Stereoselective Pharmacokinetics and Pharmacodynamics of Organic Nitrates in Rats

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ABSTRACT
Plasma concentration and vasodilating effect after i.v. bolus injection of stereoisomeric organic nitrates were evaluated. Pharmacokinetics of mononitrates was analyzed with a linear one-compartment model. The apparent volumes of distribution were almost identical, but systemic clearances were different among stereoisomers. The concentration data after dinitrate administration could be described based on a two-compartment model with elimination only from the central compartment via metabolism to mononitrate, and then mononitrate-dependent metabolic clearance was estimated. In the vasodilatation by mononitrate administered intravenously, the maximum effect was not observed. The reduction of mean arterial pressure from baseline level was related to plasma concentration with a log-linear model. The pharmacological effect following dinitrate dosing was analyzed by a sigmoidal \( E_{\text{max}} \) model assuming a simple additive effect of dinitrate and mononitrate. Although almost the same Hill’s constant and maximum effect (\( E_{\text{max}} \)) values were estimated, the concentrations required to produce 50% of \( E_{\text{max}} \) (EC\(_{50}\)) differed among stereoisomers. The clearance and EC\(_{50}\) values of stereoisomers with nitrate group at the exo position were generally higher than those with the same group at the endo position. This suggests that the stereosstructure of organic nitrates controls the vasodilator potency and duration of action.

Isosorbide dinitrate (ISDN) is widely used in various formulations and by different routes of administration as a basic vasodilator for the management of angina pectoris and congestive heart failure (Parker and Parker, 1998). A number of reports on disposition data of ISDN in human and animals have been published (Bogaert, 1983). There is substantial evidence suggesting that the vasodilating effect of organic nitrates such as ISDN requires a series of reactions, including cellular conversion to nitric oxide, activation of guanylyl cyclase, and intercellular accumulation of cyclic GMP (Ignarro et al., 1981; Kukovetz and Holxmann, 1990). However, in spite of this enormous quantity of knowledge, the relationship between plasma concentration and pharmacological response is still poorly understood (Thadani and Whitsett, 1988).

A major factor complicating the pharmacokinetic (PK)-pharmacodynamic (PD) relationship of ISDN may be the development of vascular tolerance during long-term therapy (Thadani, 1997). Another factor is the greater persistence of active metabolites, isosorbide-2-mononitrate (2-ISMN) and isosorbide-5-mononitrate (5-ISMN), making the interpretation of data difficult even after the initial dosing. The change in pulse pressure of rats following i.v. administration of 2-ISMN and 5-ISMN, which produce no active metabolites, has been successfully related with the plasma concentration (Tzeng and Fung, 1992a). ISDN and its active metabolites have the same mechanism of vasodilating action (Ignarro et al., 1981; Kukovetz and Holxmann, 1990), so the pharmacological effect after a single dose of ISDN can be described as a simple additive effect.

ISDN is a dinitrate having two pharmacologically active diastereomers, isoiodide dinitrate (IIDN) and isomannide dinitrate (IMDN), and their active metabolites, 2-ISMN, 5-ISMN, isoiodide mononitrate (IIMN), and isomannide mononitrate (IMMN) are also isomeric mononitrates. They are structurally different in a functional group, nitrate and hydroxy groups, and in their exo and endo positions (Fig. 1). Some in vitro and in situ studies have suggested that the vasodilating potency of different isomeric organic nitrates depends on the positions of functional groups (Bogaert and Rosseel, 1972; Noack, 1984). The systemic and conjugation clearances of mononitrates were also affected by their stereochemical arrangements (Tzeng and Fung, 1993). Unfortunately, little is known about the influence of stereostucture on the in vivo disposition and vasodilating action for dinitrates, because little information is available on IIDN and IMDN.

The objectives of the present study were to establish the PK-PD relationship of organic nitrates, especially dinitrates, and to comprehensively reevaluate the influence of

ABBREVIATIONS: ISDN, isosorbide dinitrate; PK, pharmacokinetic; PD, pharmacodynamic; 2-ISMN, isosorbide-2-mononitrate; 5-ISMN, isosor- bide-5-mononitrate; IIDN, isoiodide dinitrate; IMDN, isomannide dinitrate; IIMN, isoiodide mononitrate; IMMN, isomannide mononitrate; HPLC, high-performance liquid chromatography; ANOVA, analysis of variance; ΔMAP, difference in mean arterial pressure from baseline.
stereochemistry on the PK and PD properties. Plasma nitrate concentration and blood pressure were simultaneously measured in rats after a single i.v. bolus administration of dinitrates and mononitrates. The PK model incorporating PD was developed to characterize the vasodilating effect.

