[S9-3] [10/18/2002(Fri) 16:20-16:50/Hall A]

Mechanistic Pharmacokinetic/pharmacodynamic Modeling in Isolated Perfused Organs and at the Whole-Body Level

Michael Weiss

Department of Pharmacology,
Martin Luther University Halle-Wittenberg, 06097 Halle, Germany

In the past, the development of pharmacokinetic/pharmacodynamic (PK/PD) models for quantitating the time course of drug responses was mainly based on two types of models, the empirical effect compartment model that simply accounts for the delay between effect and plasma concentration (hysteresis) and the mechanism-based so-called indirect response model. The first approach traces back to a paper by Segre (1) and its application was popularized by Holford and Sheiner (2); indirect response models were introduced by Jusko's group (3). In clinical pharmacology the application of PK/PD models was especially fruitful, but this concept is equally important in experimental pharmacology where it can replace traditional steady-state experiments to construct dose-response curves. Thus, PK/PD modeling avoids not only lengthy procedures (one dose one response) but also "carryover" effects between administrations.

Since all PK/PD models developed up to now utilize only plasma concentration- and response-time data, the information on the underlying processes of drug transport to the effect site and effectuation is limited. More complex mechanistic models that include transcapillary drug exchange and the dynamics of drug-receptor interaction, for example, cannot be identified on the basis of such data. This is in accordance with the fact that the structural complexity of a model is limited by its identifiability, which is dependent on the information content of the available data. One way to overcome this problem is complexity reduction; i.e., the decomposition of the system into subsystems which can be identified separately. Since the organs represent the natural subsystems of the body, experiments in isolated perfused organs offer an efficient possibility to develop more detailed PK/PD models that provide insight into underlying processes and can be scaled-up from the organ to the whole body level.

Here we describe the development of such a concept for the cardiac glycoside digoxin. The positive inotropic effect of cardiac glycosides on cardiac muscle is mediated through inhibition of Na+/K+ ATPase (sodium pump) by binding to a specific extracytoplasmic site of this enzyme. Although digoxin is one of the most commonly prescribed of all cardiac medications less is known on its transport into the myocardium and the functional role of its binding to a heterogeneous receptor system in the intact heart. A mechanism-based PK/PD model was developed to describe the uptake kinetics, receptor interaction and positive inotropic effect of digoxin in the single-pass isolated

perfused rat heart. The PK/PD model linking the time course of inotropic response to receptor occupation was fitted to the data using Bayesian estimation incorporating prior information about model parameters taken from in vitro receptor binding experiments. Outflow concentration and left ventricular developed pressure data measured for three doses in each heart (6 data sets) were analyzed simultaneously. The uptake of digoxin by the heart was limited by capillary permeability with a permeation clearance of 2.35 ml/min/g (about 1/3 of perfusate flow). In contrast to conventional PK/PD modeling, where drug-receptor interaction does not influence PK (i.e., mass balance), specific binding was an important determinant of cardiac distribution kinetics of digoxin. Binding kinetics was determined by a mixture of two receptor subtypes, a low affinity/high capacity binding site ($K_{D,1}$ = 20.9 nmol, 89 % of total receptors) and a high affinity/low capacity binding site ($K_{D,2}$ = 1.5 nmol, 11 %). The results suggest that in the rat heart consecutive inhibition of first α_2- and then α_1-isoform of the Na^+/K^+-ATPase mediates the positive inotropic effect of digoxin with increasing dose (4).

Surprisingly, no clinical PK/PD modeling of digoxin has been reported so far (except one on drug amount in a peripheral compartment (5)). In order to deal with a potential input rate dependence due to system nonlinearity (saturation of receptor binding), we simultaneously analyzed concentration and effect (shortening of the electromechanical systole) data measured after i.v. bolus dose (1 mg) injection (5) and in a concentration-clamp experiment generating a plateau value of ~ 4.5 ng/ml over 4 h (6). Two approaches were applied: First, the conventional empirical model (delay and Hill equation) and second, the mechanistic receptor-binding model developed for the rat heart. While it was clear a priori that the available data would not allow an identification of the latter model, a good fit was possible after fixing some parameters to estimates obtained in the rat heart. This novel approach not only explains the determinants of empirical parameters like the effect site equilibration half-life, but also accounts for the change of system parameters (membrane permeability, receptor density) and its potential role in establishing optimal dosing regimes.

With advancements in molecular biology, more detailed information on receptor-ligand binding properties may become available. We suggest that mechanistic PK/PD models are valuable tools to bridge the gap between studies at the molecular level and the functioning of organ systems.

References

1. Segre G. *Il Farmaco* **1968**, 23, 907.
2. Holford, N.H.G.; Sheiner, L.B. *Clin. Pharmacokinet.* **1981**, 6, 429.
3. Dayneka, N.L.; Garg,V.; Jusko, W.J. *J. Pharmacokinet. Biopharm.* **1993**, 21, 457.
4. Kang, W.; Weiss, M. *J. Pharmacol. Exp. Ther.* **2002**, 302, 577.
5. Kramer, W.G.; Kolibash, A.J.; Lewis, R.P.; Bathala, M.S.; Visconti, J.A.; Reuning, R.H. *J. Pharmacokinet. Biopharm.* **1979**, 7, 47.
6. Weiss, M.; Sziegoleit, W.; Fahr, A.; Förster, W. *Eur. J. Clin. Pharmacol.* **1983**, 25, 455.