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ORIGINAL ARTICLE

Disposition of desipramine, a sensitive cytochrome P450 2D6 substrate, when coadministered with intravenous temsirolimus

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Abstract
Purpose Intravenous (i.v.) temsirolimus, a novel inhibitor of mammalian target of rapamycin (mTOR), is approved for treatment of renal cell carcinoma. In vitro studies with pooled human liver microsomes showed that temsirolimus and its principal metabolite, sirolimus, inhibit the CYP2D6 isozyme ($K_i = 1.5$ and 5 μM, respectively), indicating potential for pharmacokinetic interaction with agents that are substrates of CYP2D6.
Methods This 2-period study in healthy subjects investigated the pharmacokinetics of a single oral 50-mg dose of the CYP2D6 substrate desipramine, first without and subsequently with a single coadministered i.v. 25-mg dose of temsirolimus.
Results The study population consisted of 25 males and 1 female; 10 were black, 12 were white, and 4 were of other races. Plasma and whole blood samples were available from all 26 subjects in period 1 following oral desipramine and from 23 subjects in period 2 following oral desipramine and i.v. temsirolimus coadministration. The 90% confidence intervals for least squares geometric mean ratios of desipramine and 2-hydroxy-desipramine C_{max}, AUC_T, and AUC were within 80–125%, indicating that parameter differences did not manifest into clinically relevant exposure changes. A single i.v. 25-mg dose of temsirolimus, alone or with desipramine, was well tolerated in healthy subjects.
Conclusions A single i.v. 25-mg dose of temsirolimus did not alter disposition of desipramine. Temsirolimus i.v. 25 mg may be safely administered with agents metabolized through the CYP2D6 pathway, but vigilance for drug interaction is warranted in patients with advanced malignancies.

Keywords Temsirolimus · Mammalian target of rapamycin (mTOR) · Pharmacokinetics · Drug interactions

Abbreviations
CYP Cytochrome P450
mTOR Mammalian target of rapamycin

Introduction

Temsirolimus is a novel selective inhibitor of the mammalian target of rapamycin (mTOR) that is approved for the treatment of advanced renal cell carcinoma [1]. Temsirolimus is also being studied for the treatment of mantle cell lymphoma and other malignancies [2–4]. mTOR is a key regulator of tumor cell growth, apoptosis, and angiogenesis via its profound control of mRNA translation for proteins critical to these processes [5, 6]. Temsirolimus binds to FKBP12 (FK506/rapamycin-binding protein), and the complex binds to mTOR to inhibit its activity [7]. Preclinical studies of temsirolimus demonstrated significant inhibition of tumor growth and tumor angiogenesis [6, 8–10]. The pharmacokinetic parameters of temsirolimus and its principal metabolite, sirolimus, have been characterized in healthy subjects and in patients with cancer [3, 11–15].

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Metabolism of both temsirolimus and sirolimus is primarily via the CYP3A4/5 pathways [16, 17]. In vitro studies with pooled human liver microsomes have shown that the CYP2D6 isozyme is also inhibited at higher concentrations of temsirolimus [$K_i = 1.5$ μM (1,545 ng/mL)] and sirolimus ($K_i = 5$ μM 4,575 ng/mL]) [18, 19]. Although these concentrations represent moderate or large multiples of the anticipated mean peak concentrations achieved following administration of i.v. 25-mg temsirolimus in patients with cancer (temsirolimus $C_{max}/K_i \approx 0.39$; sirolimus $C_{max}/K_i \approx 0.01$) [3, 11–15], the possibility exists for interaction with drugs that are substrates of CYP2D6. Drugs metabolized by the CYP2D6 pathway include many that are commonly prescribed, such as some beta-blockers, antidepressants, antipsychotics, antiarrythmics, codeine, and dextromethorphan [20]. In patients with cancer, ondansetron, tamoxifen, and tramadol are also commonly prescribed, and are agents that are metabolized by CYP2D6 [21–24]. Single-nucleotide polymorphisms and single-base deletions within the CYP2D6 gene have been associated with a poor metabolizer phenotype and display a frequency of about 7% in the white population [25]. Therefore, understanding the metabolizer phenotype through molecular genotyping was considered important to reconcile any aberrant observations.

The tricyclic antidepressant desipramine is widely used as a probe for investigating potential CYP2D6 drug interactions. Aromatic hydroxylation of desipramine is catalyzed by the CYP2D6 isozyme [26–28]. Concomitant administration of desipramine with agents that inhibit CYP2D6 activity alters the pharmacokinetic profiles of desipramine and its principal metabolite, 2-hydroxy-desipramine, and indicates that clinically significant drug interactions may occur [29–31].

This study investigated whether the in vitro CYP2D6 inhibition by temsirolimus translates to CYP2D6 inhibition in humans. The effects of a single i.v. 25-mg dose of temsirolimus on the pharmacokinetic profile of an oral 50-mg dose of desipramine were evaluated in healthy subjects. The study was designed as a single-dose study because accumulation of temsirolimus and sirolimus at steady state is negligible compared with single-dose exposure.

