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LETTER TO THE EDITOR

Comment on the Article "Physiologically Based Modeling of Pravastatin Transporter-Mediated Hepatobiliary Disposition and Drug-Drug Interactions"

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To the Editor:

The 'bottom-up' prediction of transporter-based drug-drug interactions continues to be a challenge. In this context, we offer some comments on the recent publication of Varma *et al.* (2012) in this Journal (1). These authors describe the development of physiologically-based pharmacokinetic (PBPK) models to predict the kinetics of pravastatin and the impact of co-medication with cyclosporine, gemfibrozil or rifampicin. While the transporter-mediated interactions with gemfibrozil and rifampicin in healthy subjects were predicted within 20% by the dynamic models, that with cyclosporine as perpetrator was significantly underestimated.

In simulating the *in vivo* data for pravastatin given alone, it was necessary to fit the data using empirical scaling factors for hepatic sinusoidal uptake and canalicular efflux of 31 and 0.17, respectively. With regard to the second of these scaling factors, we suggest that there is prior experimental justification for the number, based on abundance data for MRP2. Thus, Li *et al.* (2009a) reported a mean (± SD) absolute abundance of the protein in human liver tissue of 0.64±0.27 fmol/μg of membrane protein (data extracted from Figure 5B in the reference (2)), and a mean (± SD) absolute abundance of 3.5±1.4 fmol/μg of membrane protein in 5-day old sandwich cultured human hepatocytes (SCHH) (data extracted from Figure 2 in the reference (3)). This gives a relative expression factor (REF), based on absolute abundance data, of 0.64/3.5=0.18, a value that is very close to the empirical scalar of 0.17. Varma *et al.* (2012) used SCHH for their *in vitro* characterisation of the canalicular efflux of pravastatin (1). In our view there is sufficient prior information to use the ADAM module within the Simcyp Simulator to define the impact of transporter kinetics on the intestinal and hepatic efflux of pravastatin more mechanistically.

On the basis of their analysis, Varma *et al.* (2012) state that cyclosporine is a more potent inhibitor of OATP1B1-mediated hepatic uptake *in vivo* than *in vitro* (1). Generally, IC_{50} and K_i values for the inhibition of OATP1B1 are calculated after co-application of inhibitor with substrate. A much lower K_i for cyclosporine is apparent when it is pre-incubated (0.014 *vs* 0.31 μM) (4), and its inhibitory effect is long-lasting after washing of the cells (5). Although Varma *et al.* (2012) used the lower value for K_i of 0.014 μM, they did assume a competitive mechanism. Thus, it seems that the exact nature of the inhibitory effect of cyclosporine on OATP1B1 merits more investigation if 'bottom-up' predictions for cyclosporine based on *in vitro* data are to be successful. Nevertheless, we agree with Varma *et al.* (2012) that currently the lower K_i value seems 'fit for purpose' to estimate cyclosporine tDDIs in healthy volunteers (6).

We note that the reference *in vivo* data for the pravastatin-cyclosporine interaction were from studies in heart transplant patients, whereas the data for pravastatin given alone were from studies in healthy volunteers. Heart transplant patients have been shown to have elevated plasma levels of tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (7), and both cytokines suppress mRNA and protein levels of OATP1B1 (and OATP2B1) in primary human hepatocytes (8,9). Healthy subjects have plasma IL-6 levels of about 6 pg/ml (10) compared to about 16 pg/ml (depending on the grade of cellular rejection) in heart transplant patients (11). As a consequence, it may be inappropriate to predict an OATP1B1 interaction in heart transplant patients using a

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simulation based on healthy volunteer data without decreasing the REF. A similar consideration applies to the prediction of the pravastatin—rifampicin interaction. In this case, predictions based on single doses of pravastatin and rifampicin in Caucasians were compared with observed single dose data for both drugs in Chinese, although the single dose data for pravastatin in the two groups were quite different. Any prediction of the extent of the DDI during multiple dosage of rifampicin would be further complicated by simultaneous inhibition and induction of OATP1B1 and MRP2 (12–16).

The above comments notwithstanding, we applaud Varma *et al.* (2012) for moving the quantitative prediction of transporter-mediated drug-drug interactions forward.

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