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Lack of a Clinically Important Effect of Moderate Hepatic Insufficiency and Severe Renal Insufficiency on Raltegravir Pharmacokinetics▽†

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Raltegravir is a human immunodeficiency virus type 1 integrase strand transfer inhibitor with potent activity in vitro and in vivo. Raltegravir is primarily cleared by hepatic metabolism via glucuronidation (via UDP glucuronosyltransferase 1A1), with a minor component of elimination occurring via the renal pathway. Since the potential exists for raltegravir to be administered to patients with hepatic or renal insufficiency, two studies were conducted to evaluate the influence of moderate hepatic insufficiency (assessed by using the Child-Pugh criteria) and severe renal insufficiency (creatinine clearance, <30 ml/min/1.73 m^2) on the pharmacokinetics of raltegravir. Study I evaluated the pharmacokinetics of 400 mg raltegravir in eight patients with moderate hepatic insufficiency and eight healthy, matched control subjects. Study II evaluated the pharmacokinetics of 400 mg raltegravir in 10 patients with severe renal insufficiency and 10 healthy, matched control subjects. All participants received a single 400-mg dose of raltegravir in the fasted state. In study I, the geometric mean ratios (GMR; mean value for the group with moderate hepatic insufficiency/mean value for the healthy controls) and 90% confidence intervals (CIs) for the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), the maximum concentration of drug in plasma (C_{max}), and the concentration at 12 h (C_{12}) were 0.86 (90% CI, 0.41, 1.77), 0.63 (90% CI, 0.23, 1.70), and 1.26 (90% CI, 0.65, 2.43), respectively. In study II, the GMRs (mean value for the group with renal insufficiency/mean value for the healthy controls) and 90% CIs for $AUC_{0-\infty}$, C_{max}, and C_{12} were 0.85 (90% CI, 0.49, 1.49), 0.68 (90% CI, 0.35, 1.32), and 1.28 (90% CI, 0.79, 2.06), respectively. Raltegravir was generally well tolerated by patients with moderate hepatic or severe renal insufficiency, and there was no clinically important effect of moderate hepatic or severe renal insufficiency on the pharmacokinetics of raltegravir. No adjustment in the dose of raltegravir is required for patients with mild or moderate hepatic or renal insufficiency.

Raltegravir (Isentress, MK-0518), a human immunodeficiency virus (HIV) type 1 (HIV-1) integrase strand transfer inhibitor, is a member of a promising new class of drugs for the treatment of patients infected with HIV-1. Raltegravir has been demonstrated to have potent activity in vitro and in the clinic (10) and may become a useful tool in antiretroviral treatment regimens. The pharmacokinetic properties of raltegravir have been characterized (7, 8, 9). Raltegravir demonstrates dose-proportional pharmacokinetics over 100 to 800 mg. At the clinical dose of 400 mg, the apparent terminal elimination half-life ($t_{1/2\beta}$) is approximately 9 h and the distribution-phase half-life ($t_{1/2\alpha}$) is shorter (approximately 1 h) and accounts for much of the area under the concentration-time curve (AUC). Raltegravir is relatively rapidly absorbed, with the median time to the maximum plasma concentration (T_{max}) being ~3 h in the fasted state. Raltegravir is cleared primarily by metabolism, with a minor component of elimination occurring via renal excretion (~9%) (8). Metabolism is primarily hepatic, and the major metabolite is derived through the UDP glucuronosyltransferase 1A1 (UGT1A1) isozyme (8). As the elimination of raltegravir is dependent upon both hepatic and renal processes, there is the potential for the pharmacokinetics of raltegravir to be altered in patients with hepatic or renal organ dysfunction. However, the likelihood of an interaction is projected to be low on the basis of the modest renal clearance (CL_R) of raltegravir and the fact that UGT1A1 metabolism is not as likely to be affected by moderate hepatic insufficiency (3, 4). The intended patient population for raltegravir includes patients with hepatic insufficiency and renal insufficiency, and an investigation of the effects of hepatic and renal impairment on the pharmacokinetics of raltegravir was thus performed.

