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# Pharmacokinetics and Cell Trafficking Dynamics of 2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol Hydrochloride (FTY720) in Cynomolgus Monkeys after Single Oral and Intravenous Doses

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## ABSTRACT

The pharmacokinetics and cell trafficking dynamics of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (FTY720), a novel immunosuppressive agent, were examined in cynomolgus monkeys (three males and three females). After single doses of 0.1 mg/kg p.o. or i.v. bolus and 1 mg/kg p.o. were administered to the animals, the concentrations of FTY720, and the numbers of lymphocytes, CD20+CD2-B cells, and CD2+CD20-T cells in blood were measured over 23 days. A linear three-compartment model characterized the time course of FTY720 concentrations with a terminal half-life of about 31 h, clearance of about 0.53 l/h/kg, and bioavailability of about 38%. The dynamic responses were not area under the curve (or dose) proportional for either males or females. An indirect response model with a distribution pool captured the cell trafficking data for all doses for each cell type, where initial blood counts ($R_0$) were about 7650, 2100, and 5250 cells/$\mu$l; maximum fractional inhibition ($I_{max}$) about 0.88, 0.85, and 0.91; influx ($k_{in}$) about 6014, 1312, and 5662 cells/$\mu$l/h; efflux ($k_{out}$) about 0.798, 0.555, and 1.08 $h^{-1}$; intercompartmental $k_{cp}$ about 0.134, 0.192, and 0.082 $h^{-1}$; and intercompartmental $k_{pc}$ rate constants about $3.9 \times 10^{-4}$, and 0.016 and $8.9 \times 10^{-6}$ $h^{-1}$ for lymphocytes, B cells, and T cells, respectively. The inhibition concentration $IC_{50}$ was about 0.48 $\mu$g/l for all cells, which was remarkably low. The apparent distribution volumes of peripheral pool ($V_p$) were markedly larger than blood volume ($V_b$) for all cells. The $I_{max}$ for cell trafficking was achieved at doses smaller than that producing graft protection, indicating stronger central than peripheral effects of this drug. The profound cell trafficking effects of FTY720 can be readily captured and interpreted with an extended indirect response model.

2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (FTY720), a novel immunosuppressant found in *Isaria sinclairii* (a fungus) metabolite (Fujita et al., 1994), protects solid organ grafts with strong potency (Kahan, 1998); acts synergistically with cyclosporin, sirolimus, or tacrolimus (Kawaguchi et al., 1996; Stepkowski et al., 1998; Hoshino et al., 1999); and prevents experimental autoimmune myocarditis, autoimmune diabetes, and arthritis (Yan et al., 1998; Kitabayashi et al., 1999; Matsuura et al., 2000). Diverse pharmacological mechanisms of action were found for FTY720: it can produce cell cycle arrest of lymphocytes (Nagahara et al., 2001), and it can alter production (Yagi et al., 2000), trafficking (Chiba et al., 1998; Brinkmann et al., 2000, 2001; Pinschewer et al., 2000), infiltration (Yanagawa et al., 2000), and apoptosis (Enosawa et al., 1996; Bohler at al., 2000; Nagahara et al., 2000) of lymphocytes. Perplexities about FTY720 regarding preclinical and clinical data include that the maximum effects of FTY720 on cell trafficking were achieved at doses smaller than those producing protection

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**ABBREVIATIONS:** PK, pharmacokinetics; PD, pharmacodynamics; $k_{10}$, systemic elimination rate constant; F, bioavailability; $k_a$, first-order absorption rate constant of drug; $T_{lag}$, lag time of drug being absorbed; $A_{GI}$, drug amount in gastrointestinal tract; $A_i$ (i = 1–3), drug amount in compartment i; $V_i$ (i = 1–3), distribution volume of drug in compartment i; $C_1$, drug concentration in compartment 1; $k_{ij}$ (i, j = 1, 2, 3), transfer rate constant of drug between compartments i and j; $\lambda_i$ (i = 1–3), exponential disposition slopes; $k_{in}$, zero order input constant of cells into central compartment; $k_{out}$, first-order output constant of cells; $k_{cp}$ and $k_{pc}$, transfer rate constants of cells between compartments; $R_0$, initial blood counts; $R$, lymphocyte concentration in blood; $R_p$, total cell content in peripheral pool; $V_b$, blood volume; $V_p$, apparent distribution volume of cells in peripheral pool; $I_{max}$, maximal fractional inhibition; ABEC, area between baseline and effect curve; AUC, area under the curve; MRT, mean residence time; CL, clearance; AIC, Akaike's information criterion; Y-32919, 2-amino-2-[2-(4-octyloxyphenyl)ethyl]propane-1,3-diolhydrochloride.

