Pharmacokinetic and Pharmacodynamic Studies of a Thromboxane Synthetase Inhibitor, Ozagrel, in Rabbits

Nian Xin Zheng, Hitoshi Sato, Isao Adachi, Ikuo Kanamoto, and Isamu Horikoshi

Department of Hospital Pharmacy, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan and Department of Pharmacy, Hokuriku Central Hospital, 2124-1 Hanyu, Oyabe, Toyama 932, Japan.
Received April 6, 1995; accepted August 22, 1995

The pharmacokinetic and pharmacodynamic (PK/PD) characteristics of ozagrel, a new potent and selective thromboxane synthetase inhibitor, were investigated in rabbits after its intravenous, oral, and rectal administration. Serum level of TXB₂ (the stable metabolite of TXA₂), a direct pharmacological marker, was measured after each dosing. A marked reduction of serum TXB₂ within 30 min was shown after the three routes of administration, reflecting rapid onset of action. Due to rapid and complete absorption (i.e., T_max; 20 min, bioavailability; 100%) and longer duration of pharmacological action after rectal dosing, the rectum offers a practical delivery route for ozagrel. An E_max model was employed to fit the pharmacological data, and IC₅₀ and E_max for thromboxane synthetase inhibition were estimated to be 56.0 ng/ml and 94%, respectively. These pharmacodynamic parameters were incorporated into an integrated mathematical model to simulate the PK/PD profiles of ozagrel after i.v., oral, and rectal administration at lower (50 mg) and higher (200 mg) doses, and good agreement between the experimental and calculated values was achieved. The present PK/PD model may be useful for optimizing the therapeutic regimens of ozagrel.

Key words ozagrel; thromboxane synthetase inhibitor; pharmacokinetics; pharmacodynamics; rabbit; Stella model

Ozagrel, (E)-3-[p-(1H-imidazole-1-ylmethyl)phenyl]-2-propenoic acid, is a selective thromboxane A₂ (TXA₂) synthetase inhibitor.¹ It is commercially available as tablet and solution for injection; the former is used for the treatment of bronchial asthma and the latter to improve motor disturbance after cerebral thrombosis.²,³ The possibility of rectal absorption of ozagrel from suppository form has been reported in rabbits.⁴ The pharmacokinetic and pharmacological profiles of ozagrel after intravenous (i.v.) and oral administration have been reported in human,⁵,⁶ but its pharmacokinetics and pharmacodynamics (PK/PD) have not been quantitatively correlated in a comprehensive manner. Therefore, we investigated the relationship of PK/PD of ozagrel after i.v. infusion, oral, and rectal administration in rabbits, and developed an integrated mathematical model to simulate its PK/PD. The pharmacodynamics of ozagrel was characterized by serum levels of TXB₂ (the stable metabolite of TXA₂), which is a pharmacological marker for thromboxane synthetase inhibition. Rabbits are known to be a good animal model with which to study the pharmacological characteristics of ozagrel.⁷ A pharmacodynamic model previously developed for another thromboxane synthetase inhibitor⁸ required data on platelet distribution of the drug; nevertheless, predicted effect–time curves did not successfully fit the observed data. In this study, we developed a model which requires only the plasma concentration of drug and serum TXB₂ activity, both of which can be easily measured in a clinical setting. The pharmacodynamic part of our model is based on a scheme that TXB₂ is synthesized with a zero-order rate constant (R₀) and degraded with a first-order rate constant (kᵣ), and that ozagrel inhibits the production of TXB₂ by inhibition of R₀. Thus, the pharmacodynamic model of ozagrel is analogous to those of an anticoagulant drug, warfarin,⁹ a fibrinogen receptor antagonist, L-703 014,¹⁰ and an aldose reductase inhibitor, AL 1576,¹¹

MATERIALS AND METHODS

Materials Ozagrel hydrochloride powder was supplied by Kissei Pharmaceutical Ind., Ltd. (Matsumoto, Japan). Ozagrel hydrochloride tablets (Domenan)⁵ were obtained from Kissei Pharmaceutical Ind., Ltd. Sodium ozagrel powder was supplied by Ono Pharmaceutical Ind., Ltd. (Osaka, Japan). Witepsol H-15 was obtained from Maruishi Pharmaceutical Co., Ltd. (Osaka, Japan). ²¹²⁵-I-RIA kit for TXB₂ was purchased from New England Nuclear (Mass., U.S.A.). Other reagents were commercially available and of analytical grade.

