Molecular Aspects of Medicine 34 (2013) 711–718

Contents lists available at SciVerse ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Transporter biology in drug approval: Regulatory aspects ☆

Kazuya Maeda [a], Yuichi Sugiyama [b,*]

[a] Department of Molecular Pharmacokinetics, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Japan
[b] Sugiyama Laboratory, RIKEN Innovation Center, RIKEN Research Cluster for Innovation, Japan

Guest Editor Matthias A. Hediger
Transporters in health and disease (SLC series)

ARTICLE INFO

Article history:
Received 18 April 2012
Accepted 23 August 2012

Keywords:
Transporter-mediated drug–drug interaction
False-negative predictions
Static model
Dynamic model
Drug interaction number (DIN)
Organic anion transporting polypeptide (OATP)1B1 (*SLCO1B1*)
OATP1B3 (*SLCO1B3*)
Organic anion transporter (OAT)1 (*SLC22A6*)
OAT3 (*SLC22A8*)
Organic cation transporter (OCT)2 (*SLC22A2*)
Multidrug resistance 1 (MDR1, P-glycoprotein (P-gp))
Multidrug and toxin extrusion (MATE)1 (*SLC47A1*)
MATE2-K (*SLC47A2*)

ABSTRACT

Previous *in vitro* and clinical research have indicated that a wide variety of drug transporters as well as metabolic enzymes dominate the pharmacokinetics of drugs and that some drugs modified the expression/function of drug transporters in humans, which lead to the altered pharmacokinetics and subsequent pharmacological/toxicological effects. Thus, regulatory authorities in US and EU have recently emphasized the needs to evaluate the risk of transporter-mediated drug–drug interactions (DDIs) in the (draft) guidance for pharmaceutical industries. The revised guidance includes the key transporters governing pharmacokinetics of drugs and decision trees to determine whether NMEs are substrates or inhibitors of each key transporter and when an *in vivo* clinical study is needed. In the evaluation of the potency of clinical DDIs, estimation of the inhibitor concentration at the target site is essential, but difficult since its direct measurement is almost impossible. Thus, people are now discussing what kind of inhibitor concentration should be used and how much is the appropriate cutoff value of the ratio of plasma AUC in the presence of inhibitor drugs to that in its absence (AUCR) to avoid false-negative predictions and maximize prediction accuracy. This minireview briefly summarizes the current status of the criteria for risk management of transporter-mediated DDIs in the regulatory guidelines, and describes scientific achievements that may affect regulatory decisions. Target transporters include OATP1B1 (*SLCO1B1*) and OATP1B3 (*SLCO1B3*) in the liver, and OAT1 (*SLC22A6*), OAT3 (*SLC22A8*), OCT2 (*SLC22A2*), MATE1 (*SLC47A1*), and MATE2-K (*SLC47A2*) in the kidney, and MDR1 (*ABCB1*) in the intestine.

Contents

☆ Publication in part sponsored by the Swiss National Science Foundation through the National Center of Competence in Research (NCCR) TransCure, University of Bern, Switzerland; Director Matthias A. Hediger; Web: http://www.transcure.ch.

* Corresponding author. Address: Head of Sugiyama Laboratory, RIKEN Innovation Center, RIKEN Research Cluster for Innovation, Yokohama Bio Industry Center 2F, 1-6 Suehiro-Cho, Tsurumi-ku, Yokohama 230-0045, Japan. Tel.: +81 45 506 1814; fax: +81 45 506 1800.
E-mail address: ychi.sugiyama@riken.jp (Y. Sugiyama).

