CARDIOVASCULAR EFFECT AND SIMULTANEOUS PHARMACOKINETIC AND PHARMACODYNAMIC MODELING OF PIMOBEAN IN HEALTHY NORMAL SUBJECTS

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ABSTRACT:

Pimobendan is a new inotropic agent with vasodilator properties. We have reported the pharmacokinetics of enantiomers of pimobendan in healthy humans. The present report focuses on the pharmacodynamic effect of pimobendan and a simultaneous pharmacokinetic-pharmacodynamic modeling. Eight normal healthy volunteers were studied with oral administration of 7.5 mg and i.v. administration of 5 mg of racemic pimobendan. Concentrations of enantiomers of pimobendan were determined by high performance liquid chromatography. Cardiovascular effects of pimobendan were evaluated by echocardiography. Oral pimobendan significantly reduced 29.0% and 16.5% of the left ventricle end-systolic dimension (LVESD) and end-diastolic dimension, respectively. The mean velocity of circumferential fiber shortening, ejection fraction, and fractional shortening significantly increased 105.9%, 29.8%, and 46% from their baseline values, respectively. The cardiovascular effects of i.v. pimobendan were similar but to a lesser extent. Plots of effect versus plasma concentration (Cp) showed counterclockwise hysteresis loops. A hypothetical effect compartment was established and incorporated into a sigmoid Emax model to describe the time courses of Ce of pimobendan and effects on LVESD. The maximal changes (Emax) in LVESD would be 2.60 ± 0.51 cm and 2.30 ± 0.13 cm as estimated from plasma data of (+)- and (−)-pimobendan, respectively. The estimated effect-site concentrations corresponding with 50% of the maximal effect (Ce50) were 6.54 ± 1.35 and 6.64 ± 1.35 ng/ml for (+)- and (−)-pimobendan, respectively. A simultaneous pharmacokinetic-pharmacodynamic model could be established to suppress the hysteresis loop and to predict the pharmacological effect based on Cp.

Pimobendan [4,5-dihydro-6–2-(4-methoxyphenyl)-1H-benzimidazole-5-yl-3-methyl-3(2H)-pyridazinone] (pimo)1 is a new benimidazole-pyridazine derivative that exhibits both positive inotropic and vasodilator properties (Ruegg et al., 1984; Von Meel, 1985; Verdouw et al., 1986) by specific type III phosphodiesterase inhibition (Scholz and Meyer, 1986; Schmitz et al., 1989) and by directly increasing the calcium sensitivity of the cardiac myofilaments (Ruegg et al., 1984; Fujino et al., 1988). Oral and i.v. pimo has been shown to increase cardiac output (CO), heart rate (HR), ejection fraction (EF), maximum rate of change in pressure over time (dP/dt), and decrease systemic vascular resistance, left ventricle filling pressure, and pulmonary capillary wedge pressure in a dose-dependent manner in animals and patients with chronic congestive heart failure (Walter et al., 1988; Renard et al., 1988; Hagemeyer et al., 1989a,b; Baumann et al., 1989; Remme et al., 1989). However, no hemodynamic data are available from healthy volunteers.

We have reported the pharmacokinetics of enantiomers of pimo in healthy humans (Chu et al., 1995a). The present report focuses on the pharmacodynamic (PD) effect of pimo. In addition, a simultaneous pharmacokinetic (PK)-PD modeling was established to describe and predict the hemodynamic effect of pimo after oral and i.v. administration.

