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PREDICTION OF DRUG-DRUG INTERACTION POTENTIAL OF SULFONYL UREAS ON THE DISPOSITION OF ANTI-HYPERLIPIDEMIA DRUGS-MATHEMATICAL MODELING APPROACH.

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Abstract:

As similar to metabolic pathways or metabolism of drug is inhibited competitively or by other pathways, the inhibition can be happening at the drug transport level which is also critical alongside other disposition pathways. Advances in the understanding of drug metabolic pathways and drug transport process help in the estimation of degree of invivo interaction in vitro through certain parameters like the [I]/Ki ratio. Such equations employ a blend of in vivo and in vitro derived parameters to estimate the fold change in the AUC ratio in the presence and absence of inhibitor. In the current investigation, the change in the AUC was predicted when two most commonly used drugs (Rosuvastatin and Glimepiride) were used to manage anti hyperlipidemia and diabetes. Current investigation employed the hepatic inlet concentration (determined majorly by the presence of OATP drug transporters) of Rosuvastatin which is the major rate limiting step in determining the active concentration reaching the site to elicit its therapeutic response. Alternately Glimepiride disposition is also effected by OATP transporters although at a higher affinity as shown in certain studies reported in the literature.

The results indicate a change in the rosuvastatin AUC upon long term usage of Glimepiride. However, such study need to be validated in the clinical scenario as elevated concentrations in the clinic for Rosuvastatin would precipitate the devastating Rhabdomylosis in patients who are on co-medication with the drugs under current investigation.

Keywords: Rosuvastatin, Glimepiride, Hepatic inlet concentration, OATP transporters, C_{max}

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INTRODUCTION:

Once administered, drugs undergo disintegration, dissolution and get absorbed in the body by various pathways present in the intestinal lumen and enter into systemic circulation. In the systemic circulation, the drug (s) are exposed to variety of proteins to which these drugs bind and the level or degree of such binding play a major role in affecting the drug disposition and producing the therapeutic response (Borga A, Borga B, 1997). Among several proteins involved in the disposition of the drug like albumin, globulins etc a wide variety of drug transporter proteins are present along the intestinal lumen, hepato cellular junction, bile canalicular surface which are equally important and play a major role in determining the trough and maximum concentrations in the clinical scenario (Matsushima H et al., 1999).

Such drug transporters play a major role in determining the pharmacokinetics of drugs and also in determining the right clinical dose if the compound is proven to be a substrate or inhibitor of drug transporter proteins.

Among the wide varieties of transporter proteins available, OATP`s are studied widely and serve a deterministic parameter for drugs under development. Such compounds are to be studied for their substrate or inhibitor properties towards these proteins as specified by the regulatory agencies (Shugarts S, Benet LZ, 2009).

OATP1B1 and OATP1B3 are the transporters which belong to OATP family of transporters that are present on the sinusoidal membrane of the hepatocytes and are majorly involved in the uptake of drugs or xenobiotics or endogenous compounds into the liver for clearance from the systemic circulation or to exert their therapeutic effect (Shitara Y et al., 2005). These transporters function serve as the rate limiting step for a variety of drugs specially the statins and as such the pathway is also susceptible to inhibition by co-administered drugs (Shitara Y, Sugiyama Y., 2017).

Compounds whose elimination via hepatic route or biliary excretion is more than 25 % are to be evaluated for their tendency to be a substrate for these transporters. Also, these two transporters exhibit substrate overlap among them. So, it becomes ideal for the sponsor to evaluate the inhibition of drugs while under development for their inhibition potential on the uptake of the transport of drugs (FDA 2012). Such calculations employ the systemic plasma concentration and the maximum dose of the compound administered.

Drugs (statins) are demonstrated to be substrate for OATP transporters and a chance of drug-drug interaction at this pathway exists for inhibition by co-administered drugs. In such case, the plasma concentration of the statins or the victim drug are increased to a significant extent leading to increased muscle exposure and hence rhabdomylosis (Egan and Colman, 2011). Furthermore, DDIs can also result from inhibition of OATP1B1 either alone (e.g. with gemfibrozil; simvastatin acid AUC ratio (AUCR) = 2.85), or in combination with inhibition of CYP3A4 (e.g. with cyclosporine; simvastatin acid AUCR = 8.0) (Elsby et al., 2012). Such clinical drug-drug interaction poses a significant risk for the development of compounds both at pre-clinical and clinical level. Hence, evaluation of the drug under development for their inhibition towards either drug metabolising enzymes or drug transporters to determine Ki and extrapolating to the clinical scenario with the help of equations proposed under the DDI guidance by the regulatory agencies becomes evident. Such information can be used for effective decision making and protocol design for the clinical studies (Williamson and Riley, 2017).

