Pharmacokinetics of the co-administration of boceprevir and St John’s wort to male and female healthy volunteers

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Background: St John’s wort (SJW; Hypericum perforatum) induces CYP3A4 that is involved in the metabolism of the hepatitis C virus (HCV) protease inhibitor boceprevir. Reduced boceprevir exposure and efficacy would contribute to therapeutic failure and increase the risk for resistance development. Boceprevir is co-administered with interferon/ribavirin, and depression has been described frequently in patients undergoing HCV treatment. Patients may purchase over-the-counter herbals to manage depression, and knowing the interaction between SJW and boceprevir is desirable.

Methods: This Phase I, open-label, three-period, cross-over pharmacokinetic study enrolled healthy males and females who, following consent and screening procedures, were randomized to receive SJW on days 1–14, SJW plus boceprevir (SJW on days 22–35 and together on days 31–35) and boceprevir on days 52–56, separated by 7 day washout periods, or the same treatment in the opposite order. Pharmacokinetic sampling was performed at the end of each phase.

Results: Seventeen (11 female) subjects completed the study and no serious adverse events were reported. Geometric mean ratios (GMRs) and 90% CIs for boceprevir (with SJW versus alone) AUC0–8, Cmax and C8 were 0.91 (0.87–0.96), 0.94 (0.82–1.07) and 1.00 (0.79–1.27), respectively. GMRs and 90% CIs for hypericin, the active component of SJW, (with boceprevir versus alone) AUC0–8, Cmax and C8 were 1.23 (1.10–1.38), 1.32 (1.16–1.52) and 1.37 (1.19–1.58), respectively.

Conclusions: SJW did not have a clinically significant effect on boceprevir plasma concentrations (or those of its metabolite), suggesting that SJW and boceprevir can be safely co-administered.

Keywords: drug interactions, hepatitis C, depression

Introduction

St John’s wort (SJW; Hypericum perforatum) is commonly used for the treatment of mild to moderate depression in the Western world.1 SJW extracts contain a variety of chemical components, of which hypericin, pseudohypericin and hyperforin are pharmacologically active. SJW is a potent inducer of the transmembrane transporter P-glycoprotein (P-gp)3,4 and cytochrome P450-3A4 (CYP3A4) in the intestinal wall and liver,5 and has been shown to affect the plasma exposure of various drugs and significantly influence therapy outcomes.6,7 Boceprevir is an NS3 serine protease inhibitor approved for the treatment of chronic hepatitis C virus (HCV) genotype-1 infection, in combination with pegylated interferon-alfa and ribavirin.8 Boceprevir is orally administered three times daily and consists of a 1:1 mixture of two diastereomers: SCH534128, the active S-diastereomer, and SCH534129, the inactive R-diastereomer. These rapidly interconvert in vivo forming a 2:1 ratio in favour of SCH534128 at steady-state. It is primarily metabolized by aldo-keto reductases to form different inactive keto-reduced metabolites (SCH783007, SCH783005, SCH783006 and SCH783004; known collectively as SCH629144) and by CYP3A4.9 Boceprevir is a substrate of P-gp and an inhibitor of the organic anion uptake transporter 1B1 (OATP1B1).8

Importantly, although a formal study to investigate the effect of SJW on boceprevir plasma exposure has not been done, the US prescribing information for boceprevir recommends avoiding co-administration with SJW.10 SJW is bought over the counter with different brand names, and individuals undergoing treatment for chronic hepatitis C may purchase SJW and take it to relieve the symptoms of depression11 associated with interferon-alfa use12 (and for other reasons).
This Phase I study was performed to investigate the effect of steady-state SJW on the pharmacokinetics of boceprevir and vice versa.

Methods

Study design

This pharmacokinetic study was conducted in accordance with the Declaration of Helsinki (Ethics and United Kingdom Regulatory Authority approvals were obtained before study initiation; EudraCT 2009-018055-16).

The safety/tolerability of the study medications were evaluated throughout the study by vital signs measurements, physical examinations and clinical laboratory investigations.

Following written informed consent and screening, eligible subjects were given SJW for 14 days if randomized to group A (days 1–14) or boceprevir for 5 days if randomized to group B (days 10–14); on day 14 all individuals underwent a full pharmacokinetic drug assessment and then a 7 day washout period (days 15–21). On days 22–35 all individuals were given SJW, and on days 31–35 boceprevir was added; on day 35 all individuals underwent a full pharmacokinetic drug assessment and then a 7 day washout period (days 36–42). Finally, group A was given boceprevir on days 52–56 and group B was given SJW on days 43–56; the last pharmacokinetic drug assessment took place on day 56.