Materials and Methods

Procedures. The study protocol was approved by the Human Subjects Institutional Review Board of the National Defense Medical Center and the Department of Health, Executive Yuan, Republic of China. The criteria for the selection of the eight volunteers, the laboratory tests, and the general procedure have been described previously. Briefly, three 2.5-mg (7.5 mg) capsules of pimo (Boehringer Ingelheim GmbH, Ingelheim, Germany) were administered to the selection of the eight volunteers, the laboratory tests, and the general procedure have been described previously. Briefly, three 2.5-mg (7.5 mg) capsules of pimo (Boehringer Ingelheim GmbH, Ingelheim, Germany) were administered to the eight volunteers in a single-blind and placebo-controlled manner after an overnight fast. The effect of pimo was evaluated by measuring hemodynamic and echocardiographic parameters. The pharmacokinetic (PK) and pharmacodynamic (PD) effects of pimo were evaluated after oral and i.v. administration of 7.5 mg and 5 mg, respectively. The PK and PD effects were determined by analyzing plasma samples and measuring the hemodynamic parameters. The PK and PD effects were fitted to two- or three-compartment models by using a non-linear regression program PCNONLIN (Weiner, 1986). The PK and PD effects were fitted to an Emax model to describe the time courses of Ce of pimo and effects on LVESD. The maximal changes (Emax) in LVESD would be 2.60 ± 0.51 cm and 2.30 ± 0.13 cm as estimated from plasma data of (+)- and (−)-pimobendan, respectively. The estimated effect-site concentrations corresponding with 50% of the maximal effect (Ce50) were 6.54 ± 1.35 and 6.64 ± 1.35 ng/ml for (+)- and (−)-pimobendan, respectively. A simultaneous pharmacokinetic-pharmacodynamic model could be established to suppress the hysteresis loop and to predict the pharmacological effect based on Cp.

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1 Abbreviations used are: pimo, pimobendan; AOPV, aortic flow peak velocity; BP, blood pressure; Cp, effect-site concentration; Cmax, effect-site concentration corresponding with 50% of the maximal effect; CI, cardiac index; CO, cardiac output; Cplasma, plasma concentration; CV, coefficient of variation; dP/dtmax, rate of change in pressure over time; EF, ejection fraction; Emax, maximal effect; Emax, calculated baseline effect; Ce50, observed baseline effect; Emax, estimated effect; Emax, observed effect; HR, heart rate; k0, elimination rate constant of the hypothetical effect compartment; LA, left atrium; LVESD, left ventricle end-diastolic dimension; LVET, left ventricular ejection time; MVCf, mean velocity of circumferential fiber shortening; MPV, mitral valve flow peak velocity; PD, pharmacodynamic; PEP, pre-ejection period; PK, pharmacokinetic; SV, stroke volume; SVI, stroke volume index; ΔTmax, lag-time between Tmax and Tmax; Tmax, time to reach peak concentration; T1/2, half-life of plasma drug levels.

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model gave the better fit to the data as assessed by the Akaike information criterion (Yamaoka et al., 1978). Blood pressure (BP) and HR were checked and the hemodynamic effects of pimo were evaluated by echocardiography at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 h after drug administration. A Hewlett-Packard Ultrasound Imaging System-1500 (Hewlett-Packard Co., Palo Alto, CA) was used for echocardiographic recording.