Experimental Procedures

Materials. Organic nitrates (I1DN, IMDN, and ISDN) and mononitrates (IIMN, IIMNN, 2-ISMN, and 5-ISMN) were synthesized and purified by Toshin Chemical Co. (Tokyo, Japan). Their purities were more than 98%. Other chemicals and solvents were of reagent grade.

Animals. Male Wistar rats (Japan SLC Inc., Hamamatsu, Japan) aged 8 weeks were used. Rats were allowed free access to water and laboratory rat chow and housed in a room with a 12 h light/dark cycle for at least 1 week before the day of experiment. One day prior to the experiment, the right jugular vein was cannulated for nitrate administration and blood sampling, and the left carotid artery was for blood pressure measurement, according to Hatanaka et al. (1998a). After a one-night recovery period, each rat was studied in a conscious and unrestrained state.

Dosing. Twenty-one groups of rats (n = 3 in each group) received a single i.v. bolus dose of 50, 100, or 200 mg/kg of either a dinitrate or a mononitrate via jugular venous cannula. N,N-Dimethylacetamide was as a solvent for dinitrates due to their low aqueous solubilities, and only 0.2 ml of the solution was administered to minimize the toxicity. Mononitrates were dissolved in normal saline, making the injection volume less than 2 ml/kg. The dose was delivered over 5 s followed by a saline flush of the cannula.

PK Study. Blood samples (0.25 ml) were withdrawn from the jugular vein just prior to nitrate administration and at appropriate postdose times, which were predetermined based on the detection limit for each nitrate. The blood samples were immediately transferred to heparinized micro test tubes and centrifuged at 12,000 rpm for 3 min. The separated plasma samples were stored at −20°C until assay.

The plasma concentrations of organic nitrates were determined by HPLC. The plasma samples after dinitrate dosing were divided into two for dinitrate and mononitrate determinations. Two volumes of acetonitrile containing an internal standard was added to the plasma samples and vortexed. After centrifugation at 12,000 rpm for 3 min, 50 µl of the supernatant was injected into the HPLC system.

The system consisted of a pump (LC-10AD, Shimadzu, Kyoto, Japan), a 4.6 × 150 mm stainless-steel column packed with Nucleosil 100-5C18 (Machery Nagel, Duren, Germany), an ultraviolet detector (SDP-10A, Shimadzu) and an integrator (C-R6A, Shimadzu). The mobile phases were acetonitrile/water (33.67 for dinitrates, 10:90 for IIMN, 7:93 for 2-ISMN and 5-ISMN, and 2:98 for IIMNN). The flow rates were 1.5 and 1.2 ml/min for IIMN and other nitrates, and the internal standards were ethyl p-hydroxybenzoic acid and phenol for dinitrates and mononitrates. The detector wavelength was set at 240 nm. The lower limit of quantitation was 50 ng for all nitrates.

PD Study. Blood pressure of rats was measured with a biophysigraphe (180 system, San-ei Instrument Co., Tokyo) connected to the carotid arterial cannula via a pressure transducer (MPU-0.5, Toyo Baldwin Co., Tokyo) and digitized with an A/D converter (GP-IB, Shoei Densi Laboratories, Nagoya, Japan). Three direct hemodynamic parameters, systolic blood pressure, diastolic blood pressure and heart rate, and the mean arterial pressure calculated by direct parameters were recorded every minute on a personal computer (HP-85, Hewlett-Packard, Corvalis, OR). After about a 30-min stabilization period, the measurement was carried out for 15 min to obtain the baseline level, and continued after nitrate administration until the last blood sampling.

PK-PD Modeling. To relate the vasodilating effect with plasma concentration of organic nitrates, a PK-PD model was developed as shown in Fig. 2. The following assumptions were made: 1) dinitrates distribute into a central compartment (compartment 1) and a peripheral compartment (compartment 2); 2) the elimination of dinitrates occurs only via metabolism to the active metabolites; 3) the disposition of mononitrates is described by a conventional one-compartment model (compartment 3 or 4); 4) the site of action is in the central and metabolite compartments; and 5) both dinitrates and mononitrates have an identical mechanism of action.