Preparation Sodium ozagrel was dissolved in saline for i.v. injection. Ozagrel powder suppository was prepared by the fusion method as described.⁴

Plasma Protein Binding The binding of ozagrel to plasma proteins was examined using a micropartition system, Centrifree® (Amicon, MA, U.S.A.), at ozagrel concentrations of 1 and 10 μg/ml in rabbit plasma.

Animals Throughout the experiments, normal white Japanese male rabbits weighing 2.5—3.0 kg (Sankyo Laboratory, Toyama, Japan) were used after being fasted for 48 h.

Drug Administration A group of rabbits (n = 3) was used for the cross-over study of i.v. infusion, oral and rectal administration (200 mg) with one-week resting intervals. For i.v. infusion, ozagrel was injected via the right marginal ear vein at the rate of 1.67 mg/min for 2 h; for oral dosage, it was introduced into the stomach using a catheter; and for rectal administration, an ozagrel suppository was inserted into the anus. Another group of rabbits (n = 3) was used only for the rectal administration at a lower dose (50 mg), in order to further examine the relationship between the plasma concentration and effect of the drug. In these two groups, blood (approximately 1.1 ml) was withdrawn via the left marginal ear vein with a disposable syringe at designated times after each dosing.

© 1995 Pharmaceutical Society of Japan

* To whom correspondence should be addressed.
An aliquot (500 µl) of blood was sampled in a heparinized tube and plasma was separated for drug analysis. For
TXB₂ quantification, another portion (500 µl) of blood was incubated at 37 °C for 1 h and serum was separated. The
obtained samples were kept at −80 °C until further analysis.

Drug Assay  The plasma concentrations of ozagrel were measured by a HPLC method.² Briefly, 0.2 ml of plasma was
added with 0.4 ml of methanol and mixed well. The mixture was then centrifuged at 1 × 10⁴ rpm for 2 min, the supernatant was filtered and used for HPLC analysis. The HPLC system consisted of a pump (LC-6AD, Shimadzu, Kyoto, Japan), a UV detector (SPD-6A, Shimadzu) and an autoinjector (SIL-9A, Shimadzu). A reversed-phase TSK-Gel ODS-80 TM column (150 × 4.6
mm i.d.; pore size 5 µm) (Toyoda Soda, Tokyo, Japan) was used. The mobile phase was acetonitrile: 0.01 M acetate
buffer (pH 4.0) (15 : 85). The drug was detected at a wavelength of 274 nm and quantified by an integrator (C-R6A, Shimadzu).

Assay of Serum TXB₂ Since TXA₂ is extremely short-lived, serum TXB₂ was measured by a specific
radioimmunoassay. Serum concentrations of TXB₂ were expressed as percentage of the basal level before drug
administration, and used for the pharmacological effect evaluation of ozagrel.

Pharmacokinetic Analysis  Plasma concentration–time profiles of ozagrel in one group of rabbits were charac-
terized by a moment method¹² to obtain model-independent pharmacokinetic parameters. Subsequently, the following model-dependent equations were used to fit the observed data during and after i.v. infusion, and after oral and rectal doses (200 or 50 mg), respectively, to obtain the average pharmacokinetic parameters of ozagrel.

During i.v. infusion:

\[
C_p = \frac{R}{V_1} \left\{ \frac{k_{21} - z}{\alpha - \beta} e^{-\alpha t} + \frac{(k_{21} - \alpha)}{\alpha - (\alpha - \beta)} e^{-\beta t} \right\} 
\]

(1)

After 120-min i.v. infusion:

\[
C_p = \frac{R}{V_1} \left\{ \frac{(e^{-120\alpha} - 1)(k_{21} - z)}{\alpha - (\alpha - \beta)} e^{-\alpha t} + \frac{(e^{-120\beta} - 1)(k_{21} - \beta)}{\alpha - (\alpha - \beta)} e^{-\beta t} \right\}
\]

(2)

where \( C_p \) is the plasma concentration of ozagrel; \( R \) is the i.v. infusion rate; \( V_1 \) is the volume of distribution in the central compartment; \( k_{21} \) is the rate constant for drug transfer from the peripheral to the central compartment; \( t \) is the time after dosing; and \( \alpha \) and \( \beta \) are the hybrid rate constants expressing exponential slopes of a plasma concentration–time curve.

