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PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetics of desipramine HCl when administered with cinacalcet HCl

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Abstract *Objective:* In vitro work has demonstrated that cinacalcet is a strong inhibitor of cytochrome P450 isoenzyme (CYP) 2D6. The purpose of this study was to evaluate the effect of cinacalcet on CYP2D6 activity, using desipramine as a probe substrate, in healthy subjects. *Methods:* Seventeen subjects who were genotyped as CYP2D6 extensive metabolizers were enrolled in this randomized, open-label, crossover study to receive a single oral dose of desipramine (50 mg) on two separate occasions, once alone and once after multiple doses of cinacalcet (90 mg for 7 days). Blood samples were obtained predose and up to 72 h postdose. *Results:* Fourteen subjects completed both treatment arms. Relative to desipramine alone, mean AUC and C_{max} of desipramine increased 3.6- and 1.8-fold when coadministered with cinacalcet. The $t_{1/2,z}$ of desipramine was longer when desipramine was coadministered with cinacalcet (21.0 versus 43.3 hs). The t_{max} was similar between the regimens. Fewer subjects reported adverse events following treatment with desipramine alone than when receiving desipramine with cinacalcet (33 versus 86%), the most frequent of which (nausea and headache) have been reported for patients treated with either desipramine or cinacalcet. *Conclusion:* This study demonstrates that cinacalcet is a strong inhibitor of CYP2D6. These data suggest that during concomitant treatment with cinacalcet, dose adjustment may be necessary for drugs that demonstrate a narrow therapeutic index and are metabolized by CYP2D6.

Keywords Cinacalcet · CYP2D6 · Desipramine · Drug interaction · Pharmacokinetics

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Introduction

The calcimimetic cinacalcet hydrochloride (Sensipar®/Mimpara®) increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium, thereby reducing parathyroid hormone, serum calcium, and phosphorus levels in patients with secondary hyperparathyroidism (HPT) [1] and serum calcium levels in patients with primary HPT [2, 3] or parathyroid carcinoma [4]. An in vitro study has demonstrated that cinacalcet is a strong inhibitor of cytochrome P450 isoenzyme (CYP) 2D6 [50% inhibitory concentration (IC_{50}) <0.1 μM] [5]. A multitude of drugs from different therapeutic categories are metabolized by CYP2D6, including antifungal agents, β-adrenergic blockers, antiarrhythmic agents, serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), antipsychotics, and opioids [6]. Deleterious clinical effects of coadministration of a CYP2D6 substrate and inhibitor have been documented in case reports [7–9], and the potential for such interactions has been suggested and documented in clinical studies [10–12].

Desipramine hydrochloride, a commonly used TCA, is metabolized into 2-hydroxydesipramine almost exclusively by CYP2D6, making it a sensitive and selective probe substrate for CYP2D6 inhibition. Increased exposure of desipramine has been documented following coadminis-

tration with CYP2D6 inhibitors such as sertraline [10], deramciclane [13], duloxetine [14], paroxetine [10, 13, 15], fluoxetine [16], and terbinafine [11] and in individuals who are genetically deficient in CYP2D6 (poor metabolizers) [17].

To assess the potential for drug interactions involving CYP2D6 substrates following cinacalcet therapy, this study evaluated the effect of cinacalcet on the pharmacokinetics of a prototypical CYP2D6 substrate, desipramine.

Methods

Study design

This phase 1, randomized, open-label, single-center, two-treatment, two-period, two-sequence crossover study enrolled 17 healthy subjects between the ages of 18 and 55 years. The study was conducted in accordance with Good Clinical Practice guidelines, with Institutional Review Board approval, and written informed consent by all subjects prior to study participation.

Subjects were required to be CYP2D6 extensive metabolizers (determined by genotyping) (Genaissance Pharmaceuticals, New Haven, CT, USA), to have normal clinical laboratory tests (complete blood count, blood chemistries), a normal physical exam and electrocardiogram (ECG), and a negative urine alcohol and drug screen. Subjects were ineligible if they had a history or evidence of a clinically significant medical disease or condition (e.g., seizure disorder, cardiac arrhythmia), drug or alcohol abuse, hepatitis B surface antigens, or hepatitis C or human immunodeficiency virus antibodies. Subjects were excluded for tobacco use or participation in another investigational study within 30 days, or medication use, including over-the-counter (with exception of acetaminophen) or herbal products within 14 days before dosing. All of the aforesaid medications were prohibited during the study unless approved by the investigator. Subjects were also excluded if they were unwilling to use adequate contraception (women only), were pregnant or lactating, or for any other condition that would impede the study.

