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Prediction of Apparent Oral Clearance of Small-Molecule Inhibitors in Pediatric Patients

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ABSTRACT

The purpose of this study was to build regression models for the prediction of apparent oral clearance (CL/F) for small-molecule inhibitors in the pediatric population using data obtained from adults. Two approaches were taken; a simple allometric regression model which considers no interdrug or interindividual variability and an allometric regression model with mixed-effects modeling where some variability parameters are included in the model. Average CL/F values were obtained for 15 drugs at various dosages from 31 literatures (a total of 139 data sets) conducted in adults and for 15 drugs from 26 literatures (62 data sets) conducted in children. Data were randomly separated into the "modeling" or "validation" data set, and the 2 allometric regression models were applied to the modeling data set. The predictive ability of the models was examined by comparing the observed and model-predicted CL/F in children using the validation data set. The percentage root mean square error was 17.2% and 26.3% in the simple allometric regression model and the allometric regression model with mixed-effects modeling, respectively. The predictive ability of the 2 models seems acceptable, suggesting that they could be useful for predicting the CL/F of new small-molecule inhibitors and for determining adequate doses in clinical pharmacotherapy for children.

Introduction

The initial doses of drugs used to treat pediatric patients require thorough consideration of the physiological differences, the variation in body composition, and the functions of the liver and kidneys in children.[1] In the recent years, there has been greater emphasis on evaluating the pharmacokinetics of drugs for conducting clinical studies in pediatric patients,[2] and appropriate doses in children in terms of both safety and efficacy are often determined based on pharmacokinetic knowledge of the drug in adults. To evaluate the pharmacokinetics of a drug in pediatric subjects, a clinical study is required; but this is often difficult, primarily due to ethical issues (e.g., a series of blood samples cannot be easily obtained from children). Therefore, information regarding the pharmacokinetics of drugs is often limited in clinical situations. Nevertheless, clinicians are facing the problem of determining what constitutes an adequate dose of a drug in a clinical pharmacotherapy context with respect to drug safety and efficacy. In such a situation, it is useful and usually necessary to be able to predict the pharmacokinetics of drugs, especially pharmacokinetic parameters such as clearance (CL) or exposure (area under the curve [AUC]) in children.[2]

Small-molecule inhibitors exert an antitumor effect by inhibiting tumor cell proliferation and several types of these have been developed.[3] Although these drugs were originally developed for use in adult patients with cancer, several drugs have been reported to be effective in pediatric patients.[4,5] When clinicians prescribe these drugs for pediatric patients, the appropriate dose should be determined; however, information on the pharmacokinetics and dose recommendation of small-molecule inhibitors is unavailable in documents such as package inserts.

Over the years, several methods for predicting CL in children from data obtained from adults have been reported.[6-12] In the recent years, there has been growing interest in physiologically based pharmacokinetic (PBPK) models for the prediction of pharmacokinetic parameters in pediatric medicine.[6] Maharaj et al. reported on the prediction of the pharmacokinetics and dose requirements of lorazepam in pediatric patients aged 0-18 years,[7] and CL and the volume of distribution at steady state ($V_{d,ss}$) in children are predicted with reasonable accuracy. In another approach,

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allometric modeling is used to predict pharmacokinetic parameters in pediatric subjects.[8] Allometric modeling using body weight or age as independent variables is simple and useful in predicting pediatric CL from CL in adults.[9] Other models, for example, those including maturation processes, have also been proposed.[10,11] In this study, we also constructed regression models based on allometric modeling. In addition, a mixed-effects modeling (MEM) approach was applied for the prediction of pharmacokinetic parameters in pediatric subjects. Shimamura et al.[12] demonstrated that 15 selected β-lactam antibiotics could be defined as a "drug population," and pharmacokinetic parameters in children were predicted based on an empirical Bayesian method. This was a unique strategy whereby a selection of drugs with similar structures was grouped into a "population," and the concept of population analysis was applied. In a similar way, we assumed that some small-molecule inhibitors could be defined as a "drug population" and attempted to build an allometric regression model to predict apparent oral clearance (CL/F, where F is oral bioavailability).

The purpose of this study was to build regression models for predicting CL/F in the pediatric population using data derived from the adult population for small-molecule inhibitors. Two allometric approaches, a simple allometric model, which did not consider interdrug variability, and an allometric regression model with MEM where variability parameters were included, were tested in this study. The model used here can be mathematically called a log-transformed "power model," but we use a term "allometric model" which we thought more familiar in the pharmacokinetic field.

