Effects of Trimethoprim on the Clearance of Apricitabine, a Deoxycytidine Analog Reverse Transcriptase Inhibitor, and Lamivudine in the Isolated Perfused Rat Kidney

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ABSTRACT

Apricitabine (ATC) is a novel deoxycytidine analog reverse transcriptase inhibitor in development for the treatment of human immunodeficiency virus infection. Studies were performed to characterize the excretion of ATC and its metabolite, BCH-335 (=1-(2-hydroxymethyl-[1,3]oxathiolan-4-yl)-1H-pyrimidine-2,4-dione), in the isolated perfused rat kidney (IPK). A second objective was to investigate the effect of trimethoprim on ATC excretion because trimethoprim inhibits the excretion of lamivudine, structurally similar to ATC, in the IPK. ATC excretion was nonlinear at doses of 80 to 1600 μg. The excretion ratio (ratio of clearance to glomerular filtration rate, assuming negligible protein binding) was greater than 1.0, indicating net tubular secretion. In contrast, the excretion of BCH-335 was independent of the dose of BCH-335. Concomitant administration of ATC and BCH-335 did not affect the excretion of either compound. Trimethoprim significantly inhibited the excretion of both ATC and BCH-335, with IC50 values of 0.45 and 0.54 μg/ml, respectively. In the presence of trimethoprim, the excretion ratios for both compounds were less than 1.0, indicating tubular reabsorption. Trimethoprim inhibited the excretion of ATC and lamivudine to similar extents. Following concomitant administration of ATC, lamivudine, and trimethoprim, there was no evidence of an interaction between ATC and lamivudine. These results suggest that ATC undergoes active tubular secretion in the kidney. Because the renal excretion of both ATC and lamivudine is inhibited by trimethoprim to similar extents, in clinical practice exposure to ATC, it would be expected to increase in the presence of therapeutic concentrations of trimethoprim to a similar extent as has been shown previously for lamivudine.

Apricitabine (ATC; Fig. 1; previously referred to as SPD754 and AVX754) is a novel deoxycytidine analog reverse transcriptase inhibitor that is undergoing clinical development for the treatment of human immunodeficiency virus (HIV)-1 infection (Taylor et al., 2000; Cahn et al., 2006). Pharmacokinetic studies in healthy volunteers have shown that this agent is eliminated primarily by renal excretion of unchanged drug. After oral administration, 65 to 80% of the dose is excreted unchanged in the urine after 24 h (Holdich et al., 2006). ATC undergoes conversion in vivo (<10% of administered dose) to an inactive metabolite, BCH-335. The most likely metabolic pathway for the generation of BCH-335 is metabolism in the bowel by normal intestinal flora (A vexa Limited, personal communication). Given the structural similarity between ATC and BCH-335 (Fig. 1), it is likely that both compounds are excreted by similar mechanism(s).

Studies using the isolated perfused rat kidney (IPK) model suggested that the renal clearances of ATC and BCH-335 were reduced when the two compounds were applied to the perfusate concomitantly (D. R. Taft, unpublished observations). The reason for this finding is unclear. Decreased clearance of ATC in the presence of its metabolite would be consistent with a capacity-limited transport mechanism for both compounds in the luminal membrane of the kidney; luminal transport is an active process, and given the structural similarity between the two compounds, it would be anticipated that they may compete for such a process. Alternatively, the reduction in clearance might reflect the formation of a complex between ATC and BCH-335, which would prevent the efflux of either compound across the cell membrane or a mass effect due to the greater concentration of drug applied to the perfusate when the two compounds were administered together.

Trimethoprim is widely used in combination with sulfamethoxazole for the prophylaxis of Pneumocystis jirovecii pneumonia in patients receiving treatment for HIV infection. A
previous study with lamivudine in the IPK model showed that the renal excretion of this agent was reduced in the presence of trimethoprim (Sweeney et al., 1995), and subsequent clinical trials confirmed that this interaction might be clinically relevant (Moore et al., 1996; Sabo et al., 2002), although no dose adjustment is recommended (Epivir SmPC). Given the structural similarities between ATC and lamivudine, it is possible that ATC might be subject to a similar interaction with trimethoprim. In view of these findings, studies were performed to characterize the excretion of ATC and BCH-335 in the IPK model and to investigate the effect of trimethoprim on the renal excretion of the two compounds.

