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Effect of Omeprazole on the Pharmacokinetics of Paricalcitol in Healthy Subjects

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ABSTRACT: Paricalcitol capsules are indicated for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease (CKD). Proton pump inhibitors are prescribed to CKD patients to treat gastroesophageal reflux. This was a single dose, crossover study evaluating the effect of omeprazole, change in gastric pH as a result thereof, on the pharmacokinetics (PK) of paricalcitol. Twenty-six healthy subjects were administered paricalcitol capsules (16 μg) alone (regimen A), and following a single dose of OMP (40 mg) (regimen B), with a washout of at least 7 days. Plasma samples for paricalcitol concentrations were collected for 48 h post-paricalcitol dose. The plasma paricalcitol concentrations were measured using an LC–MS/MS assay (LOQ = 0.02 ng/ml) and paricalcitol pharmacokinetic parameters were estimated using non-compartmental methods. The point estimates and the corresponding 90% confidence intervals for C_{max} and $AUC_{0\text{-}\infty}$ to evaluate paricalcitol–omeprazole interaction were 1.032 [0.920–1.158] and 1.041 [0.951–1.139], respectively. No significant differences in T_{max} (regimen A: 2.9 h vs regimen B: 2.6 h) or $t_{1/2}$ (6.83 h vs 6.6 h) between the regimens were observed. Hence, the co-administration of omeprazole does not affect the PK of paricalcitol. Both regimens were well tolerated and no apparent differences among the regimens with respect to safety were observed.

Key words: vitamin D; drug interaction; pharmacokinetics; proton pump inhibitors; kidney disease; Zemplar

Introduction

Paricalcitol capsules (Zemplar®) are approved for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD). Secondary hyperparathyroidism can occur early in the course of kidney disease and progresses along with the deterioration of kidney function.

In healthy subjects, the mean absolute bioavailability of paricalcitol capsules, administered as a single oral capsule, was 66.4% and 72.1%, under fasting and nonfasting conditions, respectively [1]. The mean half-life ranged from 5 to 7 h. The pharmacokinetics were dose linear over the 0.06 to 0.48 μg/kg dose range and were not influenced by gender [2]. Paricalcitol is extensively bound (>99.9%) to plasma proteins over the range 1–100 ng/ml. Paricalcitol is eliminated primarily by hepato-biliary excretion; approximately 70% of the radiolabeled dose is recovered in the feces with no parent drug in the urine. Following multiple-dose administration in healthy subjects,

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steady-state concentrations were reached by study day 7 with either 4 μg daily (q.d.) or 8 μg three times a week (t.i.w.) and paricalcitol pharmacokinetics were time-linear [3].

Gastrointestinal abnormalities are prominent manifestations of CKD [4,5]. There is a high frequency of gastritis, gastroesophageal reflux disease (GERD) and peptic ulcer disease in subjects with end stage renal disease (ESRD) [6,7]. Omeprazole, a proton pump inhibitor, is commonly used in this patient population to treat gastroesophageal reflux [8]. Prilosec™ delayed-release capsules contain an enteric-coated granule formulation of omeprazole, so that absorption of omeprazole begins only after the granules leave the stomach. Omeprazole suppresses gastric acid secretion by inhibiting H^+/K^+ ATPase at the secretory surface of the gastric parietal cells. A single 40 mg dose of omeprazole has been shown to raise the gastric pH by about 2 units in about 2 h [9].

Paricalcitol undergoes extensive metabolism and is eliminated primarily by hepato-biliary excretion. The primary metabolic route is renal CYP24 hydroxylation, but recent evidence indicates CYP3A mediated oxidation and UGT1A4 mediated glucuronidation. Paricalcitol is not known to be a substrate of transporters. Omeprazole is metabolized by CYP2C19 [10] and a strong inhibitor of CYP2C19 activity [11]. In addition, omeprazole has been shown to be a weak inhibitor of CYP1A2 activity [12]. There is minimal evidence to indicate that omeprazole is a significant inhibitor of CYP3A and/or CYP24 hydroxylase. As a result, a metabolism or elimination based drug interaction is not expected between paricalcitol and omeprazole.

