

Predicted metabolic drug clearance with increasing adult age

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The clearance of drugs metabolized by CYP enzymes is decreased in the elderly.
- *In vitro-in vivo* extrapolation coupled with physiological-based pharmacokinetic (IVIVE-PBPK) modelling and simulation is used widely to predict metabolic drug clearance.

WHAT THIS STUDY ADDS

- Similar to the broad body of clinical literature for drugs metabolized by CYP enzymes, IVIVE-PBPK modelling and simulation using Simcyp® predicts decreased weight-normalized metabolic clearance of 20–40% in the elderly.
- This prediction is a direct consequence of age-related decreases in the physiological parameters used for IVIVE of metabolic drug clearance; mean microsomal protein g⁻¹ of liver, liver weight, hepatic blood flow and human serum albumin concentration.
- Predictions of decreased metabolic drug clearance with increasing adult age are similar for drugs with different hepatic extraction ratios and protein binding characteristics, and appear to be independent of drug-specific physiochemical parameters, the CYP enzymes responsible for metabolism and their fractional contribution to metabolic clearance.
- Decreased clearance in the elderly may be similar for all drugs eliminated exclusively by CYP enzymes.

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AIM

To determine the effect of increasing adult age on predicted metabolic drug clearance.

METHOD

Predicted metabolic drug clearances (CL_{PT}) were determined using *in vitro-in vivo* extrapolation coupled with physiological-based pharmacokinetic modelling and simulation (IVIVE-PBPK) in Simcyp®. Simulations were conducted using CYP-selective 'probe' drugs with subjects in 5 year age groups (20–25 to 90–95 years). CL_{PT} values were compared with human pharmacokinetic data stratified according to age (young = 20–40 years and elderly = 65–85 years) and gender. Age-related changes in the physiological parameters used for IVIVE of CL_{PT} were described.

RESULTS

Predicted metabolic drug clearances decreased with increasing adult age to approximately 65–70 years: caffeine from 1.5 to 1.0 ml min⁻¹ kg⁻¹ (a 33% decrease), S-warfarin from 0.100 to 0.064 ml min⁻¹ kg⁻¹ (36%), S-mephenytoin from 4.1 to 2.5 ml min⁻¹ kg⁻¹ (39%), desipramine from 10.6 to 7.3 ml min⁻¹ kg⁻¹ (31%) and midazolam from 5.4 to 3.9 ml min⁻¹ kg⁻¹ (27%). Except for S-mephenytoin, predictions were within 3.5-fold of clearances from clinical studies when stratified by age and gender. A trend towards higher CL_{PT} was observed in females, but this was only statistically significant in larger virtual trials. Physiological parameters that determine CL_{PT} decreased with increasing adult age: mean microsomal protein g⁻¹ of liver, liver weight, hepatic blood flow and human serum albumin concentration.

CONCLUSION

Decreased metabolic clearance in the elderly was predicted by Simcyp® and was generally consistent with limited clinical data for four out of five drugs studied and the broader literature for drugs metabolized by CYP enzymes. IVIVE-PBPK may be increasingly useful in predicting metabolic drug clearance in the elderly.

Introduction

Clearance is the most important pharmacokinetic parameter to consider in clinical practice because it determines steady-state drug concentration at a given maintenance dose. Elderly people, defined as those over 65 years of age, are the largest users of drugs and the most susceptible to adverse drug reactions (ADRs) [1]. Decreased clearance resulting in high drug concentrations is a major cause of ADRs. In particular, it is estimated that metabolic clearance by cytochrome P450 enzymes (CYP) is approximately 30–50% lower in older compared with younger people [2–5].

Studies with high hepatic extraction ratio (E_H) drugs ('flow-limited') consistently show decreased clearance in the elderly as a result of decreased hepatic blood flow. The literature is also consistent for low E_H drugs ('capacity-limited') with low protein binding (PB), for which decreases in clearance largely reflect reduced intrinsic clearance by the liver ($CL_{int,liver}$). However, data for capacity-limited drugs with high PB are inconsistent, with studies showing decreased, unchanged, and even increased clearance in the elderly.

A possible reason for this inconsistency is variable consideration of renal function in studies that use urinary drug : metabolite ratios and urinary recovery of metabolites to measure differences in metabolic clearance i.e. these indices of enzyme activity are potentially confounded by the effect of renal function [6,7]. Another plausible explanation is the use of total drug concentration (bound + free drug) to estimate clearance (referred to as

'total drug clearance') [2,8]. If clearance is exclusively metabolic, decreases in total drug clearance from reduced $CL_{int,liver}$ may be masked by increases in the free fraction in blood, which may occur for some, but not all drugs, in the elderly [9, 10]. This is illustrated hypothetically in Figure 1. However, when the clearance of capacity-limited drugs with high PB is estimated from free drug concentrations, 'free drug clearance' is reduced in the elderly to a similar degree as total clearance (30–50%) for drugs with other E_H and PB characteristics [2]. This is because the free clearance of capacity-limited drugs with high PB is exclusively dependent on $CL_{int,liver}$ and not confounded by changes in binding protein concentrations (note that 'free drug clearance', 'whole liver intrinsic clearance', 'free metabolic clearance' and 'hepatic intrinsic clearance' are used interchangeably in the literature). Thus, although total drug clearance is a valid measure for examining changes in clearance for flow-limited drugs and capacity-limited drugs with low PB, it has limitations when applied to capacity-limited drugs with high PB [2].

