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Minimal Pharmacokinetic Interaction between the Human Immunodeficiency Virus Nonnucleoside Reverse Transcriptase Inhibitor Etravirine and the Integrase Inhibitor Raltegravir in Healthy Subjects

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Etravirine, a next-generation nonnucleoside reverse transcriptase inhibitor, and raltegravir, an integrase strand transfer inhibitor, have separately demonstrated potent activity in treatment-experienced, human immunodeficiency virus (HIV)-infected patients. An open-label, sequential, three-period study with healthy, HIV-seronegative subjects was conducted to assess the two-way interaction between etravirine and raltegravir for potential coadministration to HIV-infected patients. In period 1, 19 subjects were administered 400 mg raltegravir every 12 h (q12 h) for 4 days, followed by a 4-day washout; in period 2, subjects were administered 200 mg etravirine q12 h for 8 days; and in period 3, subjects were coadministered 400 mg raltegravir and 200 mg etravirine q12 h for 4 days. There was no washout between periods 2 and 3. Doses were administered with a moderate-fat meal. Etravirine had only modest effects on the pharmacokinetics of raltegravir, while raltegravir had no clinically meaningful effect on the pharmacokinetics of etravirine. For raltegravir coadministered with etravirine relative to raltegravir alone, the geometric mean ratio (GMR) and 90% confidence interval (CI) were 0.90 and 0.68 to 1.18, respectively, for the area under the concentration curve from 0 to 12 h (AUC0-12), 0.89 and 0.68 to 1.15, respectively, for the maximum concentration of drug in serum (Cmax), and 0.66 and 0.34 to 1.26, respectively, for the trough drug concentration (Ct); the GMR (90% CI) for etravirine coadministered with raltegravir relative to etravirine alone was 1.10 (1.03, 1.16) for AUC0-12, 1.04 (0.97, 1.12) for Cmax, and 1.17 (1.10, 1.26) for Ct. All drug-related adverse clinical experiences were mild and generally transient in nature. No grade 3 or 4 adverse experiences or discontinuations due to adverse experiences occurred. Coadministration of etravirine and raltegravir was generally well tolerated; the data suggest that no dose adjustment for either drug is necessary.

The global incidence of human immunodeficiency virus type 1 (HIV-1) infection is considerable, and the number of individuals living with HIV infection continues to grow. Despite a recent scaling up of treatment access worldwide, AIDS remains the largest infectious disease cause of mortality and a serious challenge to public health (http://www.unaids.org/en/KnowledgeCentre/Resources/Publications/). While currently available therapies have proven of substantial benefit in the management of HIV infection, new therapies are needed to treat the substantial unmet medical needs of this population.

The replication of an HIV-1 virion requires the virally encoded enzymes reverse transcriptase and DNA integrase. Once an HIV-1 virion enters a host cell, reverse transcriptase creates a DNA copy of the HIV-1 RNA genome that is then integrated into the host cell genome by the integrase (2, 3, 4). Each of these steps is an obligate part of the HIV-1 life cycle. While inhibitors of reverse transcriptase have proven to be an essential element of HIV-1 combination therapy, these agents are limited by viral resistance (17). Etravirine (formerly TMC125) is a recently approved nonnucleoside reverse transcriptase inhibitor (NNRTI) which bears a superior resistance profile relative to other available NNRTIs (1, 18) and has demonstrated good efficacy in the treatment of HIV-1 infection (9, 10). The recent introduction of raltegravir (formerly MK-0518) has demonstrated that inhibition of the strand transfer reaction catalyzed by integrase is an effective means of treating HIV infection, and such agents promise to become an important new addition to antiretroviral therapy (raltegravir [Isentress] prescribing information; Merck & Co., Inc., Whitehouse, NJ). Due to the possibility of resistance development, anti-HIV agents are given in combination, generally with agents from different mechanistic classes. It is likely that patients will benefit from the combined use of raltegravir with etravirine.

