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Physiologically Based Pharmacokinetic Modeling of FTY720 (2-Amino-2[2-(-4-octylphenyl)ethyl]propane-1,3-diol hydrochloride) in Rats After Oral and Intravenous Doses

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ABSTRACT:

FTY720 (2-amino-2[2-(-4-octylphenyl)ethyl]propane-1,3-diol hydrochloride) is a new sphingosine-1-phosphate receptor agonist being developed for multiple sclerosis and prevention of solid organ transplant rejection. A physiologically based pharmacokinetic model was developed to predict the concentration of FTY720 in various organs of the body. Single oral and intravenous doses of FTY720 were administered to male Wistar rats, with blood and tissue sampling over 360 h analyzed by liquid chromatography/tandem mass spectrometry. A well stirred model (perfusion rate-limited) described FTY720 kinetics in heart, lungs, spleen, muscle, kidneys, bone, and liver, with a permeability rate-limited model being required for brain, thymus, and lymph nodes. Tissue-to-blood partition coefficients (R_T) ranged from 4.69 (muscle) to 41.4 (lungs). In lymph nodes and spleen, major sites for FTY720-induced changes in sequestration of lymphocytes, R_T values were 22.9 and 34.7, respectively. Permeability-surface area products for brain, thymus, and lymph nodes were 39.3, 122, and 176 ml/min. Intrinsic hepatic clearance was 23,145 l/h/kg for the free drug in blood (f_{ub} 0.000333); systemic clearance was 0.748 l/h/kg and terminal half-life was 23.4 h. The fraction orally absorbed was 71%. The model characterized well FTY720 disposition for this extensive dosing and tissue collection study in the rat. On scaling the model to dogs and humans, good agreement was found between the actual and predicted blood concentration-time profiles. More importantly, brain concentrations in dogs were well predicted from those of the rat. In absolute terms, the predictions were slightly lower than observed values, just under a 1.5-fold deviation, but the model accurately predicted the terminal elimination of FTY720 from the brain.

FTY720 (2-amino-2[2-(-4-octylphenyl)ethyl]propane-1,3-diol hydrochloride) is a new sphingosine-1-phosphate receptor agonist that is being developed for prevention of solid organ transplant rejection (Napoli, 2000). FTY720 exerts its immunomodulatory actions by affecting lymphocyte production (Yagi et al., 2000), trafficking (Chiba et al., 1998; Brinkmann et al., 2000, 2001), infiltration (Yanagawa et al., 2000), and apoptosis (Enosawa et al., 1996; Bohler et al., 2000; Nagahara et al., 2000). The maximum effects of FTY720 on these immune responses are achieved at doses smaller than those producing effects against graft rejection (Yanagawa et al., 1998). Regulation of gene expression may also account for pharmacological and toxicological effects of FTY720: for instance, a 26-week pharmacology study in rats using gene chips showed that, at doses of 0.3 and 1.5 mg/kg/day, genes of B and T lymphocyte markers in blood (*CD79* and *CD3*) were down-regulated (Novartis Pharma AG, internal communication).

The elimination of FTY720 from the body occurs mainly via metabolism. Two primary pathways metabolize FTY720: 1) phosphorylation at one of its two hydroxy groups (yielding FTY720-P) and 2) hydroxylation at the terminal methyl group (M12) (Novartis Pharma AG, internal communication). The blood clearance values for FTY720 in dogs, monkeys, and humans are 0.0617, 0.113, and 0.0433 ml/h/kg, respectively. The elucidation of the mechanism of action and pharmacodynamics of FTY720 on immune cells will necessitate the characterization of its disposition not only in blood but also in target organs such as lymph nodes, spleen, and thymus.

The objective of this work was to develop a physiologically based pharmacokinetic (PBPK) model in rats to characterize the kinetics of

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ABBREVIATIONS: FTY720, 2-amino-2[2-(-4-octylphenyl)ethyl]propane-1,3-diol hydrochloride; PBPK, physiologically based pharmacokinetic; Y32919, 2-amino-2-[2-(4-octyloxyphenyl)ethyl]propane-1,3-diol hydrochloride; HPLC, high-performance liquid chromatography; LN, lymph nodes; AUC, area under the concentration-time curve; R_T, tissue-to-blood partition coefficient; PS_T, permeability-surface area product; CL_{int}, intrinsic clearance.

