Absence of Effect of Rufloxacin on Theophylline Pharmacokinetics in Steady State†

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Several quinolone antibacterial agents are known to inhibit the metabolism of theophylline, with the potential to cause adverse events due to raised theophylline concentrations during coadministration. A randomized crossover study was therefore conducted with 12 healthy male volunteers (ages, 23 to 34 years; body weight, 64 to 101 kg) to evaluate a possible interaction between rufloxacin and theophylline. Both drugs were administered at steady state. Following the administration of an oral loading dose of 400 mg on day 1, rufloxacin was given orally at 200 mg once daily on days 2 to 7 during one period only. During both periods, 146 mg of theophylline was administered orally twice daily for 3 days (which were days 4 to 6 of the rufloxacin coadministration period) and intravenously once the next morning to test for an interaction. Theophylline and rufloxacin concentrations were measured by reversed-phase high-pressure liquid chromatography, the pharmacokinetics of theophylline at steady state following administration of the last dose were calculated by compartment-model-independent methods. To compare the treatments, analysis of variance-based point estimates and 90% confidence intervals (given in parentheses) were calculated for the mean ratios of the pharmacokinetic parameters from the test (rufloxacin coadministration) over those from the reference (theophylline without rufloxacin) period. These were as follows: maximum concentration at steady state, 1.01 (0.96 to 1.07); area under the concentration-time curve from 0 to 12 h, 0.98 (0.94 to 1.02); half-life, 0.99 (0.95 to 1.03); total clearance at steady state, 1.02 (0.99 to 1.06); and volume of distribution in the elimination phase, 1.01 (0.97 to 1.05). In conclusion, rufloxacin did not affect theophylline pharmacokinetics at steady state. Therefore, therapeutic coadministration of rufloxacin and theophylline is not expected to cause an increased incidence of theophylline-related adverse events.

During a clinical trial of enoxacin with patients with respiratory tract infections receiving theophylline, Wijnands et al. (51) observed an increased incidence of side effects resembling those known to occur with a theophylline overdose. Measurement of plasma theophylline concentrations revealed that these side effects were indeed due to elevated drug levels. Subsequently, several new quinolones were investigated for their potential for interactions with theophylline and caffeine. Enoxacin was found to be the strongest inhibitor of methylxanthine metabolism (24, 27, 28, 36, 41, 48, 51, 52), followed by pipemidic acid (46), tosufloxacin (31, 48), ciprofloxacin (2, 25, 34, 45, 52), and pefloxacin (27, 52). The dose-dependent reductions in the total clearance by enoxacin, pipemidic acid, and tosufloxacin are in the clinically relevant range (up to 50% and more at therapeutic doses), whereas the effects of ciprofloxacin and pefloxacin (30 to 40% reductions) are relevant only on rare occasions. Yet, these agents are labeled for this interaction. The inhibitory effects were minor for norfloxacin (5, 9, 35, 36) and negligible or absent for ofloxacin (12, 17, 35, 36, 45), fleroxacin (38, 40), lomefloxacin (32, 46), temafloxacin (25, 28, 41), and sparfloxacin (21, 26) (for reviews on drug interactions between quinolones and methylxanthines, see references 13 and 43). The mechanism of this interaction is competitive inhibition of the enzyme mediating the main fraction of primary caffeine and theophylline metabolism (16), i.e., the cytochrome P-450 isoenzyme CYP1A2 (15, 18, 49). Recently, we were able to establish in vitro tests for the inhibitory potency of a quinolone derivative to the enzyme and to assess a quantitative structure-activity relationship for this effect (14). However, discrepancies between the inhibitory potencies in vitro and in vivo observed, for example, for ciprofloxacin and pefloxacin (13) hamper prediction of a pharmacokinetic interaction of an individual compound, despite a statistically significant in vivo versus in vitro relationship. Therefore, the extent to which a particular quinolone structure will definitely affect the metabolism of theophylline in vivo cannot be predicted unless the affinity of the quinolone to CYP1A2 is very low or absent (Ki greater than 1 nM) (14). Otherwise, this question remains to be clarified for each new quinolone in a clinical study. For rufloxacin, in vitro testing as described for other gyrase inhibitors (14, 16) could not be done due to its poor solubility in aqueous solutions. Rufloxacin [MF 934; 9-fluoro-2,3-dihydro-10-(4-methyl-1-piperazinyl)-7-oxo-[1,2,3de]-1,4-benzothiazine-6-carboxylic acid hydrochloride] is a new long-acting quinolone antibacte-

