The Journal of Clinical Pharmacology

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J. Clin. Pharmacol. 2009; 49; 1220 originally published online Aug 28, 2009;
DOI: 10.1177/0091270009345689

The online version of this article can be found at:
http://www.jclinpharm.org/cgi/content/abstract/49/10/1220

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The Effect of Raltegravir on the Glucuronidation of Lamotrigine

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The authors studied the effect of raltegravir on the pharmacokinetics of the antiepileptic agent lamotrigine. Twelve healthy volunteers (group A) received 400 mg raltegravir twice daily from days 1 to 5. On day 4, a single dose of 100 mg lamotrigine was administered. After a washout period, participants received a second single dose of 100 mg of lamotrigine but now without raltegravir (day 32). In group B, 12 participants received the same treatment as in group A but in reverse order. On days 4 and 32, 48-hour pharmacokinetic curves were drawn. Geometric mean ratios (+90% confidence intervals [CIs]) of lamotrigine area under the plasma concentration-time curve ($AUC_{0\rightarrow48}$) and peak plasma concentration (C_{max}) for raltegravir + lamotrigine versus lamotrigine alone were 0.99 (0.96-1.01) and 0.94 (0.89-0.99), respectively. The mean ratio of the $AUC_{0\rightarrow48}$ of lamotrigine-2N-glucuronide to lamotrigine was similar when lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36). Raltegravir does not influence the glucuronidation of lamotrigine.

Keywords: *Drug-drug interactions; raltegravir; glucuronidation; lamotrigine*

Journal of Clinical Pharmacology, 2009;49:1220-1227

Raltegravir is a newly developed antiretroviral drug that acts by targeting the HIV-1 integrase, thereby preventing the integration of HIV-DNA into the genome of the human host cell. Raltegravir has demonstrated potent antiretroviral efficacy and is generally well tolerated.[1,2] Raltegravir is metabolized in the liver by UDP-glucuronosyltransferase 1A1 (UGT1A1). As a consequence, its pharmacokinetics can be influenced by inhibitors (eg, atazanavir) or inducers (eg, etravirine, tipranavir, rifampicin) of UGT1A1.[3-6]

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DOI: 10.1177/0091270009345689

In contrast to protease inhibitors and nonnucleoside transcriptase inhibitors, raltegravir does not inhibit or induce cytochrome P_{450} (CYP_{450}) enzymes.[7] Limited data are available on the influence of raltegravir on substances that share raltegravir's metabolic pathway: glucuronidation. In vitro studies suggest that raltegravir does not potently inhibit (IC_{50} >50 μM) UGT1A1 and UGT2B7 enzymes.[8] However, other UGT subenzymes, such as UGT1A4, have not been evaluated, and there are no clinical studies that support the in vitro data.

An example of a UGT-substrate that may be prescribed to HIV-infected patients is the antiepileptic agent lamotrigine, which is hepatically metabolized to lamotrigine-2N-glucuronide.[9] Lamotrigine is one of the recommended antiepileptic agents for the management of seizures in HIV-infected patients.[10] Seizures are not rare in HIV-infected patients: retrospective studies indicate that 2% to 20% of the HIV-infected patients will have seizures at some time during their illness.[11] In addition, lamotrigine is one of the few drugs with proven efficacy in the treatment of HIV-associated neuropathic pain.[12]

In previous studies, we demonstrated that lopinavir/ritonavir reduces plasma exposure to lamotrigine by

approximately 50%.[13] The combination of atazanavir/ritonavir is also able to induce glucuronidation of lamotrigine as demonstrated in a subsequent trial.[14] The decrease in lamotrigine exposure (32%), however, was less pronounced as with lopinavir/ritonavir; in addition, this trial showed that atazanavir alone did not influence lamotrigine pharmacokinetics, suggesting that the effect from atazanavir/ritonavir is mainly caused by ritonavir.