FTY720 both in major organs and in lymphatic tissues such as spleen, thymus, and lymph nodes.

Materials and Methods

Chemicals. Analytical grade FTY720 and Y32919 (internal standard; 2-amino-2-[2-(4-octyloxyphenyl)ethyl]propane-1,3-diol hydrochloride) were supplied by Novartis Pharma AG (Basel, Switzerland). HPLC-grade dichloromethane and water were purchased from Burdick and Jackson (Muskegon, MI). Methanol optima grade and glacial acetic acid HPLC grade were purchased from Fisher Scientific (Fairlawn, NJ). *tert*-Butyl-methyl ether HPLC grade was purchased from Sigma Aldrich (Milwaukee, WI) and ammonium acetate microselect was purchased from Fluka (Milwaukee, WI).

Animals. Normal male Wistar rats, 80 to 90 days old, with body weights ranging from 300 to 375 g, were used in this study (Harlan Sprague-Dawley Inc., Indianapolis, IN). The animals were housed in pairs in stainless steel cages in a controlled environment with a 12-h light/dark cycle. Filtered tap water and food were available ad libitum. Before the dosing day, animals were kept in the animal facility for at least 7 days for acclimatization.

Dosing and Sampling. Single i.v. bolus doses of FTY720 (0.3, 2, and 4 mg/kg) were given to rats via penal vein injection. For each group, three rats were sacrificed by aortic exsanguination under ketamine/xylazine anesthesia just before dosing and 0.5, 1, 3, 6, 12, 24, 48, 72, 120, 176, 240, and 360 h postdose. Arterial blood was collected, and lungs, heart, brain, kidneys, thymus, spleen, liver, muscle, fat, inguinal lymph nodes (LN), mesenteric LN, axillary LN, cervical LN, popliteal LN, and Peyer's patches were dissected. Tissue collection was performed only after the 0.3 and 2 mg/kg doses. Samples collected at each time point from each of the three animals were pooled in equal volumes, homogenized in physiological buffer (4 times tissue weight, pH 7.4), and stored at −20°C.

Single oral doses of FTY720 (2.8 and 7.5 mg/kg) were also administered to rats. Serial blood sampling was performed for venous blood. For the dose of 2.8 mg/kg, spleen samples were collected at 1, 8, 12, 24, 48, 72, and 120 h. After administration of 7.5 mg/kg, brain, liver, lungs, muscle, and heart tissue samples were collected at 8 and 72 h.

Eighteen male beagle dogs (3 per time point) aged 7 months and weighing 7.6 to 10.1 kg received single oral doses of 10 mg/kg. At necropsy, on days 1, 3, 7, 14, 21, and 28 after drug administration, the frontal lobe of the brain was collected.

Clinical Study. Healthy male volunteers aged between 20 and 39 years, weight 68 to 95 kg, were given 1-mg doses of FTY720. Venous blood samples were obtained before FTY720 administration and then 1, 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, 72, 96, 120, and 168 h postdose. The study was carried out in compliance with the protocol and according to Good Clinical Practice with full informed consent according to the Declaration of Helsinki. Further details are available in a prior publication (Kovarik et al., 2004).

Bioanalytical Instruments and FTY720 Assay. The liquid chromatography/tandem mass spectrometry system was a PE Sciex API 3000 with heated nebulizer interface (Applied Biosystems, Foster City, CA) together with Agilent 1100 pumps, detector, and autosampler (Agilent Technologies, Palo Alto, CA). The HPLC column was a 3.5 μ Symmetry Shield RP_8, 4.6 × 50 mm (Waters Corp., Milford, MA).