Treatment procedures

Subjects were randomized in a 1:1 ratio to receive a single 50 mg dose of desipramine alone (treatment A) or during a 7-day course of cinacalcet 90 mg (treatment B) in the first period based on a computer-generated randomization schedule prepared at Amgen, Inc. using SAS. After a washout period of at least 10 days subjects received the other treatment during period 2. For treatment A, subjects were administered a single oral dose of desipramine on day 1 following a 10-h fast. For treatment B, subjects received cinacalcet on days 1, 2, 3, 4, 6, and 7 with breakfast, and with desipramine on the morning of day 5 following a 10-h fast. Subjects remained in the research facility through day 2 for treatment A (with outpatient visits on days 3 and 4), and through the morning of day 8 for treatment B.

On day 1 of treatment A and day 5 of treatment B, blood samples for determination of plasma desipramine concentrations were collected into sodium heparinized tubes predose and 1, 2, 4, 6, 8, 10, 12, 24, 48, and 72 h postdose. Physical exams and ECGs were conducted and blood samples for complete blood count and blood chemistries were collected at screening and at the conclusion of the study. Vital signs and adverse event reporting were conducted daily during the treatment periods.

Pharmacokinetics

Plasma concentrations of desipramine were determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), with a lower limit of quantitation (LOQ) of 0.500 ng/ml (MDS Pharma Services, Lincoln, NE, USA). Desipramine plasma concentration-time data were analyzed by noncompartmental methods using WinNonlin Professional v. 3.3 (Pharsight Corporation, Mountain View, CA, USA) and were plotted on a semi-log scale. The data points that described the log-linear terminal phase were identified. The terminal phase rate constant, λ_z, was estimated using a linear regression of the log-transformed terminal data points versus time, and terminal half-life ($t_{1/2,z}$) was calculated as $0.693/\lambda_z$. The area under the concentration-time curve from 0 to the time of the last measurable concentration (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the concentration-time curve from the time of the last measurable concentration to infinity ($AUC_{t-\infty}$) was calculated by dividing the concentration for the last measurable plasma concentration by λ_z. $AUC_{0-\infty}$ was calculated by the summation of AUC_{0-t} and $AUC_{t-\infty}$. Oral clearance (CL/F) was calculated as dose/$AUC_{0-\infty}$.

Concentration values for desipramine below the LOQ were set to zero for all calculations. Concentration data and pharmacokinetic parameters were summarized using descriptive statistics. AUC and C_{max} were analyzed using a crossover analysis of variance (ANOVA) model. The subject, subject within sequence, period, and treatment effects were extracted. AUC and C_{max} were transformed to natural logarithms before analysis. All other summary statistics were based on original scale data. For AUC and C_{max}, point estimates and 90% confidence intervals (CI) were constructed for the ratio of desipramine with cinacalcet to desipramine alone using the residual variance from the ANOVA and were expressed as a percentage. Absence of an interaction was to be concluded if the 90% CIs were between 0.8 and 1.25.

Safety

The safety profile was characterized using adverse events, vital signs, clinical laboratory measurements, ECGs, and

physical examinations for subjects who received at least one dose of either study drug. Adverse events were summarized by frequency and type for each group (i.e., desipramine alone or desipramine with cinacalcet).

Results

Subjects

Seventeen subjects were enrolled, with 15 (8 women, 7 men) completing at least one treatment period. Of these 15, 9 (60%) were white, 2 (13%) were black, and 4 (27%) were of other races. Subjects had a mean±SD age of 31.5±10.8 years, and a body mass index of 24.6±3.19 kg/m^2. Two subjects were deemed ineligible due to a positive urine alcohol screen before the first dose, and one subject withdrew consent during the study. All 15 treated subjects were included in the safety analyses, and the 14 subjects who completed both treatment periods were included in the pharmacokinetics analyses.