Echocardiography Recording and Analysis. Cardiac function indices including cardiac index (CI), EF, mean velocity of circumferential fiber shortening (MVCf), systolic time intervals, and peak flow velocities were evaluated by a Hewlett-Packard SONOS ultrasound system with phased-array Doppler (model 1500). M-mode, two-dimensional echocardiographic images, and pulsed-wave Doppler velocity signals were recorded on a Panasonic standard VHS video cassette recorder (model AG7300) for a later playback and analysis. The subjects were examined in a slight left-lateral decubitus position during quiet respiration. Left parasternal long-axis, left parasternal short-axis, apical 4-chamber, and apical 5-chamber views were recorded. Mitral valve-flow peak velocity (MVPV) and aortic flow peak velocity (AOPV) were recorded using a pulsed-wave Doppler. Transmitral flow velocity recordings were obtained from an apical 4-chamber or apical 2-chamber view using a 2.5 MHz imaging transducer. The sample-volume cylinder, approximately 1 cm in axial length, was superimposed on the two-dimensional image at the level of the mitral valve orifice and oriented parallel to the apparent long-axis of blood flow. The transducer was then angled to record maximal transmitral flow velocities. Doppler tracings of aortic flow were obtained using the apical 5-chamber view, with the sample-volume placed just beyond the valve leaflets within the proximal aortic root. Slight adjustments in transducer angulation or sample-volume position were at times required to maximize the audio and graphic quality of the Doppler signal. The aortic valve motion on parasternal long-axis view and velocities of mitral and aortic flow were recorded over several cardiac cycles at a monitor sweep speed of 100 mm/s. M-mode echocardiographic measurements followed the standard method as recommended by the American Society of Echocardiography (Sahn et al., 1978). Left ventricle end-diastolic dimension (LVDD) and left ventricle end-systolic dimension (LVSD) were measured in parasternal long-axis view at the level between the papillary muscle and mitral leaflet tips. Left atrium (LA) was measured at the aortic valve level. Left ventricle volume (V) was determined by the dimension (D) using Teichholz’s equation (Teichholz et al., 1976) $V = \frac{7.0(2.4 + D)}{3}$. Stroke volume (SV) equals LVDD – LVSD; EF equals SV/LVDD and CI equals SV × HR/body surface area. Pre-ejection period (PEP) was the time duration measured from the onset of ventricular depolarization (onset of QRS complex on simultaneous electrocardiogram) to the opening of the aortic valve. Left ventricular ejection time (LVET) was measured from the opening to the closure of the aortic valve. All measurements were made with the aid of an off-line computerized analysis station equipped with internal calipers and a programmable graphic analyzer (Dextra 300, Dextra Medical Inc., Long Beach, CA). The recorded images were played back through a videocassette system equipped with a frame-by-frame bidirectional search module (Panasonic model AG7300).

Reproducibility and Validation. The variabilities of echocardiographic indices were evaluated in eight other normal subjects before conducting this study. Four levels of coefficient of variation (CV) were evaluated. Level-1 CV was determined by repeatedly measuring the cardiac function indices in one cardiac cycle 5 times to evaluate the error resulting from using the pointing device of a computer digitizer. Level-2 CV was evaluated by measuring the indices 5 times in five consecutive cardiac cycles to detect the error caused by sonographer, interpreter, and examined subject in addition to level-1 error. Level-3 CV was evaluated by examining each subject at four time points (9:00 AM, 11:00 AM, 2:00 PM, and 4:00 PM) in a day to identify the time-period variation in addition to the error of the previous two levels. Level-4 CV detected the interobserver variation by measurement of all indices by four experienced echocardiographers. The percentage of coefficient of variation (CV%) of levels-1 and -2 were less than 5% except in PEP (8.0% in level-2). Level-3 CV% was less than 10% except in MVPV (11.1%) and CO (12.0%). The interobserver CV% was less than 10% except in measuring LV posterior wall dimension (10.6%).

By assuming that the transfer of the mass of drug from the central compartment to the effect compartment is relatively small, the drug moving back to the central compartment is negligible and will not add another compartment to the original two-compartment PK model. GI: gastrointestinal compartment; C: central compartment; P: peripheral compartment; E: effect compartment.

In this study, all indices were the average of at least three measurements in different cardiac cycles. An observer who was blinded as to PK data performed all measurements.

Simultaneous PK-PD Modeling. Plasma and red blood cell concentrations of (+)- and (-)-pimo and changes in LVESD were used to characterize the simultaneous PK-PD model. Plots of (+)-pimo concentration versus percent changes in LVESD in time sequence showed counterclockwise hysteresis loops. Therefore, two different levels of effect may be seen at a single plasma concentration (Cp) and two different Cps of pimo may produce the same effect, which seems against PD principles. However, this might happen in conditions in which the site of action of pimo is kinetically distinguishable from the plasma compartment. To collapse the hysteresis loop and determine the relationship between Cp and the effect, one may: 1) sample effect-site concentration (Ces), 2) perform multiple steady-state experiments, or 3) model the effect site as a kinetic “compartment” linked to the PK compartments. We postulated a hypothetical effect compartment linked to the plasma compartment by a first order process (link PK model; Fig. 1). A two-compartment model of pimo disposition was used when modeling the PK data. It was assumed that drug enters and leaves the effect compartment by a first order process with no appreciable reflux of drug back into the PK system. In this link PK model, the concentration and time course of drug at the effect compartment are determined by the elimination rate constant of the effect-compartment ($k_{e0}$). The greater the $k_{e0}$, the less is the time lag between the central and effect compartments. To determine an appropriate $k_{e0}$, a parametric approach with sigmoid maximal effect ($E_{max}$) PD model was included in the simultaneous PK-PD model.

