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Influence of Enzyme Modulation on Drug Metabolism and Pharmacokinetics: Implications for Therapeutic Safety and Personalized Treatment

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ABSTRACT: Background: Variability in drug clearance mediated by drug-enzyme interaction can happen through three pathways, resulting in variable drug exposures; pharmacological inhibition, pharmacological induction and metaboliser phenotype, which takes a genetic approach, and these pathways are not often analysed in a single reproducible modelling approach. The goal of this study is to perform a population pharmacokinetic simulation study to quantify the impact of phenotyping of metaboliser (genotype of 2D6) on overall systemic drug exposure along with the effects of CYP3A4 enzyme inhibition and induction on the overall systemic exposure in a virtual patient population.

Methods: A single-compartment population pharmacokinetic model was moved over following the allometric principles and then 2 independent virtual populations of 900 virtual adult subjects (comprising 300 patients on each treatment arm) were simulated with 1000 patients, each with a fixed dose of the simulated model CYP2D6 substrate, and randomly distributed in silico metaboliser phenotype according to the published in vivo CYP2D6 metaboliser phenotype population frequencies. Independent t-tests, geometric

mean ratios (GMR) and perceived 90% CI, Kruskal-Wallis test were used to evaluate group differences in log transformed $AUC_{0-\infty}$.

Results: The administration of the simulated strong CYP3A4 inhibitor raised the $AUC_{0-\infty}$ by a GMR of 4.98 (90% CI 4.78–5.19; $p < 0.0001$); the strong inducer reduced the $AUC_{0-\infty}$ to a GMR of 0.31 (90% CI 0.29–0.32; $p < 0.0001$). The geometric mean $AUC_{0-\infty}$ was significantly higher in the Pm phenotype compared with the other phenotypes (519 ng·h/mL for ultrarapid metabolisers vs 8,873 ng·h/mL for poor metabolisers [$H=420.9$, $df=3$, $p < 0.0001$]); and all PMs were above a pre-specified supratherapeutic threshold of exposure, whereas none UMs were.

Conclusions: This virtual-population PK simulation shows that the enzyme inhibition/induction phenomenological model and/or the genetic-type defined phenotype are a unique and important contributor for the simulated drug exposure and can be incorporated in personalised prescribing by using enzyme-modulation-aware dosing algorithms, or by using genotype-informed dosing algorithms.

INTRODUCTION

One of the most important factors of drug exposure to the system is drug metabolism and this can have a significant effect on the amount and systemic availability of a drug- particularly considering its therapeutic index in that system (Hakkola et al., 2020). Most of the phase I oxidative biotransformation reactions are catalysed by the cytochrome P450 (CYP) superfamily and this, in combination with a few common abundant isoenzymes, contributes to the P450 mediated hepatic clearance of the majority of marketed drugs (Zanger & Schwab, 2013). A few-fold systemic exposure of victim drug may occur depending on the degree of change, and this can be designated as strong, moderate or weak depending on the amount of change (fold change) it causes to use a sensitive index substrate for the AUC to the concentration–time curve of the drug (Lee et al., 2024).

CYP3A4 is a broad hepatically metabolized substrate and has been associated with a variety of drug reactions, but notable, has high concentrations in the liver and gut wall, (higher concentrations than all other druggable class members) clinically relevant (Ainurofiq & Ismaya, 2023). Besides these inter-individual metabolic differences (biological basis) there are also differences in enzyme activity (genetic basis): poor metabolizer (P.TYPE) or fast metaboliser (U TYPE) (CYP2D6 enzyme – common polymorphisms – and CYP2C19 enzyme – common polymorphisms –). In regard to systemic exposures, there were almost a 100-fold different exposures to some of these drugs for examples of TYPE. (Bousman et al., 2023; Kee et al., 2023) A few of these examples are been adapted to specific dosages of medicines to specific phenotypes, as some Consortium organisations, for example the Clinical Pharmacogenetics Implementation Consortium (CPIC) have done, and larger pragmatic trials of pre-emptive use of panel testing for specific phenotypes have confirmed that genetically using these trials makes for a substantial reduction in clinically challenging adverse drug reactions in daily clinical practice (Sven et al., 2023). If the enzymes were truly the ones that would break down a significant amount of the types of drugs commonly taken orally (Iversen et al., 2022) then some slight change in activity would have an appreciable effect – let's hope not so much that they're no longer usable to treat diseases but that they're just a point.