In vitro-in vivo extrapolation (IVIVE) coupled with physiological-based pharmacokinetic (PBPK) modelling and simulation is used widely to predict the metabolic clearance of drugs [11]. Simcyp®, an IVIVE-PBPK programme, predicts clearance across populations and not just in individuals [12–14]. Inter-individual variability in clearance may be assessed rapidly for new drug candidates, thus aiding the appropriate selection of drugs and dosing regimens for clinical studies [15]. Given that Simcyp® is used routinely in the pharmaceutical industry, the validity of its performance in predicting clearance in

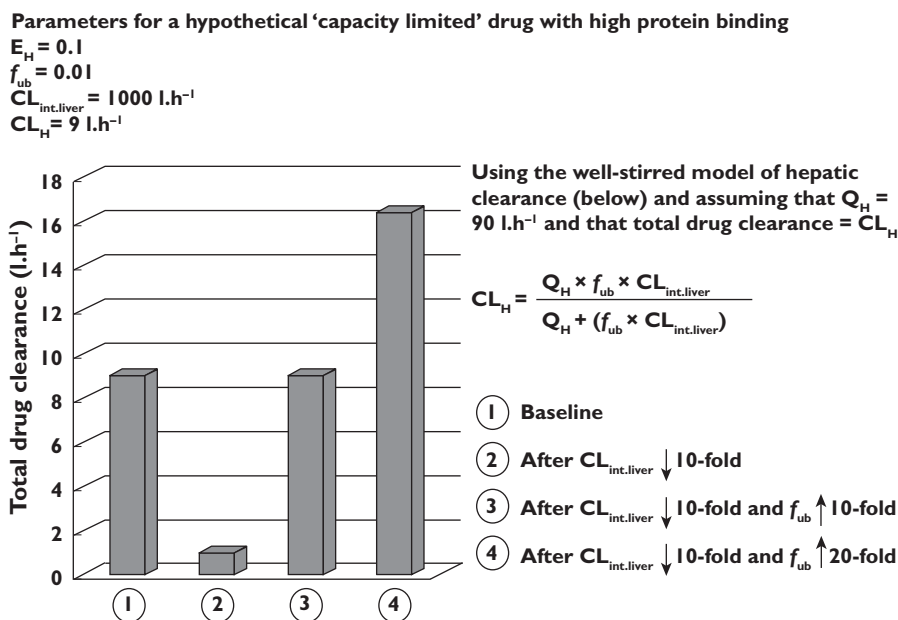


Figure 1

How total drug clearance can decrease, increase or remain unchanged following decreases in whole liver intrinsic clearance

different populations (e.g. poor metabolizers, paediatrics, the elderly etc.) is an important consideration when evaluating *in silico* data during preclinical drug development. However, an assessment of Simcyp® in predicting metabolic drug clearance with increasing adult age has not been conducted.

Thus, the primary aim of this study was to determine the effect of increasing adult age on predicted metabolic drug clearance using IVIVE-PBPK models in Simcyp®. The secondary aims were to investigate the effect of gender on predicted metabolic drug clearance, and to compare the predicted clearances with observed clearances from human pharmacokinetic studies.

Methods

Drugs used in simulations and IVIVE-PBPK of clearance

IVIVE-PBPK predicted metabolic drug clearances were determined using Simcyp® (V10). Five drugs were chosen for simulation studies based on their established use as selective *in vivo* 'probes' of the major drug metabolizing CYP enzymes [16], and because together they cover a range of E_H and PB characteristics: caffeine for CYP1A2 (low E_H with low PB), S-warfarin for CYP2C9 (low E_H with high PB), S-mephenytoin for CYP2C19 (high E_H with low PB), desipramine for CYP2D6 (intermediate E_H with high PB) and midazolam for CYP3A (low E_H with high PB) [17]. As the fraction excreted unchanged in urine (f_e) for each of these drugs is <0.05, total drug clearance was considered to equate to metabolic clearance.

In Simcyp®, IVIVE of $CL_{int,liver}$ for caffeine, S-mephenytoin, S-warfarin and midazolam is based on *in vitro* kinetic data from recombinant CYP using the following equation:

$$CL_{int,liver} = \left\{ \sum_{j=1}^n \left[\sum_{i=1}^n \frac{V_{max}(rCYP_j)_i \times CYP \text{ abundance}_j}{K_m(rCYP_j)_i} \right] \right\} \times MPPGL \times LW$$

where V_{max} (maximum reaction velocity) and K_m (Michaelis-Menten constant) describe the kinetics of metabolite formation by each recombinant CYP enzyme (j) involved in a particular metabolic pathway (i), CYP abundance is the amount of active enzyme per mg of microsomal protein, MPPGL is the mean microsomal protein per g of liver tissue and LW is liver weight [18]. For desipramine, the extrapolation in Simcyp® is conducted from human liver microsomal data using the above equation but without the CYP abundance term [18]. The well-stirred model shown in Figure 1 is then used to 'scale-up' $CL_{int,liver}$ to metabolic clearance by the liver. A model that predicts human serum albumin (HSA) concentration based on age, gender, body mass index and pregnancy status is incorporated in Simcyp® to

estimate the value of f_{ub} used in the well-stirred model. Since no covariates have been identified that may be modelled to determine accurately α_1 -acid glycoprotein concentration, variability in its concentration is randomly assigned in Simcyp® (Dr Zoe Barter, personal communication). Variability in drug clearance across populations and between population subgroups is estimated based on known variability in CYP abundance, MPPGL, LW, Q_H and f_{ub} [12–14].

