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ABSTRACT

Background: Posaconazole (POS) oral suspension is an extended-spectrum triazole that should be taken with food to maximize absorption. A new POS tablet formulation has demonstrated improved bioavailability over oral suspension in healthy adults in the fasting state. This study evaluated the effect of concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) and motility (metoclopramide) on the pharmacokinetics of POS tablet.

Methods: This was a prospective, open-label, 5-way crossover study in 20 healthy volunteers. In each treatment period, a single 400-mg (100 mg x 4) dose of POS tablets was administered alone or with 20 mL antacid (Mylanta® Ultimate Strength Liquid, aluminum hydroxide 2 g and magnesium hydroxide 2 g), ranitidine (150 mg), esomeprazole (40 mg), or metoclopramide (15 mg). There was ≥10-day washout between treatment periods.

Results: POS exposure, T_{max}, and $t_{½}$ were similar when administered alone or with medications affecting gastric pH and motility. Geometric mean ratios (90% CI) of $AUC_{0\text{-last}}$ compared with those of POS alone were antacid, 1.04 (0.90–1.20); ranitidine, 0.97 (0.84–1.12); esomeprazole, 1.02 (0.88–1.17); and metoclopramide, 0.93 (0.80–1.07). Geometric mean ratios (90% CI) of C_{max} compared with those of POS alone were antacid, 1.06 (0.90–1.26); ranitidine, 1.04 (0.88–1.23); esomeprazole, 1.05 (0.89–1.24); and metoclopramide, 0.86 (0.73–1.02).

Conclusions: In healthy volunteers, the pharmacokinetics of a single dose of POS tablet 400 mg were similar when administered alone or with medications affecting gastric pH or motility.

BACKGROUND

- Posaconazole (POS) oral suspension (Noxafil®) is a marketed extended-spectrum triazole with demonstrated efficacy as antifungal prophylaxis and treatment[1-5] that should be taken with food to maximize absorption[6,7]
- Patients at risk for invasive fungal infection may be unable to eat because of mucositis, nausea, or neutropenic enterocolitis[8-10]
- In an attempt to optimize absorption and bioavailability without regard to food intake, a new POS tablet formulation has been developed that results in substantially improved exposure compared with the oral suspension in healthy adults in the fasting state; furthermore, exposure for POS tablet was not markedly affected by food[11]
- The POS tablet formulation consists of active drug mixed with a pH-sensitive polymer (hypromellose acetate succinate); this formulation is designed to release the dose of POS within the elevated pH environment of the small intestine to maximize systemic absorption

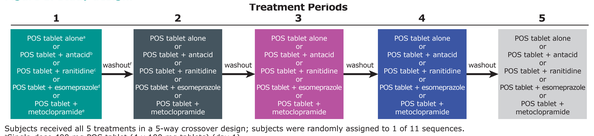
OBJECTIVES

- To evaluate the effect of concomitant medications altering gastric pH (antacid, ranitidine, and esomeprazole) and gastric motility (metoclopramide) on the pharamacokinetics (PK) of POS tablet
- To evaluate the safety and tolerability of POS tablet administered with drugs affecting gastric pH or gastric motility

METHODS

- This was a prospective, open-label, 5-way crossover study in healthy volunteers
- Subjects were excluded if they had any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of any drug
- Subjects received all 5 treatments in a randomly assigned order according to a predefined treatment schedule with a ≥10-day washout between treatment periods
- In each treatment period, a single 400-mg (100 mg x 4 tablets) dose of POS tablets was administered alone or with 20 mL antacid (Mylanta® Ultimate Strength Liquid [aluminum hydroxide 2 g/magnesium hydroxide 2g]), ranitidine (150 mg), esomeprazole (40 mg), or metoclopramide (15 mg), as shown in **Figure 1**
- On day 1
  - — POS tablets plus esomeprazole or POS tablets plus metoclopramide were administered together
  - — POS tablets were administered immediately after antacid
  - — POS tablets were administered 1 hour after ranitidine
- Study drugs were administered in the fasting state (approximately 10 hours after an overnight fast), with the first meal approximately 4 hours post dose on day 1

Figure 1. Study design.



Subjects received all 5 treatments in a 5-way crossover design; subjects were randomly assigned to 1 of 11 sequences.
[a]Single-dose 400 mg POS tablet (4 x 100 mg tablets) (day 1).
[b]400 mg POS tablet + 20 mL Mylanta® Ultimate Strength Liquid (aluminum hydroxide 2 g and magnesium hydroxide 2 g) (day 1).
[c]400 mg POS tablet + 150 mg ranitidine tablet twice daily (day 1) (POS was administered with the first dose of ranitidine).
[d]Esomeprazole 40 mg once in the morning for 5 days (days -4 to 1) + single-dose 400 mg POS tablet (day 1).
[e]Single-dose 400 mg POS tablet (day 1) + metoclopramide, 15 mg four times daily for 2 days (days -1 and 1).
[f]Washout period of 10 days between treatment periods.

