Pharmacokinetics and safety of the co-administration of the antiretroviral raltegravir and the lipid-lowering drug ezetimibe in healthy volunteers

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Received 22 September 2010; returned 23 November 2010; revised 1 December 2010; accepted 28 December 2010

Objectives: To assess the pharmacokinetics (PK) of raltegravir and ezetimibe when co-administered to healthy volunteers.

Methods: This was a prospective, open-label, crossover study, with subjects randomly assigned to group 1 (raltegravir 400 mg twice daily, raltegravir plus ezetimibe 10 mg once daily, wash-out period, ezetimibe) or group 2 (ezetimibe, raltegravir plus ezetimibe, wash-out period, raltegravir); all phases lasted for 10 days. Steady-state full PK sampling was performed at days 10, 20 and 40. Raltegravir and ezetimibe PK parameters were determined by non-compartmental methods and comparisons in the presence of the potentially interactive drug measured by geometric mean ratio (GMR) and 95% confidence intervals (CIs).

Results: Twenty subjects (10 females) completed the study. Raltegravir PK parameters did not change significantly in the presence of ezetimibe: GMRs (95% CI) were 1.16 (0.89–1.51) for AUC0–1 2, 1.13 (0.81–1.58) for maximum plasma concentration (Cmax) and 1.12 (0.72–1.74) for trough concentration (Ctrough). Ezetimibe AUC0–24 and Ctrough were lower in the presence of raltegravir [GMRs (95% CI) were 0.79 (0.68–0.91) for AUC0–24 and 0.78 (0.60–0.99) for Ctrough], while ezetimibe glucuronide Cmax was 40% higher (90% CI 1.17–1.66). There was marked inter-individual variability in the PK of the two drugs, especially during co-administration.

Conclusions: There were no significant changes in raltegravir PK parameters with or without ezetimibe. However, in the presence of raltegravir, ezetimibe AUC0–24 and Ctrough were significantly lower (>20%) and ezetimibe glucuronide Cmax was higher. Clinical data to assess the importance of the change in ezetimibe concentrations are warranted.

Keywords: PK, drug interactions, antivirals

Introduction

It is now clear that combination antiretroviral therapy (cART) has transformed the course of HIV infection, from a lethal illness to a chronic condition. Despite the benefits of cART on HIV-associated morbidity and mortality, its use is complicated by a number of factors such as adverse events, adherence challenges and drug–drug interactions.1

The increased life expectancy of HIV-infected individuals is leading to concerns about life-long toxicity of cART. The metabolic effects of some antiretrovirals in use are now becoming a major concern in patient care. The negative influence of such drugs on lipid profile leads to increased cardiovascular risk.

Therefore, when lifestyle changes and modification of cART fail to lower lipids to target values, lipid-lowering agents are co-prescribed with antiretrovirals to control this risk factor.1

The use of statins and fibrates is appropriate for the management of most cases of HIV-associated dyslipidaemia; however, it is not always fully effective. Therefore, the use of newer agents such as the cholesterol absorption inhibitor ezetimibe is increasing.1,3 Importantly, while drug interactions between statins and antiretrovirals have been studied, data on the interactions between ezetimibe and newer antiretrovirals that share the same metabolic pathways as ezetimibe, such as raltegravir, are lacking.

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RALTEGRAVIR AND EZETIMIBE IN HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Raltegravir has been recently approved for the treatment of HIV infection at a dose of 400 mg twice daily. So far, its use has shown several advantages, one of which is the low potential for drug–drug interaction. Uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT) 1A1 is the main enzyme responsible for the formation of raltegravir glucuronide and for the clearance of raltegravir in humans. Ezetimibe is available as 10 mg tablets. Ezetimibe is primarily metabolized in the liver and the small intestine via glucuronide conjugation by UGT1A1 (with some involvement of UGT1A3 and UGT2B15), with subsequent renal and biliary excretion. Both the parent compound and its active metabolite (ezetimibe glucuronide) are eliminated from plasma with a half-life of ezetimibe of ~22 h, allowing once-daily dosing. Importantly, ezetimibe has no effect on cytochrome P450 enzyme activity, suggesting a low potential for drug–drug interaction. However, whether drug–drug interactions occur when ezetimibe is co-administered with other glucuronidated drugs remains unclear.

