Pharmacokinetic and Pharmacodynamic Modeling of a Novel Thromboxane Synthetase Inhibitor, DP-1904, in Human

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Summary

Pharmacokinetic and pharmacodynamic (PK/PD) analyses for a novel thromboxane synthetase inhibitor, DP-1904, were performed to predict its PK/PD profiles in human after single and repeated oral administration. The pharmacodynamics of DP-1904 was characterized by serum levels of thromboxane B₂ (TXB₂), a pharmacological marker for thromboxane synthetase inhibition. Based on a quantitative relationship between the plasma DP-1904 and serum TXB₂ concentrations after single oral dosage, IC₅₀ and E_{max} values were estimated to be 0.54 ng/ml and 94%, respectively. An integrated, simple PK/PD model was developed to simulate the changes in serum TXB₂ levels after single oral administration of DP-1904 at various doses, and the simulation curves corresponded well with the observed data. The PK/PD model was then used to predict a pharmacological profile of DP-1904 after repeated oral doses in human; the predicted curves were in relatively good agreement with the observed data. Thus, it is suggested that our PK/PD model is feasible and practical for developing optimum dosing regimens of DP-1904 in clinical situations.

Key words : DP-1904, Thromboxane synthetase inhibitor, Pharmacokinetics, Pharmacodynamics, Human, STELLA model

Introduction

Recently, selective thromboxane synthetase inhibitors have been studied and developed for the treatment of asthma and cardiovascular diseases¹⁻⁴⁾. However, there have been only qualitative knowledge on the PK/PD relationships of these drugs in human⁵⁻⁸⁾ so far. We have fabricated an integrated mathematical model to predict the pharmacokinetics and pharmacodynamics (PK/PD) of ozagrel, a new thromboxane synthetase inhibitor, in rabbits (manuscript submitted for publication). In this study, therefore, we applied our model to predict the PK/PD profiles of DP-1904 (**Fig. 1**) in human subjects, in order to provide a rational basis for optimizing the therapeutic regimens of thromboxane synthetase inhibitors. The pharmacodynamic part of our model is based on a scheme (**Fig. 2**) that TXB₂ is synthesized with a zero-order rate constant (R_{syn}) and degraded with a first-order rate constant (k_{deg}), and that DP-1904 inhibits the production of TXB₂ by inhibition of R_{syn} . Thus, the pharmacodynamic model of ozagrel is analogous to those of an anticoagulant drug, warfarin⁹⁾, a fibrinogen receptor antagonist, L-703,014¹⁰⁾, and an aldose reductase inhibitor, AL 1576¹¹⁾.

Subjects and Methods

Plasma DP-1904 and serum TXB₂ concentration data after single and repeated oral administration of DP-1904 in normal human volunteers^{7,8)} were supplied by Daiichi Pharm. Co. (Tokyo, Japan). These

Fig. 1 The chemical structure of DP-1904.

Fig. 2 An illustration of pharmacodynamic indirect response model for DP-1904 characterized by its inhibition of TXB₂ synthesis.

data were used for further analyses to estimate the PK/PD parameters of the drug in human as described below. All the fitting procedures were conducted on a personal computer (PC-9801DA, NEC, Tokyo, Japan) using a nonlinear least-squares regression analysis, MULTI¹², implemented in S-CALC¹³.

Pharmacokinetic Analysis

For single oral administration at several different doses (i.e. 10, 20, 50, 100, 200, and 400 mg) of DP-1904, the plasma concentration data were simultaneously fitted to the following three-exponential equation, assuming linear pharmacokinetics:

$$C_p = D \cdot \{A \cdot e^{-\alpha(t-t_0)} + B \cdot e^{-\beta(t-t_0)} - (A+B) \cdot e^{-\gamma(t-t_0)}\} \quad (1)$$

where C_p is the plasma concentration ($\mu\text{g/ml}$) of DP-1904; D is the dose administered (μg); α , β , and γ represent the hybrid constants for the slopes of plasma concentration-time curves; A and B are the intercepts of monoexponential lines with the slopes of α and β , respectively; t is the time after dosing; and t_0 is the lag time for drug absorption. The above-obtained parameters (i.e., A , α , B , β , γ , and t_0) were used to predict drug concentrations in plasma after repeated oral dosing, according to the following equation:

$$C_p = D \cdot \left\{ A \cdot \frac{1 - e^{-n \cdot \alpha \cdot \tau}}{1 - e^{-\alpha \cdot \tau}} \cdot e^{-\alpha(t'-t_0)} \right\} + \left\{ B \cdot \frac{1 - e^{-n \cdot \beta \cdot \tau}}{1 - e^{-\beta \cdot \tau}} \cdot e^{-\beta(t'-t_0)} \right\} - \left\{ (A+B) \cdot \frac{1 - e^{-n \cdot \gamma \cdot \tau}}{1 - e^{-\gamma \cdot \tau}} \cdot e^{-\gamma(t'-t_0)} \right\} \quad (2)$$

where τ is the dosing interval, n is the number of doses given, and t' is the time after the n -th dosing.

Pharmacodynamic Analysis

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

$$E(\text{TXB}_2) = \frac{\text{TXB}_2^0 - \text{TXB}_2}{\text{TXB}_2^0} \times 100 \quad (3)$$

where TXB₂ denotes the serum TXB₂ level at a designated time after dosing, and TXB₂⁰ is the premedicated level of TXB₂. The relationship between the plasma DP-1904 concentration (C_p) and pharmacological effect of DP-1904, $E(\text{TXB}_2)$, was fitted to the following equation:

$$E(\text{TXB}_2) = \frac{E_{\max} \cdot C_p}{\text{IC}_{50}(\text{TXB}_2) + C_p} \quad (4)$$

where $\text{IC}_{50}(\text{TXB}_2)$ is the drug concentration which yields 50% of the maximum TXB_2 inhibition; $E_{\max}$ is the maximum TXB_2 inhibitory effect. The estimated $E_{\max}$ and $\text{IC}_{50}(\text{TXB}_2)$ after oral dosage were used to simulate the PK/PD profiles after oral single doses, and further to predict them after oral repeated dose.

Integrated PK/PD Simulation

The PK/PD model for ozagrel developed in rabbits (submitted for publication) was employed to predict the PK/PD profiles of DP-1904 in human. The simulation was conducted on a Macintosh computer (Centris 660AV) with a mathematical co-processor using a program of STELLA (High Performance System, Inc., USA). The diagram of the STELLA model is shown in **Fig. 3**. STELLA program is a tool for model development and its numerical solution that allows us to easily and rapidly simulate complex kinetic processes. Due to its efficient capability, STELLA has been utilized in recent pharmacokinetic papers.^{14,15} As shown in **Fig. 3**, submodel A represents the pharmacokinetic part for oral dosing and submodel B corresponds to the pharmacodynamic part. This model enables one to easily change the dose and dosing interval for predicting the PK/PD of the drug after single or repeated oral dosing. The pharmacodynamic part of the model (submodel B) is based on a scheme that TXB_2 is synthesized with a zero-order rate constant (R_{syn}) and degraded with a first-order rate constant (k_{deg}), and that DP-1904 inhibits the production of TXB_2 by inhibition of R_{syn} . Therefore, the effect of DP-1904 is modeled as an inhibitory factor of R_{syn} . Thus, changes in serum TXB_2 can be expressed as:

$$\frac{d\text{TXB}_2}{dt} = R_{\text{syn}} - k_{\text{deg}} \cdot \text{TXB}_2 = R_{\text{syn}}^0 \left(1 - \frac{E_{\max} \cdot C_p}{\text{IC}_{50} + C_p} \right) - k_{\text{deg}} \cdot \text{TXB}_2 \quad (5)$$

where R_{syn}^0 represents TXB_2 synthesis rate before dosing and can be expressed as:

$$R_{\text{syn}}^0 = k_{\text{deg}} \cdot \text{TXB}_2^0 \quad (6)$$

where k_{deg} is the first-order degradation rate constant of serum TXB_2 and TXB_2^0 is the basal level of serum TXB_2 before dosing. Equation 6 was derived from Eq. 5, assuming a steady state before dosing (i.e., $d\text{TXB}_2/dt = 0$ and $C_p = 0$). Since a marked reduction of serum TXB_2 was exhibited after the administration of DP-1904 even at lower doses, the value of k_{deg} was assigned to be 6.0 hr^{-1} , a value large enough to explain the rapid fall of serum TXB_2 .