Plasma concentration data in each rat receiving an i.v. dose of mononitrate were fitted to a monoexponential equation:

\[ C_i = \frac{D_i}{V_i} e^{-k_i t} \]  (1)

where \( C_i, V_i, D_i, \) and \( k_{i0} \) are the concentration at time \( t, \) apparent volume of distribution, dose and first-order elimination rate constant.

![Fig. 1. Chemical structures of stereoisomeric organic nitrates used in this study.](image)

![Fig. 2. PK-PD model for organic nitrates. C, concentration; V, volume of distribution; D, dose; k, first-order rate constant; subscripts 1 and 2, central and peripheral compartments of dinitrate; subscripts 3 and 4, compartments of mononitrate metabolites.](image)
for compartment i (i = 3 or 4). A nonlinear least squares regression program (Hatanaka et al., 1998a), which was run on a personal computer (PC-9801DA, NEC, Tokyo), was used to estimate the distribution volume and elimination rate constant. The systemic clearance (Clsys) was obtained as the product of both parameters.

When a dinitrate was administered, plasma concentrations of the nitrate and its active metabolite, mononitrate, were expressed as:

\[ C_1 = A e^{-\alpha t} + B e^{-\beta t} \] (2)

\[ C_i = \frac{V_i k_i}{V} \left( \frac{A}{k_0 - \alpha} e^{-\alpha t} + \frac{B}{k_0 - \beta} e^{-\beta t} \right) \] (3)

where \( C_1 \) is the dinitrate concentration in the central compartment, \( V_1 \) is the volume of the compartment, \( k_1 \) is the first-order metabolic rate constant from dinitrate to mononitrate, \( \alpha \) and \( \beta \) are the slopes, and \( A \) and \( B \) are the intercepts. Each data set of dinitrate and mononitrate concentrations was simultaneously fitted to eqs. 2 and 3 correcting the molecular weights and using the nonlinear least squares method described above. The elimination rate constant and distribution volume of mononitrate were fixed on the mean values obtained in the corresponding mononitrate administration study, and only hybrid parameters \((A, B, \alpha, \beta)\) were calculated. The volume of central compartment, metabolic rate constant, metabolic clearance \((CL_i)\) and steady-state volume of distribution \((VSS)\) were estimated from the hybrid parameters by traditional methods (Gibaldi and Perrier, 1982). In the analysis of ISDN dosing, \( k_{13} \) was also obtained by data-fitting and used for estimation of \( k_{14} \) together with hybrid parameters.

The difference in mean arterial pressure from the baseline level \((\Delta MAP)\) was used as a measure of pharmacological effect of organic nitrates and related to plasma concentration based on a sigmoidal \( E_{max} \) model:

\[ \Delta MAP = \frac{E_{max} C_i}{C_i + EC_{50i}} \] (4)

where \( E_{max}, \gamma, \) and \( EC_{50i} \) are the maximum effect, Hill’s constant and concentration required to produce 50% of \( E_{max} \). In the mononitrate administration studies, however, \( E_{max} \) was not observed even after the maximum dose of 200 mg/kg. When the pharmacological effect is between 20 and 80% of \( E_{max} \), the sigmoidal \( E_{max} \) model can be approximated to a log-linear model:

\[ \Delta MAP = m \log C_i + b_i \] (5)

where \( m \) and \( b_i \) are the slope and intercept, which are related with the \( E_{max}, \gamma, \) and \( EC_{50i} \) as follows (Holford and Sheiner, 1982):

\[ m = \frac{E_{max} \gamma \ln 10}{4} \] (6)

\[ b_i = \frac{E_{max}(2 - \gamma \ln EC_{50i})}{4} \] (7)

Thus, eq. 5 was used to describe the relationship between plasma concentration and \( \Delta MAP \) in each rat administered a mononitrate, and two PD parameters were determined by the data-fitting.