These 2 trials demonstrate that the conversion of lamotrigine to lamotrigine-2N-glucuronide is an appropriate marker to evaluate the effect of concomitant medications on the glucuronidation of lamotrigine. Given the unknown effect of raltegravir on the glucuronidation of UGT-substrates in vivo, we studied the effect of raltegravir on the pharmacokinetics of lamotrigine.

METHODS

Study Design

This open-label, randomized, 2-period, crossover, single-center, phase I, multiple-dose trial was conducted in March and April 2008 at the Radboud University Nijmegen Medical Centre (Nijmegen, The Netherlands). The study was designed to investigate the effect of raltegravir on the pharmacokinetics of lamotrigine and lamotrigine-2N-glucuronide as determined by intrasubject comparison. Secondary objectives were to assess the effect of lamotrigine on the pharmacokinetics of raltegravir when compared to historical controls and to evaluate the safety of the combined use of lamotrigine and raltegravir.

Twenty-four male participants were randomized to either group A or group B. In group A, 12 participants received 10 oral doses of 400 mg raltegravir twice daily (BD) during the first period of 5 days. On day 4 (together with the seventh dose of raltegravir), a single dose of 100 mg lamotrigine was administered. After a washout period of 26 days (study days 6-31), all participants received a second single dose of 100 mg lamotrigine (day 32). In group B, 12 participants received the same treatments in reverse order.

The trial was approved by the Review Board of the Radboud University Nijmegen Medical Centre.

Study Population

The trial was conducted in healthy young men aged between 18 and 55 years on the day of first dosing. For inclusion in the trial, participants had to be in a good, age-appropriate health condition as established by physical examination, medical history, electrocardiography, and biochemical, hematologic, and urinalysis testing within 4 weeks before the first dose. Participants had to be able and willing to sign the informed consent form before screening evaluations. The main exclusion criteria were as follows: a history of sensitivity or idiosyncrasy to medicinal products or excipients, a positive HIV or hepatitis B or C test result, and therapy with any drug (for 2 weeks preceding dosing), except for acetaminophen.

Study Drug and Dosing

The raltegravir dosage that was used in this trial (400 mg twice daily with or without food) is the recommended dosage for raltegravir.[8,15] At the days of pharmacokinetic sampling, both raltegravir and lamotrigine were taken on an empty stomach because at the time of study design, available data on raltegravir pharmacokinetics were obtained in the absence of food.[5] Fasting (no food, no fluid) was continued until 2 hours after dosing, followed by a standardized breakfast. Previous work demonstrated that steady-state conditions for raltegravir are present after 2 to 3 days of chronic dosing.[16] Therefore, the single dose of lamotrigine was administered on the fourth day of raltegravir administration. We used single doses of lamotrigine to minimize the risk of rash.[13,14]

Safety Assessments and Pharmacokinetic Sampling

Blood samples for pharmacokinetics were collected throughout a 48-hour period (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 24, and 48 hours) after dosing on days 4 and 32 for lamotrigine and lamotrigine-2N-glucuronide to characterize drug absorption, distribution, and elimination. Blood samples for pharmacokinetics of raltegravir were collected during an 8-hour period (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours) after dosing raltegravir on day 4 (group A) or day 32 (group B). In addition, blood samples were collected to determine trough levels of raltegravir, just before intake of the drug on days 1, 2, and 4 (group A) or days 29, 30, and 32 (group B).

Serum biochemistry and hematology test results were checked on days 1, 2, 4, 6, 29, 30, 32, and 34. Adverse events were assessed during the same visits and on days 5 and 33. Screening for drugs of abuse was performed in urine on days 1 and 29; urinalysis was carried out on days 4 and 32.

Compliance

Study personnel supervised all intake of medication at the clinical trial unit. The exact times of dosing were recorded. Drug intake at home was monitored by use of microelectronic monitoring system (MEMS) caps (Aardex Ltd, Zug, Switzerland), which records the opening of the medication bottle. Furthermore, pill counts and trough-level measurements at days 2, 4, 30, and 32 were used to assess adherence. Finally, participants were asked to write down the exact times of medication intake in a booklet.