Results

The plasma concentration vs. time curves of DP-1904 at various oral doses were fitted simultaneously to Eq. (1), and the pharmacokinetic parameters obtained by the Simplex method are; $A = 7.74 \times 10^{-7} \text{ (ml}^{-1}\text{)}$, $\alpha = 0.232 \text{ (hr}^{-1}\text{)}$, $B = 3.33 \times 10^{-5} \text{ (ml}^{-1}\text{)}$, $\beta = 1.21 \text{ (hr}^{-1}\text{)}$, $\gamma = 11.2 \text{ (hr}^{-1}\text{)}$, and $t_0 = 0.445 \text{ (hr)}$. The calculated curves corresponded well with the observed data, as shown in **Fig. 4**.

The relationships between pharmacological effect (E) and plasma concentrations (C_p) of DP-1904 after oral dosages were fitted individually to Eq. (3) (a typical result shown in **Fig. 5**), and the obtained pharmacodynamic parameters are listed in **Table I**. The IC_{50} and $E_{\max}$ values were estimated to be $0.54 \pm 0.09 \text{ ng/ml}$ and $94 \pm 1 \%$ (mean $\pm$ S.E.M.; $n=6$), respectively.

Fig. 3 A diagram of STELLA model to simulate the PK/PD of DP-1904 in normal human volunteers after single or multiple repeated oral dosing. Panels A and B illustrate the submodels for pharmacokinetics and pharmacodynamics, respectively. In the lower part, the definition of each model symbol is described.

The above-obtained PK/PD parameters were then used to simulate the pharmacological profiles of DP-1904 at various oral doses, using the STELLA model shown in Fig. 3, **Fig. 6** illustrates the observed and simulated concentrations of serum TXB₂, which are in general agreement with each other. This suggests feasibility of the method of PK/PD parameter estimation.

Moreover, the PK/PD profiles of DP-1904 after repeated oral dosing (200 mg, twice a day for two days and 400 mg, once a day for two days) were predicted using the STELLA model, in which the above-obtained PK/PD parameters are incorporated. As shown in **Fig. 7** and **Fig. 8**, the predicted curves are in good correspondence with the observed data, indicating the feasibility of our PK/PD model.

Fig. 4 Plasma concentration profiles of DP-1904 after oral administration at various doses. Lines show the computer-generated fitting curves according to Eq. (1). (●) 400 mg, (○) 200 mg, (▲) 100 mg, (△) 50 mg, (■) 20 mg, (□) 10 mg.

Fig. 5 A typical relationship between serum level of TXB₂ (E) vs. plasma concentration of DP-1904 (C_p) after oral administration of 400 mg DP-1904. The line shows the fitting curve according to Eq. (4).

Table I Pharmacodynamic parameters of DP-1904 obtained from plasma DP-1904 and serum TXB₂ concentrations after oral doses in human

Dose (mg)	IC ₅₀ (ng/ml) ^{a)}	E _{max} (%) ^{a)}
10	0.45	96
20	0.67	96
50	0.58	90
100	0.90	93
200	0.26	94
400	0.40	95
Mean ± S.E.M.	0.54 ± 0.09	94 ± 1

^{a)} Estimated by a nonlinear least-squares regression, MULTI¹²⁾, implemented in S-CALC¹³⁾.

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 Dayneka *et al.*¹⁶⁾ to describe the pharmacodynamics of drugs with mechanisms producing indirect responses, we have applied the Model I to DP-1904, where the direction of the pharmacological response is inhibition and the factor affected is the input of response control. The estimated IC₅₀ (0.54 ng/ml) for DP-1904 in human is lower than that (11.8 ng/ml) for ozagrel in human¹⁷⁾, suggesting that DP-1904 is a potent and long acting thromboxane synthetase inhibitor compared with a marketed drug with the same mechanism of