against graft rejection (Yanagawa et al., 1998b); and that lymphocytes in blood attained a trough before blood FTY720 concentrations reached $C_{max}$. Although the exact mechanism of FTY720 action is not clear (Napoli, 2000), the available fundamental literature data provide a basis for a pharmacokinetic and pharmacodynamic (PK/PD) model to quantitatively relate drug concentrations to cell trafficking responses that may assist in interpreting the above-mentioned perplexities. Kinetics and cell trafficking dynamics of FTY720 in cynomolgus monkeys (three males, three females) were studied after single intravenous and oral doses.

## Materials and Methods

**Animals.** Cynomolgus monkeys (three males and three females; 3–8 years old; body weights of 2–5 kg; China National Scientific Corporation, Beiging, China) were used in this study. Monkeys were quarantined for at least 3 months before treatment and were screened for tuberculosis, parasites, and any clinical pathological abnormalities. The monkeys were housed individually in stainless steel cages in a controlled environment with a 12-h light/dark cycle. Filtered tap water was available ad libitum and food was provided twice daily. On the dosing day, animals had catheters placed in the cephalic vein for dosing and in the femoral vein for blood sample collection. Animals were restrained in Plas-Lab medium restrainer chairs (Plas Labs, Inc., Lansing, MI) for up to 4 h on the dosing day.

**Dosing and Sampling.** A 3 × 3 crossover experiment was performed using the six monkeys with a dosing interval of 28 days. Single doses of 0.1 mg/kg p.o. or i.v. bolus and 1 mg/kg p.o. were administered to the animals; blood samples (0.2 ml) collected at 0 (predose), 0.083, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, and 120 h were obtained for FTY720 concentration measurements; and blood samples (0.5 ml) collected at 0 (predose), 1, 4, 6, 8, 24, 48, 72, 96, 120, 312, and 552 h were obtained for lymphocyte, CD20+CD2-B cell, and CD2+CD20-T cell measurements. The samples were analyzed within 24 h after collection.

**Drug Assay.** The FTY720 concentrations in blood were analyzed by liquid-liquid extraction and liquid chromatography/mass spectrometry/mass spectrometry measurement. To 0.1 ml of blood was added 0.1 ml of internal standard solution (100 ng/ml Y-32919 in methanol) and vortexed for 2 to 3 s, pH was adjusted using 0.5 ml of 0.1 N NaOH, and a 5-ml mixture of tertbutyl-methyl ether/dichloromethane (75:25, v/v) was added. Tubes were shaken for 30 min, centrifuged at 2010*g* for 10 min, and the organic layer was transferred and evaporated under pure $N_2$ gas stream. The dry extract was reconstituted with 200 $\mu$l of 0.02 M ammonium acetate/methanol (50:50) with 2- to 3-s vortexing and 3-min sonication, and centrifuged at 11,400*g* for 5 min. The supernatant was diluted 1:20 with the reconstitution solvent, and 100 $\mu$l was injected onto a 3.5-$\mu$m Symmetry Shield RP8 high-performance liquid chromatography column (50 × 4.6 mm) at 40°C, eluted at 1 ml/min using a gradient mobile phase consisting of methanol and 0.02 M $CH_3COONH_4$. The concentrations were determined by mass-spectrometry using atmospheric pressure ionization as an interface. The calibration curve ranged from 1.16 to 1010 ng/ml FTY720, and the recovery was 98% for drug and 91% for internal standard at 5 ng/sample. The limit of quantification was 0.55 ng/ml for 0.5 ml of blood.

**Cell Counting.** A flow cytometer (EPICS XL-MCL; Beckman Coulter, Inc., Fullerton, CA) was used for counting cells in blood. Lymphocyte count was determined by lymphocyte gating. The T and B cells were counted by two-color flow cytometry, where cells in samples were stained by fluorescein isothiocyanate-labeled mouse anti-human CD2 monoclonal antibody (Clone T11; Beckman Coulter, Inc.), and by phycoerythrin-labeled mouse anti-human CD20 monoclonal antibody (Clone B1; Beckman Coulter, Inc.).