For oral and rectal administration:

\[
C_p = \frac{F \cdot D \cdot k_a}{V_1} \left\{ \frac{k_{21} - z}{(\alpha - \beta) \cdot \beta} e^{-\alpha t} + \frac{k_{21} - z}{(\alpha - \beta) \cdot (\alpha - \beta)} e^{-\beta t} \right\}
\]

(3)

where \( F \) is the bioavailability; \( D \) is the dose administered; and \( k_a \) is the absorption rate constant.

Each fitting procedure was performed using a nonlinear least-squares regression analysis, MULTI⁺⁻¹¹ implemented
in S-CALC.¹⁴ Thus estimated pharmacokinetic parameters were used for subsequent simulation.

Pharmacodynamic Analysis  Serum TXB₂ levels were converted to percentage inhibition of TXB₂ as follows:

\[
E(TXB_2) = \frac{TXB_2 - TXB_2}{TXB_2} \times 100
\]

(4)

where \( TXB_2 \) is the basal level of TXB₂ before drug administration. A relationship between the plasma ozagrel
concentration and pharmacological effect of ozagrel, \( E(TXB_2) \), in individual rabbits was fitted to the following
\( E_{max} \) equation using a nonlinear least-squares regression analysis implemented in S-CALC:

\[
E(TXB_2) = \frac{E_{max} \cdot C_p}{IC_{50}(TXB_2) + C_p}
\]

(5)

where \( IC_{50}(TXB_2) \) is the concentration which yields 50% of the maximum TXB₂ inhibition and \( E_{max} \) is the
maximum TXB₂ inhibitory effect. The estimated \( E_{max} \) and \( IC_{50}(TXB_2) \) values with the lower (50 mg) and higher
(200 mg) doses were used for subsequent PK/PD simulation.

Integrated Simulation of PK/PD  A PK/PD model for ozagrel was constructed to simulate the plasma concentration
and TXB₂ vs. time curves. The numerical integration of the model-derived differential equations was conducted on a Macintosh computer using a program of STELLA (High Performance System, Inc., NH, U.S.A.). A diagram of the STELLA model is shown in Fig. 1. The route of administration can be easily selected by setting the parameter so designated in the figure. The pharmacodynamic part of the model (submodel D) is based on a scheme in which TXB₂ is synthesized with a zero-order rate constant (\( R_{syn} \)) and degraded with a first-order rate constant (\( k_{deg} \)); ozagrel inhibits the production of TXB₂ by inhibition of \( R_{syn} \). Here, the effect of ozagrel is modeled as an inhibitory factor of \( R_{syn} \). Thus, changes in serum TXB₂ can be expressed as:

\[
\frac{dTXB_2}{dt} = R_{syn} - \frac{E_{max} \cdot C_p}{IC_{50} + C_p} k_{deg} \cdot TXB_2
\]

(6)

where \( R_{syn} \) represents TXB₂ synthesis rate before dosing and can be expressed as:

\[
R_{syn} = k_{deg} \cdot TXB_2
\]

(7)

where \( k_{deg} \) is the first-order degradation rate constant of serum TXB₂, and \( TXB_2 \) is the premedicated level of serum
TXB₂. Equation 7 was derived from Eq. 6, assuming a steady state before dosing (i.e., \( dTXB_2/dt = 0 \) and \( C_p = 0 \)).

RESULTS

Plasma Protein Binding  Ozagrel was bound to plasma proteins to the extent of 74.3 ± 2.4% and 69.9 ± 6.0% (mean ± S.D.; \( n = 3 \)) at 1 µg/ml and 10 µg/ml, respectively. Thus, its protein binding was shown to be linear over the concentration range studied, and the average value of \( f_u \) (fraction unbound in plasma) was calculated to be
0.279 ± 0.047 (mean ± S.D.; n = 6).

Pharmacokinetic Analysis One group of rabbits received i.v. infusion, oral and rectal doses of 200-mg ozagrel, the other group of rabbits received a rectal dose of 50-mg, and the plasma concentration profiles are presented in Fig. 2 together with simulated curves; these curves were obtained by simultaneous fitting of all the observed values to Eqs. 1—3. The estimated values of pharmacokinetic parameters are given in the legend to Fig. 2. Since three of the rabbits used in a previous paper were in the present pharmacokinetic-pharmacodynamic study, model-independent pharmacokinetic parameters at the higher dose (200 mg) were essentially the same as those reported earlier. \( T_{\text{max}} \), \( AUC \) (area under the plasma concentration–time curve), and MRT (mean residence time) with the additional dose (50 mg) were calculated to be 18.3 ± 6.0 min, 1481 ± 346 \( \mu \)g/ml · min, and 107 ± 15 min (mean ± S.E.M.; n = 3), respectively. From the \( AUC \) values obtained with the two rectal doses, the pharmacokinetics of ozagrel was suggested to be almost linear. By comparing the \( AUC \)s after the i.v. and rectal dosing at 200 mg, the bioavailability was determined to be almost 100% after rectal administration.