Following the initiation of omeprazole therapy, increases in gastric pH have been shown to affect the absorption of other concomitantly administered drugs [9]. Paricalcitol is a lipophilic (c Log P $\sim$5.69), poorly soluble compound and is formulated as a solution in Neobee oil in a soft-elastic capsule. Absorption of poorly soluble drugs and drugs with pH-sensitive solubility are generally most affected when co-administered with omeprazole. The rationale behind this study was to evaluate the effect of altered gastric pH on paricalcitol absorption or in other words, evaluating absorption based drug interaction between paricalcitol and omeprazole. Additionally, the safety of co-administering paricalcitol and omeprazole was also assessed.

Methods

Subjects

Healthy adult male and female volunteers between the ages of 18 and 55 years were eligible to participate in the study. Subjects were in general good health based on medical history, physical examination, vital signs, laboratory profile and 12-lead ECG. The subjects had a body weight within $\pm$ 15% of the applicable range based on height, sex and body frame and was a minimum of 54.4 kg for females and 61.2 kg for males. Females were of non-childbearing potential.

Subjects were excluded from the study if they had a clinically significant abnormality, had gastric surgery, vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption, had consumed alcohol, grapefruit, or grapefruit products within 72 h of start of the study, were tobacco users within 6 months preceding study drug administration, or had taken (or were required to regularly take) over-the-counter medications within 2 weeks of dosing, had a positive test result for hepatitis B surface antigen or hepatitis C virus antibody, had a history of allergies to any medication, received any drug by injection within 30 days prior to study drug administration, had donated or lost 550 ml or more blood volume, or received a transfusion of any blood product within 8 weeks prior to study drug administration, and had received any investigational drug within 6 weeks. Subjects signed a written informed consent form prior to participation in the study.

Study design

This was a Phase 1, single-dose, open-label, fasting, randomized, single-center, and drug-interaction study conducted according to a two-period, complete crossover design. Twenty-six (26) male and female healthy subjects were

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randomly assigned, in equal numbers, into one of two sequence groups of the following regimens, under fasting conditions: regimen A: four 4 μg paricalcitol capsules (16 μg) and regimen B: one 40 mg omeprazole capsule (Prilosec®, AstraZeneca, LP, Wilmington, DE, USA) administered under fasting conditions and, 2 h later, followed by four 4 μg paricalcitol capsules (16 μg).

The sequences of regimens were such that each subject had received both regimens upon completion of the study. A washout interval of at least 7 days separated the doses of the two study periods. All medications were administered with approximately 240 ml of water. Subjects were confined for approximately $2\frac{1}{2}$ days in each period from the afternoon of day −1 through the morning of day 3.

The study protocol was approved by Institutional Review Board/Independent Ethics Committee. The study was conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP regulations and guidelines, U.S. Food and Drug Administration (FDA) regulations and guidelines governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 revision) and all applicable local regulations.

Sample collection and analysis

Blood samples (7 ml) were collected from each subject by venipuncture or intravenous cannula into evacuated EDTA containing collection tubes. The samples were collected immediately prior to dosing (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 18, 24, 36 and 48 h after paricalcitol dosing in each study period. Sufficient blood was collected to provide 2.5 ml plasma from each sample. All samples were placed in an ice bath immediately after collection.