Two phase I clinical studies were conducted to investigate the safety, tolerability, and pharmacokinetics of raltegravir. The first study included individuals with moderate hepatic impairment, and the second study included individuals with severe renal insufficiency.

(This study was presented in part at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy [12].)

MATERIALS AND METHODS

Study designs and populations. Study I was an open-label, single-dose study with patients with moderate hepatic insufficiency. Eight patients and eight healthy, matched control subjects each received a single 400-mg dose of raltegravir (Merck & Co., Inc., Whitehouse Station, NJ) in the fasted state. For patient eligibility, a diagnosis of chronic (>6 months), stable, moderate hepatic

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insufficiency was required, as defined by a Child-Pugh score of 7 to 9 (2, 13). Healthy subjects were matched to each patient by race, sex, age (within ±5 years), and body mass index (BMI) (±3.5 units). Patients were excluded from the study if they had evidence of unstable disease, had a history of renal disease (creatinine clearance, ≤60 ml/min/1.73 m^2 either measured by the use of a 24-h urine collection or estimated by use of the Cockcroft-Gault equation), were infected with HIV, had recently donated blood, or had recently experienced significant blood loss. Additional exclusion criteria for healthy control subjects included a history of any chronic and/or active hepatic disease, a significant medical history of clinical concern, or the anticipation of the need for any prescription or nonprescription drug during the study.

This patient study population specifically consisted of individuals with moderate hepatic insufficiency, as assessed by the Child-Pugh classification. On the basis of historical data assembled by the FDA (14), there is a lack of a correlation between oral drug metabolism and hepatic impairment, and this correlation supports the suggestion that all classifications of hepatic impairment do not necessarily have to be studied. For this study, only subjects with moderate hepatic insufficiency were enrolled and the findings could be extrapolated to patients with mild disease, and thus, dosing in patients with severe disease would be contraindicated if a substantial effect was seen. To ensure that the patients with hepatic impairment had laboratory abnormalities consistent with hepatic dysfunction (e.g., reduced serum albumin levels, increased serum bilirubin levels, and increased prothrombin times), at least 25% of the patients with hepatic impairment were required to have had a score of 2 or more on at least one of the Child-Pugh laboratory parameters.

Study II was an open-label, single-dose study with patients with severe renal insufficiency, defined as a creatinine clearance of <30 ml/min/1.73 m^2 (confirmed by the use of two 24-h urine collections). Ten patients and 10 healthy, matched control subjects each received a single 400-mg dose of raltegravir in the fasted state. Healthy subjects were matched to each patient by race, sex, age (within ±5 years), and BMI (±3.5 units). Patients were excluded from the study if they had evidence of unstable disease, had a history of active hepatic disease, were infected with HIV, had recently donated blood, or had recently experienced significant blood loss. Dialysis patients were excluded. Additional exclusion criteria for the healthy control subjects included a history of any chronic and/or active renal disease, any significant medical history of clinical concern, or the anticipation of the need for any prescription or nonprescription drug during the study.

In both studies, blood samples for assays for raltegravir levels were obtained predosing and at selected time points postdosing. Safety was assessed throughout the studies by clinical and laboratory evaluations. Both study designs incorporated the administration of a single dose of raltegravir. Although raltegravir is indicated to be administered as multiple doses, a single-dose study was sufficient since the single-dose pharmacokinetics of raltegravir are approximately linear and are predictive of the multiple-dose pharmacokinetics.

All subjects and patients provided written informed consent to participate in the studies. The protocols were approved by the institutional review boards of the respective study centers. Both studies were conducted in accordance with the guidelines on good clinical practice and ethical standards for human experimentation established by the Declaration of Helsinki.

Analytical and pharmacokinetic measurements. Plasma samples were collected for the quantification of raltegravir concentrations at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 32, 48, 72, and 96 h postdosing (a sample was collected at 96 h only for study I). Plasma samples were analyzed by a validated reverse-phase high-pressure liquid chromatography–tandem mass spectrometry method (11). The lower limit of quantitation (LLOQ) for the plasma assay was 2 ng/ml (4.5 nM), and the linear calibration range was 2 to 1,000 ng/ml.