Methods

Subjects

Written informed consent was obtained from all participants prior to enrollment in this study. The study protocol was approved by the Institutional Review Board of the study site, Radiant Research, Dallas, TX, and the trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Subjects were eligible for participation if they were 18–45 years of age, weighed at least 50 kg, had a body mass index of 18–30 kg/m^2, and were healthy based on their medical history, physical examination, laboratory results, vital signs, and 12-lead electrocardiogram (ECG). Women were only enrolled if they had a documented hysterectomy or oopherectomy or were postmenopausal for at least 1 year, with an estradiol concentration of 20 pg/mL or less and a follicle-stimulating hormone level of 40 mIU/mL or greater. A negative serum pregnancy test was required within 48 h prior to receiving study medications. Potential participants were not eligible if they had clinically significant cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, neurologic, or psychiatric disease, or if they experienced nausea, vomiting, fever, or diarrhea within 7 days before initiation of the first desipramine administration (study day 1). Subjects were excluded if they had human immunodeficiency virus antibodies, hepatitis B surface antigen, or hepatitis C virus antibodies, as well as any surgical or medical conditions that might interfere with the absorption, distribution, metabolism, or excretion of study medications.

Caffeine-containing products, grapefruit or grapefruit-containing products, and alcoholic beverages were not allowed within 48 h before study day 1. Over-the-counter drugs and herbal supplements (except occasional acetaminophen or vitamins at doses of 100% or lower of the recommended daily allowance) were not allowed within 14 days before study day 1, and prescription or investigational drugs were not allowed within 30 days before study day 1. Subjects with a positive urine drug screen, a history of drug or alcohol abuse within 1 year, or a history of smoking more than 10 cigarettes a day were not eligible for the study. Smoking was not allowed during the trial.

Study design

In this open-label, single-center, nonrandomized, 2-period sequential study, subjects received an oral dose of desipramine alone in period 1, then desipramine with an i.v. dose of temsirolimus in period 2. In the first treatment period, all subjects received desipramine 50 mg orally with 240-mL water on study day 1. On study day 15, subjects were pretreated with diphenhydramine 25 mg i.v. followed in 30 min by a 50-mg tablet of desipramine taken with 240-mL of water and temsirolimus 25 mg administered over 30 min by i.v. infusion. For both treatment periods, subjects fasted 10 h prior to receiving desipramine and for 4 h afterward. Water was not permitted 2 h before or after desipramine administration.

The 50-mg oral dose of desipramine was chosen to yield a modest but clinically relevant exposure that would be subject to sensitive changes in CYP2D6 metabolism. The i.v. 25-mg dose of temsirolimus was chosen as the highest dose considered safe to be administered to healthy subjects, and represents the approved dose for patients with renal cell carcinoma.

This study assessed the equivalence in desipramine and 2-hydroxy-desipramine PK exposure parameters between desipramine alone and the temsirolimus coadministered treatments. Based on power size calculations using nQuery Advisor 6.0, a sample size of 22 subjects, and a maximum estimated intrasubject coefficient of variation of 23% for desipramine and 2-hydroxy-desipramine exposure parameters, the power for concluding equivalence was expected to be 80% at the 0.05 significance level, assuming a 10% difference between the treatments.

A 6-mL blood sample was collected on study day 1 for CYP2D6 genotyping [32]. Venous blood samples (5 mL) were collected at predose and at 0.5, 2, 4, 8, 10, 12, 16, 24, 32, and 48 h after desipramine administration on study days 1 and 15 to measure plasma concentrations of desipramine and 2-hydroxy-desipramine. Blood samples were collected on study days 12, 26, and 30 for one subject identified as having a poor metabolizer CYP2D6 genotype. Venous blood samples (3 mL) were collected on study day 15 at predose and at hours 0.5, 2, 4, 8, 24, 48, 264 (study day 26), and 360 (study day 30) to measure the plasma concentration of temsirolimus and sirolimus. Urine samples for measuring desipramine and 2-hydroxy-desipramine concentrations were collected during both treatment periods from 0 to 12, 12 to 24, and 24 to 48 h after desipramine administration.

Bioanalytic assays

Desipramine and 2-hydroxy-desipramine

Concentrations of desipramine and 2-hydroxy-desipramine in sodium heparin-treated plasma and in urine were measured using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) combination method (PPD Development, Richmond, VA). Mean interday variabilities, expressed as coefficient of variation (CV), of desipramine and 2-hydroxy-desipramine quality control samples were 15.6% or less, and mean intraday CVs were 11.3% or less. Mean interday accuracy was within ±4.38%, and mean intraday accuracy was within ±5.62%. The limits of quantitation ranged from 0.25 to 100 ng/mL**.** Mean bias was minimal (−0.62% for desipramine and 1.85% for 2-hydroxy-desipramine). No interferences were observed in blank plasma or urine, or in plasma or urine spiked with internal standard.

