An Algorithm for Evaluating potential Tissue Drug Distribution in Toxicology Studies from Readily Available Pharmacokinetic Parameters

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ABSTRACT: Having an understanding of drug tissue accumulation can be informative in the assessment of target organ toxicities; however, obtaining tissue drug levels from toxicology studies by bioanalytical methods is labor-intensive and infrequently performed. Additionally, there are no described methods for predicting tissue drug distribution for the experimental conditions in toxicology studies, which typically include non-steady-state conditions and very high exposures that may saturate several processes. The aim was the development of an algorithm to provide semiquantitative and quantitative estimates of tissue-to-plasma concentration ratios (K_p) for several tissues from readily available parameters of pharmacokinetics (PK) such as volume of distribution (V_d) and clearance of each drug, without performing tissue measurement *in vivo*. The computational approach is specific for the oral route of administration and non-steady-state conditions and was applied for a dataset of 29 Genentech small molecules such as neutral compounds as well as weak and strong organic bases. The maximum success rate in predicting K_p values within 2.5-fold error of observed K_p values was 82% at low doses (<100 mg/kg) in preclinical species. Prediction accuracy was relatively lower with saturation at high doses (≥100 mg/kg); however, an approach to perform low-to-high dose extrapolations of K_p values was presented and applied successfully in most cases. An approach for the interspecies scaling was also applied successfully. Finally, the proposed algorithm was used in a case study and successfully predicted differential tissue distribution of two small-molecule MET kinase inhibitors, which had different toxicity profiles in mice. This newly developed algorithm can be used to predict the partition coefficients K_p for small molecules in toxicology studies, which can be leveraged to optimize the PK drivers of tissue distribution in an attempt to decrease drug tissue level, and improve safety margins. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3816–3829, 2013

Keywords: ADME; DMPK; disposition; distribution; partition coefficients; pharmacokinetics; tissue distribution; toxicology; volume of distribution; safety assessment

INTRODUCTION

The distribution of drugs into tissues, that is, tissue accumulation, is a recognized contributor to drug toxicity[1,2]; however, evaluation of tissue drug partitioning under *in vivo* condition is not routinely performed in toxicology studies, partly because it is resource-intensive. This issue can also be approached with physiologically based pharmacokinetics (PK) modeling, where the impacts of dosing regimen on tissue distribution can be predicted from description of its controlling processes, although this could be a data-intensive approach. Alternatively, it can be of interest to verify whether tissues can be treated as well-stirred compartments, and the influences of altered delivery through changes in blood flow can be neglected.[3–13] This premise assumes that the same physicochemical mechanisms are present in each tissue, and hence, relationships among drug tissue partitioning can be developed, comparably to a physiological approach. The challenge is that, being more empirical, the well-stirred compartment model may not totally account for the processes that determine the relationship of simple PK observations to tissue-specific and regimen-specific drug concentrations; processes such as nonlinear metabolism, saturation of binding, and non-steady-state distributions that depend on the dosing regimens and the interaction among uptake, redistribution, and tissue-specific clearance processes. Despite these limitations, consistent patterns of relative partitioning into various tissues can be identified that can allow reasonable estimate with less intensive data collection, for which the input parameters are readily available.[3–18]

Abbreviations used: AUC, area under the curve; BM, bone marrow; Clog *P*, log *n*-octanol–water ratio calculated; Cp*K*a, ionization constant calculated; Eh, hepatic extraction ratio; CL, clearance; fu_p, fraction unbound in plasma; fu_t, fraction unbound in tissue; fu_{cells}, unbound fraction in intracellular water; Gen, Genentech; *F*, bioavailability; λ, elimination rate constant; K_a, absorption rate constant; K_p, tissue-to-plasma concentration ratio; NCA, noncompartmental analyses; p*K*a, ionization constant; PO, per os; REP, erythrocyte-to-plasma ratio; V_d, volume of distribution; V_z, volume of distribution of the terminal phase.

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Theoretical Background

The endpoint is the estimation of values of tissue–plasma ratios (K_p), which are the parameters commonly used to estimate the degree to which a drug accumulate across tissues. For steady-state conditions after continuous intravenous infusions, consistent patterns of relative partitioning into various tissues were made by relaying some *in vitro* physicochemical properties of drugs to tissue composition data to predict the K_p values by considering the binding to tissue lipids and plasma proteins[14–18]; therefore, the predicted K_p values linearly correlated across tissues.[3,9] However, these *in vitro*-based calculation models did not cover the exposure conditions observed in toxicology studies such as oral route of absorption and non-steady-state conditions, and performed less accurately compared with models derived from *in vivo* data.[14,18] Alternatively, the *in vivo* K_p data may also be used to develop consistent patterns of relative tissue distribution into various tissues for any exposure condition. Moreover, several authors demonstrated that drug tissue partitioning, and, thus, the *in vivo* K_p values, correlated across tissues for several drugs.[3–7] Specifically, muscle K_p values correlate with K_p values of other tissues (e.g., brain, lung, liver, heart, skin, intestine, and red blood cells; r^2 mostly in the range of 0.60–1), irrespective of the chemical nature of the drug and exposure conditions. The established correlation methods enable the prediction of K_p values in various tissues under *in vivo* conditions on the basis of a known muscle K_p value. The linearity of the correlations between the K_p values of several tissues suggests that, as expected, the biological features related to the binding of drugs to lipids and/or proteins are common among tissues.[3–7] Recently, the principle of the correlation model has been successfully extended to further examples in veterinary, oncology, and PK studies either for steady-state and non-steady-state conditions for various routes of administration (i.e., intravenous, oral, or intraperitoneal).[8–10] Moreover, the analyses of Jansson et al.[8] and Edginton and Yun[11] incorporated descriptors of drug properties such as lipophilicity in coming up with their K_p estimates.