Etravirine is eliminated primarily by metabolism and in vitro undergoes hydroxylation through the action of several cytochrome P-450 (CYP) isozymes (CYP3A, CYP2C9, and CYP2C19 primarily), followed by glucuronidation of the metabolites (12, 15). Etravirine has been shown to be an inducer of CYP3A and an inhibitor of CYP2C9 and CYP2C19 (7). In contrast, raltegravir is not metabolized through the CYP oxidation system and is neither a clinically meaningful inducer nor an inhibitor of enzymes involved in drug metabolism (8). Consequently, raltegravir has shown minimal interactions when coadministered with other antiviral agents (5; raltegravir pre-
scribing information, Merck & Co., Inc., Whitehouse, NJ), and for this reason, raltegravir was not expected to influence the pharmacokinetics of etravirine. However, glucuronidation catalyzed by UGT1A1 is a primary route of raltegravir metabolism (8), and as a result, the pharmacokinetic profile of raltegravir may be affected by compounds that inhibit or induce this enzyme. The effect of etravirine on glucuronidation is unknown. This clinical interaction study was undertaken with healthy subjects to assess the two-way interaction of etravirine and raltegravir with respect to safety, tolerability, and pharmacokinetics and to determine whether a dose adjustment, particularly for raltegravir, would be warranted in this setting. (These data have been presented at the AIDS Society 4th International Conference, Sydney, Australia, 22 to 25 July 2007.)

MATERIALS AND METHODS

Study design. This was a phase I, open-label, three-period, fixed-sequence study performed at a single center in the United States. Healthy men and women within 30% of the ideal body weight and between 18 and 45 years of age were eligible for enrollment. HIV-infected individuals, those bearing a clinically significant medical condition, and those with a history of alcohol and/or drug abuse or requiring use of comedication were excluded from the study. Subjects who had previously received etravirine, dapivirine (TMC120), or rilpivirine (TMC278) in any trial were not eligible for this study. All subjects gave written informed consent prior to study commencement. The study protocol was approved by the Institutional Review Board of the study center. The study was conducted in accordance with the guidelines on good clinical practice and with the ethical standards for human experimentation established by the Declaration of Helsinki.

In period 1, all subjects were administered oral doses of 400 mg raltegravir q12h (every 12 h) for 4 days, followed by pharmacokinetic sampling for determination of plasma raltegravir concentrations. Period 1 was followed by a washout of at least 4 days. In period 2, the same subjects were administered 200 mg etravirine q12h for 8 days, followed by pharmacokinetic sampling for determination of plasma etravirine concentrations. In period 3, all subjects received a combination of etravirine (200 mg q12h) and raltegravir (400 mg q12h) for 4 days, followed by pharmacokinetic sampling for determination of raltegravir and plasma etravirine concentrations. There was no washout between periods 2 and 3 in order to observe the effects of potential induction by etravirine on the pharmacokinetics of raltegravir. All doses were administered in an open-label fashion. Current guidance for etravirine dosing is to administer this medication following a meal (14), whereas raltegravir may be taken without regard to food (raltegravir prescribing information; Merck & Co., Inc.). In accordance with the food guidance, all subjects were administered both study drugs after a moderate-fat meal, including days when pharmacokinetic samples were collected.

Bioanalytical and pharmacokinetic analyses. Serial blood samples were collected to determine plasma concentrations of raltegravir and etravirine. On day 4 of period 1 and on day 4 of period 3, samples were collected for raltegravir analysis at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h postadministration. On day 8 of period 2 and on day 4 of period 3, samples were collected for etravirine analysis at the same time points as for raltegravir analysis. Additional predosing samples were collected for analysis of raltegravir and etravirine on day 1 of periods 1 and 2 and for analysis of etravirine on days 3, 5, and 7 of period 2.

The analytical method for the determination of raltegravir concentrations in human plasma involved isolation, via 96-well liquid-liquid extraction, of the analyte and internal standard from plasma, followed by reverse-phase high-pressure liquid chromatography–tandem mass spectrometry analysis as previously described (11), while plasma concentrations of etravirine were determined by a validated liquid chromatography-tandem mass spectrometry method without extraction (13). For each analyte, no cross-interference was observed in the respective assays. For raltegravir, the lower limit of quantitation by the plasma assay was 2 ng/ml (4.5 nM) and the linear calibration range was 2 to 1,000 ng/ml. For etravirine, the lower limit of quantitation by the plasma assay was 2 ng/ml (4.0 nM) and the linear calibration range for undiluted samples was 2 to 5,000 ng/ml.