Temsirolimus and sirolimus

Concentrations of temsirolimus and sirolimus metabolite were measured simultaneously using a validated LC/MS/MS combination method with internal standard [11]. The combination method was validated through the quantitation range of 0.25–100 ng/mL for 1 mL of ethylenediaminetetraacetic acid-treated whole blood. Mean interday variabilities for temsirolimus and sirolimus were ≤7.3%, and intraday variabilities were ≤10.1%. The mean interday and intraday accuracies were within ±7.4%, and ±9.1%, respectively. Mean accuracy at the lower limit of quantitation (0.25 ng/mL) indicated that variability was acceptable (≤6.3%), and mean bias was minimal (9.2% for temsirolimus, 12.4% for sirolimus). No interferences were observed in blank blood or in blood spiked with internal standard.

Molecular genotyping

Blood samples from subjects were processed for isolation of DNA for CYP2D6 *3, *4, *6, *7, and *8 alleles using multiplex polymerase chain reaction [32]. Analysis of the CYP2D6 *5 allele was performed in a separate, long-range PCR assay. Genotyping and phenotype interpretations [33] were conducted by Genaissance (Morrisville, NC).

Pharmacokinetics

The pharmacokinetics for desipramine and 2-hydroxy-desipramine in plasma and for temsirolimus and sirolimus in blood were determined for subjects using a noncompartmental model [34]. The actual times of blood collection were used for all calculations. Data from all subjects were used, regardless of *CYP2D6* genotype.

The maximum plasma or blood concentration (C_{max}), the time to C_{max} (T_{max}), and the absorption lag time (T_{lag}) were determined by analysis of the concentration-time graphs. The terminal elimination rate constant (λ_z) was estimated by log-linear regression of the terminal monoexponential phase of the concentration–time curve. The terminal phase elimination half-life ($T_{1/2}$) was calculated as $0.693/\lambda_z$. Area under the concentration–time curve (AUC) at the last observed concentration at time T (AUC_T) was calculated by the trapezoidal rule using the ascending portion of the curve and the log-trapezoidal rule using the descending portion of the curve. The total AUC was estimated as $AUC = AUC_T + C_T/\lambda_z$ wherein C_T is the concentration at time T. Apparent oral dose clearance (CL) was determined by dose/AUC. The volume of distribution based on the terminal phase (V_z) was determined from the quotient of CL and λ_z, and volume of distribution at steady state (V_{dss}) was calculated as the product of CL and mean residence time (MRT). The MRT was calculated as (AUMC/AUC) + (T/2),

wherein AUMC is the area under the first moment curve and T is the duration of drug infusion. Denominators of F and f_m used for CL, V_z, and V_{dss} denote the unknown oral bioavailability and fraction of parent drug metabolized, respectively. Ratios of 2-hydroxy-desipramine AUC and desipramine AUC (AUC_{ratio}) were calculated for each subject.

Cumulative amounts of desipramine and 2-hydroxy-desipramine excreted in the urine for each collection interval were determined by the product of urine volume and analyte concentration. The fractional urinary excretion for each analyte was calculated as the ratio of the cumulative amount of analyte excreted to the desipramine dose administered.

Assessment of safety

Safety was evaluated from the results of spontaneously reported signs and symptoms, scheduled physical examinations, measurements of vital signs, 12-lead ECGs, and clinical laboratory evaluations. All adverse events were recorded. Safety was analyzed by summarizing the number and percentage of subjects with adverse events of different severities in period 1, period 2, and overall.

Statistics

A linear mixed-effects model with treatment as a fixed effect, and subject as a random effect was used to evaluate the treatment effect in pharmacokinetic parameters. For the primary analysis, the least squares geometric mean (LSGM) ratios between test and reference treatments, their 90% confidence intervals (CIs) for C_{max}, AUC_T, and AUC, and one-sided t tests were formally calculated [35]. These statistical analyses were conducted using WinNonlin Enterprise version 4.1 (Pharsight, Mountain View, CA). All bioanalytic data and the pharmacokinetics and statistical results were stored using the Pharsight Knowledgebase server (PKS) (Pharsight, Mountain View, CA).

Selection of criteria for the 90% CIs of PK data was considered most conservative, as specified by regulatory guidance [35, 36]. Predetermined criteria for potential clinical importance were used to screen vital signs, ECGs, and routine clinical laboratory tests for significant differences.

Results

Study population

Twenty-six subjects were enrolled in this study (Table 1), of whom 23 completed both treatment periods. One subject withdrew during period 2 due to an episode of syncope unrelated to study medications, one withdrew consent on day 7, and one did not return for the second treatment period. Safety and pharmacokinetic data from all subjects, including the three who withdrew from the study, were included in the analyses. One subject, who was genotype *4/*5 [heterozygous for mutation *5 (deletion of the entire *CYP2D6* gene) and *4 mutation within the *CYP2D6* gene on the other allele], was identified as a poor metabolizer [32, 33, 37].