Furthermore, the pharmacokinetics (PK) of ezetimibe have been shown to be influenced by intestinal efflux transporters and hepatic uptake transporters.

The primary objective of this study was to assess the steady-state PK of raltegravir and ezetimibe when co-administered. HIV-negative healthy volunteers were selected for this study in order to minimize the potential for the development of resistance, in the case of the occurrence of a significant drug–drug interaction between the two drugs, and preserve treatment options for HIV-infected patients.

Methods

Subjects

Male and non-pregnant, non-lactating female subjects were eligible for enrolment if they provided written informed consent and met the following criteria: age between 18 and 65 years; and body mass index (BMI) 18–35 kg/m².

Subjects were excluded if they had: any significant acute or chronic medical illness; abnormal physical examination; ECG or clinical laboratory determinations; positive screen for HIV, hepatitis B or hepatitis C; current or recent (within 3 months) gastrointestinal disease; clinically relevant alcohol or drug use that the investigator felt would adversely affect compliance with trial procedures; exposure to any investigational drug or placebo within 4 weeks of the first dose of study drug; use of any other drugs, including over-the-counter medications and herbal preparations, within 2 weeks prior to the first dose of study drug; and previous allergy to any of the constituents of the pharmaceuticals administered during the trial.

Study design

This was a 41 day, open-label, randomized, prospective, two-treatment arm, PK study conducted at the Pharmacokinetic Unit of the St Stephen’s Centre, Chelsea and Westminster Hospital, London, UK. The study protocol was reviewed and approved by the Brent Research Ethics Committee, UK. All subjects provided written informed consent and the trial was conducted in accordance with the Declaration of Helsinki, and applicable regulatory requirements (EudraCT 2007-003540-29).

Based on the wide inter-individual variability (60%) in drug PK shown in previous studies, 20 subjects completing the study will provide at least 90% power at a 5% significance level to conclude the presence of a significant interaction between the studied drugs.

At screening, subjects had a clinical assessment and routine laboratory investigations performed. The safety and tolerability of study medications were evaluated throughout the study using the NIAID Division of AIDS table for grading the severity of adult and paediatric adverse events to characterize abnormal findings (published December 2004), vital signs, physical examinations and clinical laboratory investigations.

Following successful screening, subjects were randomized 1:1 to group 1 or group 2. Subjects in group 1 were assigned to receive 400 mg of raltegravir orally twice daily for 10 days, followed by 10 days of 400 mg of raltegravir twice daily and 10 mg of ezetimibe orally once daily for 10 days, followed by a 10 day wash-out period and 10 mg of ezetimibe once daily for 10 days. Group 2 subjects received 10 mg of ezetimibe orally once daily for 10 days, followed by 10 mg of ezetimibe and 400 mg of raltegravir orally twice daily for 10 days, followed by a 10 day wash-out period and 400 mg of raltegravir twice daily for 10 days.

On days 10, 20 and 40, study drugs were administered within 15 min of completion of a standardized breakfast (orange juice, semi-skimmed milk and 50–100 g of cereal) and serial blood samples obtained at the following timepoints: pre-dose; and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 (raltegravir and ezetimibe) and 24 (ezetimibe only) h post-dose.

Analytical methods

Concentrations of raltegravir in plasma were measured by HPLC-tandem mass spectrometry substantially by the method described by Else et al. The method was validated according to FDA guidelines. Recovery of raltegravir was >90%; the lower limit of quantification was taken as the lowest point on the standard curve (1 ng/mL) and the upper limit of quantification was 2000 ng/mL. Intra-assay and inter-assay coefficients of variation at the low-, medium- and high-quality controls were <10%.

