Hybrid Pharmacokinetic Models to Describe Anti-HIV Nucleoside Brain Disposition Following Parent and Prodrug Administration in Mice

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Brain delivery of active anti-HIV compounds is important for successful treatment of the AIDS patient. As an initial step in predicting human brain drug concentrations, hybrid pharmacokinetic models were developed to characterize the disposition of anti-HIV nucleosides following parent and prodrug administrations in mice. Mouse data were obtained following intravenous administration of 3′-azido-2′,3′-dideoxyuridine (AZddU or AZDU), 3′-azido-3′-deoxythymidine (AZT), and their dihydropyridine prodrugs (AZddU-DHP and AZT-DHP). Exponential equations were fitted to the serum concentration–time data for each species, including the pyridinium ion moieties, and subsequently used in differential mass balance equations describing the brain dynamics of each compound. Model parameters for the mass balance equations were estimated by various techniques, including the utilization of *in vitro* data. In general, model-predicted brain concentrations agreed with the observed data. Similar data in larger animals will permit scale-up of the current model to predict human brain drug concentrations.

KEY WORDS: hybrid pharmacokinetic models; anti-HIV nucleosides; brain delivery.

INTRODUCTION

Brain delivery of anti-HIV nucleosides is an important aspect of effective drug treatment of AIDS patients. HIV-infected macrophages gain access to the central nervous system (CNS) and produce a number of debilitating symptoms, particularly a progressive AIDS dementia complex (1). Variable and somewhat limited entry of active anti-HIV nucleosides, such as zidovudine (AZT), into the CNS has initiated the development of novel prodrugs. The dihydropyridine–pyridinium salt redox system has been proposed as a prodrug system for anti-HIV nucleosides (2–4). In principle, the lipophilic prodrug penetrates the blood–brain barrier and, after chemical and enzymatic conversions to the parent compound, increases the brain concentrations of the pharmacologically active agent.

Pharmacokinetic models that predict prodrug and drug brain concentrations are useful in the design of prodrugs and their dosage regimens. Hybrid pharmacokinetic models which incorporate components of physiological and compartmental pharmacokinetic models have been promoted for their simplicity relative to that of global physiological models (5). Hybrid models typically focus on a single organ and, thus, require fewer data and model parameters than a comprehensive physiological pharmacokinetic model. Scale-up of a hybrid model to humans could provide predictions of drug disposition in an organ of interest in which data cannot be readily obtained. Since anti-HIV drug brain concentrations are important determinants of successful therapy, the objective of this investigation was to develop hybrid pharmacokinetic models describing the brain disposition of anti-HIV nucleosides following parent and prodrug administration in mice. Results with additional animal species could then be used for interspecies extrapolations and for predicting human brain drug concentrations.

MATERIALS AND METHODS

Chemicals

3′-Azido-2′,3′-dideoxyuridine (AZddU or AZDU), 3′-azido-3′-deoxythymidine (AZT), 3′-azido-2′,3′-dideoxy-5′-0-(1,4-dihydro-1-methyl-3-pyridinocarbonyl) uridine (AZddU-DHP), 3′-azido-3′-deoxy-5′-0-(1,4-dihydro-1-methyl-3-pyridinocarbonyl)thymidine(AZT-DHP),3′-azido-2′,3′-dideoxy-5′-0-(1-methyl-3-pyridinocarbonyl)uridine (AZddU-QS), and 3′-azido-3′-deoxy-5′-0(1-methyl-3-pyridinocarbonyl)thymidine (AZT-QS) were synthesized in our laboratory. Spectrographic and high-pressure liquid chromatographic (HPLC) analyses indicated that chemical purity of all compounds was greater than 98%.

The internal standard *o*-acetophenitidin was purchased from Eastman Organic Chemicals (Rochester, NY), and sodium lauryl sulfate was purchased from Sigma Chemical Co (St. Louis, MO). Dimethyl sulfoxide (DMSO) was obtained from EM Science (Cherry Hill, NJ). HPLC-grade acetonitrile and all other chemicals (analytical grade) were obtained from J. T. Baker (Phillipsburg, NJ). Deionized distilled water was used throughout the studies.