Methods

Collection of Pharmacokinetic Data

The pharmacokinetic data, that is, the values for CL/F of small-molecule inhibitors, were obtained by a literature search using PubMed. The literature published from 2000 to 2015 was searched using the keywords "(pharmacokinetic OR pharmacokinetics) AND "drug name" AND (children OR pediatric) OR adult," with "drug name" referring to an individual drug. The details of the procedure are shown in Figure 1. Only literatures regarding phase I were selected for adults. Exclusion criteria were (1) cases where other drugs were coadministered, (2) when no data were explicitly given for CL/F or AUC, and (3) there was an insufficient number of subjects

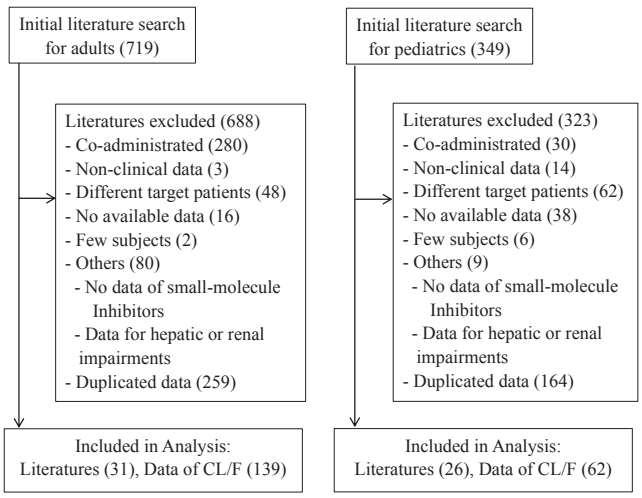

Figure 1. Flow charts of the data selection processes.

to obtain robust average values (we defined this as being less than 3). The collected data included the number of subjects, the median (or mean) age, gender, the dose of drugs, and the mean values for CL/F (CL/F/BSA for pediatric studies, where BSA is body surface area and CL/F per body for adult subjects) for each dose used in the literature. When CL/F was not given, it was calculated using the values for dose and AUC, which were provided, based on Equation 1.

$$\mathrm{CL/F(L/hr)} = \frac{\mathrm{Dose(mg)}}{\mathrm{AUC(\mu g \cdot h/mL)}} \tag{1}$$

These data were randomly divided into 2 data sets for model building (modeling data set) and for model validation (validation data set). In the following sections, we refer to CL/F in adults and in children as $\mathrm{CL/F_{adults}}$ and $\mathrm{CL/F_{ped}}$, respectively.

Simple Allometric Regression Modeling

In the simple allometric regression model, we did not consider interdrug variability for the relationship between $\mathrm{CL/F_{adults}}$ and $\mathrm{CL/F_{ped}}$. The model equation with a logarithmic scale is given as follows:

$$\log\left(\mathrm{CL}\middle/\mathrm{F_{ped}}\right) = \mathrm{A} + \mathrm{B}\cdot\log(\mathrm{CL/F_{adults}}) \tag{2}$$

where A and B are the intercept and the slope, which were estimated by a regression analysis. We assumed linear pharmacokinetics, that is, drug CL/F is theoretically the same among different doses. In cases where the mean values for CL/F at several different doses were reported in the same study, we calculated the "mean of the reported CL/F" and a pair of these means for $\mathrm{CL/F_{adults}}$ and $\mathrm{CL/F_{ped}}$ for each reference was used in the regression analysis. The predictive ability of the simple allometric regression model was evaluated using the validation data set by comparing observed values and the model-predicted values. Microsoft Excel 2013® was used for data handling and statistical analysis.

Allometric Regression With Mixed-Effects Modeling

In the allometric regression model with MEM, we regarded the drugs in the modeling data set as components of a "drug population" and a concept of MEM which is usually applied to population pharmacokinetics was applied using the software NONMEM (Ver. 7.2; Icon Development Solutions, Ellicott City, MD).[13] In contrast to the simple allometric regression model, the reported CL/F values were used separately for the regression analysis. The model equation with a logarithmic scale is given by Equation 3:

$$\log\left(\mathrm{CL}\middle/\mathrm{F_{jk}}\right) = \log(\mathrm{a_j}) + \mathrm{Flag}\cdot\log(\mathrm{b_j}) + \varepsilon_{jk} \tag{3}$$

where $\mathrm{CL/F_{jk}}$ is a parameter for j-th drug in k-th dosage in either adults or children, the variable "Flag" is defined as 0 for adults and 1 for children, and $\mathrm{a_j}$ and $\mathrm{b_j}$ are the intercept and the slope for j-th drug. The parameter ε_{jk} is a random variable for "interdosage variability" of the same drug, assumed to be normally distributed with mean zero and variance σ^2.

The parameters $\mathrm{a_j}$ and $\mathrm{b_j}$ are defined by Equation 4:

$$\log(\mathrm{a_j}) = \log(\overline{a}) + \eta_{a,j}, \log(\mathrm{b_j}) = \log\left(\overline{b}\right) + \eta_{b,j} \tag{4}$$

where $\overline{a}$ and $\overline{b}$ are the population mean values for the intercept and the slope, and $\eta_{a,j}$ and $\eta_{b,j}$ are the random variables for interdrug variability for $\overline{a}$ and $\overline{b}$ which are assumed to be normally distributed with mean zero and variance ϖ_a^2 and ϖ_b^2, respectively. Nondiagonal