**Pharmacokinetics.** The PK model for FTY720 was a linear three-compartment model depicted in the upper part of Fig. 1. Triexponential fittings of mean blood FTY720 concentrations, $C_{iv}(t)$, versus time $t$ for males and females were performed by weighted ($1/C_t^2$) nonlinear regression using WinNonlin Professional, version 2.1 (Pharsight, Apex, NC):

$$C_{iv}(t) = C_1 \cdot e^{-\lambda_1 \cdot t} + C_2 \cdot e^{-\lambda_2 \cdot t} + C_3 \cdot e^{-\lambda_3 \cdot t} \quad (1)$$

where $C_1$, $C_2$, and $C_3$ are intercepts and $\lambda_1$, $\lambda_2$, and $\lambda_3$ are disposition slopes. Parameters for the three-compartment model were then calculated by the program. These parameters included the systemic elimination constant $k_{10}$, distribution volume of central compartment $V_c$, distribution volume at steady-state $V_{ss}$, and the transfer rate constants between compartments $k_{21}$, $k_{31}$, $k_{12}$, and $k_{13}$. The oral data for the two doses were then fitted simultaneously for bioavailability ($F$), first-order absorption rate constant ($k_a$), and absorption lag time ($T_{lag}$) using $1/C_t^2$ as weights. The following equation was applied:

$$C_{po}(t) = F \cdot \text{Dose} \cdot k_a \cdot [r_1 \cdot e^{\lambda_1 \cdot (T_{lag} - t)} + r_2 \cdot e^{\lambda_2 \cdot (T_{lag} - t)} + r_3 \cdot e^{\lambda_3 \cdot (T_{lag} - t)} + r_4 \cdot e^{k_a \cdot (T_{lag} - t)}]/V_c \quad (2)$$

where $T_{lag} - t = 0$ when $t < T_{lag}$ and:

$$r_1 = \frac{(k_{21} - \lambda_1) \cdot (k_{31} - \lambda_1)}{(k_a - \lambda_1) \cdot (\lambda_2 - \lambda_1) \cdot (\lambda_3 - \lambda_1)} \quad (3)$$

$$r_2 = \frac{(k_{21} - \lambda_2) \cdot (k_{31} - \lambda_2)}{(k_a - \lambda_2) \cdot (\lambda_1 - \lambda_2) \cdot (\lambda_3 - \lambda_2)} \quad (4)$$

$$r_3 = \frac{(k_{21} - \lambda_3) \cdot (k_{31} - \lambda_3)}{(k_a - \lambda_3) \cdot (\lambda_1 - \lambda_3) \cdot (\lambda_2 - \lambda_3)} \quad (5)$$

$$r_4 = \frac{(k_{21} - k_a) \cdot (k_{31} - k_a)}{(\lambda_1 - k_a) \cdot (\lambda_2 - k_a) \cdot (\lambda_3 - k_a)} \quad (6)$$

**Pharmacodynamics.** In normal conditions, the number of any kind of lymphocyte in blood is relatively constant as controlled by the balance of influx and efflux of the recirculating cells. FTY720 inhibits thymocyte emigration (Yagi at al., 2000) and induces lymphopenia in the thoracic duct (Chiba et al., 1998) and in the whole body system (Luo et al., 1999), showing that the input of lymphocytes to blood was altered. Considering that some lymphocytes are recirculating in blood to lymph and some are resident in peripheral tissues (Smith and Ford, 1983; Butcher, 1986; Picker and Butcher, 1992; Butcher and Picker, 1996; Pinschewer et al., 2000), the transfer of cells between blood and distribution pools is requisite. Therefore, the PD model for FTY720 was established as depicted in the lower part of Fig. 1 as indirect response model 1 with a distribution compartment (Krzyzanski and Jusko, 2001). It can be described by the following equations:

$$\frac{dR}{dt} = k_{in} \cdot [1 - I(C)] - k_{out} \cdot R - k_{cp} \cdot R + k_{pc} \cdot \frac{R_p}{V_b} \quad (R)_{t=0} = R_0 \quad (7)$$

