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Report

Probenecid Inhibits the Metabolic and Renal Clearances of Zidovudine (AZT) in Human Volunteers

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The effect of probenecid on the disposition of AZT was investigated in a pilot study in two healthy volunteers. The pharmacokinetics of AZT were examined after a single oral dose of 200 mg with and without probenecid coadministration in a balanced crossover study. Administration of 500 mg probenecid every 6 hr prior to and during AZT dosing resulted in an increase in the average AUC_{AZT} from 89 μg · min/ml (control) to 191 μg · min/ml during probenecid treatment. This was manifested by a corresponding decrease in CL_{TOT}/F, which is attributed to the inhibitory effect of probenecid on the glucuronidation and renal excretion of AZT. Average CL_R and CL_{TOT}/F of AZT decreased from 4.76 and 28.7 to 2.98 and 14.1 ml/min/kg during control and probenecid treatment, respectively. AZT glucuronidation was affected to a greater extent than its renal excretion, as reflected by the decreased ratio of GAZT/AZT urinary recoveries. The terminal half-life of AZT was slightly longer during probenecid administration. That only a small change in the half-life occurred indicates that probenecid also reduced the volume of distribution of AZT. The CL_R of GAZT decreased from an average of 11.3 ml/min/kg (control) to 2.63 ml/min/kg during probenecid treatment, resulting in a greater than 3.5-fold increase in AUC_{GAZT}. Probenecid did not affect the blood/plasma distribution or the plasma protein binding of AZT. These preliminary findings suggest that it may be possible to maintain effective plasma AZT concentrations in AIDS patients receiving a reduced daily dose, in combination with probenecid.

KEY WORDS: zidovudine; pharmacokinetics; probenecid; AIDS therapy.

INTRODUCTION

Zidovudine (AZT) is a synthetic thymidine analog that has a potent and selective inhibitory effect against the human immunodeficiency virus (HIV). It is currently the only drug proven effective in the treatment of acquired immunodeficiency syndrome (AIDS) (1,2).

The pharmacokinetics of AZT have been studied in AIDS patients. After AZT administration, its glucuronide conjugate (GAZT) is the only metabolite detectable in human plasma and urine. Glucuronidation is the major route of AZT elimination, and GAZT is subsequently excreted in the urine. Following intravenous administration of AZT, 18 and 60% of the administered dose is recovered in the urine as AZT and GAZT, respectively. After oral administration 14% of the administered dose is recovered as AZT and 75% as GAZT in the urine (3,4).

The renal clearance of AZT based on the total urinary recovery of unchanged drug was 350 ml/min per 70 kg (3,4). This high renal clearance (approximately three times the glomerular filtration rate) indicates that AZT is actively secreted in the renal tubule. Because the metabolic clearance ($CL_{TOT} - Cl_R$) measured after intravenous administration approaches the hepatic blood flow and in view of the relatively high bioavailability for such a high-clearance drug, extrahepatic metabolism of AZT is likely.

Although the therapeutic window for AZT has yet to be established, it has been recommended that the plasma concentration be maintained above 0.25 μg/ml (1 μ*M*), the *in vitro* minimum inhibitory concentration of HIV (5). Because of the high CL_{TOT} of AZT, which results in its relatively short terminal half-life, frequent dosing is necessary to maintain effective plasma concentrations.

De Miranda *et al.* have shown that probenecid alters the pharmacokinetics of AZT in AIDS patients. Coadministration of 500 mg of probenecid every 6 hr with AZT increased the AZT area under the plasma concentration–time curve (AUC_{AZT}) to approximately three times its control value. From measurements of AZT and GAZT in a single pooled urine collection, it was concluded that probenecid reduced the metabolic and renal clearances of AZT (6). In a more recent report, in which probenecid in doses of 500 mg every 8 hr was coadministered with AZT in AIDS patients it was found that the AUC_{AZT} was increased by 80%. Total urine was collected over a dosing interval and analyzed for AZT and GAZT. The authors concluded that probenecid had no effect on renal elimination of AZT, attributing the interaction to an inhibition of GAZT formation (7).