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† This work is dedicated to Marika Geldmacher-von Mallinckrodt, professor emeritus and former head of the Division of Forensic Toxicology of the University of Erlangen-Nürnberg, Erlangen-Nürnberg, Germany, on the occasion of her 75th birthday.
rial agent (6, 39) developed by Mediolanum Farmaceutici, Milan, Italy. Rufloxacin has a broad spectrum of activity in vitro against clinically important gram-positive and gram-negative aerobes (37, 54). The pharmacokinetics of rufloxacin are characterized by a mean level of plasma protein binding of 60% (53), a long elimination half-life of about 30 to 35 h (19, 22), a low renal clearance (33), and a good tissue penetration (4, 53). In the rat, about 60% of the dose was absorbed (39). The drug seems to have a metabolite with relevant in vivo activity (1, 29). After oral administration of repeated doses of 200 mg (following the administration of a loading dose of 400 mg on day 1) once daily for 5 to 9 days to human volunteers and patients with lower respiratory tract infections, maximum levels in plasma of about 4 µg/ml were achieved at 3 to 5 h after administration (8, 19, 22). Steady-state concentrations in serum were reached within 4 to 5 days of administration (8, 19, 22). The level of excretion of rufloxacin in urine was 25 to 50% of the dose (19, 22). The renal clearance was about 20 ml/min and accounted for about 50% of the apparent total clearance (33, 42, 50).

Available data from clinical trials suggest that rufloxacin, besides its efficacy against other infectious diseases such as urinary tract infections (10, 20), is a suitable drug for the treatment of patients with chronic obstructive pulmonary infections (11, 23, 30). These patients often require theophylline, a bronchodilator, for the treatment of bronchospasms. When administered as a single dose, no effect of rufloxacin on the levels of theophylline and caffeine in plasma could be observed (7). However, due to the long half-life of rufloxacin, steady-state levels in a once-a-day dosing schedule exceed the levels achieved after the administration of a single dose (22) by several times. Thus, the purpose of this study was to assess whether the pharmacokinetics of theophylline at steady state are altered by chronic administration of rufloxacin, as it will be probably dosed in clinical practice.

MATERIALS AND METHODS

Volunteers. Twelve male subjects (age range, 23 to 34 years; mean age, 27.6 years) participated in the study, 64 and 101 kg: mean body weight, 76.1 kg) participated in this study after written informed consent was obtained. The study was approved by the Ethics Committee “Freiburger Ethik-Kommission,” Freiburg, Germany. All subjects were determined to be in good health prior to the study on the basis of physical examination, medical history, and the results of laboratory tests. Hematological and biochemical tests were repeated after the study. No drugs were allowed 4 weeks prior to the beginning of the study. No caffeine- or theophylline-containing foods or beverages were allowed to be ingested from 5 days prior to the first study drug administration for either treatment to the time that the last blood sample for that study period was collected. In addition, no alcohol consumption was permitted for the subjects receiving treatment A (theophylline only) from 12 h prior to the first drug administration until the time that the last sample for this period was drawn and for subjects receiving treatment B (theophylline plus rufloxacin) from 12 h prior to the first drug administration to 5 days after the time that the last sample for this period was drawn.

Study design. The study was conducted by using a randomized two-period crossover design. Treatment A, which consisted of treatment with theophylline only, consisted of treatment for 4 days; treatment B, which consisted of rufloxacin and theophylline coadministration, lasted for 7 days. The treatments were separated by washout periods of 19 and 21 days for treatment sequences A-B and B-A, respectively. For both study periods, 146 mg of theophylline was administered as two immediate-release 73-kg tablets (Euphyllin N) every 12 h for 3 days to achieve steady-state levels (treatment A, days 1 to 3; treatment B, days 4 to 6). The 146-mg theophylline test dose was given as an infusion (Euphyllin) on the last day 12 h after the last administration of theophylline tablets. Both theophylline preparations were manufactured by Byk Gulden, Konstanz, Germany. Rufloxacin (treatment B) was given as 200-kg tablets (Mediolanum Farmaceutici). The onset of rufloxacin administration was 3 days prior to the onset of theophylline administration for the treatment regimen B, starting with a loading dose of 400 mg (two tablets) on the first day. On days 2 to 6, 200 mg of rufloxacin was administered every morning and was administered simultaneously with theophylline tablets on days 4 to 6. On study day 7 of treatment B, rufloxacin (200 mg) was administered at 0.5 h before the start of theophylline administration. For both drugs, morning doses were administered after an overnight fast of 10 h, and evening doses were given after a 3-h fast. The subjects remained in the fasting state for 1 h after drug intake on study days 1 to 3 for treatment A and days 1 to 6 for treatment B. On the last day of treatment, breakfast was given exactly 1.5 h after the start of the theophylline infusion. Standard meals were provided on the last days of both treatments.

