The effects of sitaxentan on sildenafil pharmacokinetics and pharmacodynamics in healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Endothelin-A receptor antagonists (ETRA) and phosphodiesterase-type 5 inhibitors are approved monotherapies for the treatment of pulmonary arterial hypertension; combining agents from these two drug classes could be beneficial.
- There is a significant pharmacokinetic (PK) interaction between the ETRA bosentan and the phosphodiesterase-type 5 inhibitor sildenafil.
- This study assessed whether the ETRA sitaxentan similarly impacts the PK of sildenafil.

WHAT THIS STUDY ADDS

- This study demonstrates that sitaxentan has little effect on sildenafil PK and pharmacodynamics and that no dose adjustment of either agent is required upon co-administration of sildenafil with sitaxentan.

AIMS

This study evaluated the effects of sitaxentan on the pharmacodynamic [systemic blood pressure (BP)] and pharmacokinetic (PK) parameters of sildenafil in healthy volunteers.

METHODS

Healthy subjects (18–60 years, $n = 24$) were randomized into two sequence groups. Group 1 received sitaxentan sodium 100 mg daily (7 days), followed by placebo (7 days). Group 2 received placebo (7 days), followed by sitaxentan sodium 100 mg (7 days). On day 7 of each treatment period, participants received sildenafil 100 mg. PK parameters and BP were analysed on day 7 in each treatment period.

RESULTS

Sildenafil exposure was slightly higher [AUC_{∞} geometric mean ratio (GMR), 128%] when co-administered with sitaxentan 100 mg vs. placebo, demonstrating a weak, but statistically significant interaction (90% confidence interval 115.5%, 141.2%). The mean maximum positive ($E_{\max+}$) and maximum negative ($E_{\max-}$) changes from baseline in both systolic and diastolic BP were comparable for sitaxentan and placebo (range 4.8–7.3 mmHg) with three of four geometric mean ratios falling within the equivalence window, suggesting that the drug interaction was not clinically significant. Adverse events were similar between sitaxentan 100 mg (39%) and placebo (30%). No deaths or serious adverse events occurred during the study.

CONCLUSION

The dose of sildenafil does not need to be adjusted when co-administered with sitaxentan.

Introduction

Pulmonary arterial hypertension is a progressive disease characterized by vasoconstriction and vascular

remodelling of small pulmonary arteries; increased pulmonary artery pressure and vascular resistance ultimately lead to failure of the right ventricle and death. Endothelin receptor antagonists (ETRA), such as

sitaxentan, prostanoids and phosphodiesterase-type 5 inhibitors, such as sildenafil, are approved monotherapies, but combining drugs from different classes may provide additive, potentially synergistic, effects [1]. This study evaluated the effects of sitaxentan at steady state on the pharmacokinetics (PK) of sildenafil and its primary metabolite *N*-desmethylsildenafil after a single dose of sildenafil, as well as the effect on systemic blood pressure (BP), in healthy volunteers.

Methods

This was a two-arm, double-blind, placebo-controlled, randomized, crossover study in 24 healthy subjects 18–60 years of age. Subjects were randomized into two sequence groups. Group 1 received sitaxentan sodium 100 mg daily (7 days), followed after a 14-day washout by placebo (7 days). Group 2 received placebo (7 days), followed 14 days later by sitaxentan sodium 100 mg (7 days). On day 7 of each treatment period, participants received sildenafil 100 mg, concurrently with the sitaxentan dose. BP and PK were analysed on day 7 in each treatment period. The protocol was approved by the Institutional Review Board for the site (Bio-Kinetic Clinical Applications, Inc., Springfield, MO, USA) and the study was conducted in accordance with the Declaration of Helsinki (2000), Good Clinical Practice guidelines, according to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guideline (1995), and all applicable federal, state and local laws, rules and regulations. Written informed consent was obtained from all subjects.

Blood samples for the determination of sitaxentan concentrations were collected prior to dosing on days 1, 3 and 5 and for sitaxentan, sildenafil and *N*-desmethylsildenafil predose, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 (day 8) h post dose on day 7 of each treatment period. Seated systolic and diastolic BP measurements were taken predose (baseline) and at 0.5, 1, 1.5, 2, 3, 4 and 6 h post dose on day 7 in both treatment periods. All measurements were performed in triplicate at each time point, and mean values reported.