Table 1 Subject demographics and baseline characteristics

Characteristic	Total ($N = 26$)
Age mean ± SD (years)	33.6 ± 7.2
Gender (n) (%)	
Women	1 (3.8)
Men	25 (96.2)
Height mean ± SD (cm)	175.0 ± 7.1
Weight mean ± SD (kg)	80.9 ± 11.2
Body mass index mean ± SD (kg/m^2)	26.4 ± 2.8
Race/ethnicity (n) (%)	
White	12 (46.1)
Black	10 (38.5)
Other[a]	4 (15.4)

[a] Includes Native American, Hispanic or Latino, Asian, and Arabic

Pharmacokinetics

The mean pharmacokinetics of desipramine and 2-hydroxy-desipramine were calculated for 26 subjects who received desipramine alone, and for 23 subjects who received desipramine in combination with temsirolimus. Mean plasma concentration–time curves were comparable for desipramine and 2-hydroxy-desipramine for subjects administered desipramine alone or in combination with temsirolimus (Fig. 1). Desipramine and 2-hydroxy-desipramine pharmacokinetic parameters were determined for subjects who received desipramine, then the combination of temsirolimus and desipramine (Table 2). In the statistical comparisons for the primary analysis, the 90% CI for the least squares geometric mean ratios of desipramine and 2-hydroxy-desipramine C_{max}, AUC_T and AUC were assessed and found to lie within the 80–125% bounds (Table 3). As expected, when the CYP2D6 poor metabolizer was excluded from consideration, less variability in PK parameters was observed and the conclusions of the summary statistical inference were unchanged.

When specific desipramine pharmacokinetic parameters were compared, no significant differences were observed for mean T_{max} ($P = 0.494$), $T_{½}$ ($P = 0.097$), AUC ($P = 0.601$), or CL/F ($P = 0.601$). For 2-hydroxy-desipramine pharmacokinetic parameters for subjects receiving the

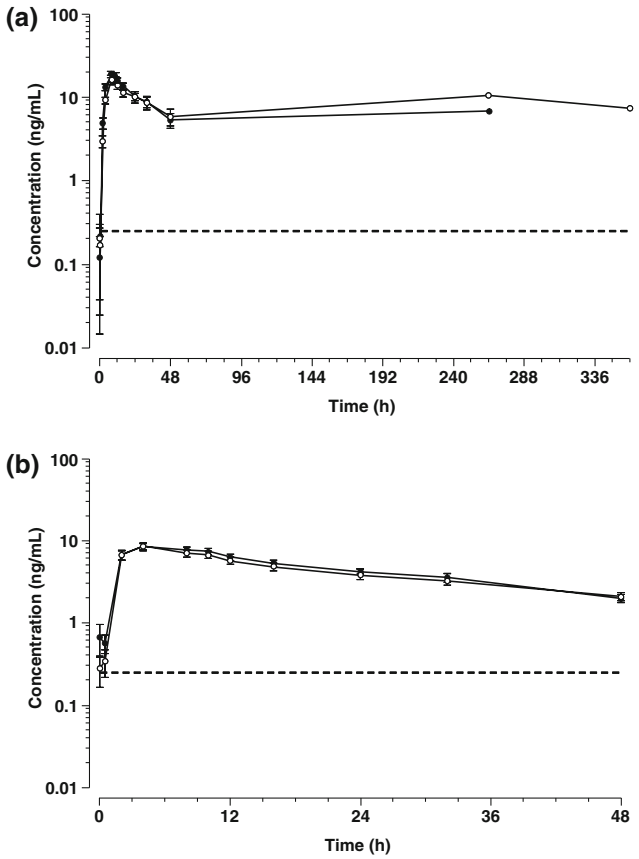

Fig. 1 Mean (±SE) plasma concentration versus time profiles of desipramine (**a**) and 2-hydroxy-desipramine (**b**) following a single 50-mg oral dose of desipramine alone and in combination with a single i.v. 25-mg dose of temsirolimus in healthy subjects. Closed circles denote desipramine 50-mg treatment, open circles denote desipramine 50 mg plus temsirolimus 25-mg treatment, and the dashed line denotes the lower limit of quantitation of the bioanalytic method

combination of temsirolimus and desipramine were compared with desipramine alone, no significant differences were observed for mean C_{max} ($P = 0.281$), T_{max} ($P = 0.165$), $T_{½}$ ($P = 0.347$), AUC_T ($P = 0.083$), AUC ($P = 0.579$), or CL/f_m ($P = 0.579$). Albeit, some statistically significant observations were observed for desipramine (mean C_{max} ($P = 0.001$), AUC_T ($P = 0.043$), and V_z/F ($P < 0.001$). The mean C_{max} of desipramine decreased from 19.6 ± 8.4 to 17.1 ± 8.4 ng/mL, and the V_z/F increased from 2,974 ± 1,821 to 3,548 ± 1,909 L when desipramine was administered with temsirolimus. For 2-hydroxy-desipramine, mean V_z/f_m was significantly different ($P = 0.023$). Differences observed in discrete pharmacokinetic parameters did not manifest into clinically relevant effects.

