Selective Inhibition of Cytochrome P450 2D6 by Sarpogrelate and Its Active Metabolite, M-1, in Human Liver Microsomes

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ABSTRACT

The present study was performed to evaluate the in vitro inhibitory potential of sarpogrelate and its active metabolite, M-1, on the activities of nine human cytochrome (CYP) isozymes. Using a cocktail assay, the effects of sarpogrelate on nine CYP isozymes and M-1 were measured by specific marker reactions in human liver microsomes. Sarpogrelate potently and selectively inhibited CYP2D6-mediated dextromethorphan O-demethylation with an IC50 (K) value of 3.05 μM (1.24 μM), in a competitive manner. M-1 also markedly inhibited CYP2D6 activity; its inhibitory effect with an IC50 (K) value of 0.201 μM (0.120 μM) was more potent than that of sarpogrelate, and was similarly potent as quinidine (K, 0.129 μM), a well-known typical CYP2D6 inhibitor. In addition, sarpogrelate and M-1 strongly inhibited both CYP2D6-catalyzed bufuralol 1'-hydroxylation and metoprolol α-hydroxylation activities. However, sarpogrelate and M-1 showed no apparent inhibition of the other following eight CYPs: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5. Upon 30-minute preincubation of human liver microsomes with sarpogrelate or M-1 in the presence of NADPH, no obvious shift in IC50 was observed in terms of inhibition of the nine CYP activities, suggesting that sarpogrelate and M-1 are not time-dependent inactivators. Sarpogrelate strongly inhibited the activity of CYP2D6 at clinically relevant concentrations in human liver microsomes. These observations suggest that sarpogrelate could have an effect on the metabolic clearance of drugs possessing CYP2D6-catalyzed metabolism as a major clearance pathway, thereby eliciting pharmacokinetic drug–drug interactions.

Introduction

Sarpogrelate ((R,S)-1-{2-[2-(3-methoxyphenyl)ethyl]-phenoxy}-3-(dimethyl amino)-2-propyl hydrogen succinate hydrochloride; Fig. 1) is a highly specific 5-HT2A receptor antagonist widely used in China, Japan, and South Korea to treat peripheral arterial disease (Rashid et al., 2002; Doggrell, 2004). Sarpogrelate has inhibitory effects on serotonin-induced platelet aggregation (Hara et al., 1991a; Nakamura et al., 1999), thrombus formation (Hara et al., 1991b; Yamashita et al., 2000), vascular constriction, and vascular smooth muscle cell proliferation (Sharma et al., 1999), all of which are mediated by 5-HT2A receptors, and consequently reduces the ischemic symptoms associated with peripheral arterial disease. Additionally, sarpogrelate has beneficial effects in restenosis after coronary stenting (Fujita et al., 2003; Saini et al., 2004), pulmonary hypertension (Saini et al., 2004), angina pectoris (Kinguwara et al., 2002), and diabetes mellitus (Pietraszek et al., 1993; Ogawa et al., 1999), although the precise mechanisms remain unknown. Sarpogrelate is metabolized to (S)-1-{2-[2-(3-methoxyphenyl)ethyl]-phenoxy}-3-(dimethylamino)-2-propanol hydrochloride (M-1; Fig. 1), formed by hydrolysis from sarpogrelate (Nagatomo et al., 2004; Saini et al., 2004). The M-1 is an active sarpogrelate metabolite, which has inhibitory effects exceeding those of sarpogrelate in vitro (Pertz and Elz, 1995).

General sarpogrelate dosing in patients is one 100-mg tablet taken three times per day after meals (Shinohara et al., 2008). After oral administration of 100 mg of sarpogrelate to healthy male subjects, sarpogrelate is rapidly absorbed from the gastrointestinal tract with a mean maximum plasma concentration (Cmax) of 856.3 ng/mL at 0.7 hour and is rapidly eliminated from plasma with a half-life of 0.8 hour (Kim et al., 2013a). The active metabolite, M-1, reaches a Cmax of 49.3 ng/mL at 0.9 hour and exhibits slower elimination than sarpogrelate, with a half-life of 4.4 hours (Kim et al., 2013a). After absorption, sarpogrelate and M-1 further undergo glucuronide conjugations to form several metabolites, which are mainly excreted in bile (Kim et al., 2013b). Despite the wide use and excellent pharmacological properties of sarpogrelate, to date there is no information regarding the potential inhibitory effects of sarpogrelate and M-1 on human P450 isozymes. In the present study, the inhibitory effects of sarpogrelate and M-1 on the nine cytochrome P450 (CYP) isozymes were evaluated using a cocktail assay to assess the potential of sarpogrelate to cause drug–drug interactions with other concomitantly administered drugs. We report in this work that especially M-1 is a selective competitive inhibitor of CYP2D6 in vitro.