Simulations

The 'PK Profiles' mode in Simcyp® was used to run virtual trials of single oral doses of each CYP-selective probe drug; 150 mg caffeine, 10 mg S-warfarin, 200 mg S-mephenytoin, 50 mg desipramine and 5 mg midazolam. North European Caucasian subjects (1:1 males to females) were used for all simulations. 'Duration of study' was set to record the area under the plasma concentration–time curve for each drug from the time of dose to infinity ($AUC(0,\infty)$). To determine the effect of increasing adult age on clearance, simulations were conducted for sequential 5 year age groups (20–25, 25–30, 30–35 etc.) up to 90–95 years. Simulations were repeated for each age group using three trial sizes; 1 trial \times 10 subjects ($n = 10$), 10 trials \times 10 subjects ($n = 100$), and 10 trials \times 100 subjects ($n = 1000$).

Drug clearances from clinical studies

The human clinical pharmacokinetic studies on caffeine, S-warfarin, desipramine and midazolam that were cited by the major review articles on decreased metabolic clearance in the elderly [2–4] were retrieved from the literature. An extensive literature search (Medline and Google-Scholar®) was also conducted to identify additional studies that could provide further clinical data for the five drugs studied. A total of seven studies were identified for which mean total plasma drug clearances (CL_{obs}) could be estimated for each probe drug in the following groups: young female (20–40 years), elderly female (65–85 years), young male (20–40 years) and elderly male (65–85 years). The basic characteristics of these studies are shown in Table 1. For the purpose of the comparisons with simulations, preference was given to data published in studies specifically designed to compare the pharmacokinetics of drugs in the young and elderly (e.g. the single studies on this topic for caffeine [19], desipramine [20] and midazolam [21]). Although there are numerous studies with clinical data on S-warfarin clearance in different age groups, data for the comparisons with simulations were taken from a recent publication for which access to the original data was possible [22] (see discussion for further details). Clearance data for S-mephenytoin was only available for young males and females [23], and data for the clearance of caffeine in young females were retrieved from two studies [24, 25]. All the clearance data from clinical studies were then normalized for mean total body weight and the units standardized to $ml \text{ min}^{-1} \text{ kg}^{-1}$.

Table 1

Characteristics of the clinical studies used to estimate observed clearances in the young and elderly

Drug	Subjects identified	Study location	Ethnicity of subjects	Reference
Caffeine	8 young males and 8 elderly males	UK	Caucasian	[19]
	18 young females	USA	17 Caucasian, 1 African American	[24]
	3 young males and 6 young females	Germany	NR	[25]
S-warfarin	10 young males, 10 young females, 10 elderly males, 10 elderly females	New Zealand	~90% New Zealand Europeans	[22]
S-mephenytoin	7 young males and 5 young females (23–49 years)	USA	NR	[23]
Desipramine	12 young males, 7 young females, 7 elderly males, 9 elderly females	USA	NR	[20]
Midazolam	10 young males, 10 young females, 9 elderly males, 11 elderly females	USA	NR	[21]

NR, not reported.

Data analysis

Mean predicted total drug clearances (CL_{PT}), ‘systemic plasma clearance’ in Simcyp®, were recorded from the ‘Clearance Trials SS’ tab on the Excel® output from Simcyp®. Mean predicted free drug clearances (CL_{PF}) were estimated by calculating ‘time-averaged $CL_{int,liver}$ ’ from the ‘ CL_{int} Profiles’ tab according to a previously published approach [15]. All predicted clearances were normalized for total body weight and the units standardized to $ml\ min^{-1}\ kg^{-1}$.

To allow comparison between the predicted and observed clearances (CL_{PT} and CL_{obs}) based on age and gender, mean CL_{PT} values were calculated from the results of simulation studies ($n = 100$) for each probe drug in the following groups: young female (20–40 years), elderly female (65–85 years), young male (20–40 years) and elderly male (65–85 years). The data were then normalized for mean total body weight and the units standardized to $ml\ min^{-1}\ kg^{-1}$. The mean CL_{PT} that was stratified in this way was then compared with mean CL_{obs} using the mean fold error (MFE):

$$MFE = \frac{CL_{PT(\text{mean,predicted})}}{CL_{obs(\text{mean,observed})}}$$

Differences in mean clearance between groups were analyzed using *t*-tests (R Program Suite 2.8). The significance level of all tests was $P < 0.05$.

The mean unbound drug fraction in blood ($f_{u,b}$) for virtual individuals was calculated from the unbound drug fraction in plasma ($f_{u,p}$) and the ratio of blood to plasma drug concentration (BP) according to the relationship $f_{u,b} = f_{u,p}/BP$. Mean MPPGL, LW and HSA concentration were calculated for each age group in simulations using caffeine ($n = 100$ trial design). Mean hepatic blood flow (Q_H) in each age group was estimated by multiplying mean cardiac output for females by 0.285 and mean cardiac output for males by 0.255.