In Vitro Biotransformation of AZddU-DHP and AZT-DHP

Three-milliliter samples of mouse serum or brain homogenate containing AZddU-DHP or AZT-DHP were maintained at 37°C under mixing. Aliquots of 100 μl were removed at time 0 and for up to 10 hr after adding the prodrugs to the samples. The aliquots were measured for prodrug, quaternary salt, and parent drug by the method described below.

Animals

Female NIH Swiss mice (Taconic Farms, NY) weighing 25 to 30 g were housed in a 12-hr light/12-hr dark constant-temperature (20°C) environment and had free access to standard laboratory chow and water. Mice were acclimatized to this environment for 1 week prior to experiments.

Parent Drug Animal Studies

AZddU or AZT were dissolved in DMSO (50 mg/ml)

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and administered intravenously through a tail vein over 30 sec at a dose of 50 mg/kg. Animals were momentarily restrained during dosing and then placed in individual cages and allowed food and water ad libitum. Three mice each were killed at 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600, and 720 min following drug administration. Animals were killed by exsanguination via a left ventricle heart puncture after anesthetization with diethyl ether. Serum was harvested from blood collected from the heart. The brain was excised, rinsed with normal saline, blotted dry, and weighed. A brain homogenate was prepared at a 1:1 (g:ml) ratio with ice-cold pH 7.4 isotonic phosphate buffer. Serum and brain homogenate samples were stored at −20°C until analysed by a previously developed HPLC method (6).

Prodrug Animal Studies

AZddU-DHP or AZT-DHP was dissolved in DMSO (50 mg/ml) and administered intravenously through a tail vein over 30 sec at a dose of 73.9 or 72.7 mg/kg (equimolar to 50 mg/kg of AZddU or AZT), respectively. Animal dosing, sample collection, and processing procedures were the same as described for the parent drug studies above. Serum and brain samples were processed immediately for the analysis of prodrugs and quaternary salts by an ion-pair HPLC method (see below). AZddU and AZT were analyzed separately by an HPLC method (6).

Analysis of AZddU-DHP and AZddU-QS or AZT-DHP and AZT-QS

To 100 μl of serum or brain homogenate in a 1.5-ml polyethylene tube containing 10 μl of *o*-acetophenitidin and 40 μl of DMSO, 300 μl of cold acetonitrile was added while vortexing to precipitate proteins. Vortexing was continued for 30 sec, and then 100 mg of sodium chloride was added to each tube. The tubes were briefly vortexed and then centrifuged at 10,000 rpm for 5 min. For serum, 200 μl of supernatant obtained from centrifugation was evaporated to dryness under nitrogen gas at 25°C, whereas for brain homogenate all the supernatant was evaporated to dryness. The residual film was reconstituted in 100 μl of mobile phase and an aliquot injected onto the HPLC system. Inter- and intraday coefficients of variation for all compounds and procedures were 15% or less. The lowest concentration that was quantitated for all compounds was 100 ng/ml.

HPLC Conditions

All samples were analyzed on a chromatographic system that consisted of a Varian Model 2510 pump, 9090 autosampler, 2550 variable wavelength detector, and 4290 integrator. Chromatographic separations were achieved on a Hypersil ODS column (5-μm particle size, 150 × 4.6 mm) preceded by a guard column packed with 30 to 40-μm pellicular RP-18 material. The mobile phase consisted of 30% (v/v) acetonitrile/water at a final concentration of 40 m*M* sodium acetate, 4 m*M* sodium lauryl sulfate, and an apparent pH of 7 (adjusted with acetic acid). The mobile phase flow rate was 2 ml/min, and all compounds were detected at 260 nm.

Model Development

Parent Drugs

The brain was represented as a two-compartment model consisting of a serum or vascular compartment and an extravascular compartment (see Fig. 1). In this model, the blood–brain barrier (BBB) would provide a membrane limitation to drug transport, and the interstitial and intracellular compartments are lumped into the extravascular compartment.

