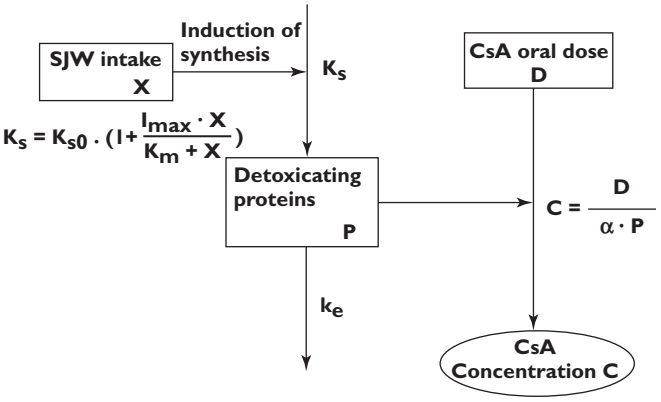

Figure 1

Pharmacokinetic and pharmacodynamic model of the interaction between SJW and CsA. X is the daily intake of SJW (mg day^{-1}), K_s is the rate constant of synthesis of detoxicating proteins (AU/month), k_e is the elimination rate constant of the detoxicating proteins (/month), P is the amount of the detoxicating proteins (AU), D is the daily dose of CsA (mg day^{-1}), C is CsA trough blood concentration (ng ml^{-1}), K_{s0} is the rate constant of detoxicating proteins in the absence of SJW (AU/month), I_{max} is the maximal induction potency of SJW for detoxicating proteins, K_m is the dose of SJW required to induce half-maximal induction (mg day^{-1}), and α is a constant ((ng ml^{-1})/(mg day^{-1})/AU)

The intake of SJW is considered to increase K_s. The analysis in the previous section demonstrated that the extent of decrease in the C/D ratio of CsA is saturable and SJW dose-dependent. Therefore, K_s can be described by equation 2:

$$K_s = K_{s0} \cdot \left(1 + I_{max} \cdot \frac{X}{X + K_m}\right) \quad (2)$$

where K_{s0}, X, I_{max} and K_m represent a zero-order synthesis rate constant of P in the absence of SJW (AU/month), the daily dose of SJW (mg day^{-1}), the maximal induction potency of SJW for P and the dose of SJW required to induce half-maximal induction (mg day^{-1}), respectively. In each case, the C/D ratio was assumed to be in inverse proportion to P for each patient. The relationship between C and D can be represented by equation 3:

$$C = \frac{D}{\alpha \cdot P} \quad (3)$$

where C, D and α represent the trough blood concentration of CsA (ng ml^{-1}), the daily dose of CsA (mg day^{-1}) and a constant ((mg day^{-1})/(ng ml^{-1})/AU), respectively. Equation 3 can be rewritten as follows:

$$P = \frac{1}{\alpha} \cdot \frac{D}{C} \quad (3')$$

Substituting equation 3′ into equation 1 gives equation 4:

$$\frac{d\frac{D}{C}}{dt} = \alpha \cdot K_s - k_e \cdot \frac{D}{C} \quad (4)$$

Substituting equation 2 into equation 4 gives equation 4′:

$$\frac{d\left(\frac{C}{D}\right)^{-1}}{dt} = \alpha \cdot K_{s0} \cdot \left(1 + \frac{I_{max} \cdot X}{X + K_m}\right) - k_e \cdot \left(\frac{C}{D}\right)^{-1} \quad (4')$$

Model analysis

Equation 4′ was simultaneously fitted to the time profiles of C/D ratio for all the cases, taking the dose profiles of SJW as input functions, by using a nonlinear least-squares method (MLAB, Civilized Software Inc., MD, USA) to obtain common pharmacokinetic parameters, I_{max}, K_m and k_e, and an individual parameter for each case, $\alpha \cdot K_{s0}$. The K_m value was modelled based on a log-normal distribution.

Results

Analysis of the dose–response relationship of SJW for the induction of the detoxicating proteins

The increase in the steady-state D/C ratio of CsA by SJW was dose-dependent and described by saturable Michaelis-Menten kinetics, suggesting that the induction of detoxicating proteins by SJW is saturable (Figure 2).

Model analysis

As a result of model analysis, I_{max}, K_m and k_e were calculated to be 2.61, 428 (mg day^{-1}) and 4.72 (/month), respectively. Moreover the individual parameter values $\alpha \cdot K_{s0}$, ranged from 3.33 to 10.0 ((mg day^{-1})/(ng ml^{-1})/month) (Table 2). The developed model could adequately explain the observed time profile of the C/D ratio in each case (Figure 3).

Discussion

We have reported a pharmacokinetic model to explain the mechanism-based inhibition of CYP3A4 by grapefruit juice in which the turnover of CYP3A4 protein was incorporated. The model provided the dosing-interval dependency of the extent of interaction based on the time-dependent changes of the active CYP3A4 content [14]. With regard to the induction of detoxicating protein(s), model analysis based on the turnover of protein(s) has not been carried out. CsA concentration is decreased as a result of the induction of detoxicating proteins by SJW intake. Therefore, we employed the C/