Sample collection. Venipuncture was performed on the mornings of study days 1 to 3 (treatment A) and study days 1 to 6 (treatment B) to retrieve blood samples. Blood was taken from an indwelling intravenous cannula on study day 4 (treatment A) immediately before and 0.17, 0.33, 0.50 (end of infusion), 0.58, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 3.50, 4.50, 5.50, 6.00, 8.50, 10.00, 12.00, 12.50, and 24 h after the start of the theophylline infusion. On study day 7 (treatment B) the same blood sampling scheme was used, but in addition, blood samples were collected immediately before rufloxacin dosing and 0.50, 1.00, 1.50, 2.00, and 2.50 h (the sample collected at 2.5 h was identical to the sample taken before the start of infusion) after rufloxacin administration. Blood samples were collected in NaH2-heparinized tubes (Monovette; Sarstedt, Nümbrecht, Germany), shaken slightly at room temperature, and centrifuged for 10 min to remove the blood cells. The resulting plasma was transferred to plastic tubes. Immediately after the samples were pipetted into the test tubes, the samples were frozen and stored under light protection conditions at approximately –20°C.

Drug analysis. Plasma samples were analyzed for theophylline and rufloxacin by reversed-phase high-pressure liquid chromatography assays. For both compounds but not the internal standard, the same sample preparation procedure was used. Plasma (100 µl) samples were deproteinized by addition of 2 µl of a precipitation agent (acetone and methanol, 80/20 [vol/vol]). After vigorous mixing and centrifugation, 50 µl of the supernatant was injected onto the high-pressure liquid chromatography system. Turbowchrom 3 software (version 3.2, 1991; PF Nelson, Cupertino, Calif.) was used to evaluate the chromatograms. Peak heights were used for quantification of rufloxacin, theophylline, and the internal standards.

(i) Theophylline. The chromatographic separation of theophylline was performed on a Lichrospher RP18 column (M. Grom, Herrenberg, Germany) with a solvent consisting of 0.1 M potassium phosphate buffer, methanol, and acetonitrile (80/15/5 [vol/vol/vol]). 8-Chlorotheophylline was used as an internal standard. The retention times of theophylline and 8-chlorotheophylline were 7.3 and 15 to 17 min, respectively. The eluent was monitored with UV light (273 nm).

(ii) Rufloxacin. The samples used for quantification of rufloxacin were always handled under conditions that protected the samples from light. The chromatographic separation of rufloxacin was performed on a Spherisorb ODS II column with a solvent consisting of 0.1 M citric acid buffer containing ammonium perchlorate and acetonitrile containing tetrabutylammonium hydrogen sulfate (16/84 [vol/vol]). Sparfloxacin was used as an internal standard. The retention times of rufloxacin and sparfloxacin were 5 and 11 min, respectively. The eluent was monitored with UV light (300 nm).

The calibration graphs were linear from 0.00691 to 9.99 ìg/ml with a coefficient of correlation greater than 0.999. The lower limit of quantitation in plasma was set equal to 0.152 ìg/ml.

The within-day precision (coefficient of variation) was found to be 4.2% for 0.487 ìg/ml (relative error, –1.9%), 1.2% for 1.96 ìg/ml (relative error, 1.5%), and 0.5% for 13.9 ìg/ml (relative error, 2.1%). The between-day precision was 3.5% for 0.487 ìg/ml (relative error, –1.9%), 1.8% for 1.96 ìg/ml (relative error, 0.8%), and 1.3% for 13.9 ìg/ml (relative error, 1.7%). The absolute recovery of theophylline in plasma was 87.6% ± 6.1% over the whole concentration range tested. The recovery of the internal standard (8-chlorotheophylline) was 85.6% ± 1.6%.

