A Phase I study to assess the safety, tolerability and pharmacokinetic profile of boceprevir and sildenafil when dosed separately and together, in healthy male volunteers

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Objectives: Boceprevir is a first-generation direct-acting antiviral licensed for the treatment of hepatitis C infection. Sildenafil is an oral therapy for erectile dysfunction. As boceprevir is a potent inhibitor of CYP3A4, potential pharmacokinetic interactions may occur when it is coadministered with sildenafil. The aim of this study was to assess the pharmacokinetic profile of sildenafil and boceprevir when dosed separately and together in healthy volunteers.

Methods: Thirteen male subjects completed the following study procedures: phase 1 (Day 0), a single dose of 25 mg of sildenafil was administered; washout period (Days 1–9); phase 2 (Days 10–15), 800 mg of boceprevir three times a day was administered; and phase 3 (Day 16), 800 mg of boceprevir and 25 mg of sildenafil were administered. All drugs were administered in the fed state. Intensive pharmacokinetic sampling was undertaken on Days 0, 15 and 16. Differences in the pharmacokinetic parameters of sildenafil, N-desmethyl-sildenafil and boceprevir between phase 3 and the earlier phases were evaluated by changes in the geometric mean ratios (GMRs).

Results: All the drugs were well tolerated with no safety concerns arising. In the presence of boceprevir (phase 3 versus phase 1), the GMR for the plasma Cmax and the AUC24 for sildenafil increased by 1.9-fold (95% CI 1.5–2.4) and 2.7-fold (95% CI 2.1–3.4), respectively, whereas a reduction in the Cmax of N-desmethyl-sildenafil was observed (GMR 0.5, 95% CI 0.4–0.7). No significant changes in boceprevir exposure were observed between phases 3 and 2.

Conclusions: Exposure of sildenafil is increased in the presence of boceprevir. A dose adjustment of sildenafil is therefore necessary. An initial dose of 25 mg of sildenafil is suggested.

Keywords: PK, HCV, erectile dysfunction

Introduction

Several direct-acting antivirals (DAAs) have recently been approved for the treatment of hepatitis C virus (HCV) infection, including boceprevir, a PI recommended for the treatment of genotype-1 infection. Boceprevir is a potent, reversible inhibitor of the cytochrome P450 isoenzyme group (CYP450), and clinically relevant increases in the exposure of other drugs dependent on CYP450 have been observed when they are administered simultaneously.

As DAAs are used more widely, clinically relevant drug–drug interactions are likely to become apparent in patients receiving concomitant medication. Sildenafil, used for the management of erectile dysfunction, is metabolized via CYP450, and increases in plasma exposure have been described when it is administered with CYP450 inhibitors such as HIV PIs. Therefore, increased exposure of sildenafil would be expected when it is administered with boceprevir; however, the magnitude of this interaction is unknown and unpredicted pharmacokinetic interactions often occur. The aim of this study was to assess the pharmacokinetic interactions of sildenafil and boceprevir when administered separately and together.

Methods

Subject selection

Healthy male volunteers, aged 18–60 years, with no clinically significant abnormalities on screening laboratory testing and a BMI between 18 and 32 kg/m² were eligible to participate. Exclusion criteria included...
HIV-1 or HCV infection, current alcohol abuse, drug dependence, a positive urine test for drugs of abuse (InstAlert™; Innovcon Inc., San Diego, CA, USA) and the use of concomitant medication with potential drug–drug interactions.

This study was registered in the European Clinical Trials Database (EudraCT number 2011-000680-27) and national human ethics committee approval was granted prior to recruitment. All patients signed an informed consent before screening.

Study design and procedures

This Phase I pharmacokinetic study was conducted at Imperial College Healthcare NHS Trust (St Mary’s Hospital, London, UK) between December 2012 and June 2013.

During phase 1 (Day 0), a single dose of 25 mg of sildenafil (Viagra™) was administered and intensive pharmacokinetic sampling was undertaken (at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose). Days 1–9 were a washout with no medication allowed. During phase 2 (Days 10–15), subjects commenced 800 mg of boceprevir three times a day with food. On Day 15 at steady-state, witnessed dosing and intensive pharmacokinetic sampling over 8 h took place (at 0, 0.5, 1, 2, 3, 4, 6 and 8 h post-dose). During phase 3 (Day 16), subjects attended for witnessed dosing of 800 mg of boceprevir and a single dose of 25 mg of sildenafil (Viagra™). Intensive pharmacokinetic sampling was performed over a 24 h period (at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose). Subsequently, the study medication was stopped and the subjects attended a final follow-up visit. For safety monitoring, haematology and chemistry panels were undertaken throughout. A meal containing 20 g of fat was administered with all the witnessed doses.

A 25 mg dose of sildenafil (lower than the 50 mg or 100 mg generally used in clinical practice) was chosen for several reasons. First, this is the recommended dose when administered with CYP3A4 inhibitors. Second, given the unknown actual interactions between boceprevir and sildenafil, this dose was used in order to minimize potential adverse effects associated with excessively high peak concentrations. Finally, such an approach has been undertaken in similar pharmacokinetic studies.

