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Lack of a clinically significant drug–drug interaction in healthy volunteers between the HCV protease inhibitor boceprevir and the proton pump inhibitor omeprazole

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Objectives: Proton pump inhibitors (PPIs) can limit the solubility of concomitant drugs, which can lead to decreased absorption and exposure. Reduced efficacy can be a consequence and in the case of an antimicrobial agent this may contribute to development of resistance. Patients chronically infected with the hepatitis C virus can be treated with a boceprevir-containing regimen and it is relevant to know if interactions between PPIs and boceprevir exist. This study was designed to investigate the influence of a frequently used PPI, omeprazole, on the pharmacokinetics of boceprevir and vice versa.

Methods: In this open-label, three-period, randomized, cross-over, Phase I study, healthy subjects were randomly assigned to 40 mg of omeprazole once daily for 5 days, 800 mg of boceprevir three times daily for 5 days and 40 mg of omeprazole once daily+800 mg of boceprevir three times daily for 5 days, or the same treatment in a different order. Every treatment was followed by a wash-out period. At day 5 of every treatment pharmacokinetic blood sampling was performed for 8 h after medication intake. ClinicalTrials.gov: NCT01470690.

Results: All 24 subjects (15 males) completed the study and no serious adverse events were reported. Geometric mean ratios (90% CI) of the area under the plasma concentration–time curve up to 8 h (AUC_{0-8}) and maximum plasma concentration (C_{max}) of boceprevir with omeprazole versus boceprevir alone were 0.92 (0.87–0.97) and 0.94 (0.86–1.02), respectively. For omeprazole these values were 1.06 (0.90–1.25) for AUC_{0-8} and 1.03 (0.85–1.26) for C_{max} for the combination versus omeprazole alone.

Conclusions: Omeprazole did not have a clinically significant effect on boceprevir exposure, and boceprevir did not affect omeprazole exposure.

Keywords: drug interactions, pharmacokinetics, hepatitis C virus, PPIs

Introduction

Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide, as they are (self-)prescribed for several acid-related disorders. It is well known that they can affect the bioavailability of other drugs.[1] By their ability to increase the pH in the stomach, PPIs can limit the solubility of other drugs and hence lead to decreased absorption and lower plasma concentrations.[1] For example, PPIs decrease the absorption of some oral tyrosine kinase inhibitors (e.g. dasatinib and erlotinib),[2,3] various antifungal agents (e.g. ketoconazole, itraconazole and posaconazole),[4–7] mycophenolate mofetil[8,9] and a number of drugs used to treat HIV (e.g. rilpivirine, atazanavir, nelfinavir and indinavir).[10–15]

Boceprevir is an NS3 serine protease inhibitor that is approved for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection, in combination with pegylated interferon alfa and ribavirin.[16] Since PPIs are widely prescribed it is very likely that HCV-infected patients will use boceprevir and a PPI simultaneously. The effect of gastric pH elevation by a PPI on boceprevir

solubility and absorption is currently unknown. It is, however, relevant to know whether there is a drug–drug interaction that can significantly influence the bioavailability of boceprevir, in order to prevent inadequate exposure to boceprevir, which might lead to reduced efficacy or even resistance to this protease inhibitor. At the moment a pharmacokinetic drug–drug interaction study is lacking.

This pharmacokinetic study in healthy volunteers was performed in order to assess the effect of steady-state omeprazole, the prototype PPI, on the pharmacokinetics of boceprevir and vice versa, and to evaluate the safety and tolerability of the combination.

Methods

Study design

This open-label, three-period, randomized, cross-over, Phase I study was conducted from October to December 2011 at the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. The study was designed to determine the effect of multiple-dose omeprazole on the pharmacokinetics of boceprevir by intra-subject comparison. The secondary objective was to examine the effect of steady-state boceprevir on the pharmacokinetics of omeprazole, again by intra-subject comparison, and to study the safety of steady-state boceprevir combined with multiple-dose omeprazole.

Healthy volunteers were equally randomized to one of the following regimen sequences: ABC; ACB; BCA; BAC; CAB; or CBA. The regimens were: regimen A, 40 mg of omeprazole once daily for 5 consecutive days (omeprazole alone); regimen B, 800 mg of boceprevir three times daily (8 h intervals) for 4 consecutive days + a single dose of 800 mg on day 5 (boceprevir alone); and regimen C, 40 mg of omeprazole once daily for 5 consecutive days + 800 mg of boceprevir three times daily (8 h intervals) for 4 consecutive days + a single dose of 800 mg on day 5 (combination). Every treatment regimen was followed by a wash-out period of 9 days. After observed intake of the medication with a standardized breakfast at day 5 of every treatment period, blood samples for assessment of pharmacokinetic parameters were collected during an 8 h period.

