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Semi-mechanistic physiologically-based pharmacokinetic modeling of clinical glibenclamide pharmacokinetics and drug–drug-interactions

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ABSTRACT

We studied if the clinical pharmacokinetics and drug–drug interactions (DDIs) of the sulfonylurea-derivative glibenclamide can be simulated via a physiologically-based pharmacokinetic modeling approach. To this end, a glibenclamide PBPK-model was build in Simcyp using *in vitro* physicochemical and biotransformation data of the drug, and was subsequently optimized using plasma disappearance data observed after i.v. administration. The model was validated against data observed after glibenclamide oral dosing, including DDIs. We found that glibenclamide pharmacokinetics could be adequately modeled if next to CYP metabolism an active hepatic uptake process was assumed. This hepatic uptake process was subsequently included in the model in a non-mechanistic manner. After an oral dose of 0.875 mg predicted C_{max} and AUC were 39.7 (95% CI:37.0–42.7) ng/mL and 108 (95% CI: 96.9–120) ng/mL h, respectively, which is in line with observed values of 43.6 (95% CI: 37.7–49.5) ng/mL and 133 (95% CI: 107–159) ng/mL h. For a 1.75 mg oral dose, the predicted and observed values were 82.5 (95% CI:76.6–88.9) ng/mL vs 91.1 (95% CI: 67.9–115.9) for C_{max} and 224 (95% CI: 202–248) vs 324 (95% CI: 197–451) ng/mL h for AUC, respectively. The model correctly predicted a decrease in exposure after rifampicin pre-treatment. An increase in glibenclamide exposure after clarithromycin co-treatment was predicted, but the magnitude of the effect was underestimated because part of this DDI is the result of an interaction at the transporter level. Finally, the effects of glibenclamide and fluconazol co-administration were simulated. Our simulations indicated that co-administration of this potent CYP450 inhibitor will profoundly increase glibenclamide exposure, which is in line with clinical observations linking the glibenclamide-fluconazol combination to an increased risk of hypoglycemia. In conclusion, glibenclamide pharmacokinetics and its CYP-mediated DDIs can be simulated via PBPK-modeling. In addition, our data underline the relevance of modeling transporters on a full mechanistic level to further improve pharmacokinetic and DDI predictions of this sulfonylurea-derivative.

1. Introduction

Sulfonylurea-type (SU-type) oral antidiabetic drugs comprise a mainstream therapy to achieve blood glucose control in type II diabetic patients. The predominant side effect of the SU derivatives is hypoglycemia and especially second generation SU compounds are associated with this adverse effect. Second generation compounds include drugs such as glibenclamide, glimepiride and gliclazide, and the higher incidence of hypoglycemia of these drugs is attributed to the longer plasma half-life and higher potency of the second generation compounds as compared to first generation drugs such as tolbutamide (Hardman et al., 2001). Moreover, pharmacokinetic drug–drug interactions (DDIs) between SU-derivatives and concomitantly administered medications may lead to unexpected enhanced hypoglycemic effects and therefore morbidity. Recently, Schelleman et al. found an increased incidence of hypoglycemic

Abbreviations: DDI, drug–drug interaction; CYP450, cytochrome P450; SU, sulfonylurea; PBPK-model, physiologically-based pharmacokinetic model; C_{max}, maximum plasma concentration; AUC, area under the plasma concentration time curve; ADME, absorption, distribution, metabolism, excretion; V_{ss}, volume of distribution at steady state; V_{max}, maximum enzymatic biotransformation rate; K_m, concentration at which half-maximum biotransformation rate is reached; K_i, concentration resulting in 50% inhibition; K_{app}, concentration of mechanism-based inhibitor associated with half maximal inactivation rate; k_{inact}, inactivation rate of the enzyme (1/h); $IndC_{50}$, inducer concentration that supports half maximal induction. Ind_{max}, maximal fold induction over control. IVIVE, *in vitro–in vivo* extrapolation; $IndC_{50}$, inducer concentration that supports half maximal induction. Ind_{max}, maximal fold induction over control; IVIVE, *in vitro–in vivo* extrapolation; FDA, food and drug administration; EMA, European medicines agency; f_u, fraction unbound; f_a, fraction absorbed..

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events in glibenclamide users that were treated simultaneously with CYP450-inhibiting anti-infective agents, compared to glibenclamide users that were treated with an antibiotic that does not interact with Phase I metabolism (Schelleman et al., 2010). Also Tirkkonen et al. demonstrated that simultaneous administration of CYP2C9 inhibitors with glibenclamide, glimepiride or glipizide was associated with an increased blood glucose-lowering effect of the SU-derivatives in patients with diabetes mellitus type II (Tirkkonen et al., 2010).

In recent years, the *in silico* simulation of DDIs using physiologically-based pharmacokinetic models has emerged as an approach to predict the likelihood and magnitude of potential changes in the systemic exposure of a drug, resulting from the concomitant administration of drugs (Peters, 2012). Physiologically-based pharmacokinetic modeling (PBPK modeling) aims to predict the clinical pharmacokinetics of drugs by combining drug-specific permeability, biotransformation and physicochemical data that are obtained *in vitro* with an *in silico* model describing the physiology and anatomy of the human body. In this way, the handling of a drug by the body can be simulated in a mechanistic manner, taking molecular processes as a starting point. This contrasts with a population pharmacokinetic modeling and simulation approach, which is an empirical method to build models taking clinical pharmacokinetic data obtained from prior clinical trials as a starting point. A combination of these two approaches can be very powerful to understand and predict the pharmacokinetics and DDIs of a drug with other, concomitantly administered compounds (Rostami-Hodjegan and Tucker, 2007). In the clinic, PBPK simulations can help to estimate the potential consequences of administering concomitant medications for SU pharmacokinetics, especially in cases in which clinical DDI trials for the prescribed combination of drugs have not been conducted earlier. With respect to clinical drug development, PBPK modeling and simulation has been advocated by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) to provide a mechanistic understanding of the clinical pharmacokinetics of drugs and predict the likelihood and magnitude of possible DDIs occurring with the investigational new drug after admission of new compounds to the market (Peters, 2012; Rostami-Hodjegan and Tucker, 2007; Peters et al., 2009).

