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Preincubation-dependent and long-lasting inhibition of organic anion transporting polypeptide (OATP) and its impact on drug-drug interactions

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ABSTRACT

Preincubation with cyclosporin A (CsA), a potent inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3, enhanced its inhibitory effects on these transporters *in vitro*. A similar effect was observed upon preincubation with some other inhibitors. Removing these from the incubation media did not readily reverse the inhibition on OATP1B1 and OATP1B3. This preincubation-dependent long-lasting inhibition appeared to be related to CsA concentration in the cells in addition to that in the incubation media. Thus, we hypothesized that CsA inhibits OATP1B1 and OATP1B3 from inside (*trans*-inhibition) as well as outside (*cis*-inhibition) the cells and constructed the *cis*- and *trans*-inhibition model. The enhanced inhibitory effect of CsA on OATP1B1 observed after preincubation was quantitatively described using $K_{i,out}$ and $K_{i,in}$ as inhibition constants for *cis*- and *trans*-inhibitions, respectively. In addition, a long-lasting inhibition was also described by this model. Additional factors taken into consideration when simulating *in vivo* pharmacokinetic alterations by CsA are potential inhibition by AM1, a major metabolite of CsA, which has been reported to inhibit OATP1B1 and OATP1B3. Based on the physiologically based pharmacokinetic model incorporating *trans*- and *cis*-inhibition of OATP1B1 by CsA, the simulation showed that OATP1B1-mediated drug–drug interaction with CsA was suggested to be time-dependent also *in vivo* although further clinical studies are required for confirmation.

Contents

Abbreviations: AUC, area under the plasma concentration-time curve; AUCR, increase ratio in the area under the plasma concentration-time curve; BIM-I, bisindolylmaleimide I; BSP, sulfobromophthaleine; CCK8, cholecystokinine octapeptide; CsA, cyclosporin A; DDI, drug-drug interaction; E_1S, estrone 3-sulfate; E_2G, estradiol 17β-D-glucuronide; f_u, unbound fraction; IC_{50}, concentration to produce 50% inhibition; I_{in}, inhibitor concentration at the inside of cells; I_{out}, inhibitor concentration at the outside of cells; $I_{u,sys}$, unbound concentration of inhibitor in systemic circulation; $I_{u,liver}$, unbound concentration of inhibitor in the liver; K_i, inhibition constant; M&S, modeling and simulation; PBPK, physiologically based pharmacokinetic; PS, permeation clearance for unbound compound across membrane; OATP, organic anion transporting polypeptide; PKC, protein kinase C; PMA, phorbol-12-myristate-13-acetate; V_{cell}, intracellular volume; V_{medium}, volume of incubation medium.

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1. Introduction

Drug–drug interaction (DDI) is recognized as one of the biggest problems in drug development in the pharmaceutical industry (Tucker, Houston, & Huang, 2001; Zhang, Reynolds, Zhao, & Huang, 2010). DDIs cause an increase or reduction in systemic exposure of victim drugs unless their doses are adjusted, potentially resulting in adverse events (Giacomini & Sugiyama, 2011). DDIs have resulted in discontinuation of drug development or withdrawal of drugs from the market, due to severe side effects and/or potential adverse reactions (Alexandridis, Pappas, & Elisaf, 2000; Beijnen & Schellens, 2004; Schmassmann-Suhijar, Bullingham, Gasser, Schmutz, & Haefeli, 1998). Thus, prediction of the extent of DDIs using modeling and simulation (M&S) is encouraged to avoid these issues (Peters, Schroeder, Giri, & Dolgos, 2012; Wagner et al., 2015; Zhang, Zhang, Zhao, & Huang, 2009; Zhao et al., 2012). The guidelines or draft guidance for evaluation of DDIs that have been published by regulatory agencies in USA, EU and Japan, also recommend using M&S techniques to predict the extent of DDIs (European Medicines Agency, 2012; Ministry of Health, Labour and Welfare, Japan, 2014; U.S. Department of Health and Human Services, 2012). As a result, there have been increasing numbers of new drug applications utilizing this innovative technique.

However, there are still DDIs with a complex mechanism involving multiple enzymes, multiple inhibition mechanisms and/or enzyme plus transporter, which cannot be easily predicted based on simple M&S techniques (Kudo, Hisaka, Sugiyama, & Ito, 2013; Rowland-Yeo, Jamei, Yang, Tucker, & Rostami-Hodjegan, 2010). In such cases, it is desirable to predict the extent of DDIs with an elucidation of the underlying mechanisms. It is notable that a transporter-mediated hepatic uptake process can be a rate-determining factor of hepatic elimination even for drugs which undergo metabolism (Shitara, Maeda, et al., 2013; Watanabe, Kusuhara, Maeda, Shitara, & Sugiyama, 2009). In such cases, extended clearance concept needs to be considered and physiologically based pharmacokinetic (PBPK) models incorporating drug transporters help more precise prediction of the DDIs (Shitara, Maeda, et al., 2013; Varma, Steyn, Allerton, & El-Kattan, 2015; Yamazaki, Suzuki, & Sugiyama, 1996; Yoshikado et al., 2016).