Urine samples were collected in study II for determination of the raltegravir concentrations predosing and during the following intervals: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdosing. The analytical method used for the determination of the raltegravir concentration in human urine involved sample dilution and direct injection onto the high-pressure liquid chromatography–tandem mass spectrometry system (7). The LLOQ for the urine assay was 0.25 μg/ml, and the linear calibration range was 0.25 to 25 μg/ml.

Plasma concentrations, converted into molar units (nM) by using a molecular weight of 444.4, were used to determine pharmacokinetic parameter values, including the concentration at 12 h (C_{12}), the AUC from 0 h to infinity ($AUC_{0-\infty}$), and the maximal plasma concentration (C_{max}). Values below the quantitation limit (BQL) for the plasma assay (BQL, 2 ng/ml) were replaced according to the following rules: the BQL value predosing was 0; the first BQL value in the terminal phase was (1/2) · LLOQ, which was equal to 1 ng/ml, or 2.3 nM; and second and subsequent BQL values in the terminal phase were equal to 0 (1). The software program WinNonlin (version 5.0.1; Pharsight Corporation, Mountain View, CA) was used for the calculation of the pharmacokinetic parameter values. The distribution and elimination phases of each plasma concentration profile (α and β, respectively) were fit to a biexponential equation (concentration = $A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$, where A and B are fitting constants and t is time) by using the Gauss-Newton (Levenberg and Hartley) minimization method and a weighting of 1/predicted concentration^2. The onset of the α phase was determined by inspection. The $t_{1/2}$s for each phase were calculated as the quotient of ln(2) and α or β. The AUC from predosing (0 h) to the last time point with a detectable plasma concentration (AUC_{0-last}) was calculated by using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. $AUC_{0-\infty}$ was estimated as the sum of AUC_{0-last} and the extrapolated area given by the quotient of the last measured concentration. C_{max} and T_{max} were obtained by inspection of the plasma concentration data. Since the actual observed T_{max}s did not differ in a meaningful way from the nominal plasma sampling times, the nominal plasma sampling times were used to determine T_{max}. C_{12}s were taken as the plasma concentrations determined for the nominal sampling time at 12 h postdosing.

Urine drug concentrations, urine volumes from individual collection intervals, and the nominal times of the collection intervals were used to calculate urinary pharmacokinetic parameter values. BQL values for the urine assay (BQL, 250 ng/ml) were replaced according to the following rules: the predose BQL value was 0; the first postdose BQL value was (1/2) · LLOQ, which was equal to 125 ng/ml; and the second and subsequent postdose BQL values were equal to 0 (1). The amount of raltegravir excreted unchanged in urine over each collection interval was determined from the product of the urine concentration and the urine volume. The percentage of the raltegravir dose that was excreted unchanged in urine over the collection interval (f_e) was determined from the quotient of the sum of raltegravir collected over all collection intervals and the dose administered multiplied by 100%. The AUC over the total urine collection interval to 24 h (AUC_{0-24}) was calculated by using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. CL_R was determined as the quotient of total f_e and AUC_{0-24}.

Statistical methods. Study sample sizes were determined from variance estimates on the basis of prior raltegravir pharmacokinetic data. For both studies, the raltegravir parameters C_{12}, C_{max}, and $AUC_{0-\infty}$ 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. With the exception of T_{max} and the apparent $t_{1/2}$, all CIs were based on the least-squares means arising from an analysis of covariance (ANCOVA) model with population and sex as fixed effects and with age and BMI as continuous covariates. Ninety percent CIs were calculated for the geometric mean ratios (value for subjects with organ impairment/value for healthy subjects) of the raltegravir $AUC_{0-\infty}$, C_{max}, and C_{12}. An ANCOVA model was also used to assess the interaction terms population by BMI and population by age. Ninety-five percent CIs were constructed for the geometric means of the raltegravir $AUC_{0-\infty}$, C_{max}, and C_{12} for each population. The Hodges-Lehman estimate of the median difference (value for subjects with organ impairment − value for healthy subjects) was computed for the raltegravir T_{max} and apparent $t_{1/2}$, as were the corresponding 90% CIs. These CIs were based on the test statistic used for the Wilcoxon signed-rank test.