To facilitate the prediction of DDIs with SU derivatives we now used the Simcyp population-based ADME simulator for the PBPK-modeling of glibenclamide pharmacokinetics (Jamei et al., 2009). Next, we validated the glibenclamide model by investigating whether clinically relevant CYP450-mediated DDIs with glibenclamide can be simulated correctly. In this paper we focused on the interaction of glibenclamide with three anti-infective agents, clarithromycin, rifampicin, and fluconazole.

2. Materials and methods

2.1. Simcyp simulations

PBPK-simulations were performed using the Simcyp software package version 11.00 (Simcyp Limited, a Certara company, Sheffield, UK). Simcyp performs *in vitro* to *in vivo* extrapolations of clearance, based on *in vitro* biotransformation and physicochemical parameters. Details on the algorithms to calculate *in vivo* pharmacokinetic parameters, a description of the Simcyp *in vitro–in vivo* extrapolation (IVIVE) methods, the structure of the physiological model and a description of the differential equations used, have been published earlier (Howgate et al., 2006; Almond et al., 2009; Jamei et al., 2009; Rowland et al., 2010; Yang et al., 2006). Simulations were performed using the default Simcyp population of virtual healthy volunteers. For each simulation, number of subjects, gender and age range of the virtual population were matched to the reported trial population as much as possible, as well as other trial conditions, including fasting/fed state, dosing time. For the individual trials, details of the virtual trial populations are indicated in the legends of Figs. 1 and 4.

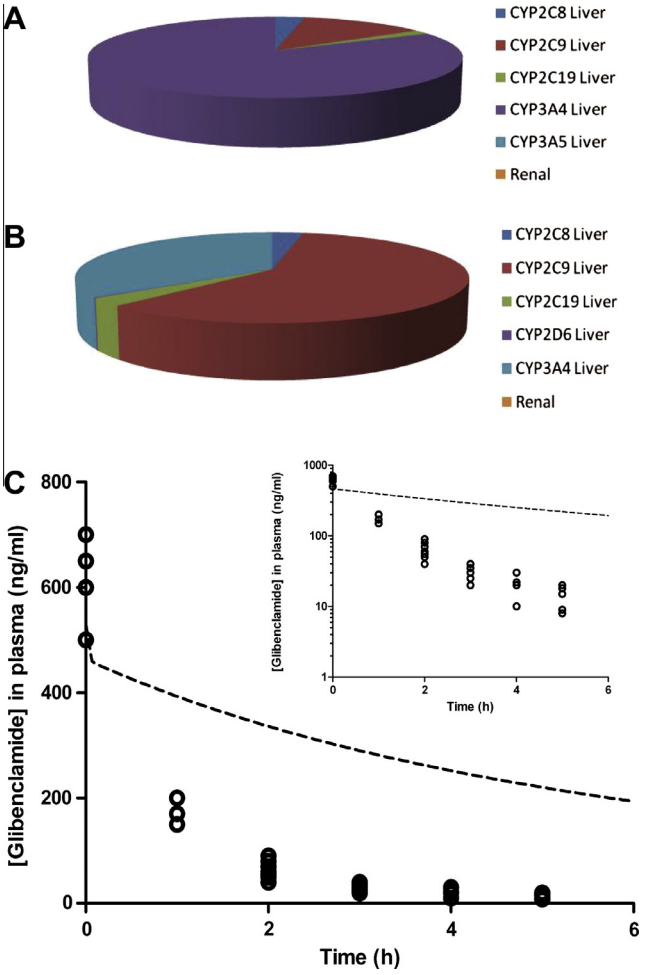

Fig. 1. Predicted median fraction of glibenclamide metabolized by specific CYP enzymes using the data reported by Zhou et al. (2010) (A) or Zharikova et al. (2009) (B). (C): Simulated (dashed line) and observed (open spheres), plasma disappearance of glibenclamide after i.v. administration of 3.5 mg, applying the Zharikova data set in simulations. Observed data were described prior by Rydberg et al. (1997). Simulated plasma concentration–time data are derived from 10 virtual trials in 8 healthy subjects (4 males, 4 females), ranging in age from 21 to 33 years, in this way matching the reported trial population by Rydberg et al. as much as possible.

2.2. Input parameters

In Table 1 the input parameters of Simcyp for the initial simulations are given, references to the sources describing the data are included in this table. In case of oral dosing, absorption of glibenclamide was modeled using a first-order absorption model. The glibenclamide absorption rate constant (k_a) and fraction absorbed (f_a) were predicted by Simcyp from P_{eff} values published earlier (Yu et al., 1996a, 1996b). Intravenous administration of glibenclamide was performed via simulation of bolus injections. The volume of distribution of glibenclamide was taken from clinical trial data (Morrison et al., 1982), since prediction with the full PBPK-Simcyp model resulted in an over-prediction of distribution volume (data not shown). Parameters to estimate metabolic clearance were based on *in vitro* drug metabolism data, using two published data sets that quantitatively describe CYP-mediated glibenclamide