Differential mass balance equations for the parent drugs are given in Appendix I, and all terms are defined in Appendix III. The serum concentrations, C_s, for AZddU and AZT were represented by exponential equations,

$$C_s = \sum_{i=1}^{n} A_i e^{-\lambda_i t} \quad (1)$$

where A_i is the y-axis intercept for the ith phase, λ_i is the disposition rate constant for the ith phase, and t is time. Exponential equations, i.e., Eq. (1), were fitted to the mean serum concentration–time data for AZddU and AZT by nonlinear regression analysis (7). The exponential equations for C_s, thus, served as an input or forcing function in the mass balance equations. Organ serum flow rate (Q) and compartmental volumes (V_1, V_2) were estimated from the literature (8–10). Partition coefficients (r) and mass transfer coefficients (h) for AZddU and AZT were determined by nonlinear regression analysis of the observed brain concentration–time data. These parameters, except the mass transfer coefficient for AZT, were estimated by alternate means for the prodrug models (see below).

Prodrugs

Figure 2 illustrates the hybrid pharmacokinetic model for the prodrugs. Similar to the parent drug model, the brain consists of a vascular and an extravascular compartment. AZddU-DHP and AZT-DHP are converted in parallel to their respective quaternary ion and parent drug species in each compartment. The quaternary ion moieties are converted to the parent drugs in each compartment, yet it has been assumed the charged species are unable to cross the BBB. In support of this, it was found that intravenous administration of AZddU-QS did not produce detectable AZddU-QS or AZddU brain concentrations. The differential

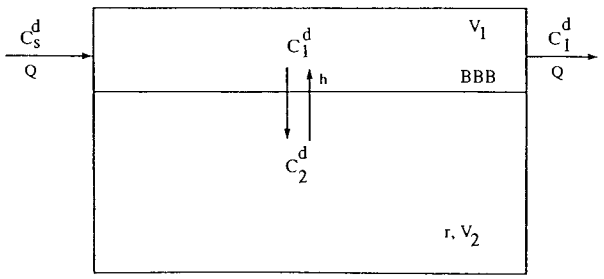

Fig. 1. Representation of the hybrid pharmacokinetic model used for parent drug administrations, AZT and AZddU. BBB, blood–brain barrier. See Appendix III for definition of other terms.

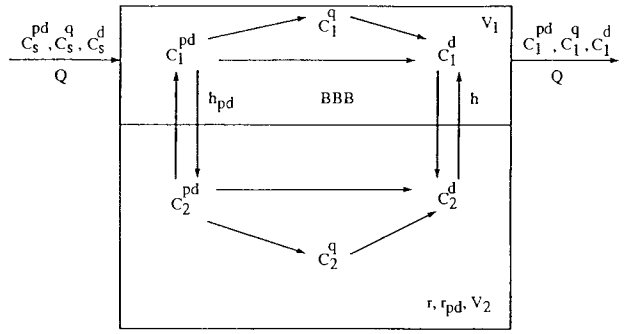

Fig. 2. Representation of the hybrid pharmacokinetic model used for prodrug administrations, AZT-DHP and AZddU-DHP. BBB, blood–brain barrier. See Appendix III for definition of other terms.

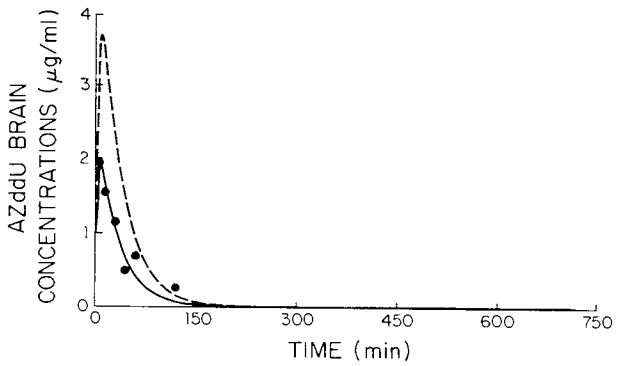

Fig. 3. AZddU brain concentrations versus time in mice following AZddU administration. (●) Observed; (——) predicted from fitted parameters, h = 0.0038 (ml/min), r = 0.034; (--) predicted from parameters in prodrug model. See text for details.

mass balance equations and the definition of terms are given in Appendixes II and III, respectively.