Bioanalysis of Raltegravir, Lamotrigine, and Lamotrigine-2N-Glucuronide in Plasma

Plasma concentrations of lamotrigine and lamotrigine-2N-glucuronide were analyzed by use of a validated reversed-phase high-performance liquid chromatography (HPLC) method.[13] The accuracy values for lamotrigine were 103%, 103%, and 104% for concentrations of 0.358, 1.79, and 11.94 mg/L, respectively. At these same concentrations, the precision values (within day, coefficient of variation) were 2.34%, 1.82%, and 1.87%, respectively. For lamotrigine-2N-glucururonide, the accuracy values were 99%, 100%, and 99% at concentrations of 0.218, 1.09, and 7.25 mg/L, respectively. The precision values (within day, coefficient of variation) were 4.08%, 2.43%, and 1.06%, respectively, for the same concentrations.

Plasma concentrations of raltegravir were analyzed by means of liquid-liquid extraction followed by reversed-phase HPLC with fluorescence detection. In brief, to 500 µL of plasma was added 500 µL acetate buffer (pH 4.0, 0.2 M), 5 mL hexane/dichloromethane 1:1 (v/v), and 50 µL of internal standard (lormetazepam in methanol/water 1:1 [v/v]). The sample was mixed on a vortex mixer for 5 minutes, followed by centrifugation at 11 000 rpm for 5 minutes. Afterwards, the organic phase was evaporated at 37°C under a gentle stream of nitrogen gas and reconstituted in 200 µL of eluens (acetonitrile/phosphate buffer [pH 4.80, 20 mM] [35:65 v/v]). Then, 40 µL of the resulting solution was run on a 10-cm SymmetryShield reversed-phase C18 column (flow rate 1.5 mL/min), and raltegravir was detected by use of a fluorescence detector ($\lambda_{excitation}$ 240 nm, $\lambda_{emission}$ 412 nm).

The accuracy values for raltegravir were 99%, 101%, and 97% at 0.050, 0.140, and 0.500 mg/L, respectively. At the same concentrations, the precision values (within day, coefficient of variation) were 2.4%, 2.5%, and 1.9%, respectively. The calibration curve was linear over a concentration range of 0.014 to 1.40 mg/L.

Pharmacokinetic Analysis

Pharmacokinetic parameters for lamotrigine, lamotrigine-2N-glucuronide, and raltegravir were calculated by noncompartmental methods using the WinNonlin software package (Version 4.1; Pharsight, Mountain View, California) and the log-linear trapezoidal rule. Based on the individual plasma concentration-time data, the following pharmacokinetic parameters of lamotrigine were determined: the area under the plasma concentration-time curve from 0 to 48 hours after intake ($AUC_{0\rightarrow48}$; in h·mg/L), the maximum plasma concentration of the drug (C_{max}; in mg/L), the time to reach C_{max} (t_{max}; in hours), and the apparent elimination half-life ($t_{1/2}$; in hours). For raltegravir, the same pharmacokinetic parameters were calculated. To be able to compare raltegravir AUC with historical data, we calculated steady-state $AUC_{0\rightarrow12}$ by extrapolation to 12 hours.

Sample Size and Statistical Analysis

The study was powered to detect a 20% difference in lamotrigine AUC. In our previous single-dose lamotrigine trial, the intersubject coefficient of variation in lamotrigine AUC was 22.2%.[14] With a conservative approach, we assumed intrasubject variability to be equal to intersubject variability, and we calculated the required number of participants as 20. With an estimated dropout rate of 15%, 24 participants were included in the trial to ensure complete data from 20 participants.

For the identification of a clinically relevant drug interaction, we used the bioequivalence approach.[17] Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) were calculated for $AUC_{0\rightarrow48}$, C_{max}, and $t_{1/2}$ after log transformation of within-subject ratios. GMRs with 90% CIs falling entirely within the range of 0.80 to 1.25 were considered to indicate no significant interaction.