Whilst individual clinical reports or consortium guidance describe the individual drug–gene or drug–drug interactions, there are few studies that quantifies the three relevance of enzyme inhibition, induction of these enzymes and/or the genetically determined phenotype to alter difference in exposure at the population level, compared to statistically similar to the pharmacokinetics from phase 2 (no modulation) under a controlled (covariate adjusted) conditions within a single reproducible modelling system. The real life data on PK is often limited in number, it may be skewed due to the use of dosage, there are many other variables with regard to the illness, such as co-morbidity and other medications, etc., which all make the data "noisy" (difficult to work with) when attempting to answer this question. It may be a daunting problem to build a big population of PK's for different distribution of the covariate levels for a single condition, but can be achieved through a simulation model with a controlled model population. Thus, we conducted a Monte Carlo simulated (simulated throughout all of the study) population pharmacokinetic analysis on the 2 hypotheses: (i) statistically significantly higher (or lower) simulated $AUC_{0-\infty}$ with co-administration of the resident drug compared to an unmodulated simulated population and (ii) statistically significantly more or less simulated $AUC_{0-\infty}$ with the different drug metaboliser phenotypes compared to the normal metabolite phenotype,

which we deemed to be the base one. Therefore, we performed a Monte Carlo simulated population pharmacokinetic study on these 2 hypotheses: (i) statistically significantly higher (or lower) simulated $AUC_{0-\infty}$ with co-administration of the resident drug compared to an unmodulated simulated population and (ii) statistically significantly more or less simulated $AUC_{0-\infty}$ at the drug doses studied with the different drug metaboliser phenotypes than with the normal one. That simulation study is described, analyzed and presented as it is the focus of this Paper.

METHODOLOGY

Study design: A population pharmacokinetic simulation (in silico virtual cohort) was used. The virtual clinical trial cohorts, covariates and pharmacokinetic outcomes were created by computational modelling, which was pre-specified for this trial, with no identifiable real patient data used or required which meant formal ethics committee approval was not relevant.

Computational implementation: All the values were printed and reported, and the simulation was performed using Python 3.11 code with fixed pseudo-random seed, using the NumPy and SciPy libraries. A one compartment model was used, with first order oral absorption, that had been accepted for regulatory evaluation of drug interactions and is becoming more popular in the context of physiologically-based pharmacokinetic (PBPK) analysis (Shaik et al., 2019; Chou et al., 2025). The clearance - simulated body weight relation, total clearance (CL) to simulated body weight (WT), was also allometric with each virtual subject, just as in most population studies of coefficient of variance of the unexplained inter-individual coefficient of variance, 25% ($CL = CL_{typ} \times (WT/70)^{0.75} \times e^{\eta}$).

Experiment 1 (enzyme modulation): Three separate virtual arms of 300 subjects, each were generated using the following equations: an unmodulated control arm, a strong inhibitor arm, the clearance was multiplied by a factor of 0.21 log normally distributed (79% median reduction, in the range that defines a strong CYP3A4 inhibitor) (Lee et al., 2024); a strong inducer arm, the clearance was multiplied by a factor of 3.40 log normally distributed (median, No lower limit defined) (Lee et al., 2024). The above-mentioned clearance and volume of distribution parameters were simulated in each subject, and then $AUC_{0-\infty}$, C_{max} and half-life were calculated.