Polyexponential equations [*viz.* Eq. (1)] were fitted to prodrug, quaternary ion, and parent drug mean serum concentration data obtained following AZddU-DHP and AZT-DHP administrations by nonlinear regression analysis (7). The serum flow rate (Q) and compartment volumes (V_1,V_2) were set equal to the values used in the parent drug model. Parent drug partition coefficients (r) were estimated by the area method (11). The prodrug partition coefficients (r_{pd}) were set equal to the octanol:water partition coefficient determined *in vitro*. The mass transfer coefficient (h) for AZddU was empirically adjusted based on the value used in the parent drug model, whereas for AZT this parameter was set equal to the value used in the parent drug model. The prodrug mass transfer coefficients (h_{pd}) were estimate empirically. All rate constants (k_i) were assumed to be first-order and were initially estimated from the *in vitro* data. For the *in vitro* data, rate equations describing first-order conversions of the prodrugs to the quaternary salts and parent drugs and of the quaternary salts to the parent drugs in serum and brain homogenates were fit by nonlinear regression methods (12). The *in vitro* rate constants adequately predicted the *in vivo* parent drug brain concentrations but not the quaternary salt and prodrug brain concentrations. Thus, further empirical optimization of the rate constants was done to obtain better agreement between observed and predicted brain concentrations for all species. Empirical optimizations, or trial-and-error approaches, may not result in parameter sets that achieve optimal predictions since only a portion of the parameter space is investigated. Improved predictions may be achieved with statistical optimization procedures, however, parameters may be obtained that have little physiological meaning. In the current study, optimizations based on a log-likelihood function did not improve the prodrug model predictions, no doubt due to the large number of parameters to be estimated relative to the number of observations. All differential mass balance equations for the parent and prodrug models (see Appendixes I and II) were solved using a Gears algorithm in the SIMUSOLV program (12).

RESULTS AND DISCUSSION

Parent Drugs

Figures 3 and 4 illustrate the observed and model predicted AZddU and AZT brain concentrations following administration of AZddU and AZT, respectively. Table I lists the parameters for the best-fit exponential equations that describe the serum concentrations from both the parent and the prodrug studies. Weights of $1/y$ and $1/y^2$ provided the best fit to the data based on the randomness of the residuals. Standard deviations of some parameter estimates were high (i.e., >100% coefficients of variation) and were due to the small number of observed serum concentrations. This was particularly true for the DHP moieties; however, in all cases the fitted equations produced small residual values. Tissue uptake and relatively rapid hydrolysis of the prodrugs did not permit the measurement of the prodrug concentrations at more time points. The exponential equations, for the purposes of this investigation, are considered functional, since they serve as input functions into the differential mass balance equations, rather than as means to estimate pharmacokinetic parameters. Although numerical identifiability of some of the input function parameters is problematic, the possibility of attaining large concentration–time data sets for the prodrugs is unrealistic.

Organ serum flow and compartmental volumes were equal to the values used in the prodrug models (see Table II). Close agreement between observed and predicted AZddU and AZT brain concentrations were obtained by fitting (solid line in Figs. 3 and 4) the data through varying the partition (r)

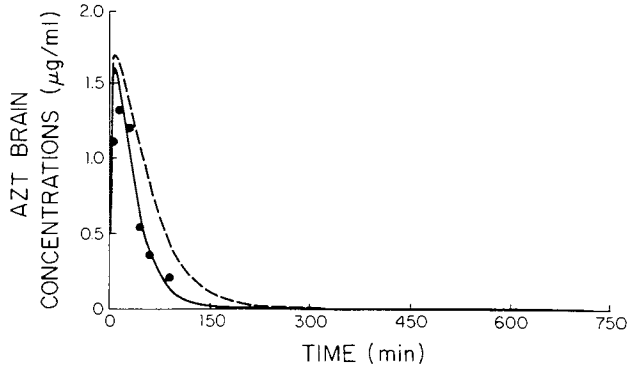

Fig. 4. AZT brain concentrations versus time in mice following AZT administration. (●) Observed; (——) predicted from fitted parameters, h = 0.0005 (ml/min), r = 0.02; (---) predicted from parameters in prodrug model. See text for details.