To establish a simultaneous PK-PD model, the first step is to obtain PK parameters. In all subjects the 2-compartment PK model gave the best fit for the data as assessed by the Akaike information criterion (Yamaoka et al., 1978).

The PK model: (see appendix eq. 1)

$$C_p = \alpha e^{-k_1 t} + \beta e^{-k_2 t} + \gamma e^{-k_3 t}$$

where $C_p$ represents plasma concentration, $t$ is time, $k_i$ is the first-order absorption rate constant, $\lambda_1$ and $\lambda_2$ are the disposition rate constants, and $\alpha$, $\beta$, and $\gamma$ represent hybrid constants.
FIG. 2. This plot represents the cardiovascular effects of pimo in eight normal healthy volunteers after oral administration of 7.5 mg of racemic pimo. SBP and DBP: systolic and diastolic blood pressure.

Decrease in cardiac chamber dimensions and increase in ejection-phase indices, HR, and CI developed gradually toward their maxima in 2 to 5 h and lasted for 8 to 10 h. Data were expressed in mean ± S.E. *represents p < .05 by using repeated measured ANOVAs followed by Dunnett’s multiple comparisons.
The second step is to apply the PK parameter in the link PK model (Sheiner et al., 1979). In the link PK model, the following equation was used to describe the time course of the concentration in the effect-compartment (Ce):

\[ Ce = C_{\text{e0}} \left( \frac{\alpha}{(k_e - k_h)} (e^{-k_h t} - e^{-k_e t}) + \frac{\beta}{(k_e - k_h)} (e^{-k_h t} - e^{-k_e t}) + \frac{\gamma}{(k_e - k_h)} (e^{-k_h t} - e^{-k_e t}) \right) \]

The third step is to integrate the link PK model into a PD model, which becomes a simultaneous PK-PD model (Schuttler et al., 1987).

The simultaneous PK-PD model:

\[ E = E_0 - E_{\text{max}} \times \frac{C_e}{C_{\text{e,lo}} + C_e} \]

In this equation, E is effect, E₀ is the calculated baseline effect, E_{max} is the maximum change in predicted response that can be produced by the drug. C_{e,lo} is the concentration at the effect site causing 50% of E_{max} and n is the Hill coefficient (or slope factor), which determines the sigmoidicity of the concentration-effect curve.

Using a nonlinear curve fitting program PCNONLIN, the parameters: E₀, E_{max}, n, C_{e,lo}, and k_{e,lo} were obtained to best fit the model to the data of effect and time.

For i.v. administration the third exponential term in the PK and the link PK models were omitted.

**Statistical Analysis.** The changes in the PD data according to time were evaluated by repeated measured analysis of variances followed by Dunnnett’s multiple comparisons. A paired \( t \) test was used to compare the parameters of the simultaneous PK-PD model in oral and i.v. studies. Differences in the \( p \) values of < .05 (two-tailed) were considered significant. Results were reported as mean ± S.E.