Safety. Safety and tolerability were assessed by clinical evaluation and laboratory measurements. Adverse experiences were monitored throughout the study. Investigators evaluated all clinical adverse experiences in terms of intensity (mild, moderate, or severe), duration, seriousness, outcome, and relationship to the study drug.

RESULTS

Demographics and baseline characteristics. In study I, eight patients with hepatic insufficiency and eight matched, healthy control subjects were enrolled. Each group consisted of six males and two females. All patients and subjects met the inclusion criteria. The mean body weights in each group were 75.5 kg and 72.1 kg for the patient and subject groups, respectively; the mean ages were 56.3 and 55.8 years for the patient and subject groups, respectively. In each group, one individual was an African-American male and the remaining participants were Caucasian. Individual Child-Pugh's classification scores and associated laboratory values are provided in Table 1. Of the patients with moderate hepatic insufficiency, 25% (n = 2)

TABLE 1. Individual Child-Pugh's classification scores and laboratory values for patients with moderate hepatic insufficiency enrolled in study I[a]

Patient AN[b]	Albumin		PT		Bilirubin		Total CP score
	Concn (g/dl)	CP Score	Value (s)[c]	CP score	Concn (mg/dl)	CP score[d]	
0275	5.1	1	0.8	1	1.1	1	7
0276	4.9	1	0.6	1	1.3	1	7
0277	4.0	1	0.7	1	1.0	1	7
0278	4.4	1	0.9	1	1.1	1	7
0279	3.2	2	0	1	0.8	1	8
0280	4.1	1	3.7	1	2.0	2	8
0281	4.0	1	2.0	1	0.8	1	7
0282	4.7	1	0.3	1	0.6	1	7

[a] Abbreviations: AN, allocation number; CP, Child-Pugh; PT, prothrombin time.
[b] The encephalopathy and ascites Child-Pugh scores were 2 for all patients.
[c] Number of seconds over that for the controls.
[d] For patients with nonprimary biliary cirrhosis.

had a score of 8 on the Child-Pugh scale, with the remaining patients having a score of 7. As specified in the protocol, 25% ($n = 2$) of the patients had a score of 2 or higher on at least one of the laboratory parameters on the Child-Pugh scale. Concomitant medication was allowed in the patient group. Three patients continued maintenance therapy for chronic medical conditions, including hypertension, hyperlipidemia, ascites management, gastroesophageal reflux, and anticoagulation.

In study II, 10 patients with renal insufficiency and 10 matched, healthy control subjects were enrolled. Each group consisted of seven males and three females. All patients and subjects met the inclusion criteria. The mean body weights in each group were 77.2 kg and 80.8 kg for the patient and subject groups, respectively; the mean ages were 53.0 and 52.9 years for the patient and subject groups, respectively. Creatinine clearance values in the patient group ranged from 13.0 to 28.8 ml/min/1.73 m^2. All participants were Caucasian. Concomitant medication was allowed in the patient group. All patients continued maintenance therapy for chronic medical conditions, including hypertension, hyperlipidemia, anticoagulation, depression, asthma, gout, gastroesophageal reflux, diabetes, anemia, arthritis, and electrolyte imbalance.

None of the concomitant medications in either study (see the supplemental material) were expected to have a clinically meaningful effect on raltegravir metabolism; however, subsequent data obtained in a drug interaction study conducted with healthy subjects (6) indicated a potential influence of proton pump inhibitors on the bioavailability of raltegravir that increased the overall plasma concentrations. The effect of proton pump inhibitors on the pharmacokinetics of raltegravir in the patient populations with chronic renal and hepatic insufficiency is unknown and may differ due to the presence of chronic underlying disease. An exploratory analysis examining the three patients receiving proton pump inhibitors in the study with patients with renal insufficiency and the one patient in the study of patients with hepatic insufficiency did not indicate a substantive difference in pharmacokinetics in this subgroup, although the population affected was limited in number. There were no patients receiving H_2 blockers. Six patients in the study of patients with hepatic insufficiency received concomitant medications of calcium, magnesium, or bicarbonate salts, with the concomitant medications being administered more than 1 h after the administration of raltegravir. The effect of salt on gastric pH is transient and likely of minor influence regarding sustained pH elevation and of minor consequence since administration was subsequent to the time of peak absorption.