If the vasodilating effect caused by administration of a dinitrate is an additive effect of the nitrate and a metabolized mononitrate \((IIDN \) and \( IMDN \) or \( IMMN \) and \( IMDN \) and \( IMMN \) ), which act via the same mechanism of action, the PK-PD relationship is expressed as the following equation (Koizumi et al., 1993):

\[ \Delta MAP = \frac{E_{max} \left( C_1 \frac{C_i}{EC_{50i}} \right) \gamma}{1 + \left( C_1 \frac{C_i}{EC_{50i}} \right) \gamma} \] (8)

Similarly, the relationship following administration of ISDN, which has two active metabolites, is:

\[ \Delta MAP = \frac{E_{max} \left( C_1 \frac{C_i}{EC_{50i}} + C_4 \frac{C_i}{EC_{50i}} \right) \gamma}{1 + \left( C_1 \frac{C_i}{EC_{50i}} + C_4 \frac{C_i}{EC_{50i}} \right) \gamma} \] (9)

From eqs. 6 and 7, \( E_{max}, \gamma, \) and \( EC_{50i} \) can be expressed as follows:

\[ E_{max} = \frac{2(b_i \ln 10 + m \ln EC_{50i})}{\ln 10} \] (10)

\[ \gamma = \frac{2m}{b_i \ln 10 + m \ln EC_{50i}} \] (11)

\[ EC_{50i} = EC_{50} e^{-\left(\frac{m}{b_i \ln 10}\right)} \] (12)

Two PD parameters, \( EC_{50i} \) and \( EC_{50} \), were calculated for each rat by fitting the \( \Delta MAP \) data after \( IIDN \) or \( IMDN \) dosing to eqs. 8, 10, and 11 and those after ISDN dosing to eqs. 9 through 12 using the mean values of PD parameters \((m \) and \( b_i)\) of the corresponding mononitrate, and \( E_{max}, \gamma, \) and \( EC_{50i} \) were generated as secondary parameters from eqs. 10 and 11.

Statistics. Statistical significance of difference was evaluated by one-way ANOVA, and then by Scheffe’s multiple comparison method. In all cases, \( P < 0.05 \) was considered to be significant.

Results

PK-PD of Dinitrates. Figure 3 shows the typical time courses of plasma concentration and mean arterial pressure in rats receiving a single i.v. dose of 100 mg/kg \( IIDN \), \( IMDN \), or \( ISDN \). In all cases, the plasma concentration of dinitrate declined rapidly in a biphasic manner, whereas the mononitrate concentration peaked soon after dosing and then reduced slowly, maintaining higher levels than the dinitrate. The peak concentrations and terminal slopes of mononitrate, and the slopes of dinitrate decline differed among stereoisomers. The mean arterial pressure decreased to a minimum at the earliest recording time (1 min) after dosing and then recovered gradually to the baseline level. The duration to recovery of blood pressure level varied depending on the dinitrate administered.

PK of Organic Nitrates. Plasma concentration profile after i.v. injection of a mononitrate to a rat showed a monoeponential decline. The average profiles are shown in Fig. 4. The slope of decline was independent of dose but clearly differed among mononitrate isomers. The PK parameters obtained by fitting the data for each rat to a linear one-compartment model are summarized in Table 1. Although the apparent volumes of distribution are almost the same among stereoisomeric mononitrates except for 5-ISMN, the elimination rate constant and systemic clearance were highest for \( IIMN \), followed by \( IMMN \), 2-ISMN, and 5-ISMN.

The pharmacokinetics of dinitrates was linear at the dose levels of 50 to 200 mg/kg, as shown in the plasma concentra-
tion profiles after ISDN dosing (Fig. 5). The parameters determined by the data-fitting to the PK model shown in Fig. 2 are listed in Table 2, and the representative fitting values are shown in Fig. 3 as solid curves. The differences in the distribution volume of the central compartment and steady-state volume of distribution were roughly 2-fold among dinitrate stereoisomers, whereas metabolic rate constant and metabolic clearance had about 7-fold variation between the maximum values of denitration from IIDN to IIMN and the minimum from ISDN to 2-ISMN.

**PD of Organic Nitrates.** A rapid decrease immediately after administration and then a slower increase to the baseline level in mean arterial pressure were found for doses of mononitrates as true for dinitrates. The hemodynamic effect after dosing of 100 mg/kg IMMN and 5-ISMN, and 50 mg/kg of all mononitrates, however, was too weak and brief to analyze the PK-PD relationship. Figure 6 shows representative relationships between plasma concentration and ΔMAP in rats from 200 mg/kg mononitrates administration groups. Although no distinct maximum effect was observed, there was a log-linear relationship in data below 10% of mean arterial pressure at the baseline (above about 10 mm Hg of ΔMAP) for each diastereomer. The best-fit lines to the log-linear model are shown in this figure and the estimated PD parameters are summarized in Table 3.