We calculated AUC ratios of lamotrigine-2N-glucuronide versus lamotrigine obtained by use of lamotrigine alone and by use of lamotrigine in combination with raltegravir to determine the effect of raltegravir on the glucuronidation of lamotrigine. To check whether autoinduction of lamotrigine metabolism might have influenced our results, we also compared the AUC ratios of lamotrigine-2N-glucuronide and lamotrigine in participants who took lamotrigine alone on day 32 (group A) to those obtained in participants who took lamotrigine alone on day 4 (group B).

Statistical evaluations were carried out using SPSS for Windows, Version 16.0.1 (SPSS, Chicago, Illinois, 1989-2005).

RESULTS

Baseline Characteristics

Twenty-four healthy male participants were included in this trial. The mean (range) age, body weight, and body mass index were 34 (20-52) years, 79 (63-94) kg, and 24 (20-28) kg/m^2, respectively. There was 1 black participant and 1 Hispanic participant; the other participants were white. There were no dropouts: all participants completed the trial and were available for statistical analyses.

Compliance

The compliance of all 24 participants was good, as indicated by their statements about the intake of the drug doses, the number of tablets in the returned vials, the raltegravir trough concentrations, the booklets, and the MEMS caps (data not shown).

Pharmacokinetics

All included participants completed day 34 of the trial and were included for statistical evaluation. Figure 1 shows the lamotrigine and lamotrigine-2N-glucuronide plasma concentration versus time curves obtained in the presence and absence of steady-state raltegravir. The mean pharmacokinetic parameters of lamotrigine are shown in Table I. Raltegravir did not appear to influence the pharmacokinetics of single-dose lamotrigine. The geometric mean ratios of lamotrigine $AUC_{0\rightarrow48}$, C_{max}, and $t_{1/2}$ for lamotrigine + raltegravir versus lamotrigine alone were all close to 1.0, and the corresponding 90% CIs were within the predefined interval of 0.80 to 1.25, indicating no interaction occurred (see Table I). In agreement with this observation, the mean (SD) ratio of the $AUC_{0\rightarrow48}$ of lamotrigine-2N-glucuronide/lamotrigine was similar when lamotrigine was taken alone or when taken with raltegravir. The geometric mean (95% CI) $AUC_{0\rightarrow48}$ of lamotrigine-2N-glucuronide was 11.0 (10.1-12.0) h·mg/L after intake of 100 mg lamotrigine alone, leading to a mean (SD) AUC ratio of metabolite versus parent compound of 0.35 (0.08). The mean (SD) ratio was 0.36 (0.10) when lamotrigine was taken in the presence of steady-state raltegravir (P = .35, paired samples t test).

The mean (SD) AUC ratios of lamotrigine-2N-glucuronide versus lamotrigine were 0.37 (0.07) and 0.32 (0.08) in participants who took lamotrigine alone on day 4 and day 32, respectively (P = .16, independent samples t test), indicating no period effect occurred. In addition, the elimination half-life of lamotrigine was not significantly different in participants who took lamotrigine alone on day 4 versus on day 32: the mean elimination half-lives were 37.0 and 36.0 hours, respectively (P = .83, independent samples t test).

The arithmetic mean plasma raltegravir concentration-time curve following administration of raltegravir with lamotrigine is shown in Figure 2. One participant was excluded from the pharmacokinetic analyses of raltegravir because raltegravir's half-life and thus $AUC_{0\rightarrow12}$ could not be determined reliably. The geometric mean of the $AUC_{0\rightarrow8}$ of raltegravir was 3.70 h·mg/L. Extrapolation in WinNonlin to the $AUC_{0\rightarrow12}$ resulted in a slightly higher (4.6%) geometric mean: 3.87 h·mg/L. The pharmacokinetic parameters of raltegravir, which are presented in Table II, were similar to those of historical controls.[6,18]

Raltegravir pharmacokinetics displayed large interindividual variability: the coefficient of variation (CV) for raltegravir $AUC_{0\rightarrow8}$ was 77%. In addition, we observed that steady-state raltegravir trough levels in the morning were 3 to 4 times higher than raltegravir levels obtained 8 hours after dosing (see Figure 2).

