Rifabutin Absorption in the Gut Unaltered by Concomitant Administration of Didanosine in AIDS Patients

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Didanosine (ddI) is currently used in the management of patients infected by the human immunodeficiency virus. Rifabutin (RBT) is being extensively used for prophylaxis against Mycobacterium avium complex (MAC) infections. Due to its acid-labile characteristics, ddI must be administered with a buffer. Recent reports have indicated that absorption of ketoconazole, ciprofloxacin, and dapsone, etc., in the gut is altered by concomitant ddI dosing. We have assessed whether concomitant dosing of ddI as antiretroviral therapy modifies RBT absorption in the gut, its steady-state pharmacokinetics, and/or safety in 15 patients with AIDS. Of the 15 patients enrolled, 12 completed the study and 3 receiving 600 mg of RBT with concomitant ddI administration withdrew prematurely from the study. Steady-state RBT pharmacokinetics were assessed on day 13 (ddI plus RBT) and day 16 (RBT alone). The ddI doses (adjusted for body weight) were 167 to 375 mg twice daily, while RBT was administered as a single 300- or 600-mg daily dose. No statistically significant (P > 0.05) differences were seen in RBT absorption parameter estimates between days 13 and 16: maximum concentration in plasma (Cmax; 511 ± 341 ng/ml versus 525 ± 254 ng/ml) and the time at which Cmax was observed (3.0 versus 2.5 h). The mean RBT estimates for area under the concentration-time curve from 0 to 24 h (AUC0–24) (5,650 versus 5,023 ng·h/ml) and for oral clearance (1.28 versus 1.18 liter/h/kg) on both study days were also similar. Assessment based on urinary recovery of RBT (3.1 versus 3.7 mg) and its predominant deacetyl metabolite, LMS565 (1.6 versus 1.4 mg), showed no apparent effect of ddI. The fraction of the RBT dose converted to LM565, as suggested by the ratio of AUC of the metabolite to AUC of the parent drug, was also unaltered (0.15 versus 0.12). A ratio analysis (day 13/day 16) of the RBT pharmacokinetic estimates showed that the 95% confidence intervals for all parameters were inclusive of one. Furthermore, the brief interruption of ddI therapy over this short study period at steady state produced no clinically significant changes in body weight, hematology, and renal and pancreatic functions. Therefore, concomitant administration of ddI appears not to affect RBT absorption in the gut and its disposition or safety in patients with AIDS.

Rifabutin (RBT) has shown a broad spectrum of antibacterial activity against a number of gram-positive and gram-negative organisms, as well as mycobacteria, including Mycobacterium avium complex (MAC) (11). In North America, RBT is currently an approved agent for MAC prophylaxis in patients with advanced AIDS.

RBT appears to be readily but incompletely absorbed from the gastrointestinal tract in humans and animals (2, 15). RBT also distributes extensively in the body; the apparent volume of distribution is 8 to 9 liter/kg of body weight (15). Linear drug disposition at doses up to 600 mg in healthy volunteers (17) in healthy volunteers but also at doses up to 900 mg in patients with AIDS-related complex (ARC) has been established (15). Two main metabolites, an equiactive 25-deacetyl derivative (LM565) and a 31-hydroxy derivative, which contribute 5% of the dose (2). However, some 30% of the urinary drug excretion is accounted for as polar metabolites (2). From a physiochemical perspective, RBT has a low aqueous solubility and carries a tertiary amide group (R3NH+) which has a pKa of approximately 7.2 (10). The solubility and octanol-to-water partitioning coefficient of RBT at neutral pH have been measured to be 0.23 mg/ml and 2,562, respectively (10). Because of changes in the degree of ionization of the tertiary amide group, the solubility of RBT decreases by 16-fold and the octanol-to-water partitioning coefficient increases by 8-fold when the pH increases from 5 to 7.4. As a result, changes in gastric pH may have an impact on the solubility and possibly dissolution of RBT.