Procedures

The study was approved by the Investigational Review Board of the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT01470690). An advertisement for the study was published in local newspapers and online. All participants signed informed consent prior to screening evaluations and received monetary compensation for their time. Subjects were admitted to the Clinical Research Centre Nijmegen for the pharmacokinetic study days.

Study population

Healthy male and female subjects between the ages of 18 and 55 years and with a body mass index (BMI) of 18–30 kg/m^2 (extremes included) were eligible for enrolment. Included participants had to be in a good, age-appropriate health condition as established by physical examination, medical history, electrocardiography and biochemical, haematological and urine analyses within 4 weeks prior to day 1. Main exclusion criteria were a history of sensitivity or idiosyncrasy to medicinal products or excipients, a positive HIV, hepatitis B virus or HCV test result or the use of any medication (for 2 weeks preceding dosing) except for acetaminophen. Other exclusion criteria were participation in another drug trial or blood donation within 60 days prior to day 1 of the study. Pregnant or breast-feeding females were also not eligible.

Study drug and dosing

Omeprazole (Losec®, AstraZeneca, Zoetermeer, The Netherlands) was administered as commonly used 40 mg enteric coated tablets. Omeprazole (with or without boceprevir) was taken between 08:00 h and 09:00 h with a breakfast. A treatment duration of five consecutive days was chosen to reach a maximally elevated gastric pH.[17] Subjects were not allowed to eat or drink acidic foods or beverages.

The approved dose of boceprevir (Victrelis®, Merck Sharp & Dohme Ltd, Hoddesdon, UK) is 800 mg every 8 h with food.[16] In this study, subjects took four capsules of 200 mg of boceprevir at approximately 08:00 h, 16:00 h and 0:00 h with a meal or snack.

On the pharmacokinetic sampling days the medication was taken at the trial site and the subjects consumed a standardized breakfast within 5 min prior to the dose. The breakfast consisted of two slices of wheat bread with butter [one slice with cheese and one with cervelat (cooked smoked sausage)] and one glass of milk (in total 291 kcal, 21% protein, 15% carbohydrate and 64% lipids).

Intake of medication at the clinical trial unit was supervised and recorded by the study personnel. Drug intake at home was monitored by the use of microelectronic monitoring system (MEMS) caps (Aardex Ltd, Zug, Switzerland), which record the opening of the medication bottle. The number of omeprazole tablets in the bottles and the weight of the bottles containing the boceprevir capsules were recorded on each visit day to assess adherence. Subjects were asked to write down the exact times of medication intake in a booklet. Additionally, blood samples were taken pre-dose on days 1 and 4 of every treatment period to measure plasma concentrations of omeprazole and boceprevir for determination of treatment adherence.

Pharmacokinetic sampling and safety assessments

Blood samples for assessment of pharmacokinetic parameters of boceprevir and omeprazole were collected during an 8 h period at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h after intake of the medication on day 5 of every treatment period. Blood samples for boceprevir were collected into pre-chilled potassium-EDTA-containing tubes and centrifuged for 15 min at 1500 **g** at 4°C within 30 min after blood collection. Plasma (1.5 mL) was transferred to pre-chilled cryovials containing 75 μL of 85% phosphoric acid, mixed with a vortex mixer and stored at ≤20°C within 1 h of sample collection.

Blood samples for omeprazole were collected into heparinized tubes and centrifuged for 5 min at 1900 **g** at 20°C. Plasma was transferred to polypropylene tubes and stored at −40°C until further bioanalysis.

Blood samples for serum biochemistry and haematology were taken on the day before every treatment period (day −1) and on day 4 of every treatment period. Screening for drugs of abuse in urine was carried out at day 5 of every treatment period. A pregnancy test was done by performing a human chorionic gonadotropin blood test in all females at screening and on the day before starting treatment. Subjects were asked about the presence of adverse events on each visit day.

Bioanalytical methods

Boceprevir (SCH 503034) is an approximately equal mixture of two diastereomers: SCH 534128, the active diastereomer, and SCH 534129, which is inactive. The predominant metabolic pathway produces inactive stereoisomers, together called SCH 629144.[18] Concentrations of boceprevir were determined as the sum of concentrations of the two diastereomers of boceprevir: SCH 534128 and SCH 534129. Concentrations of

SCH 629144 were obtained as the sum of concentrations of four analytes, namely, SCH 783004, SCH 783005, SCH 783006 and SCH 783007. The overall lower limit of quantification (LLOQ) was 0.0048 mg/L for boceprevir and 0.0025 mg/L for SCH 629144. The calibration range for SCH 534128, SCH 534129 and the four metabolites were from the LLOQ to 5.20, 4.80 and 2.50 mg/L, respectively. Concentrations of both diastereomers and their metabolites in collected plasma samples were determined using HPLC–tandem mass spectrometry at PPD Global Central Labs (Middleton, WI, USA).

