Accepted Manuscript

Discussions on the hepatic well-stirred model: Re-derivation from the dispersion model and re-analysis of the lidocaine data

Jin Dong, Miki Susanto Park

PII: S0928-0987(18)30376-2
DOI: doi:10.1016/j.ejps.2018.08.011
Reference: PHASCI 4648

To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 7 December 2017
Revised date: 9 July 2018
Accepted date: 9 August 2018

Please cite this article as: Jin Dong, Miki Susanto Park , Discussions on the hepatic well-stirred model: Re-derivation from the dispersion model and re-analysis of the lidocaine data. Phasci (2018), doi:10.1016/j.ejps.2018.08.011

Discussions on the Hepatic Well-Stirred Model: Re-Derivation from the Dispersion Model and Re-Analysis of the Lidocaine Data

Jin Dong and Miki Susanto Park*

Department of Pharmaceutics & Medicinal Chemistry, Thomas J. Long School of Pharmacy & Health Sciences, University of the Pacific

mpark@pacific.edu

ABSTRACT

Roberts and Rowland explained the well-stirred model as an extreme case of the dispersion model when the dispersion number is infinity. However, the inconsistency within and discrepancy between the theoretical explanation and experimental observations of the well-stirred model are discovered. In this paper, the well-stirred model is examined from both mathematical and physiological points of view. The well-stirred model is re-derived from the convection-elimination equation using the finite difference method. The well-stirred model is a subset of the parallel-tube model when the dispersion number is zero and concentration gradient is ignored. The relative errors and sensitivities of the well-stirred and the parallel-tube models are compared using numerical simulations. The well-stirred model should not be used to estimate *in vivo* apparent intrinsic clearance from hepatic extraction ratio for high extraction ratio drugs and predicting availability is not recommended for high extraction ratio drugs with either the well-stirred or the parallel-tube models. Based on our theoretical derivation and numerical simulations, we found lidocaine data analysis in Pang and Rowland's 1977 paper was based on an unfair comparison of these two models at two different efficiency number ranges. The high sensitivity of the parallel-tube model at a relatively lower efficiency number range versus the lack of sensitivity of the well-stirred model at an extremely high efficiency number range leads one to believe that the well-stirred model fit the data of high extraction ratio drugs such as lidocaine better. However, the intrinsic clearance values estimated by the parallel-tube model are much more consistent with both *in vitro* data and those estimated by the dispersion model than those by the well-stirred model. In addition, a key assumption used in the data analysis that the intrinsic clearance is independent of changes in blood flow may not be true. Both theoretical discussions and experimental results indicate that apparent intrinsic clearance and intrinsic clearance could be affected by blood flow and protein binding. Moreover, the lidocaine data analysis in 1977 paper could be control condition dependent and misleading when it is applied to data from other drugs, such as diazepam and diclofenac. The distinction between the well-stirred and parallel-tube models is a result of the mathematical treatment of concentration gradient rather than the flow pattern or extent of physical mixing. The well-stirred model is not likely better than the parallel-tube model. One should be cautious of using the well-stirred model for comparing *in vitro* intrinsic clearance and estimated *in vivo* "intrinsic clearance" for high clearance drugs.

Keywords: pharmacokinetics, well-stirred model, parallel-tube model, dispersion model, hepatic clearance, intrinsic clearance

Abbreviations: AAG, α_1-acid glycoprotein; IPRL, isolated perfused rat liver; IVIVE, *in vitro-in vivo* extrapolation; PBPK, physiologically based pharmacokinetic(s); PK, pharmacokinetic(s).