Didanosine or 2′,3′-dideoxyinosine (ddI) is an antiretroviral nucleoside which has shown activity against human immunodeficiency (HIV). Therapy with ddI doses exceeding 20 mg/kg/day has been associated with peripheral neuropathy and pancreatitis (4). Hyperuricemia has also been observed at ≥30 mg/kg/day (4). The elimination half-life for ddI, which averages 0.5 to 2.0 h, is short. However, the intracellular half-life of the active moiety (ddI triphosphate) is much longer and varies from 12 to 24 h (12). This long intracellular half-life is the reason why the drug is given twice daily. Perhaps the most prominent characteristic for ddI is its instability in an acidic environment. Therefore, this antiviral agent has to be properly buffered prior to oral administration. It has been shown that 10% of the dose, if unbuffered, would be decomposed to hypoxanthine at pH <3 at 37°C in 2 min (12).

ddI, in the presence of various buffering agents in its formulations, has caused altered drug availability for a number of compounds, including dapsone (14), ranitidine (7), zidovudine (1), ciprofloxacin (13), and itraconazole (9). Although the mechanisms of interaction between these agents may vary, it is believed that the increase in gastric pH as a result of the buffering agents may affect drug absorption for some agents.
Although the availability of newer agents, e.g., protease inhibitors and nonnucleoside analogs, has expanded the options for the treatment of HIV infection, most dosing strategies that are promoted employ drug combination regimens that are inclusive of nucleoside reverse transcriptase inhibitors to guard against resistance development (3, 19). Therefore, the numbers of patients, i.e., those with ARC or AIDS, receiving ddI along with their MAC prophylaxis RBT therapy are expected to increase. From the perspective of pharmacotherapy, the impact of possible alteration in RBT absorption and bioavailability (F) when both drugs are concomitantly administered needs to be addressed. The present study explored the potential for changes in the absorption and other pharmacokinetic characteristics of RBT at steady-state and safety when the study patients received the two drugs in combination.

MATERIALS AND METHODS

Study protocol. Patients who had been receiving ddI as the only antiretroviral therapy for ≤6 weeks before initiation of the study were recruited. The patients who participated in this study also had to satisfy the following inclusion-exclusion criteria to be enrolled: male or female patients of 18 years or older with laboratory evidence of HIV infection and clinical symptoms consistent with the diagnosis of AIDS as per criteria defined by the Centers for Disease Control: ≤500 CD4 cells/μl, an absolute neutrophil count of ≥1,000/mm³, and no evidence of active pulmonary disease or significant liver or kidney impairment. Written informed consent was obtained from each of the study patients. At the study initiation, the protocol required participating patients to receive a 600-mg/day dose of RBT (Adria Labs, Columbus, Ohio) with ddI (Bristol-Myers Squibb, Syracuse, N.Y.). Due to an apparently higher incidence (three of six) of adverse events in the first six enrolled patients and the revised RBT dosage per the phase III study plan, the protocol was amended to change the RBT dose from 600 to 300 mg daily. RBT was administered as a single daily dose, while ddI (doses, 167 to 375 mg, based on body weight) was given orally on a twice-a-day regimen. On days 2 to 13, patients receiving oral ddI doses daily were also given RBT prior to the morning meal. ddI was discontinued after the morning dose on day 13, such that RBT was given alone daily from days 13 to 16, thus permitting steady-state drug absorption and other pharmacokinetic assessments of RBT before (day 13) and after (day 16) ddI withdrawal. To minimize any unnecessary interruption of the sole antiretroviral therapy, the patients were allowed to return to their normal ddI schedule beginning on day 17. The goal of this protocol was to allow comprehensive assessments of steady-state RBT absorption and pharmacokinetics with minor disturbance of other therapies the patients should have received.

Biological samples were obtained on days 13 and 16 from the study patients. Blood sampling on day 13 was scheduled at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h. An additional blood sample representing the minimum concentration of drug in plasma at steady state (C_{ss}) before the morning dose on day 12 was drawn to confirm the steady-state pharmacokinetic condition for RBT. On day 16, blood sampling schedule simulated that for day 13 was followed. At each sampling time, blood samples were collected in heparinized tubes and centrifuged for separation of the plasma. Urine samples were collected for a 24-h period on days 13 and 16 over the 0- to 2-, 2- to 4-, 4- to 8-, 8- to 12-, and 12- to 24-h intervals and were kept refrigerated throughout all collection periods. After volume and pH measurements, an aliquot of the urine sample from each collection was stored in plastic tube. All biosamples were frozen at -50°C prior to RBT assaying. Concurrent with the pharmacokinetic evaluations, safety measurements including those of pancreas, liver, and other vital organ functions were assessed by determining the levels of amylase in serum, hematologic, chemistries, and urinalysis on both days 13 and 16.