Adverse Events and Safety Assessments

Study medication was generally well tolerated. Thirteen participants reported a total of 37 nonserious adverse events. The majority of these events (n = 25, 68%) were classified as grade I; the remaining 12 events were classified as grade II (n = 11, 30%) or grade III (n = 1, 3%).

Three adverse events were considered possibly or probably drug related. One participant reported transient nausea on the first day of raltegravir administration, which disappeared within 6 hours without need of additional treatment. The other 2 adverse events were reported in 1 participant who developed a grade III aspartate aminotransferase (AST) elevation (385 U/L) and a grade II alanine aminotransferase (ALT) elevation (101 U/L) on day 6, following 5 days of raltegravir administration. The participant reported no complaints, and ALT and AST values returned to normal values within 10 days.

DISCUSSION

The primary objective of this study was to determine the effect of raltegravir on the pharmacokinetics of single-dose lamotrigine. The lamotrigine pharmacokinetics clearly met the

Table I Comparison of Lamotrigine Pharmacokinetics Following Administration of a Single Dose of 100 mg Lamotrigine in the Presence or Absence of Coadministration of Multiple Doses of 400 mg Raltegravir Twice Daily to Healthy Male Participants

	Lamotrigine Alone	Lamotrigine + Raltegravir	Lamotrigine + Raltegravir: Lamotrigine Alone
Pharmacokinetic Parameter	**Geometric Mean (95% CI)**	**Geometric Mean (95% CI)**	**GMR (90% CI)**
$AUC_{0\rightarrow48}$, h·mg/L	33.1 (31.3, 35.0)	32.6 (30.7, 34.7)	0.99 (0.96, 1.01)
C_{max}, mg/L	1.28 (1.20, 1.37)	1.20 (1.13, 1.28)	0.94 (0.89, 0.99)
$t_{1/2}$, h	35.0 (31.0, 39.5)	36.0 (31.9, 40.7)	1.03 (0.97, 1.09)

AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration; $t_{1/2}$, elimination half-life; GMR, geometric mean ratio; CI, confidence interval.