Pharmacokinetics. The raltegravir plasma concentration-time profiles following the administration of single 400-mg oral doses of raltegravir to patients with moderate hepatic insufficiency and severe renal insufficiency and to the corresponding matched, healthy control subjects are shown in Fig. 1 and 2. Pharmacokinetic parameter values are shown in Tables 2 and 3. Appreciable variability was seen in the values of the pharmacokinetic parameters $AUC_{0-\infty}$, C_{max}, C_{12}, T_{max}, and apparent $t_{1/2}$; however, there were no clinically important differences between the groups with organ impairment and the respective matched, healthy control groups. f_e and CL_R were both lower for patients with renal insufficiency than for the healthy subjects (reduced 90% and 92%, respectively).

Additional analyses investigating the potential interaction terms population by age and population by BMI were conducted; but with one exception, none of these interactions was significant at the level of α equal to 0.05 for $AUC_{0-\infty}$, C_{max}, and

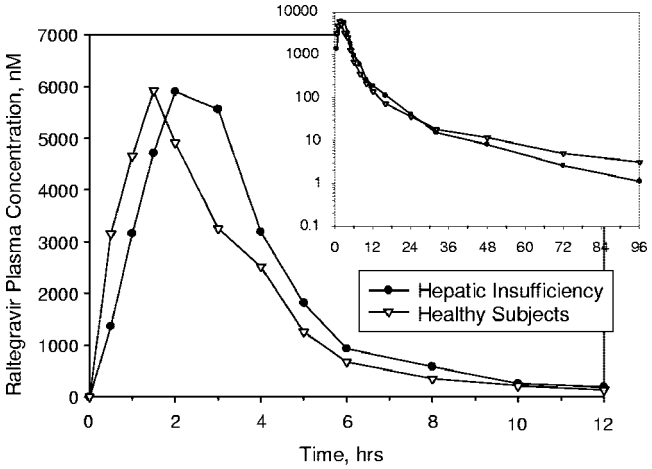

FIG. 1. Arithmetic mean plasma raltegravir concentration profiles following administration of single oral doses of 400 mg raltegravir to patients with moderate hepatic insufficiency and matched, healthy control subjects ($n = 8$ per panel; inset, semilogarithmic scale).

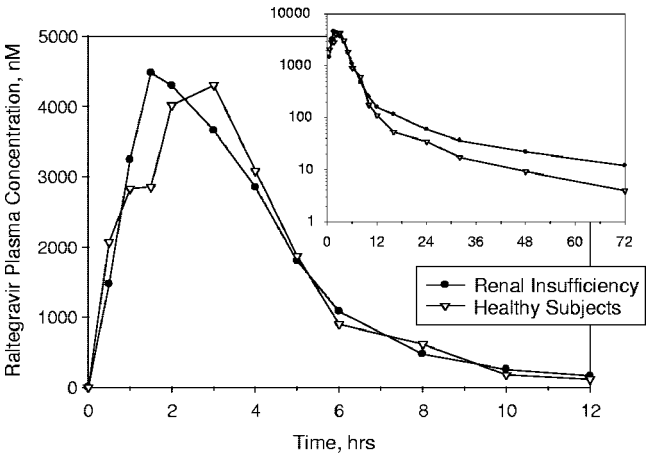

FIG. 2. Arithmetic mean plasma raltegravir concentration profiles following administration of single oral doses of 400 mg raltegravir to patients with severe renal insufficiency and matched, healthy control subjects ($n = 10$ per panel; inset, semilogarithmic scale).

C_{12} in both studies. The exception was the population-by-BMI interaction for C_{12} in the study with patients with renal insufficiency, in which a significant ($P = 0.0458$) interaction was seen at the level of α equal to 0.05 (data not shown). However, this interaction is believed to be of little consequence, given the marginal significance combined with the failure to adjust for multiplicity over all interactions.