If probenecid inhibits the renal secretion of AZT, it may also alter the transport of this antiviral nucleoside to or from

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tissues and may therefore modify the efficacy and/or toxicity of AZT. For example, in addition to its inhibitory effect on the renal and nonrenal elimination of AZT in the rabbit, probenecid enhances the distribution of AZT into cerebrospinal fluid (8–10). Whether similar effects on AZT transport occur in man during probenecid coadministration is not known.

The main objectives of this study were to quantitate the extent to which renal and metabolic clearances of this antiviral agent are affected by probenecid, to examine the effect of probenecid on GAZT elimination, and to study the effect of probenecid on AZT blood/plasma distribution and plasma protein binding.

MATERIALS AND METHODS

Chemicals

We used AZT and GAZT obtained from Burroughs Wellcome Co. to prepare standard solutions for analysis. Probenecid, 3-chlorobenzoic acid, β-hydroxyethyl theophylline, β-hydroxypropyl theophylline, and bacterial β-glucuronidase were supplied by Sigma Chemical Co.; acetonitrile, ether, and chloroform were obtained from Burdick and Jackson Laboratories; and ammonium phosphate monobasic, acetic acid, isopropyl alcohol, and methyl alcohol were purchased from Mallinckrodt, Inc. All solvents were HPLC grade.

Effect of Probenecid on the Blood/Plasma Distribution of AZT *in Vitro*

The blood/plasma distribution and plasma protein binding experiments were performed in quadruplicate in a temperature-controlled room maintained at 37°C.

To study the blood/plasma distribution of AZT and the effect of probenecid on this distribution process, two sets of 3-ml aliquots of heparinized freshly drawn blank human whole blood were used. The first set of samples was supplemented with AZT to produce concentrations of 0.1, 0.25, 1.0, and 2.5 μg/ml. The second was supplemented with probenecid in addition to AZT. Samples with 0.1 and 1.0 μg/ml AZT contained 50 μg/ml probenecid, and those with 0.25 and 2.5 μg/ml AZT contained 150 μg/ml probenecid. Samples were shaken gently for 3 hr, and plasma was then obtained by centrifugation. Aliquots of the plasma were kept frozen at −20°C until analysis for AZT.

Effect of Probenecid on the Plasma Protein Binding of AZT *in Vitro*

The effect of probenecid on AZT plasma protein binding was determined by measuring free (unbound) AZT plasma concentrations in aliquots of the plasma obtained from the blood/plasma distribution experiment by ultrafiltration at 37°C, using disposable microfilters (Centrifree, Amicon Corp.). Ultrafiltrate was stored at −20°C until analysis.

Effect of Probenecid on AZT and GAZT Pharmacokinetics

Two healthy volunteers, age 31 and 34, weighing 80 and 77 kg, received a single oral dose of 200 mg AZT (two 100-mg capsules, Burroughs Wellcome Co., Lot. No. 8N2026) alone (control) and during concurrent probenecid treatment in a balanced crossover experiment. Probenecid treatment consisted of probenecid, 500 mg (Danbury Pharmacal, Inc., Lot No. 32026) every 6 hr for 3 days before AZT administration. Dosing continued throughout the day on which AZT was administered. The probenecid dosing schedule was chosen such that, on the day of AZT dosing, the probenecid morning dose was administered 3 hr before AZT administration. There was a 1-week washout period between treatments. The study was balanced to eliminate any treatment sequence effect.

The subjects were instructed not to take any other drugs or alcohol for the 2 days prior to AZT administration. Subjects were fasted overnight and food was not allowed for 4 hr after AZT administration. On the day of AZT dosing, an indwelling catheter with a heparin lock was inserted into the forearm of each subject to allow for frequent blood sampling. The catheters were flushed between sampling with a solution of heparin, 10 U/ml, in normal saline.

After AZT administration, 8-ml blood samples were drawn at 0 (blank), 10, 20, 30, and 45 min and 1, 1.25, 1.75, 2.25, 2.75, 3.5, 4.5, 5.5, 6.5, 8, 10, and 12 hr. Blood samples were collected in heparinized vacutainers. Plasma was obtained by centrifugation and was stored at −20°C until analysis. Urine samples were collected every 0.5 hr for the first 3 hr, and hourly until 12 hr, followed by a single collection between 12 and 24 hr. The volume of each urine sample was measured and aliquots were stored at −20°C until analysis. Urine and plasma samples were analyzed for AZT and GAZT. Plasma samples obtained during the treatment period were further analyzed for probenecid.