Pharmacokinetics

Relative to when desipramine was administered alone, a 3.6-fold increase in $AUC_{0-\infty}$ and 1.8-fold increase in C_{max} of desipramine was observed when cinacalcet was administered for 5 days before and 2 days after dosing with desipramine (Table 1, Fig. 1). Administration with cinacalcet resulted in an increase in the $AUC_{0-\infty}$ and C_{max} of desipramine for all subjects (Fig. 2). Coadministration of desipramine and cinacalcet also resulted in a notable reduction in desipramine oral clearance. The terminal half-life of desipramine was also increased by approximately twofold when desipramine was coadministered with cinacalcet. The median t_{max} was 6 h following administration of desipramine alone and following administration with cinacalcet.

Safety

Overall, treatment-related adverse events (as determined by the investigator) occurred in 33% (5/15) of the subjects during the desipramine alone period and 86% (12/14) during the desipramine with cinacalcet period. The most common treatment-related adverse events (>1 in either group) are reported in Table 2.

All adverse events were mild to moderate in severity. There were no clinically significant changes in laboratory results, vital signs, or ECGs over the course of the study. No deaths occurred during the study and no subjects withdrew due to adverse events.

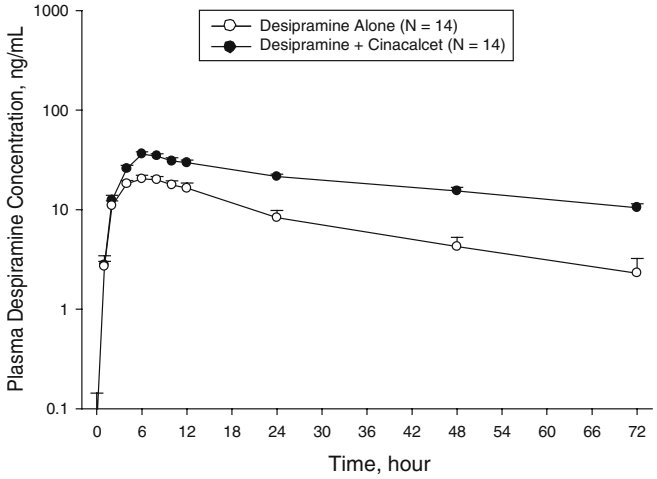

Fig. 1 Mean (SE) plasma concentration-time profiles of desipramine alone and with cinacalcet. Mean (SE) plasma concentrations of desipramine (ng/ml) over 72 h postdose are shown when desipramine was administered alone (*open circles*) and with cinacalcet (*closed circles*)

Discussion

Coadministration of cinacalcet (90 mg once daily for 7 days) and a single oral dose desipramine 50 mg on day 5 resulted in a 3.6-fold and 1.8-fold increase in the AUC and C_{max}, respectively, of desipramine, a CYP2D6 substrate. The terminal half-life of desipramine was significantly prolonged, and clearance was correspondingly reduced when cinacalcet was coadministered. These in vivo findings are consistent with in vitro data which demonstrated that cinacalcet is a strong inhibitor of CYP2D6 [18]. The approximate threefold increase in desipramine exposure observed in this study was slightly less than the largest (approximately fourfold to fivefold) increases in AUC

Table 1 Pharmacokinetic data (mean±SD), point estimates, and 90% confidence intervals (CI)

Parameter	Desipramine alone	Desipramine with cinacalcet[a]	Point estimate[a]	90% CI
AUC_{0-t} (ng*h/ml)	541±314	1351±318	2.79	2.29–3.38
$AUC_{0-\infty}(ng*h/ml)$	656±521	2048±665	3.64	2.97–4.47
C_{max} (ng/ml)	21.8±6.5	37.2±6.9	1.75	1.58–1.95
t_{max}[b] (h)	6.0 (4.0–12.0)	6.0 (6.0–10.0)		–
$t_{1/2,z}$ (h)	21.0±10.8	43.3±12.6		–
CL/F (l/h)	108.7±55.6	27.2±10.4		–

[a]Ratio (cinacalcet + desipramine: cinacalcet alone) of geometric means
[b]Median (range)