Materials and Methods

Chemicals and Reagents. Pooled human liver microsomes from a mixed pool of 24 donors (17 males and 7 females), S-benzylNirvanol, and 1'-hydroxybufuralol were purchased from BD Gentest (Woburn, MA). Sarpogrelate and M-1 were obtained from Kunwha Pharmaceutical Company (Seoul, Republic of Korea). Acetaminophen, bufuralol, chlorpropamide, chloroxazone, coumarin, desflurane, dextildihydcarbamate, furafylline, α-hydroxymetoprolol, ketocona- zole, metoprolol, phenacetin, propranolol, quercetin, quinidine, rosiglitazone,
preincubated for 5 minutes at 37°C. The reaction was initiated by adding an aliquot of sarpogrelate or M-1 (concentration range: 0–50 μM) and incubated for 15 minutes at 37°C in a shaking water bath. When sarpogrelate as an inhibitor was incubated, a 10-μL aliquot of 1 M KF in 0.1 M phosphate buffer (pH 7.4) was added before incubation to inhibit esterase activity (Clarke and Waskell, 2003). After incubation, reactions were stopped by addition of 50 μL of ice-cold acetonitrile containing 2 μM chloropropamide as an internal standard, and they were chilled and centrifuged (13,000 rpm, 8 minutes, 4°C). The supernatant was then diluted 100-fold with acetonitrile and then injected into the LC-MS/MS system. All incubations were performed in triplicate, and mean values were used for analysis. Additionally, identical parallel incubation samples containing well-known reversible CYP inhibitors were included as positive controls. Two different microsomal protein concentrations, 0.05 and 0.1 mg/mL, were also used to evaluate the inhibitory potential for CYP2D6 activities.

Additionally, sarpogrelate or M-1 was tested as an inhibitor of bufuralol 1'-hydroxylase (Boobis et al., 1985; Kronbach et al., 1987), metoprolol O-hydroxylase (Otton et al., 1988), and other CYP2D6-specific biotransformation pathways. Concentrations of bufuralol (5 μM) and metoprolol (20 μM) were used in this study. Other procedures were similar to those used in the cocktail assays.

**Determination of the Ki of Sarpogrelate and M-1 for CYP2D6.** Based on the IC50 values, the Ki values of sarpogrelate and M-1 for CYP2D6 were determined. Briefly, dextromethorphan, a specific substrate for CYP2D6, was incubated with sarpogrelate, M-1, or quinidine, a well-known typical CYP2D6 inhibitor. For determination of Ki values, dextromethorphan concentrations used were 2.5, 5, and 10 μM. The concentrations of quinidine, sarpogrelate, and M-1 were as follows: 0–1 μM for quinidine, and 0–10 μM for sarpogrelate and M-1. All incubations were performed in triplicate, and mean values were used for the analysis. Other procedures were similar to those of the reversible inhibition studies.

**Time-Dependent Inhibitory Effects of Sarpogrelate and M-1 on the Activities of Nine Cytochrome P450 Enzymes.** The IC50 shift assay is one of the most efficient and convenient methods of evaluating the time-dependent inhibitory effects of sarpogrelate and M-1. Changes in enzymatic activity are usually detected with and without preincubation of the test compound for a defined period. A shift in IC50 to a lower value (shift) following preincubation indicates time-dependent inactivation (Obach et al., 2007).