Materials and Methods

Materials. ATC, BCH-335, and lamivudine were obtained from Shire BioChem (Laval, QC, Canada). All other chemicals were obtained from Sigma Chemical Co. (St. Louis, MO).

Surgical Technique. Male Harlan Sprague-Dawley rats, weighing approximately 300 g, were used in all experiments. The animals were housed in stainless steel cages and allowed free access to standard laboratory chow and water. The experimental protocols were approved by the Institutional Animal Care and Usage Committee of Long Island University.

The right kidney was isolated by means of the Bowman (1975) modification of the Nishiiatsuji-Uwo procedure (Nishiiatsuji-Uwo et al., 1967). In brief, rats were anesthetized by i.p. injection of pentobarbital sodium (40 mg/kg) and a midline incision made from the pelvis to the sternum. The right ureter was isolated and cannulated to facilitate urine collection. The superior mesenteric artery, aorta, and right renal artery were exposed, and a cannula was inserted into the right renal artery via the superior mesenteric artery. The cannula was secured, and the kidney was excised from the animal and placed in the perfusion apparatus.

Perfusion of the isolated kidney was performed as described by Bekersky (1983a,b). The perfusate consisted of the following: Krebs-Henseleit buffer, pH 7.4, 4.00% bovine serum albumin, 1.67% dextan, 100 mg/dl glucose, and 60 mg/dl inulin and amino acids. Inclusion of physiologic amino acids in the IPK perfusate has been shown to improve functional performance of the IPK preparation (Epstein et al., 1982). The perfusate was oxygenated, and the pH was maintained at 7.4 by bubbling a mixture of 95% O2/5% CO2 continuously through the perfusate, commencing 1 h before the start of each perfusion. The initial volume of perfusate was 80 ml, and this volume was maintained throughout the experiment by the addition of a 50:50 mixture of perfusate and deionized water to replace fluid lost due to urine collection or perfusate sampling. The perfusion pressure was maintained at 100 ± 10 mm Hg by adjusting the perfusion flow rate as necessary. Parameters monitored to assess kidney function during perfusion included glomerular filtration rate (GFR), fractional reabsorption of glucose, fractional reabsorption of sodium, urine flow rate, and urine pH. A 10-min stabilization period preceded all pharmacokinetic experiments.

Dose Linearity Experiments. Initial experiments were performed to investigate the dose linearity of ATC and BCH-335 excretion in the IPK model. ATC or BCH-335 was added to the perfusate as a bolus at doses of 80, 160, 320, 640, or 1600 μg (n = 3 per dose) to yield concentrations of 1, 2, 4, 8, and 20 μg/ml, respectively. In other experiments, ATC and BCH-335 were given together at doses of 640 (8 μg/ml) and 160 (2 μg/ml) μg, respectively. Perfusion was sampled 5 min after dosing and at 10-min intervals thereafter. Urine was collected over 10-min periods for 90 min.

Concentrations of sodium, potassium, chloride, and glucose in perfusate and urine were measured by means of a Beckman CX-3 Clinical Chemistry Analyzer (Beckman-Coulter, Brea, CA). Inulin was measured by means of a validated colorimetric technique (Poolla et al., 2002).

Nonspecific binding of ATC within the IPK circuit was assessed by perfusing the system with 80 ml of phosphate-buffered saline and adding a bolus of ATC intended to produce a concentration in the perfusate of 20 μg/ml (equivalent to the 1600-μg bolus). Perfusion samples were obtained 5 min after administration and every 10 min thereafter for 1.75 h.

Perfusion binding of ATC and BCH-335 was measured by ultrafiltration. Perfusion (2 ml) containing ATC or BCH-335 was incubated at 37°C in a shaker bath for 1 h to ensure binding equilibrium. Studies were conducted over a concentration range between 0.5 and 20 μg/ml (0.5, 1, 2, 5, 10, and 20 μg/ml). After incubation, an aliquot was collected for determination of total drug concentration. A second aliquot (1 ml) was added to an Amicon Centrifree ultrafiltration device (Millipore Corporation, Billerica, MA) and centrifuged at 1500g for 15 min. After centrifugation, the resulting ultrafiltrate was stored at −20°C for subsequent determination of unbound concentration. Preliminary studies determined that the drug binding to the device was negligible. All studies were performed in triplicate.

