Antidepressants, anxiolytics and statins: prediction of exposure changes due to aging.

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Manoranjenni Chetty, Felix Stader,* Krishna Machavaram.

Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK

* Current address: Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel and University of Basel, Basel, Switzerland

Background

Antidepressants, anxiolytics and statins are commonly prescribed in elderly patients. Case studies and anecdotal evidence suggest that dosage adjustments may be appropriate when some of these drugs are used in elderly patients. This group of patients are generally not included in clinical trials that determine the relevant doses of these drugs. Drug dose regimens used in the older patients are frequently determined by trial and error or extrapolated from doses relevant to young adults. Physiological changes that may potentially impact drug exposure in the elderly are frequently reported. However, adequately powered clinical studies to determine the impact of the physiological changes on the pharmacokinetics and pharmacodynamics of drugs in the elderly patient population are not usually conducted.

Physiologically based pharmacokinetic (PBPK) modelling offers the opportunity to explore and predict such changes in large virtual patient populations. The Simcyp population-based PBPK Geriatrics model accounts for age-related physiological changes such as demographic distribution, intestinal transit time, liver volume, kidney weight, renal function and some metabolic enzymes. This model does not account for frailty.

The objective of this study was to predict potential differences in drug exposure between elderly and young patients, using the geriatrics and healthy Caucasian models within the Simcyp simulator.

Methods

PBPK models and simulation of concentration profiles

Two drugs from each of the above mentioned drug classes were selected from the Simcyp library for this analysis. They included fluoxetine, desipramine, midazolam, triazolam, pravastatin and rosuvastatin. Using the compound files within the Simcyp simulator (Version 16), simulations were run using 500 subjects who were healthy Caucasians aged between 18 and 46 years, while another 500 subjects were geriatric Caucasians aged between 66 and 80 years. Drug exposures, as assessed by area under the plasma concentration versus time curve (AUC_{0-t}) and maximum plasma concentration (C_{max}) or clearance (CL) of 40 mg fluoxetine, 50 mg desipramine, 0.03mg/kg midazolam, 0.25 mg triazolam, 20 mg pravastatin and 40 mg rosuvastatin were simulated and compared with observed values. Dosage selections for these drugs were based on that of available clinical studies that could be used to verify the models. The ratio of the predicted and observed drug exposure in both young and elderly subjects were first evaluated to verify the performance of the PBPK models. Drug exposures in elderly subjects were then compared with that in young subjects to determine whether dosage changes are necessary.

Model Verification

The PBPK models were verified by comparison of the predicted and clinically observed differences in pharmacokinetic parameters between the young and elderly. Prediction ratios (predicted % difference between elderly and young : observed % difference between elderly and young) within 2 –fold range were considered to be acceptable and indicated that the model could recover the clinical data.

Results

The simulated profiles of the six drugs in young and elderly subjects are shown in Figure 1.

Ratios of the predicted (Pred) difference between young and elderly and observed (Obs) difference between young and elderly are shown in Table 1.
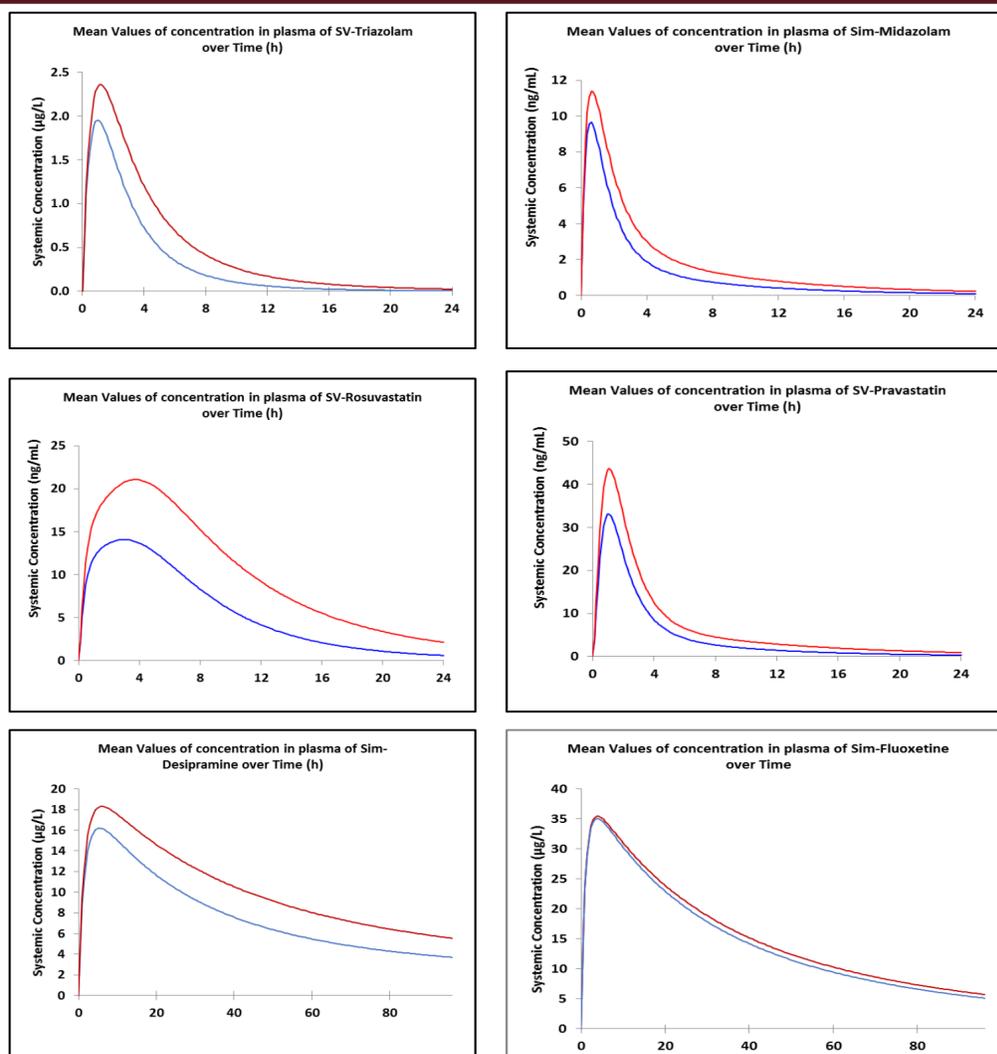
Figure 1: Simulated concentration profiles in young (blue line) and elderly subjects (red line).

Table 1: Pred : Obs ratios for comparative % decrease in exposure between young and elderly, for each drug

Drug	Pred:Obs Ratio
Midazolam	0.96
Triazolam	1.26
Pravastatin	0.93
Rosuvastatin	0.75
Desipramine	1.23
Fluoxetine	1.31

Conclusions

The PBPK models were able to recover the clinical data adequately, as indicated by the ratios in Table 1.

Comparison of the concentration-time profiles of the drugs in the young and elderly indicated a difference in exposure C_{max}, AUC and CL between the two populations, except with fluoxetine, where the difference in exposure is negligible.

This study will be extended further to predict dosage adjustments for the five drugs with increased exposure in the elderly.

References

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