Results

Simulations of CL_{PT} with increasing adult age

Figures 2(A) to (E) show the effect of increasing adult age on CL_{PT} . These simulations used a trial size of $n = 100$. The same trends were observed using $n = 10$ and $n = 1000$ (data not shown). For all drugs, mean CL_{PT} decreased with increasing adult age until approximately 65–70 years and was similar in magnitude for drugs with different E_H and PB characteristics: caffeine from 1.5 to 1.0 $ml\ min^{-1}\ kg^{-1}$ (a 33% decrease), S-warfarin from 0.100 to 0.064 $ml\ min^{-1}\ kg^{-1}$ (36%), S-mephenytoin from 4.1 to 2.5 $ml\ min^{-1}\ kg^{-1}$ (39%), desipramine from 10.6 to 7.3 $ml\ min^{-1}\ kg^{-1}$ (31%) and midazolam from 5.4 to 3.9 $ml\ min^{-1}\ kg^{-1}$ (27%). Women generally had slightly higher mean CL_{PT} than men.

Comparison of CL_{PT} with CL_{obs}

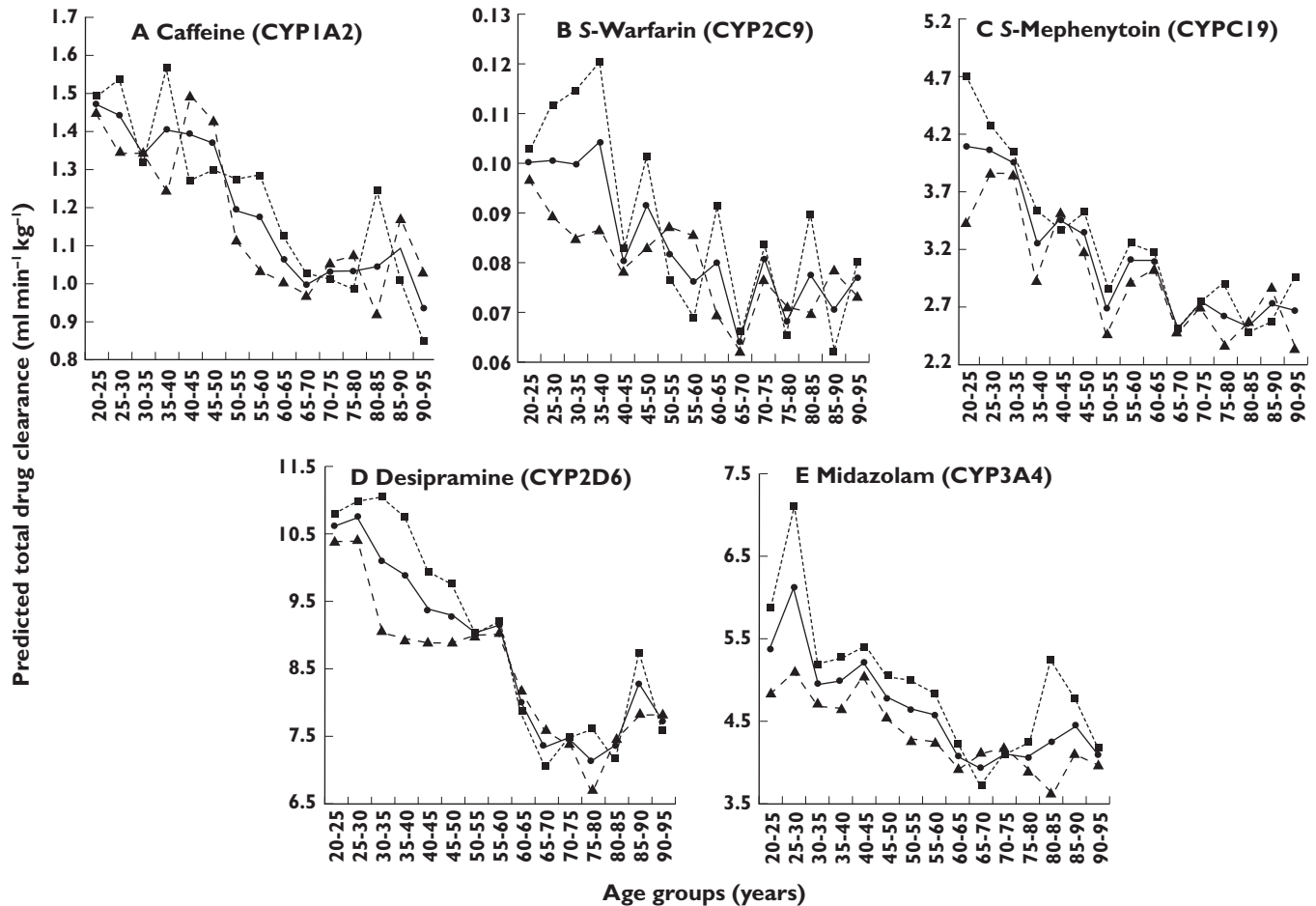
Mean CL_{PT} values stratified according to age (young vs. elderly) and gender were within 3.5-fold of estimated CL_{obs} values for caffeine, S-warfarin, desipramine and midazolam (Table 2). The mean fold errors of these predictions are shown in brackets next to the predicted clearances in Table 2. The mean CL_{PT} of S-mephenytoin was <10% that of the CL_{obs} in young men and women (Table 2).