In order to examine the effect of probenecid on the *in vivo* protein binding of AZT, free (unbound) plasma AZT concentrations were determined by ultrafiltration as described above in five samples during each treatment for each subject.

The plasma samples obtained at 12 hr and the urine samples obtained during the 12- to 24-hr collection were analyzed for creatinine to estimate the creatinine clearance for each subject during each treatment.

Sample Analysis

Plasma and urine samples were analyzed for AZT using the HPLC method developed in our laboratory (11). This method was also used to determine GAZT concentrations in urine and plasma after hydrolysis of GAZT with β-glucuronidase (12). Probenecid was also quantified in plasma by HPLC as described previously (9).

Pharmacokinetic Analysis

The area under the plasma concentration–time curve (AUC) and the area under the moment curve (AUMC) were calculated by the linear trapezoidal rule up to the last data point. The total areas were calculated by extrapolation to infinity using the terminal half-life.

Because the bioavailability (F) was not determined in these subjects, estimates of the clearance and volume of distribution are expressed as the apparent clearance and apparent volume, i.e., CL_{TOT}/F and Vd_{ss}/F. CL_{TOT}/F is calculated according to Eq. (1).

$$\frac{CL_{TOT}}{F} = \frac{dose}{AUC} \quad (1)$$

Because AZT is rapidly absorbed after oral administration resulting in a short mean absorption time, Vd_{ss}/F can be approximated from Eq. (2) (13).

$$\frac{Vd_{ss}}{F} = \frac{dose \cdot AUMC}{AUC^2} \quad (2)$$

AZT and GAZT renal clearances were calculated from the amounts of AZT and GAZT recovered in the urine (0–∞) and AUC_{AZT} and AUC_{GAZT}, respectively.

RESULTS

Effect of Probenecid on the Blood/Plasma Distribution of AZT *in Vitro*

The results from the blood/plasma distribution experiment are summarized in Table I. AZT blood/plasma distribution was concentration independent in the range of concentrations examined (one-way ANOVA), with an average distribution ratio of 0.98 ± 0.04 (mean ± SD; $n = 16$). This blood/plasma distribution ratio of unity is consistent with the AZT erythrocyte distribution ratio reported previously (14). In the presence of probenecid, the average blood/plasma distribution ratio determined at the range of concentrations examined was 0.96 ± 0.04 ($n = 16$), which was not significantly different from control (Student's t test). However, the blood/plasma distribution ratio determined at 0.1 μg/ml AZT was statistically different from the ratios at the higher concentrations in presence of probenecid (Tukey's W, $P < 0.05$).

Effect of Probenecid on the Plasma Protein Binding of AZT *in Vitro*

The results of the plasma protein binding experiment are summarized in Table II. The free fraction of AZT in plasma measured by ultrafiltration was concentration independent in the range of concentrations examined (one-way ANOVA). The average AZT free fraction measured at concentrations ranging from 0.1 to 2.5 μg/ml was 0.93 ± 0.056 ($n = 14$). The measured free fraction was significantly different from unity (Student's t test, $P < 0.001$). The average free fraction of AZT in the presence of probenecid was concentration independent in the range of concentrations examined (one-way ANOVA), with an average of 0.90 ± 0.040 ($n = 15$), and was significantly different from unity (Student's t test, $P < 0.001$). The average AZT free fractions measured in the presence and the absence of probenecid were not different (Student's t test). When the free fraction of AZT measured at each concentration in the presence of probenecid was compared with the corresponding control, the free fraction determined at 2.5 μg/ml AZT was significantly smaller in the presence of probenecid (Student's t test, $P < 0.05$).

Probenecid did not affect the protein binding in plasma samples obtained after AZT administration. The free (unbound) fraction measured in the plasma samples obtained from the subjects who received AZT were 0.90 ± 0.05 and 0.93 ± 0.05 ($n = 10$ in each group) during control and probenecid treatment situations, respectively.

Effect of Probenecid on AZT and GAZT Pharmacokinetics

Stability studies performed in our laboratory have shown that AZT and GAZT are stable when incubated at 70°C for 1 hr with 1 *M* HCl or 1 *M* NaOH (unpublished data). This indicates that the degradation of AZT or GAZT during incubation at 37°C during GAZT hydrolysis with β-glucuronidase is unlikely. The average hydrolysis efficiency of GAZT was 104 ± 11% ($n = 12$), indicating complete hydrolysis of GAZT by the β-glucuronidase enzyme preparation.