Pharmacodynamic Analysis The basal TXB₂ level fell in the range of 1.55 ± 0.30 ng/ml (mean ± S.E.M.; n = 12); the average change of basal TXB₂ levels was approximately 20% between the first and second dosages in our cross-over study. Ozagrel caused a marked reduction of serum TXB₂ with a maximum effect of 98% acquired within 30 min after i.v. infusion, oral, and rectal administration (Figs. 3A and 3B). This observation led us to set \( k_{\text{deg}} \) at 0.1 min⁻¹, a value large enough to explain the rapid fall of serum TXB₂ after the dosing. The sigmoidal nature of the TXB₂ inhibition by ozagrel after its
Fig. 2. Plasma Concentration Profiles of Ozagrel after Intravenous Infusion (A), Oral (B) and Rectal (C, 200 mg; D, 50 mg) Administration to Rabbits

Each point and bar represent the mean ± S.D. of three rabbits. Solid lines show the fitted curves according to Eqs. 1-3. The optimized pharmacokinetic parameters for the three rabbits are: $k_{on} = 0.00522 ± 0.00077 \text{min}^{-1}, V_1 = 340 ± 80 \text{ml/kg}, k_{12} = 0.00555 ± 0.00473 \text{min}^{-1}, a = 0.0856 ± 0.0231, \beta = 0.00507 ± 0.00386$ and $k_{34} = 0.0136 ± 0.0018 \text{min}^{-1}$ (mean ± S.D.).

Fig. 3. Serum TXB$_2$ Profiles after Intravenous Infusion (□, 200 mg), Oral (△, 200 mg) and Rectal (○, 30 mg; ●, 200 mg) Administration of Ozagrel to Rabbits

Each point and bar represent the mean ± S.E.M. of three rabbits.

Fig. 4. Relationship between Pharmacological Effect ($E$) and Plasma Concentration of Ozagrel ($C_p$) after Intravenous Infusion, Oral and Rectal (50 mg and 200 mg) Administration of Ozagrel to Rabbits

The shaded part represents a variable range simulated using inter-individual variations (S.D.) of $IC_{50}$ and $E_{max}$.

lower and higher dosing is illustrated in Fig. 4. The curve in the middle of the shaded area represents a simulation of the plasma concentration and effect relationship of ozagrel, calculated by Eq. 5 using average values of $IC_{50}$ and $E_{max}$, i.e. $56.0 ± 44.0 \text{ng/ml}$ and $94 ± 6\%$ (mean ± S.D.; $n = 6$), respectively. Clearly, the observed data fall in the variable range (i.e., shaded part) estimated from the

Fig. 5. Changes in Serum TXB$_2$ Levels after Intravenous Infusion (A), Oral (B) and Rectal (C, 200 mg; D, 50 mg) Administration of Ozagrel to Rabbits

Each point and bar represent the mean ± S.D. of three rabbits. The solid lines show the simulated curves according to the STELLA model illustrated in Fig. 1. The pharmacokinetic parameters used in the simulation model are given in the legend to Fig. 2, and the pharmacodynamic parameters used are $IC_{50} = 56.0 ± 44.0 \text{ng/ml}$ and $E_{max} = 94 ± 6\%$ (mean ± S.D.; $n = 6$). The shaded parts represent variable ranges simulated using inter-individual variations (S.D.) of $IC_{50}$ and $E_{max}$.

Integrated Simulation of PK/PD

The estimated $IC_{50}$ and $E_{max}$ were utilized in an integrated PK/PD model (Fig. 1) to simulate the TXB$_2$ vs. time profiles after i.v. infusion, oral, and rectal (200 or 50 mg) administration, and the obtained result is presented in Fig. 5. Clearly, a good fit between the experimental and simulated values was achieved.