Analytical methods

Plasma concentrations of the individual isomers SCH534128 and SCH534129 of boceprevir were determined (PPD Global Central Labs, Middleton, WI, USA) and summed to give total boceprevir (SCH503034) concentrations. Plasma concentrations of sildenafil and its main metabolite N-desmethyl-sildenafil were analysed by a validated HPLC–tandem MS method at the University of Liverpool (UK). The lower limits of quantification for boceprevir SCH534128, boceprevir SCH534129, sildenafil and N-desmethyl-sildenafil were 5.20, 4.80, 2.60 and 1.275 ng/mL, respectively. Inter- and intra-assay precision did not exceed 10% for any compound.

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters were calculated using non-compartmental methods (WinNonlin; Pharsight Corporation, Mountain View, CA, USA). The 95% CIs were constructed for the ratios of geometric means (GMs) of the AUC24 for sildenafil and N-desmethyl-sildenafil or the AUC0–24 for total boceprevir, the observed plasma concentration (Cmax) values, the T1/2 trough, defined as the concentration at 24 h after the observed dose for sildenafil and N-desmethyl-sildenafil or at 8 h after the observed dose for total boceprevir and the T1/2 (defined as the period of time required for the plasma drug concentration to be reduced by one-half from the Cmax). All statistical calculations were performed and analysed using SPSS (version 22.0; SPSS Inc., Chicago, IL, USA). Within-subject changes in the assessed pharmacokinetic parameters between phase 3 versus the earlier phase were evaluated by assessment of the GM ratios (GMRs) and corresponding 95% CIs. The CIs were determined using logarithms of the individual GM values; the calculated values were then expressed as linear values.

Table 1. Pharmacokinetic results (n=13)

<table>
<thead>
<tr>
<th></th>
<th>Phase 1: sildenafil single dose GM</th>
<th>Phase 2: boceprevir steady-state GM</th>
<th>Phase 3: sildenafil single dose+b-ceboprevir steady-state GM</th>
<th>GMR phase 3/earlier phase (95% CI)</th>
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<tbody>
<tr>
<td>Sildenafil</td>
<td></td>
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<td></td>
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<tr>
<td>T1/2 (h)</td>
<td>5.1 (4.3–6.1)</td>
<td>1.6 (1.2–2.3)</td>
<td>4.5 (3.9–5.2)</td>
<td>0.9 (0.7–1.1)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>79.9 (59.9–106.5)</td>
<td>356.8 (271.1–469.6)</td>
<td>150.9 (126.2–180.5)</td>
<td>1.9 (1.5–2.4)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>356.8 (271.1–469.6)</td>
<td>50</td>
<td>954.0 (801.4–1135.5)</td>
<td>2.7 (2.1–3.4)</td>
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<tr>
<td>AUC24 (ng.h/mL)</td>
<td></td>
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<td>N-desmethyl-sildenafil</td>
<td></td>
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<tr>
<td>T1/2 (h)</td>
<td>8.1 (7.2–9.2)</td>
<td>1.5 (1.1–2.0)</td>
<td>7.8 (6.7–9.0)</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>10.0 (7.9–12.6)</td>
<td>48.5 (39.1–60.0)</td>
<td>4.9 (3.7–6.6)</td>
<td>0.5 (0.4–0.7)</td>
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<tr>
<td>Cmax (ng/mL)</td>
<td>48.5 (39.1–60.0)</td>
<td>48.5 (39.1–60.0)</td>
<td>52.8 (42.1–66.3)</td>
<td>1.1 (0.9–1.3)</td>
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<tr>
<td>AUC24 (ng.h/mL)</td>
<td></td>
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<tr>
<td>Boceprevir</td>
<td></td>
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<tr>
<td>T1/2 (h)</td>
<td>1.3 (1.1–1.4)</td>
<td>1.3 (1.2–1.4)</td>
<td>1.3 (1.2–1.4)</td>
<td>1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.5 (2.2–2.9)</td>
<td>2.5 (2.2–2.9)</td>
<td>1.9 (1.3–2.7)</td>
<td>0.7 (0.5–1.04)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>3.0 (1276.1–1607.7)</td>
<td>1432.3 (1276.1–1607.7)</td>
<td>1440.5 (1211.7–1712.4)</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>Ctrough (ng/mL)</td>
<td>63.0 (42.0–94.4)</td>
<td>63.0 (42.0–94.4)</td>
<td>82.3 (55.4–122.2)</td>
<td>1.3 (0.97–1.7)</td>
</tr>
<tr>
<td>AUC8 (ng.h/mL)</td>
<td>4512.3 (3839.7–5302.7)</td>
<td></td>
<td>4842.8 (4117.2–5697.7)</td>
<td>1.1 (0.97–1.2)</td>
</tr>
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</table>
Interpatient variability in the pharmacokinetic parameters was expressed as a coefficient of variation (CV) [(standard deviation/mean) × 100].