**Results**

**Pharmacodynamics.** After oral administration of 7.5 mg of pimo, the dimension of the heart decreased (Fig. 2 and Table 1). The LVESD and LVEDD significantly reduced 29.0% and 16.5% of their baseline values at 2 to 5 h, respectively. This effect lasted for at least 10 h. In a similar trend, the LA dimension, LVET, and PEP were significantly reduced 20 to 30%. The parameters of LV contractile force including MVCf, EF, and fractional shorting were significantly increased to 105.9%, 29.8%, and 46%, respectively. BP showed no significant change, whereas HR increased 38%. The AOPV, which was determined by the SV, aortic valve area, afterload, and contractility, was also increased significantly to 29.3% in 2 to 4 h. The stroke volume index (SVI) reduced insignificantly in 2 to 4 h and returned toward baseline after 5 h. The CI, calculated by SVI × HR, increased gradually but not significantly until 5 h. This increase in CI resulted from an increase in HR. The hemodynamic change after i.v. administration of 5 mg of pimo showed a similar change in the parameter but to a lesser extent (Fig. 3). Because the bioavailability of pimo was about 50% (Chu et al., 1995a), a greater effect was seen with a smaller available dose of pimo (3.75 versus 5 mg), which suggested that the demethylated metabolite formed in first pass metabolism was contributing to the overall hemodynamic effect.

The adverse effect was unremarkable. One subject experienced dizziness while voiding at 1.75 h after the oral dose, whereas others had lightheadedness or palpitations. There were no arrhythmias found on the electrocardiogram tracings in echocardiographic recording.

**Simultaneous PK-PD Model.** There was a delay between the peaking time of plasma pimo concentration and the E_{max} (changes in LVESD; Fig. 4). When the effects were plotted against C_p at time sequence, large counterclockwise hysteresis loops were observed for oral and i.v. administration, respectively (Fig. 5A and B). After applying the simultaneous PK-PD model, the hypothetical C_p was obtained along with the estimated effect (E_{est}; Fig. 4). It is worth noting that observed effect (E_{obs}) is unable to fit or estimate unless the effect site concentration of drug is known. This figure demonstrates a good fitting between E_{obs} and E_{est}. When effects were plotted against the effect-compartment concentrations, the hysteresis loop collapsed (Fig. 5, C and D). This demonstrated that concentration-effect relationships or pharmacodynamics of pimo could be found by using the simultaneous PK-PD model.

Table 2 shows the parameters of the simultaneous PK-PD model by fitting the effect with concentration of enantiomers of pimo in plasma using the simultaneous PK-PD model in oral and i.v. studies. Differences in the \( p \) values of < .05 (two-tailed) were considered significant. Results were reported as mean ± S.E.
Fig. 3. This plot demonstrates the cardiovascular effects of pimo in eight normal healthy volunteers after i.v. administration of 5 mg of racemic pimo.

Legends are the same as in Fig. 1. The changes are similar to those in the oral study but to a lesser extent. Diastolic BP decreased significantly in 2 to 6 h. CI did not change significantly.
Pharmacodynamics. We have reported the hemodynamic effects of pimo in patients with congestive heart failure (Chu et al., 1995b). In patients, the HR, SV, and CO were increased and the BP and the filling pressure of the cardiac chambers were decreased. In our study of normal volunteers, the decrease in chamber size and increase in HR and CO were also significant, but BP and SV were decreased insignificantly. These different effects on SV in patients and in normal subjects might be due to different preload and inotropic response.

Simultaneous PK-PD Model. One of the major goals in clinical pharmacology is to have a drug given in a proper way, proper dose, and suitable duration to achieve and maintain an ideal therapeutic effect in patients of variable disease entities. To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. In most cases, the concentration of drug in the systemic circulation will be parallel to that at the sites of action. There is then a direct link between PK and PD models. For some drugs, there is no clear or simple relationship between pharmacological effect and concentration in plasma. Many factors, such as formation of active

![Graph](image)

**Fig. 4.** Observed $C_p$ of $(*)$-pimo and $E_{obs}$ and $E_{est}$ versus time curves after oral administration of 7.5 mg of racemic pimo in eight normal healthy volunteers.

A simultaneous PK and PD model was established using observed $C_p$ and $E_{obs}$. There is a good correlation between $E_{obs}$ and $E_{est}$. The dotted line represents hypothetical effect compartment concentration of $(*)$-pimo. Data are presented as mean ± S.E.