There were no significant effects of temsirolimus on urinary excretion of desipramine or 2-hydroxy-desipramine. Urinary excretion of desipramine was 1% after administration of desipramine alone and 2% after administration of desipramine and temsirolimus. The mean urinary excretion of 2-hydroxy-desipramine was 27% of the dose.

The mean pharmacokinetic parameters for temsirolimus and its metabolite sirolimus obtained for these healthy subjects are summarized in Table 4. For the poor metabolizer of CYP2D6, temsirolimus and sirolimus pharmacokinetic parameters were within the range of variability observed for the summary dataset of all subjects.

Adverse events

Adverse events occurred in 77% of subjects. All adverse events were considered to be mild in severity, except for 1 of 13 cases of stomatits, which was considered to be moderate. There were no severe adverse events or safety-related discontinuations.

The most frequently occurring adverse events (≥10% of all subjects) were stomatitis (50%), headache (23%), acne (23%), pain (15%), nausea (15%), pharyngitis (15%), rash (15%), accidental injury (12%), chills (12%), fever (12%), and vomiting (12%) (Table 5). The adverse events considered possibly, probably, or definitely related to temsirolimus included stomatitis, headache, acne, pain, nausea, pharyngitis, rash, chills, fever, and vomiting. These were typically transient and resolved either without treatment or with symptomatic management. The accidental injuries reported were unrelated to treatment and consisted of a burn on the arm, a burn on the tongue (from a hot drink), and a paper cut. The most commonly occurring laboratory test abnormalities of potential clinical importance (percentage of subjects receiving desipramine, percentage of subjects receiving temsirolimus + desipramine) were low glucose (31, 0%), elevated triglycerides (8, 17%), and decreased hematocrit (12, 17%). There were no trends of clinical importance in vital sign measurements or ECG interval results.

Discussion

Despite the low concentration of CYP2D6 in the liver [25], many widely prescribed drugs are metabolized by this enzyme [25, 38]. In this regard, interaction is a concern when metabolic substrates compete for clearance through a common, limited capacity pathway. Therefore, the likelihood for drug interactions exists between agents that interact with the CYP2D6 pathway. These findings indicate that the previously observed in vitro inhibition of CYP2D6 activity by temsirolimus did not translate into a clinically relevant drug interaction in humans.

The relevance of including subjects with varying phenotypes of metabolizer status stems from the goal to study a population that was somewhat representative of the population at large. To understand potential contributions of metabolizer status on substrate disposition, all subjects

Table 2 Mean pharmacokinetic parameters of desipramine and 2-hydroxy-desipramine in plasma following administration of desipramine alone or in combination with temsirolimus

Analyte	Desipramine		2-Hydroxy-desipramine	
Treatment	Desipramine 50 mg	Desipramine 50 mg + temsirolimus 25 mg	Desipramine 50 mg	Desipramine 50 mg + temsirolimus 25 mg
C_{max} (ng/mL)	19.6 ± 8.35	17.1 ± 8.44	9.14 ± 3.38	9.18 ± 4.69
T_{max} (h)[a]	8.0 (8.0, 12.15)	8.0 (4.0, 16.0)	4.0 (2.0, 16.0)	4.0 (2.0, 10.0)
$T_{½}$ (h)	24.7 ± 21.5	29.5 ± 31.4	33.9 ± 37.7	32.2 ± 26.2
AUC_T (ng h/mL)	602 ± 784	656 ± 1206	215 ± 77.5	203 ± 89.9
AUC (ng h/mL)	845 ± 1047	952 ± 1583	365 ± 342	316 ± 140
T_{lag} (h)[a]	0.25 (0, 0.57)	0.48 (0, 0.52)	0 (0, 0.57)	0.48 (0, 2.0)
CL/F (L/h)[b]	123 ± 114	144 ± 136	185 ± 80.9	193 ± 96.0
V_Z/F (L)[b]	2,974 ± 1,821	3,548 ± 1,909	8,411 ± 13,499	8,389 ± 8,685

Data represented as mean ± SD

[a] Values for T_{max} and T_{lag} are median (min, max)

[b] For 2-hydroxy-desipramine = CL/f_m L/h, V_Z/f_m L

were genotyped for CYP2D6 polymorphisms, and one subject was identified as having a poor metabolizer genotype, *4/*5. This subject had a high desipramine AUC of 7,794 ng h/mL and a low apparent clearance of 6.4 L/h, affirming the genotyping results. When the poor metabolizer was excluded from the pharmacokinetic analyses, the intersubject variability (CV%) for desipramine AUC decreased from 166 to 85%. However, the 90% CI for the least squares geometric mean ratios of C_{max}, AUC_T, and AUC remained within the range of 80–125%. This subject did not report more frequent or more severe adverse events than did other study participants. All other subjects were predicted to be extensive metabolizer phenotypes based on genotype. Despite the challenges in predicting CYP2D6 phenotype from genotype due to the large number of alleles, their range of activity, and ethnic influences [39], none of these other patients exhibited desipramine AUC values indicative of a CYP2D6 poor or intermediate metabolizer phenotype, even using this sensitive CYP2D6 substrate.