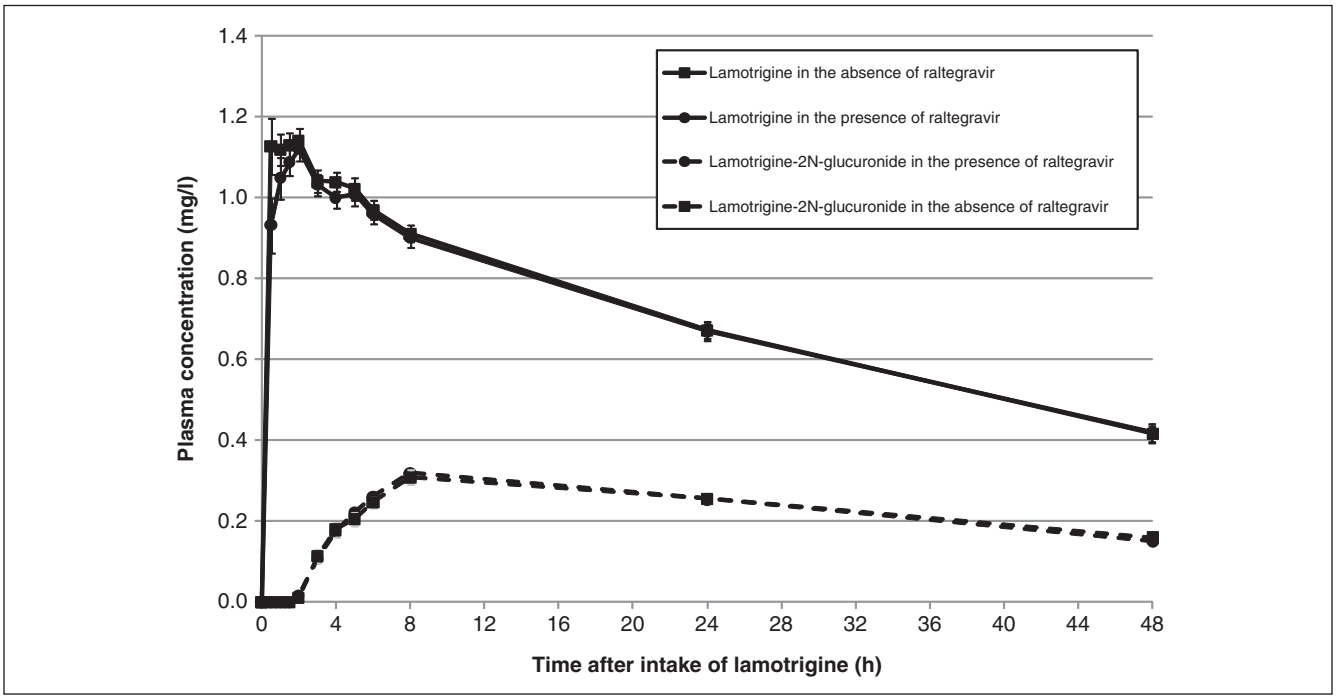

Figure 1. Arithmetic mean plasma concentrations of lamotrigine and lamotrigine-2N-glucuronide following the administration of a single dose of 100 mg lamotrigine in the presence and absence of raltegravir. Error bars represent the standard error of the mean.

predefined bioequivalence criteria for no clinically relevant interaction. In addition, the mean ratio of the $AUC_{0\rightarrow48}$ of lamotrigine-2N-glucuronide to lamotrigine was similar when lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36), which indicates that raltegravir does not inhibit or induce the glucuronidation of lamotrigine.

In our previous single-dose lamotrigine study, the AUC ratio of lamotrigine-2N-glucuronide versus lamotrigine was slightly higher (0.45) after the same dose of lamotrigine.[14] This is probably caused by the longer sampling period in that study (120 hours vs 48 hours in the current study).[14] Lamotrigine-2N-glucuronide has a longer elimination half-life than lamotrigine (see Figure 1). As a consequence, determining the $AUC_{0\rightarrow\infty}$ for both lamotrigine and lamotrigine-2N-glucuronide instead of the $AUC_{0\rightarrow48}$, which we did in the current study, will increase the absolute value of the AUC of lamotrigine-2N-glucuronide relatively more when compared to the AUC of lamotrigine, which results in a higher ratio of lamotrigine-2N-glucuronide versus lamotrigine.

Because raltegravir and lamotrigine share a common metabolic pathway, we hypothesized that raltegravir might inhibit lamotrigine glucuronidation, although results from in vitro experiments had indicated that

Table II Pharmacokinetic Parameters of Raltegravir When Compared to Historical Controls

Pharmacokinetic Parameter	This Study (n = 23[a])	Wenning et al[18] (n = 9)	Anderson et al[6] (n = 19)
$AUC_{0\rightarrow12}$, h·mg/L	3.9 (2.7, 5.7)[b]	5.0[c]	3.4 (2.4, 4.7)[c]
C_{max}, mg/L	1.2 (0.8, 1.8)	1.4 (0.8, 2.3)[c]	0.8 (0.6, 1.2)[c]
t_{max}, h	1.5 (0-8)	1.5	1.5 (0-12)

Data are geometric means + 95% confidence intervals, except for t_{max} (median + range). AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration; t_{max}, time to reach C_{max}.

[a]One participant was excluded from the pharmacokinetic analyses of raltegravir because raltegravir's half-life and thus $AUC_{0\rightarrow12}$ could not be determined reliably in this individual.

[b]The raltegravir $AUC_{0\rightarrow12}$ was obtained by extrapolation from the raltegravir $AUC_{0\rightarrow8}$.