Concentrations of omeprazole and its pharmacologically inactive metabolites, 5-hydroxyomeprazole and omeprazole sulfone, in plasma were analysed by use of a validated ultra-performance liquid chromatography (UPLC) method with tunable UV detection. Sample preparation consisted of liquid–liquid extraction by adding 50 μL of internal standard [phenacetine (400 μg/mL)] and 2.5 mL of methyl *tert*-butyl ether/dichloromethane (60:40; v/v) to 500 μL of plasma. The samples were shaken for 5 min at 1500 rpm, followed by centrifugation at 1910 **g** for 5 min. After freezing at −40°C for 5 min the organic supernatant was decanted and evaporated at 37°C under a stream of nitrogen gas. The residue was reconstituted in 200 μL of acetonitrile/10 mM phosphate buffer, pH 7.05 (25:75; v/v), washed with 1.5 mL of hexane and mixed on a vortex mixer for 5 min, followed by centrifugation at 1910 **g** for 5 min. Ten microlitres of the reconstituted solution was injected into an Acquity UPLC System. The mobile phases were (A) 10 mM phosphate buffer pH 7.05 and (B) acetonitrile/10 mM phosphate buffer pH 7.05 (65:35; v/v). Chromatographic separation was achieved on a BEH C18 column (1.7 μm, 100×2.1 mm) at a flow rate of 0.35 mL/min. Gradient run was programmed from 35% mobile phase B to 55% in 4.8 min. Omeprazole and its metabolites were detected by the use of a UV detector at 302 nm. The lower limit of quantification and detection limit was 0.0100 mg/L for omeprazole, 0.0028 mg/L for 5-hydroxyomeprazole and 0.0033 mg/L for omeprazole sulfone. The linear calibration ranges in plasma were from 0.010 to 3.03 mg/L for omeprazole, from 0.0028 to 2.75 mg/L for 5-hydroxyomeprazole and from 0.0033 to 3.32 mg/L for omeprazole sulfone. Validation results of the quality control samples showed an accuracy in the linear calibration range varying from 98.8% to 101.3% for omeprazole, from 97.5% to 106.3% for 5-hydroxyomeprazole and from 97.6% to 100.2% for omeprazole sulfone. In this concentration range, the intra-day precision (coefficient of variation) values varied from 1.9% to 4.3% for omeprazole, from 1.9% to 6.0% for 5-hydroxyomeprazole and from 1.7% to 4.7% for omeprazole sulfone. The inter-day precision (coefficient of variation) values were 0–2.6%, 0–2.4% and 0–2.8%, respectively. The omeprazole assay was performed at the laboratory of the Pharmacy Department of the Radboud University Nijmegen Medical Centre (Nijmegen, The Netherlands).

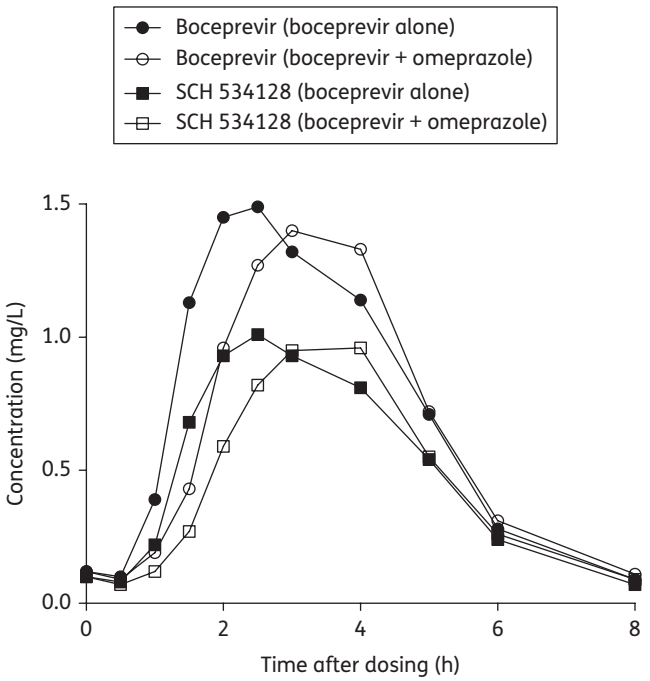

Figure 1. Geometric mean plasma concentrations of boceprevir (SCH 534128+SCH 534129) and the active diastereomer (SCH 534128) after multiple doses of 800 mg of boceprevir in the presence and absence of steady-state omeprazole.

