mg aprepitant dose, which is that used for prevention of PONV, produced induction of CYP2C9, as observed by mean percentage decreases in plasma tolbutamide $AUC_{0-\infty}$ fold-change from a baseline of 8% on Day 2, 16% on Day 4, 15% on Day 8, and 10% on Day 15. However, for each of these days, the 90% CI for the geometric mean ratio (aprepitant/placebo) for tolbutamide AUC mean fold-change from baseline fell within the interval prespecified as the criterion for similarity. Although measures of tolbutamide Cmax, t½, and Tmax were not part of the study's hypothesis, several additional observations were made when these data were evaluated. The aprepitant/placebo ratios of geometric means for tolbutamide Cmax fold-change from baseline also suggested similarity between treatment groups on each of Days 2, 4, 8, and 15. By contrast, slight decreases in the half-life values for plasma tolbutamide were noted on Days 2 and 4 in both treatment groups. This was further suggestive of similarity between treatment groups, and there was no meaningful change in tolbutamide Cmax on Days 2 and 4. The median Tmax values for plasma tolbutamide on Days 2, 4, and 15 were similar between the treatment groups, but the median Tmax

value on Day 8 in the aprepitant group was 3.0 hours, compared with 4.0 hours in the placebo group.

The genotyping results of the subjects in this study for CYP2C9 genotype comprised the most common alleles recommended for measurement in all population groups. The two most common polymorphisms, the *2 and *3 alleles, reportedly account for the majority of intersubject variation. The CYP2C9*2 allele occurs at an allelic frequency of ~10% in Caucasian subjects. 2% to 4% in African-American subjects and has not been reported in Asian populations. The CYP2C9*3 allele occurs at an allelic frequency of 8% in Caucasian subjects, less than 1% in African-American subjects, and ~2% in Asian subjects.8 Due to the small number of subjects with *2 and *3 alleles in this study, comparison of tolbutamide pharmacokinetics by allele was not conducted, but the distribution of CYP2C9 alleles in this study was generally consistent with frequencies reported for these alleles in the Caucasian population.[5]

Clinical implications and conclusions

CYP2C9 represents the primary CYP2C protein found in the human liver and it accounts for about 20% of the total hepatic CYP content.[8] CYP2C9 is the major CYP pathway involved in the metabolism of several drugs. In addition to tolbutamide, it also includes glipizide, phenytoin, warfarin, losartan, fluvastatin, and many nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac, naproxen, piroxicam, and tenoxicam. Many drug substrates for CYP2C9 have narrow therapeutic indices including tolbutamide, S-warfarin, and phenytoin. Post-dose monitoring and individualization of dose is the appropriate and currently recommended practice. In a patient taking tolbutamide, monitoring is recommended to be individualized according to the patient's blood glucose response to the drug; in the case of warfarin, according to the patient's PT/INR response to the drug; and in the case of phenytoin, individualized to provide maximum benefit. In some cases,

serum blood level determinations may be necessary for optimal dosage adjustments as the clinically effective serum level is usually 10 to 20 mcg/mL.[5, 9-11]

The inductive effect on CYP2C9 activity seen in this study with aprepitant 40 mg (as observed by mean percentage decreases in plasma tolbutamide $AUC_{0-\infty}$ fold-change from baseline of 8% on Day 2, 16% on Day 4, 15% on Day 8, and 10% on Day 15) is unlikely to be clinically significant for drugs that are CYP2C9 substrates. For CYP2C9-metabolized drugs with a narrow therapeutic window such as tolbutamide, a 30% or greater reduction in plasma concentration could be clinically significant; the changes noted in this study were of lesser magnitude and were therefore determined to be not clinically relevant. In a broader context, induction of CYP2C9 activity by rifampin results in ~55 and 58% reductions of tolbutamide and warfarin AUC, respectively.[12, 13] In a previous study that assessed the potential effect of the 3-day aprepitant CINV regimen (125 mg on Day 1; 80 mg on Days 2 and 3) on CYP2C9 activity, tolbutamide 500 mg p.o. was given prior to aprepitant on Day 1 and again on Days 4, 8, and 15. Decreases were observed in tolbutamide $AUC_{0-\infty}$ by 23% on Day 4, 28% on Day 8, and 15% on Day 15.[3] Moreover, another study evaluated the 3-day aprepitant CINV regimen in healthy subjects stabilized on chronic warfarin therapy.[4] Although no effect of aprepitant on the plasma $AUC_{0-\infty}$ of R(+) or S(-) warfarin was observed on Day 3, there was a 34% decrease in S(-) warfarin trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with aprepitant.[4]

Although the degree of CYP2C9 induction with the 3-day aprepitant regimen and that observed in the present study following single-dose aprepitant 40 mg are both modest compared with the CYP2C9-inductive effect of rifampin, the changes noted with aprepitant 40 mg were of lesser magnitude

than those following the 3-day aprepitant CINV regimen. This suggests a dose-dependent difference in the CYP2C9-inductive potential of aprepitant. The results of this drug-drug interaction study evaluating the CYP2C9 inductive potential of a single 40-mg aprepitant capsule when coadministered with the CYP2C9 probe substrate, tolbutamide (500 mg), support the conclusion that a single 40 mg oral dose of aprepitant has no clinically relevant effect on CYP2C9 activity and is generally well tolerated. These are important findings because the 40 mg dose of aprepitant is the dose approved for administration within 3 hours of induction of anesthesia to prevent post-operative nausea and vomiting (PONV). Complications of PONV can cause disabling and serious consequences for the patient. Also of concern are potential drug interactions in anesthesia whereby a coadministered CYP2C9 inducer along with a CYP2C9 substrate could pose the risk of diminished or loss of efficacy for the CYP2C9 substrate.[14]

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CONFLICT OF INTEREST/DISCLOSURES

All authors are responsible for the work described in this paper and were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data, drafting the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

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