The mean temsirolimus C_{max} of 639 ng/mL and mean AUC 2,368 ng h/mL observed in the present study are consistent with those observed in previous studies wherein administration of a single 25-mg i.v. dose of temsirolimus to patients with advanced renal cell carcinoma (RCC) resulted in a mean C_{max} of 595 ng/mL (CV = 17%) and a mean AUC of 1,580 ng h/mL (CV = 17%) [3, 11–15]. Similarly, the mean sirolimus C_{max} of 58 ng/mL in the present study was comparable to the mean C_{max} obtained in RCC patients (66 ng/mL) [3, 11–15].Therefore, the fractions for peak concentrations of temsirolimus and sirolimus in blood relative to their K_i values for CYP2D6 in vitro were as expected (temsirolimus, $C_{max}/K_i = 0.41$; sirolimus, $C_{max}/K_i = 0.01$).

Coadministration of i.v. temsirolimus and oral desipramine was well tolerated in these healthy adults. Only one of the reported adverse events was considered to be of moderate severity (stomatitis); all others were mild. The frequency and type of temsirolimus-related adverse events

Table 3 Least squares geometric mean ratios of desipramine and 2-hydroxy-desipramine following administration of 50-mg oral desipramine

Pharmacokinetic metric	LSGM ratio (% of reference[a])	Lower 90% CI	Upper 90% CI
All subjects[b]			
Desipramine Ln(C_{max})	87	81	93
Desipramine Ln(AUC_T)	91	85	98
Desipramine Ln(AUC)	96	85	109
2-hydroxy-desipramine Ln(C_{max})	91	78	105
2-hydroxy-desipramine Ln(AUC_T)	92	85	100
2-hydroxy-desipramine Ln(AUC)	95	83	110
With poor metabolizer excluded[b]			
Desipramine Ln(C_{max})	86	80	92
Desipramine Ln(AUC_T)	89	84	96
Desipramine Ln(AUC)	94	83	107
2-hydroxy-desipramine Ln(C_{max})	91	78	106
2-hydroxy-desipramine Ln(AUC_T)	91	84	99
2-hydroxy-desipramine Ln(AUC)	95	82	109

LSGM least squares geometric mean, *CI* confidence interval, *Ln* logarithmic normal

[a] Reference = single 50-mg oral dose of desipramine alone, and test = single 50-mg oral dose of desipramine coadministered with a single 25-mg i.v. dose of temsirolimus

[b] Reanalysis with exclusion of one subject exhibiting a poor metabolizer phenotype for CYP2D6

Table 4 Mean pharmacokinetic parameters of temsirolimus and sirolimus in whole blood following administration of 25-mg i.v. temsirolimus with 50-mg oral desipramine

Pharmacokinetic parameter	Temsirolimus (n = 23)	Sirolimus (n = 23)
C_{max} (ng/mL)	639 ± 69.8	57.8 ± 12.9
T_{max} (h)	0.47 ± 0.07	2.26 ± 1.26
$T_{½}$ (h)	13.7 ± 1.08	74.6 ± 29.3
AUC_T (ng h/mL)	2,203 ± 232	5,094 ± 1,599
AUC (ng h/mL)	2,368 ± 264	5,710 ± 2,252
CL (L/h)[a]	10.7 ± 1.19	4.81 ± 1.24
V_Z (L)[a]	210 ± 25.2	485 ± 83.3
V_{dss} (L)[a]	156 ± 14.7	493 ± 83.5

Data represented as mean ± SD

[a] For sirolimus, CL/f_m L/h, V_Z/f_m L, V_{dss}/f_m L

Table 5 Number (%) of subjects reporting adverse events occurring in at least 10% of the total population

Adverse event	Desipramine 50 mg (n = 26)	Desipramine 50 mg + temsirolimus 25 mg (n = 23)	Total (N = 26)
Any adverse event	11 (42)	19 (83)	20 (77)
Body as a whole			
Accidental injury	1 (4)	2 (9)	3 (12)
Chills	1 (4)	2 (9)	3 (12)
Fever	0	3 (13)	3 (12)
Headache	2 (8)	6 (26)	6 (23)
Pain	1 (4)	3 (13)	4 (15)
Digestive system			
Nausea	2 (8)	2 (9)	4 (15)
Stomatitis (all/moderate severity)	0	13 (57)/1 (4)	13 (50)/1 (4)
Vomiting	0	3 (13)	3 (12)
Respiratory system			
Pharyngitis	1 (4)	3 (13)	4 (15)
Skin and appendages			
Acne	0	6 (26)	6 (23)
Rash	0	4 (17)	4 (15)

seen with the coadministration of desipramine in this study were similar to those observed in studies of cancer patients who received multiple doses of temsirolimus [2, 3, 12, 13, 15]. Clinical manifestations of desipramine overexposure are generally observed when plasma concentrations approach 500 ng/mL and they include excessive sedation, anticholinergic effects, and orthostatic hypotension [40]. In this study, the highest observed C_{max} following a single 50-mg dose of desipramine was much lower than this threshold (39.8 ng/mL), and was observed in the subject with a CYP2D6 poor metabolizer phenotype.