Pharmacokinetic analysis

Based on the individual plasma concentration–time data, the following pharmacokinetic parameters of boceprevir (both diastereomers and metabolites) were determined: the AUC from 0 to 8 h after intake (AUC_{0-8}), the maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), the concentration at 8 h after intake (C_8), the bioavailability-adjusted volume of distribution (V/F), the apparent oral clearance (CL/F) and the apparent elimination half-life ($t_{1/2}$). $t_{1/2}$ was only calculated if there were two or more points (not including C_{max}) in the elimination phase of the plasma concentration–time curve with $r^2 > 0.80$.

For omeprazole and metabolites the same parameters were determined. All pharmacokinetic parameters were calculated by non-compartmental methods using the linear log trapezoidal rule.

Statistical analysis

The data obtained in this study were analysed according to an equivalence approach that is recommended for pharmacokinetic interaction studies.[19,20] The main pharmacokinetic parameter to be evaluated in this respect was the exposure to boceprevir, as expressed by AUC_{0-8}. The required sample size was calculated (power of 80%) assuming no difference in AUC_{0-8} of boceprevir with or without omeprazole and an intra-subject coefficient of variation of 22.5% of boceprevir AUCs. The required number of participants was 20. Taking dropouts into account, a total of 24 subjects were included in the study.

The geometric mean ratio estimates of all determined pharmacokinetic parameters of boceprevir (diastereomers and metabolites) with omeprazole versus boceprevir alone and for omeprazole (and metabolites) with versus without boceprevir, except for T_{max}, were calculated using mixed model analysis, with the Kenward–Roger approach for the evaluation of fixed effects. In addition, the non-parametric Wilcoxon signed rank test was used for T_{max} values between the two different regimens. Geometric mean ratio estimates with 90% CI entirely within the range of 0.80–1.25 were considered to indicate no significant interaction.

Statistical analyses were carried out using SPSS software version 16.0 or higher (SPSS Inc., Chicago, IL, USA, 1989–2007) and SAS 9.2. Descriptive pharmacokinetic statistics were calculated using WinNonlin version 5.3 (Pharsight Corporation, CA, USA).

Results

Baseline characteristics

Twenty-four healthy volunteers (15 males) were included in the study. Subjects were all of Caucasian ethnicity and the median (IQR) age and BMI were 31 (22–44) years and 23 (22–24) kg/m^2, respectively. The subjects were in good general health according to medical history, physical examination, vital signs and laboratory

data. All subjects completed the trial and were included in the demographic, safety and pharmacokinetic analyses.

Adherence

The adherence to both boceprevir and omeprazole treatment was good. Two subjects took omeprazole more than once per day during the combination treatment and one subject missed one dose of boceprevir during the boceprevir alone treatment. All other subjects took all doses of boceprevir and omeprazole according to pill count, diary, MEMS cap recordings and blood concentrations. Twelve subjects (one to four times/subject) took the dose of boceprevir (and/or omeprazole) outside a 2 h time frame (07:00–09:00 h/15:00–17:00 h/23:00–01:00 h). These deviations did not lead to exclusion of subjects from the analysis.

Pharmacokinetics

Pharmacokinetic parameters were calculated on all available data from the 24 subjects who were included in the trial. The plasma concentration–time curves of boceprevir and the active diastereomer SCH 534128 with and without omeprazole are shown in Figure 1. The pharmacokinetic parameters of boceprevir, both diastereomers and the metabolites together as SCH 629144, after intake of boceprevir alone or in combination with omeprazole, are given in Table 1. For boceprevir co-administered with omeprazole relative to boceprevir alone, the geometric mean ratio estimates (90% CI) of boceprevir AUC_{0-8} and C_{max} were 0.92 (0.87–0.97) and 0.94 (0.86–1.02), respectively. For the active diastereomer SCH 534128, the geometric mean ratio estimates (90% CI) of AUC_{0-8} and C_{max} were 0.91 (0.87–0.97) and 0.94 (0.86–1.02) when boceprevir was co-administered with omeprazole relative to boceprevir alone.