Effects of Trimethoprim on ATC and BCH-335 Excretion. Further experiments were performed to investigate the effect of trimethoprim on the renal excretion of ATC and BCH-335. Trimethoprim (lactate salt) was added to the perfusate at doses selected to achieve concentrations in perfusate of 0.5, 1, 5, 10, or 50 μg/ml (n = 3–4 per group), and after 10 min, ATC or BCH-335 was added to the perfusate at target concentrations of 1 and 2 μg/ml, respectively. Urine was collected over 10-min periods for 1 h after administration of trimethoprim, and perfusate samples were obtained at the midpoint of each collection period. Renal function was monitored, and ATC and BCH-335 were measured as described above.

Effect of Trimethoprim on Lamivudine Excretion. In other experiments, trimethoprim was added to the perfusate as described above, followed after 10 min by lamivudine at a target concentration of 2.5 μg/ml. A further experiment investigated the effect of concurrent administration of trimethoprim, ATC, and lamivudine (target concentrations, 5, 1, and 2.5 μg/ml, respectively).

Sample Analysis. ATC, BCH-335, and lamivudine were analyzed in perfusate and urine samples by LC-MS/MS. Sample analysis was performed by HFL (Fordham, Cambridgeshire, UK). For ATC and lamivudine, separation was accomplished using a Phenomenex Synergy Max-RP column, 50 × 2.0-mm i.d. (Phenomenex, Torrence, CA). BCH-4556 was used as an internal standard. Mobile phase consisted of a 50:50 mixture of methanol and water, involving gradient elution (methanol increased from 0–20% over 4 min) at a flow rate of 1 ml/min. Turbo- IonSpray in positive ion mode was used to detect each analyte. MS/MS detection involved monitoring the fragmentation of 230 →
112 (m/z) for ATC and lamivudine and 214 → 112 for BCH-4556. The retention times were 1.9 min for BCH-4556, 2.7 min for ATC, and 3.0 min for lamivudine. The lower limit of quantitation for both compounds was 50 ng/ml in perfusate and 200 ng/ml in urine. The coefficient of variation percentage for the assay (at the lower limit of quantitation) was as follows: ATC, 9.7% (perfusion) and 5.9% (urine); and lamivudine, 5.9% (perfusion) and 9.0% (urine).

BCH-335 was analyzed using an isocratic method. The mobile phase was composition was 10 mM ammonium formate, pH 3.5/ methanol/water (50:15:35 (v/v)) at a flow rate of 0.3 ml/min. BCH-335 and internal standard (BCH-4556) were separated using a Phenomenex Luna Phenyl Hexyl, 50 × 2.0-mm i.d. (5 mm). MS/MS detection involved monitoring the fragmentation of 231 → 113 (m/z) for BCH-335 and 214 → 112 for BCH-4556. The retention times were approximately 0.8 min for BCH-4556 and 2.0 min for BCH-335. The coefficient of variation percentage for the assay was 5.7% in perfusate and 4.3% in urine.

**Data Analysis.** GFR was calculated as the inulin clearance during each urine collection period, using the formula:

\[
GFR = \frac{UFR \times U_{\text{inulin}}}{P_{\text{inulin}}} \tag{1}
\]

where UFR represents the urine flow rate, \(U_{\text{inulin}}\) represents the concentration of inulin in urine, and \(P_{\text{inulin}}\) represents the concentration of inulin in the perfusate at the midpoint of the urine collection period. The fractional reabsorption of glucose or electrolytes was calculated from the formula:

\[
FR = 1 - \frac{U_{\text{substance}} \times P_{\text{inulin}}}{U_{\text{inulin}} \times P_{\text{substance}}} \tag{2}
\]

where \(U_{\text{substance}}\) represents the concentration of analyte in the urine, and \(P_{\text{substance}}\) represents the concentration of analyte in the perfusate at the midpoint of the urine collection period. The renal clearances of ATC and BCH-335 were calculated from eq. 1, above. The excretion ratio (XR) (Tucker, 1981) was calculated as the ratio of clearance to GFR (assuming negligible binding to protein in the perfusate, discussed below). XR values above 1.0 indicate net tubular secretion by the kidney, whereas values below 1.0 indicate net tubular reabsorption.