Fig. 6 Serum TXB₂ changes after oral administration of DP-1904 in various doses. Lines show the simulated curves using pharmacokinetic parameters (see text) and pharmacodynamic parameters (Table I). Each point and vertical bar represent the mean $\pm$ S.D. ($n=5$). A; 10 mg, B; 20 mg, C; 50 mg, D; 100 mg, E; 200 mg, F; 400 mg.

action. The PK/PD model thus developed were in general agreement with the data taken at the wide dose range, as shown in Fig. 6. The exact reason for the moderate inconsistency between the simulated and observed TXB₂ values at the middle dose range (i.e., 50–100 mg) is not known in this study, but there might be another pharmacokinetic and/or pharmacodynamic factor to consider to fully accommodate the pharmacological effect of DP-1904 in human at various doses. Perhaps, the pharmacodynamic bias in the effect–drug concentration relationship (as in a typical example shown in Fig. 5) at 0.001–0.1

Fig. 7 Changes in plasma DP-1904 (A) and serum TXB₂ (B) concentrations after repeated oral administration (200 mg, twice a day for two days). The lines show the computer-generated predicted curves using pharmacokinetic parameters (see text) and pharmacodynamic parameters (Table I). Each point and vertical bar represent the mean $\pm$ S.D. ($n=5$).

Fig. 8 Changes in plasma DP-1904 (A) and serum TXB₂ (B) concentrations after repeated oral administration (400 mg, once a day for two days). The lines show the computer-generated predicted curves using pharmacokinetic parameters (see text) and pharmacodynamic parameters (Table I). Each point and vertical bar represent the mean $\pm$ S.D. ($n=5$).

μg/ml may be related to the inconsistency at the middle dose range.

In the present pharmacodynamic model, the pharmacological effect of DP-1904 was modeled as an inhibiting factor of R_{syn} ; this is because of the fact that the level of TXB₂ is the function of the rates of TXB₂ synthesis and degradation¹⁸⁾, and that DP-1904 inhibits TXA₂ synthetase²⁾. 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., the middle of the two sampling times), we first estimated the IC_{50} value from the plasma DP-1904 concentration vs. serum TXB₂ relationship (a typical result shown in Fig. 5) and incorporated this 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 $E(R_{syn})$ ($= (R_{syn}^0 - R_{syn}) / R_{syn}^0 \times 100$) had a ratio of nearly 1. This should 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 sample blood from patients in frequent times.

In conclusion, a simple mathematical model was assembled for predicting the PK/PD of DP-1904 in

human after single and repeated oral dosing. The PK/PD model was successfully applied to various doses and multiple dosing of DP-1904, and thus may be useful for developing optimum dosing regimens of the drug in clinical situations. Moreover, the present modeling procedure should be applied to other thromboxane synthetase inhibitors.

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Appendix 1. Equations for a PK/PD Model Described in Fig. 3.

Submodel A:

$$A = 0.000774 * \text{dose}$$

$$B = 0.0333 * \text{dose}$$

$$C_p = \text{if TIME} \geq \text{lag_time then } A * (1 - \text{EXP}(-n * \alpha * \tau)) / (1 - \text{EXP}(-\alpha * \tau)) * \text{EXP}(-\alpha * t') + B * (1 - \text{EXP}(-n * \beta * \tau)) / (1 - \text{EXP}(-\beta * \tau)) * \text{EXP}(-\beta * t') - (A + B) * (1 - \text{EXP}(-n * \gamma * \tau)) / (1 - \text{EXP}(-\gamma * \tau)) * \text{EXP}(-\gamma * t') \text{ else } 0.00001$$

$$n = \text{INT}((\text{TIME} - \text{lag_time}) / \tau) + 1$$

$$t' = \text{TIME} - (n - 1) * \tau - \text{lag_time}$$

Submodel B:

$$\text{TXB2}(t) = \text{TXB2}(t - dt) + (\text{Synthesis} - \text{Degradation}) * dt$$

$$\text{INIT TXB2} = 100$$

INFLOWS:

$$\text{Synthesis} = R_{\text{syn0}} - E_{\text{max}} * C_p / (EC_{50} + C_p)$$

OUTFLOWS:

$$\text{Degradation} = k_d * \text{TXB2}$$

$$R_{\text{syn0}} = 100 * k_d$$