Table 1. Comparison of pharmacokinetic parameters of steady-state boceprevir with and without co-administration of multiple doses of omeprazole in healthy volunteers

	Boceprevir			Boceprevir + omeprazole			Boceprevir + omeprazole/boceprevir alone		
Pharmacokinetic parameter	*n*	GM	95% CI	*n*	GM	95% CI	*n*[a]	GM ratio estimate	90% CI
Boceprevir									
T_{max} (h)[b]	24	2.5	(1.5–5.0)	24	3.0	(2.0–5.0)	24		
C_{max} (mg/L)	24	1.78	(1.56–2.02)	24	1.66	(1.47–1.89)	24	0.94	(0.86–1.02)
AUC_{0-8} (mg · h/L)	24	5.34	(4.75–6.00)	24	4.89	(4.37–5.48)	24	0.92	(0.87–0.97)
C_8 (mg/L)	24	0.08	(0.07–0.10)	24	0.09	(0.07–0.12)	24	1.17	(0.97–1.42)[c]
V/F (L)	23	235.0	(207.0–266.9)	19	249.7	(218.9–285.0)	19	1.07	(0.95–1.20)
CL/F (L/h)	24	149.8	(133.3–168.4)	24	163.6	(146.0–183.2)	24	1.09	(1.03–1.15)
$t_{1/2}$ (h)	23	1.1	(1.0–1.2)	19	1.1	(1.0–1.2)	19	1.03	(0.95–1.12)
SCH 534128 (active)									
T_{max} (h)[b]	24	2.5	(1.5–5.0)	24	3.5	(2.0–5.0)	24		
C_{max} (mg/L)	24	1.17	(1.03–1.32)	24	1.14	(1.01–1.29)	24	0.94	(0.86–1.02)
AUC_{0-8} (mg · h/L)	24	3.73	(3.33–4.19)	24	3.46	(3.09–3.87)	24	0.91	(0.87–0.97)
C_8 (mg/L)	24	0.07	(0.05–0.08)	24	0.08	(0.06–0.10)	24	1.17	(0.97–1.42)[c]
$t_{1/2}$ (h)	23	1.1	(1.0–1.2)	19	1.1	(1.1–1.2)	19	1.02	(0.94–1.11)
SCH 534129 (inactive)									
T_{max} (h)[b]	24	2	(1.5–5.0)	24	2.7	(1.0–5.0)	24		
C_{max} (mg/L)	24	0.63	(0.54–0.73)	24	0.55	(0.47–0.63)	24	0.86	(0.78–0.96)[c]
AUC_{0-8} (mg · h/L)	24	1.59	(1.39–1.81)	24	1.42	(1.25–1.61)	24	0.89	(0.84–0.95)
C_8 (mg/L)	24	0.01	(0.01–0.02)	24	0.02	(0.01–0.02)	24	1.21	(0.94–1.55)[c]
$t_{1/2}$ (h)	23	1	(0.9–1.1)	18	1.1	(1.0–1.2)	18	1.13	(1.00–1.28)[c]
SCH 629144 (metabolites)									
T_{max} (h)[b]	24	4	(2.5–5.0)	24	4	(3.0–6.0)	24		
C_{max} (mg/L)	24	4.85	(4.22–5.57)	24	5.37	(4.76–6.06)	24	1.11	(1.00–1.23)
AUC_{0-8} (mg · h/L)	24	22.10	(19.06–25.63)	24	22.35	(19.61–25.46)	24	1.01	(0.92–1.11)
C_8 (mg/L)	24	1.35	(1.15–1.58)	24	1.70	(1.48–1.96)	24	1.27	(1.14–1.41)[c]
$t_{1/2}$ (h)	13	1.8	(1.7–1.9)	13	1.8	(1.6–2.1)	9	1.01	(0.89–1.14)

AUC_{0-8}, area under the plasma concentration–time curve up to 8 h after intake; C_{max}, maximum plasma concentration; T_{max}, time to reach C_{max}; C_8, concentration 8 h after intake; V/F, volume of distribution; CL/F, apparent oral clearance; $t_{1/2}$, elimination half-life; GM, geometric mean.

[a]The number of paired samples per parameter is given.

[b]For T_{max}, median + range is reported; the results of the Wilcoxon signed rank tests were $P = 0.013$ for boceprevir, $P = 0.006$ for SCH 534128, $P = 0.056$ for SCH 534129 and $P = 0.149$ for SCH 629144.

[c]GM ratio estimate for pharmacokinetic parameter is not bioequivalent with and without omeprazole.

The plasma concentration–time curves of omeprazole and the two metabolites 5-hydroxyomeprazole and omeprazole sulfone after administration of omeprazole alone and with boceprevir are shown in Figure 2(a and b), respectively. The pharmacokinetic parameters of omeprazole and the metabolites 5-hydroxyomeprazole and omeprazole sulfone, with and without boceprevir, are shown in Table 2. For omeprazole co-administered with boceprevir relative to omeprazole alone, the geometric mean ratio estimates (90% CI) of AUC_{0-8} and C_{max} were 1.06 (0.90–1.25) and 1.03 (0.85–1.26), respectively.