Evaluations of absorption and pharmacokinetics. Rates of drug absorption were estimated from the maximum concentration of drug in plasma (C_{max}) and the time at which C_{max} was observed (T_{max}), which were directly from the individual concentration versus time data. The extent of drug absorption (area under the plasma concentration versus time curve [AUC]) after a dosing interval [AUC_{CL,INF}] = 24 h), where oral clearance (CL_{INF}), and renal clearance (CL_{R}) were estimated as noncompartmental analysis (5). In addition to AUC_{CL,INF}, urinary drug excretion over dosing interval X_{[0-t] INF}, another estimator for drug absorption, was also measured for individual patients. The pharmacokinetic parameters obtained for the deacetyl metabolite LM565 were analyzed in a similar manner and are distinguished from the parent drug by the subscript m, (e.g., AUC_{m}). The AUC_{CL,INF}/AUC_{m} ratios (where p represents the parent drug) were calculated to provide further information on the formation and disposition CL of LM565. Because two RBT doses, i.e., 300 and 600 mg, were studied and because the steady-state pharmacokinetics of RBT have shown to be linear up to 900 mg (15), both C_{max} and AUC_{m} values obtained for the 600-mg dose were normalized to those for the 300-mg dose to facilitate the comparison.

Statistical analysis. Based on previous pharmacokinetic estimates from HIV-positive patients, computation of power estimates suggested that a sample size of 12 (assuming a 40% coefficient of variation [CV]) was adequate for the detection of a 35% difference in the AUC for RBT. The paired t test was used to assess the effect of removal of ddI on the absorption, disposition, and safety of RBT and LM565. Steady-state pharmacokinetic and safety parameters obtained before (day 13) and after (day 16) the removal of ddI were compared. The significance level (α) was chosen to be 0.05. To confirm these changes more vigorously, the day 13/day 16 ratios of individual pharmacokinetic parameters and their respective 95% CI were computed. The ratio of one or unity was used as a point of reference suggesting no effect on RBT by ddI coadministration.

Drug assay. Concentrations of RBT and LM565 in plasma and urine were determined by a high-performance liquid chromatography assay at Harris Laboratories, Lincoln, Neb. The assay was developed at the Bioanalytical Laboratory of Adria Laboratories (8) and was properly validated by the analytical site before its use.

RESULTS

A total of 15 patients, of whom 12 completed the study as required per protocol, were enrolled. All patients were Caucasian except for patient 12, who was black. One female (patient 6) also participated in the study. At screening, a mean (± standard deviation [SD]) age of 36.3 ± 5.3 years (range, 29 to 50), a mean height of 176 ± 6 cm (range, 160 to 184), and a mean weight of 69.4 ± 8.3 kg (range, 54.8 to 87.0) were recorded for the 15 patients. Six patients (patients 1, 2, 3, 4, 103, and 104) received 600 mg of RBT daily, while the other 9 received a 300-mg dose. All patients receiving ddI were on a twice-a-day regimen. Eleven of the 15 patients received a 250-mg dose of ddI, two patients (1 and 7) received 167 mg, and two others (3 and 104) received 375-mg dose. Three patients (patients 3, 4, and 104) receiving RBT (600 mg/day) and ddI (375 mg [patient 3]) 250 mg [patient 4], and 375 mg [patient 104]) were prematurely discontinued from the study.

Bioanalytically, for both RBT and LM565, least-squares regression estimates for calibration showed a relative SD (RSD) of <18.2% in slope. Precision from the low and the high quality controls (OQC) for RBT showed RSDs of 12.8 and 7.8%, respectively. Accuracy expressed as bias were +4.44 and +3.37% from the low and the high RBT QCs, respectively. Assay accuracy and bias for LM565 were similar to those for RBT. Precision-accuracy in the urine matrix for the low (300-ng/ml) and the high (2,500-ng/ml) QCs showed interday RSD and bias values of 4.7% (low QC) and -2.23% (high QC) and 5.5% (low QC) and -4.92% (high QC), respectively. These data adequately supported the assay performance for both compounds in the present study.