Concentrations of ezetimibe, and its active metabolite ezetimibe glucuronide, were determined using a new validated HPLC-single mass spectrometry assay. The method was validated according to FDA guidelines and UNI EN ISO 9001:2000 certification planning rules currently used in the certified laboratory of Turin, Italy (www.tdm-torino.org). The lower limits of quantification were taken as the lowest points on each standard curve (0.31 ng/mL for ezetimibe and 3.12 ng/mL for ezetimibe glucuronide) and the upper limits of quantification were 40 ng/mL for ezetimibe and 400 ng/mL for ezetimibe glucuronide. The recovery of each analyte was >90%. Intra-assay and inter-assay coefficients of variation for ezetimibe and ezetimibe glucuronide, at the low-, medium- and high-quality controls, were <11.9% and <12.4%, respectively.

PK and statistical analysis

Raltegravir and ezetimibe maximum plasma concentrations (Cmax) and trough concentrations (Ctrough) were derived. Area under the curve (AUC) from 0 to 12 and 0 to 24 h for raltegravir and ezetimibe, respectively, were calculated using WinNonLin version 5.2 (Mountain View, CA, USA), by a non-compartmental linear–linear trapezoidal method. Inter-individual variability in plasma concentrations was assessed by measuring the coefficient of variation (CV = standard deviation/mean × 100). Within-subject changes of drug concentration (drug alone versus drug combination) were assessed by calculating geometric means (GMs) and geometric mean ratios (GMRs) and 95% confidence intervals (CIs). The CIs were first determined using logarithms of the individual GMR values and then expressed as linear values. The changes in PK parameters were considered significant when the CI for the GMR did not cross the value of 1.
Results

Demographic and clinical characteristics

Twenty-three subjects signed the study informed consent and were screened, one had a positive illicit drug screen at baseline and two withdrew consent during the study period. Twenty subjects (12 in group 1 and 8 in group 2) completed all PK phases. Median (range) age, weight and BMI were 37 (21–62) years, 80 (50–115) kg and 26 (19–32) kg/m². Ten subjects were female; 15 were Caucasian, 2 were of Asian origin and 3 were Black.

The study drugs were well tolerated and no grade 3 or 4 adverse events were reported.

Raltegravir PK

Raltegravir PK parameters in the absence and presence of ezetimibe are shown in Table 1, and steady-state raltegravir concentrations are shown in Figure 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GM (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (ng/mL)</td>
<td>605.1 (430.6–1252.2)</td>
</tr>
<tr>
<td>C_trough (ng/mL)</td>
<td>24.1 (16.2–74.4)</td>
</tr>
<tr>
<td>AUC_0–24 (ng h/mL)</td>
<td>2264.1 (1895.1–3534.9)</td>
</tr>
<tr>
<td>GMR (95% CI)</td>
<td>1.13 (0.81–1.58)</td>
</tr>
</tbody>
</table>

Ezetimibe and ezetimibe glucuronide PK

Ezetimibe and its active metabolite PK parameters in the absence and presence of raltegravir are shown in Table 1, and steady-state concentrations of the two compounds are shown in Figure 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GM (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (ng/mL)</td>
<td>5.4 (4.8–8.3)</td>
</tr>
<tr>
<td>C_trough (ng/mL)</td>
<td>2.0 (1.8–3.3)</td>
</tr>
<tr>
<td>AUC_0–24 (ng h/mL)</td>
<td>71.2 (63.9–100.2)</td>
</tr>
<tr>
<td>GMR (95% CI)</td>
<td>0.90 (0.71–1.15)</td>
</tr>
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Discussion

We report here the steady-state PK of raltegravir, a recently approved integrase inhibitor for the treatment of HIV, and the cholesterol-lowering drug ezetimibe.