After oral administration of 200 mg AZT during the control period, the drug was absorbed rapidly resulting in an average peak plasma concentration of 1.6 μg/ml achieved after 30 min. AZT plasma concentrations exhibited an initial distributive phase, with an average terminal half-life of 1.7 hr. The GAZT average peak plasma concentration was 3.3 μg/ml, achieved 45 min after AZT administration. GAZT plasma concentrations declined in parallel to AZT concentrations, indicating that GAZT follows formation rate-limited pharmacokinetics. Figures 1A and B show AZT and GAZT plasma concentration–time profiles for one subject during control and probenecid treatment periods, respectively. Higher AZT and GAZT plasma concentrations were ob-

Table I. Effect of Probenecid on AZT Blood/Plasma Distribution

Blood concentration (μg/ml)	Blood/plasma conc. ratio (mean[a] ± SD) Control	Added probenecid	Statistical significance[b]
0.1	0.95 ± 0.07	0.91 ± 0.03[c,*]	NS
0.25	1.00 ± 0.04	0.97 ± 0.02[d]	NS
1.0	0.97 ± 0.01	0.98 ± 0.02[c]	NS
2.5	0.99 ± 0.02	1.00 ± 0.05[d]	NS

[a] Mean of four observations.
[b] Student's t test ($P = 0.05$).
[c] Contains 50 μg/ml probenecid.
[d] Contains 150 μg/ml probenecid.
* Statistically different from the ratios at other AZT concentrations (Tukey's W, $P < 0.05$).

Table II. Effect of Probenecid on AZT Protein Binding

Plasma concentration (μg/ml)	Free fraction (mean[a] ± SD) Control	Added Probenecid	Statistical significance[b]
0.1	0.91 ± 0.07	0.90 ± 0.06[c]	NS
0.25	0.94 ± 0.06[d]	0.91 ± 0.02[e]	NS
1.0	0.91 ± 0.07[d]	0.90 ± 0.06[c,d]	NS
2.5	0.96 ± 0.01	0.89 ± 0.05[e]	$P < 0.05$

[a] Mean of four observations.
[b] Student's t test ($P = 0.05$).
[c] Contains 50 μg/ml probenecid.
[d] Mean of three observations.
[e] Contains 150 μg/ml probenecid.

served during probenecid administration. Figure 2 shows AZT plasma concentration–time profile during control and probenecid treatment periods. Probenecid plasma concentrations measured during probenecid administration were at steady state, ranging from 115 to 165 and from 80 to 145 μg/ml in subjects 1 and 2, respectively. Figure 3 shows probenecid plasma concentration–time profiles in the two subjects during the entire sampling period.

The results obtained from noncompartmental analysis are summarized in Table III. Probenecid administration caused an increase in AUC_{AZT} to more than twice its control value, resulting from a proportional decrease in CL_{TOT}/F. The terminal half-life was slightly longer during probenecid administration. That only a small change in the half-life occurs indicates that probenecid also reduces the apparent volume of distribution of AZT.

AZT renal clearance calculated from the amounts recovered in the urine (0–∞) and AUC_{AZT} was 350 and 395 ml/min during the control period and 214 and 251 ml/min during probenecid treatment for subjects 1 and 2, respectively. Similar estimates for AZT renal clearance were calculated from renal excretion rate and midpoint plasma concentration during each urine collection interval. Figure 4 represents a plot of AZT renal excretion rate vs AZT average plasma concentration during control and probenecid treatment in one subject. Figures 5A and B show AZT plasma concentration and renal excretion rate time profiles during control and probenecid treatment, respectively.