Table I. Parameters for the Exponential Equations Used in the Hybrid Pharmacokinetic Models

Compound/study[a]	A_1[b]	A_2	A_3	λ_1[c]	λ_2	λ_3
AZddU/1	38.74	0.09762	—	0.02954	1.3 E-6	—
AZT/2	56.09	—	—	0.03733	—	—
AZddU-DHP/3	1.22	0.31	—	0.1823	0.00646	—
AZddU-QS/3	24.99	1.96	—	0.458	0.048	—
AZddU/3	44.0984	43.99	0.1084	0.1394	0.0272	4.0 E-6
AZT-DHP/4	13.37	—	—	0.1677	—	—
AZT-QS/4	4.73	0.12	—	0.14	2.2 E-6	—
AZT/4	27.36	27.2	0.16	0.20	0.021	8.0 E-5

[a] 1 = 50 mg/kg AZddU iv; 2 = 50 mg/kg AZT iv; 3 = 73.9 mg/kg AZddU-DHP iv; 4 = 72.7 mg/kg AZT-DHP iv.
[b] Units for A_i are μg/ml.
[c] Units for λ_i are min^{-1}.

and mass transfer (h) coefficients. AZddU and AZT brain concentrations predicted by utilizing the r and h values from the prodrug models (dashed lines in Figs. 3 and 4) overpredict the observed concentrations, especially for AZddU. The mass transfer coefficient for AZT was the same for both parent and prodrug models, as would be expected. However, the mass transfer coefficient for AZddU was empirically increased for the prodrug model to obtain agreement between observed and predicted AZddU brain concentrations.

AZddU and AZT brain concentrations predicted by the fitted parameters clearly demonstrate that hybrid modeling can be applied to characterize anti-HIV nucleoside brain disposition.

Prodrugs

Figures 5 and 6 show the observed and predicted brain concentrations derived from the administration of AZddU-DHP and AZT-DHP. Tables I and II give the parameter values used for the *in vitro* and empirical model predictions.

Table II. Hybrid Pharmacokinetic Model Parameters

	AZddU-DHP		AZT-DHP	
Parameter	Empirical[a]	*In vitro*[b]	Empirical	*In vitro*
Q (ml/min)	0.233	0.233	0.233	0.233
V_1 (ml)	0.0104	0.0104	0.0104	0.0104
V_2 (ml)	0.3376	0.3376	0.3376	0.3376
r	0.1	0.1	0.05	0.05
r_{pd}	20.0	20.0	50.0	50.0
h (ml/min)	0.009	0.009	0.0005	0.0005
h_{pd} (ml/min)	2.0	2.0	0.01	0.01
k_{pd1} (min^{-1})	0.001	1.1 E-7	0.001	0.0037
k_{pd2} (min^{-1})	0.035	0.035	0.01	0.039
k_{pq1} (min^{-1})	0.25	0.0234	0.01	0.0025
k_{pq2} (min^{-1})	0.875	0.035	0.08	0.022
k_{qd1} (min^{-1})	0.09	0.0233	0.0075	0.012
k_{qd2} (min^{-1})	0.09	0.020	0.01	0.0097

[a] The parameters listed were used in the solid-line model predictions in Figs. 5 and 6.
[b] The *in vitro* parameters (dashed lines in Figs. 5 and 6) are the same as the empirical except the rate constants were determined by analysis of the *in vitro* serum (compartment 1) and brain homogenate (compartment 2) stability data.

The differences in these models are that the rate constants (i.e., k_i) were determined empirically based on the values obtained from the *in vitro* stability studies. All other parameters were equal in the two models.

The hybrid model predictions (solid lines, Fig. 5) following AZddU-DHP administration agree with the observed brain concentrations for all species. The dihydropyridine and quaternary salt species disappear relatively rapidly, with neither species being detected past 2 hr. The active drug, AZddU, was measured for up to 8 hr after prodrug administration, whereas it was observed for only 2 hr (see Figure 3) after parent drug administration. The *in vitro* hybrid model predictions (dashed lines, Fig. 5) predict only AZddU brain concentrations well, while overpredicting the other compounds.