Pharmacokinetics of raltegravir and etravirine were converted into nano-molar values, and actual sampling times, converted to elamed times relative to dosing times, were used to estimate the pharmacokinetic parameters with WinNonLin (version 5.0.1; Pharsight, Mountain View, CA), with the exception of the time to the maximum concentration of drug in serum (Tmax), for each treatment and each subject. The area under the concentration curve from 0 to 12 h (AUC0–12) was calculated by the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. The maximum concentration of drug in serum (Cmax) and Tmax were obtained by inspection of the plasma concentration data.

Safety evaluation. The tolerability of raltegravir with etravirine was assessed by clinical evaluation, including vital signs, physical examination, electrocardiogram, and laboratory safety assessment (hematology, chemistry, and urinalysis) throughout the study. The Division of AIDS toxicity scale was used to grade laboratory and adverse experiences. As a class, NNRTIs, including etravirine, harbor the potential to induce a skin rash, and for this study, occurrences of rash were events of clinical interest.

Statistical methods. The trough drug concentration (C12), Cmax, and AUC0–12 were natural log transformed before analysis, and all corresponding confidence intervals (CIs) for means (for the difference of two means) were constructed on the natural log scale. Exponentiation was performed on the means (mean differences) and lower and upper limits of these CIs prior to reporting.

Analysis of raltegravir pharmacokinetic parameters was conducted separately from analysis of etravirine pharmacokinetic parameters. All statistical analyses were conducted with SAS version 8. With the exception of those for Tmax all CIs were based on an analysis of variance (ANOVA) model with the treatment as a fixed effect and the subject as a random effect (compound symmetric covariance structure assumed). Given the fixed-sequence design of this study, the method of analysis employed confounded any underlying period effects with treatment.

For each drug, a 90% CI was constructed for the geometric mean ratio (GMR) (raltegravir and etravirine coadministered/raltegravir or etravirine alone) of C12, Cmax, or AUC0–12. For Tmax the Hodges-Lehman estimate of the true median difference (raltegravir and etravirine coadministered/raltegravir or etravirine alone) was computed, as was a 90% CI for the true median difference.

RESULTS

Demographics. A total of 20 HIV-seronegative subjects were enrolled in this study, all of whom were within 30% of the ideal body weight and in good general health as judged by routine medical history, physical examination, vital signs, and laboratory data. Study subjects had not donated or experienced significant loss of blood in the 4 weeks preceding the study start and did not anticipate the use of prescription or nonprescription drugs during the course of the study. Of the 20 subjects enrolled, 16 were Caucasian (80%) and the remaining 4 were African-American (20%). Thirteen subjects were male (65%). All subjects were nonsmokers, with a mean (range) age and weight of 29.8 years (19 to 45 years) and 78.5 kg (58.2 to 103.2 kg), respectively. Nineteen subjects completed the study. One subject voluntarily withdrew consent early in period 1. All subjects who enrolled in the study were included in the safety analysis, while the 19 subjects who completed the study were included in the pharmacokinetic analyses.

Pharmacokinetics. The arithmetic mean plasma raltegravir concentration-time profiles following administration of raltegravir with and without coadministration of etravirine are shown in Fig. 1. The mean pharmacokinetic parameters of raltegravir are described in Table 1. Etravirine had only modest effects on the pharmacokinetics of raltegravir. For raltegravir coadministered with etravirine relative to raltegravir alone, the GMR (90% CI) was 0.90 (0.68 to 1.18) for AUC12, 0.89 (0.68 to 1.15) for Cmax, and 0.66 (0.34 to 1.26) for C12.