SJW was administered as two tablets of Ucald (300 mg of SJW extract per tablet) once daily and boceprevir at 800 mg three times daily. The dose of SJW studied is within those previously studied in formal pharmacokinetic studies and well above the doses that showed no effect on midazolam (a CYP3A4 substrate) metabolism.

On the full pharmacokinetic drug assessment days, blood samples were drawn pre-dose and (after a standard breakfast) 1, 2, 3, 4, 6 and 8 h post-dose.

Analytical methods

Concentrations of boceprevir were determined as the sum of concentrations of SCH534128 and SCH534129. The overall lower limit of quantification (LLOQ) of boceprevir was 4.8 ng/mL. The calibration ranges for SCH534128 and SCH534129 were from the LLOQ to 5200 and 4800 ng/mL, respectively. All boceprevir and metabolite plasma concentrations were determined using a validated method by HPLC–tandem mass spectrometry at PPD Global Central Labs (Middleton, WI, USA).

Plasma SJW concentrations, quantified as hypericin, were determined using a validated method by HPLC–tandem mass spectrometry at PPD Global Central Labs (Middleton, WI, USA). The LLOQ was 0.03 ng/mL. The intra-assay and inter-assay coefficients of variation were ≤15%.

Pharmacokinetic and statistical analysis

The calculated boceprevir pharmacokinetic parameters were the concentration measured 8 h after the observed dose (Cmax), the maximum concentration (Cmax, 8), and the area under the concentration–time curve from 0 to 8 h (AUC0–8). All parameters were calculated by non-compartmental modelling techniques (WinNonlin Phoenix, version 6.1; Pharsight Corp., Mountain View, CA, USA). Descriptive statistics, including geometric means (GMs) and 95% CIs, were calculated for all parameters.

Within-subject changes in drug concentrations (drug alone versus combination) were assessed by calculating GM ratios (GMRs) and 90% CIs. The CIs were first determined using logarithms of the individual GM values and then expressed as linear values. The changes in parameters were considered significant when the CI for the GMR did not cross the value of one.

Results

Demographic and clinical characteristics

Seventeen (11 female) subjects completed the study. Median (range) age and body mass index were 35 (26–49) years and 25.7 (19.1–34.8) kg/m2, respectively. Twelve individuals were Caucasian, three black and two defined themselves as ‘other’. The study drugs were well tolerated and no grade 3/4 adverse events or serious adverse events were reported.

Boceprevir pharmacokinetics

Boceprevir pharmacokinetic parameters in the absence and presence of SJW are illustrated in Table 1. Plasma steady-state boceprevir concentrations are shown in Figure 1(a).

The steady-state boceprevir AUC was 9% lower (90% CI for GMR: 0.87–0.96) in the presence of SJW. This was confirmed by calculating the active enantiomer (SCH534128) GMR and 90% CI (0.91, 0.86–0.96).

Table 1. Plasma pharmacokinetic parameters of steady-state boceprevir (BOC) and its active metabolite SCH534128 in the absence and presence of SJW, and of steady-state hypericin (the active ingredient of SJW) in the absence and presence of BOC

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>BOC</th>
<th>BOC + SJW</th>
<th>BOC + SJW versus BOC alone</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>1477 (1312–1833)</td>
<td>1385 (1222–1736)</td>
<td>0.94 (0.82–1.07)</td>
<td></td>
</tr>
<tr>
<td>C0, ng/mL</td>
<td>63 (53–87)</td>
<td>63 (51–97)</td>
<td>1.00 (0.79–1.26)</td>
<td></td>
</tr>
<tr>
<td>AUC0–8, ng·h/mL</td>
<td>4599 (4160–5317)</td>
<td>4204 (3795–4886)</td>
<td>0.91 (0.87–0.96)</td>
<td></td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>1001 (892–1228)</td>
<td>932 (829–1146)</td>
<td>0.93 (0.82–1.06)</td>
<td></td>
</tr>
<tr>
<td>C0, ng/mL</td>
<td>50 (42–66)</td>
<td>49 (60–72)</td>
<td>0.98 (0.79–1.22)</td>
<td></td>
</tr>
<tr>
<td>AUC0–8, ng·h/mL</td>
<td>3222 (2929–3687)</td>
<td>2935 (2653–3403)</td>
<td>0.91 (0.87–0.96)</td>
<td></td>
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hypericin