During probenecid treatment there was a greater than 3.5-fold increase in the AUC_{GAZT} when compared with control, resulting from a proportional decrease in its clearance. The average renal clearance of GAZT measured from the total amount of GAZT recovered in the urine and AUC_{GAZT} was 890 and 210 ml/min during control and probenecid treat-

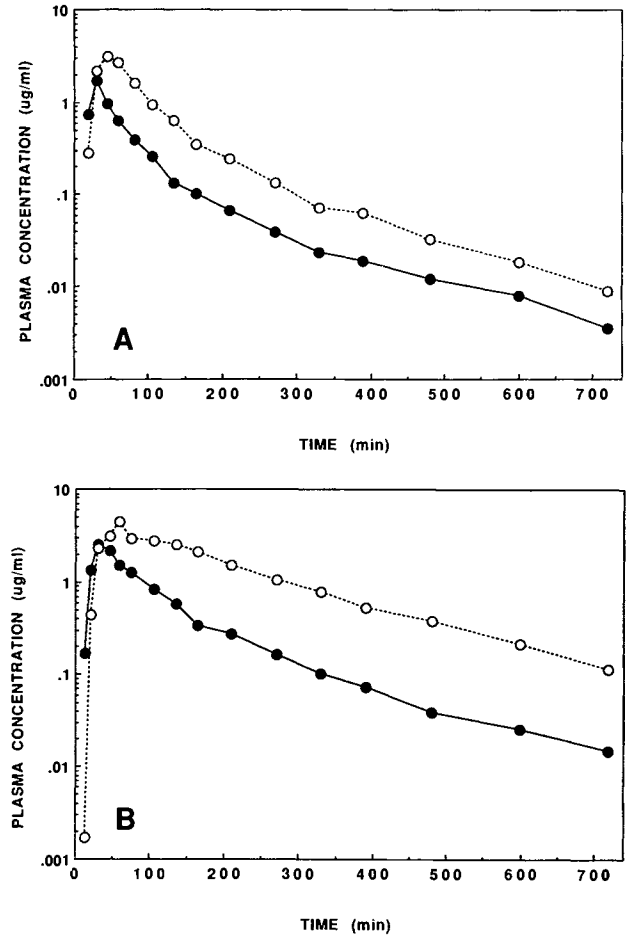

Fig. 1. Plasma concentration–time profiles of AZT (●) and GAZT (○) in subject 1 during (A) control and (B) probenecid treatment periods.

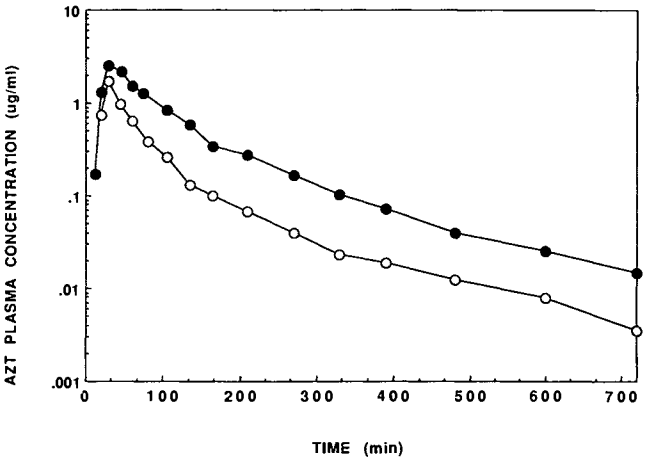

Fig. 2. AZT plasma concentration–time profiles in subject 1 during (○) control and (●) probenecid treatment periods.

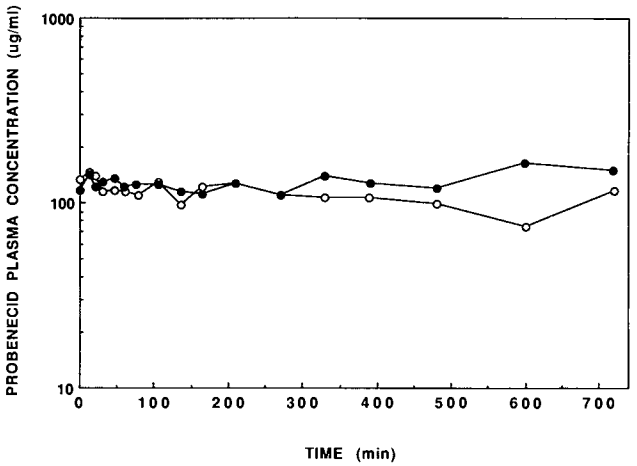

Fig. 3. Probenecid plasma concentration–time profiles in subject 1 (●) and subject 2 (○), during the 12-hr sampling period.