Irreversible inhibition of drug metabolism enzymes may also cause a complexity in the prediction of DDIs (Ito et al., 1998; Kanamitsu, Ito, Green, et al., 2000; Lin & Lu, 1998). The extent of DDIs caused by irreversible inhibition is more marked than estimated from simple reversible inhibition and the effect of perpetrator drugs is possibly extended. Mechanism-based inhibition is an example of the irreversible inhibition, and some studies have quantitatively predicted the DDIs caused by this mechanism using M&S methods (Ito et al., 1998; Kanamitsu, Ito, Green, et al., 2000; Kanamitsu, Ito, Okuda, et al., 2000). In this case, the contents of active metabolic enzymes change when they are incubated in the presence of mechanism-based inhibitors *in vitro*, depending on the incubation time with them. Thus, not only the pharmacokinetics of perpetrator and victim drugs but the activity/content of metabolic enzymes were included in the PBPK models and they changed with respect to time after administration of inhibitor drugs. More recently, irreversible inhibition has been reported also for drug transporters. In this article, preincubation-dependent and long-lasting inhibition of

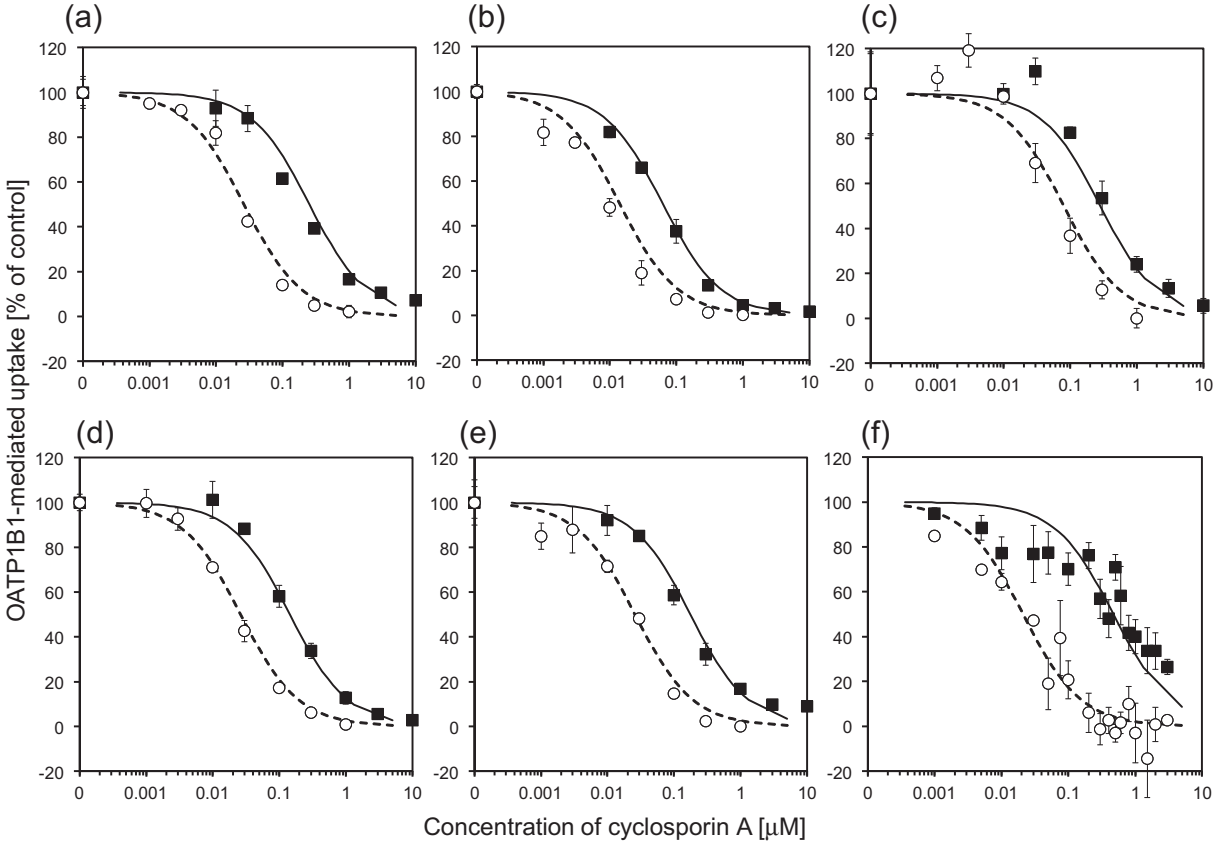

Fig. 1. Preincubation-dependent enhancement of the inhibitory effect of CsA on OATP1B1-mediated uptake. Inhibitory effect of CsA on the OATP1B1-mediated uptake was examined with (○) or without (■) CsA preincubation. E_1S (a), E_2G (b), BSP (c), pitavastatin (d), and atorvastatin (e and f) were used as OATP1B1 substrates. Data are shown as mean ± S.D. (a ~ e) or mean ± S.E. (f). Solid and dotted lines represent fitted curves for OATP1B1-mediated uptake *vs.* CsA concentration in the absence and presence of preincubation with CsA, respectively. Preincubation with CsA markedly enhanced its inhibitory effects on OATP1B1, with a reduction in its IC_{50} values on the OATP1B1-mediated uptake. Figures are cited and modified from the references shown below with permission.
References: (a) to (e) Izumi et al. (2015), (f) Amundsen et al. (2010).