Experiment 2 (genetic polymorphism): One thousand independent virtual patients were provided with a dosage of Cyp3A4 drug (50mg) with a constant bioavailability of 0.7. Relative clearance multipliers (medians of 0.15, 0.50, 1.00 and 2.50, for the poor, intermediate, normal and ultrarapid metabolisers, respectively) were stochastically assigned to each subject based on population frequencies derived from CPIC and pharmacogenomic population studies (Bousman et al., 2023, Shubbar et al., 2024) and then applied to allometrically scaled clearance.

In Experiment 1, group differences were compared for statistical analysis with log transformed $AUC_{0-\infty}$ which were then compared by an independent-samples t-test or using geometric mean ratios (GMR) and 90% confidence interval (CI) according to standard method for drug interaction/bioequivalence. In Experiment 2 the differences among the four groups of CYP2D6 phenotypes were checked with the Kruskal-Wallis test and the agreement of assigned/planned and target phenotype frequencies were confirmed with the Chi-Square goodness of fit test. The percentage of each phenotype expected to have exposure levels at or above the a priori supratherapeutic exposure dilution target for 2x the geometric mean $AUC_{0-\infty}$ of the normal metabolisers was used in the calculations for the normal metaboliser group at the standard dose. A significance level of $\alpha = 0.05$ (two-tailed) was used; all the analyses were done within SciPy 1.17.

RESULTS

Virtual population characteristics

Considering the Experimental group of 900 subjects - mean weight of 75.5kg (standard deviation of 14.6kg); mean age of 52.3 years (SD 15.9 years) little difference was seen among the three groups. Also the 1 000 virtual poor, and intermediate CYP2D6 metabolisers were randomly allocated a CYP2D6 metaboliser sub-type and the 1 000 virtual extended and ultra-extended CYP2D6 metabolisers were also arbitrarily assigned a CYP2D6 metaboliser sub type (Table 1 and Fig. 1). This basic information was common for all experiments and may not have been common between experiments in real exposure since the differences in exposure were measured against this particular exposure model, but not the differences between the rather basic information of the different experiments.

Table 1. Baseline characteristics of the two simulated virtual-population cohorts. PM, poor metaboliser; IM, intermediate metaboliser; NM, normal metaboliser; UM, ultrarapid metaboliser.

Cohort	n (total)	Arms / phenotype groups	Mean weight, kg (SD)	Mean age, years (SD)
Experiment 1 (CYP3A4 modulation)	900	Control (n=300); Strong inhibitor (n=300); Strong inducer (n=300)	75.5 (14.6)	52.3 (15.9)
Experiment 2 (CYP2D6 phenotype)	1,000	PM (n=54); IM (n=96); NM (n=785); UM (n=65)	75.2 (14.6)	52.8 (15.7)

Effect of CYP3A4 inhibition and induction on simulated exposure (Experiment 1)

In the unmodulated control arm, the model CYP3A4 substrate achieved a geometric mean $AUC_{0-\infty}$ of 5,752 ng·h/mL (90% CI 5,603–5,905), a geometric mean C_{max} of 404.3 ng/mL (90% CI 402.6–406.0), and a median elimination half-life of 7.85 hours. They found, when taken at the same time as the simulated strong CYP3A4 inhibitor, that geometric mean $AUC_{0-\infty}$ increased by 4.98-fold, to 28,652 ng·h/mL (90% CI 27,744–29,589) compared with reading group 1 (90% CI 4.78–5.19; independent t-test on log-AUC, $t=63.82$, $p<0.0001$), with a median half-life of 39.63 hours. Coadministration of the simulated strong CYP3A4 inducer reduced the geometric mean $AUC_{0-\infty}$ to 1,755 ng·h/mL (90% CI 1,697–1,815), a GMR of 0.305 relative to control (90% CI 0.292–0.318; $t=-46.00$, $p<0.0001$), and shortened the median half-life to 2.44 hours (Table 2).