Pooolen human liver microsomes (1 mg/mL) were incubated with sarpogrelate or M-1 (0–50 μM) in the absence or presence of a NADPH-generating system for 30 minutes at 37°C (i.e., the inactivation incubation). After inactivation incubation, aliquots (10 μL) were transferred to fresh incubation tubes (final volume 100 μL) containing a NADPH-generating system and each P450-selective substrate cocktail set. When sarpogrelate was studied, a 10-μL aliquot of 1 M KF was added into both inactivation and incubation mixtures. The reaction system (100 μL total volume) was incubated for 15 minutes at 37°C in a shaking water bath. After incubation, reactions were stopped by addition of 50 μL of ice-cold acetonitrile containing 2 μM chloropropamide, as an internal standard, and they were chilled and centrifuged (13,000 rpm, 8 minutes, 4°C). The supernatant was then diluted 10-fold with acetonitrile and injected into the LC-MS/MS system.

**Determination of the Unbound Fraction of Sarpogrelate or M-1 in Human Liver Microsomes and Human Plasma.** Equilibrium dialysis was conducted to assess the unbound fraction of sarpogrelate or M-1 in human liver microsomes and human plasma using a single-use plate rapid equilibrium dialysis device with dialysis membranes with a molecular weight cutoff of ~8000 Da (Thermo Scientific, Rockford, IL) (Ba et al., 2013). Human liver microsome samples containing sarpogrelate or M-1 at concentrations of 0.5 and 10 μM, respectively (100 μL), were dialyzed against 50 mM phosphate buffer (300 μL) at pH 7.4. The loaded dialysis plate was covered with sealing tape, placed on an orbital shaker at approximately 500 rpm, and incubated at 37°C for 4 hours. All incubations were performed in triplicate, and mean values were used for the analysis. Nonspecific binding in microsome/buffer mixed matrix was evaluated for sarpogrelate or M-1 concentrations using the LC-MS/MS method. In plasma protein-binding studies, the final concentrations of sarpogrelate or M-1 were both 0.5 and 10 μM. The LC-MS/MS conditions for determination of sarpogrelate and M-1 were optimized based on the conditions used in a previous study (Kim et al., 2013a).

**LC-MS/MS Analysis.** Metabolites of nine P450-selective substrates were analyzed using a tandem quadrupole mass spectrometer (QTrap 5500 LC-MS/MS; Applied Biosystems, Foster City, CA) equipped with an electrospray
ionization interface, as reported previously (Bae et al., 2013). Single reaction monitoring mode using specific precursor/product ion transition was used for quantification. The mass transitions of the metabolites of the nine P450-selective substrates and collision energies are listed in Supplemental Table 1. Peak areas for all of the analytes were integrated automatically using the Analyst software (version 1.5.2; Applied Biosystems, Foster City, CA).

The mass transitions used for quantification of 1′-hydroxybufuralol or α-hydroxymetoprolol were optimized based on the conditions used in a previous study (VandenBrink et al., 2012).

**Data Analysis.** For reversible inhibition and time-dependent inhibition screening, the P450-mediated activities in the presence of the inhibitor, sarpogrelate or M-1, were expressed as percentages of the corresponding control values at 0 μM sarpogrelate or M-1. From plots of percent inhibition versus inhibitor concentrations, corresponding IC₅₀ values were calculated by nonlinear regression using the WinNonlin software (version 4.0; Pharsight, Mountain View, CA). The apparent kinetic parameters for inhibitory potential (Kᵢ values) were estimated from the fitted curves using the WinNonlin software. The most appropriate inhibition model selected based upon the goodness-of-fit criteria of a visual inspection of the data, correlation of determination (R²), and corrected Akaike’s Information Criterion.

**Results**

The inhibitory effects of sarpogrelate and M-1 on the activities of nine CYP isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) at microsomal protein concentrations of 0.25 mg/mL are shown in Figs. 2 and 3, respectively. The IC₅₀ values of sarpogrelate and M-1 at a microsomal protein concentration of 0.25 mg/mL are listed in Table 1. The IC₅₀ values for the positive controls used in the reversible inhibition studies were in good agreement with published values to an acceptable degree of accuracy (data not shown). Of the nine P450 isoforms tested, CYP2D6-catalyzed dextromethorphan hydroxylation was most strongly inhibited by sarpogrelate and M-1, with IC₅₀ values of 3.05 and 0.201 μM, respectively (Table 1).