The application of such correlation models in toxicology was limited because the K_p value for muscle used as input parameter in the correlation equations is not commonly generated. To overcome this difficulty, Jansson et al.[8] proposed to combine the correlation equations with the overall volume of distribution (V_d) measured *in vivo*, which is a readily available parameter because it can be estimated from the measured plasma concentration–time profiles by using noncompartmental analyses (NCA)[12] as part of routine PK studies in drug discovery. This will yield quantitative estimates of K_p values for several tissues based on *in vivo* V_d values, without conducting any tissue measurement *in vivo*. In addition, in the early stages of drug discovery, it could be of interest to predict whether a drug has low or high potential for tissue accumulation, and to be able to rank-order drugs based on this potential. In other words, when drugs have similar V_d values, the additional information on clearance (CL) may help to rank-order drugs; therefore, when plasma concentration over time is increased because of a lower CL effect, the tissue distribution should also increase, and inversely, under non-steady-state conditions.[13] Therefore, our hypothesis was that semiquantitative (rough) estimates of K_p values under non-steady-state conditions in toxicology studies could also be made by including CL effects in addition to V_d. The CL data are also routinely generated in drug discovery using NCA analyses.[12]

In the work described herein, an algorithm was provided for evaluation of tissue drug distribution from readily available PK parameters by combining semiquantitative and quantitative estimates of K_p values for common target organs identified in toxicological studies, thus avoiding the need to measure actual drug levels in tissues. This algorithm expands from the current correlation models used in the PK studies, as it was applied for wide dose ranges that include high doses, and an approach to perform low-to-high doses extrapolations of K_p values is presented in addition to an interspecies extrapolation approach. The current computational approach is specific for the oral route of administration under non-steady-state conditions. Finally, the utility of the proposed algorithm in drug discovery was also challenged in a case study to predict differential tissue distribution of two small molecule MET kinase inhibitors from their *in vivo* V_d and CL values. Accordingly, Diaz et al.[1] recently reported that minimal structural changes lowering ionization constant (p*K*a) for one small molecule MET kinase inhibitor compared to another caused significant changes in V_d (decreased) and CL (increased), which resulted in lowered tissue distribution and reduced toxicity profiles in mice. Overall, this provides a novel tool for toxicologists to guess tissue drug partitioning in the interpretation of toxicological data.

METHODS

Figures 1, 2, 3 illustrate the overall algorithm for tissue distribution model development and predictive assessment strategy to conduct semiquantitative and quantitative assessments in a stepwise fashion. Test set of compounds is presented in Table 1.

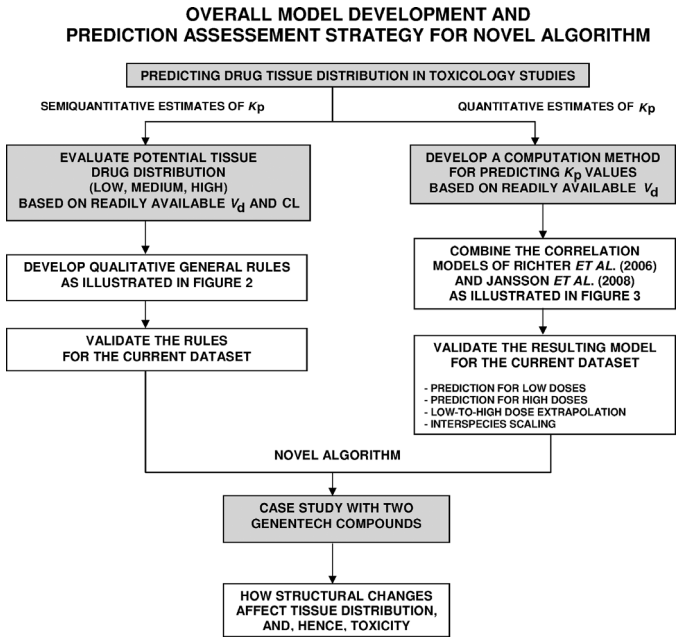

Figure 1. Illustration of the overall model development and prediction assessment strategy for the development of a novel semiquantitative and quantitative algorithm to estimate tissue drug distribution (K_p).