All there was was an equal exposure difference with respect to the one that was created by the same pharmacokinetics as the reference dose of 1.0 (the average exposures of both were the same), or a difference of 1.0-fold. The 90% upper and lower bound of GMR, however, was definitely separating the differences in exposure and pharmacokinetics between the groups of "exposed" and "non-exposed" subjects, and gave a "statistical" contrast between the differences of simulated exposure compared to non-exposure. The latter, that is to say "a clearance-based interaction", would have been predicted to influence total exposure (AUC) and not the rate of rise in the drug's plasma concentration (C_{max}) and this prediction was confirmed by proportional changes in C_{max} in the inhibitor arm (1.18) as well as the inducer arm (0.76).

Table 2. Simulated pharmacokinetic outcomes for a model CYP3A4 substrate (dose 200 mg, $F = 0.9$) under baseline, inhibited, and induced conditions ($n = 300$ per arm). *Independent t-test on log-transformed $AUC_{0-\infty}$ versus control.

Arm	n	Geometric mean $AUC_{0-\infty}$, ng·h/mL (90% CI)	GMR vs control (90% CI)	Geometric mean C_{max} , ng/mL (90% CI)	Median $t_{1/2}$, h	p-value*
Control (no interacting drug)	300	5,752 (5,603–5,905)	1.00 (reference)	404.3 (402.6–406.0)	7.85	—
+ Strong CYP3A4 inhibitor	300	28,652 (27,744–29,589)	4.98 (4.78–5.19)	476.7 (475.8–477.7)	39.63	<0.0001
+ Strong CYP3A4 inducer	300	1,755 (1,697–1,815)	0.305 (0.292–0.318)	306.5 (303.3–309.7)	2.44	<0.0001

Effect of CYP2D6 genotype-predicted phenotype on simulated exposure (Experiment 2)

The present study did not reveal any differences for the normal-metabolisers genetic polymorphism (78.5%) ($p=0.378$), 96 subjects in the intermediate and 54 in the poor groups respectively and 65 subjects in the normal group, indicating the internal validity of the random selection procedure adopted for the assignment of the phenotype. At the standard dose, there was a roughly 17-fold difference in exposure due to the difference in geometric mean $AUC_{0-\infty}$: 8,873 ng·h/mL (90% CI 8,109–9,709) in poor metaboliser phenotype; 2,634 ng·h/mL (90% CI 2,480–2,798) in intermediate metaboliser; 1,384 ng·h/mL (90% CI 1,352–1,416) in normal metaboliser and 519 ng·h/mL (90% CI 480–561) in an ultrarapid metaboliser phenotype (Table 3).

The Kruskal–Wallis test was used for four groups of exposure and the difference was demonstrated to be statistically significant ($H = 420.89$, $df = 3$, $p < 0.0001$).

When using the supratherapeutic exposure threshold of $2,767 \text{ ng}\cdot\text{h}/\text{mL}$ (double the geometric mean $\text{AUC}_{0-\infty}$ of the normal metaboliser group), simulations indicated that 100% of poor metabolisers, 46.9% of intermediate and 3.4% of normal metabolisers, but no ultrarapid metabolisers, exceeded this threshold at the fixed dose of 200 mg twice daily (Table 3). It reflects the dose difference in exposure that can be expected in a population of high and low activity CYP2D6 individuals and should be considered and taken into account when considering the same risk of efficacy and toxicity when dosaging the metabolites.

Table 3. Simulated CYP2D6 metaboliser-phenotype distribution and $\text{AUC}_{0-\infty}$ outcomes at a fixed standard dose ($n = 1,000$). Kruskal–Wallis $H = 420.89$, $df = 3$, $p < 0.0001$; phenotype-assignment goodness-of-fit $\chi^2 = 3.09$, $df = 3$, $p = 0.378$.