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>hypericin</th>
<th>hypericin + BOC</th>
<th>hypericin + BOC versus hypericin alone</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>2.2 (1.7–3.3)</td>
<td>2.9 (2.2–4.3)</td>
<td>1.32 (1.16–1.52)</td>
<td></td>
</tr>
<tr>
<td>C0, ng/mL</td>
<td>1.8 (1.4–2.8)</td>
<td>2.5 (2.1–3.5)</td>
<td>1.37 (1.19–1.58)</td>
<td></td>
</tr>
<tr>
<td>AUC0–8, ng·h/mL</td>
<td>11.6 (9.3–17.0)</td>
<td>14.3 (11.2–20.8)</td>
<td>1.23 (1.10–1.38)</td>
<td></td>
</tr>
</tbody>
</table>
The boceprevir AUCs observed were still within the range of those measured in HCV genotype-1-infected patients and associated with HCV RNA declines.9

**Hypericin pharmacokinetics**

Hypericin pharmacokinetic parameters in the absence and presence of boceprevir are illustrated in Table 1. Plasma steady-state hypericin concentrations are shown in Figure 1(b).

Boceprevir co-administration caused 23% (90% CI for GMR: 1.10–1.38), 32% (1.16–1.52) and 37% (1.19–1.58) increases in hypericin AUC, $C_{\text{max}}$, and $C_{\text{ss}}$, respectively.

**Discussion**

This study demonstrates that concomitant administration of SJW and boceprevir does not remarkably alter the pharmacokinetics of boceprevir (9% decrease in AUC) and increases hypericin $C_{\text{max}}$ by 32%.

Because of the common depression symptoms experienced by patients undergoing treatment for hepatitis C with peginterferon, ribavirin and nowadays boceprevir, and the possibility for these patients to self-medicate by purchasing SJW over the counter, this is important information for clinical practice.

The different active components of SJW (hypericin, hyperforin etc.) are known to be potent inducers of intestinal and hepatic...
P-gp and CYP3A4 via pregnane X receptor activation.\textsuperscript{15–17} As a consequence, several therapeutic agents’ summaries of product characteristics strongly recommend against SJW intake, even in the absence of formal pharmacokinetic data.

Boceprevir is mainly metabolized by aldo–keto reductases 1C3 and 1C2, and only partly by CYP3A4. This may explain why the co-administration of SJW did not lead to a remarkable alteration in boceprevir steady-state plasma exposure, and underlines the complexity of drug interactions involving agents metabolized by different metabolic pathways, especially in view of the fact that different CYP3A4 inducers, e.g. efavirenz, lead to a decrease in boceprevir exposure.\textsuperscript{9}

Hypericin exposure was moderately increased by boceprevir co-administration. This might be due to the inhibiting effect of boceprevir on CYP3A4 metabolism of hypericin. However, its metabolic pathway remains unclear and the clinical significance of a mild increase in hypericin $C_{\text{max}}$ is unknown.

Our data are very reassuring for clinical use, as SJW has been shown to decrease the concentrations of different antimicrobial drugs (e.g. indinavir\textsuperscript{18}) and its co-administration with numerous antibiotics or antivirals is contraindicated to avoid therapeutic failure.

One of the study limitations is that it was conducted in healthy volunteers, who may differ from HCV-infected individuals in terms of hepatic metabolic activity, drug absorption, protein binding etc., especially in the presence of hepatic impairment that leads to higher boceprevir concentrations.\textsuperscript{9,10} However, boceprevir pharmacokinetics do not seem to differ between healthy volunteers and HCV-infected individuals in the absence of hepatic impairment.\textsuperscript{9,10} Furthermore, we have chosen a commonly used brand of SJW, containing a relatively high and frequently self-administered dose of the drug. Nevertheless, different doses may be used in different countries and different formulations may contain different quantities of the active ingredients. As no significant impact of SJW intake on boceprevir exposure has been measured, suggesting the lack of a significant CYP3A4 involvement, it is unlikely that higher doses of SJW affect boceprevir pharmacokinetics.

We are not aware of a formal pharmacokinetic study of SJW with other currently approved HCV NS3/4A protease inhibitors (telaprevir and simeprevir), but their summaries of product characteristics list SJW co-administration as contraindicated.\textsuperscript{15,16} Telaprevir is mainly metabolized in the liver by CYP3A4 and aldo–keto reductase, but it is unclear which is the predominant metabolic pathway.\textsuperscript{10} The effect of SJW must be studied with every specific agent and type of IFN-\alpha.

In conclusion, co-administration of multiple doses of SJW did not have a clinically significant impact on boceprevir plasma exposure. Boceprevir increased hypericin $C_{\text{max}}$, by only $\sim$30\%, suggesting that SJW and boceprevir can be safely co-administered.

### Acknowledgements

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### Transparency declarations

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### References

Boceprevir and St John’s wort