RBT and LM565 steady-state pharmacokinetics (day 13): before ddI removal. The dependence of RBT pharmacokinetic parameters on the length of ddI RBT coadministration were assessed. The significance level (α) was chosen to be 0.05; paired t test) were detected. Thus, parameter estimates of RBT for all patients were employed for day 13 versus day 16 comparisons. When RBT was given concomitantly with ddI on day 13, the drug was readily absorbed, with an average T_{max} of 3.0 h. Mean (± SD) dose-normalized C_{max} and AUC_{CL,INF} estimates at steady state were 511 (± 341) ng/ml and 5,650 (± 4,420) ng·h/ml, respectively. Estimated CL_{INF}/F was 1.28 liters/h/kg. Similar pharmacokinetic estimates for LM565 are shown in Table 1. Along with other metabolite/parent ratios shown in Table 2, the mean (± SD) AUC_{CL,INF}/AUC_{m} ratio estimate was 0.153 (± 0.063). Mean amounts of RBT and LM565 excreted over a 24-h dosing interval on day 13 totalled <1.6% of the oral dose. However, the cumulative urinary excretion reported is slightly underestimated due to missing samples or to levels being below the limit of quantitation. Nevertheless, by using matched urine collection and AUC intervals, the respective CL_{INF} and CL_{R} values were reliably assessed (Table 1).

RBT and LM565 steady-state pharmacokinetics (day 16): after ddI removal. Following the removal of ddI from the
combination regimen, a mean (± SD) dose-normalized $C_{\text{max}}$ for RBT of 525 (± 255) ng/ml was achieved within 2.5 h postdose on day 16. Mean (± SD) AUC$_{0-\text{t}}$ and CL$_{\text{R}}$/F were 5023 (± 2780) ng · h/ml and 1.18 (± 0.67) liter/h/kg, respectively. Similar parameter estimates for LM565 are also listed in Table 1. The AUC$_{0-\text{t}}$/AUC$_{\text{R}}$ ratio, which is an index for metabolite formation-disposition, was 0.12 (Table 2). Similar to the results for day 13, total urinary recovery of RBT and LM565 post-ddI removal remained low, i.e., 1.8%. The corresponding CL$_{\text{R}}$ and CL$_{\text{R(free)}}$ estimates on day 16 were similar to those for day 13 (Table 1).

Statistical analysis of RBT absorption and LM565 pharmacokinetics: effect of ddI removal. Absorption parameters (such as $C_{\text{max}}$, $T_{\text{max}}$, and AUC) for RBT and LM565 obtained on day 16 closely matched those for day 13, suggesting that both the rate and the extent of RBT absorption were not altered by concomitant administration with ddI. No statistically significant differences ($P > 0.05$) were detected in other disposition parameters between days 13 and 16 by the paired $t$ tests for both RBT and LM565. Although from a statistical design perspective, the study might be subjected to period effects which were imposed by the constraint of brief interruption of ddI therapy, given the short elimination half-life of ddI, the impact of such effects should be pharmacologically minimal. The day 13/day 16 ratios for all pertinent RBT and LM565 parameters were not different from unity; the 95% CIs of all ratios were inclusive of 1 (Table 3). The results of these statistical analyses clearly suggest the lack of an impact by ddI on RBT absorption, distribution, metabolism, and elimination. To depict these results graphically, Fig. 1 shows the mean (± SD) dose-normalized RBT and LM565 concentration versus time profiles obtained on both study days.

As for urinary excretion over the 24-h dosing interval, which was estimated by using matched collection intervals on both study days, the day 16/day 13 ratios for RBT and LM565 were 0.85 (95% CI, 0.63 to 1.05) and 1.22 (95% CI, 0.70 to 1.75), respectively (Table 3). Since these CIs encompass unity in both cases, changes in renal excretion for either the parent drug or its metabolite are not apparent.