The geometric mean ratio estimate with 90% CI of the main pharmacokinetic parameter boceprevir AUC_{0-8} fell entirely within the range of 0.80–1.25, which indicates no significant interaction with omeprazole. The AUC_{0-8} of omeprazole also lay within these limits and therefore no influence of boceprevir on omeprazole exposure was found.

Bio-equivalence was also found or suggested for the other pharmacokinetic parameters of boceprevir, both diastereomers and their metabolites, as well as for all the parameters of omeprazole and its metabolite 5-hydroxyomeprazole. Only T_{max} was found to be statistical significantly later for boceprevir and the active diastereomer SCH 534128 when omeprazole and boceprevir were taken together compared with boceprevir alone. Inequivalence was also found in exposure to omeprazole sulfone. Concentrations of this metabolite, formed by CYP3A4, were lower in the presence of the CYP3A4 inhibitor boceprevir.

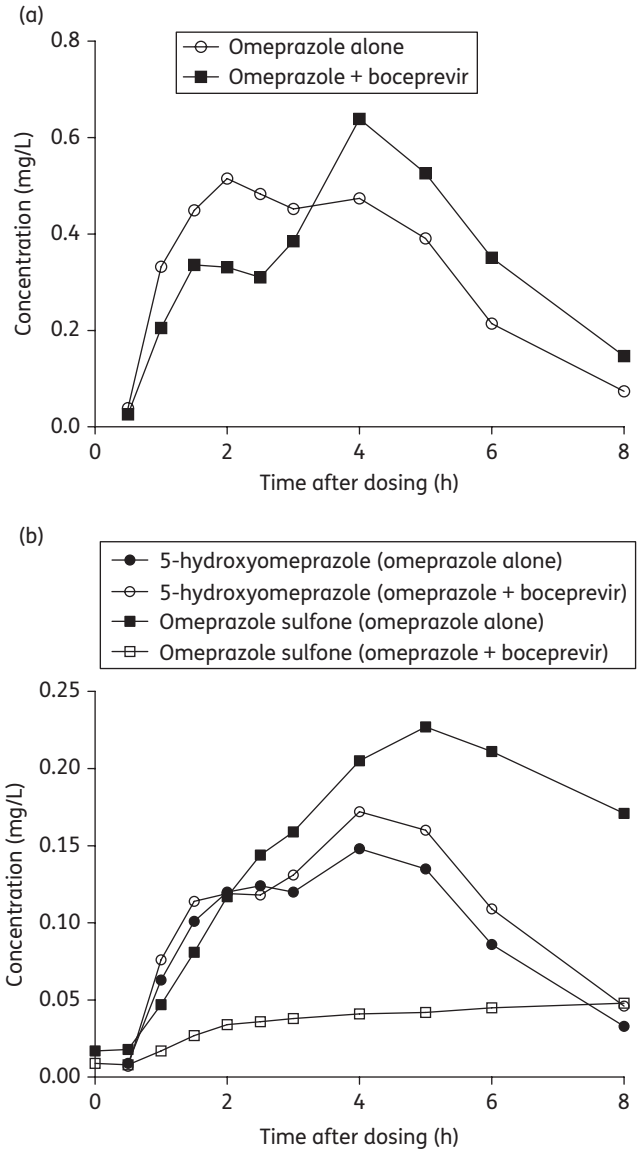

Figure 2. Geometric mean plasma concentrations of omeprazole (a) and 5-hydroxyomeprazole and omeprazole sulfone (b) at steady-state of 40 mg of omeprazole with and without multiple doses of 800 mg of boceprevir.

Adverse events and safety assessments

No serious adverse events were reported. In total 131 adverse events were reported by 22 subjects after intake of study medication. Most frequently reported adverse experiences that were possibly, probably or definitely drug related were dysgeusia ($n=21$ subjects), nausea ($n=7$), abdominal pain ($n=6$), headache ($n=5$), dry mouth ($n=4$), fatigue ($n=4$) and diarrhoea ($n=4$) (see Table S1, available as Supplementary data at *JAC* Online). All adverse events were grade 1 or 2 in intensity. No additional side effects were seen when omeprazole and boceprevir were co-administered.

Discussion

This study demonstrates that the concomitant intake of omeprazole and boceprevir does not influence the pharmacokinetics of either drug. Because omeprazole and other PPIs are widely prescribed, available as over-the-counter drugs and frequently used for long time periods, this is relevant information for clinical practice.