The effects of age and gender on CL_{PT}

The differences in mean CL_{PT} with age (young vs. elderly) were statistically significant for all drugs even in virtual trials of 10 subjects ($P < 0.05$). Larger virtual trials ($n = 100$ and 1000) were required to demonstrate statistically significant differences in CL_{PT} between genders (data not shown).

The effects of covariates on CL_{PT} and CL_{PF}

For all drugs, the decreases in mean CL_{PF} (‘time-averaged $CL_{int,liver}$ ’) with increasing adult age were marginally greater than the decreases in CL_{PT} . Comparing the 20–25 and 65–70 year age groups, the decreases in CL_{PF} were 36, 39,


Figure 2

Effect of increasing adult age on the predicted total drug clearance of CYP-selective probe drugs in Simcyp®. Data points represent mean clearances for all subjects (●), for female subjects only (■) and for male subjects only (▲) in the $n = 100$ simulations

47, 40 and 32% for caffeine, S-warfarin, S-mephenytoin, desipramine and midazolam, respectively (Figure 3). As stated above, corresponding decreases in CL_{PT} were 33, 36, 39, 31 and 27% (Figure 2).

The physiological parameters used in Simcyp® to predict metabolic drug clearance are shown in Figure 4. Lower mean MPPGL and LW contribute to decreases in CL_{PF} in older subjects. With respect to the determinants of CL_{PT} , mean Q_H decreased from 82 to 68 $l\ h^{-1}$ (18%). Mean HSA concentration decreased from 45.6 to 44.0 (3.5%) between 20–25 and 65–70 years (Figure 4). Consequently, the mean f_{ub} increased by 2, 7, 2 and 6% for caffeine (0.692 to 0.708), S-warfarin (0.014 to 0.015), S-mephenytoin (0.818 to 0.834) and midazolam (0.050 to 0.053), respectively. The mean f_{ub} of desipramine decreased 1% (0.218 to 0.216).

Discussion

This is the first study to investigate systematically the effect of increasing adult age on predicted metabolic drug clear-

ance. IVIVE-PBPK using Simcyp® predicted a weight-normalized metabolic drug clearance 20–40% lower in elderly compared with younger adults. Although simulation data should always be interpreted in the context of the limitations of IVIVE approaches, this result is generally consistent with the changes reported in clinical studies for drugs eliminated by CYP enzymes (see discussion on specific drugs below) [2–5]. Age-related changes in Q_H , LW and the hepatic endothelium are considered to be primarily responsible for decreased metabolic clearance with age rather than changes in CYP activity or expression [1]. This decline with age is replicated in the functions for extrapolation factors in Simcyp® – MPPGL, LW and Q_H . As these are physiological parameters, the clearance of any drug eliminated exclusively via CYP will be affected similarly by increasing adult age in Simcyp®. Indeed, Figures 2 and 3 show comparable percentage decreases in CL_{PT} and CL_{PF} for each probe drug. Clearance predictions for drugs metabolized by multiple CYP enzymes will therefore be insensitive to the fraction of drug metabolized by each enzyme ($f_{m_{CYP}}$). Thus, the current status of Simcyp® in

Table 2

Comparison of predicted total drug clearance (CL_{PT}) with observed clearance from clinical studies (CL_{obs}) when stratified according to age (young = 20–40 years and elderly = 65–85 years) and gender. The mean fold error between observed and predicted total drug clearance is given in brackets next to the predicted value

CYP-selective probe drug	Young female (ml min ⁻¹ kg ⁻¹)		Elderly female (ml min ⁻¹ kg ⁻¹)		Young male (ml min ⁻¹ kg ⁻¹)		Elderly male (ml min ⁻¹ kg ⁻¹)		Estimated reduction in clearance (male)		
	Predicted (CL _{PT})	Clinical (CL _{obs})	Predicted (CL _{PT})	Clinical (CL _{obs})	Predicted (CL _{PT})	Clinical (CL _{obs})	Predicted (CL _{PT})	Clinical (CL _{obs})	Predicted	Clinical	
Caffeine	1.48 (0.87)	1.75 [24] 1.66* [25]	1.07 (NA)	NA	1.35 (0.83)	1.42 [19]	1.88* [25]	1.01 (0.63)	1.60 [19]	25.2%	-12.7 to 14.9%
S-warfarin	0.112 (1.47)	0.076† [22]	0.076 (1.90)	0.040† [22]	0.090 (1.88)	0.048† [22]		0.070 (1.15)	0.061† [22]	22.2%	-27.1%
S-mephenytoin	4.14 (0.09)	59.0‡ (CL/F) [23]	2.66 (NA)	NA	3.53 (0.06)	59.0‡ (CL/F) [23]		1.54 (NA)	NA	56.4%	NA
Desipramine	10.9 (0.49)	22.0 (CL/F) [20]	7.32 (0.35)	20.9 (CL/F) [20]	9.72 (0.34)	28.7 (CL/F) [20]		7.27 (0.42)	17.3 (CL/F) [20]	25.2%	39.7%
Midazolam	5.86 (0.63)	9.39 [21]	4.33 (0.58)	7.50 [21]	4.84 (0.62)	7.75 [21]		3.97 (0.90)	4.41 [21]	18.0%	43.1%