Blood samples were collected into tubes containing ethylenediamine tetraacetic acid, processed to plasma by centrifugation, and stored (–20°C) until analysis using liquid chromatography/tandem mass spectrometry methods (sitaxentan: MDS Pharma Services, Montreal, Canada; sildenafil and *N*-desmethylsildenafil: CEDRA Corp., Austin, TX, USA) validated to meet the specifications set out in the Food and Drug Administration Bioanalytical Method Validation guidance [2]. Analytes were extracted by organic solvent extraction using isotopic internal standardization. The mass transitions monitored were m/z 475→58 (sildenafil), m/z 461.5→283 (*N*-desmethylsildenafil) and m/z 453→417 (sitaxentan). The

analytical range, within-study assay precision (coefficient of variation) and accuracy were 5.00–750 ng ml^{–1}, 3.5–4.4% and 93.1–101.0% for sildenafil; 2.00–300 ng ml^{–1}, 4.9–7.6% and 98.3–105.8% for *N*-desmethylsildenafil; and 0.005–2.0 µg ml^{–1}, 3.8–6.7% and 100.0–111.5% for sitaxentan. Interference evaluations conducted prior to analysis ensured that each analyte did not adversely influence the quantification of the other analytes.

Routine laboratory tests (haematology, clinical chemistry, urinalysis), physical examinations, vital signs and ECG readings were conducted at screening and on day 8 of each treatment period. At baseline, an additional physical examination and vital signs check was performed, with the latter repeated multiple times throughout day 7. Adverse events (AEs) and use of concomitant medications were recorded.

PK parameters C_{max} , T_{max} , λ_z [first-order rate constant associated with the terminal (log-linear) portion of the curve, estimated via linear regression of time vs. log concentration], $t_{1/2}$, AUC over a 24-h dosing interval at steady state (AUC_{0–24}; sitaxentan), and AUC_{0–t} and AUC_∞ (sildenafil and *N*-desmethylsildenafil) were calculated using non-compartmental analysis. AUC_{0–t} was calculated using the linear trapezoidal method, where t is the time of last measurable concentration. AUC_{0–∞} was calculated as AUC_{0–t} + C_t/λ .

Pharmacodynamic (PD) parameters were the maximum positive change (E_{max+}), maximum negative change (E_{max-}) and the mean change (E_{avg}) at all seven time points in seated systolic and diastolic BP values.

PK calculations and statistical analyses used SAS for Windows Version 9.1 (SAS Institute Inc., Cary, NC, USA). Comparisons of sildenafil and *N*-desmethylsildenafil PK parameters with respect to placebo and sitaxentan treatments used an analysis of variance (ANOVA) model with sequence, subject within sequence, treatment, and period as the classification variables. Confidence intervals (CI, 90%) were constructed for the treatment ratios (sitaxentan to placebo) of all parameters using the log-transformed data and the two one-sided t -tests procedure.

The PD parameters (E_{max+} , E_{min-} and E_{avg}) for the change from baseline (predose, day 7) systolic and diastolic BP were compared between sitaxentan and placebo treatments using the same ANOVA model with data on the original scale. CIs (90%) were constructed for the treatment ratios (sitaxentan to placebo) using the two one-sided t -tests procedure.

Results

Twenty-four subjects were recruited and randomized (Table 1). Twenty-two (92%) completed both treatment periods and were included in the PK and PD analyses.

Mean PK values for sitaxentan (day 7) and sildenafil and *N*-desmethysildenafil given with either placebo or sitaxentan 100 mg are shown in Table 2.

Sildenafil mean plasma concentrations 3 and 10 h post dose were slightly higher when co-administered with sitaxentan 100 mg vs. placebo, resulting in an 18% and 28% increase in mean C_{max} and AUC_{∞} , respectively. For both parameters the upper limits of the 90% CIs for the geometric mean ratios (sitaxentan to placebo) were outside the 80–125% equivalence window, indicating a statistically significant interaction between the two drugs, consistent with CYP3A4/5 inhibition. *N*-desmethysildenafil C_{max} and AUC_{∞} increased by 1 and 6%, respectively, and were not statistically significant. There was no effect on sildenafil or *N*-desmethysildenafil $t_{1/2}$ values.