**Fig. 5.** $E_{obs}$ and $E_{est}$ versus $C_p$ of $(*)$-pimo in plasma plotted in time sequence in eight normal healthy volunteers after oral (A) and i.v. (B) administrations of pimo showed counterclockwise hysteresis loops.

The curves of $E_{est}$ showed good fitting with the observed data. It was unable to fit the data without knowing the $C_e$, which was obtained by applying the simultaneous PK-PD model. When effect was plotted against the hypothetical effect compartment concentration (C, D), the hysteresis loop collapsed and the concentration-effect relationship could be found.
metabolites, enzyme induction, enzyme inhibition, receptor desensitization, indirect or irreversible pharmacological effect, delayed equilibrium in concentration between plasma and sites of action, and endoniters with different elimination rates and potency (Holford and Sheiner, 1981; Mehrvar, 1992) may account for the lack of correlation. Although the growth of pharmacodynamics is less than that in pharmacokinetics because difficulties exist in the quantitative determination of meaningful responses, it is possible to use mathematical models to describe the effect-concentration relationship. The simultaneous PK-PD model is first proposed by Segre (1968) and later by Galeazzi et al. (1976), Hull et al. (1978), and subsequently elaborated by Sheiner et al. (1979). These modeling techniques have been applied to various drugs including neuromuscular blocking agents (Evans et al., 1984), anesthetics (Stanski et al., 1984), bronchodilators (Oosterhuis et al., 1984), antihypertensives (Reid and Meredith, 1990), benzodiazepines (Buhrer et al., 1990), antibiotics (Garrison et al., 1990), steroids (Kong et al., 1989), and diuretics (Hammarlund et al., 1985). We herein applied this integrated model to a cardiotonic agent.

To quantitatively evaluate cardiac performance is a complicated process. There are a number of methods to evaluate cardiac performance, such as cardiac catheterization, radionuclide angiography, echocardiography, etc., using a number of parameters based on pressures, flows, volumes, and dimensions. Echocardiography was used because it is reliable, noninvasive, and relatively inexpensive for the monitoring of the cardiovascular effect of a drug without neurohumoral disturbances. However, there are a number of limitations. First, it is difficult to clarify whether the increased cardiac performance was due to either an inotropic effect or vasodilatation effect alone or both without direct measurement of intracardiac pressure and volume changes. Second, an echocardiography examination takes 5 to 10 min, or even longer in some cases with a small “cardiac window”, to obtain a series of images at one time. To monitor the rapidly changing effect, as in the initial phase of some i.v. studies, only limited numbers of views can be obtained. Third, calculations of the 3-dimensional volume or CO from a linear dimension primary measurement will cube the error and subsequently affect the model fitting.

We therefore used the changes in LVESD as a meaningful PD response to establish a combined PK-PD model.

The slope factor “n” was about 2.4 in the oral study and 4 to 6 in the i.v. study. Theoretically, an n value greater than one indicates positive cooperativity in receptor binding. This means that the occupancy of one binding site by a ligand enhances the likelihood that other couple sites on the molecule will preferentially bind the same ligand. However, interpreting this n value from a entire body point of view, we would consider this is an overall systemic effect integrated from the effects on different organ systems. The overall changes in LVESD might result from an increased inotropic effect, a vasodilating effect, and an increase in HR directly or indirectly. The more the organs respond to the drug, the greater the n value could be. Nevertheless, this cannot explain the higher n value in the i.v. study. Examination of standard errors showed the greatest uncertainty in the estimates of n. This might be due to the estimated C_l, which was smaller than C_{e0} and fell in the lower left half of the sigmoidal effect-log concentration curve.