Blood Collection for Assessment of POS PK Parameters

- Blood samples (4 mL each) for PK evaluation of POS in plasma were collected in each treatment period at predose (0 hours) and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, and 168 hours post POS dose
- Plasma samples were assayed for POS using validated liquid chromatography with tandem mass spectrometric detection[12] with a lower limit of quantitation of 5.00 ng/mL and a calibration range of 5.00 to 5000 ng/mL

PK Evaluations

- Area under the curve from time 0 to the time of the last quantifiable sample ($AUC_{0\text{-last}}$) and maximum plasma concentration (C_{max}) were analyzed using a linear mixed-effect model extracting the effects due to treatment, period, and sequence as fixed effects and subject as random effect; a log transformation was applied and back-transformed
- Geometric mean ratios (GMRs) of $AUC_{0\text{-last}}$ and C_{max} (treatment B/C/D/E versus A) and 90% confidence intervals (CIs) were provided from the above linear mixed-effect model. If the 90% CI fell within the range of 0.5 to 2.0, then there was no clinically meaningful effect of gastric pH/motility on POS PK

Safety

- Safety assessments included reporting of adverse events (AEs), vital signs, physical examination, electrocardiograms, hematology, and blood chemistry through day 8 of the last treatment period

RESULTS

- Twenty-one subjects were enrolled in the study. Subject demographics are shown in **Table 1**
- 20 of 21 subjects completed the study; 1 subject withdrew consent after treatment period 1 and discontinued the study

Table 1. Subject Demographics

	All Subjects (N = 21)
Age, y, median (range)	38 (24–53)
Sex, n (%)	
Male	18 (86%)
Female	3 (14%)
Race, n (%)	
White	7 (33%)
Black/African American	13 (62%)
Asian	1 (5%)
Ethnicity, n (%)	
Hispanic/Latino	0
Weight, kg, median (range)	78.2 (52.5–105.1)
Height, cm, median (range)	175 (158–186.5)
Body mass index, kg/m², median (range)	25.9 (21.0–31.7)

PK Evaluations

- POS $AUC_{0\text{-last}}$, T_{max}, and $t_{½}$ were similar whether POS was administered alone or with medications affecting gastric pH and gastric motility (**Table 2**)

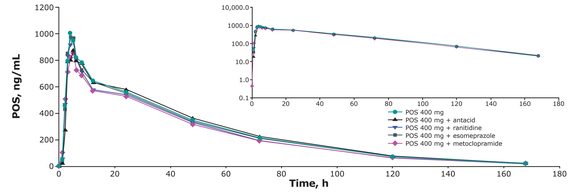
Table 2. Arithmetic Mean (%CV) of the Pharmacokinetic Parameters of POS Following Single-Dose Administration of 400 mg POS Tablet Alone or With Concomitant Medications to Healthy Volunteers

Treatment	C_{max}, ng/mL	$AUC_{0\text{-last}}$, h · ng/mL	T_{max}*, h	$t_{½}$, h
POS alone	1090 (43)	40,967 (47)	4 (2-8)	27.3 (37)
POS + antacid	1112 (36)	41,247 (39)	4.8 (3-12)	27.7 (29)
POS + ranitidine	1094 (37)	38,046 (35)	4 (3-5)	26.9 (35)
POS + esomeprazole	1104 (35)	40,083 (40)	4.5 (3-24)	28.0 (30)
POS + metoclopramide	935 (44)	36,975 (40)	4 (2-6)	29.0 (38)

*Median (minimum-maximum).
$AUC_{0\text{-last}}$, area under the curve from time 0 to time of last quantifiable sample; C_{max}, maximum observed concentration; CV, coefficient of variation; POS, posaconazole; T_{max}, time to C_{max}; $t_{½}$, terminal half-life.

- Mean plasma concentration-time profiles of POS tablet administered alone and with antacid, ranitidine, esomeprazole, and metoclopramide were similar (**Figure 2**)

Figure 2. Arithmetic mean plasma concentration time profiles following single-dose administration of 400 mg POS tablet alone or with concomitant medications to healthy volunteers (inset: semi log scale).



N = 20 for treatments with POS alone, POS + ranitidine, POS + esomeprazole, POS + metoclopramide; N = 21 for treatment with POS + antacid. POS, posaconazole.

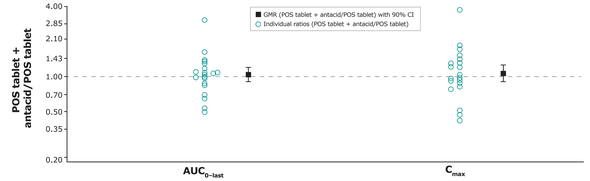
- GMRs (90% CI) of $AUC_{0\text{-last}}$ of POS tablet plus treatment versus POS tablet alone are summarized in **Table 3** and presented graphically in **Figures 3–6**
- The 90% CIs of $AUC_{0\text{-last}}$ and C_{max} for each comparison to POS alone were fully contained within 0.5, 2.0; POS tablet PK was therefore considered to be similar when a single POS dose of 400 mg was administered alone or with medications affecting gastric pH or gastric motility