After thawing and rehomogenization of samples, FTY720 was extracted as follows. Aliquots (0.1 ml) of calibration standards, quality controls, or unknowns were added to 0.1 ml of 100 ng/ml Y32919 in methanol, 0.5 ml of 0.1 N sodium hydroxide solution added, followed by 6 ml of *tert*-butyl-methyl ether and dichloromethane (75:25 v/v). After shaking for 45 min followed by centrifugation for 10 min at 2000*g*, the organic phase was transferred and evaporated under N_2, reconstituted with 150 μl of HPLC eluent, sonicated for 5 min, mixed, and centrifuged for 5 min at 15,000*g*, and then injected into the liquid chromatograph/tandem mass spectrometer.

The chromatography system was eluted with 70% methanol plus 30% 0.02 M ammonium acetate at 1 ml/min. The parent molecular ion for FTY720 is 308.3 Da ($+1^+$ proton) with a daughter ion of 255.3 *m/z*. Y32919 has a parent of 324.4 Da and daughter of 271.4 *m/z*. The integrity of the original compounds was checked using the mass spectrometer, and there was no carryover into either the FTY720 or the Y32919 detection channels. The lower limit of quantitation was 0.5 ng/ml (11.9% CV) and the upper limit 2000 ng/ml (2.33% CV). The recovery was 86.1% at 30 ng/ml and 95.8% at 1250 ng/ml. The intraday and interday CV% ranges were 4.15 to 5.94% and 5.01 to 5.96%, respectively.

Partition Coefficients. The AUC (area under the concentration-time curves) of drug in blood and tissues was calculated by

$$\mathrm{AUC} = \sum_{i=0}^{n-1} [(C_{i+1} + C_i) \cdot (t_{i+1} - t_i)/2] + \frac{C_n}{\lambda_z} \quad (1)$$

where C_i is the drug concentration at $t = t_i$ and λ_Z is the terminal slope of the concentration-time curve. The tissue-to-blood partition coefficient (R_T) for noneliminating tissues was obtained from

$$R_T = \frac{\mathrm{AUC_T}}{\mathrm{AUC_V}} \approx \frac{\mathrm{AUC_T}}{\mathrm{AUC_A}} \quad (2)$$

where AUC_T, AUC_V, and AUC_{art} are derived from drug concentration versus time profiles for tissues and venous and arterial blood. This equation was used to calculate R_T for lungs, heart, brain, kidneys, thymus, spleen, muscle, and lymph nodes for the 0.3 and 2 mg/kg i.v. doses.

The volume of distribution at steady state ($V_{B,ss}$) was calculated as

$$V_{B,ss} = \sum_{\text{Tissue}}^{\text{non-elim}} [R_{T/B} \cdot V_T] + R_{H/B} \cdot V_{liver} \cdot (1 - E_{liver}) + V_{blood} \quad (3)$$

where V_T represents specific tissue volumes and E_{liver} is the hepatic extraction ratio.

Compartmental Analysis. Arterial blood concentration-time data for FTY720 after i.v. administration of 0.3 and 2 mg/kg doses were analyzed by compartmental analysis using the computer software WinNonlin ver. 4.0 (Pharsight Corporation, Mountain View, CA).

Model Development. Local models were developed with blood and organ concentration-time data obtained after single i.v. doses of 0.3 and 2 mg/kg. Data from each tissue were first considered individually. The choice of final structural models was based upon inspection of quality of fits to the data and the Akaike information criterion. Parameter values obtained with local models were then used as initial estimates for the whole body model. The fitted parameters were tissue-to-blood partition coefficients (R_T), permeability-surface area products (PS_T), and liver intrinsic clearance (CL_{int}). The first-order absorption rate constant (k_{abs}) and fraction of drug absorbed (F_{abs}) were determined by adapting the i.v. PBPK model to oral data obtained after the single doses of 2.8 and 7.5 mg/kg. For the oral PBPK model, all parameters (R_T, PS_T, and CL_{int}) were maintained as constant. Only parameters k_{abs} and F_{abs} were optimized. To verify the linearity of FTY720 kinetics with respect to dose, blood and tissue data obtained after the single 4 mg/kg i.v. dose were superimposed on the corresponding simulated curve based upon the parameters determined with the 0.3 and 2 mg/kg doses. Single i.v. bolus doses were regarded as a 7.5-s i.v. infusion, and drug was assumed to distribute evenly in the whole vein pool once injected. Based on metabolism and clearance data (Novartis Pharma AG, internal communication), the liver was considered as the sole eliminating organ.

