

Lack of a Clinically Relevant Effect of an Antacid on the Pharmacokinetics of Lersivirine[∇]

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Lersivirine (UK-453,061) is a next-generation nonnucleoside reverse transcriptase inhibitor that displays potent antiviral activity. Lersivirine solubility is pH dependent; therefore, the effect of coadministration of antacid on the pharmacokinetics of lersivirine in healthy subjects was investigated. The ratio of adjusted geometric means (750 mg lersivirine plus 20 ml Maalox Max/750 mg lersivirine alone) for the area under the curve from time zero extrapolated to infinite time (AUC_{inf}) was 101.86%, showing that coadministration of an antacid had no effect on lersivirine exposure. Coadministration appeared to be safe and relatively well tolerated.

Patients with HIV are treated with a combination of anti-retroviral medications and often receive additional agents for the treatment of comorbidities (3). Consequently, the occurrence and extent of drug-drug interactions must be investigated.

Lersivirine is a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), currently in phase 2b development, with *in vitro* antiretroviral activity against wild-type virus and a broad spectrum of clinically relevant NNRTI-resistant strains, including viruses with transmitted resistance to NNRTIs (5). A phase 2a study demonstrated that 7-day monotherapy with 500 and 750 mg lersivirine once daily (QD) achieved mean HIV-1 RNA reductions of 1.7 and 1.8 \log_{10} copies/ml, respectively; in this study and other phase 1 studies lersivirine was safe and well tolerated (2, 4). *In vitro* studies indicate that lersivirine is predominantly cleared by metabolism, with glucuronidation (UGT2B7) being the major metabolic pathway and oxidation via cytochrome P450 (CYP3A4) also being important (8).

Gastrointestinal symptoms are common in patients with HIV, and a substantial subset receive gastric pH-altering therapies (7). Lersivirine exhibits pH-dependent solubility; its solubility at acidic pH (<2) is approximately 3-fold greater than that over the remainder of the physiologically relevant pH range (pH 2 to 7). Therefore, in the presence of an antacid (or in a patient with hypochlorhydria) the oral bioavailability of lersivirine may be decreased. This phase 1 study was conducted to investigate the effects of an antacid on single-dose pharmacokinetics (PK) of lersivirine and the safety and tolerability of single-dose lersivirine when coadministered with an antacid.

This was an open-label, randomized, 2-way crossover study. Healthy subjects, 18 to 55 years of age, with a body mass index (BMI) of 18 to 30 kg/m^2 and total body weight of >50 kg were eligible. Exclusion criteria included HIV infection, significant

medical history, and use of prescription or nonprescription drugs within 7 days prior to the first dose of study medication. All subjects provided written informed consent. The protocol was approved by the Institutional Review Board of the investigational center and was conducted in accordance with the ethical principles established by the Declaration of Helsinki and International Conference on Harmonization good clinical practice (ICH-GCP) guidelines.

Subjects received each of two treatments in a randomized order. Treatment A consisted of 20 ml antacid (Maalox Max) administered 5 min prior to a single 750-mg dose of lersivirine; treatment B consisted of a single 750-mg dose of lersivirine. There was at least a 7-day washout between treatments. Plasma samples for PK analysis were taken predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 h postdose.

Plasma samples were analyzed using a validated, sensitive, and specific high-performance liquid chromatography-tandem mass spectrometry method. Natural log-transformed PK parameters (area under the curve from time zero extrapolated to infinite time [AUC_{inf}], plasma concentration at 24 h [C_{24}], and maximum plasma concentration [C_{max}]) were analyzed using a

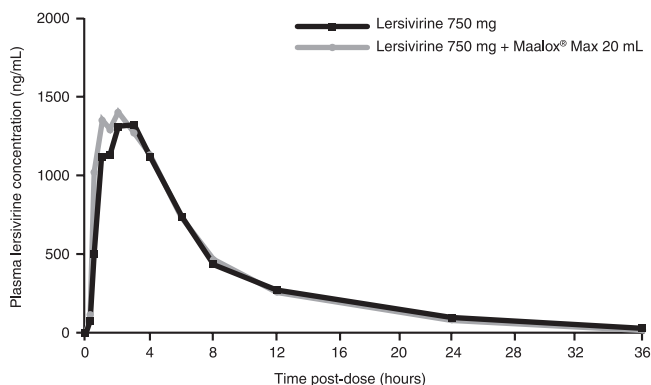


FIG. 1. Median lersivirine concentration-time profiles in healthy subjects after single-dose administration of 750 mg lersivirine with or without concomitant antacid (20 ml Maalox Max).

