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Robust parameter estimation for physiologically based pharmacokinetic model of Tegafur with dissolution dynamics

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ABSTRACT

Physiologically based pharmacokinetics (PBPK) model can predict absorption, distribution, elimination and metabolism in a drug delivery system. While PBPK model is generally expressed as a set of ordinary differential equations with a large number of parameters, *in vivo* experimental data are often noisy and sparse. This makes it difficult to estimate parameters with conventional least squares approach. To address this problem and improve prediction accuracy of PBPK model, this work proposes a covariance based parameter estimation scheme and dissolution dynamics model for PBPK of Tegafur after oral administration. Unknown parameters of the PBPK model are estimated by a maximum a posteriori method where the covariance matrix of the parameter estimates is calculated by simulation. Its diagonal entries represent the prior information of the parameters, while off-diagonal entries represent correlations among the parameters. The proposed estimation scheme demonstrated an improved performance in terms of variance of the parameter estimates and concentration predictions. In addition, incorporation of dissolution dynamics provided more accurate prediction than conventional PBPK models.

1. Introduction

The drug discovery process takes an enormous amount of time, money, and effort. Nevertheless, to prevent side-effects of a drug and find an optimal dosage, a large number of tests need to be conducted on various subjects. However, experiments of a new drug on human carry a great risk, because the toxicity and side-effects of a new drug are often unknown. Mathematical models describing drug delivery mechanisms in terms of drug concentrations in each organ over a time course can be of significant help in reducing the cost of development and the risk of failure. Therefore, time-course data are collected to construct physiologically based pharmacokinetics (PBPK) models during animal and human trials (Phases I–III) (Gehring et al., 1979). Pharmacokinetics (PK) is the study of absorption, distribution, metabolism, and excretion of the chemicals in a living body, and plays an important role in the development of drugs (Kang et al., 1997; Lindsey et al., 2000). The PBPK model includes mechanistic and physiological basis describing the pharmacokinetics of drugs within a biological entity (Andersen et al., 1987). If a PBPK model is constructed, it can be used not only for the

Abbreviations: PBPK, physiologically based pharmacokinetic; DDM, drug dissolution model; MLE, maximum likelihood estimation; MAP, maximum a posteriori; MCMC, Markov chain Monte Carlo; Var-MAP, variance-based maximum a posteriori; Cov-MAP, covariance-based maximum a posteriori.

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prediction of PK profiles of drugs, but also for dose regulation as in feedback control strategies (Gehring et al., 1979). Therefore, the PBPK model can also allow for determination of the optimal dosage and administration time (Zhao et al., 2010).

Because PBPK models are only concerned with the dynamics inside a body, they commonly include a number of organs and blood vessels. However, drug dissolution dynamics is usually not considered. In the past, most medicines with serious side-effects or dosage sensitivity were usually in the form of a liquid, because they need to be absorbed quickly (Lasagna and Beecher, 1954). Since this type of drugs is absorbed at a high rate, drug dissolution dynamics could be ignored. However, with the recent development of various drug dosage forms, some drugs are produced in the form of a tablet or capsule to control the dissolution rate (Davis et al., 1986; Dressman et al., 1998). Since the dissolution dynamics of medicine in a non-liquid form is an important part of the drug's PK profile, it is necessary to describe the dissolution dynamics when constructing a PBPK model. In addition, the dissolution rate of drugs for individuals will be very different with a large variance because of their physical properties and individual genotypic variations (Kroetz et al., 2010). It is also impossible to collect dissolution data for every patient to estimate a personal dissolution rate. In this manner, the dissolution parameter would be better described as a probability distribution to reflect personal differences. Nevertheless, PBPK and drug dissolution models have been developed and their parameters have been estimated independently. Therefore, development of a model that combines PBPK and drug dissolution dynamics in a compatible manner can help to provide reasonable estimates of the dissolution parameters in a lumped form, which can also reflect personal differences of each patient.