The arithmetic mean plasma etravirine concentration-time profiles following administration of etravirine with and without coadministration of raltegravir are shown in Fig. 2. The mean pharmacokinetic parameters of etravirine are described in Table 2. Raltegravir had minimal to no effect on the pharmacokinetics...
kinetics of etravirine. For etravirine coadministered with raltegravir relative to etravirine alone, the GMR (90% CI) was 1.10 (1.03, 1.16) for AU_{C12}, 1.04 (0.97, 1.12) for C_{max}, and 1.17 (1.10, 1.26) for C_{12}.

Safety and tolerability. Coadministration of etravirine and raltegravir was generally well tolerated. Sixteen subjects reported a total of 44 nonserious clinical adverse experiences, 21 of which were deemed by the investigator to be possibly drug related. All adverse experiences were transient and rated mild to moderate in intensity. The most commonly reported, nonserious, possibly drug-related clinical adverse experiences (reported by two or more subjects) were somnolence, headache, vaginal bleeding, and rash. Three subjects had grade 1 rashes, all of which were judged not drug related by the investigator and therefore did not qualify as events of clinical interest. No Division of AIDS grade 3 or 4 adverse experiences were observed, and no discontinuations due to an adverse experience occurred. No laboratory adverse experiences were reported during the study.

DISCUSSION

Both raltegravir and etravirine have recently been approved for the treatment of HIV-1 infection and represent a significant addition to the armamentarium available to physicians to treat HIV infection and AIDS. It is likely that patients will benefit from regimens that include both raltegravir and etravirine. Etravirine has been shown to possess a relatively complex drug interaction profile with known inductive and inhibitory properties (7). In contrast, raltegravir is not an inducer or inhibitor of enzymes involved in drug metabolism, including those involved in etravirine metabolism (5, 6, 20; raltegravir prescribing information, Merck & Co., Inc.). Thus, the assessment of an effect of etravirine on the pharmacokinetics of raltegravir was supported by the drug interaction profile associated with etravirine. Although a clinically meaningful effect of raltegravir on the pharmacokinetics of etravirine was thought to be of low probability, investigation of raltegravir effects on etravirine was also warranted to confirm prior clinical and in vitro findings.

![FIG. 1. Arithmetic mean plasma raltegravir concentration profiles following the administration of multiple doses of 400 mg raltegravir twice daily with or without the coadministration of multiple doses of 200 mg etravirine twice daily to healthy adult subjects (inset = semilog scale). Error bars represent the standard error of the mean.](image1)

![FIG. 2. Arithmetic mean plasma etravirine concentration profiles following the administration of multiple doses of 200 mg etravirine twice daily with or without the coadministration of multiple doses of 400 mg raltegravir twice daily to healthy adult subjects (inset = semilog scale). Error bars represent the standard error of the mean.](image2)

| TABLE 1. Comparison of plasma raltegravir pharmacokinetics following administration of multiple doses of 400 mg raltegravir twice daily with or without coadministration of multiple doses of 200 mg etravirine twice daily to healthy adult subjects |
|---|---|---|
| Pharmacokinetic parameter | Raltegravir + etravirine | Raltegravir | Raltegravir + etravirine/raltegravir | P value |
| | Geometric mean | 95% CI for geometric mean | Geometric mean | 95% CI for geometric mean | Geometric mean | 95% CI for geometric mean | Geometric mean | 95% CI for geometric mean | n | GMR | 90% CI for GMR | P value |
| C_{12} (nM)^{b} | 19 | 141.6 | (77.2, 259.6) | 19 | 216.0 | (117.8, 396.0) | 19 | 0.66 | (0.34, 1.26) | 0.2769 |
| AU_{C12} (μM · h)^{b} | 19 | 6.28 | (4.48, 8.78) | 19 | 7.01 | (5.02, 9.81) | 19 | 0.90 | (0.68, 1.38) | 0.4950 |
| C_{max} (μM)^{b} | 19 | 1.54 | (1.09, 2.18) | 19 | 1.74 | (1.23, 2.46) | 19 | 0.89 | (0.68, 1.15) | 0.4310 |
| T_{max} (h) | 19 | 3.00 | 0–12^{c} | 19 | 1.50 | 0–12^{c} | 19 | 1.80^{d} | (0.3, 3.0)^{d} | 0.0408 |

*a n, number of subjects.