$$\frac{dR_p}{dt} = k_{cp} \cdot R \cdot V_b - k_{pc} \cdot R_p \quad (R_p)_{t=0} = k_{cp} \cdot R_0 \cdot V_b / k_{pc} \quad (8\text{ a, b})$$

$$I(C) = \frac{I_{max} \cdot C(t)}{IC_{50} + C(t)} \quad (9)$$

In eqs. 7 and 8, $R$ is the cell concentration in blood, $R_p$ is the total cell amount in the peripheral pool, $k_{in}$ is a zero order input rate of cells from a general pool, and $k_{out}$ is the first-order rate constant for cells returned to the general pool. It is assumed that the general pool is sufficiently large such that changes in cell content are too small to require use of a first-order rate constant and that the zero order $k_{in}$ thus is sufficient. The $k_{in}$ is altered by a nonlinear inhibition fraction $I(C)$ expressed by eq. 9, where $C(t)$ is FTY720 concentration in blood

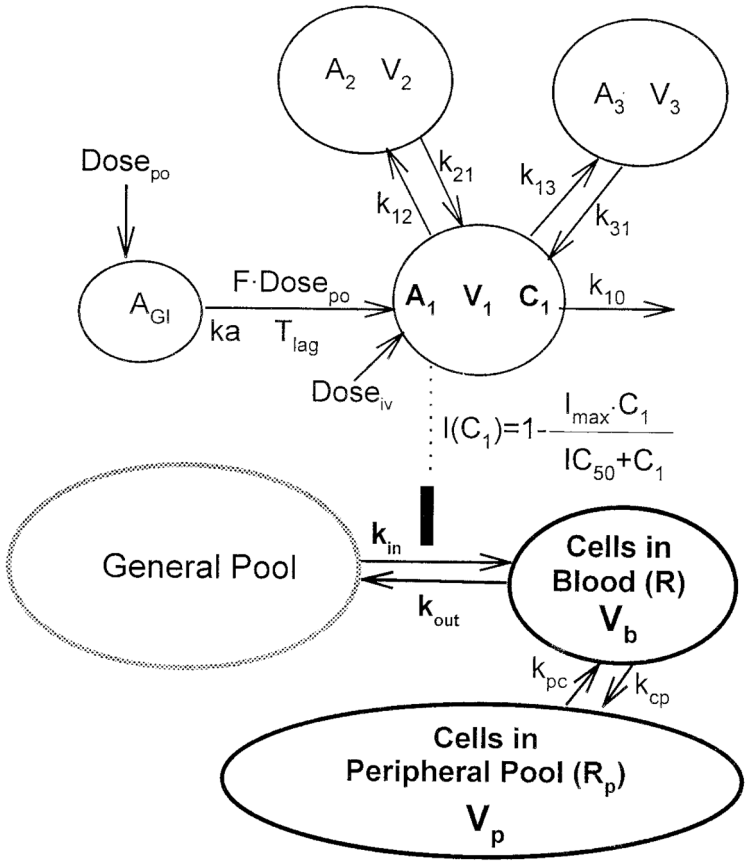


**Fig. 1.** Three-compartmental pharmacokinetic model for the time course of FTY720 concentrations and the indirect response model with a distribution compartment for the dynamics of lymphocytes, B cells, and T cells. Parameters are defined in the text or in the abbreviation list.

at time $t$ (eqs. 1 and 2), $I_{max}$ is the fractional inhibition capacity of FTY720, and $IC_{50}$ is the blood FTY720 concentration producing 50% inhibition of $I_{max}$. The $k_{cp}$ and $k_{pc}$ are first-order transfer rate constants between the distribution pool and blood.

Before FTY720 was given, the lymphocyte amounts in blood and peripheral pools (baselines) are at homeostasis, which means eqs. 7, 8, and 9 = 0, based on which the initial condition for $R_p(t)$ was set as eq. 8b, as well as the following:

$$k_{in} = R_0 \cdot k_{out} \tag{10}$$

$$V_p = k_{cp} \cdot V_b / k_{pc} \tag{11}$$

where $V_p$ is the apparent distribution volume of the cells in peripheral pool. This parameter, although a multiple of $V_b$, is considered "apparent" because it reflects the volume needed if the peripheral and blood pool concentrations were equal at steady state.