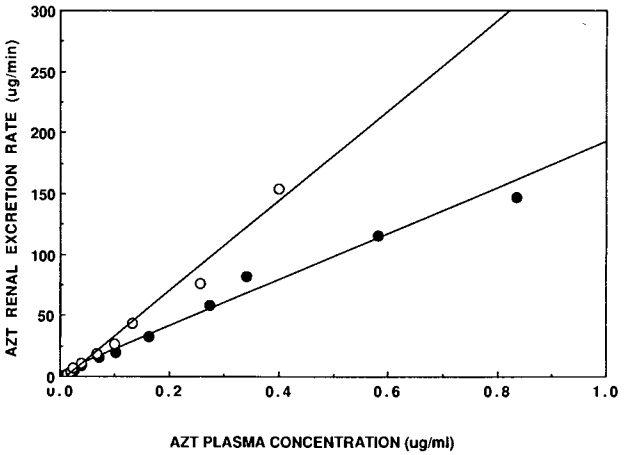

Fig. 4. AZT renal excretion rate vs plasma concentration at the midpoint of the urine collection interval for subject 1 during control (○) (slope = 369 ml/min) and probenecid treatment (●) (slope = 190 ml/min).

ment periods, respectively. Figure 6 represents a plot of GAZT renal excretion rate vs GAZT midpoint plasma concentration during control and probenecid treatment in one subject.

The fraction of the AZT dose recovered in the urine as AZT and GAZT calculated from the cumulative amounts of AZT and GAZT excreted in the urine during 24 hr and extrapolated to infinity were, on average, 86.3 and 77.9% during control and probenecid treatment periods, respectively. During the control period, 16.6% of the dose was recovered in the urine as AZT and 69.7% as GAZT, while during probenecid treatment 21.8% of the dose was recovered as AZT and 56.1% as GAZT.

Both the metabolic and the renal elimination processes were affected by probenecid administration as determined by the decrease in CL_R and CL_{TOT}/F. On average, CL_R decreased by approximately 40%, and CL_{TOT}/F by 50% when compared with controls. This indicates that probenecid affected AZT glucuronidation to a greater extent, resulting in the decrease in the ratio of GAZT/AZT urinary recoveries (calculated from fraction of dose recovered as GAZT/fraction recovered as AZT) from 4.2 during the control period to 2.6 during probenecid treatment.

DISCUSSION

Probenecid is a uricosuric agent with a high therapeutic index. It is the classical competitive inhibitor of the active transport of organic anions in the renal tubule (15,16). Although the presence of specific active transport systems for anions and cations is well documented (17,18), functional overlap between these transport systems has been demonstrated. Probenecid has been shown to inhibit the renal excretion of neutral compounds such as 17-ketosteroid (19) and nucleosides such as acyclovir (20) in humans. It has also been demonstrated to reduce the renal clearance of cimetidine, a basic imidazole derivative, in human volunteers (21).

Probenecid can also alter the pharmacokinetics of drugs that undergo glucuronide conjugation. It significantly decreases the clearance of acetaminophen and lorazepam by inhibition of ether glucuronide formation (22). *In vitro,* probenecid was found to inhibit the uptake of uridine-5′-diphosphoglucuronic acid into rat liver microsomes (23). Thus, probenecid can inhibit the clearance of drugs not

Table III. Noncompartmental Pharmacokinetic Parameter Estimates During Control and Probenecid Treatment

	Control		Probenecid	
Parameter	Subject 1	Subject 2	Subject 1	Subject 2
$AUC_{(AZT)}$ (μg · min/ml)	90.3	88.0	231	150
$CL_{TOT(AZT)}/F$ (ml/min/kg)	27.8	29.5	10.8	17.3
$CL_{R(AZT)}$ (ml/min/kg)	4.38	5.13	2.68	3.27
$Vd_{ss(AZT)}/F$ (L/kg)	2.85	2.80	1.44	2.19
$AUC_{(GAZT)}$ (μg · min/ml)	257	266	773	1060
$CL_{R(GAZT)}$ (ml/min/kg)	11.6	11.0	2.82	2.44
Fraction of dose[a] (%) eliminated in the urine as				
AZT	15.8	17.4	24.7	18.9
GAZT	71.6	67.7	52.4	59.7
AZT + GAZT	87.4	85.1	77.1	78.6

[a] Corrected for molecular weight.