^b Geometric mean computed from least-squares estimate from an ANOVA performed on the natural-log-transformed values.

^c Median and range reported for T_{max}.

^d Hodges-Lehman estimate of median treatment difference with corresponding 90% CI for true median treatment difference.
Etravirine had an overall modest suppressive effect on the pharmacokinetics of raltegravir. Etravirine exerted the greatest effect on the raltegravir C$_{12}$, reducing this parameter by a mean 34%, but lowered the AUC$_{0-12}$ and C$_{\text{max}}$ to lesser degrees (10 and 11%, respectively) and not to a statistically significant degree. No substantial differences were observed in the T$_{\text{max}}$ of raltegravir in the presence versus the absence of etravirine.

This diminution of the raltegravir C$_{12}$ is presumably attributable to an inductive effect of etravirine on metabolic enzymes, particularly UGT1A1, the major clearance route for raltegravir. Interestingly, of the pharmacokinetic parameters assessed, there was the broadest distribution in C$_{12}$ as reflected in the breadth of the 90% CI, implying some uncertainty in the effect of etravirine on this parameter. This variation within the study cohort could be a reflection either of individual variation in inductive potential or of relatively large intraindividual variability in raltegravir C$_{12}$ values. In addition, as this study was conducted with all subjects administered both study drugs following a moderate-fat meal, including pharmacokinetic sampling days, this enhanced pharmacokinetic variability of raltegravir may be due, in part, to a food effect (19). However, if the true change in the raltegravir C$_{12}$ were on the order of the lower end of the 90% CI seen, then this overall level of induction should have resulted in more substantial decreases in other associated pharmacokinetic parameters (e.g., AUC) than those observed. The lack of a substantive effect on AUC, C$_{\text{max}}$, and T$_{\text{max}}$ suggests that the overall effect is minor.

In support of this viewpoint, it is important to consider the implications of changes in these pharmacokinetic values with respect to the comparability bounds that define a meaningful effect in the context of the larger study database. Such population pharmacokinetic analyses and pharmacokinetic/pharmacodynamic correlation analyses based on the safety and efficacy data collected in the phase II and III studies of this clinical program have determined that a 60% decrease in the C$_{12}$ does not result in clinically meaningful reductions in efficacy (16). Thus, the mean reduction of the C$_{12}$ by 34% (i.e., a GMR of 0.66) does not define a clinically meaningful decrease. Although the lower end of the 90% CI falls just below this cutoff (0.34 versus 0.4), the weight of the pharmacokinetic and clinical data suggests that there is a low risk of reduced efficacy of raltegravir in patients administered the combination, supporting coadministration of etravirine with raltegravir without a dose adjustment.

From these same analyses, a twofold increase in the AUC has been shown to define an upper safety boundary for raltegravir exposure (16). In this study, coadministration of raltegravir with etravirine did not result in a clinically meaningful change in the AUC (GMR of 0.9), with the upper end of the 90% CI only slightly elevated (GMR of 1.18) beyond unity.

In contrast, the effect of raltegravir on the pharmacokinetics of etravirine (C$_{12}$, C$_{\text{max}}$ and AUC$_{0-12}$) is negligible, as reflected in the close correspondence of the pharmacokinetic profile in the presence or absence of coadministered raltegravir across the entire 12-h dosing interval. This result is consistent with the studied preclinical and clinical interaction profile of raltegravir wherein raltegravir has been demonstrated to show only modest to insignificant effects on the pharmacokinetics of coadministered drugs (5, 6, 20; raltegravir prescribing information, Merck & Co., Inc.).

As stated earlier, drug-drug interactions are particularly important considerations in the management of HIV-infected patients and may pose significant challenges. The degree of interaction between raltegravir and etravirine is overall likely to be of no clinical importance. The combined safety and pharmacokinetic data support the coadministration of 400 mg raltegravir with 200 mg etravirine twice a day without a dose adjustment.

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