0098-2997/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mam.2012.10.012

1. The need to evaluate the importance of transporters in the pharmacokinetics of drugs during drug development

In the process of drug development, to understand the pharmacokinetic profiles of new molecular entities (NMEs) is one of the critical factors for selecting appropriate drug candidates and considering the proper use of drugs. Since many human drug transporters have been identified and characterized, clinical studies have also directly demonstrated the importance of selected transporters in the regulation of the pharmacokinetics of substrate drugs in humans *in vivo*. Several genetic polymorphisms in transporter genes, which alter the function/expression of transporters *in vitro*, were reported to affect the intestinal absorption and/or systemic clearance of substrate drugs. Some drugs are known to inhibit potently the function of certain transporters and subsequently change the pharmacokinetics of substrates in humans. Drug–drug interactions (DDIs) sometimes lead to the withdrawal of drugs from the market, despite their potential to clinically benefit many patients. For example, cerivastatin, a potent HMG-CoA reductase inhibitor, was voluntarily withdrawn from the market by the manufacturer because a number of patients died from lethal myotoxicity, including rhabdomyolysis, induced by cerivastatin. After thorough inspection of the data, it was found that some of the victims simultaneously took cerivastatin and gemfibrozil, an antihyperlipidemic drug, and the plasma AUC of cerivastatin was reported to be increased 4.4 times by coadministration of gemfibrozil (Backman et al., 2002). We now know that this DDI is mainly caused by the mechanism-based inhibition of CYP2C8-mediated metabolism and inhibition of organic anion transporting polypeptide (OATP)-mediated hepatic uptake of cerivastatin by gemfibrozil glucuronide (Ogilvie et al., 2006; Shitara et al., 2004). Because the substrate specificities of transporters are generally very broad, a functional change in a single transporter affects the pharmacokinetics of a wide variety of structurally unrelated compounds. Transporter inhibitors can also affect the pharmacokinetics of a range of drugs with different classes of pharmacological action. At present, we cannot accurately judge from a compound's chemical structure whether it interacts with transporters, so it is essential to know in the early stage of drug development which transporters can recognize a new drug candidate as a substrate and/or an inhibitor. It must also be noted that drugs that inhibit transporters *in vitro* do not always change the pharmacokinetics of substrate drugs in humans *in vivo*, because many factors modify the influence of coadministration of inhibitors on the total clearance of substrate drugs. Such factors include the ratio of the unbound concentration of an inhibitor at the site of the interacting molecule to its inhibition constant, contribution of a target transporter to the overall membrane transport process of substrate drugs and the rate-determining process (transport vs. metabolism; blood flow rate vs. intrinsic clearance) in the overall clearance of substrate drugs (Maeda and Sugiyama, 2007).

Under such circumstances, the US Food and Drug Administration (FDA) launched the International Transporter Consortium (ITC), which consists of scientists in the field of drug transporter science from the US, EU and Asia, and from industry, academia and the FDA. The ITC is intended to facilitate intensive discussion of the key transporters related to therapeutic and adverse drug responses, and to develop *in vitro* and *in vivo* tools and techniques to evaluate transporter function. It has also developed a decision tree for each key transporter, to judge whether a new molecular entity (NME) is a substrate or inhibitor of a certain transporter at relevant clinical concentrations and whether a clinical DDI study is recommended in the development of NMEs. This achievement was published as a review article in Nature Reviews Drug Discovery, and is recognized as the "FDA transporter white paper" (Giacomini et al., 2010). The US FDA recently released a revised draft guidance titled "Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations", which basically follows the contents of the white paper with some modifications (FDA, 2012). In April 2010, the European Medicines Agency (EMA) released a revised guideline titled "Guideline on the Investigation of Drug Interactions", which added to the discussion of transporter-mediated DDIs and it was finalized in June 2012. (EMA, 2012).

2. Key transporters as determinants of the pharmacokinetics of drugs

Fig. 1 illustrates the tissue distribution and membrane localization of major drug transporters in the "FDA transporter white paper" (Giacomini et al., 2010). The US FDA draft guidance on DDIs indicates that OATP1B1, OATP1B3, organic anion transporter 1 (OAT1), OAT3 and organic cation transporter 2 (OCT2) are key uptake transporters and that P-gp (P-glycoprotein) and BCRP (breast cancer resistance protein) are key efflux transporters. In addition, the EMA guideline suggests that DDIs mediated by OCT1, MATEs (multidrug and toxin extrusions) and BSEP (bile salt export pump) should also be considered. Both documents note that transporters might be added to or removed from the list of key transporters based on future advances in transporter science.

OATP1B1 and OATP1B3, encoded by the *SLCO1B1* and *SLCO1B3* genes, respectively, are exclusively expressed on the basal side of hepatocytes and are responsible for the hepatic uptake of several clinically important anionic drugs including HMG-CoA reductase inhibitors (statins) and angiotensin II type 1 receptor antagonists (sartans) (Fahrmayr et al., 2010). OAT1 and OAT3, encoded by the *SLC22A6* and *SLC22A8* genes, respectively, are mainly expressed on the basal side of renal tubular epithelial cells and are involved in the renal secretion of several anionic drugs (Rizwan and Burckhardt, 2007). OAT1 accepts hydrophilic compounds with relatively low molecular weight such as nucleotide analog antiviral drugs (adefovir, tenofovir,