If multiple-doses of FTY720 were given daily for a long period, the blood cell concentrations should come to a steady-state $R_{ss}$, which means eqs. 7 and 8 = 0 again but eq. 9 > 0, and therefore

$$I_{max} = \left(1 - \frac{R_{ss}}{R_0}\right) \cdot \left(\frac{IC_{50}}{C_{ss}} + 1\right) \tag{12}$$

When the dosage is large enough, $C_{ss} \gg IC_{50}$, and $R_{ss}$ attains to $(R_{min})_{ss}$, yielding

$$I_{max} = 1 - \frac{(R_{min})_{ss}}{R_0} \tag{13}$$

As will be shown, all cells for the three doses attained a minimum in blood; this made $(R_{min})_1$, the $R_{min}$ for the first FTY720 dose, approximate $(R_{min})_{ss}$, thus

$$I_{max} = 1 - \frac{(R_{min})_1}{R_0} \tag{14}$$

With the observed data for $R_0$ and $(R_{min})_1$, $I_{max}$ values were calculated using eq. 14 for each type of cell. With $R_0$, $I_{max}$, and fixed PK parameters, and $V_b$ set as blood volume (0.07 l/kg), a subroutine of ADAPT II-Release IV (D'Argenio and Schumitzky, 1997) based on eqs. 1 to 10 was used to fit the cell data to generate $k_{in}$, $IC_{50}$, $k_{cp}$, and $k_{pc}$, whereas $k_{out}$ and $V_p$ were calculated as secondary parameters.

After the PD fitting, the area between the baseline and the effect curve (ABEC), the ratio of ABEC/AUC, and the mean reduction percentage of peripheral counts were calculated using the trapezoidal method for each dose, gender, and cell type.

## Results

**Pharmacokinetics.** The PK profiles of mean FTY720 concentrations for male and female monkeys for the 1-mg/kg oral dose and the 0.1-mg/kg oral and i.v. bolus doses with the fitted curves are shown in Fig. 2. The relevant PK parameters for a three-compartment model are depicted in Table 1. For the i.v. bolus dose, the disposition kinetics were triexponential, with a brief first distribution phase ($\lambda_1$), a longer second distribution phase ($\lambda_2$), a longest terminal phase ($\lambda_3$), and a corresponding long mean residence time (MRT). For

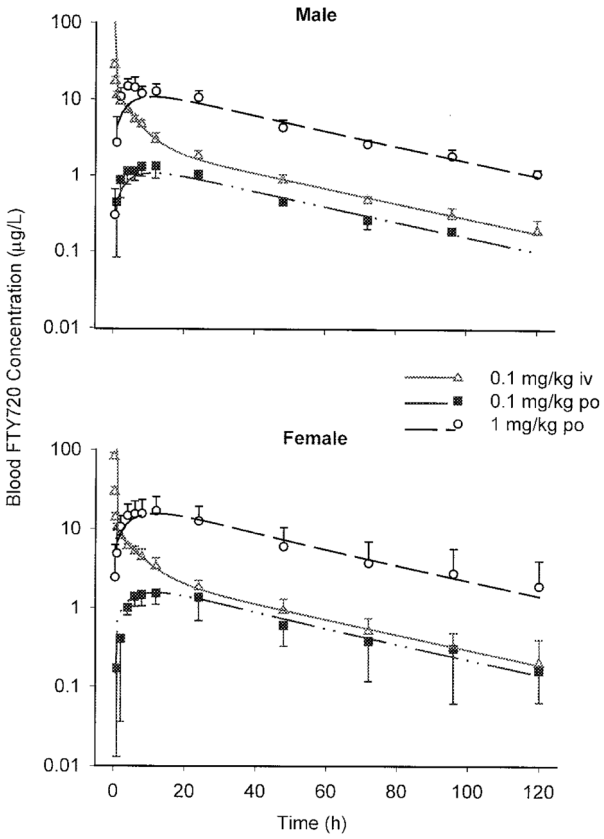


**Fig. 2.** Blood FTY720 concentrations after dosing of 0.1 mg/kg i.v. bolus (triangles), 0.1 mg/kg p.o. (squares), and 1 mg/kg p.o. (circles) for male and female monkeys. The lines are fittings based on eqs. 1 and 2.