The pharmacological data following i.v. injection of dinitrates were analyzed assuming a simple additive effect of the dinitrate and metabolized mononitrates. The estimated PD parameters are listed in Table 4, and the typical time courses of mean arterial pressure calculated from the best-fit values are drawn in Fig. 3. The estimated $E_{\text{max}}$ values were almost identical and $\gamma$ values were about 1 for all dinitrates. On the other hand, the $EC_{50}$ values were 20 to 200 times higher for dinitrates than mononitrates and varied about 3-fold among stereoisomers. The contribution of dinitrates and mononitrates to the total vasodilating effect was also calculated based on sigmoidal $E_{\text{max}}$ model (Fig. 3). Although the vasodilating effect was mainly attributed by dinitrates, the contribution of mononitrates increased at later recording times.

**Discussion**

PK of mononitrates, particularly 5-ISMN, has been well investigated in human and animals (Chasseeand, 1987; Tzeng and Fung, 1993). The PK properties obtained here were essentially consistent with those reported previously. The volumes of distribution of all mononitrates were of the same order of magnitude as the volume (0.9 liters/kg) of total body water (Rothwell and Stock, 1979), although the value of 5-ISMN was significantly higher than that of other isomers (Table 1). The systemic clearance was highest for IIMN followed by IMM, 2-ISMN, and 5-ISMN. No remarkable non-
rates (Fig. 3). The metabolic clearances of all dinitrates (Table 2) exceeded hepatic plasma flow in rat (Bischoff et al., 1971). The extensive metabolism of nitroglycerin and ISDN by extrahepatic tissues including blood vessels has been confirmed in vitro (Fung et al., 1984). The clearances were always higher than systemic clearances of mononitrates capable of being denitratated at the same position (Tables 1 and 2). The faster denitration in dinitrates might be due to their larger distribution volume and thus better access to enzymes catalyzing denitration. Another explanation could be higher binding affinity, by analogy with experimental results for nitroglycerin and the corresponding dinitrates (Needleman and Hunter, 1965). Compared among dinitrate diastereomers, the metabolic clearance had about 7-fold variation, and the values were significantly different from one another (Table 2).

Organic nitrates introduced into systemic circulation partition into vascular cells where they undergo transformation involving denitration with the subsequent liberation of nitric oxide (Ignarro et al., 1981). Nitric oxide simulates guanylyl cyclase, which leads to the conversion of GTP to cyclic GMP, which in turn causes vasodilation (Kukovetz and Holzmann, 1990). The series of reactions following generation of nitric oxide is very rapid (Keith et al., 1982; Kelm et al., 1988). These facts allow us to assume that the vasodilating effect after dinitrate administration is a simple additive effect of both the nitrate and its mononitrate metabolites with an identical mechanism of action. In the vasodilation by mononitrates, the experimental $E_{\text{max}}$ was not obtained even at the maximum dose of 200 mg/kg (Fig. 6), nor was $E_{\text{max}}$ observed in the reduction of rat pulse pressure (Tzeng and Fung, 1992a) or relaxation of aortic ring (Tzeng and Fung, 1992b). Although the hemodynamic and antianginal actions of organic nitrates are mediated through vasodilation of veins and arteries, the venodilation predominates and dilation of arteries and arterioles occurs to a lesser extent (Imhof et al., 1982). A log-linear model was therefore used to describe the PK-PD relationship of mononitrates (Fig. 6). In contrast, the pharmacological effect after dinitrate dosing was so strong that it could be analyzed by a sigmoidal $E_{\text{max}}$ model (Fig. 3).

Regardless of stereoisomers, the estimated $E_{\text{max}}$ and $\gamma$ values were about 50 mm Hg and 1 (Table 4). The slopes of log-linear regression line for the vasodilation after mononitrate dosing, which is a function of $E_{\text{max}}$ and $\gamma$ (eq. 6), were identical among isomers (Table 3). These results support that the vasodilating effect of all organic nitrates is caused by a common mediator, cyclic GMP. The EC$_{50}$ values of dinitrates were remarkably lower than those of mononitrates (Table 4). The higher vasodilator potency of dinitrates might be due to their higher lipophilicity and thus greater partition into the vascular cells, as pointed out in previous in situ and in vitro studies (Bogaert and Rosseel, 1972; Noack, 1984). Although EC$_{50}$ showed a large interindividual difference, the vasodilating potency also seemed to depend on the stereostructure of organic nitrates.