In conclusion, no clinically significant alterations in the pharmacokinetic disposition of desipramine were caused by 25 mg i.v. temsirolimus. This indicates that dosage adjustments of CYP2D6 substrates are not required for patients receiving 25 mg of i.v temsirolimus. Despite the low risk for CYP2D6 drug interaction, vigilance is warranted in patients with advanced malignancies.

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References

1. Torisel [package insert] (2007) Wyeth Pharmaceuticals Inc., Philadelphia, PA
2. Witzig TE, Geyer SM, Ghobrial I, Inwards DJ, Fonseca R, Kurtin P, Ansell SM, Luyun R, Flynn PJ, Morton RF, Dakhil SR GH, Kaufmann SH (2005) Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. J Clin Oncol 23:5347–5356
3. Chan S, Scheulen ME, Johnston S, Mross K, Cardoso F, Dittrich C, Eiermann W, Hess D, Morant R, Semiglazov V, Borner M, Salzberg M, Ostapenko V, Illiger HJ, Behringer D, Bardy-Bouxin N, Boni J, Kong S, Cincotta M, Moore L (2005) Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. J Clin Oncol 23:5314–5322
4. Galanis E, Buckner JC, Maurer MJ, Kreisberg JI, Ballman K, Boni J, Peralba JM, Jenkins RB, Dakhil SR, Morton RF, Jaeckle KA, Scheithauer BW, Dancey J, Hidalgo M, Walsh DJ (2005) Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. J Clin Oncol 23:5294–5304
5. Bjornsti MA, Houghton PJ (2004) The TOR pathway: a target for cancer therapy. Nat Rev Cancer 4:335–348
6. DelBufalo D, Ciuffreda L, Trisciuoglio D, Desideri M, Cognetti F, Zupi G, Milella M (2006) Antiangiogenic potential of the mammalian target of rapamycin inhibitor temsirolimus. Cancer Res 66:5549–5554
7. Abraham RT, Gibbons JJ (2007) The mammalian target of rapamycin signaling pathway: twists and turns in the road to cancer therapy. Clin Cancer Res 13:3109–3114
8. Peralba JM, DeGraffenried L, Friedrichs W, Fulcher L, Grunwald V, Weiss G, Hidalgo M (2003) Pharmacodynamic evaluation of CCI-779, an inhibitor of mTOR, in cancer patients. Clin Cancer Res 9:2887–2892
9. Thomas GV, Tran C, Mellinghoff IK, Welsbie DS, Chan E, Fueger B, Czernin J, Sawyers CL (2006) Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. Nat Med 12:122–127
10. Teachey DT, Obzut DA, Cooperman J, Fang J, Carroll M, Choi JK, Houghton PJ, Brown VI, Grupp SA (2006) The mTOR inhibitor CCI-779 induces apoptosis and inhibits growth in preclinical models of primary adult human ALL. Blood 107:1149–1155
11. Punt CJ, Boni J, Bruntsch U, Peters M, Thielert C (2003) Phase I and pharmacokinetic study of CCI-779, a novel cytostatic cell-cycle inhibitor, in combination with 5-fluorouracil and leucovorin in patients with advanced solid tumors. Ann Oncol 14:931–937