TABLE 1
Pharmacokinetic parameters (CV%) for FTY720 in cynomolgus monkeys

| Parameters | Males | | Females | |
|---|---|---|---|---|
| Fitted from i.v. data | | | | |
| $C_1$ (μg/l) | 191.0 | (18.5) | 125.4 | (10.9) |
| $\lambda_1$ ($h^{-1}$) | 9.773 | (12.2) | 7.284 | (8.3) |
| $C_2$ (μg/l) | 11.1 | (9.2) | 7.88 | (7.5) |
| $\lambda_2$ ($h^{-1}$) | 0.200 | (12.6) | 0.164 | (11.5) |
| $C_3$ (μg/l) | 2.60 | (12.2) | 2.70 | (9.2) |
| $\lambda_3$ ($h^{-1}$) | 0.022 | (6.7) | 0.022 | (5.0) |
| AUC (μg × h/l) | 191.7 | (2.9) | 187.9 | (2.0) |
| CL (l/h/kg) | 0.522 | (2.9) | 0.532 | (2.0) |
| $V_c$ (l/kg) | 0.487 | (17.3) | 0.735 | (10.1) |
| $V_{ss}$ (l/kg) | 14.9 | (5.5) | 16.6 | (3.7) |
| $t_{1/2}$ (h) | 30.8 | (6.7) | 31.6 | (5.0) |
| Fitted from p.o. data | | | | |
| $k_a$ ($h^{-1}$) | 0.0524 | (10.2) | 0.0609 | (6.7) |
| F (%) | 31.8 | (7.3) | 44.8 | (4.4) |
| $T_{lag}$ (h) | 0.49 | (0.5) | 0.42 | (3.6) |

males, the half-lives for the three phases were $t_{1/2,\ \lambda1}$ = 0.07 h; $t_{1/2,\ \lambda2}$ = 3.46 h; and $t_{1/2,\ \lambda3}$ = 30.82 h, consisting 10.2, 28.9, and 60.9% of the total AUC, with an MRT of 28.54 h. For females, $t_{1/2,\ \lambda1}$ = 0.10 h; $t_{1/2,\ \lambda2}$ = 4.24 h; and $t_{1/2,\ \lambda3}$ = 31.55 h, consisting 9.2, 25.6, and 65.2% of the total AUC, and MRT was 31.26 h.

The blood clearance of FTY720 of about 0.52 l/h/kg can be compared with hepatic blood flow in monkey of 2.6 l/h/kg (Davies and Morris, 1993), indicating that the drug is of low-to-moderate clearance. Thus, the incomplete bioavailability (32–45%) is not likely due to hepatic first-pass. The $V_{ss}$ of 15 l/kg is very large, indicative of appreciable tissue binding. Furthermore, the long terminal $t_{1/2}$ is probably determined by this extensive distribution and binding in tissues.

For males or females, the parameters obtained from the i.v. data characterized the oral data well as shown in Fig. 2. For the oral doses, the absorption was slow and obviously delayed, and bioavailabilities were moderate. The absorption half-life ($t_{1/2,\ ka}$) and the time for maximum blood concentration ($T_{max}$) were 13.22 and 12.01 h for males, and 11.38 and 12.12 h for females. The fitted $F$ and $T_{max}$ values were almost equal to those calculated by PK analysis. The ratio AUC/dose for 0.1 and 1 mg/kg were 0.655 and 0.670 kg × h/l for males, and 0.866 and 0.940 kg × h/l for females. Analysis of variance for CL, $V_{ss}$, and $V_c$ showed no significant difference between the two oral dose levels ($p > 0.05$); and the CL/$F$, $V_{ss}/F$, $V_c/F$, and MRT of mean data were almost equal for the two dose levels for each gender. Thus, FTY720 exhibited linear PK within the oral dose range of 0.1 to 1 mg/kg in monkeys.