The k_{e0} obtained in the i.v. study is generally smaller than that calculated in an oral study (p < 0.05 in (-)pimo). There are several possibilities. First, it may be a statistical type-one error. Second, this discrepancy was caused by underestimated disposition rate constants α and β in the i.v. study because fewer data points were measurable in the elimination phase (Chu et al., 1995a). In the link PK model, the higher α and β value will lead to a lower k_{e0} and hence k_{e0} will be underestimated. Third, the amount and peaking time of the active metabolite may affect the overall effect and result in a relatively delayed peaking changes of LVESD in the i.v. study. In isolated canine ventricular muscle, Endoh et al. (1991) found that the demethylated metabolite of pimo is one-third the efficacy and 500 times the potency as compared with pimo. However, to apply these PD parameters in humans one should be cautious that a metabolite is usually hydrophilic and thus has a different volume of distribution and tissue affinity. The ratio of a parent drug to its metabolite in plasma may be different from that in the effect site. Thus, the in vivo efficacy and potency may be different from those of an in vitro study. Therefore, to determine the percentage of contribution of pimo and its metabolite to the overall effect based on their C_l is difficult. In our study, it is worth noticing that the time to reach E_{max} is over 3 h after i.v. administration, which seems longer than that in oral administration. In a normal situation, the effect is usually seen earlier in i.v. administration than oral administration with the exception that the drug acts more like a prodrug requiring biotransformation in the liver to become active. This suggests that the metabolite of pimo contributes to the overall effect. However, it is yet to be clarified by direct administration of the demethylated metabolite in humans.

The effect compartment concentration has been compared with a steady-state concentration. Schwartz et al. (1989) studied verapamil in 22 normal subjects in a single dose and steady-state infusions to compare the estimated and real effect site concentration. They found that use of the PK model to estimate effect site concentration provided a closer estimate of the true steady-state concentration than the estimation from the postinfusion C_l. However, the model was limited in describing higher concentration versus effect relationships.

In summary, this study demonstrated the cardiovascular effect of pimo in normal subjects after oral and i.v. dosings. A simultaneous PK-PD model was developed to suppress the hysteresis loop and to predict the pharmacological effect based on C_l. It can provide valuable information on dose-effect relationships and on a choice of optimal dosing intervals in drug development. It is possible that in patients with variable disease entities and impaired hepatic and renal functions the changes in the time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral study</th>
<th>Plasma (Mean ± S.E.)</th>
<th>Red Blood Cell (Mean ± S.E.)</th>
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<tr>
<td></td>
<td>(+)-pimo</td>
<td>(-)-pimo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-)-pimo</td>
<td>(+)-pimo</td>
<td>(-)-pimo</td>
</tr>
<tr>
<td>K_{e0}</td>
<td>l/h</td>
<td>0.33 ± 0.07</td>
<td>0.33 ± 0.06</td>
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<tr>
<td></td>
<td></td>
<td>0.35 ± 0.07</td>
<td>0.30 ± 0.07</td>
</tr>
<tr>
<td>n</td>
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<td>2.43 ± 0.57</td>
<td>2.37 ± 0.57</td>
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<td></td>
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<td>C_{e0}</td>
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<td></td>
<td>34.62 ± 6.30</td>
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</tr>
<tr>
<td>F_{max}</td>
<td>cm</td>
<td>2.60 ± 0.51</td>
<td>2.30 ± 0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.16 ± 0.42</td>
<td>1.75 ± 0.34</td>
</tr>
<tr>
<td>E_{0}</td>
<td>cm</td>
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<td>3.36 ± 0.13</td>
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<td></td>
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<td>3.35 ± 0.12</td>
<td>3.39 ± 0.11</td>
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| E_{0}(t我知道，这个研究为什么用LVESD来衡量？
to reach peak effect and the therapeutic duration might be predicted based on different PK parameters, yet this remains unproved.