*Data are mean values excluding subjects 4, 9 and 12 (>40 years). †Reported CL/F taken as CL since F_i is assumed to be complete [36]. ‡Data are mean values for 12 volunteers (23–49 years) after weight normalization using 70 kg. NA, data not available.

predicting 20–40% lower metabolic clearance in elderly people is independent of drug-specific physiochemical parameters, the CYP enzymes responsible for metabolism, and their fractional contributions to clearance (e.g. specific *f*_{mCYP} values).

Simulated CL_{PT} and CL_{PF} decreased with increasing adult age until approximately 65–70 years (Figures 2 and 3). The lack of further decreases in predicted clearances after this age appears to result from plateauing of the MPPGL decrease (Figure 4). The exact reason why MPPGL fails to decrease further with advancing age is unknown. However, this pattern may simply reflect bias in the mean MPPGL derived from liver samples in those >65 years, since they may be relatively healthy individuals who have outlived their counterparts.

IVIVE-PBPK modelling of CL_{PT} in elderly vs. young males and females was compared with clinical data that describe the clearance of caffeine, S-warfarin, desipramine and midazolam, but such a comparison was not possible for S-mephenytoin (Table 2). In each of these cases, comparisons were limited by the small sample sizes in the clinical studies. For example, the only study to investigate the effects of age on caffeine clearance showed slightly higher total clearance in elderly men, although this difference was not statistically significant [19]. In contrast, when clearance data from separate studies in young and elderly men are compared, a modest decrease in total caffeine clearance with ageing is found (14.9%) [19, 25]. However, this approach introduces additional sources of uncertainty and provides unconvincing evidence for a negative correlation between increasing adult age and caffeine clearance. Interestingly, the effects of adult age on caffeine CL_{PT} resemble clinical data with theophylline, another capacity-limited CYP1A2-selective probe with low PB. Clinical data show that the total clearance of theophylline is significantly decreased in the elderly (22–35%) [3] despite increases in the fraction unbound (20–25%) [9]. When theophylline is studied in Simcyp®, CL_{PT} decreases to a similar degree as shown in clinical studies (21%, simulations not shown). Thus, the effects of increasing adult age on the clearance of drugs predominantly metabolized by CYP1A2 may require consideration on a case-by-case basis.

Clinical data on S-mephenytoin clearance are scarce. The decrease in CL_{PT} shown here (39%) is consistent with lower recovery of 4-hydroxymephenytoin (35%) and a decreased S : R enantiomeric ratio (25%) in the urine of patients ≥50 years [26, 27], although the effect of changes in renal function may contribute to this result. In the eight studies that report changes in total S-warfarin clearance with ageing, most found a significant decrease with age, although in two of the studies this was only a trend [2, 22]. The majority of these studies were not designed to investigate specifically changes in clearance with age and data are not available to allow for a direct comparison with the Simcyp® data generated here. However, for the studies in which multiple regression analysis or population pharma-