Table 1

Subject demographics

Parameter	Treatment sequence 1 (n = 12)	Treatment sequence 2 (n = 12)
Age (years), median (range)	27.5 (21.0–47.0)	26.5 (19.0–50.0)
Male/female	10/2	11/1
Body mass index (kg m ⁻²), median (range)	25.0 (20.1–29.5)	26.1 (21.5–29.7)
White/Black or African-American	11/1	11/1

Table 2

Pharmacokinetic parameters for sitaxentan, and sildenafil and *N*-desmethysildenafil following administration of sildenafil 100 mg after either sitaxentan 100 mg or placebo for 7 days

Parameter*	Sitaxentan 100 mg*	Placebo*	Geometric mean ratio (%)†	90% CI
Sildenafil (n = 22)				
C_{max} (ng ml ⁻¹)	440 ± 232	377 ± 208	117.61	93.81, 147.46
AUC_{∞} (h ng ⁻¹ ml ⁻¹)	1648 ± 692	1295 ± 488	127.69	115.46, 141.22
$t_{1/2}$ (h)	2.82 ± 0.45	2.76 ± 0.45	–	–
T_{max} (h)‡	1.25	1.00	–	–
AUC_{0-t} (h ng ⁻¹ ml ⁻¹)	1575 ± 671	1222 ± 474	124.95	113.40, 137.68
<i>N</i>-desmethysildenafil (n = 22)				
C_{max} (ng ml ⁻¹)	104 ± 40.8	109 ± 53.1	100.70	82.72, 122.60
AUC_{∞} (h ng ⁻¹ ml ⁻¹)	425 ± 115	440 ± 112	105.78	96.21, 116.30
$t_{1/2}$ (h)	5.14 ± 2.13	5.13 ± 1.63	–	–
T_{max} (h)‡	1.00	1.00	–	–
AUC_{0-t} (h ng ⁻¹ ml ⁻¹)	389 ± 105	372 ± 107	112.43	98.50, 128.32
Sitaxentan (n = 22)				
C_{max} (µg ml ⁻¹)	10.2 ± 4.73			
AUC_{0-t} (h µg ⁻¹ ml ⁻¹)	25.2 ± 10.2			
$t_{1/2}$ (h)	8.42 ± 1.46			
T_{max} (h)‡	2.48			

*Values are expressed as arithmetic mean ± SD. †Statistical comparison of pharmacokinetic parameters between sitaxentan and placebo based on analysis of natural log-transformed data. ‡Median. AUC, area under the plasma concentration–time curve (AUC_{0-t} was calculated using the linear trapezoidal method where t is the time of last measurable concentration. $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + C_t/\lambda$); CI, confidence interval; C_{max} , maximum plasma concentration; $t_{1/2}$, elimination half-life; T_{max} , time to maximum plasma concentration.

Mean systolic and diastolic BPs were similar after concomitant dosing of sildenafil 100 mg with either sitaxentan 100 mg or placebo. The mean maximum positive (E_{max+}) and maximum negative (E_{max-}) changes from baseline in both systolic and diastolic BP were comparable for sitaxentan and placebo (range 4.8–7.3 mmHg), with three of four geometric mean ratios falling within the equivalence window. Mean average changes (E_{avg}) were very variable, ranging from –0.07 (± 6.00) to 0.86 (± 5.14) and 1.92 (± 5.18) to 0.65 (± 3.68) mmHg for systolic and diastolic BP, respectively.

A similar proportion of subjects reported AEs during dosing with sitaxentan 100 mg (39%) and with placebo (30%), with headache as the most common (26% subjects on sitaxentan and 30% on placebo, in all cases on day 7). No AEs were related to hypotension. There were no clinically significant changes in laboratory tests.

Discussion

Co-administration of sitaxentan increased sildenafil exposure slightly, probably due to the weak inhibition by sitaxentan of CYP3A4, the principal hepatic metabolic enzyme for sildenafil, but had no effect on *N*-desmethysildenafil exposure. The effect of sildenafil on sitaxentan PK was not examined, but steady-state sitaxentan plasma concentrations in the presence of sildenafil were similar to steady-state sitaxentan plasma concentrations from other PK

studies when sitaxentan was administered alone [3]. Given that there were no clinically relevant changes in BP and single oral doses of sildenafil are well tolerated up to 800 mg [4] the increased exposure to sildenafil should not be clinically relevant and no dose adjustment of either agent is required upon co-administration of sildenafil with sitaxentan.

In contrast, combining the nonselective endothelin receptor antagonist bosentan (125 mg day⁻¹) with sildenafil (20–80 mg) decreased sildenafil $C_{\max}$ by 55.4% (90% CI 40.3, 66.6); and conversely, after 6 days' co-administration, sildenafil increased bosentan $C_{\max}$ by 42.0% (90% CI 15.4, 74.8) [5, 6].

Competing interests

None to declare.

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