Phenotype	n (% of cohort)	Geometric mean $\text{AUC}_{0-\infty}$, $\text{ng}\cdot\text{h}/\text{mL}$ (90% CI)	% exceeding supratherapeutic threshold ($>2,767 \text{ ng}\cdot\text{h}/\text{mL}$)
Poor metaboliser (PM)	54 (5.4%)	8,873 (8,109–9,709)	100.0%
Intermediate metaboliser (IM)	96 (9.6%)	2,634 (2,480–2,798)	46.9%
Normal metaboliser (NM)	785 (78.5%)	1,384 (1,352–1,416)	3.4%
Ultrarapid metaboliser (UM)	65 (6.5%)	519 (480–561)	0.0%

Summary of findings

In both cases (with enzyme reduction both positive and inhibitory) the activity statistically significance in presence of systemic actions in the direction positive and negative as expected for the enzyme activity. The amount of systemic exposure to enzymes (either increased or decreased) changed very much according to the type of enzyme, and generally by a similar degree as isolated changes reported in the clinical literature, either as enzyme inhibitors or enzyme activators. The results have been confirmed in two virtual experiments, in both of which the level of the drug in the population was manipulated either by altering the level of an enzyme in a virtual model (either pharmacologically or by a desired heritable genetic variation designed for the purpose), or both.

DISCUSSION

The consequence of a different exposure (as a result of modification by the pharmacologic effect of the drug), and consequence of a different availability (due to the genetic difference [phenotype]) gives the same convenient modelling framework, relative size and statistical significance of 'exposure-variability', which simulate consequence of a different exposure (interaction), and consequence of a different pharmacologic effect (pharmacogenomic studies). The simulated $\text{AUC}_{0-\infty}$ under strong CYP3A4 inhibition of 4.98 is in the range of empirically observed potent inhibitors co-administered with sensitive CYP3A4 substrates and the underlying predicted 79% inhibition of clearance is similar to the magnitude of the inhibition reported for mechanism-based CYP inhibition with clinically investigated compounds (Hakkola et al., 2020; Lee et al., 2024). Similarly, the same size of simulated (GMR 0.305) clearance decrease was seen during induction, as compared to when other potent CYP3A4 substrates were coadministered with the potent CYP3A4 inducer published in the literature (Hakkola et al., 2020). While the chemical agent itself was not used as a real compound which was approved for FDA use, the similarity of the different parameterisations of the virtual arms demonstrated face validity of the modelling approach.

The extent to which dose-response studies of classical PK have been inhibited by gemfibrozil, which results in clinically relevant interactions with cerivastatin (and presumably other CYP2C8/CYP2C9 substrates), indicates that more than an artefact, this type of inhibition is a generally occurring effect amongst all members of the CYP superfamily (Shitara et al., 2004; Wen et al., 2001). This exposure gradient was also observed by the CYP2D6 phenotype simulation where none of the 100 PM simulated exposure was below the pre-specified supratherapeutic limit while all 100 UR simulated exposure was above this supratherapeutic limit, nearly 17-fold more. The finding appears to have provided a solid quantitative rationale for CPIC/other

genotype-specific dosing recommendations for warfarin in patients with these CYP2C9/VKORC1 polymorphisms (Bousman et al., 2023) and is consistent with the improved anticoagulation control observed in trials of using panel-based pharmacogenomic tests in warfarin to make goal pre-emptive dosing recommendations (Swen et al., 2023) and with the reduction in the number of clinically relevant ADRs shown to be associated with such pharmacogenomic tests in warfarin patients during the PREPARE implementation project (Swen et al., 2023). And in formalized genotype-to-dose translation tools, such as are available for warfarin, a blueprint exists to provide translation tools for others that are CYP2D6- and CYP2C19-dependent drugs. The structure of genotype-to-dose translation tools like the warfarin is a blueprint for how to incorporate AllStar tools into other CYP2D6- and CYP2C19-dependent drugs (Pirmohamed et al., 2013; Johnson et al., 2011).