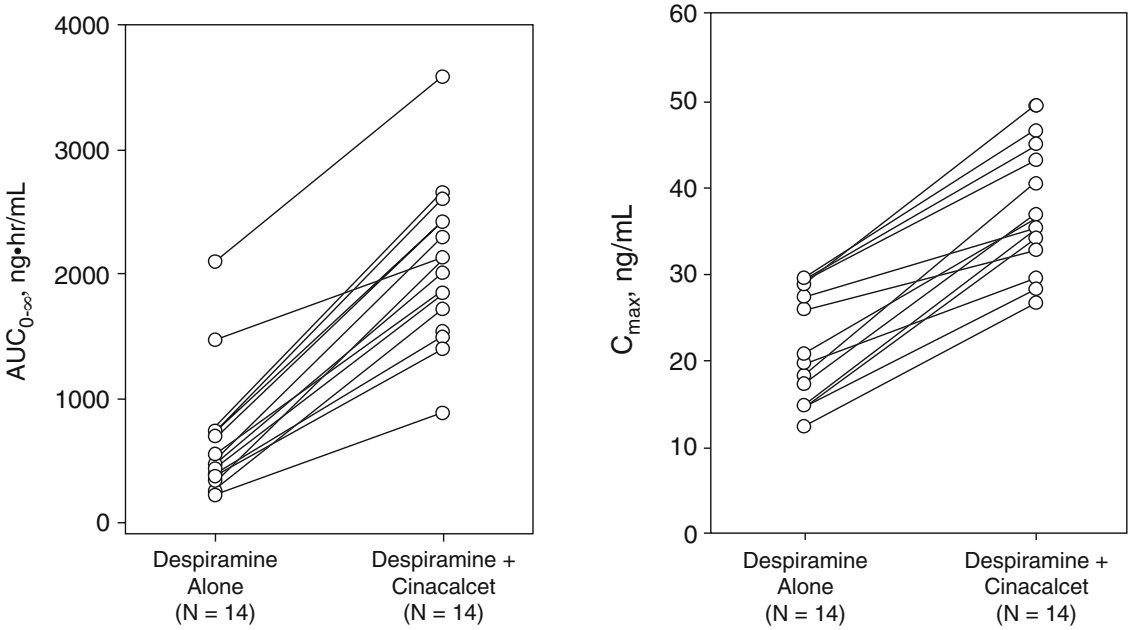

Fig. 2 Individual $AUC_{0-\infty}$ and C_{max} values for desipramine after subjects received desipramine alone and with cinacalcet

observed in studies of coadministration of desipramine with other known strong CYP2D6 inhibitors: paroxetine [10, 13], fluoxetine [16], and terbinafine [11]. Assuming that these other CYP2D6 inhibitors completely abolish CYP2D6 activity, the 3.6-fold increase in desipramine AUC resulting from coadministration of cinacalcet corresponds to an approximately 90% inhibition of CYP2D6 activity. Presumably, higher doses of cinacalcet could result in even greater inhibition, and therefore, cinacalcet should be classified as a strong inhibitor of CYP2D6.

An increased incidence of adverse events was observed during coadministration of desipramine and cinacalcet compared with administration of desipramine alone. Although this study was not designed to draw a definitive link between either agent and a particular adverse event, some associations based on previous findings can be made. Paresthesia is a known adverse effect of desipramine, and increased exposure of desipramine may increase the probability of subjects experiencing this side effect. Conversely, nausea is among the most commonly reported adverse events in clinical studies of cinacalcet [1, 19, 20] and is, therefore, not necessarily the result of CYP2D6 inhibition.

Deleterious clinical effects have been reported following coadministration of TCAs and CYP2D6 inhibitors [7–9]. In this study, an increase in the number of treatment-related adverse events was observed during the desipramine with cinacalcet treatment arm in relation to the desipramine alone arm, the most frequent of which (nausea and headache) have been reported for patients treated with either desipramine or cinacalcet.

In conclusion, these in vivo findings confirm the in vitro findings that cinacalcet is a strong CYP2D6 inhibitor. Coadministration of desipramine with cinacalcet resulted in a significant increase in exposure to desipramine. Therefore, caution should be undertaken when cinacalcet is coadministered with known CYP2D6 substrates that have narrow therapeutic windows.

Table 2 Treatment-related adverse events (>1 subject in either group)

	Desipramine alone, *n*=15 (%)	Desipramine + cinacalcet, *n*=14 (%)
Nausea	0	6 (43)
Headache	0	5 (36)
Paresthesia	1 (7)	4 (29)
Disturbances in attention	0	2 (14)
Vomiting	0	2 (14)
Flushing	2 (13)	1 (7)
Somnolence	3 (20)	0

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