For dose linearity studies, a saturable excretion model was fitted to the experimental data (XR as a function of perfusate concentration) by nonlinear regression using Winnonlin software (version 5.0.1; Pharsight, Mountain View, CA). The following equation was used:

\[
XR = \left(1 + \frac{T_{\text{max}} \times GFR}{K_m + C}\right) \times (1 - R) \tag{3}
\]

Equation 3 assumes that drug is excreted by a combination of mechanisms (filtration, secretion, reabsorption) and that secretion is saturable over the range of concentrations studied. In the equation, \(T_{\text{max}}\) represents the maximum transport rate, and \(K_m\) is the perfusate concentration where then transport rate is 50% of \(T_{\text{max}} \times R\) indicates the fraction of drug that is reabsorbed.

The trimethoprim concentration producing a 50% reduction in clearance of ATC, BCH-335, or lamivudine (IC_{50}) was determined by nonlinear regression. XR was related to trimethoprim concentrations using the following empirical equation:

\[
XR = \text{Baseline} \times \left(1 - \frac{I_{\text{max}} \times C_{\text{TMP}}}{C_{\text{50}} + C_{\text{TMP}}}\right) \tag{4}
\]

where baseline indicates the excretion ratio of compound (ATC, BCH-335, or lamivudine) in the absence of trimethoprim, \(C_{\text{50}}\) is the initial concentration of trimethoprim in the perfusate, and \(I_{\text{max}}\) represents the maximum reduction in excretion ratio produced by trimethoprim (corrected for the baseline value).

The mean parameter estimates of IPK viability criteria for control and drug treatment groups were compared using one-way analysis of variance. Dunnett's test was used to identify study groups that differed from control perfusions in terms of viability criteria. Likewise, renal excretion parameters estimates were also compared using analysis of variance. Post hoc analysis (Tukey's Honestly Significant Differences) was used to assess the effect of increased dose and trimethoprim coadministration on drug excretion.

**Results**

**Dose Linearity of ATC and BCH-335.** The functional viability of the perfused kidneys following administration of ATC or BCH-335 is summarized in Table 1. Viability parameters were within acceptable limits and were consistent between study groups.

Over the range of concentrations studied (0.5–20 µg/ml), perfusate binding of ATC and BCH-335 was negligible, as determined by ultrafiltration. Thus, the excretion ratio for both compounds was calculated as the ratio of clearance to GFR.

Renal excretion parameters following administration of ATC or BCH-335 are summarized in Table 2, and the excretion ratios are shown graphically in Figs. 2 and 3, respectively. The excretion of ATC in urine was nonlinear with respect to concentration, and clearance and excretion ratio tended to decrease with increasing dose (Fig. 2). A saturable excretion model (eq. 3) was fitted to the data in Fig. 2, generating the following parameter estimates: \(T_{\text{max}}\) 2.92 µg/min (confidence interval, 0.75–6.61); \(K_m\) 1.15 µg/ml (confidence interval, 0.071–2.38); \(R\) 0.21 (confidence interval, 0.13–0.56).

The clearance and excretion ratios of BCH-335 were highest with the 320-µg dose. The excretion ratio showed considerable variability in relation to concentration (Fig. 3), although there was a tendency for excretion to decrease with increasing concentration of BCH-335 in the perfusate. Attempts to model the data using eq. 3 were unsuccessful because the saturation model produced a poor fit to the data (data not shown). Concomitant administration of ATC and BCH-335 had no significant effect on the clearance or excretion ratio of either compound.

In experiments performed to assess nonspecific binding of ATC within the perfusion circuit, the mean (n = 3) concentrations of ATC measured over 2 h after administration of a bolus intended to produce a concentration in perfusate of 20 µg/ml ranged from 18.5 to 20.6 µg/ml. Thus, nonspecific binding of ATC within the circuit seems to be minimal.