Both theophylline and rufloxacin were stable in plasma at room temperature over a period of at least 4 h. After sample workup, no instability was observed over a period at least 48 h at either room temperature or approximately –20°C. Rufloxacin was stable for at least 6 months when it was stored in plasma in a freezer at approximately –20 and approximately –80°C. No instability of rufloxacin in plasma was observed over three freeze-thaw cycles.

Pharmacokinetic calculations. The following pharmacokinetic parameters were determined for treatment regimens. Predose trough concentrations were measured on days 2, 3, and 4 (treatment A) and on days 5, 6, and 7 (treatment B). Maximum plasma concentrations at steady state (Cmax) were taken directly from the measured data obtained on study days 4 (treatment A) and 7 (treatment B). The area under the plasma concentration-time curve from the start of the theophylline infusion to steady state (AUC0–ss) was calculated from the measured data from the start of
infusion up to 12 h after the start of infusion by the linear trapezoidal rule. The terminal elimination constant (b) was calculated by log-linear regression of the data from the concentration-time profile from 2 to 24 h after the onset of theophylline infusion. Total clearance at steady state (CLss) was calculated by the formula CLss = dose/AUCssmax. The b-phase volume of distribution (Vb) was calculated as Vb = dose/(AUCbssmax * b).

The following pharmacokinetic parameters were determined for rufloxacin. The predose trough concentrations on days 2 to 7 (treatment B), Cmaxss, and the time to Cmaxss were taken directly from the measured data. A one- or two-compartment model was fitted to all datum points including trough values by proportional weighting. The model used for further calculation was selected according to the Akaike Information Criterion. The following parameters were estimated from the fitted models: apparent clearance, apparent volume of distribution at steady state, mean absorption time, and mean residence time of rufloxacin.

Confidence intervals for the ratios of the pharmacokinetic parameters for rufloxacin between both treatments, the parametric point estimates of the ratio μtest/μreference, and the corresponding 90% confidence intervals were always within the bioequivalence interval of 0.80 to 1.25 (Table 1). Accordingly, the null hypothesis that “rufloxacin has a relevant effect on theophylline pharmacokinetics” was rejected for all pharmacokinetic parameters. Thus, there was no evidence that rufloxacin has any effect on either the distribution or the elimination of theophylline.

The pharmacokinetics of rufloxacin were best described by a one-compartment model for five volunteers and by a two-compartment model for the remaining seven volunteers. Mean ± SD pharmacokinetic parameters are presented in Table 2. N-

### RESULTS

The mean concentrations of theophylline in plasma after the administration of six multiple oral doses of 146 mg of theophylline and one intravenous infusion of 146 mg of theophylline without and with chronic coadministration of rufloxacin at 200 mg once daily (n = 12). Rufloxacin administration was started with the administration of a loading dose of 400 mg (two tablets) on the first day. On days 2 to 6, 200 mg of rufloxacin was administered every morning. On day 7, the last 200-mg rufloxacin dose was administered 21.5 h after the administration of the previous rufloxacin dose.

(Fig. 2). The mean ± SD pharmacokinetic parameters for theophylline as well as the results of the statistical analysis are summarized in Table 1. The Cmaxss values of 7.08 ± 0.85 and 7.00 ± 0.90 μg/mL (mean ± SD) with and without coadministration of rufloxacin, respectively, were almost identical, as were the AUCssmax values: 42.6 ± 9.89 and 43.4 ± 9.35 μg · h/mL, respectively (mean ± SD). For the comparison of the pharmacokinetic parameters for theophylline between both treatments, the parametric point estimates of the ratio μtest/μreference and the corresponding 90% confidence intervals were always within the bioequivalence interval of 0.80 to 1.25 (Table 1). Accordingly, the null hypothesis that “rufloxacin has a relevant effect on theophylline pharmacokinetics” was rejected for all pharmacokinetic parameters. Thus, there was no evidence that rufloxacin has any effect on either the distribution or the elimination of theophylline.