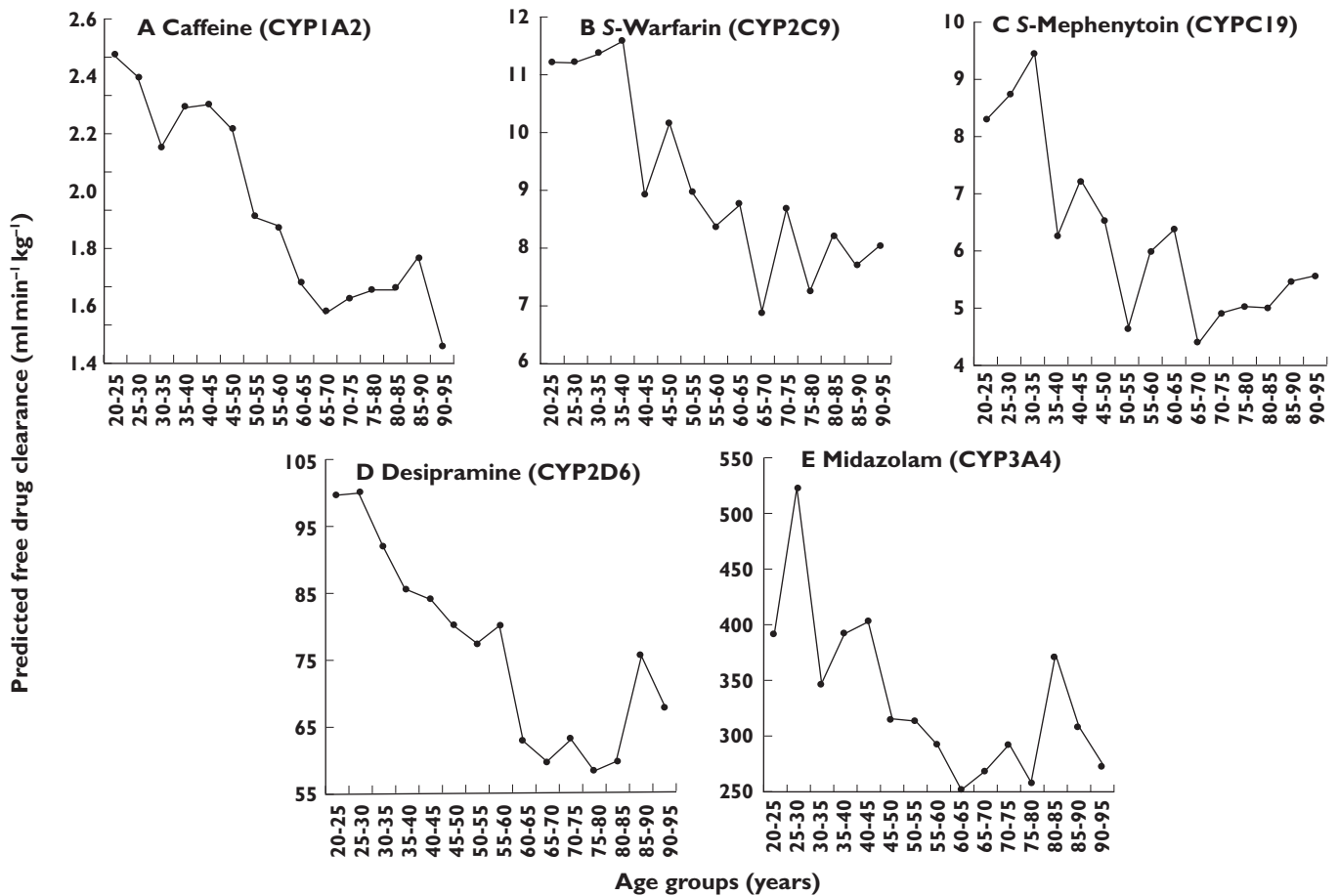


Figure 3

Effect of increasing adult age on the predicted free drug clearance of CYP-selective probe drugs in Simcyp®. Data points represent mean clearances for all subjects in the $n = 100$ simulations

cokinetic modelling was used on populations of 39–306 patients, the decline in S-warfarin clearance with age was reported to be 0.3–1% per year [22], which roughly translates to a 14–45% decline between the young and elderly age groups used in the Simcyp® simulations. For one recent study that specifically investigated the influence of adult age on warfarin clearances [22], it was possible to stratify the results as shown in Table 2. This analysis showed a significant decrease (48%) in total S-warfarin clearance in women but an increase (27%), although not statistically significant, in men. When females and males were combined, a modest decrease in total S-warfarin clearance was found between the young and the elderly (<15%, data not shown). Since the CL_{PT} of S-warfarin was decreased by 36%, this falls within the range of reported studies, although it may slightly over-predict the effects of adult age on decreased total clearance of CYP2C9 substrates (note that sub-analysis of CYP2C9 genotype was not conducted). There are two small clinical studies showing decreased total desipramine and midazolam clearance with age [20, 21], and Simcyp® was moderately successful in reproducing the observed % decreases (Table 2).

For low E_H drugs with high PB, total drug clearance does not reliably assess changes in clearance and free drug clearance is preferred [2]. As shown in Figure 1, this is because decreased $CL_{int,liver}$ may be masked by increased f_{ub} (from decreased binding proteins) when total drug concentration is used to estimate drug clearance. In this study, the percentage decreases in CL_{PT} were similar (27 to 39%) for all probes which have different E_H and PB characteristics. Therefore, minor increases in the predicted f_{ub} of caffeine, S-warfarin, S-mephenytoin and midazolam did not significantly affect the relationship between decreased CL_{PT} and increasing adult age (note that the non-significant increases in predicted f_{ub} , along with the small decrease for desipramine, are consistent with clinical data [19–22]). Clinical comparisons of free drug clearance between young and elderly people are limited. Of the five drugs studied here, sufficient data are available only for caffeine and S-warfarin. The free clearance of S-warfarin decreases by 0.4% per year in the absence of statistically significant decreases in PB [22], and the simulations of CL_{PF} are consistent with this trend (Figure 3). Here, the free clearance of caffeine was accurately predicted in the