Safety and tolerability. Administration of a single 400-mg dose of raltegravir was generally well tolerated by individuals with moderate hepatic insufficiency and severe renal insufficiency. In study I, no clinical or laboratory adverse experiences were reported. In study II, clinical adverse experiences were reported; however, there were no serious clinical or laboratory adverse experiences. Thirty-three nonserious clinical adverse experiences were reported by 11 study participants (5 patients in the renal insufficiency group and 6 individuals in the healthy control group). Of these adverse experiences, 15 were judged by the investigator to be related to the study drug. All adverse experiences were generally transient in nature and mild to moderate in intensity. The most common drug-related clinical adverse experiences reported (by two or more subjects or patients) were headache (one patient, three control subjects) and mouth ulceration (one patient, one control subject). No adverse experiences were detected according to laboratory analyses.

DISCUSSION

Two studies with patients with organ dysfunction were conducted to investigate the effects of moderate hepatic insufficiency and severe renal insufficiency on the pharmacokinetics of raltegravir. The clearance of raltegravir from human plasma is primarily driven by metabolism, with a minor component of elimination occurring from renal excretion. In that the target population for raltegravir includes patients with renal insufficiency as well as patients with hepatic insufficiency, characterization of the pharmacokinetics of raltegravir in these patient populations was performed to determine if the levels in plasma would be altered with renal or hepatic organ impairment.

Investigation of the pharmacokinetics of raltegravir in the population with moderate hepatic insufficiency revealed there was no clinically meaningful effect of moderate hepatic insufficiency on the pharmacokinetics of raltegravir, although appreciable variability in pharmacokinetics was seen. The comparability bounds that define a clinically meaningful effect have been established and are a twofold increase in AUC (which defines a upper safety boundary) or a 60% decrease in the trough concentration or C_{12} (which defines a lower efficacy boundary) (9); these parameter boundaries were determined through population pharmacokinetic analyses and pharmacokinetic/pharmacodynamic correlation analyses arising from safety and efficacy data collected in the phase II and III studies. For AUC, the geometric mean ratio of patients to matched,

TABLE 2. Mean raltegravir plasma pharmacokinetic parameter values following administration of single oral doses of 400 mg raltegravir to patients with moderate hepatic insufficiency and matched, healthy control subjects

Group and parameter[a]	$AUC_{0-\infty}$ ($\mu M \cdot hr$)[b]	C_{max} (μM)[b]	C_{12} (nM)[b]	T_{max}[c] (h)	$t_{1/2}$[d] (h)	
					α phase	β phase
Patients with hepatic insufficiency						
GM	17.67	4.41	143.4	2.5	1.49	7.0
95% CI for GM	8.93, 34.99	1.74, 11.20	77.3, 266.1			
Healthy subjects						
GM	20.66	6.99	113.8	1.5	1.12	9.3
95% CI for GM	10.29, 41.47	2.70, 18.09	60.6, 213.8			
Patients with hepatic insufficiency/healthy subjects						
GMR	0.86	0.63	1.26	0.4[e]	0.26[e]	−1.9[e]
90% CI for GMR	0.41, 1.77	0.23, 1.70	0.65, 2.43	−1.0, 1.5[e]	−0.15, 0.74[e]	−7.7, 6.8[e]
P value	0.649	1.208	0.532	0.654	0.235	0.773

[a] Each group had eight patients or subjects. GM, geometric mean; GMR, geometric mean ratio.
[b] The geometric means were computed from the least-squares estimate from an ANCOVA performed with the natural-log-transformed values, with fixed-effect terms for hepatic status, age, sex, and BMI.
[c] The medians are reported.
[d] The harmonic means are reported.
[e] Hodges-Lehman estimate of median difference with corresponding 90% CI for true median difference.

TABLE 3. Mean raltegravir plasma pharmacokinetic parameter values following administration of single oral doses of 400 mg raltegravir to patients with severe renal insufficiency and matched, healthy control subjects