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### TABLE 1. Pharmacokinetic parameters for theophylline

<table>
<thead>
<tr>
<th>Treatment or parameter</th>
<th>Cmaxss (μg/mL)</th>
<th>AUCssmax (μg · h/mL)</th>
<th>t1/2 (h)</th>
<th>CLss (mL/min)</th>
<th>Vb (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7.00 ± 0.90</td>
<td>43.4 ± 9.35</td>
<td>7.12 ± 1.50</td>
<td>59.1 ± 15.6</td>
<td>35.0 ± 5.03</td>
</tr>
<tr>
<td>B</td>
<td>7.08 ± 0.85</td>
<td>42.6 ± 9.89</td>
<td>7.05 ± 1.67</td>
<td>60.0 ± 17.1</td>
<td>35.3 ± 5.48</td>
</tr>
<tr>
<td>PEb</td>
<td>1.012</td>
<td>0.978</td>
<td>0.985</td>
<td>1.022</td>
<td>1.007</td>
</tr>
<tr>
<td>90% CI†</td>
<td>0.955–1.072</td>
<td>0.942–1.015</td>
<td>0.945–1.026</td>
<td>0.985–1.060</td>
<td>0.966–1.051</td>
</tr>
<tr>
<td>CV (%)</td>
<td>7.9</td>
<td>5.0</td>
<td>5.6</td>
<td>5.0</td>
<td>5.8</td>
</tr>
</tbody>
</table>

*Values are means ± SDs for theophylline after the administration of six multiple oral doses of 146 mg of theophylline twice daily and one intravenous infusion of theophylline ethylenediamine monohydrate equivalent to 146 mg of theophylline without and with steady-state coadministration of 200 mg of rufloxacin once daily (n = 12); the results of statistical analysis are also presented (ANOVA-based point estimates [PE], 90% confidence intervals [90% CI] for the comparison test [coadministration of rufloxacin] versus the reference test [theophylline alone] and intrapatient coefficients of variation [CV]).

†Treatment A, theophylline without rufloxacin coadministration; treatment B, theophylline with rufloxacin coadministration; t1/2, half-life; the other abbreviations are defined in the text.

*For comparisons between treatments, individual ratios (treatment B/treatment A) of parameters were used.

FIG. 1. Mean ± SD levels of theophylline in plasma following the administration of the last dose of theophylline after the administration of six multiple oral doses of 146 mg of theophylline twice daily and one intravenous infusion of theophylline ethylenediamine monohydrate equivalent to 146 mg of theophylline without and with steady-state coadministration of rufloxacin at 200 mg once daily (n = 12).

FIG. 2. Mean ± SD levels of rufloxacin in plasma following the administration of the last 200-mg dose of rufloxacin after the administration of multiple oral doses during steady-state coadministration of 146 mg of theophylline twice daily (n = 12). Rufloxacin administration was started with the administration of a loading dose of 400 mg (two tablets) on the first day. On days 2 to 6, 200 mg of rufloxacin was administered every morning. On day 7, the last 200-mg rufloxacin dose was administered 21.5 h after the administration of the previous rufloxacin dose.
Desmethylerufloxacin, a major urinary metabolite of rufloxacin, was not found in the plasma samples (limit of detection, 0.01 μg/ml).

**DISCUSSION**

In this steady-state study we could demonstrate that no statistically significant changes in the total clearance, volume of distribution, or half-life of theophylline occurred when it was administered together with rufloxacin. Inspection of the individual data as well as comparison of the mean values suggests that there is no evidence of a significant interindividual variability in the possible inhibitory potency of rufloxacin. This result is in accordance with that of a study on the effect of a single dose of rufloxacin on theophylline and caffeine pharmacokinetics (7). Rufloxacin therefore does not seem to have any potential for interaction with theophylline pharmacokinetics. This is in contrast to the case for some other quinoline antibiotic agents which have clinically relevant effects on theophylline concentrations, such as enoxacin (24, 27, 28, 36, 41, 48, 51, 52), pipemidic acid (46), tosulfloxacin (31, 48), ciprofloxacin (2, 25, 34, 45, 52), and pefloxacin (27, 52) and to the case for norfloxacin (5, 9, 35, 36), which has a minor but clearly reproducible inhibitory action. Rufloxacin thus belongs to the same group of compounds as ofloxacin (12, 17, 35, 36, 45), feroxacin (38, 40), lomefloxacin (32, 46), temafloxacin (25, 28, 41), and sparfloxacin (21, 26), for which no clinically relevant inhibition of theophylline metabolism has been described.