The hybrid model predictions (Fig. 6A) for AZT-DHP brain concentrations overpredict the observed concentrations at 5 and 15 min. However, the predicted values do fall off rapidly and are consistent with the lack of measurable values after 15 min. The predicted AZT-QS brain concentrations (Fig. 6B, solid line) adequately describe the observed values, especially when considering the variability in the mean concentration data. The *in vitro* model predictions (Fig. 6B, dashed line) do not agree nearly as well. Model predicted AZT brain concentrations (Fig. 6C, solid line) describe the observed data for up to 3 hr and then underpredict the terminal concentrations by approximately 0.3 μg/ml. The *in vitro* model predicted AZT brain concentrations (Fig. 6C, dotted line) overpredict early concentration values and then underpredict the terminal concentrations.

There were a number of similarities in the values for the rate constants used for the empirical and *in vitro* hybrid models. For the AZddU-DHP model, all empirical rate constants were equal to or greater than the *in vitro* values (see Table II). This would be consistent with greater *in vivo* enzyme concentrations or activity. In both cases, the favored conversion pathway to AZddU was through AZddU-QS rather than by direct hydrolysis of AZddU-DHP. Also, all conversion rates were essentially equal to or greater in compartment 2 than in compartment 1 for both the *in vitro* and the empirical models. For the AZT-DHP model, the ratio of the rate constants in compartment 1 to compartment 2 were similar for the *in vitro* and empirical models. Analagous to the AZddU-DHP model, rate constants were generally greater in compartment 2 than in compartment 1.

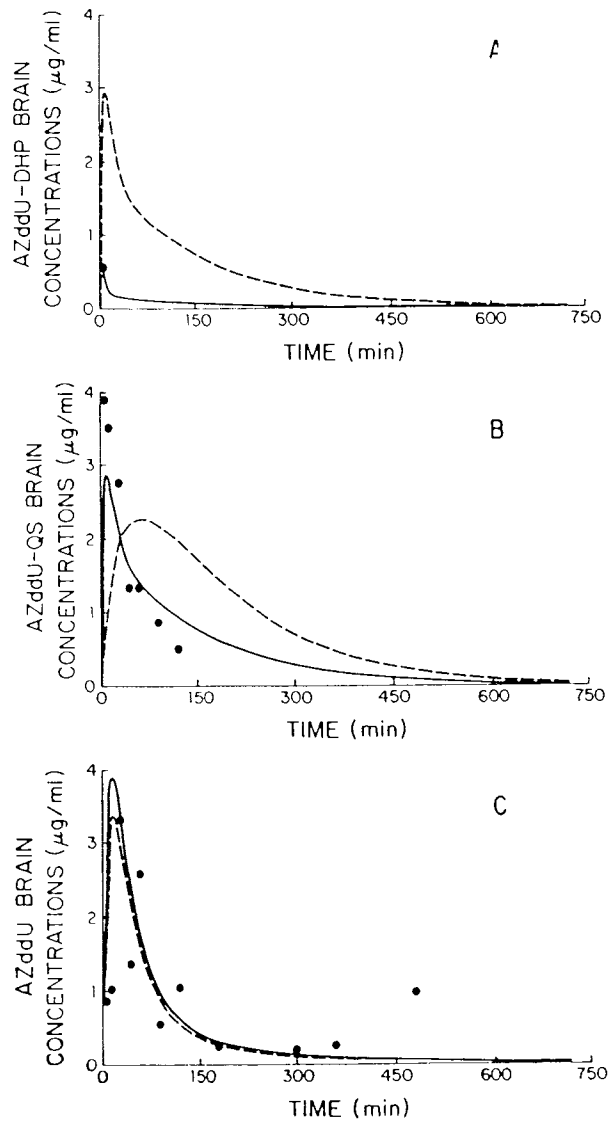

Fig. 5. AZddU-DHP (A), AZddU-QS (B), and AZddU (C) brain concentrations versus time in mice following AZddU-DHP administration. (●) Observed; (——) predicted by empirical parameters; (---) predicted by conversion rate constants determined *in vitro*. See text for details.