Raltegravir PK did not change in the presence of ezetimibe. Ezetimibe C_trough and AUC were lower during co-administration with raltegravir. Ezetimibe glucuronide C_max was increased by 40% in the presence of raltegravir but its C_trough and AUC were not affected.

Both raltegravir and ezetimibe and the co-administration of the two drugs were well tolerated without major adverse events being described.

Importantly, drug interactions involving antiretroviral agents are often not identified until after their approval for the treatment of HIV infection. Although the number of drug interaction studies during antiretroviral drug development phases has increased, Phase I trials, such as this one, are still conducted following drug approval in order to understand how new compounds may interact with drugs used to treat HIV-associated co-morbidities.

With raltegravir and ezetimibe administration to HIV-infected patients increasing, it is tempting to speculate that the PK changes (albeit relatively small) are due to the fact that both drugs are metabolized through glucuronidation by UGTs. Therefore, an interaction at the enzyme level during the absorption phase in either the intestine or the liver is possible.

However, the reason for the limited decrease in ezetimibe total exposure coupled with the increase in ezetimibe glucuronide C_max observed in the presence of raltegravir is difficult to explain.
determine since it would be necessary to infer that raltegravir is an inducer of UGTs; this has not been shown to date.11

Other major variables in the disposition of ezetimibe are the efflux transporter proteins P-glycoprotein (ABCB1) and multidrug resistance protein 2 (MRP2, ABCC2), and the hepatic uptake carrier OATP1B1 (organic anion transporting polypeptides).7,8 The 40% increase in ezetimibe glucuronide $C_{\text{max}}$ observed during co-medication with raltegravir suggests a significant influence of the latter on the clearance of ezetimibe glucuronide. This may be explained hypothetically by the inhibition of biliary efflux transporters or an effect on hepatic efflux. However, the evidence to date is that raltegravir has very limited impact on transmembrane transporters.12

Finally, wide inter-individual variability has been observed for both studied drugs, especially during co-administration. This could be due to various reasons including food intake prior to drug administration (as the variability of raltegravir concentrations is increased in the presence of food), genetic variability of UGTs and transmembrane transporters, and competition for binding to UGTs and transmembrane transporters.

In conclusion, HIV-infected individuals who have dyslipidaemia related to HIV infection and cART may benefit from cholesterol-lowering therapy with ezetimibe, a substrate of UGT. Since raltegravir is also a substrate of UGT1A1 we considered there was the potential for an adverse PK interaction. However, in this randomized, multiple-dose study in healthy volunteers, the interaction between raltegravir and ezetimibe did not seem to be of major clinical relevance. This should be confirmed by clinical data in HIV-infected patients, as the most common adverse events observed in individuals treated with ezetimibe monotherapy are diarrhoea, fatigue, upper respiratory tract infection and arthralgia.13 Whether these are correlated with ezetimibe or its active metabolite concentrations is uncertain and the clinical significance of the 40% increase in ezetimibe glucuronide $C_{\text{max}}$ is unclear.

**Figure 1.** (a) GM steady-state raltegravir plasma concentrations in the absence (diamonds) and in the presence (squares) of ezetimibe. GM steady-state ezetimibe (b) and ezetimibe glucuronide (c) plasma concentrations in the absence (diamonds) and in the presence (squares) of raltegravir.

**References**


**Acknowledgements**

Some of the results of this study were presented at the Tenth International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam, The Netherlands, 2009, Abstract P25.

We would like to thank the St Stephen’s AIDS Trust Research Team for their hard work and the volunteers who took part in the study.

**Funding**

This work was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck. Funding support was also provided by the St Stephen’s AIDS Trust.

**Transparency declarations**

A. J., S. B., D. B., B. G., G. M. and M. B. have received travel and research grants from and have been advisers for Tibotec, Roche, Pfizer, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp & Dohme, Abbott and Boehringer Ingelheim. All other authors: none to declare.

**Disclaimer**

The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck.
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