**Effect of Trimethoprim on Excretion of ATC and BCH-335.** Renal function was within acceptable limits in all trimethoprim interaction experiments (data not shown). Viability parameters were consistent with previous data in the IPK model (Hall and Rowland, 1984; Statkevich et al., 1993; Sweeney et al., 1995; Kugler et al., 1996).

Renal excretion parameters of ATC and BCH-335 alone and in the presence of trimethoprim are summarized in Table 3. Trimethoprim was associated with a marked decrease in the clearance of ATC and the corresponding excretion ratio. The IC_{50} for trimethoprim, determined by fitting eq. 4 above to the observed data, was 0.45 µg/ml (confidence interval, 0.09–0.80), and \(I_{\text{max}}\) was 1.86 (confidence interval, 1.44–2.28). Likewise, the clearance and excretion ratio of BCH-335 were reduced in the presence of trimethoprim. IC_{50} was 0.54
Effects of Trimethoprim on the Renal Excretion of Lamivudine. The effect of trimethoprim on the renal excretion of lamivudine is summarized in Table 3. Negligible per fusate binding of lamivudine has been reported previously (Sweeney et al., 1995). The clearance and excretion ratio of lamivudine were similar to those of ATC and were reduced in the presence of trimethoprim, to a similar extent to that seen with ATC. The IC$_{50}$ of trimethoprim was 0.27 µg/ml (confidence interval, 0.15–0.38), and $I_{\text{max}}$ was 2.53 (confidence interval, 2.25–2.80).

Discussion

These IPK studies were performed to characterize the renal excretion of ATC and its metabolite BCH-335 and to investigate potential interactions between trimethoprim, ATC and lamivudine. Such potential interactions are relevant since it can be anticipated that various combinations of antiviral and antibacterial agents will be required in patients with HIV infection.

The renal excretion of ATC was nonlinear with respect to concentration. The findings that the excretion ratio of ATC was higher than 1.0 and that clearance and excretion ratio decreased at higher concentrations suggest that ATC undergoes active, saturable tubular secretion. Similar findings have been reported in the IPK model with lamivudine (Sweeney et al., 1995). Likewise, in in vivo studies in rats, the renal clearances of zidovudine (Patel et al., 1989) and dideoxyinosine (Wientjes et al., 1992) have been shown to decrease with increasing dose.

In contrast to the findings with ATC, the renal excretion of the metabolite BCH-335 was relatively unchanged over the range of concentrations studied. The clearance of BCH-335 tended to be higher with a dose of 320 µg than with other doses, and this was associated with higher urine flow rates. This might suggest that BCH-335 undergoes passive reabsorption because this process is urine flow-dependent. However, alterations in urine flow rates are unlikely to account for the increased clearance of BCH-335 seen with the 320-µg dose because the highest clearances were seen in experiments in which urine flow rate was within normal ranges. Nonlinear excretion of BCH-335 would have been expected, given the similarity in structure between this compound and ATC. It is possible that BCH-335 is subject to two opposing saturable processes (with different concentration dependencies), such as tubular secretion and reabsorption, which together mask any dose dependence.

Concomitant administration of ATC and BCH-335 had no significant effect on the renal excretion of either compound. This finding contrasts with those of a previous study (D. R. Taft et al., unpublished observations), which suggested that the clearances of both compounds might be reduced when they were administered together. In that study, however, a direct comparison within the study could not be performed because the compounds were only administered in combination and not given alone. The conclusion that clearance may have been decreased for the combination was based on comparison with earlier data generated for each compound alone. The results of the present study suggest that ATC and BCH-335 do not compete for the same saturable transport process.
It is not possible from the present data to preclude the possibility that ATC is converted to BCH-335 in the kidney. However, we are aware of no data or mechanistic rationale to suggest that such a conversion occurs.

Trimethoprim completely inhibited the tubular secretion of ATC at all concentrations studied, as shown by a decrease in the excretion ratio of ATC. A surprising finding in this study was that in the presence of trimethoprim concentrations above 5 μg/ml, the excretion ratio of ATC was below 1.0. Likewise, the excretion ratios of BCH-335 were below 1.0 at trimethoprim concentrations above 0.5 μg/ml. Such low ratios suggest that the compounds are reabsorbed in the kidney. Because ATC is hydrophilic, it is unlikely to undergo passive reabsorption. However, nucleoside transporters have been identified in both the basolateral and luminal membranes of the kidney (Yao et al., 1996; van Aubel et al., 2000; Mangravite et al., 2003), and active transport by these mechanisms would explain the low excretion ratios of ATC and BCH-335 observed in the presence of trimethoprim.