Local Models. FTY720 concentration-time data after i.v. doses were fitted to

$$C_{art} = A \times e^{-\alpha \times t} + B \times e^{-\beta \times t} + C \times e^{-\gamma \times t} \quad (4)$$

Equations for well stirred organs (heart, lungs, muscle, spleen, liver, and kidneys) were

$$\frac{dX_T}{dt} = Q_T \times \frac{X_{art}}{V_T} - Q_T \times \frac{X_T}{(R_T \times V_T)} \quad (5)$$

Equations for permeability rate-limited transport (brain, thymus, lymph nodes) were:

Blood compartment

$$\frac{dX_{T1}}{dt} = Q_T \times \frac{X_{art}}{V_{T1}} - Q_T \times \frac{X_{T1}}{V_{T1}} - PS_T \times f_{ub} \times \frac{X_{T1}}{V_{T1}} + PS_T \times \left(\frac{f_{ub}}{R_T}\right) \times \frac{X_{T2}}{V_{T1}} \quad (6)$$

TABLE 1

Standard physiologic parameters for rats weighing 250 g

Organ	Mass	Q	Organ	Mass	Q
	g	*ml/min*		*g or ml*	*ml/min*
Lungs	1.0	43.0	Muscle	122	7.5
Brain[a,b]	1.7	1.33	Lymph nodes[a,b,c]	0.9	0.16
Heart	0.8	3.92	Liver	10.3	2.0
Stomach	1.1	1.13	Skin	40	5.83
Gut	10	7.52	Bone	15.8	2.53
Pancreas	1.3	0.52	Fat	10	0.4
Spleen	0.6	0.63	Arterial blood	5.6	
Kidneys	2.3	9.23	Venous blood	11.3	
Thymus[a,b]	0.7	0.3			

[a] Fractional volume of vascular space: brain, 0.014; thymus and lymph nodes, 0.009.
[b] Fractional volume of interstitial space: brain, 0.188; thymus and lymph nodes, 0.150.
[c] Sum of mesenteric, axillary, inguinal, cervical, Peyer's patches, and popliteal lymph nodes.

Interstitial and intracellular compartments

$$\frac{dX_{T2}}{dt} = PS_T \times f_{ub} \times \frac{X_{T1}}{V_{T2}} - PS_T \times \left(\frac{f_{ub}}{R_T}\right) \times \frac{X_{T2}}{V_{T2}} \quad (7)$$

where Q_T is organ blood flow rate, V_T is organ volume, X_{art} is input from arterial blood, PS_T is permeability-surface area product, R_T is tissue-to-blood partition coefficient, fw_T is fractional volume of vascular and/or interstitial space, V_{T1} is volume of blood + interstitial fluid ($V_{T1} = fw_T \times V_T$), V_{T2} is volume of intracellular space ($V_{T2} = V_T - V_{T1}$), and f_{ub} is free fraction of FTY720 in blood.

Organ volumes (V_i) were scaled from published data for a 250-g rat (Bernareggi and Rowland, 1991; Davies and Morris, 1993) using

$$V_2 = \frac{BW_2 \cdot V_1}{BW_1} \quad (8)$$

where BW_1 is the rat standard body weight (250 g) and BW_2 is the actual body weight of animals used in the current study (mean 362 g). Blood flow of tissues except thymus and lymph nodes was similarly scaled using

$$Q_2 = \frac{BW_2 \cdot Q_1}{BW_1} \quad (9)$$

Blood flow for thymus and lymph nodes was scaled from Cahill and Trnka (1978). All physiologic parameters used for this analysis are listed in Table 1. Drug concentrations for each tissue were converted to ng/ml from ng/g using tissue density.