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TABLE 1. Summary of statistical analysis of lersivirine exposure

Parameter ^c	Value for:		Ratio of adjusted geometric means (%)	90% CI (%)
	750 mg lersivirine + 20 ml Maalox Max (n = 13)	750 mg lersivirine (n = 13)		
AUC _{inf} (ng · h/ml) ^a	11,167.68	10,967.32	101.86	97.09, 106.86
C ₂₄ (ng/ml) ^a	64.41	83.41	74.82	61.49, 91.05
C _{max} (ng/ml) ^a	1,454.48	1,524.06	95.43	82.82, 109.97
T _{max} (h) ^b	2.00 (0.50–4.00)	2.00 (1.00–6.00)	— ^d	—
t _{1/2} (h) ^c	6.223 (16)	6.910 (16)	—	—

^a Adjusted geometric mean.^b Median (range).^c Arithmetic mean (% coefficient of variation).^d —, not applicable.^e T_{max}, time to maximum drug concentration; t_{1/2}, half-life.

mixed-effect model with sequence, period, and treatment as fixed effects and subjects within the sequence as the random effect and the eNCA version 2.2 software package (Pfizer Inc.). Estimates of the adjusted mean differences (lersivirine plus antacid versus lersivirine alone) and corresponding 90% confidence intervals (CIs) were obtained from the model and were exponentiated to provide estimates of the adjusted geometric means (lersivirine plus antacid versus lersivirine alone) and 90% CIs for the ratios.

Fourteen subjects (8 men and 6 women) were enrolled. Subjects ranged in age from 23 to 54 years, had a mean (standard deviation [SD]) body weight of 73.4 kg (13.8 kg), mean (SD) BMI of 25.3 kg/m² (2.7 kg/m²), and mean (SD) height of 169.7 cm (10.2 cm). Median plasma lersivirine concentration-time profiles with and without coadministration of antacid are shown in Fig. 1. PK parameter values are summarized in Table 1.

There were no deaths, serious adverse events (AEs), dose reductions, or temporary discontinuations during this study. Two subjects withdrew after only one treatment period: one who received 750 mg lersivirine was lost to follow-up; one who received 750 mg lersivirine plus antacid was discontinued due to a severe AE. Both subjects provided PK samples for the treatment period completed. A total of 7 subjects reported 18 treatment-emergent all-causality AEs (16 treatment related) while receiving lersivirine plus antacid; 6 subjects reported 11 treatment-emergent all-causality AEs (7 treatment related) while receiving lersivirine alone. The most frequently occurring AEs in both treatment groups were gastrointestinal tract related. The majority of treatment-related AEs were mild in intensity with the exception of 3 events in the lersivirine-plus-antacid group: 1 event of vomiting (moderate), 1 event of dizziness (moderate), and 1 event of left lower quadrant abdominal pain (severe) that led to discontinuation.

Despite the pH-dependent solubility of lersivirine, coadministration with antacid had no significant effect on lersivirine exposure. Hence, it is likely that exposure of lersivirine is driven by the rate of absorption in the small intestine and not by solubility in the stomach.

To date, studies indicate that the concomitant use of acid-reducing treatments (H₂ receptor antagonists and proton pump inhibitors [PPIs]) with the next-generation NNRTIs rilpivirine (TMC-278) and RDEA806 alters the exposure of the NNRTI. Coadministration of 20 mg omeprazole QD with

150 mg rilpivirine QD resulted in a 40% decrease in steady-state rilpivirine AUC₂₄ and C_{max} (1). Furthermore, coadministration of a single dose of 40 mg famotidine 2 h before a single dose of 150 mg rilpivirine decreased rilpivirine exposure by approximately 76%, while administration of famotidine 4 h after rilpivirine increased rilpivirine exposure by 13% (6). Hence, PPIs cannot be coadministered with rilpivirine (1) and H₂ antagonists can be used only if taken more than 12 h before or 4 h after rilpivirine (6). In a single-dose study, coadministration of ranitidine with 300 mg RDEA806 resulted in an approximately 25% decrease in RDEA806 AUC (9). It must be noted that H₂ receptor antagonists and PPIs are more potent acid-reducing agents than antacids, and consequently a direct comparison with the results of this study cannot be made.

In addition to the lack of a pharmacokinetic effect of antacid on lersivirine exposure shown in this study, concomitant administration of lersivirine with antacid appeared to be safe and relatively well tolerated in healthy subjects. Thus, lersivirine can be coadministered with antacids with no effect on lersivirine PK, offering an advantage to patients with HIV who require antacid therapy.

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