Group and parameter[a]	$AUC_{0-\infty}$ ($\mu M \cdot h$)[b]	C_{max} (μM)[b]	C_{12} (nM)[b]	T_{max}[c] (h)	$t_{1/2}$[d] (h)		f_e[e]	CL_R[e]
					α phase	β phase		
Patients with renal insufficiency								
GM	16.8	3.85	135	3.5	1.38	17.2	0.5	2.7
95% CI for GM	9.96, 28.35	2.06, 7.20	85.9, 211.9					
Healthy subjects								
GM	19.7	5.68	105.5	3.0	1.10	11.4	4.1	31.5
95% CI for GM	11.84, 32.76	3.09, 10.43	68.0, 163.7					
Patients with renal insufficiency/healthy subjects								
GMR	0.85	0.68	1.28	0.0[f]	0.26[f]	5.8[f]		
90% CI for GMR	0.49, 1.49	0.35, 1.32	0.79, 2.06	−1.5, 1.0[f]	0.03, 0.46[f]	1.2, 10.4[f]		
P value	0.623	0.322	0.382	0.97	0.05	0.055		

[a] Each group had 10 patients or subjects. GM, geometric mean; GMR, geometric mean ratio.
[b] The geometric means were computed from a least-squares estimate from an ANCOVA performed with the natural-log-transformed values, with fixed-effect terms for renal status, age, sex, and BMI.
[c] Medians are reported.
[d] Harmonic means are reported.
[e] Arithmetic mean are reported.
[f] Hodges-Lehman estimate of the median difference with the corresponding 90% CI for true median difference.

healthy control subjects was 0.86 and the 90% CI was (0.41, 1.77), with the upper bound of the 90% CI being less than 2.00. For C_{12}, the geometric mean ratio of patients to matched, healthy control subjects was 1.26 and the 90% CI was (0.65, 2.43), with the lower bound of the 90% CI being greater than 0.40. These data, which take into consideration the overall variability in pharmacokinetics, indicate that there is a low risk of reduced efficacy and a low risk of decreased tolerability in patients with moderate hepatic insufficiency. These findings can be further extrapolated to the population with mild hepatic insufficiency. Because the population with severe hepatic insufficiency was not studied, the effect in that population is not known. Although the primary mechanism of raltegravir clearance is through hepatic metabolism, suggesting a higher likelihood of a resultant clinically meaningful effect in hepatic dysfunction, metabolism is mediated by UGT1A1. Unlike cytochrome-based metabolism, glucuronidation is found to be relatively unaffected by hepatic disease in a number of instances (3, 4). The mechanism has not been completely elucidated but may be due in part to extrahepatic metabolism, the microsomal location of glucuronosyltransfereases, or perhaps, the liberation or activation of latent enzyme (4). The findings for raltegravir in patients with moderate hepatic insufficiency are consistent with the results of other studies with patients with moderate hepatic insufficiency and other compounds which are primarily clearly by glucuronidation (3, 4).

Investigation of the pharmacokinetics of raltegravir in the population with severe renal insufficiency also revealed no clinically meaningful effect of renal insufficiency on the pharmacokinetics of raltegravir, although there was evidence of pharmacokinetic variability. For AUC, the geometric mean ratio for patients to matched, healthy control subjects was 0.56 and the 90% CI was (0.49, 1.49), with the upper bound of the 90% CI being less than 2.00. For C_{12}, the geometric mean ratio for patients to matched, healthy control subjects was 1.28 and the 90% CI was (0.79, 2.06), with the lower bound of the 90% CI being greater than 0.40. These data, which take into account the overall pharmacokinetic variability, indicate that there is low risk of reduced efficacy and a low risk of decreased tolerability in patients with severe renal insufficiency. These findings can be safely extrapolated to the populations with moderate and mild renal insufficiency. In contrast to the drug exposure parameters, clear evidence of alterations in the amount of raltegravir excreted in urine, CL_R, and $t_{1/2\beta}$ was seen. f_e and CL_R were both considerably lower (~90%) for patients with renal insufficiency than for the healthy subjects. The lower rate of CL_R appears to have prolonged the β phase of plasma elimination by ~50%. Because the overall elimination of raltegravir via the renal pathway is minor in subjects with normal renal function, the differences in f_e and in CL_R did not result in a similarly large alteration in the exposure parameters (AUC, C_{max}, and C_{12}). Because the β phase has a minor contribution to AUC and C_{max}, the prolongation of $t_{1/2}$ in this phase did not result in meaningful elevations in AUC or C_{max}. As the level of renal elimination of raltegravir is modest relative to the levels of other plasma clearance pathways, raltegravir may be used in patients with creatinine clearance values of <10 ml/min/1.73 m^2, including subjects on dialysis. The extent to which raltegravir is dialyzable is unknown; therefore, dosing immediately prior to a dialysis session should be avoided.