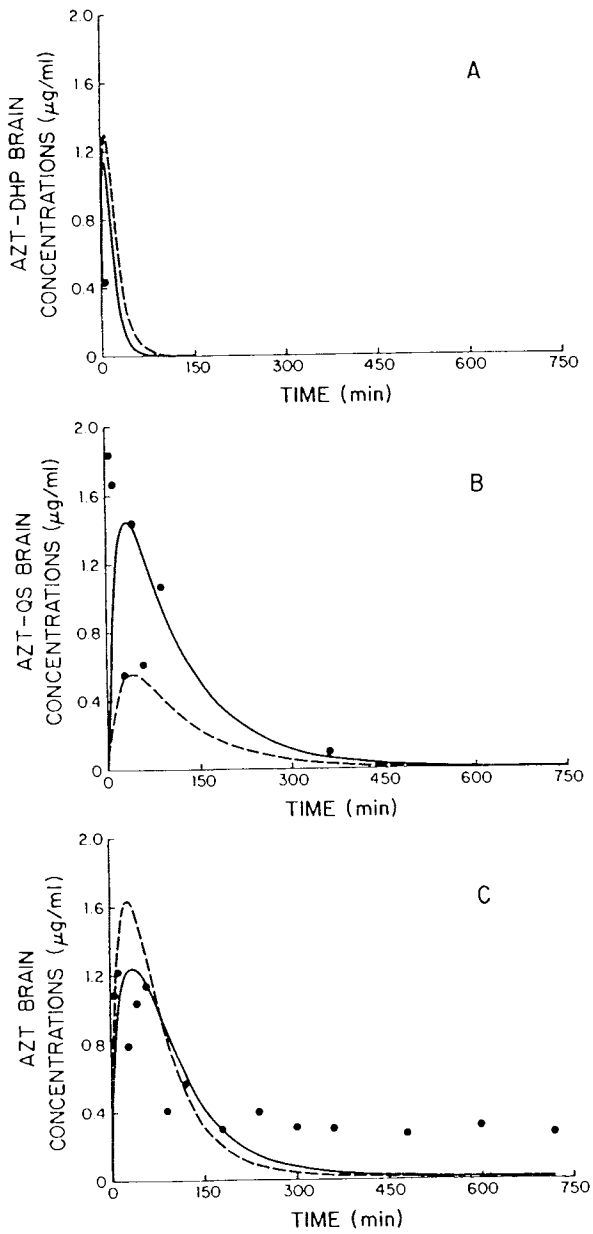

Fig. 6. AZT-DHP (A), AZT-QS (B), and AZT (C) brain concentrations versus time in mice following AZT-DHP administration. (●) Observed; (——) predicted by empirical parameters; (---) predicted by conversion rate constants determined *in vitro*. See text for details.

The hybrid modeling technique was considered an attractive approach in that it is simpler than a global physiological pharmacokinetic model since fewer data and parameters are required, yet the model can be scaled to humans. An ultimate goal of the models is to predict human brain anti-HIV drug concentrations. Scale-up of the current hybrid model will require collection of similar data in larger animals such as dogs and monkeys. The combined animal data could be used to explore and develop interspecies extrapolation techniques for the model parameters. Allometric equations based on animal body weight have been successfully applied to scale physiological and pharmacokinetic parameters. It has been demonstrated that exponential equations used to characterize serum drug concentration–time profiles can be related by allometric equations (13), thus the forcing functions used in the hybrid model mass balance equations can be scaled. Scale-up of other model parameters (i.e., partition coefficients and rate constants), if necessary, can also be accomplished and, as for the exponential functions, would be based on additional *in vitro* and animal data.

Revisions to the current models may occur in a number of areas. Prodrug metabolic and membrane transport processes have been assumed to be first-order rather than saturable. *In vitro* and *in vivo* concentration–time data, obtained over a range of concentrations or doses, would be needed to justify Michaelis–Menton kinetics and saturable membrane transport. Previous representations (14) and *in vitro* (3) investigations of dihydropyridine prodrug biotransformations have utilized first-order reactions. Membrane transport of AZT into human erythrocytes and lymphocytes