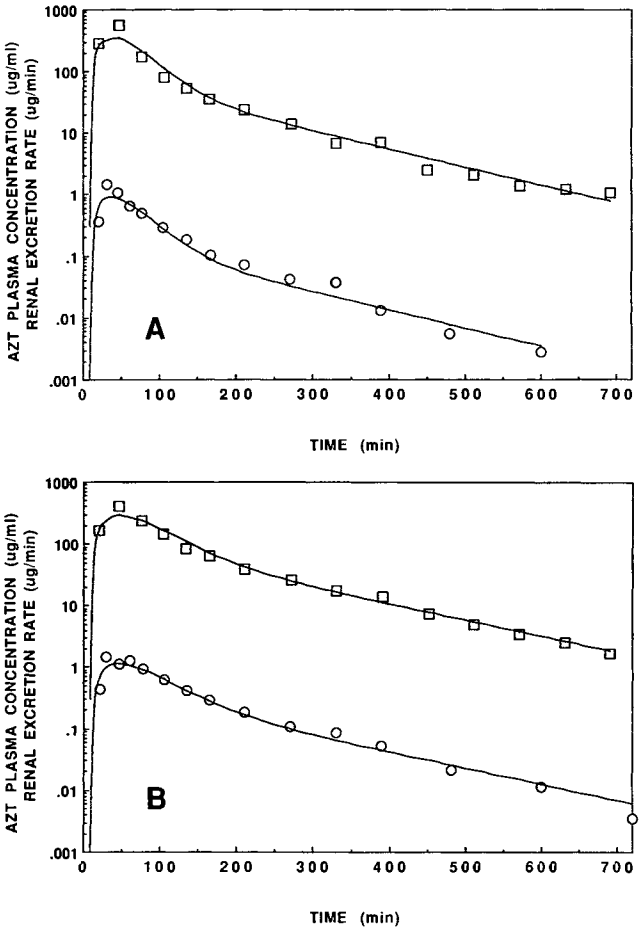

Fig. 5. AZT plasma concentration–time (○) and renal excretion rate–time (□) profiles for subject 2 during (A) control and (B) probenecid treatment periods. The solid lines are the model-fitted curves obtained from simultaneously fitting the plasma and urine data by nonlinear regression analysis, using a two-compartment open model.

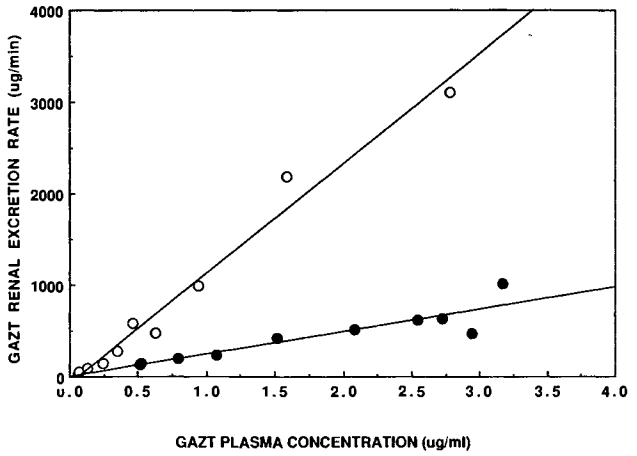

Fig. 6. GAZT renal excretion rate vs plasma concentration at the midpoint of the urine collection interval for subject 1 during control (○) (slope = 1190 ml/min) and probenecid treatment (●) (slope = 246 ml/min).

only by inhibition of renal tubular secretion but also by inhibition of glucuronide formation.

AZT is actively secreted in the renal tubules and is metabolized to an ether glucuronide conjugate, two parallel processes that can be inhibited by probenecid. In the present study, frequent sampling of plasma and urine allowed an examination of how both renal and metabolic clearances of AZT are affected by probenecid.

Because probenecid did not affect the blood/plasma distribution or plasma protein binding of AZT, this decrease in clearance may be attributed to the inhibitory effect of probenecid on the glucuronidation and renal excretion of AZT. Noncompartmental analysis showed that CL_{TOT}/F decreased by more than 50%, while CL_R decreased by approximately 40%. This indicates that AZT glucuronidation was affected to a slightly greater extent than its renal excretion, as reflected by the decreased ratio of GAZT/AZT urinary recoveries.