**Appendix**

Laplace transform and anti-Laplace transform of 2-compartment model with first order input and the link PK model (Fig. 1)

List of symbols:
F: bioavailability
D: dose
\(i_{in,c}:\) Laplace transform for the input function of central compartment
\(d_{dis,c}:\) Laplace transform for the disposition function of central compartment
\(a_{s,c}:\) Laplace transform for the amount of drug in the central compartment
\(i_{in,e}:\) Laplace transform for the input function of effect site compartment
\(d_{dis,e}:\) Laplace transform for the disposition function of effect site compartment
\(a_{s,e}:\) Laplace transform for the amount of drug in the effect site compartment
\(X_c:\) amount of drug in the central compartment
\(X_e:\) amount of drug in the effect site compartment
\(C_p:\) plasma concentration
\(C_e: \) effect site concentration
\(V_c: \) volume distribution of central compartment
\(V_e: \) volume distribution of effect site compartment
\(k: \) Laplace operator
\(k_{11}, k_{21}, \lambda_1, \lambda_2: \) rate constants

Laplace transform for 2-compartment model with first order input:

\[
in_{in,c} = \frac{FDk_c}{s + k_c} \quad d_{dis,c} = \frac{(s + k_c)}{(s + \lambda_1)(s + \lambda_2)}
\]

\[
a_{s,c} = \frac{FDk_c}{(s + k_c)} \quad \text{eq. 1:}
\]

\[
a = \frac{FDk_c(k_{21} - \lambda_1)}{V_c(k_{21} - \lambda_1)(\lambda_2 - \lambda_1)} \quad \beta = \frac{FDk_c(k_{21} - \lambda_2)}{V_c(k_{21} - \lambda_2)(\lambda_1 - \lambda_2)} \quad \gamma = \frac{FDk_c(k_{21} - k_{21})}{V_c(\lambda_1 - k_{21})(\lambda_2 - k_{21})}
\]

Laplace transform for hypothetical effect compartment (so called link PK model, assuming the effect site receiving negligible actual mass of drug and not affecting 2-compartment model):

\[
in_{in,e} = \frac{FDk_c k_{1e}}{(s + k_{21}) (s + \lambda_1)(s + \lambda_2)}
\]

\[
d_{dis,e} = \frac{1}{(s + k_{21})}
\]

\[
a_{s,e} = \frac{FDk_{1e}(s + k_{21})}{(s + k_{21})(s + \lambda_1)(s + \lambda_2)(s + k_{21})}
\]

Anti-Laplace transform:

\[
X_c = \frac{X_e V_c}{FDk_c} \quad \text{eq. 2:}
\]

\[
C_e = \frac{k_{21}}{(s + k_{21})} \quad \text{Le}^{-k_{21}t} + \text{Me}^{-k_{21}t} + \text{Ne}^{-k_{21}t} + \text{Oe}^{-k_{21}t}
\]

\[
L = \frac{(k_{21} - \lambda_1)}{(k_{21} - \lambda_1)(\lambda_2 - \lambda_1)(k_{21} - \lambda_2)} \quad M = \frac{(k_{21} - \lambda_2)}{(k_{21} - \lambda_2)(\lambda_1 - \lambda_2)(k_{21} - \lambda_1)}
\]

\[
N = \frac{(k_{21} - k_{21})}{(\lambda_1 - k_{21})(\lambda_2 - k_{21})(k_{21} - k_{21})} \quad O = \frac{(k_{21} - \lambda_2)}{(\lambda_1 - k_{21})(\lambda_2 - k_{21})(k_{21} - \lambda_2)}
\]

When \(t = 0\), \((L + M + N + O) = 0\), then eq. 2 becomes:

\[
C_e = \frac{FDk_c}{(s + k_{21})} \quad \text{Le}^{-k_{21}t} - \text{Le}^{-k_{21}t} + \text{Me}^{-k_{21}t}
\]

\[- \text{Me}^{-k_{21}t} + \text{Ne}^{-k_{21}t} - \text{Ne}^{-k_{21}t} + (O + L + M + N)e^{-k_{21}t}\]
Combining eq. 1 and 2, the effect site concentration is:

\[ C_e = \frac{\alpha}{(k_{e0} - \lambda_1)} (e^{-\lambda_1 t} - e^{-k_{e0} t}) + \frac{\beta}{(k_{e0} - \lambda_2)} (e^{-\lambda_2 t} - e^{-k_{e0} t}) + \frac{\gamma}{(k_{e0} - \lambda_3)} (e^{-k_{e0} t} - e^{-k_{e0} t}) \]

References