Model Equations for Whole Body Model. The whole body PBPK model for FTY720 is depicted in Fig. 1. It depicts the body as composed of 13 tissue compartments and 2 blood compartments (arterial and venous pools) with the lungs closing the loop. Drug is placed in the venous compartment. All equations were solved simultaneously using the maximum likelihood estimator in ADAPT II.4 (D'Argenio and Schumitzky, 1997). Although FTY720 concentrations in bone, gastrointestinal tract, and skin were not collected, these organs were included as lumped compartments representing the gastrointestinal tract—splanchnic compartment—and "rest-of-body". It was assumed that these compartments obey the distribution characteristics of a well stirred model.

Interspecies Scale-Up. The PBPK model developed for rat was scaled-up to dog and humans. Physiological values (organ volume and blood flow rate) were taken from the literature. Unbound equilibrium distribution ratio (R_Tu) in dogs and humans for each tissue was calculated from R_T values obtained with the rat model and corresponding f_{ub} values for each species (f_{ub} values were 0.000241 in dogs and 0.000361 in humans). The PS_T values for brain, thymus, and lymph nodes for dog and human were predicted from the measurement in rat by use of an allometric equation

$$PS_T = A(M)^B \quad (10)$$

where M is organ mass (or weight) and A and B are allometric coefficients. The B value of 0.67 was fixed, assuming that permeability of tissue cellular membrane and organ structure is geometrically similar among mammals.

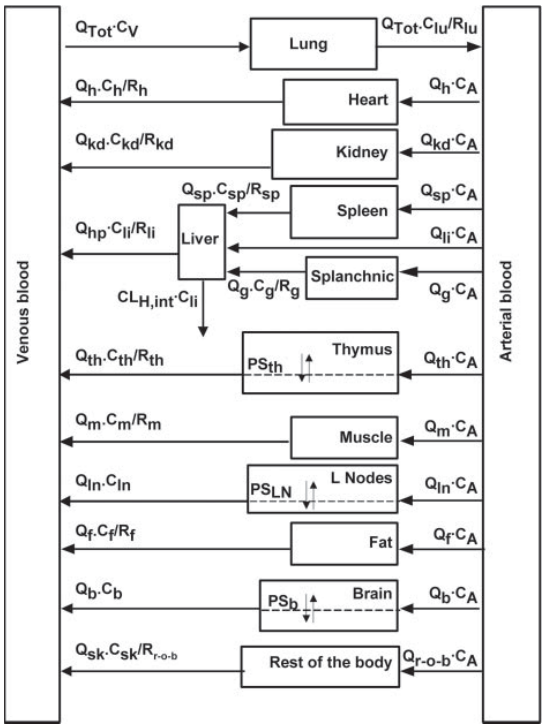

FIG. 1. Whole body PBPK model for FTY720. Subscripts are: A, arterial blood; V, venous blood; b, brain; h, heart; li, liver; sp, spleen; lu, lungs; g, gut-stomach-pancreas; kd, kidney; f, fat; sk, skin; m, muscle; th, thymus; ln, lymph nodes; and bn, bone.

To predict the blood concentration versus time profile for FTY720 in dogs, a first-order absorption rate constant (k_{abs}) and bioavailability values were taken from the results of a compartmental analysis. Because no in vitro data were available for the biotransformation of FTY720 in dogs, the intrinsic clearance in dogs (CL_{intD}) was calculated by nonlinear regression analysis with the whole body PBPK model, keeping all distribution parameters (R_T and PS_T) identical to those from the rat after correction for binding in blood.

To predict the concentration versus time profile for FTY720 in human blood, the first-order absorption rate constant (k_{abs}) was taken from the results of compartmental analysis. Because no i.v. formulation for FTY720 is available for humans, we assumed that humans had the same bioavailability (F) as rats. The intrinsic clearance in humans ($CL_{int,H}$) value was calculated in two ways. First, $CL_{int,H}$ was predicted from the product of the human in vitro clearance determined with liver microsomes and the in vivo to in vitro CL_{int} ratio from rats. Second, when human FTY720 concentration data became available, they were used to improve the estimate of human $CL_{int,H}$, keeping all distribution parameters (R_T and PS_T) identical to those from the rat after correction for binding in blood.