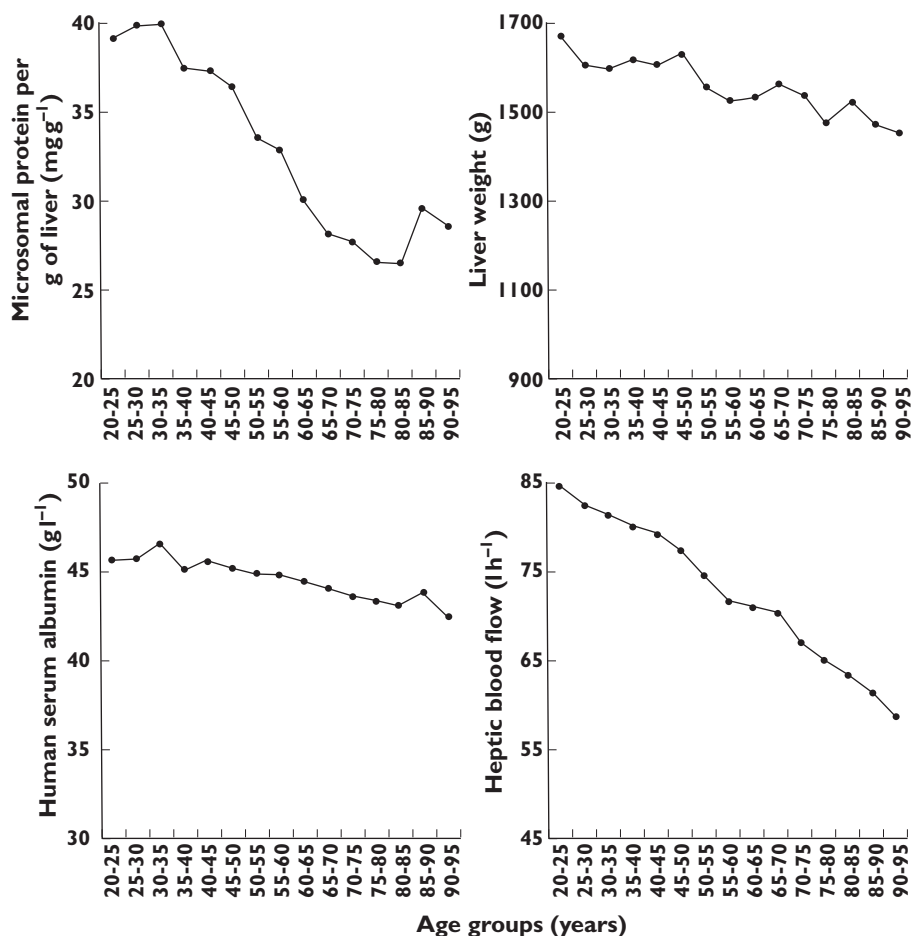


Figure 4

Changes with increasing adult age in the physiological parameters that determine IVIVE of metabolic drug clearance in Simcyp®. Data points represent mean values for all subjects in the $n = 100$ simulations with caffeine

young ($CL_{PF} = 2.3$ vs. clinical = $2.14 \text{ ml min}^{-1} \text{ kg}^{-1}$ [19]), but the decrease in simulated caffeine free clearance with age did not correspond with the increase observed in elderly non-smoking men ($CL_{PF} = 1.6$ vs. clinical = $2.55 \text{ ml min}^{-1} \text{ kg}^{-1}$ [19]).

Gender difference in drug metabolism is a controversial topic that has been extensively reviewed in the literature [28–32]. In the simulations, women generally had higher CL_{PT} than men (Figure 2). This results from differences between women and men in the physiological parameters that determine IVIVE of metabolic clearance, although analysis of these differences was not undertaken here (see Chetty *et al.* for more on this topic [33]). Most investigators concur that a small but statistically significant increase in the size adjusted clearance of CYP3A substrates, including midazolam, occurs in women [34]. Similarly for S-mephenytoin, women have significantly lower S : R enantiomeric ratios in urine (35%) as a result of greater CYP2C19 activity [27]. However, for the other CYP-selective probes studied here, increased CL_{PT} in women is not supported by available clinical data. For example, a recent population

pharmacokinetic analysis of S-warfarin in predominantly older patients showed men to have 12% higher clearance than women [35]. Our sub-analysis of the elderly in Jensen *et al.* [22] showed a trend of an even greater difference, although the opposite gender difference for S-warfarin is seen in the young (Table 2). Lower CYP1A2 and CYP2D6 activities in women have also been suggested [20, 25]. It must be emphasized, however, that many studies on gender difference in clearance are problematic, as many are underpowered to consider large inter-individual variability in clearance, they employ different probes with varying degrees of selectivity, they use total drug concentration to estimate clearance in the absence of PB information, and urinary drug : metabolite ratios are measured to assess differences in metabolic clearance without considering the impact of renal function [6, 7]. Therefore, there are no simple answers on whether particular CYPs differ significantly between men and women. We noted that large numbers of virtual subjects ($n = 100$ and 1000) were required to show statistically significant gender differences in predicted metabolic drug clearance (data not

shown). Thus, in the absence of superior clinical studies, it is difficult to assess accurately the current performance of Simcyp® in predicting gender differences in the clearances of caffeine, S-mephenytoin and desipramine.

In conclusion, the primary aim of this study was to investigate the effect of increasing adult age on predicted metabolic drug clearance. IVIVE-PBPK using Simcyp® predicted 20–40% lower weight-normalized metabolic drug clearance in the elderly. This is generally consistent with limited clinical data for four out of five drugs studied here and the broader literature on drugs metabolized by CYP enzymes [2–5]. Decreased metabolic clearance with increasing adult age was similar for probe drugs of major CYP enzymes with different E_H and PB characteristics. Observed decreases in predicted drug clearance with age were attributable to the physiological changes of ageing. IVIVE-PBPK modelling and simulation may be used with increasing confidence to predict metabolic drug clearance in the elderly and to inform clinical study design.

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Competing Interests

Part of this work was published as a poster at the Annual Scientific Meeting of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) in Perth, Australia, 4–7 December 2011.

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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