Similar inhibitory potencies of sarpogrelate and M-1 at the different microsomal protein concentrations (0.05 and 0.1 mg/mL) were observed (data not shown), indicating that nonspecific microsomal binding of sarpogrelate and M-1 did not affect the inhibitory potencies. However, sarpogrelate and M-1 showed no apparent inhibition of the other eight
CYPs tested (Table 1; Figs. 2 and 3); the remaining activities at the tested highest concentration (50 μM) were greater than 90%.

To determine whether the inhibitory activities of sarpogrelate and M-1 were substrate specific, we examined the inhibitory effects on other CYP2D6-specific biotransformation pathways (i.e., bufuralol 1'-hydroxylation and metoprolol α-hydroxylation) and found that sarpogrelate also markedly inhibited their activities, with IC50 values of 4.02 and 3.37 μM, respectively (data not shown). M-1 also potently inhibited CYP2D6 activity; corresponding IC50 values were 0.360 and 0.545 μM, respectively (data not shown).

To characterize the type of reversible inhibition of CYP2D6 by sarpogrelate or M-1 based on the IC50 values, enzyme kinetic assays were conducted with varying concentrations of sarpogrelate or M-1 and dextromethorphan. Identical parallel incubation samples containing a known potent inhibitor of CYP2D6, quinidine, were included. The Ki values of sarpogrelate, M-1, and quinidine are listed in Table 2. Representative Dixon plots for the inhibition of CYP2D6 by sarpogrelate, M-1, and quinidine in human liver microsomes are shown in Fig. 4. Sarpogrelate and M-1 strongly and selectively inhibited CYP2D6 with Ki values of 1.24 μM and 0.120 μM, respectively. Specifically, inhibition of CYP2D6 by M-1 was more potent than that of sarpogrelate and was similarly potent as quinidine (Ki, 0.129 μM) (Table 3). Visual inspection of the Dixon plots and further analysis of the enzyme inhibition modes

<table>
<thead>
<tr>
<th>CYPs</th>
<th>Reactions</th>
<th>IC50</th>
</tr>
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<tbody>
<tr>
<td>CYP1A2</td>
<td>Phenacetin O-deethylation</td>
<td>&gt;50 &gt;50</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin 7-hydroxylase</td>
<td>&gt;50 &gt;50</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Bupropion hydroxylation</td>
<td>&gt;50 &gt;50</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Paclitaxel 6α-hydroxylation</td>
<td>&gt;50 &gt;50</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Tolbutamide 4-hydroxylation</td>
<td>&gt;50 &gt;50</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>S-Mephenytoin 4'-hydroxylation</td>
<td>&gt;50 &gt;50</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Dextromethorphan O-demethylation</td>
<td>3.05 0.201</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chloroxazone 6-hydroxylation</td>
<td>&gt;50 &gt;50</td>
</tr>
<tr>
<td>CYP3A4/5</td>
<td>Midazolam 1'-hydroxylation</td>
<td>&gt;50 &gt;50</td>
</tr>
</tbody>
</table>

The assay conditions are described in Materials and Methods. Data are expressed as the mean of triplicate determinations.
suggested that the inhibition data of sarpogrelate, M-1, and quinidine all fit well to a competitive inhibition type.

A shift in the inhibition curve to a lower IC\textsubscript{50} value by 30-minute preincubation in the presence of NADPH is an indicator of time-dependent inhibition. After 30-minute preincubation of sarpogrelate or M-1 with human liver microsomes in the presence of NADPH, no obvious shift in IC\textsubscript{50} was observed for inhibition of the nine CYPs (data not shown). Representative IC\textsubscript{50} shift plots for CYP2D6 activity by sarpogrelate or M-1 are shown in Supplemental Fig. 1. These suggest that sarpogrelate and M-1 are not time-dependent inhibitors.