DISCUSSION

Dosage regimens of thromboxane synthetase inhibitors in clinical practice have been based mainly on empirical
grounds. However, in order to maximize the efficacy/toxicity ratio of these drugs, therapeutic protocols should be designed based on adequate understanding of their PK/PD in a quantitative and comprehensive manner. Among the four basic models (models I–IV) recently proposed by Dayekha et al.15 to describe the pharmacodynamics of drugs with mechanisms producing indirect responses, we have applied model I to ozagrel, where the direction of the pharmacologic response is inhibition and the factor affected is the input of response control.

A marked reduction of serum TXB2 was exhibited after the three routes of administration, reflecting rapid onset of action. Serum TXB2 returned to the basal levels more slowly after oral dosing than after i.v. dosing, due to slower absorption and elimination of ozagrel after the oral route. Due to rapid and complete absorption (i.e., T_{max}: 20 min, bioavailability: 100%) and longer duration of pharmacological action after rectal dosing, the rectum offers a practical delivery route for ozagrel.

In the present pharmacodynamic model, the pharmacologic effect of ozagrel was modeled as an inhibiting factor of R_{syn}, this is due to the fact that the level of TXB2 is the function of the rates of TXB2 synthesis and degradation,16 and that ozagrel inhibits TXA2 synthetase.17 However, since the interval of blood sampling was not always short enough to accurately calculate the synthesis rate of TXB2 at a specific time point (i.e., middle of the two sampling times), we first estimated the IC_{50} value from the plasma ozagrel concentration vs. serum TXB2 relationship (Fig. 4) and incorporated the value into the IC_{50} of TXA2 synthetase inhibition. The feasibility of this procedure was confirmed by our preliminary simulation which showed that the two IC_{50} values for \( E(TXB_2) \) and \( E(R_{syn}) \) had a ratio of nearly 1. This can be explained by the large \( k_{deg} \) value that made the time-lag between the inhibition of \( R_{syn} \) and TXB2 negligible. Clearly, the serum TXB2 is a direct pharmacological marker for a TXA2 synthetase inhibitor, and can be easily monitored in clinical settings where one cannot frequently sample blood from patients.

A sigmoid \( E_{max} \) model, in which another parameter \( N \) is added to Eq. 5, is expressed as follows:

\[
E(TXB_2) = \frac{E_{max} \cdot C_R}{IC_{50}(TXB_2) + C_R} \tag{8}
\]

The number \( N \) makes the curve steeper when it is greater than 1 and shallower when less than 1. When Eq. 8 was employed to fit the data (Fig. 4), \( N \) values were determined to be about 1.0. Therefore, for simplification of the pharmacodynamic analysis, \( N \) was fixed at unity so that the sigmoid \( E_{max} \) model was reduced to the \( E_{max} \) model (Eq. 5).

The PK/PD model developed in this study provided good agreement between simulated and experimental data, indicating the feasibility of the model to simulate the pharmacological effect of ozagrel. The \textit{in vivo} IC_{50} was estimated to be 56 ng/ml (or 245 nM) in rabbit. This is a reasonable value, because the product of this \textit{in vivo} IC_{50} value and the fraction unbound in plasma (i.e., \( f_u = 0.28 \)) is 69 nM, which is relatively close to an \textit{in vitro} IC_{50} value (4–21 nM) for rabbit platelets.17 Moreover, we have found that the same pharmacodynamic model can be successfully applied to human subjects (manuscript in preparation).

In conclusion, we have established a PK/PD model to simulate the plasma concentrations and pharmacological effects of ozagrel after i.v. infusion, oral, and rectal administration in rabbits. Provided that the TXB2 concentrations reflect the clinical benefit of ozagrel, the integrated PK/PD model may be useful for optimizing its therapeutic regimens.

**APPENDIX**

Equations for the PK/PD model described in Fig. 1.

**Submodel A:**

\[
X_1(\cdot) = X_1(\cdot) + (\text{Transer21}_{1} + \text{dosing} - \text{Elimination}_{1} - \text{Transfer12}_{1}) \cdot dt
\]

\[
\text{INIT} X_1(\cdot) = 0
\]

**INFLOWS:**

\[
\text{Transer21}_{1} = k_{21} \cdot X_2(\cdot)
\]

\[
\text{dosing} = \text{Dose}_{1}\cdot \text{inf}_{1}\cdot \text{duration}_{inf} \cdot \text{inf}_{duration}
\]

