Special Section on Prediction of Human Pharmacokinetic Parameters from In Vitro Systems—Commentary

Prediction of Human Pharmacokinetics in 2013 and Beyond

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ABSTRACT
The utility of in vitro generated kinetic data to provide quantitative prediction of in vivo pharmacokinetic behavior is well established and forms a cornerstone of many research projects in drug metabolism and disposition, particularly within the pharmaceutical industry. This issue provides several excellent examples of the use of in vitro techniques for prediction of human pharmacokinetics (PK). The general area of in vitro–in vivo extrapolation (IVIVE) is broad and hence the spectrum of topics covers various aspects drug clearance and distribution and drug–drug interactions. Some articles were commissioned whereas others were identified during the reviewing process. Overall they provide a snapshot of activity at the end of 2013. They document that whereas the translation of some in vitro approaches is now established, other areas are in their infancy and need more development.

Prediction of metabolic clearance is an example of a mature in vitro–in vivo extrapolation (IVIVE) area. Di et al. (2013a) provide here an overview of best practices and illustrate a wide application. The area is dominated by examples of hepatic cytochrome P450 (P450), but application beyond P450 enzymes to UDP-glucuronosyltransferases (UGTs) and aldehyde oxidase are now evident. Clearance prediction, and IVIVE in general, is increasingly coupled with physiologically based pharmacokinetic (PBPK) models to allow prediction not limited to specific parameters but to generate a time course that can further inform quantitative aspects of drug absorption, distribution, metabolism, and excretion processes (as outlined here by Shardlow et al., 2013). The dynamic rather than static approaches with a time dimension rather than a time-averaged estimate results in far more comprehensive usage of the in vitro data. An excellent example is contained in this issue (Xu et al., 2013), where the importance of CYP2B6 polymorphisms is explored in defining efavirenz clearance.

Prediction of transporter hepatic clearance is an area of great interest and contrasts markedly with the state of play for metabolic hepatic clearance. The complexity of this is becoming evident when delineating the interrelationships between not only enzymes and transporters but also between uptake and efflux transporters and between transporters and passive processes acknowledged (Parker and Houston, 2008; Yabe et al., 2011; Jones et al., 2012; Menochet et al., 2012). It would appear that multiple in vitro models are required, and to integrate these different sources of data requires PBPK modeling procedures. This and other aspects of best practices for transporter-related parameter estimations and predictions have been collated by the International Transporter Consortium (Zamek-Gliszczynski et al., 2013).

The balance of active and passive processes in membrane transport of drugs is often helped by consideration of the Biopharmaceutical Drug Disposition Classification System (BDDCS) (Wu and Benet, 2005). Here Kikuchi et al. (2013) review the evidence for the utility of the BDDCS in predicting brain penetration from in vitro–derived P-gp efflux ratios.

A limitation of standard in vitro methodologies for obtaining drug clearance, whether metabolic or transporter-mediated, is the relatively short lifetime of enzymes in the in vitro incubation. The particularly short time of microsomal incubations is one of several reasons why hepatocytes have become more widely employed. However, even hepatocytes in traditional culture (suspension or monolayer) can only be useful for a few hours. The need to measure the metabolic clearance of low turnover drugs is becoming increasingly important with the design of new drugs that do not use the well characterized enzymes P450 and UDP-glucuronosyltransferases. Hence the articles by Di et al. (2013b) and Chan et al. (2013), concerned with evaluating novel approaches to hepatocyte incubation that provide increased longevity for hepatocyte incubations, should be of great interest to many.

The importance of the gut to clearance of certain drugs and also drug–drug interactions (DDIs) has been appreciated for some time. However the most useful way of building this in with liver has received limited attention. Karlsson et al. (2013) provide a useful analysis of the current position in this area.

Prediction of metabolic DDI has also been an IVIVE area that has been extensively studied. This has benefited particularly from the use of PBPK and the availability of commercial software. We now appreciate the potential of metabolites’ contributions to metabolic DDI and here Callegari et al. (2013) provide a retrospective analysis of this complexity. Fueled by the regulatory adoption of MIST (Metabolites in Safety Testing)
(Smith and Obach, 2010), this has become routinely investigated. Ways in which we can adapt existing models to include metabolites for parent drug perpetrators are explored here by Lutz et al. (2013).

Enzyme (particularly P450) induction as a DDI mechanism for increased clearance has received much attention. In contrast other mechanisms for increased clearance, such as activation (for example through CYP3A4 allosteric effects), are less studied and regarded by many as purely an in vitro phenomenon. Blobaum et al. (2013) provide an interesting case example for in vivo relevance using a rat model, which will lend itself to wider use to explore the wider application of this potential player in DDIs.

Beyond 2013 there is little doubt that the in vitro kinetics of transporters and the factors controlling intracellular drug concentrations will continue to be a major focus for achieving successful in vivo human prediction. Clearer understanding and maturation of approaches, both experimental and modeling, together with integration into the existing metabolic clearance and DDI strategies, will be achieved to keep pace with the drugs of the future. As the in vitro toolbox continues to expand and PBPK models are refined, our ability to make valuable in vivo predictions of complex events from comparatively simple in vitro to expand and PBPK models are refined, our ability to make valuable in vivo predictions of complex events from comparatively simple in vitro processes involved in drug metabolism and disposition.

References


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