**Results**

**Patient characteristics and drug tolerability**

Among the 13 subjects who completed all the study procedures, the ethnic origin was distributed as follows: six white (46%), four Asian (31%) and three black (23%) subjects. The median age was 36 years (range, 22–47 years) and the median BMI was 26.2 kg/m² (range, 19.9–30.6 kg/m²). Study medications were well tolerated and no safety or laboratory concerns were observed. All patients reported 100% adherence to the therapy.

**Plasma pharmacokinetic parameters over the study phases**

The pharmacokinetic profile parameters for total boceprevir, sildenafil and N-desmethyl-sildenafil are shown in Table 1. No significant changes in boceprevir exposure were observed between the study phases.

In the presence of boceprevir, the total exposure of sildenafil was increased by 2.7-fold (95% CI 2.1–3.4) and the $C_{\text{max}}$ was increased by 1.9-fold (95% CI 1.5–2.4). No changes in the elimination rate or $T_{\text{max}}$ for sildenafil were observed (Figure 1). A 50% reduction in the $C_{\text{max}}$ of N-desmethyl-sildenafil was observed with no significant changes in elimination rate or $T_{\text{max}}$. An increase in the ratio of the $C_{\text{max}}$ values of sildenafil to those of N-desmethyl-sildenafil was observed between phases 3 and 1 [8 (95% CI 6.3–10) and 30 (95% CI 23–41) in phase 1 versus phase 3, respectively].

**Discussion**

We assessed the pharmacokinetic interactions of sildenafil and boceprevir when administered together in healthy volunteers with no safety concerns observed.

An initial 25 mg oral dose of sildenafil was administered with no evidence of direct toxicity. The maximum plasma exposure of sildenafil observed was 279 ng/mL in phase 3. This is lower than the mean concentration observed after a single oral dose of 100 mg without enzyme-inhibiting drugs (~440 ng/mL). As we observed a 190% increase in the $C_{\text{max}}$ of sildenafil when it was administered with boceprevir, and assuming that the pharmacokinetic parameters were dose-proportional, one could expect $C_{\text{max}}$ values of approximately ~1110 ng/mL if the 100 mg dose of sildenafil was to be administered with boceprevir. Although there is not a clearly defined maximum tolerated exposure of sildenafil, oral doses of 200 mg achieving $C_{\text{max}}$ values of 1150 ng/mL have resulted in an increased frequency and intensity of adverse events.

Sildenafil and boceprevir were administered with food in all phases since the bioavailability of boceprevir depends greatly on its administration in the fed state. The absorption of sildenafil is slowed in the presence of food, resulting in the $C_{\text{max}}$ for sildenafil being reduced by 29%. Therefore, our observations, in particular the increase in plasma $C_{\text{max}}$, may underestimate these effects if sildenafil is administered without food, as often happens when treating erectile dysfunction. These findings suggest that 25 mg of sildenafil may be a suitable dose to commence in such subjects.

The increases in total plasma exposure (270%) and observed $C_{\text{max}}$ (190%) of sildenafil are similar in magnitude to the effects on sildenafil reported for other CYP3A4 inhibitors. The total plasma exposure of sildenafil has been shown to increase by 210% and 1110%, respectively, in the presence of the HIV PIs saquinavir and ritonavir. The main route of metabolism of sildenafil is via...
the CYP450 isoforms, predominantly CYP3A4 and to a lesser extent CYP2C9. Boceprevir is a strong inhibitor of CYP3A4/3A5 but does not inhibit CYP2C9. The increase in sildenafil exposure and plasma $C_{\text{max}}$ with no changes in absorption parameters ($T_{\text{max}}$) or elimination parameters ($t_{1/2}$) suggests the underlying mechanism to be a reduction in first-pass metabolism secondary to CYP3A4 inhibition by boceprevir. Since our study is limited by the assessment of pharmacokinetic parameters in healthy volunteers rather than HCV-infected individuals, this inhibition of CYP3A4 may occur in addition to a previously observed moderate reduction in CYP3A4 activity in HCV-infected patients receiving IFN/ribavirin therapy.\textsuperscript{13}

Interestingly, the exposure of N-desmethyl-sildenafil, the main metabolite of sildenafil, although unchanged, was reduced in proportion to the maximum sildenafil exposure. These results suggest the metabolic pathway for the production of the N-desmethyl-sildenafil metabolite is not solely through CYP3A4, and that there might be an involvement of other pathways that boceprevir may not have an effect on, such as CYP2C9.

Several other DAAs, such as telaprevir, paritaprevir/ritonavir and simeprevir, also affect the hepatic CYP450 isoenzyme group.\textsuperscript{14–16} As DAAs are increasingly used in HCV treatment, drug-drug interactions will continue to be of clinical relevance, and future work to assess such interactions remains imperative in order to maintain the safest approaches in clinical practice.

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Transparency declarations
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References