Boceprevir is to be administered with food as this increases its bioavailability substantially.[16,21] Administration without food is associated with a net loss of efficacy due to insufficient exposure.[21] In response to food ingestion, the stomach pH increases and gastric emptying is delayed.[22] For drugs with either pH-dependent solubility or poor aqueous solubility, postprandial changes in gastrointestinal pH and gastric emptying can influence the absorption of these drugs. Gastric pH is important for the solubility and thus absorption of weakly acidic or basic drugs. Boceprevir is a non-ionizable drug and its solubility is therefore not expected to be pH dependent,[23] which is confirmed by the results of this study.

Boceprevir is poorly soluble in water[23] and, in general, a slowing of gastric emptying can increase the absorption of poorly water-soluble drugs by increasing the time available for dissolution.[22] Although the T_{max} of boceprevir was slightly, but statistically significantly, delayed by adding omeprazole, this did not result in a changed C_{max} or AUC of boceprevir (Table 1).

Besides drug–drug interactions involving the absorption of medications, interactions can also occur on drug metabolism. Omeprazole is metabolized by CYP2C19 and CYP3A4 and known to inhibit CYP2C19 and, possibly, to induce CYP1A2.[1] Boceprevir is a potent inhibitor of CYP3A4/5 and is not metabolized by CYP1A2 or CYP2C19. Therefore, no interaction on the metabolism of boceprevir is expected. However, boceprevir inhibits the CYP3A4 metabolism route of omeprazole, resulting

Table 2. Comparison of pharmacokinetic parameters of steady-state omeprazole with and without co-administration of multiple doses of boceprevir in healthy volunteers

	Omeprazole			Omeprazole + boceprevir			Omeprazole + boceprevir/omeprazole alone		
Pharmacokinetic parameter	*n*	GM	95% CI	*n*	GM	95% CI	*n*[a]	GM ratio estimate	90% CI
Omeprazole									
T_{max} (h)[b]	24	3.5	(1.0–5.0)	24	4.0	(1.0–5.0)	24		
C_{max} (mg/L)	24	0.78	(0.61–0.98)	24	0.80	(0.64–1.01)	24	1.03	(0.85–1.26)[c]
AUC_{0-8} (mg · h/L)	24	1.98	(1.51–2.61)	24	2.10	(1.56–2.83)	24	1.06	(0.90–1.25)
C_8 (mg/L)	24	0.05	(0.03–0.08)	24	0.05	(0.03–0.10)	24	1.12	(0.75–1.67)[c]
V/F (L)	18	27.24	(22.57–32.87)	17	28.65	(24.38–33.68)	13	1.03	(0.92–1.16)
CL/F (L/h)	24	20.18	(15.33–26.57)	24	19.02	(14.14–25.58)	24	0.95	(0.81–1.11)
$t_{1/2}$ (h)	18	1.06	(0.89–1.26)	17	1.18	(0.92–1.53)	13	1.04	(0.91–1.19)
5-Hydroxyomeprazole									
T_{max} (h)[b]	24	3.5	(1.0–5.0)	24	3.0	(1.0–5.0)	24		
C_{max} (mg/L)	24	0.23	(0.19–0.27)	24	0.26	(0.23–0.30)	24	1.13	(1.01–1.27)[c]
AUC_{0-8} (mg · h/L)	24	0.70	(0.62–0.79)	24	0.82	(0.74–0.91)	24	1.16	(1.07–1.27)[c]
C_8 (mg/L)	23	0.03	(0.02–0.04)	24	0.04	(0.03–0.05)	23	1.25	(0.92–1.69)[c]
$t_{1/2}$ (h)	17	1.45	(1.23–1.71)	19	1.58	(1.29–1.94)	14	1.08	(0.97–1.19)
Omeprazole sulfone									
T_{max} (h)[b]	24	4.0	(2.5–8.0)	24	5.0	(2.0–8.2)	24		
C_{max} (mg/L)	24	0.21	(0.16–0.27)	24	0.04	(0.03–0.06)	24	0.19	(0.15–0.25)[c]
AUC_{0-8} (mg · h/L)	24	0.95	(0.69–1.31)	24	0.18	(0.11–0.28)	24	0.19	(0.14–0.26)[c]
C_8 (mg/L)	24	0.13	(0.09–0.18)	24	0.03	(0.02–0.04)	24	0.20	(0.16–0.25)[c]
$t_{1/2}$ (h)	13	4.03	(2.88–5.62)	7	3.19	(2.17–4.68)		not feasible	(*n* = 4)