[c]Data for AUC and C_{max} from historical controls were converted from h·μM and μM to h·mg/L and mg/L, respectively, using the molecular weight of raltegravir (482.51 g/mol).[8]

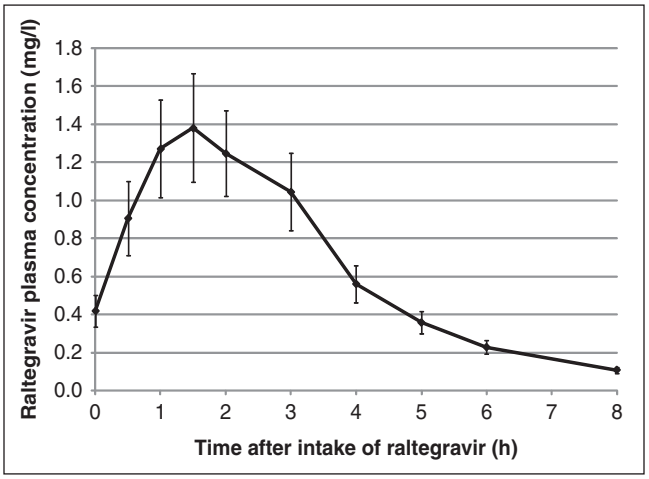

Figure 2. Arithmetic mean plasma raltegravir concentration profile following the administration of multiple doses of 400 mg raltegravir twice daily. Error bars represent the standard error of the mean.

raltegravir did not potently inhibit (IC_{50} >50 μM) UGT2B7-mediated glucuronidation. However, as explained by Kiang and colleagues,[19] one must be cautious when predicting in vivo effects of UGT enzymes based on data obtained from in vitro experiments. Moreover, there are several examples of drug-drug interactions between drugs that are both metabolized via glucuronidation, potentially based on hepatic competition for glucuronidation.[20,21] Therefore, and because of the importance of drug-drug interactions in the management of seizures in HIV-infected patients,[10] we felt it was appropriate to investigate raltegravir's influence on the glucuronidation of the UGT substrate lamotrigine in a clinical study.

In our previous lamotrigine study, we considered lamotrigine a phenotypic probe for UGT1A4 and possibly UGT2B7 substrates.[14] On the basis of this view, we originally designed the current study as a "phenotypic probe" study to investigate the influence of raltegravir on UGT1A4 and UGT2B7 enzymes in vivo. Meanwhile, lamotrigine metabolism by UGT1A4 and UGT2B7 has become in part controversial: a recent publication suggests that lamotrigine is metabolized by UGT1A3 and UGT1A4 but not by UGT2B7.[22] Thus, it is possible that lamotrigine is metabolized by at least 3 different UGT enzymes, which questions the appropriateness of using lamotrigine as a selective probe for UGT phenotyping. For instance, if raltegravir inhibits UGT1A4 enzymes and not UGT1A3 or UGT2B7, it is possible that lamotrigine is still glucuronidated at a similar velocity by using UGT1A3 and/or UGT2B7 as escape routes.

As depicted in Table II, pharmacokinetic parameters of raltegravir were comparable to those of healthy volunteers in other studies, indicating no significant effect of a single dose of lamotrigine on raltegravir pharmacokinetics. Because assessing the effect of a single dose of lamotrigine on the pharmacokinetics of raltegravir was a secondary objective of our trial, we did not include a 12-hour pharmacokinetic sample in our study. We extrapolated the raltegravir $AUC_{0\rightarrow8}$ to $AUC_{0\rightarrow12}$ to compare our data to historical controls. Because the percentage of the AUC extrapolated was smaller than 5%, we do not expect the extrapolation to confound the comparison to the historical controls.