A few notes of caution for the interpretation of these findings. First and most importantly, the following is not an empirical clinical or laboratory trial, but a computation simulation of an hypothetical substrate and as such, the values of absolute exposures should not be relied upon and shall only be considered illustrative, but is compound specific because the parameters of the model were anchored to ranges reported in the literature, which also reported background clearance and background bioavailability and magnitude of interaction. Secondly, one-compartment, linear pharmacokinetic models fail to represent non-linear (saturable) elimination, displacement of plasma-protein binding by other drugs (plasma-protein binding) or transporter-mediated interactions, which are all important in some instances of real drug–drug interaction (Lee et al., 2024). Moreover, hepatitis and renal impairment were not incorporated into the model and the model did not take into account multiple drug co-usage common in older people which may cause adverse drug reactions that are enzyme mediated (Khurshid et al., 2025) known to be a real world pharmacokinetic variation. Though enterically metabolizing orally ingested drugs is well known to depend upon the host microbiome, emerging evidence suggests that this ability will also significantly vary across individuals and should therefore be a new stochastic covariate in future simulation frameworks (in addition to host genotype) (Cai et al., 2023; Mastroiilli et al., 2026; Pant et al., 2023).

The internal consistency of the simulation, given the high significance of the random part of the simulation which arises from the Gaussian response/dose relationship and the deterministic part of the simulation arising from the very large simulation, however, offers good reason to use it as a hypothesis-generating tool; and an educational tool to quantify the risk of focussed clinical interaction studies used to investigate drug efficacy and toxicity in a patient-centred approach prior to, and as well as, after exposure to a large simulation. The modelling process could be elaborated to include patient level pharmacokinetic parameters of individual approved CYP3A4 and CYP2D6 substrates and extended to other covariates (hepatic function, multiple drug interactions etc.) which could be useful and may pave the way for further prospective testing on whether the use of patient level adaptive dose recommendations based on chromosomal CYP3A4 and/or CYP2D6 phenotyping and the inclusion of these covariates into the models can help reduce the number of adverse drug reactions that occur in clinical decision support systems, as discussed in a previous paper (panel based pharmacogenomic dosing) (Swen et al., 2023).

CONCLUSION

The simulation study of the population pharmacokinetic (PK) evidence statistically supported the presence of clinically-relevant differences between it in terms of drug exposure for the different populations due to pharmacologic induction by a drug (e.g. an inhibitor) or caused by the genetically determined CYP2D6 phenotype. When coadministered with a strong CYP3A4 inhibitor, it resulted in a nearly 5-fold increased amount of simulated exposure, as well as less than 1/3rd of the simulated exposure when coadministered with a strong inducer, magnitudes similar to the real-world drug–drug interactions reported in the clinical literature. When the standard dose was used with the CYP2D6 phenotype, the spread of exposure was even wider: the low CYP2D6 phenotype had exposures that were above a prespecified "supratherapeutic" threshold with a broad distribution, while the high CYP2D6 had exposures below a prespecified "subtherapeutic" threshold, with a broad distribution and distinct quantitative shape. Since the parameters derived from the literature were, by their nature, dependent on the simulation, and since there was no fixed environment (set up) for the simulation, the multitude of "virtual" cohorts obtained was not a "real" cohort but rather a straightforward approach with the clinical data represented by the "covariates". The results support: (1) the usefulness of enzyme-modulation-aware dosages and genotype-informed dosages; (2) population based polypharmacy groups – the groups that have higher risk of developing enzyme-mediated ADRs and the groups that are more likely to get ADRs mediated by enzymes – should be targeted to these types of dosages. This framework should be expanded to individual-tailored up to approved pharmacokinetics/pharmacodynamics-informed dosing prediction scenarios to individual patient pharmacokinetics data, taking into account other pharmacovigilance-related parameters such as liver dysfunction, multi-

drug treatment (polypharmacy), clearance by gut microbiome and testing the efficacy of recommended extensions derived from simulation when applied to pharmacovigilance scenarios (as a drug-safety decision support tool for preventing adverse drug reactions).

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