AUC_{0-8}, area under the plasma concentration–time curve up to 8 h after intake; C_{max}, maximum plasma concentration; T_{max}, time to reach C_{max}; C_8, concentration 8 h after intake; V/F, volume of distribution; CL/F, apparent oral clearance; $t_{1/2}$, elimination half-life; GM, geometric mean.
[a]The number of paired samples per parameter is given.
[b]For T_{max}, median + range is reported; the results of the Wilcoxon signed rank tests were $P = 0.716$ for omeprazole, $P = 0.600$ for 5-hydroxyomeprazole and $P = 0.140$ for omeprazole sulfone.
[c]GM ratio estimate for pharmacokinetic parameter is not bioequivalent with and without boceprevir.

in formation of a smaller amount of the metabolite omeprazole sulfone. This led to somewhat higher concentrations of omeprazole itself and the 5-hydroxyomeprazole metabolite, although the increases were not statistically significant.

PPIs are often (self-)prescribed for many acid-related diseases as well as for the prevention of gastrointestinal bleeding. By specific inhibition of H^+/K^+-ATPase in gastric parietal cells, PPIs suppress gastric acid secretion and elevate intra-gastric pH. This increased pH can lead to reduced solubility of concomitantly administered drugs, resulting in lower plasma concentrations. This has been shown for several classes of currently used medications, including some oral tyrosine kinase inhibitors used in oncology,[2,3] various antifungal agents[4–7] and a number of drugs used in HIV treatment.[10–15] For example, the AUC_{24} of atazanavir was 62% lower when 300/100 mg of atazanavir/ritonavir was combined with 40 mg of omeprazole.[14] Another example is lower exposure to nelfinavir when 40 mg of omeprazole was administered 30 min before intake of nelfinavir. This resulted in a 36% lower AUC and a 39% lower C_{min} of nelfinavir.[24] As a consequence, reduced efficacy can be expected. In the case of lower exposure to antimicrobial drugs, besides treatment failures, the development of drug resistance is likely to occur. It would be very unfortunate if this were to happen with boceprevir as ~60%–70% of patients achieve a sustained virological response with triple therapy containing boceprevir, a percentage substantially higher than with dual therapy consisting of pegylated interferon alfa and ribavirin.[25,26]

This study was conducted in healthy volunteers, which can limit its interpretation in patients chronically infected with HCV. The pharmacokinetics of boceprevir are not different in HCV-positive or -negative patients, but in patients with hepatic impairment higher plasma concentrations of boceprevir are found.[16] It is, however, not likely that higher concentrations of boceprevir will affect the possibility of an interaction between boceprevir and omeprazole. Another limitation could be that we used a 40 mg dose of omeprazole, which is the highest approved dose for many indications.[27] Since no interactions occurred with the 40 mg dose, lower doses of omeprazole will probably also not affect the solubility and absorption of boceprevir. For a number of indications, e.g. in peptic ulcer bleeding, higher doses of omeprazole are used.[28] However, these higher doses of omeprazole are generally not used for long periods of time and therefore their influence, if any, on boceprevir absorption is not expected to be substantial.

For most indications omeprazole is administered every 24 h, but in this study omeprazole was sampled over only 8 h. We

chose to do so since no large influence of boceprevir on omeprazole pharmacokinetics was expected and the dosing interval and sampling time for boceprevir was 8 h.

In this study the PPI omeprazole was used. Although other PPIs with boceprevir have not been studied, they have a similar mechanism of action as they also strongly inhibit gastric acid secretion in the parietal cells of the stomach. Because of the physical and pharmaceutical properties of boceprevir and the absence of significant drug–drug interaction with omeprazole, it is very unlikely that other PPIs will reduce the solubility and absorption of boceprevir.

To our knowledge, no drug–drug interaction studies with boceprevir and histamine H2-antagonists or antacids have been performed. No interaction is expected based on their ability to increase intra-gastric pH, but interactions based on other mechanisms, e.g. CYP3A4 inhibition by cimetidine, can occur.

In conclusion, co-administration of multiple-dose omeprazole did not have a clinically significant affect on boceprevir exposure. Boceprevir did not meaningfully affect omeprazole exposure, but did cause a 5-fold decrease in the formation of the omeprazole sulfone (CYP3A4-mediated) metabolite. This reflects the known CYP3A4 inhibitory property of boceprevir. This did not lead to a clinically relevant increase in omeprazole or 5-hydroxyomeprazole levels.

Due to the absence of clinically significant drug–drug interaction, boceprevir and omeprazole can be safely combined. In the groups of healthy volunteers participating in this study, co-administration of boceprevir and omeprazole was well tolerated.

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D. M. B. has served as a speaker, a consultant or an advisory board member for Merck Sharp & Dohme BV. All other authors: none to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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