Evaluation of $C_{\text{min}}$SS levels. The mean steady-state trough levels ([$C_{\text{min}}$SS]) (± SD) of RBT measured prior to the withdrawal of ddI on the mornings of days 12, 13, and 14 were 155 (± 103), 180 (± 95), and 161 (± 67) on the 3 consecutive days. The consistency in these mean $C_{\text{min}}$SS values indicates that steady-state pharmacokinetics for RBT were achieved after 12 days of concomitant RBT-plus-ddI dosing. Also apparent from these $C_{\text{min}}$SS estimates is the large variation in these patients with advanced disease, i.e., ranges from 31 to 258, <20 to 306, and 29 to 339 ng/ml on days 12, 13, and 14, respectively. Nevertheless, these data provide important estimates of both inter- and intrapatient variability. Contributions from the assay method, impact of concomitant medications, patient compliance, and disease status are important determinants of this variability. The magnitude of intrapatient variability (%CV) in RBT $C_{\text{min}}$SS levels ranged from ~4 to 29%. The interpatient component was estimated to be ~50 to 70%. As expected, interpatient variability was much higher than that of the intrapatient component. A similar degree of interpatient variability (~67%) was also observed for the dose-normalized $C_{\text{max}}$ for RBT on day 13. This may reflect a relatively constant interpatient variation over the whole dosing interval. By comparing the 50 to 70% interpatient variability of $C_{\text{min}}$SS over days 12 to 14 to the 50% variability of dose-normalized $C_{\text{max}}$ on day 16, the removal of ddI appears to have minimal effect on the pharmacokinetic variability of RBT under steady-state conditions. Likewise, the respective degrees of interpatient variability, i.e., 64 and 61%, observed for $C_{\text{min}}$SS on days 16 and 17 were similar to that for dose-normalized $C_{\text{max}}$ on day 16.

Safety assessment. Three patients (3, 4, and 104) receiving RBT (600 mg/day) and ddI (250 to 375 mg) prematurely withdrew from the study. Patient 3 had a ddI-related elevation in the level of amylase, and patient 104 reported increased thirst and showed signs of dehydration. Patients 104 and 4 developed some nonspecific signs and symptoms. The subsequent safety

### Table 1. Summary of steady-state absorption and disposition estimates for RBT and LM565

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parameter for day 13</th>
<th>Parameter for day 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (ng/ml)$^a$</td>
<td>$T_{\text{max}}$ (h)</td>
</tr>
<tr>
<td>RBT</td>
<td>Mean 511.0 3.0 5,650 1.28 0.009 3.08</td>
<td>525.0 2.5 5023 1.18 0.012 3.74</td>
</tr>
<tr>
<td></td>
<td>SD 341.0 1.2 4,420 0.82 0.003 1.70</td>
<td>255.0 1.1 2780 0.67 0.004 1.77</td>
</tr>
<tr>
<td></td>
<td>n 12 12 12 12 11$^c$ 11$^c$</td>
<td>12 12 12 12 12 12</td>
</tr>
<tr>
<td>LM565</td>
<td>Mean 76.6 3.6 953 NA$^d$ 0.035 1.64</td>
<td>66.6 3.0 667 NA 0.041 1.39</td>
</tr>
<tr>
<td></td>
<td>SD 66.0 1.4 952 0.021 1.32</td>
<td>40.9 0.8 587 0.016 0.96</td>
</tr>
<tr>
<td></td>
<td>n 12 12 12 12 11 11</td>
<td>12 12 12 12</td>
</tr>
</tbody>
</table>

$^a$ Values are for the 12 patients with AIDS from this study. Values for day 13 are for RBT plus ddI, while those for day 16 are for RBT alone.

$^b$ Normalized to the 300-mg dose.

$^c$ Urine samples not available; excluded from the calculation of mean and SD values.

$^d$ NA, not applicable.

### Table 2. Summary of metabolite/parent ratios for steady-state pharmacokinetic estimates$^e$ day 13 (RBT + ddI) and day 16 (RBT Alone)

<table>
<thead>
<tr>
<th>Value</th>
<th>Ratio for the following parameters and study days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 13</td>
<td>Day 16</td>
</tr>
<tr>
<td>$C_{\text{max}}$ $^a$</td>
<td>0.138</td>
</tr>
<tr>
<td>SD</td>
<td>0.051</td>
</tr>
<tr>
<td>n</td>
<td>12</td>
</tr>
</tbody>
</table>

$^a$ Values are for RBT plus ddI (day 13) and RBT alone (day 16).

$^b$ $P > 0.05$ for day 13 versus day 16 ratios.

$^c$ $P > 0.05$ for day 13 versus day 16 ratios.

$^d$ $P > 0.05$ for day 13 versus day 16 ratios.

$^e$ $P > 0.05$ for day 13 versus day 16 ratios.

$^f$ Urine samples for patient 1 on day 13 were not available.
assessments was based on the available data collected from the 12 patients who completed the study as per protocol.