Plasma concentrations of paricalcitol were determined using a validated liquid/liquid extraction HPLC tandem mass spectrometric method (LC–MS/MS). Samples were analysed by subject such that both regimens for each subject were analysed in the same analytical run with the exception of re-assayed samples. The lower limit of quantification (LLOQ) for paricalcitol was established as 0.021 ng/ml using 600 μl of plasma. In-study quality control (QC) samples, supplemented with concentrations of 0.06, 1.10 and 14.99 ng/ml of paricalcitol, were analysed with the unknowns. All calibration curves had a coefficient of determination (r^2) greater than 0.9937. The percent coefficients of variation (%CV) values for the accepted data at QC concentrations ranged from 7.1% to 33.8%. The excessively high %CV was at the low concentration and is attributed to the small statistical sample for this QC level. The mean analytical recoveries of the QC samples ranged from 98.5% to 119.3%.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed on the paricalcitol plasma concentration-time data for each individual subject and the estimates of pharmacokinetic parameters were obtained by noncompartmental methods using WinNonlin-Pro™, version 3.3 (Pharsight Corporation, Mountain View, CA). The maximum plasma concentration post-paricalcitol dose (C_{max}) and the time to reach C_{max} (T_{max}) were determined directly from the observed blood concentration vs time data. The terminal elimination phase rate constant (λ_z) was derived by linear regression of the log-linear disposition of the concentration vs time profile. The terminal elimination half-life ($t_{1/2}$) was calculated as $(\ln 2)/\lambda_z$. The area under the curve from time zero to infinity ($AUC_{0\text{-}\infty}$) was calculated as $AUC_{0\text{-last}} + (C_{last}/\lambda_z)$, where $AUC_{0\text{-last}}$ was the area under the curve between zero and the time of the last measurable concentration (C_{last}) calculated using the linear trapezoidal rule. Oral clearance (CL/F) was calculated as Dose/$AUC_{0\text{-}\infty}$. The apparent volume of distribution in the terminal phase (Vd_β/F) value was calculated by dividing the CL/F by λ_z.

Safety assessment

Adverse events were monitored throughout the study. Physical examinations were performed at the beginning and completion of the study, and vital signs measurement were performed daily, and clinical laboratory profile and ECG were obtained several times during confinement.

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Statistical analysis

The pharmacokinetic parameters were analysed using SAS (version 6.11). An analysis of variance (ANOVA) was performed for T_{max}, λ_z and the natural logarithms of C_{max} and AUC. The model included effects for sequence, subject nested within sequence, period and regimen. The effects of sequence, period and regimen were fixed, while the effect of subject was random. For the test on sequence effects, the denominator sum of squares for the F statistic was the sum of squares for subject nested within sequence. For the tests on period and regimen effects, the denominator sum of squares was the residual sum of squares. Within the ANOVA modeling framework, the two regimens (paricalcitol with omeprazole vs paricalcitol alone) were compared by a test with a significance level of 0.05.

The 90% confidence intervals (CI) for paricalcitol C_{max} and AUC were provided with concomitant administration of paricalcitol and omeprazole as the test regimen and paricalcitol alone as the reference regimen. These confidence intervals were obtained by exponentiating the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model. No pharmacokinetic drug interaction between paricalcitol and omeprazole was concluded if the 90% CI from the analyses of log-transformed $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} were within the 0.80 to 1.25 range.

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by COSTART V [13] term and body system with a breakdown by regimen. Laboratory test values that were outside the reference ranges were flagged in the data listings, and evaluated for clinical significance.

Results

A total of 26 healthy (13 male and 13 female) volunteers were randomized to the two treatment regimens. However, one subject (23 years, 69 kg, 161.2 cm, White male) discontinued from the study on day 1 of period 1 due to a vasovagal episode not related to either paricalcitol or omeprazole administration. For the remaining 25 subjects who completed both regimens of the study, the subject demographics are shown in Table 1.

The mean plasma concentration-time profiles following the administration of paricalcitol alone and co-administration of omeprazole were similar (Figure 1). Based on the ANOVA analysis, the C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ were similar in both regimens (Table 2). Additionally, the T_{max} value, when paricalcitol was administered alone (2.9 ± 1.6 h) was similar to that when paricalcitol was co-administered with omeprazole (2.6 ± 1.1 h). Co-administration of omeprazole with paricalcitol did not alter the $t_{1/2}$ of paricalcitol. No statistical comparisons were performed on CL/F and Vd_β/F, however, the mean values of these parameters were similar between the two regimens. The test statistic for period effect was not statistically significant for any of the tested pharmacokinetic parameters suggesting a lack of carry-over effects.