**OUTFLOWS:**

\[
\text{Elimination}_{1} = k_e \cdot X_1(\cdot)
\]

\[
\text{Transfer12}_{1} = k_{12} \cdot X_1(\cdot)
\]

\[
X_2(\cdot) = X_2(\cdot) + (\text{Transfer12}_{1} - \text{Transfer21}_{1}) \cdot dt
\]

\[
\text{INIT} X_2(\cdot) = 0
\]

**INFLOWS:**

\[
\text{Transfer12}_{1} = k_{12} \cdot X_1(\cdot)
\]

**OUTFLOWS:**

\[
\text{Transert1}_{2} = k_{21} \cdot X_2(\cdot)
\]

\[
G_{iv} = X_1(\cdot)\cdot Vc
\]

**Submodel B:**

\[
X_{1,p0}(\cdot) = X_{1,p0}(\cdot) + (\text{Absorption}_{po} + \text{Transfor21}_{po} - \text{Elimination}_{po} - \text{Transfer12}_{po}) \cdot dt
\]

\[
\text{INIT} X_{1,p0} = 0
\]

**INFLOWS:**

\[
\text{Absorption}_{po} = k_a \cdot po \cdot X_d
\]

\[
\text{Transfor21}_{po} = k_{21} \cdot X_2(\cdot)
\]

**OUTFLOWS:**

\[
\text{Elimination}_{po} = k_e \cdot X_{1,po}
\]

\[
\text{Transfer12}_{po} = k_{12} \cdot X_1(\cdot)
\]

\[
X_{2,p0}(\cdot) = X_{2,p0}(\cdot) + (\text{Transfer12}_{po} - \text{Transfer21}_{po}) \cdot dt
\]

\[
\text{INIT} X_{2,p0} = 0
\]

**INFLOWS:**

\[
\text{Transfer12}_{po} = k_{12} \cdot X_1(\cdot)
\]

**OUTFLOWS:**

\[
\text{Transert1}_{2} = k_{21} \cdot X_2(\cdot)
\]

\[
X_d(\cdot) = X_d(\cdot) + (\text{Absorption}_{po} \cdot dt)
\]

\[
\text{INIT} X_d = 0
\]

**INFLOWS:**

\[
\text{Absorption}_{po} = k_a \cdot po \cdot X_d
\]

\[
G_{po} = X_1(\cdot) \cdot V_c
\]

**Submodel C:**

\[
X_{1,ir}(\cdot) = X_{1,ir}(\cdot) + (\text{Absorption}_{ir} + \text{Transfor21}_{ir} - \text{Elimination}_{ir} - \text{Transfer12}_{ir}) \cdot dt
\]

\[
\text{INIT} X_{1,ir} = 0
\]

**INFLOWS:**

\[
\text{Absorption}_{ir} = k_a \cdot ir \cdot X_d
\]

\[
\text{Transfor21}_{ir} = k_{21} \cdot X_2(\cdot)
\]

**OUTFLOWS:**

\[
\text{Elimination}_{ir} = k_e \cdot X_{1,ir}
\]

\[
\text{Transfer12}_{ir} = k_{12} \cdot X_1(\cdot)
\]

\[
X_{2,ir}(\cdot) = X_{2,ir}(\cdot) + (\text{Transfer12}_{ir} - \text{Transfer21}_{ir}) \cdot dt
\]

\[
\text{INIT} X_{2,ir} = 0
\]
December 1995

IN defends:
Transfer12._ir = k12*X1._ir

OUT defense:
Transfer21._ir = k21*X2._ir
Xd_ir(t) = Xd_ir(t - dt) + (Absorption._ir) * dt
INIT Xd_ir = Dose_ir * F_ir

OUT defense:
Absorption._ir = ka._ir * Xd_lr
Cp_ir = X1._ir / V

Submodel D:

TXB2(t) = TXB2(t - dt) + (Synthesis_ - Degradation_)* dt
INIT TXB2 = 100

IN defense:
Synthesis_ = Rsyn_ - Emax_*Cp_ / (IC50_+Cp_)

OUT defense:
Degradation_ = km_ * TXB2
Rsyn_ = 100 * km
Cp_ = if Route_of_administration=0 then Cp_lv else if Route_of_administration=1 then Cp_po else if Route_of_administration=2 then Cp_ir else 0
Route_of_administration = 0

DOCUMENT: One can select a route of administration by setting this parameter as follows:
Intravenous: 0
Oral: 1
Rectal: 2

REFERENCES