Among all the safety parameters in Table 4, a slight decrease ($P = 0.01$) in body weight was observed. However, removal of ddI did not produce any statistically significant ($P > 0.05$) effect on any hematological parameter. In addition, removal of ddI showed no significant ($P > 0.05$) effect on hepatic function estimators, i.e., serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxalacetic transaminase (SGOT). However, albumin levels were slightly elevated on day 16 ($P = 0.07$). Renal function estimators showed some improvements following the removal of ddI; levels of uric acid and creatinine in the plasma on day 16 were significantly ($P < 0.05$) lower compared to day 13 values. Pancreatic function tests showed a borderline increase ($P = 0.06$) in amylase levels in the serum, and triglyceride levels remained unchanged ($P > 0.05$). A similar comparison of safety parameters obtained on days 13 and 1 (baseline) did not reveal any significant differences except for SGPT values, which were lower (27.5 versus 40.9 IU/liter) over the 12-day period when the patients received both study drugs in combination. However, it should be stressed that any continuous changes of these organ function tests might not be readily detected, even if they were clinically significant, because of the relatively short study period.

**DISCUSSION**

Buffering agents in the sachet formulation of ddI have been shown to reduce the $P$ of many drugs used in the management of patients with AIDS, e.g., dapsone, ciprofloxacin, and itraconazole. The citrate-phosphate buffer used in the ddI sachet formulation did not show any effect on the rate or the extent of RBT absorption in patients with AIDS. Apparently, the magnitude of effect of these buffers on the gastric pH was not substantial enough to cause a shift in the extent of ionization of the RBT tertiary amide group to have an impact on its solubility and/or dissolution characteristics.

Although this study shows high interpatient variability, both the pharmacokinetic parameters (Table 1) and plasma level profiles for RBT and LM565 on days 13 and 16 were comparable (Fig. 1) and revealed no significant differences in the presence or the absence of ddI. This lack of an effect of ddI on RBT (and LM565) was further reinforced by day 13/day 16 pharmacokinetic parameter ratios (Table 3), which were not statistically different from unity ($P > 0.05$), and the 95% CIs encompassed unity. Moreover, the stability of the $AUC_{0-\infty}/AUC_{\infty}$ ratios (Table 2) reflected no effect on the formation-disposition CLs of LM565. RBT is not extensively metabolized via the deacetylation pathway to LM565, as is evident from the low $AUC_{0-\infty}/AUC_{\infty}$ ratios (0.12 to 0.15) and low urinary recovery (0.5 to 0.6% of dose). The pharmacokinetic stability of $AUC_{t}/AUC_{\infty}$ ratios in the presence and absence of ddI further suggests no apparent changes in absorption in the gut. Concomitant ddI dosing showed no effect on this metabolic pathway involving deacetylation of RBT. However, the $CL_{R}$ and $CL_{L}$ are low, the renal excretion of the latter is three to four times faster than that of the parent, and a lack of effect on renal elimination is also evident from the day 13/day 16 ratio of $CL_{R}$. Similarly, $CL_{S}/F$ estimates were also unaffected by concomitant ddI administration. RBT autoinduction, which has been shown to be complete after 3 to 4 days of daily dosing (16), was unlikely to impact steady-state assessments on study days 13 and 16.

Although the distribution volume of RBT ($V_{d}/\lambda_{R}$) was not assessed due to the lack of $\lambda_{R}$ estimation in the current steady-state design, the superimposibility of the RBT plasma concentration versus time profiles with and without ddI allows one to conclude that the extensive cellular uptake of RBT is not affected by ddI.

From a safety perspective, discontinuation of ddI resulted in an apparent improvement in two parameters associated with renal function, i.e., a significant decrease ($P < 0.05$) in the levels of creatinine and uric acid in the serum (Table 4). The lowering of uric acid levels may be directly related to the withdrawal of ddI, since ddI is intracellularly metabolized to uric acid through the purine pathway (6). Borderline significant increases ($0.05 < P < 0.1$) in amylase and albumin levels in the serum were also observed. Although these observations may be a result of ddI therapy, a possible impact of the small sample size and its clinical relevance to the study population should be kept in perspective.