The IC50 values of trimethoprim for the inhibition of ATC and BCH-335 excretion (approximately 0.5 μg/ml) were substantially lower than the plasma concentrations achieved with the doses of trimethoprim normally used in the prophylaxis or treatment of P. jirovecii pneumonia in HIV-infected

<table>
<thead>
<tr>
<th>ATC Dose (μg/ml)</th>
<th>BCH-335 Dose (μg/ml)</th>
<th>ATC (8 μg/ml) + BCH-335 (2 μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>Clearance (ml/min)</td>
<td>Excretion ratio</td>
</tr>
<tr>
<td>0.76 (0.33)</td>
<td>1.9 (0.86)</td>
<td>2.5 (1.1)</td>
</tr>
<tr>
<td>0.84 (0.17)</td>
<td>1.7 (0.67)</td>
<td>2.1 (0.76)</td>
</tr>
<tr>
<td>0.65 (0.15)</td>
<td>1.1 (0.23)</td>
<td>1.6 (0.28)</td>
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<td>0.64 (0.089)</td>
<td>1.0 (0.31)</td>
<td>1.6 (0.43)</td>
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<tr>
<td>0.63 (0.15)</td>
<td>0.59 (0.14)</td>
<td>0.97 (0.26)</td>
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<td>0.78 (0.17)</td>
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<td>0.84 (0.17)</td>
<td>1.6 (0.69)</td>
<td>2.2 (0.95)</td>
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<td>0.84 (0.080)</td>
<td>2.8 (0.96)</td>
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</tr>
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<td>0.77 (0.20)</td>
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</tr>
<tr>
<td>0.62 (0.14)</td>
<td>0.97 (0.14)</td>
<td>1.6 (0.55)</td>
</tr>
<tr>
<td>0.73 (0.18)</td>
<td>1.3 (0.40)</td>
<td>2.0 (0.73)</td>
</tr>
</tbody>
</table>

TABLE 2
Dose linearity experiments: renal excretion of ATC and BCH-335
Data are presented as mean (SD) (five excretion periods were analyzed for each perfusion experiment).
patients; in one study, for example, mean concentrations of 6.7 µg/ml were achieved after administration of trimethoprim, 15 to 23 mg/kg/day (Klinker et al., 1998). Because the half-life of trimethoprim is approximately 9 to 12 h (Odlind et al., 1984; Hutt et al., 1988; Srinivas et al., 1996), it seems likely that trimethoprim concentrations above the IC50 would be sustained throughout the day in clinical practice. However, a recent pharmacokinetic study in healthy volunteers found that the magnitude of the interaction between ATC and trimethoprim was modest compared with IPK findings. Coadministration of trimethoprim (480–960 mg/day) was associated with increased Cmax values for ATC and BCH ranging between 30 and 42%, whereas area under the concentration time curve (AUC) estimates for these compounds increased between 37 and 69% (Sawyer et al., 2005).

The magnitude of this interaction is consistent with that seen for trimethoprim and lamivudine (discussed below) and does not warrant dose adjustment of ATC when coadministered with trimethoprim.

The effect of trimethoprim on the excretion of lamivudine was greater than expected from previous studies. In a previous IPK study, the excretion of lamivudine was reduced approximately 2.4-fold in the presence of 4 µg/ml trimethoprim (Sweeney et al., 1995); from the present results, this concentration would be expected to produce a greater than 4-fold reduction in lamivudine excretion. Clinical data, however, suggest that the interaction between trimethoprim and lamivudine is less pronounced in vivo than in vitro. In a clinical study in HIV-infected patients, the AUC for lamivudine was increased by only 23% in the presence of trimethoprim (Moore et al., 2003). The effect of trimethoprim on the excretion of lamivudine was greater than predicted from the in vitro results presented here.

**References**


Pharmacokinetics of nevirapine and lamivudine in patients with HIV-1 infection. AAPS PharmSci 2:1–8.


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