PBPK models involve both physiological and kinetic parameters. Physiological parameters, include organ volume, blood flow rate, and blood volume, etc. Kinetic parameters include absorption rate and Michaelis–Menten constants for enzyme reactions. Whereas physiological parameters can be measured or specified easily, kinetic parameters are generally difficult to specify (Brown et al., 1997). Therefore, unknown parameters should be estimated with experimental data. However, experiments to collect *in vivo* data are expensive, and often have poor repeatability (Coleman and Block, 2006). Estimating the parameters of a PBPK model with such poor data sets is further complicated by the concentration profiles, which show a pattern of declining exponential functions, with amplitudes and decay times (Gelman et al., 1996). In addition, since each individual may have different parameter values depending on their own physiological properties, the drug concentration profiles can vary between test subjects. With these uncertainties, parameters can be treated as random variables and described by probability distributions. The least squares method is the most widely used estimation method, and finds the point estimate of the parameters by minimizing the sum of squared errors between actual observations and predictions. Since there is no probabilistic structure in the least squares method, it is sensitive to the presence of unusual data points; one or two outliers can sometimes seriously skew the results, thus raising the requirement for a large number of data points. However, the number of available *in vivo* drug concentration data points is often limited, and involves a high degree of uncertainty. This requires a robust estimation method which would be suitable for PBPK models.

Statistical inference based on Bayes' rule can be used for parameter estimation of the PBPK model. In particular, the maximum a posteriori (MAP) principle is one of the Bayesian inference methods considering the prior information on the parameter and differences between model outputs and experimental observations (Kay, 1993). Because the prior knowledge is incorporated into the estimation, MAP methods can be more robust than the least squares or maximum likelihood estimation (MLE) methods (Harrison and Stevens, 1976; Marrelec et al., 2003), and can provide more accurate estimates when the data are contaminated with noise, or when the number of data points is small (Kay, 1993). For simple PK models with one or two model equations, the MAP method is easy to implement because the model parameters are nearly uncorrelated. In this case, the parameter distribution obtained from *in vitro* experiments can be used as the prior information (Laínez et al., 2011). However, model parameters are often correlated since the organs are interconnected by blood vessels. While the prior information cannot be incorporated into a MAP method without information on the parameter correlations, i.e., covariance matrix, a large number of experimental data sets are necessary for estimating the correlations between each pair of parameters (Jang and Gopaluni, 2011).

This study presents a PBPK model augmented with dissolution dynamics and a robust parameter estimation scheme, given a limited number of data sets. The maximum a posterior (MAP) method is used to estimate the parameters of the PBPK model. The covariance matrix in prior distribution is calculated by simulation. With the prior distribution and likelihood, the objective function of the MAP method is minimized for optimal parameter estimation. The proposed model and estimation scheme are illustrated with a PBPK model for a rat with Tegafur administration, and are also compared with a conventional least squares method and a MAP estimation method ignoring parameter correlations.

2. Materials and methods

2.1. Materials

Tegafur is widely used in the treatment of a range of cancers, especially colorectal cancer (Jonsson and Johanson, 2003). It is an orally administrated drug, and is transformed to 5-fluorouracil by the enzyme CYP450 in the liver, thereby performing pharmacological action. 5-fluorouracil is subsequently degraded by the enzyme DPD in the liver (Sakata et al., 1998). The *in vivo* data collected from experiments on rats and orally administrated Tegafur were adapted from Sung et al. (2009).

2.2. Model development

The PBPK model can be constructed by three kinds of differential equations. The first describes the transportation and metabolism of the medicine, based on mass balance:

$$V \cdot \frac{dC}{dt} = Q \cdot \left(C_{in} - \frac{C}{P} \right) - R_e \quad (1)$$

where V is the organ volume, Q is the volumetric flow rate of blood in the organ, C_{in} is the drug concentration going into the organ, and C is the drug concentration in the organ. P is the tissue/blood partition coefficient of the organ, and describes the proportion of blood volume in the organ. R_e is the consumption term due to the metabolism in the organ, such as degradation, transformation and excretion. Since a drug is transformed by