The pharmacokinetics of raltegravir were characterized by large interindividual variability (CV 77%), which was reported by others as well.[23] Proposed explanations for large interindividual variability are differences in coadministration with food and concomitant medications.[8] Nonetheless, in our study, raltegravir was taken on an empty stomach, and concomitant medications, except for lamotrigine, were not allowed. Because omeprazole increases raltegravir exposure by 321%,[15] differences in gastric pH might have contributed to interindividual variability. Another contributing factor may be genetic polymorphism of UGT1A1, the enzyme that metabolizes raltegravir. Genetic polymorphism of UGT1A1 is relatively common: 7% to 19% of the white population is homozygous for UGT1A1*28, which leads to decreased UGT1A1 expression and reduced elimination of UGT1A1 substrates, such as irinotecan and raltegravir.[19]

Raltegravir trough concentrations taken in the morning of study day 4 (ie, around 8 AM), before drug intake for pharmacokinetic sampling, were on average 3 to 4 times higher than raltegravir concentrations obtained 8 hours after dosing (see Figure 2). Because this might have been caused by too late intake of the raltegravir evening dose before the day of pharmacokinetic sampling, we checked our MEMS data thoroughly. However, according to MEMS, all participants opened the medication bottle between 7:42 PM and 8:56 PM in the evening of day 3 or 31 (scheduled intake time 8:00 PM).

Further investigation learned that the same phenomenon can be noted in the work of Anderson et al.[6] In their article, raltegravir (morning) trough concentrations were about 2-fold higher than C_{8h} or C_{12h} raltegravir concentrations. A possible explanation for these findings could lie in circadian variations in pharmacokinetics.[24] For instance, acetaminophen glucuronidation occurs at a higher rate in the daytime compared to the night.[25] Glucuronidation rates of raltegravir might vary in a similar way, although this hypothesis requires further investigation. Another factor that may have contributed to this phenomenon is that raltegravir morning C_{trough} levels may have been increased in participants who took raltegravir with food at the evening before pharmacokinetic sampling days. The food effect on raltegravir is substantial (35% decrease in C_{max} and 8.5-fold increase in C_{min}), although not considered clinically relevant.[26] Unfortunately, we cannot test this hypothesis because we did not note whether participants took raltegravir with or without food at home.

Combined use of single-dose lamotrigine and raltegravir was generally well tolerated. However, there was 1 participant with a reversible grade III AST and grade II ALT elevation after 5 days of raltegravir administration. Lamotrigine as the causal agent seems unlikely in this case because AST had already risen from 16 to 190 U/L between day 1 and day 4 (ie, before intake of lamotrigine). Indeed, hepatitis is among the serious drug-related adverse events of raltegravir, although its frequency is defined as "uncommon" (≥1/1000 to <1/100).[8,15]

This is the third study in which we studied the influence of antiretroviral drugs on the glucuronidation of lamotrigine. In the first trial, we encountered a relatively high incidence (25%) of lamotrigine-related rashes,[13] especially among women (42%). Therefore, we decided to include only male participants in future trials with lamotrigine. In an attempt to further reduce the incidence of rash, we used single doses of lamotrigine instead of chronic dosing. The effect of these measures is satisfactory: rash occurred in only 1 participant in the second trial (4.8%), and it did not occur in the present trial.

In the first study that used single doses of lamotrigine, we used a sequential design—that is, all participants received a single dose of lamotrigine on day 1 (reference) and again on days 13 and 27, after administering atazanavir without and with ritonavir, respectively. In this situation, it could not be excluded that autoinduction of lamotrigine metabolism had confounded our results.[9,14] Therefore, we modified the design of the current study and used a randomized crossover design with a washout period of 26 days. In addition, we were now able to check whether our data were confounded by lamotrigine autoinduction, which clearly did not occur. Therefore, we consider the current study design optimal for testing whether drugs influence the glucuronidation of lamotrigine.

In conclusion, our study shows that raltegravir does not affect exposure to the UGT substrate lamotrigine.

We thank the healthy volunteers for participating in this trial. The technicians at the Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, are kindly acknowledged for processing and analyzing the plasma samples of lamotrigine, lamotrigine-2N-glucuronide, and raltegravir.

Financial disclosure: This study was funded by a research grant from Merck. David M. Burger has received honoraria for serving on advisory boards, speaker's fees, and educational grants for clinical research from Merck, the manufacturer of raltegravir. Matthijs van Luin has received honoraria for serving on advisory boards of Merck Sharp & Dohme. Hugo Gomes da Silva is an employee of Merck. All other authors declared no conflict of interest.

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