MATERIALS AND METHODS:

Using the pharmacokinetic data from the literature, several assumptions, inactivation kinetics constants, the [I] /K i ratios for the drugs known to be inhibitors or substrates of drug transporters. Such data is corrected for the unbound concentration using the in-vitro derived parameters of free fractions determined experimentally through Rapid equilibrium dialysis.

Since the interaction is supposed to be happening at the hepatic canalicular junction where these OATP transporters are expressed abundantly, a more robust parameter employing the hepatic blood flow (Q_h), absorption rate constant, fraction of drug available from the intestine would be best at predicting the drug-drug interaction potential of the co-administered drug. Maximum concentration obtained in the clinic at the maximum recommended therapeutic dose is also used as input for determining the inhibition potential manifested as the fold increase in the area under the curve when two drugs are administered together.

Therefore the aim of the current prediction is to estimate the “R” value- the predicted ratio of the victim drug’s AUC in the presence and absence of the investigational drug as the inhibitor employing static equations. It is derived from the equation $1+ [I]_{inlet,\ max}/Ki$. $[I]_{inlet,max}$ was estimated as C_{max} + (ka x Dose x FaFg/Qh), where Qh is the hepatic blood flow

(1,500 mL/min), ka is the absorption rate constant, and F_aF_g is the fraction of oral dose that reaches the liver. Dose is the highest dose approved for clinical use. K_a is the absorption rate constant of the drug which can be determined experimentally and can be assumed to be theoretical value of 0.1 min^{-1} in case of unavailability. The value of F_aF_g can be assumed to be 1.0, the theoretical value in case of no experimental determination. This usage of theoretical value can be useful to avoid false-negative prediction. C_{max} is the maximum plasma concentration obtained in humans or corresponding species at the highest clinical dosage. Q_h is the liver blood flow in humans which is measured as 1500 mL/min (Ito K et al.,2002).

For Glimepiride, the values of K_i were measured in earlier experiments (E. van de Steeg et.al. 2012). The concentration of the Estradiol-β-Glucuronide used in the final assay conditions was 1.0 µM and such concentration is well below the K_m of Estradiol-β-glucuronide, the inhibition showed by Glimepiride towards OATP1B1 was assumed to be competitive in nature. Accordingly, the K_i for the current prediction will be calculated as $IC_{50}/2$ (Haupt LJ et al., 2015). The guidelines from the regulatory agencies implicate a possibility for in-vivo DDI, if the R value calculated from the above equation resulted as $\geq$1.1.However, the magnitude of the changes in the pharmacokinetic parameters can be exactly measured with an in-vivo outcome.

For Glimepiride:

The maximum concentration, at an approved maximum dose of 8 mg in the clinic during a 14 day multiple dose clinical study is 578 ng/mL (Product monograph). Accordingly, with a molecular weight of 490.32, the maximum concentration observed will be 1.18 µM. The increase in the AUC for Rosuvastatin upon co-administration of Glimepiride is calculated as mentioned below:

Dose	8 mg
Cmax	578 ng/mL
Mol.Wt	490.62
C_{max} (µM)	1.18
Dose (mMol)	0.016
Fa*Fg	1
Ka	0.1 min^{-1}
IC_{50} (µM)	3.55
Ki ($IC_{50}/2$)	1.77
Inlet $_{max}$	1.09
Inlet/K_i	0.612
1+ [I] inlet, max /K i	1.612

DISCUSSION AND CONCLUSION:

Data from the above predictions result and classify that Glimepiride as an inhibitor for OATP transporter and a chance of drug-drug interactions in the clinic can be anticipated with co-administered drugs. Since, sulfonyl ureas like Glimepiride are used with statins in patients who are suffering from metabolic syndrome chronically; there is high possibility to see interaction associated at the drug transport level. The results from the R-value approach suggest Glimepiride may interact with drugs that rely on OATP1B1/1B3 for hepatic uptake.

However, such data is to be interpreted carefully in the clinic. Hence, the role of therapeutic monitoring come in to the place with drugs designated to be substrate for single metabolic enzyme or drug-transporter to avoid any untoward effects to the patient in the clinic.

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