The free fractions of sarpogrelate at concentrations of 0.5 and 10 \( \mu \)M in human plasma were 96.8 \( \pm \) 4.29\% and 95.1 \( \pm \) 3.12\%, respectively (\( n = 3 \), each). However, incubation in human liver microsomes for 4 hours prohibited the measurement of microsomal binding for sarpogrelate due to its instability in microsomes. When M-1 was added at concentrations of 0.5 and 10 \( \mu \)M to human liver microsomes (human plasma), the free fractions of M-1 were 72.0 \( \pm \) 6.12\% (97.3 \( \pm \) 4.28\%) and 68.1 \( \pm \) 5.18\% (97.8 \( \pm \) 3.09\%), respectively (\( n = 3 \) each). The free fractions of sarpogrelate and M-1 were not affected by the concentrations added.

### Discussion

To our knowledge, there are no reports of in vitro drug interactions of sarpogrelate via CYP isozymes. In this study, we demonstrated that sarpogrelate is a potent and selective competitive inhibitor of CYP2D6 in vitro. Additionally, M-1, an active metabolite of sarpogrelate, significantly inhibited CYP2D6 activities; its inhibitory effects with an IC\textsubscript{50} (\( K_i \)) value of 0.201 \( \mu \)M (0.120 \( \mu \)M) were more potent than those of sarpogrelate, with an IC\textsubscript{50} (\( K_i \)) value of 3.05 \( \mu \)M. Sarpogrelate and M-1 strongly inhibited other CYP2D6-catalyzed bufuralol 1'-hydroxylation and metoprolol \( \alpha \)-hydroxylation activities. However, sarpogrelate and M-1 showed no apparent inhibition of the other following eight CYPs: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1. Preincubation of sarpogrelate or M-1 with human liver microsomes and a NADPH-generating system did not alter the inhibition potencies against the nine CYPs, suggesting that sarpogrelate or M-1 are not time-dependent inactivators.

Generally, alterations in the activities of hepatic CYPs, inhibition or induction, in vivo represent the major mechanisms underlying pharmacokinetic drug–drug interactions (Clarke and Jones, 2002; Leucuta and Vlase, 2006). Although it accounts for only 2–5\% of all hepatic CYP isozymes, CYP2D6 metabolizes approximately 25\% of all clinically used medications, such as some cytotoxins, tamoxifen, and many agents used to treat associated complications such as antiarrhythmics, antidepressants, antipsychotics, and analgesics (Wolf and Smith, 1999; Ingelman-Sundberg and Evans, 2001). In addition, the CYP2D6 gene is highly polymorphic with more than 112 variants described to date (http://www.imm.ki.se/CYPalleles/cyp2d6.htm), and such variations in CYP2D6 expression are thought to increase the potential for drug–drug interactions (Bernard et al., 2006).

The in vitro inhibition potency alone does not dictate the likelihood of pharmacokinetic drug interactions because the in vivo concentration of the inhibitor should also be considered. For reversible inhibitors, the magnitude of the increase in exposure is related to the inhibitory potency (\( K_i \)), the concentration of inhibitor, and the fraction of the affected drug that ordinarily goes through the inhibited enzyme (\( f_m \)) (Yao & Levy, 2002; Ito et al., 2004; Obach et al., 2006). As stated previously, the \( C_{\text{max}} \) of sarpogrelate was 856.3 ng/mL (1.99 \( \mu \)M) following a single 100-mg sarpogrelate oral dose in healthy subjects. In addition, our clinical trial data indicate that the \( C_{\text{max}} \) values of sarpogrelate and M-1 in steady state are 657 \( \pm \) 302 ng/mL (1.56 \( \mu \)M) at 0.9 hour with a half-life of 0.64 hour and 53.0 \( \pm \) 16.1 ng/mL (0.161 \( \mu \)M)

### Table 2

\( K_i \) values of the inhibition for CYP2D6 by sarpogrelate, M-1, and quinidine at microsomal protein concentrations of 0.25 mg/mL.

<table>
<thead>
<tr>
<th>CYPs</th>
<th>( K_i ) Sarpogrelate ( \mu )M</th>
<th>( K_i ) M-1 ( \mu )M</th>
<th>( K_i ) Quinidine ( \mu )M</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>1.24*</td>
<td>0.120*</td>
<td>0.125*</td>
</tr>
</tbody>
</table>

\*Inhibition type was determined by the best fit to competitive mode based on AICs.