The creatinine clearance measured during probenecid coadministration was not different from that measured during the control period in the two subjects and AZT plasma protein binding was not affected by the presence of probenecid. This indicates that the filtration clearance of AZT was not affected by probenecid and the reduction in the renal clearance was due to a decreased net secretion clearance. Although CL_R decreased by approximately 40%, the net secretion clearance, which reflects the active secretion process, decreased to a much larger degree. The inhibition by probenecid of the renal excretion of AZT has been shown to be due to competitive inhibition of the active secretion in renal tubules in an animal model (8,9).

The increase in the terminal half-life during probenecid coadministration was very small compared to the decrease in CL_{TOT}/F, indicating that probenecid decreased the volume of distribution of AZT. This effect is similar to that seen when probenecid is coadministered with penicillin (24).

The CL_R of GAZT during the control period was on average 890 ml/min in the two subjects. This clearance is close to renal blood flow, suggesting that the GAZT renal extraction ratio from the blood is approaching unity. The apparently high extraction may be an overestimate of the true value if the kidney is involved in metabolic conversion of AZT to GAZT. GAZT CL_R was reduced to approximately 25% of its control value by probenecid, resulting in an increased AUC_{GAZT}. This is presumably due to the inhibition by probenecid of the active secretion of GAZT in the kidney.

The effect of probenecid on the distribution of AZT into different tissues, particularly those in which HIV resides, has yet to be examined. Recent studies in the rabbit (9,10) demonstrated that probenecid can enhance the distribution of AZT into cerebrospinal fluid (CSF). This effect was attributed in part to the inhibition of CSF to plasma active transport of AZT (10). If probenecid can effectively increase the brain tissue uptake of AZT in humans, this may be extremely beneficial in treating the neurological complications of AIDS.

Because of the effect of probenecid on the metabolic and renal clearances and on the volume of distribution of AZT, higher AZT plasma concentrations were observed during probenecid treatment compared to control when similar doses were administered. If AZT and probenecid are coadministered, average plasma concentrations similar to those obtained when AZT is administered alone would be achieved with lower doses or less frequent administration of AZT.

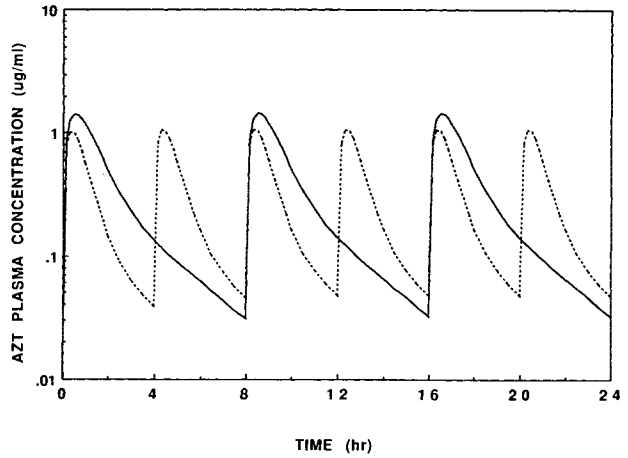

Fig. 7. Simulation of AZT plasma concentration–time profiles during multiple oral dosing of (-------) 200 mg AZT alone (control) every 4 hr and (——) 200 mg AZT every 8 hr in combination with probenecid. The average pharmacokinetic parameter estimates for the two subjects during control and probenecid treatment were used in this simulation.

The average pharmacokinetic parameters obtained in this pilot study were used to simulate the plasma concentration–time profiles shown in Fig. 7. These simulations suggest the potential for significant reduction of the total daily dose in AIDS patients while maintaining effective plasma concentrations. The results of this work will be used to design a larger study to investigate further this interaction in AIDS patients.

In summary, probenecid inhibits the renal and metabolic elimination of AZT and reduces its volume of distribution. These findings suggest that it may be possible to maintain effective plasma AZT concentrations in AIDS patients at a reduced daily dose, in combination with probenecid. The effect of probenecid on the distribution of AZT to tissues is yet to be determined. Studies of AZT efficacy and toxicity associated with this combination therapy in AIDS patients are required before this potentially beneficial drug interaction can be evaluated.

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