Results

Blood Profiles. Figures 2 and 3 depict blood concentration-time profiles for FTY720 after i.v. and oral administration. It appears from the graphs that the model captured the venous blood concentration-time profiles relatively well for the 0.3, 2, and 4 mg/kg i.v. doses. In contrast, arterial concentration-time profiles were somewhat overestimated. Venous blood concentration-time profiles for the 2.8 and 7.5 mg/kg oral doses were also well captured by the PBPK model. The model yielded a liver intrinsic clearance (CL_{int}) value based upon free FTY720 concentrations in blood of 23,145 l/h/kg. The corresponding systemic clearance value, according to the well stirred model, was 0.748 l/h/kg (f_{ub} = 0.000333). After oral administration, the first-

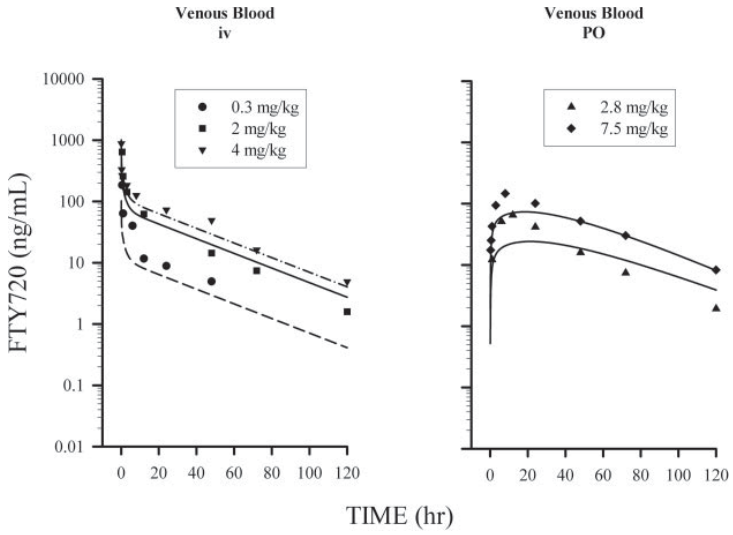

FIG. 2. Time course of FTY720 concentrations in rat venous blood after the indicated i.v. and oral doses. Symbols are experimental values and lines are PBPK model predictions.

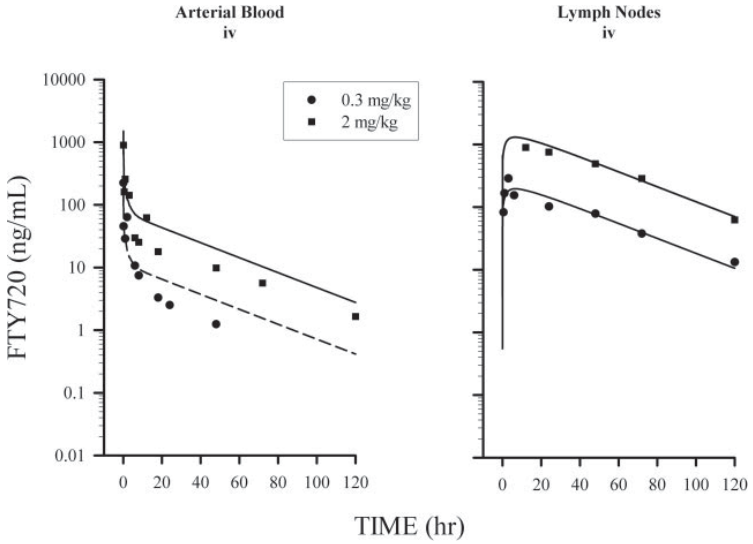

FIG. 3. Time course of measured (symbols) and predicted (lines) FTY720 concentrations in rat arterial blood and lymph nodes.

order absorption rate constant was 0.052 h^{-1} and fraction of drug absorbed was 0.45.