Table 1. Subject demographics

	Mean $\pm$ SD ($n = 25$)	Min–Max
Age (years)	41.0 ± 6.9	26–54
Weight (kg)	69.0 ± 8.5	55.8–84.8
Height (cm)	163.8 ± 8.5	147.3–177.8
Sex	12 Males (48%), 13 Females (52%)	
Race	24 White (96%), 1 Black (4%)	

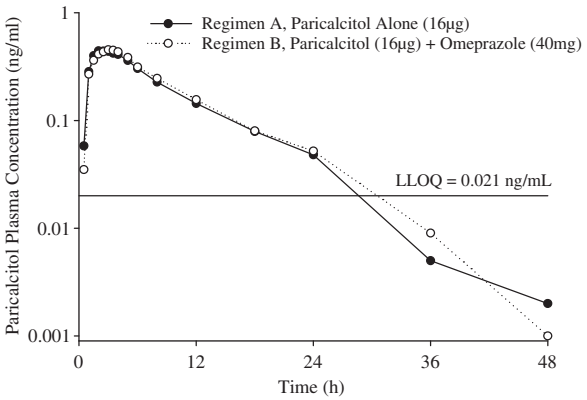

Figure 1. Mean plasma paricalcitol concentration vs time profile

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The 90% confidence intervals of C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ for evaluating the paricalcitol–omeprazole interaction were completely contained in the 0.80–1.25 range (Table 3). There was a high degree of overlap in individual C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ values between the two regimens (Figure 2).

The regimens tested were generally well tolerated by the subjects. No clinically significant physical examination results, vital sign changes or laboratory measurements were observed during the course of the study. No differences were seen among regimens for their adverse event profiles. The proportion of subjects reporting at least one treatment-emergent adverse event (mild to moderate in severity) was similar among subjects who received paricalcitol alone and paricalcitol with omeprazole. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for vital signs, ECGs and physical examinations were unremarkable for each regimen.

Table 2. Mean ± SD pharmacokinetic parameters of paricalcitol

	Regimen	
Pharmacokinetic parameters (units)	Paricalcitol alone ($n = 25$)	Paricalcitol with omeprazole ($n = 25$)
T_{max} (h)	2.9 ± 1.6	2.6 ± 1.1
C_{max} (ng/ml)	0.542 ± 0.178	0.550 ± 0.171
$AUC_{0\text{-last}}$ (ng·h/ml)	4.482 ± 1.308	4.716 ± 1.298
$AUC_{0\text{-}\infty}$ (ng·h/ml)	5.032 ± 1.412	5.183 ± 1.334
λ_z (h^{-1})	0.102 ± 0.030	0.105 ± 0.032
$t_{1/2}$[a] (h)	6.83 ± 2.01	6.60 ± 2.06
CL/F[b] (l/h)	3.50 ± 1.33	3.31 ± 0.94
Vd_{β}/F[b] (l)	38.2 ± 22.8	33.3 ± 11.5

[a] Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.
[b] Parameter was not tested statistically.

Table 3. Effect of omeprazole and paricalcitol co-administration on paricalcitol bioavailability

		Central value[a]		Relative bioavailability	
Regimens test vs reference	Pharmacokinetic parameter	Paricalcitol with omeprazole (B)	Paricalcitol alone (A)	Point estimate[b]	90% confidence interval
Omeprazole+paricalcitol vs Paricalcitol alone	C_{max}	0.525	0.509	1.032	0.920–1.158
	$AUC_{0\text{-last}}$	4.559	4.267	1.068	0.968–1.180
	$AUC_{0\text{-}\infty}$	5.028	4.832	1.041	0.951–1.139

[a] Antilogarithm of the least squares means for logarithms.
[b] Antilogarithm of the difference (regimen B minus regimen A) of the least squares means for logarithms.