12. Raymond E, Alexandre J, Faivre S, Vera K, Materman E, Boni J, Leister C, Korth-Bradley J, Hanauske A, Armand JP (2004) Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. J Clin Oncol 22:2336–2347
13. Hidalgo M, Buckner JC, Erlichman C, Pollack MS, Boni JP, Dukart G, Marshall B, Speicher L, Moore L, Rowinsky EK (2006) A phase I and pharmacokinetic study of temsirolimus (CCI-779) administered intravenously for 5 days every 2 weeks to patients with advanced cancer. Clin Cancer Res 12:5755–5763
14. Boni JP, Leister C, Bender G, Fitzpatrick V, Twine N, Stover J, Dorner A, Immermann F, Burczynski ME (2005) Population pharmacokinetics of CCI-779: correlations to safety and pharmacogenomic responses in patients with advanced renal cancer. Clin Pharmacol Ther 77:76–89
15. Atkins MB, Hidalgo M, Stadler WM, Logan TF, Dutcher JP, Hudes GR, Park Y, Liou SH, Marshall B, Boni JP, Dukart G, Sherman ML (2004) Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. J Clin Oncol 22:909–918
16. Cai P, Tsao R, Ruppen ME (2007) In vitro metabolic study of temsirolimus: preparation, isolation, and identification of the metabolites. Drug Metab Dispos 35:1554–1563
17. Boni J, Leister C, Burns J, Cincotta M, Hug B, Moore L (2007) Pharmacokinetic profile of temsirolimus with concomitant administration of cytochrome P450-inducing medications. J Clin Pharmacol 47:1430–1439
18. Hoffman M (2002) Data on file, CCI-779 (WAY-130779): evaluation as an inhibitor of cytochrome P450 enzymes CYP3A4/5, CYP2D6, CYP2C8 and CYP2C9 in human liver microsomes (Protocol 98901). Wyeth Pharmaceuticals, Collegeville, PA
19. Torisel Clinical Pharmacology (2007) Available at: http://www.rxlist.com/cgi/generic/torisel_cp.htm. Accessed 24 January 2008
20. Zanger UM, Raimundo S, Eichelbaum M (2004) Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch Pharmacol 369:23–37
21. Desta Z, Ward BA, Soukhova NV, Flockhart DA (2004) Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. J Pharmacol Exp Ther 310:1062–1075
22. Fischer V, Vickers AE, Heitz F, Mahadevan S, Baldeck JP, Minery P, Tynes R (1994) The polymorphic cytochrome P-4502D6 is involved in the metabolism of both 5-hydroxytryptamine antagonists, tropisetron and ondansetron. Drug Metab Dispos 22:269–274
23. Eap CB, Lessard E, Baumann P, Brawand-Amey M, Yessine MA, O'Hara G, Turgeon J (2003) Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. Pharmacogenetics 13:39–47
24. Subrahmanyam V, Renwick AB, Walters DG, Young PJ, Price RJ, Tonelli AP, Lake BG (2001) Identification of cytochrome P-450 isoforms responsible for *cis*-tramadol metabolism in human liver microsomes. Drug Metab Dispos 29:1146–1155
25. Mizutani T (2003) PM frequencies of major CYPs in Asians and Caucasians. Drug Metab Rev 35:99–106
26. Brosen K, Gram LF, Kragh-Sorensen P (1991) Extremely slow metabolism of amitriptyline but normal metabolism of imipramine and desipramine in an extensive metabolizer of sparteine, debrisoquine, and mephenytoin. Ther Drug Monit 13:177–182
27. Steiner E, Dumont E, Spina E, Dahlqvist R (1988) Inhibition of desipramine 2-hydroxylation by quinidine and quinine. Clin Pharmacol Ther 43:577–581
28. Dahl ML, Iselius L, Alm C, Svensson JO, Lee D, Johansson I, Ingelman-Sundberg M, Sjoqvist F (1993) Polymorphic 2-hydroxylation of desipramine. A population and family study. Eur J Clin Pharmacol 44:445–450
29. Leucht S, Hackl HJ, Steimer W, Angersbach D, Zimmer R (2000) Effect of adjunctive paroxetine on serum levels and side-effects of tricyclic antidepressants in depressive inpatients. Psychopharmacology (Berl) 147:378–383
30. Alderman J, Preskorn SH, Greenblatt DJ, Harrison W, Penenberg D, Allison J, Chung M (1997) Desipramine pharmacokinetics when coadministered with paroxetine or sertraline in extensive metabolizers. J Clin Psychopharmacol 17:284–291
31. Madani S, Barilla D, Cramer J, Wang Y, Paul C (2002) Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. J Clin Pharmacol 42:1211–1218
32. Stamer UM, Bayerer B, Wolf S, Hoeft A, Stuber F (2002) Rapid and reliable method for cytochrome P450 2D6 genotyping. Clin Chem 48:1412–1417
33. Ingelman-Sundberg M, Daly AK, Nebert DW (eds) (2008) Home page of the human cytochrome P450 (CYP) Allele Nomenclature Committee. Available at: http://www.cypalleles.ki.se/. Accessed 7 October 2008
34. Jusko WJ (1992) Guidelines for collection and analysis of pharmacokinetic data. In: Evans WE, Schentag JJ, Jusko WJ (eds) Applied pharmacokinetics: principles of therapeutic drug monitoring. Applied Therapeutics Inc, Vancouver, pp 2.1–2.43
35. Schuirmann DJ (1987) A comparison of the two-one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 15:657–680
36. Guidance for industry: in vivo drug metabolism/drug interaction studies—study design, data analysis, and recommendations for dosing and labeling. (1999) Center for Drug Evaluation and Research (CDER), Rockville, MD
37. Daly AK, Brockmoller J, Broly F et al (1996) Nomenclature for human CYP2D6 alleles. Pharmacogenics 6:193–201
38. Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP (1994) Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 270:414–423
39. Gaedigk A, Simon SD, Pearce RE et al (2008) The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clin Pharmacol Ther 83:234–242
40. Baldessarini RJ (1996) Drugs and the treatment of psychiatric disorders. In: Goodman LS, Limbird LE, Milinoff PB, Ruddon RW, Goodman GA (eds) Goodman and Gilman's The pharmacological basis of therapeutics. McGraw-Hill, New York, pp 431–460