Well Stirred Organs. Concentration versus time profiles for heart, lungs, liver, kidneys, muscle, fat, and spleen captured by the PBPK model are depicted in Figs. 4 to 7. Concentration-time curves of these organs declined in parallel with that of venous and arterial blood. Tissue-to-blood partition coefficients (R_T) calculated by noncompartmental analysis and those obtained with the PBPK model are reported in Tables 2 and 3. Model-defined R_T values were obtained with relatively good precision, with CV% on parameters generally $<20\%$. In most organs, the deviation between the noncompartmental and PBPK-defined R_T values never exceeded 3-fold. Among these well stirred organs, FTY720 distributed most extensively into lungs and liver. The extent of distribution into fat and skeletal muscle was moderate.

Permeability-Limited Organs. The concentration-time curves for FTY720 in lymph nodes, brain, and thymus are shown in Figs. 3, 4, and 6. The model captured the observed data fairly well, with the exception of thymus, for which an overprediction of tissue concentration levels was noticed. Nevertheless, the model still captured the trend in the data as well as the terminal slope of the drug in that organ. To develop the organ model for lymph nodes, it was assumed that fractional volumes of vascular and interstitial spaces were identical to those of thymus because the two organs belong to the immune system. The PBPK model captured fairly well the features of the data. Tissue-to-blood partition coefficient values were 22.9 for lymph nodes, 27.1 for brain, and 15.7 for thymus. The corresponding PS_T values were 176, 39.3, and 122 ml/min (Table 3).

Other Organs. Organs that were not sampled, such as bone and skin, were lumped into a single compartment labeled "rest of body". A nonsampled splanchnic compartment comprising stomach and intestinal tract was also incorporated to account for the flow of blood

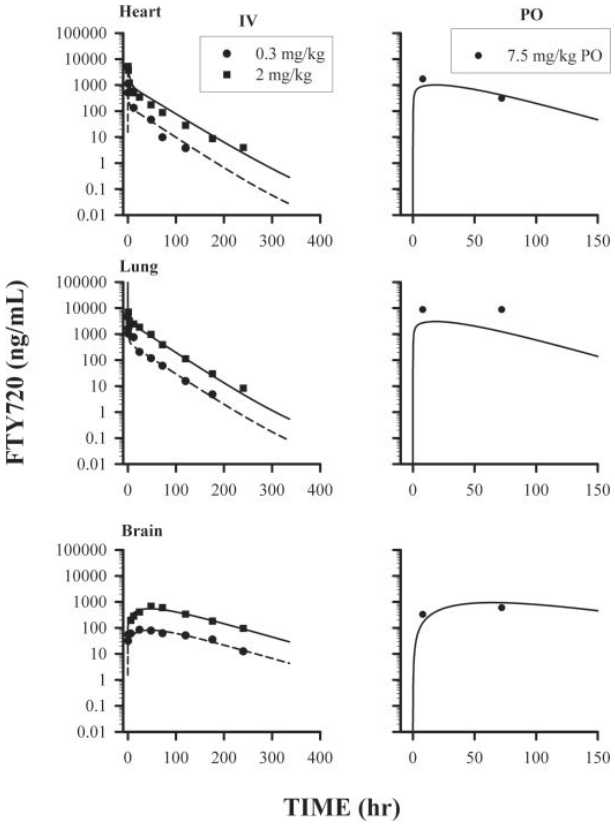

FIG. 4. Time course of measured (symbols) and predicted (lines) FTY720 concentrations in rat heart, lungs, and brain after i.v. and oral administration.