has been shown to occur by nonfacilitated diffusion (15) and is consistent with the linear transport processes used in the current models. Another potential area for model refinement would be to include the intracellular conversions of the parent drugs, AZddU and AZT, to active phosphorylated derivatives. Phosphorylation of dideoxynucleosides through cellular kinases is cell species dependent (16), and direct measurement of phosphorylated metabolites has not been undertaken in mouse brain homogenate. The *in vitro* bioconversion studies conducted for this investigation showed no evidence of AZT or AZddU metabolism, and thus, intracellular metabolism was not included in the current models. Another model revision could include separation of the extravascular compartment into an extracellular space–cerebrospinal fluid (ECS-CSF) compartment and an intracellular compartment. This division has been considered in other central nervous system drug distribution models (17,18) and allows predictions of CSF concentrations, which are assumed to be equal to ECS brain concentrations. Verification of models that distinguish between CSF and intracellular brain concentrations will require experimental procedures to measure CSF drug concentrations independently of brain concentrations. The current models have lumped CSF into the extravascular compartments, since independent measurement of CSF concentrations in mice is technically unrealistic.

Prediction of human brain anti-HIV drug concentrations via a scaled hybrid model will provide valuable feedback prior to initiating clinical studies. Predictions can be made for different multiple dose regimens, and comparisons between generated steady-state brain concentrations and accepted therapeutically active concentrations will provide a quantitative assessment of the dosage regimen design and of the brain delivery potential of the drug or prodrug. The current hybrid models make a first attempt at attainment of a predictive model for anti-HIV target organ drug delivery.

APPENDIX I: DIFFERENTIAL MASS BALANCE EQUATIONS FOR PARENT DRUG HYBRID PHARMACOKINETIC MODELS

For compartment 1,

$$V_1 \frac{dC_1^d}{dt} = Q(C_s^d - C_1^d) - h(C_1^d - C_2^d/r)$$

For compartment 2,

$$V_2 \frac{dC_2^d}{dt} = h(C_1^d - C_2^d/r)$$

APPENDIX II: DIFFERENTIAL MASS BALANCE EQUATIONS FOR PRODRUG HYBRID PHARMACOKINETIC MODELS

For compartment 1,

$$V_1 \frac{dC_1^{pd}}{dt} = Q(C_s^{pd} - C_1^{pd}) - h_{pd}(C_1^{pd} - C_2^{pd}/r_{pd}) - k_{pd1}V_1C_1^{pd} - k_{pq1}V_1C_1^{pd}$$

$$V_1 \frac{dC_1^q}{dt} = Q(C_s^q - C_1^q) + k_{pq1}V_1C_1^{pd} - k_{qd1}V_1C_1^q$$

$$V_1 \frac{dC_1^d}{dt} = Q(C_s^d - C_1^d) - h(C_1^d - C_2^d/r) + k_{pd1}V_1C_1^{pd} + k_{pq1}V_1C_1^{pd}$$

For compartment 2,

$$V_2 \frac{dC_2^{pd}}{dt} = h_{pd}(C_1^{pd} - C_2^{pd}/r_{pd}) - k_{pd2}V_2C_2^{pd} - k_{pq2}V_2C_2^{pd}$$

$$V_2 \frac{dC_2^q}{dt} = k_{pq2}V_2C_2^{pd} - k_{qd2}V_2C_2^q$$

$$V_2 \frac{dC_2^d}{dt} = h(C_1^d - C_2^d/r) + k_{pd2}V_2C_2^{pd} + k_{pq2}V_2C_2^q$$

APPENDIX III: DEFINITION OF PARAMETERS USED IN THE HYBRID PHARMACOKINETIC MODEL

C_i^m	Concentration of chemical m in compartment i or serum (μg/ml)
h	Mass transfer coefficient for parent compounds (ml/min)
h_{pd}	Mass transfer coefficient for prodrugs (ml/min)
k_{pdi}	Prodrug-to-parent drug conversion rate constant in compartment i (min − 1)
k_{pqi}	Prodrug-to-quaternary salt conversion rate constant in compartment i (min − 1)
k_{qdi}	Quaternary salt-to-parent drug conversion rate constant in compartment i (min − 1)
Q	Brain serum flow rate (ml/min)
r	Partition coefficient for parent drug
r_{pd}	Partition coefficient for prodrug
V_i	Volume of brain compartment i (ml)

Subscripts for *i*:

1	Compartment 1 or brain vascular compartment
2	Compartment 2 or brain extravascular compartment.

Superscripts for m:

d	Parent drug
pd	Prodrug
q	Quaternary salt.

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