Comparison of the data for the healthy controls from the current study to the single-dose renal elimination data for healthy subjects from earlier studies shows that the mean recovery of 4.1% was slightly lower than the mean range of 7 to 14% (7). Accordingly, the mean CL_R in healthy subjects was also lower in this study (mean of 31.4 ml/min relative to the mean range of 42 to 78 ml/min). The mean urinary recovery in the human absorption, distribution, metabolism, and elimination study was 9% (8). The differences between the data for the healthy population in this study and the healthy population in earlier studies is not understood. As determined in vitro, the fraction of raltegravir that is unbound to plasma proteins in

humans is 17%, so if a typical glomerular filtration rate of 120 ml/min is assumed, a CL_R value of approximately 20 ml/min would be anticipated for raltegravir on the basis of filtration alone. The observed mean CL_R value for healthy subjects in this study was similar to slightly higher than that value, implying that raltegravir may be actively excreted into urine. However, these data also confirm that an overall low percentage of the dose is excreted unchanged in urine; therefore, CL_R plays a fairly minor role in the overall elimination of raltegravir.

A limitation of the study with patients with moderate hepatic insufficiency was the method used to screen the patients to confirm a lack of renal insufficiency. The Cockcroft-Gault equation was used to estimate creatinine clearance, and this equation has been documented to overestimate this value in patients with severe liver disease (5); the effect in patients with moderate disease is probably similar. As such, there was a risk of the inclusion of patients with combined hepatic and renal impairment in the study with patients with hepatic insufficiency. As there was no clinically meaningful effect of renal organ dysfunction on the pharmacokinetics of raltegravir, the potential inclusion of patients with renal insufficiency in the study with patients with hepatic insufficiency would not affect the overall conclusion.

A limitation of both studies was the inclusion of patients receiving proton pump inhibitors. Subsequent to the conduct of the studies discussed in this report, it was found that proton pump inhibitors increase plasma raltegravir concentrations in healthy subjects, with the values of AUC and C_{max} being increased approximately three- to fourfold (6). The potential mechanism for the increase is likely an increase in gastric pH, resulting in the increased solubility of raltegravir and increased absorption and bioavailability. However, in the HIV-infected population, exploratory data did not reveal the same effect (6). A total of four patients with organ impairment (three in the study with patients with renal insufficiency and one in the study with patients with hepatic insufficiency) received raltegravir concomitantly with a proton pump inhibitor. Exploratory data for these few subjects indicated that there was no substantive difference in the raltegravir concentration profiles relative to those for the other patients. It is unclear why the differences seen in the healthy subject population is not reflected in this study population, but it may be related to the underlying chronic disease in the population with organ impairment or perhaps to the intrinsic variability of the pharmacokinetics of raltegravir. It was hypothesized that if hepatic or renal insufficiency affected the pharmacokinetics of raltegravir, an increase in plasma concentrations would have been seen due to the decreased CL_R or decreased metabolism. Furthermore, the potential effect of proton pump inhibitors could have had a similar effect of increasing the plasma raltegravir concentrations and could have exacerbated the pharmacokinetic effect of organ impairment. Such a finding was not seen. An argument could also be made that the inclusion of concomitant proton pump inhibitor use could misleadingly increase the overall mean for the patient population and negate a decrease in the plasma raltegravir levels; however, review of the data do not suggest such a trend. Overall, no clinically meaningful effect was seen, which continues to support the suggestion that hepatic and renal insufficiencies do not have a clinically meaningful effect on the pharmacokinetics of raltegravir.

In summary, the administration of single 400-mg dose of raltegravir was generally well tolerated by patients with moderate hepatic insufficiency and severe renal insufficiency. There were no clinically important effects of moderate hepatic insufficiency or severe renal insufficiency on the pharmacokinetic profile of raltegravir. No dose adjustment of raltegravir is required for patients with mild or moderate hepatic insufficiency or for patients with renal insufficiency.

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