Based on the PK and PD parameters obtained here, the influence of stereochemistry on the PK and PD of organic nitrates is discussed. The metabolic clearance from dinitrate to mononitrate showed that two nitrate groups rather than one at the exo position rather than just one at the endo position are easily denitratated (Table 2). The EC$_{50}$ values of dinitrates had a tendency to decrease with increase in the number of exo
nitrates and, thus another advantage of exo position to denitration was found (Table 4). The nitrates group at the exo position interacts with the lone-pair electrons of the oxygen atom in the adjacent ring and thus lends itself less easily to enzymatic attack than the same group at the endo position (Hayward et al., 1967). Comparison of EC₅₀ among mononitrate isomers showed that exo hydroxy groups are helpful to denitration (Table 4). This can be explained by the hypothesis that enzymes metabolizing nitrates to nitric oxide contain two attachment sites that can bind to the oxygen atoms and are separated by a distance of 5.8 Å (Tseng and Fung, 1992c). The effect of stereostructure on the elimination of mononitrates is not simple, because the compounds are cleared from the body via not only denitration but also glucuronidation (Wood et al., 1984). The urinary conjugation clearances were around 10% except for 43% of IMMN (Tzeng and Fung, 1992c). The hydroxy groups at the endo position are also involved in intermolecular interactions via hydrogen bonding to an oxygen atom in the same ring (Anteunis and Verhegghe, 1971), but the interaction is favorable to glucuronidation, which requires a backside attack (the so-called S_N2 mechanism). The intermolecular interaction of both nitrates and hydroxy groups might cause the exceptionally extensive conjugation and then systemic elimination of IMMN (Table 1).

In conclusion, the PK-PD relationship of organic mononitrates and dinitrates was established, and the stereoselective clearances and vasodilating effects were demonstrated. Stereoisomers having exo nitrate groups generally showed high vasodilating potency, but their duration of action was short due to high systemic and metabolic clearances. It is understandable that ISDN and 5-ISMN, whose potency and clearance are in the middle among isomers, showed high vasodilating potency, but their duration of action was short due to high systemic and metabolic clearances.
1998). Some information obtained here may not be directly utilized in the improvement of nitrate treatment of angina pectoris and congestive heart failure. However, the present study is a thorough PK-PD study of several organic dinitrates and mononitrates in conscious rats and thus a worthwhile step to establish the clinical PK-PD relationship.

References


TABLE 3
Pharmacodynamic parameters of organic mononitrates in rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IIMN</th>
<th>IMMN</th>
<th>2-ISMN</th>
<th>5-ISMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m$ (mm Hg)</td>
<td>29.5 ± 7.6</td>
<td>29.7 ± 7.0</td>
<td>26.9 ± 6.5</td>
<td>30.5 ± 13.0</td>
</tr>
<tr>
<td>$b_0$ or $b_1$ (mm Hg)</td>
<td>−28.1 ± 4.0</td>
<td>−49.1 ± 13.9</td>
<td>−38.7 ± 12.2</td>
<td>−45.8 ± 21.5</td>
</tr>
</tbody>
</table>

* Each value represents the mean ± S.D. of six rats administered a 200 or 100 mg/kg dose.

* Each value represents the mean ± S.D. of three rats administered a 200 mg/kg dose.

TABLE 4
Pharmacodynamic parameters of organic dinitrates in rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IIDN</th>
<th>IMDN</th>
<th>ISDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{max}}$ (mm Hg)</td>
<td>54.4 ± 6.8</td>
<td>44.2 ± 8.1</td>
<td>49.0 ± 9.6</td>
</tr>
<tr>
<td>γ</td>
<td>0.956 ± 0.127</td>
<td>1.19 ± 0.17</td>
<td>1.05 ± 0.19</td>
</tr>
<tr>
<td>EC$<em>{503}$ or EC$</em>{504}$ (μg ml$^{-1}$)</td>
<td>1.39 ± 0.68</td>
<td>4.67 ± 2.15$^a$</td>
<td>1.86 ± 1.19</td>
</tr>
<tr>
<td>EC$<em>{503}$ or EC$</em>{504}$ (μg ml$^{-1}$)</td>
<td>$77.9 ± 19.6^b$</td>
<td>$254 ± 101$</td>
<td>$184 ± 75$</td>
</tr>
</tbody>
</table>

* Significantly different from the values of other isomers ($P < 0.05$).

* Significantly different from the values of IMMN and 5-ISMN ($P < 0.05$).
Stereoselective PK-PD of Organic Nitrates

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