The concentrations of rufloxacin and its derived pharmacokinetic parameters observed in this study were very similar to those observed in previous studies of multiple doses of 200 mg given twice daily (22, 50). Likewise, data on theophylline pharmacokinetics corresponded to published data (34). A major shortcoming of the current data on interactions between methylxanthines and quinoline antibiotic agents is that only a few comparative studies with a randomized crossover design have been reported (25, 27, 28, 35, 36, 41, 52). In studies comparing different groups of subjects or using the same sequence of treatments for all volunteers, the nonspecific differences may easily be as large as the potential differences between agents. As a consequence, in clinical studies by various investigators, considerable variability in study outcome was observed for the pharmacokinetic parameters (Table 1) documents the fact that the study design eliminated most sources of nonspecific variation. The comparison with ofloxacin is of special interest in view of our recent findings on quantitative structure-activity relationships (14). Ofloxacin is chemically closely related to rufloxacin (6). The two structural differences are the sulfur atom in rufloxacin that yields a benzothiazine derivative (ofloxacin is a benzoxazine derivative) and the missing methyl group at position 3 of the benzothiazine group of rufloxacin (3-methylbenzoxazine in ofloxacin). Both ofloxacin and rufloxacin have an N-methyl substituent at position 4’ of the piperazinyl ring. This substitution was related to a lower level of inhibitory activity against CYPIA2 in vitro for several quinoline derivatives compared to the activities of their unmethylated congeners (14). Accordingly, ofloxacin did not alter the pharmacokinetics of theophylline (or caffeine) in several studies (see above). In one study, however, ofloxacin administration was reported to have decreased theophylline clearance by 12% (43). Additionally, in vivo investigations with human liver microsomes, ofloxacin was a competitive inhibitor, albeit a very weak competitive inhibitor, of the cytochrome P-450 isof orm CYPIA2 (16), which mediates theophylline metabolism (15, 18, 49). We therefore assumed that rufloxacin, if it had an affinity to the binding site of CYPIA2 in vitro similar to that of ofloxacin, might reach sufficient concentrations at the enzyme to translate this property into a drug interaction in vivo, since steady-state levels of rufloxacin at therapeutic doses exceed those of ofloxacin by more than twofold (8, 22, 42, 44, 50). Thus, the possibility that rufloxacin had at least a minor inhibitory effect on theophylline pharmacokinetics that exceeded that of ofloxacin could not be excluded from data on chemical structure and rufloxacin pharmacokinetics only. Despite these considerations, however, which made it desirable to evaluate the possible inhibitory effect of rufloxacin on theophylline metabolism under conditions close to those in the therapeutic situation, rufloxacin did not alter theophylline pharmacokinetics in this study. In conclusion, this study demonstrated unequivocally that at a chronic daily rufloxacin dose of 200 mg, no interaction of rufloxacin with theophylline is to be expected. There is no reason not to extend these findings with healthy volunteers to patients treated with this or other combinations of doses of rufloxacin and theophylline.

**ACKNOWLEDGMENTS**

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**REFERENCES**


<table>
<thead>
<tr>
<th>$C_{\text{ssmax}}$ (μg/ml)</th>
<th>$T_{\text{ssmax}}$ (h)</th>
<th>$V_{\text{ss/f}}$ (liters)</th>
<th>$CL/f$ (ml/min)</th>
<th>MAT (h)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.80 ± 0.52</td>
<td>1.34 ± 0.70</td>
<td>133.0 ± 31.2</td>
<td>44.4 ± 7.3</td>
<td>0.60 ± 0.45</td>
<td>50.8 ± 13.0</td>
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</table>

* Values are means ± SDs for rufloxacin following the last administration of a 200-mg dose of rufloxacin after the administration of multiple oral doses during steady-state coadministration of 146 mg of theophylline twice daily (n = 12) (treatment B). Rufloxacin administration was started with a loading dose of 400 mg (two tablets) on the first day. On days 2 to 6, 200 mg of rufloxacin was administered every morning. On day 7, the last 200-mg rufloxacin dose was administered 21.5 h after the time of administration of the previous rufloxacin dose. $T_{\text{ssmax}}$, time to $C_{\text{ssmax}}$; $V_{\text{ss/f}}$, apparent volume of distribution at steady state; CL/f, apparent clearance; MAT, mean absorption time; MRT, mean residence time of disposition.