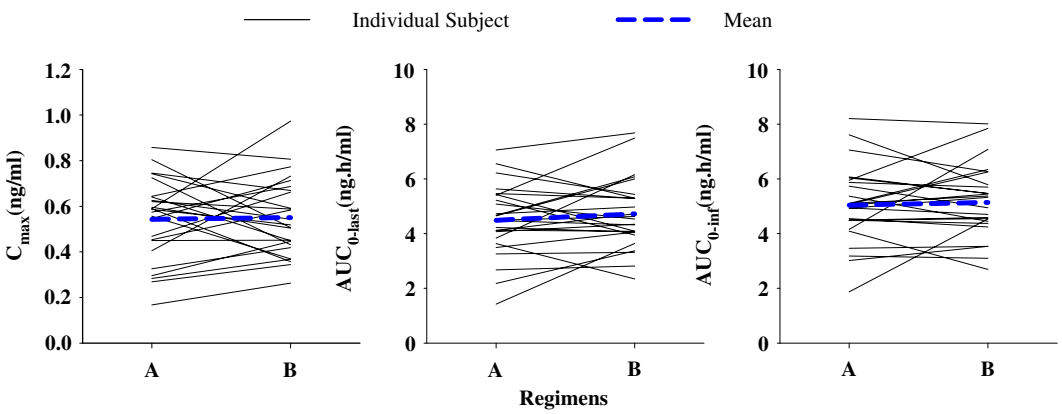

Figure 2. Comparison of individual (solid line) and mean (dashed line) pharmacokinetic parameters, paricalcitol alone vs paricalcitol with omeprazole, regimen A: paricalcitol alone; regimen B: omeprazole with paricalcitol

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Discussion

The pharmacokinetic parameters observed in the paricalcitol alone regimen were in accordance to those reported in previous studies [2]. The results of this study showed that omeprazole administered as a single dose 2 h prior to oral paricalcitol dose does not affect the rate and extent of paricalcitol absorption. The results of ANOVA show that C_{max}, T_{max} and *AUC* were similar when paricalcitol was administered alone or with omeprazole. Additionally, the 90% confidence intervals for evaluating paricalcitol–omeprazole interaction were contained within the 0.80–1.25 range. The harmonic mean $t_{1/2}$ and elimination rate constant of paricalcitol were similar when administered alone or when administered with omeprazole. The comparison of the individual pharmacokinetic parameters between the two regimens showed that no individual had any meaningful change in the paricalcitol pharmacokinetics following concomitant administration of paricalcitol and omeprazole.

It has been well documented that vitamin D and its analogs when administered orally have adequate intestinal absorption. Similar to other vitamin D analogs, paricalcitol is a lipophilic molecule ($c\,\mathrm{Log}\,P \sim 5.69$) and is administered as a solution in Neobee oil in a soft-elastic capsule formulation. *In vitro* Caco-2 cell permeability measurements have shown that the absorptive (A to B) apparent permeability (P_{app}) value at 5 or 50 μM concentration ranged from 3.76 to 12.02×10^{-6} cm/s at pH of 6.8–7.4, suggesting paricalcitol to be a high permeability drug. However, the aqueous solubility of paricalcitol is very low ($\leqslant 50$ ng/ml) (unpublished data). Thus, paricalcitol can be classified as a BCS class 2 drug.

It is known that one of the determinants of aqueous solubility could be gastric pH. Omeprazole, a commonly prescribed drug, inhibits the secretion of acid from gastric parietal cells. Concomitant omeprazole administration has been shown to induce modest, but clinically relevant changes in the absorption of some drugs (phenytoin, digoxin) because of the strong and long lasting decrease in the intragastric acidity [10,14]. Although gastric pH was not monitored in this study, a single dose of omeprazole has been shown to raise the gastric pH from less than 2 to greater than 4 in 2 h [9].

Since the current study did not show even a minimal effect of omeprazole co-administration on paricalcitol bioavailability following single dose administration of omeprazole and a metabolism or elimination based drug interaction is not likely between paricalcitol and omeprazole because of their dissimilar metabolic pathways, a drug-interaction between omeprazole and paricalcitol is not likely following chronic administration.

The regimens tested were generally well tolerated by the subjects. No clinically significant physical examination results, or vital signs or laboratory measurements were observed during the course of the study. No differences were seen among regimens for their adverse event profiles. There were no apparent differences among the regimens with respect to safety.

In conclusion, these findings demonstrate that omeprazole has no effect on paricalcitol pharmacokinetics. Additionally, both paricalcitol alone and when coadministered with omeprazole were generally well tolerated and no apparent differences among the regimens with respect to safety were observed.

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