The CV% for the PK parameters of the mean data were 0.5 to 18.5% for males, and 2.0 to 11.5% for females, with most of

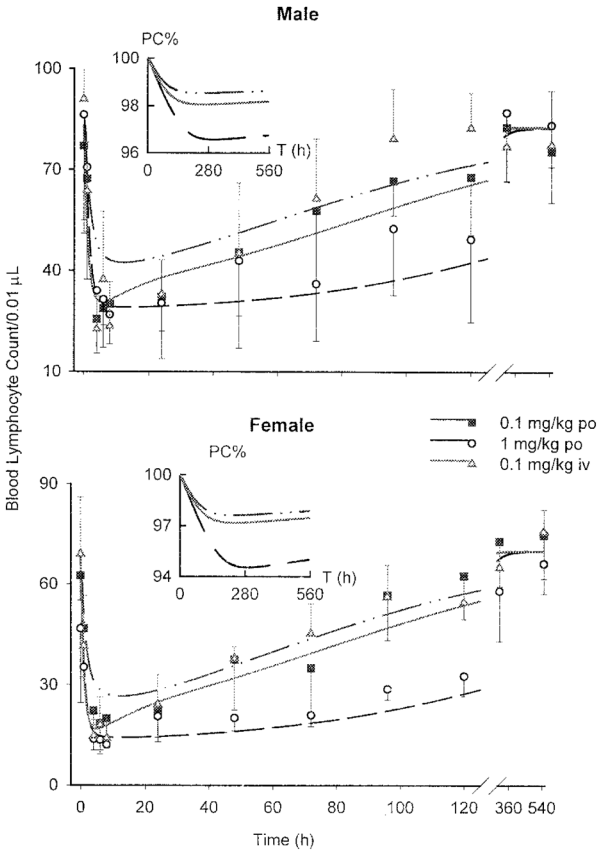


**Fig. 3.** Lymphocyte counts in blood and the lymphocyte count fluctuation percentages in the peripheral compartment (PC%) after dosing of 0.1 mg/kg i.v. bolus (triangles), 0.1 mg/kg p.o. (squares), and 1 mg/kg p.o. (circles) for male and female monkeys. The lines in the panels are fittings based on eqs. 7 to 9.

them below 10%. The analysis of variance for each PK parameter showed no significant difference between males and females ($p > 0.05$).

**Pharmacodynamics.** As shown in Figs. 3, 4, and 5, the mean lymphocyte, B cell, and T cell numbers in blood for all monkeys decreased quickly after the doses were given, attained a trough at about 4 to 24 h, and then returned slowly to the baselines at 312 to 552 h. As seen from the fitted lines in these figures, the indirect response model with a distribution compartment captured all the PD data well, with characteristics of response slopes and troughs for different i.v./p.o. doses being caught simultaneously. The fitted lines went down quickly to a trough at 6 to 14 h, and rose back through the data points to baselines when blood drug concentrations approached zero (Figs. 3–5).

For each type of cell, the count reductions in blood and peripheral pools (Figs. 3–5) were driven by blood FTY720 concentrations in the nonlinear inhibition function of eq. 9. The fittings for B cells were better than for other cells, and those for females were better than for males. These were shown by AIC values of the fittings: for B cells, lymphocytes, and T cells, the AIC values were 186.0, 280.4, and 252.1 for males, and 109.5, 233.9, and 240.4 for females. The net PD effects of the three doses were 1 mg/kg p.o. > 0.1 mg/kg i.v. > 0.1 mg/kg p.o. in both blood and peripheral compartments. Blood ABEC values were not proportional to AUC values for each cell or gender, nor were the mean reduction percentages of peripheral cell counts (Figs. 3–5; Table 2). Peripheral B cells were more susceptible to FTY720 than T cells and lymphocytes for each dose or gender shown by the higher $k_{pc}$ value (Table 3) and the higher mean reduction percentages (Table 2).

For each gender, the $R_0$ and $k_{in}$ values for lymphocytes were close to the sum of those for B and T cells, and other parameters for lymphocytes were almost the average of those for B and T cells. This reflected the fact that CD20+CD2-B cells and CD2+CD20-T cells were the majority subtypes of lymphocytes in these monkeys. The CV% for PD parameters was greater than PK parameters, especially when the parameter was very small (Table 3). It was particularly difficult to estimate $k_{pc}$ as indicated by the large CV% values.