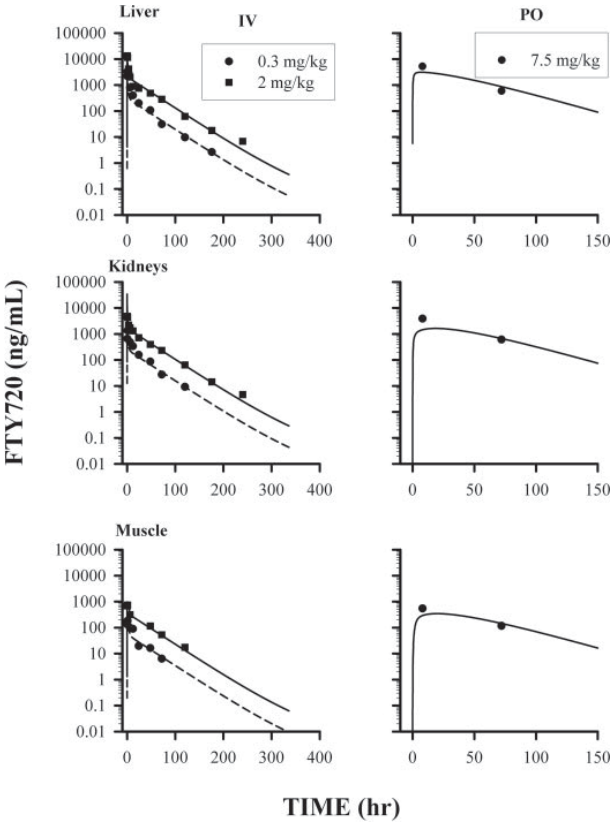

FIG. 5. Time course of measured (symbols) and predicted (lines) FTY720 concentrations in rat liver, kidneys, and muscle after i.v. and oral administration.

through the liver. The model-predicted R_T values were 50.9 for the rest-of-body and 11.1 for the splanchnic compartment. Being unobserved, these tissue-to-blood partition coefficients may not reflect the real extent of FTY720 distribution in these organs.

Prediction of FTY720 Kinetics in Dogs and Humans. Figure 8 depicts FTY720 blood concentration-time profile in the dog after i.v. (Fig. 8, top) and oral (Fig. 8, middle) administration. The PBPK model was able to capture the experimental data reasonably well. Despite an overestimation of C_{max} after oral administration, the model described the terminal slope with good accuracy. FTY720 concentrations in dog brain were simulated for a single oral dose of 10 mg/kg. We used the appropriate dog physiology and the extrapolated organ distribution parameters from the whole body PBPK model. As shown in Fig. 8 (bottom), the predictions were slightly lower than the observed values, by just under 1.5-fold, but the model predicted accurately the slope of decay of FTY720.

Figure 9a shows the FTY720 concentration-time profile in human blood after a single oral dose of 1 mg, as predicted from the rat PBPK model with the in vitro intrinsic clearance determined from human liver microsomes. Although the prediction was not perfect, it was within interindividual variability. It was noted that the predicted C_{max} value for FTY720 was different from the observed values. Figure 9b shows the FTY720 concentrations in human blood obtained after optimizing the intrinsic clearance to fit the human data. A great improvement was observed and the observed concentration data were better described by the PBPK model.

Discussion

The present analysis characterizes the concentration-time profiles for FTY720 in venous and arterial blood and in an extensive array of organs after i.v. and oral administration to rats. Gaining insight into the pharmacokinetic behavior of a drug in different organs is highly desirable, especially in therapeutic target organs or those for which the compound may be potentially harmful. We were able to analyze FTY720 concentration versus time profiles in the typical major organs, but also in other rather unusual ones, viz. lymph nodes, spleen, and thymus. FTY720 is an immunomodulator that exerts its pharmacological action by sequestering lymphocytes in secondary immune organs. Thus, being able to characterize the behavior of the drug in pharmacological targets such as spleen and lymph nodes constitutes a unique achievement.

There are several advantages of developing PBPK models. Two obvious advantages are the possibility to investigate, in animals, organs that could otherwise never be assessed in humans, and the possibility to extrapolate the model to higher species by adjusting organ volumes and perfusion rates, and adjusting for differences in metabolism, plasma protein binding, and blood cell distribution between species.

The results of the investigation showed that FTY720 distributed extensively into various organs. More importantly, distribution and clearance appeared to be linear in the dose range of 0.3 to 4 mg/kg. The model-predicted R_T values were similar to those calculated by noncompartmental analysis. On average, a 3-fold deviation was observed between the two analyses (Table 2 versus Table 3).

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