![Dixon plots to determine \( K_i \) values for CYP2D6 of sarpogrelate (A), M-1 (B), and quinidine (C). The concentrations of dextromethorphan were determined 2.5 (\( \bullet \)), 5 (\( \circ \)), and 10 (\( \blacktriangledown \)) \( \mu \)M, respectively. \( V \) represents formation rate of dextrophan (pmol/min/mg protein). Data are the mean values of triplicate determinations. The solid lines of sarpogrelate, M-1, and quinidine fit well to all competitive inhibition types.](downloaded from dmd.aspetjournals.org at ASJP Journals on November 20, 2016)
at 1.08 hours with a half-life of 4.98 hours, respectively (our unpublished data).

In human in vivo interaction studies, the degree of interaction is usually expressed as the ratio of the area under the plasma concentration–time curve (AUC) in the presence (AUC,) and absence of an inhibitor. When the in vivo inhibition potency of sarpogrelate against completely CYP2D6-cleared drug (\(I_{\text{in vitro}}\)) is determined from the plasma concentration of sarpogrelate described above, the \(K_i\) values of sarpogrelate (1.24 \(\mu\)M) for CYP2D6, and the unbound fractions in both human liver microsomes and plasma by the methods of Obach et al. (2006), the AUC, to AUC ratio is estimated to be 1.17–11.5 (Table 3). These estimates of the magnitude of drug–drug interactions for a CYP2D6-cleared drug range from 1.17 to 11.5, largely due to whether the unbound or total sarpogrelate concentrations are most relevant to enzyme inhibition in vivo. However, all the AUC, to AUC ratios had >1.1 when either total or unbound concentrations were used for the calculation of ratios. Thus, we cannot exclude the possibility of the in vivo inhibitory potency of CYP2D6 by sarpogrelate.

There are some limitations to our calculations. First, the effects of M-1 were not considered, although its inhibitory effect was more potent than that of sarpogrelate. Second, the free fraction of sarpogrelate in human liver microsomes is assumed to be the same as that of M-1. The fraction of the affected drug cleared by CYP2D6 and \(F_i\) is assumed to be unity. The estimate for \(k_e\) was calculated from the expression \(T_{\max } = \ln \left( \frac{[I]_0}{K_i} \right) / k_e - k_i\), where \(k_i\) is the elimination rate constant. The value of \(k_e\) was calculated from half-life, 0.64 h, and \(T_{\max }\) value was 0.9 h (our unpublished data).

### Table 3

<table>
<thead>
<tr>
<th>([I]_{\text{in vitro}})</th>
<th>Equation Used to Estimate the ([I]_{\text{in vitro}})</th>
<th>Fold Increase in Exposure (AUC/AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic total (C_{\text{max}})</td>
<td>(\frac{[I]<em>{\text{in vitro}}}{C</em>{\text{in vitro}}} = \frac{C_{\text{max}}}{C_{\text{in vitro}}}) at steady state</td>
<td>1.17</td>
</tr>
<tr>
<td>Systemic free (C_{\text{max}})</td>
<td>(\frac{[I]<em>{\text{in vitro}}}{C</em>{\text{in vitro}}} = \frac{fu \times C_{\text{max}}}{C_{\text{in vitro}}}) at steady state</td>
<td>1.17</td>
</tr>
<tr>
<td>Estimated total portal (C_{\text{max}})</td>
<td>(\frac{[I]<em>{\text{in vitro}}}{C</em>{\text{in vitro}}} = \frac{C_{\text{max}} + k_e \times F_i \times D/Qh}{C_{\text{in vitro}}})</td>
<td>11.5</td>
</tr>
<tr>
<td>Estimated total free (C_{\text{max}})</td>
<td>(\frac{[I]<em>{\text{in vitro}}}{C</em>{\text{in vitro}}} = \frac{fu \times (C_{\text{max}} + k_e \times F_i \times D/Qh)}{C_{\text{in vitro}}})</td>
<td>1.42</td>
</tr>
</tbody>
</table>

\(D\), dose of inhibitor; \(F_i\), fraction absorbed from the gastrointestinal tract; \(fu\), unbound fraction of sarpogrelate in plasma; \([I]\), concentrations of sum of inhibitors; \(k_e\), absorption rate constant; \(Qh\), human hepatic blood flow rate.

### References


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