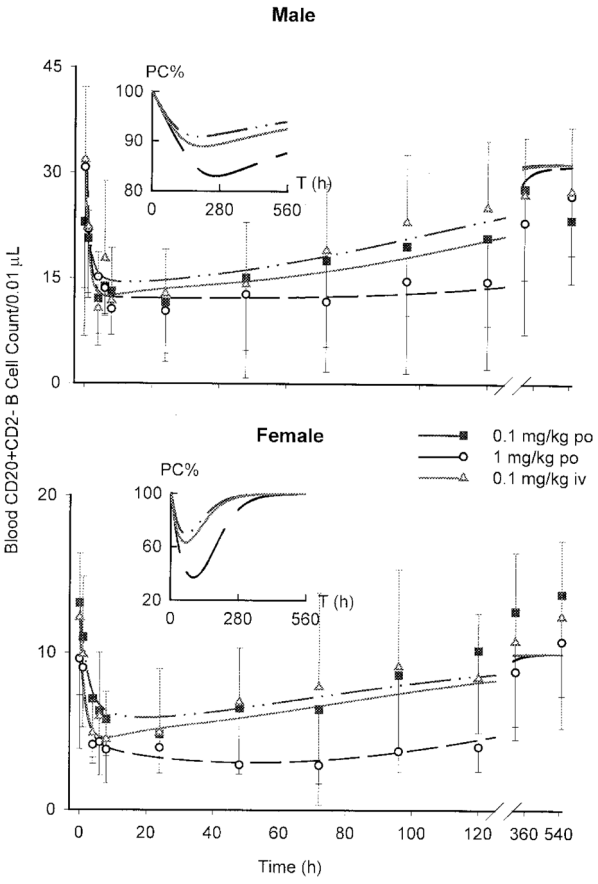


**Fig. 4.** CD20+CD2-B cell counts in blood and the lymphocyte count fluctuation percentages in the peripheral compartment (PC%) after dosing of 0.1 mg/kg i.v. bolus (triangles), 0.1 mg/kg p.o. (squares), and 1 mg/kg p.o. (circles) for male and female monkeys. The lines in the panels are fittings based on eqs. 7 to 9.

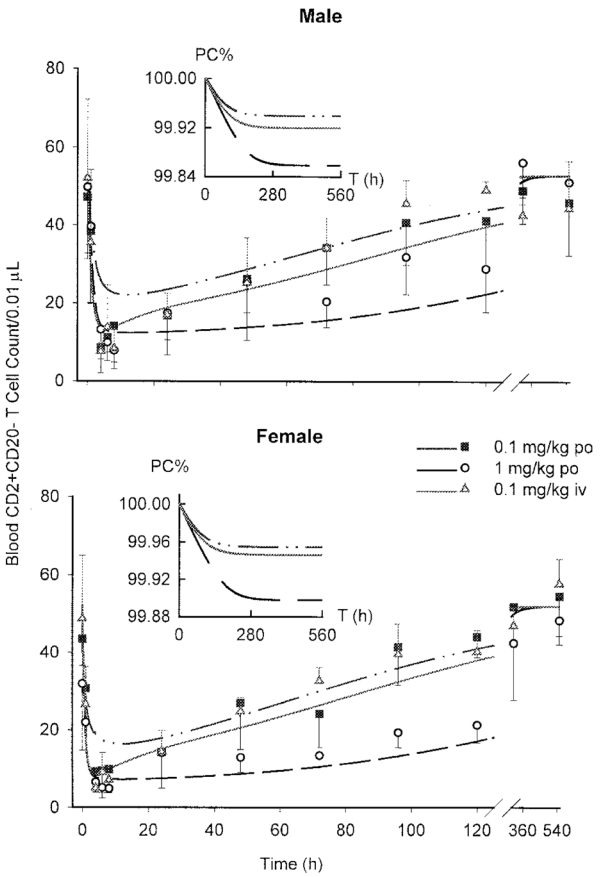


**Fig. 5.** CD2+CD20-T cell counts in blood and the lymphocyte count fluctuation percentages in the peripheral compartment (PC%) after dosing of 0.1 mg/kg i.v. bolus (triangles), 0.1 mg/kg p.o. (squares), and 1 mg/kg p.o. (circles) for male and female monkeys. The lines in the panels are fittings based on eqs. 7 to 9.

## Discussion

**Pharmacokinetics.** As shown in Fig. 2, the three-compartment model reasonably characterized the PK data in

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