It is apparent from this study that concomitant administration of ddI (range, 167 to 375 mg or 2.4 to 4.6 mg/kg twice daily) with 300 or 600 mg of daily RBT dosing to patients with AIDS does not affect the absorption and steady-state pharmacokinetics of RBT and its metabolite LM565. The high degree of variability in RBT pharmacokinetic estimates seen in this

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**TABLE 3. Day 13/day 16 ratios of individual RBT and LM565 pharmacokinetic estimates**

<table>
<thead>
<tr>
<th>Parameter for RBT</th>
<th>Mean</th>
<th>SD</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
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<tbody>
<tr>
<td>$C_{max}$</td>
<td>1.00</td>
<td>0.5</td>
<td>0.51</td>
<td>1.67</td>
<td>0.37</td>
</tr>
<tr>
<td>$T_{max}$</td>
<td>1.06</td>
<td>0.38</td>
<td>0.38</td>
<td>1.08</td>
<td>0.87</td>
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<tr>
<td>$AUC_{0-\infty}$</td>
<td>0.85</td>
<td>0.30</td>
<td>0.30</td>
<td>0.95</td>
<td>0.93</td>
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<tr>
<td>$CL_{R}$</td>
<td>1.21</td>
<td>0.95</td>
<td>0.95</td>
<td>1.34</td>
<td>1.51</td>
</tr>
<tr>
<td>$X_{t(0-\infty)}$</td>
<td>1.22</td>
<td>0.44</td>
<td>0.44</td>
<td>1.22</td>
<td>0.70</td>
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<table>
<thead>
<tr>
<th>Parameter for LM565</th>
<th>Mean</th>
<th>SD</th>
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<th>SD</th>
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<tr>
<td>$X_{t(0-\infty)}$</td>
<td>1.22</td>
<td>0.44</td>
<td>0.44</td>
<td>1.22</td>
<td>0.70</td>
</tr>
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</table>

$P < 0.05$ for all comparisons. A similar comparison of safety parameters obtained on days 13 and 1 (baseline) did not reveal any significant differences except for SGPT values, which were lower (27.5 versus 40.9 IU/liter) over the 12-day period when the patients received both study drugs in combination. However, it should be stressed that any continuous changes of these organ function tests might not be readily detected, even if they were clinically significant, because of the relatively short study period.

**FIG. 1.** Mean plasma concentration versus time (h) profiles of RBT (RIF) and LM565 before and after removal of ddI.
TABLE 4. Effect of ddI removal (day 13 versus day 16) on pertinent safety parameters

<table>
<thead>
<tr>
<th>Assessment day</th>
<th>Platelet count (10^9/liter)</th>
<th>Leukocyte count (10^9/liter)</th>
<th>Body wt (kg)</th>
<th>Hematocrit (%)</th>
<th>Hemoglobin (g/liter)</th>
<th>SGOT (IU/liter)</th>
<th>SGPT (IU/liter)</th>
<th>Triglycerine (mmol/liter)</th>
<th>Creatine (mol/liter)</th>
<th>Uric acid (mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>6.74 ± 7.1 (12)</td>
<td>3.5 ± 5.0 (12)</td>
<td>62.4 ± 7.9 (12)</td>
<td>36.5 ± 5.5 (11)</td>
<td>36.5 ± 5.3 (11)</td>
<td>26.0 ± 6.7 (12)</td>
<td>36.3 ± 7.1 (11)</td>
<td>17.7 ± 6.8 (11)</td>
<td>0.006</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>16</td>
<td>6.68 ± 7.9 (12)</td>
<td>3.5 ± 5.0 (12)</td>
<td>62.2 ± 8.0 (12)</td>
<td>36.5 ± 5.5 (11)</td>
<td>36.5 ± 5.3 (11)</td>
<td>25.7 ± 6.0 (12)</td>
<td>36.3 ± 7.1 (11)</td>
<td>17.7 ± 6.8 (11)</td>
<td>0.006</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

P-value (day 13 vs day 16)

- 0.05
- 0.05
- 0.05
- 0.05
- 0.05
- 0.05
- 0.05
- 0.05
- 0.05
- 0.05

study may in fact be associated with the severity of disease and possible changes in the gastrointestinal milieu. No changes of clinical significance were apparent in select RBT safety parameters due to concomitant ddI administration. Should RBT blood levels be a determinant for its efficacy against MAC infection, concomitant ddI administration is unlikely to modulate that effect.

REFERENCES