Table 3. GMR (90% CI) of $AUC_{0\text{-last}}$ and C_{max} of POS Tablet + Treatment vs POS Tablet Alone

POS Tablet + Treatment Listed vs POS Tablet Alone	$AUC_{0\text{-last}}$ GMR (90% CI)	C_{max} GMR (90% CI)
Antacid	1.04 (0.90–1.20)	1.06 (0.90–1.26)
Ranitidine	0.97 (0.84–1.12)	1.04 (0.88–1.23)
Esomeprazole	1.02 (0.88–1.17)	1.05 (0.89–1.24)
Metoclopramide	0.93 (0.80–1.07)	0.86 (0.73–1.02)

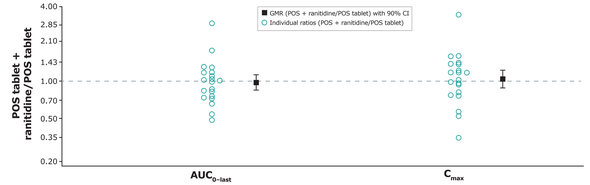
$AUC_{0\text{-last}}$, area under the curve from time 0 to time of last quantifiable sample; C_{max}, maximum observed concentration; GMR, geometric mean ratio; POS, posaconazole.

Figure 3. Individual ratios, GMR (POS tablet + antacid/POS tablet) and 90% CI of $AUC_{0\text{-last}}$ and C_{max} for 400 mg POS tablet alone or 400 mg POS tablet + antacid.



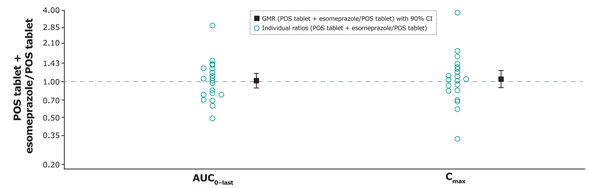
$AUC_{0\text{-last}}$, area under the curve from time 0 to time of last quantifiable sample; C_{max}, maximum observed concentration; GMR, geometric mean ratio; POS, posaconazole.

Figure 4. Individual ratios, GMR (POS tablet + ranitidine/POS tablet) and 90% CI of $AUC_{0\text{-last}}$ and C_{max} for 400 mg POS tablet alone or 400 mg POS tablet + 150 mg ranitidine.



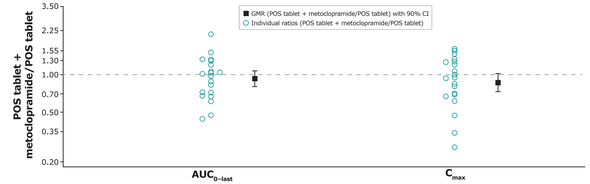
$AUC_{0\text{-last}}$, area under the curve from time 0 to time of last quantifiable sample; C_{max}, maximum observed concentration; GMR, geometric mean ratio; POS, posaconazole.

Figure 5. Individual ratios, GMR (POS tablet + esomeprazole/POS tablet) and 90% CI of $AUC_{0\text{-last}}$ and C_{max} for 400 mg POS tablet alone or 400 mg POS tablet + 40 mg esomeprazole.



$AUC_{0\text{-last}}$, area under the curve from time 0 to time of last quantifiable sample; C_{max}, maximum observed concentration; GMR, geometric mean ratio; POS, posaconazole.

Figure 6. Individual ratios, GMR (POS tablet + metoclopramide/POS tablet) and 90% CI of $AUC_{0\text{-last}}$ and C_{max} for 400 mg POS tablet alone or 400 mg POS tablet + 15 mg metoclopramide.



$AUC_{0\text{-last}}$, area under the curve from time 0 to time of last quantifiable sample; C_{max}, maximum observed concentration; GMR, geometric mean ratio; POS, posaconazole.

Safety

- Overall, 19/21 (90%) subjects reported at least 1 treatment-emergent AE
- All AEs were mild to moderate in severity
- There were no deaths, serious AEs, or significant AEs, and no subjects discontinued because of AEs
- A total of 14 (67%) subjects reported one or more AEs considered treatment-related; the most frequent treatment-related AEs were somnolence (7 subjects [33%]), diarrhea (5 subjects [24%]), and flatulence (3 subjects [14%])
- In 2 subjects dosing was temporarily halted because of AEs (elevated creatine phosphokinase and dystonia/oromandibular dystonia); the AEs were transient and the subjects remained on-study through completion
  - — Elevated creatine phosphokinase was not considered to be treatment related; dystonia/oromandibular dystonia was considered to be probably related to treatment with the coadministered drug metoclopramide

SUMMARY AND CONCLUSIONS

- The PK of a single 400-mg dose of POS tablet is similar when the drug is administered alone or with medications affecting gastric pH or gastric motility in healthy volunteers
- POS tablet may be coadministered with gastric agents (antacid, ranitidine, esomeprazole, or metoclopramide) without decreasing POS exposure
- POS 400-mg tablet was safe and well tolerated by healthy volunteers when administered alone or in combination with antacid, ranitidine, esomeprazole, or metoclopramide

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