Prediction of the pharmacokinetics of renally-excreted antiretrovirals in older patients, using physiologically based pharmacokinetic (PBPK) modelling.

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Introduction

Despite our knowledge of diminishing renal function with advancing age, information on the impact of aging on the pharmacokinetics (PK) of antiretroviral drugs that are mainly excreted unchanged by the kidney is sparse. In a clinical study that compared the PK of 100mg lamivudine in 6 older males (over 65 years) and 6 young males, a significant difference was observed, where the renal clearance of the drug in the older subjects was 0.67 times that in young subjects.[2]

The objective of this study was to use PBPK modelling to predict changes in the exposure to tenofovir, emtricitabine and lamivudine in older patients and to evaluate whether the changes warrant dosage adjustments in this patient group.

Methods

Tenofovir, lamivudine and emtricitabine were selected for this study since excretion via the kidney is >70%. PBPK models[1] were verified in version 16 of the Simcyp Simulator using available clinical data[3-5] and then used to predict PK profiles for 300mg tenofovir, 300mg lamivudine and 200mg emtricitabine, in Caucasian subjects aged 20 to 49 years; 50 to 64 years and 65 to 75 years. 10 trials with 10 individuals were simulated. The Simcyp Geriatric Caucasian population was used for the 65 to 75 year age group. Since drug response has been associated with the area under the plasma concentration versus time curve (AUC) for these drugs, differences in exposure (AUC) were compared.

Results

PBPK models[1] for tenofovir, lamivudine and emtricitabine were verified in V16 of the Simcyp Simulator using available clinical data. The models were then used to predict pharmacokinetic (PK) profiles for the three drugs using standard doses in Caucasian population groups aged 20 to 49 years; 50 to 64 years and 65 to 75 years respectively.

A decrease in CL and an increase in AUC with advancing age was observed for all three drugs. The mean ratio of the increase in exposure (AUC) between the oldest and youngest age groups were 1.4 for emtricitabine, 1.4 for lamivudine and 1.2 for tenofovir.

Simulations indicated that the PBPK models were able to recover the clinical data acceptably during verification (Figure 1) as well as when applied to the predictions in the Geriatric population (Figure 2).

For all three antiretrovirals, a decrease in systemic clearance (Figure 3) with a corresponding increase in AUC (Figure 4) was predicted with an increase in age. Predicted mean CL of lamivudine in the geriatric population was 73% of that in young subjects (20 to 49 years) while the clinically observed value was 71%.[2] Predicted median CL of emtricitabine in geriatrics was 72% that in young subjects while the clinically observed value was 69%.[6]

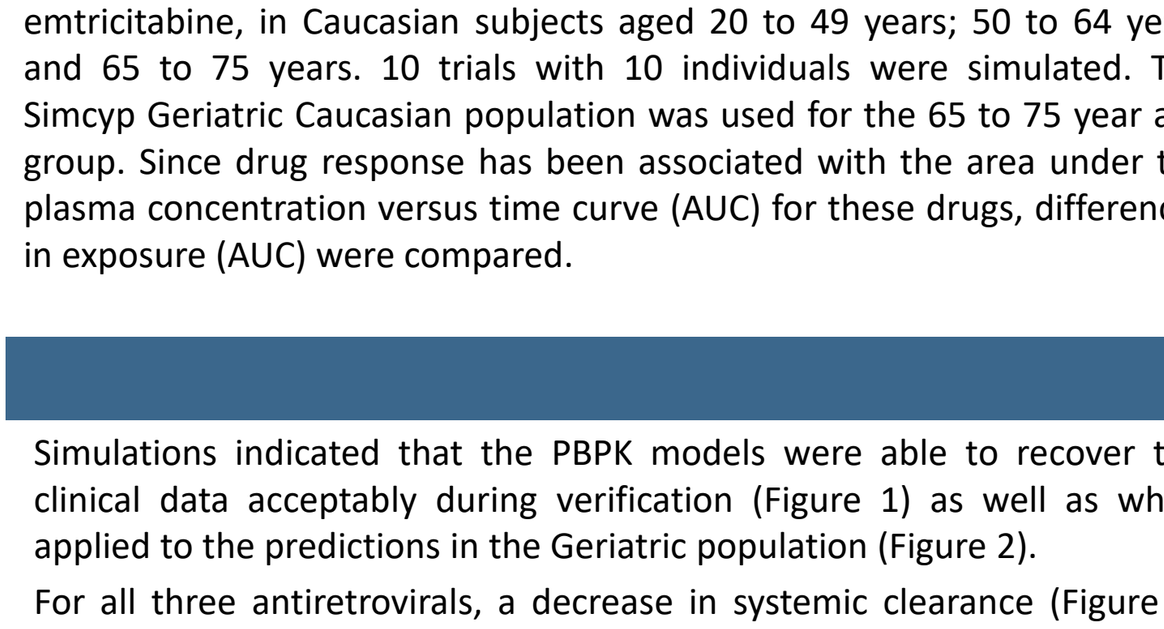

Figure 1: Predicted (lines) and observed (circles)[2-4] concentration-time profiles used for model verification

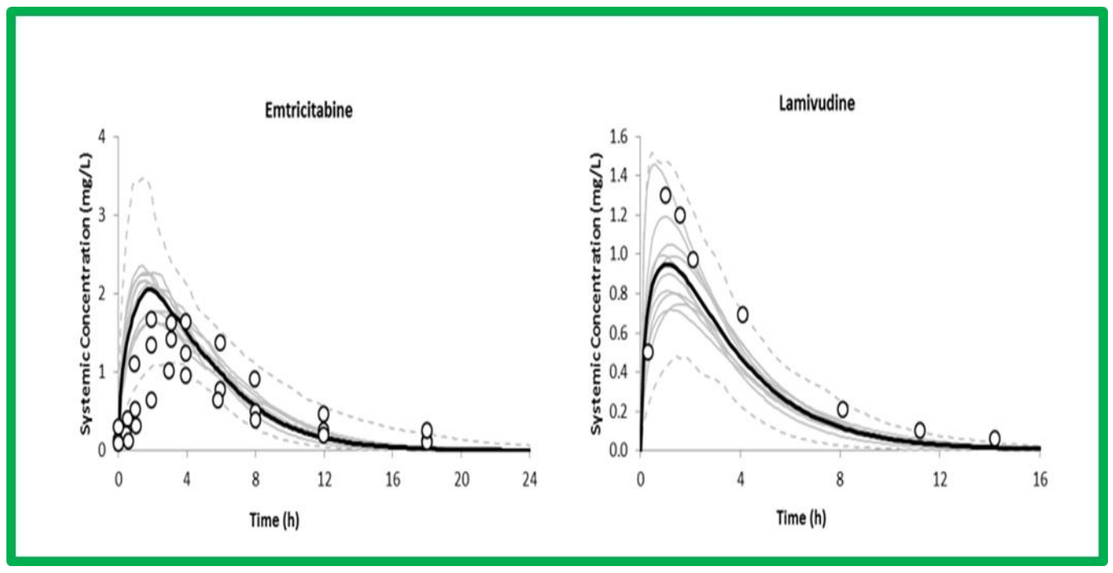

Figure 2: Predicted (lines) and observed (circles) concentration-time profiles of emtricitabine and lamivudine in elderly subjects

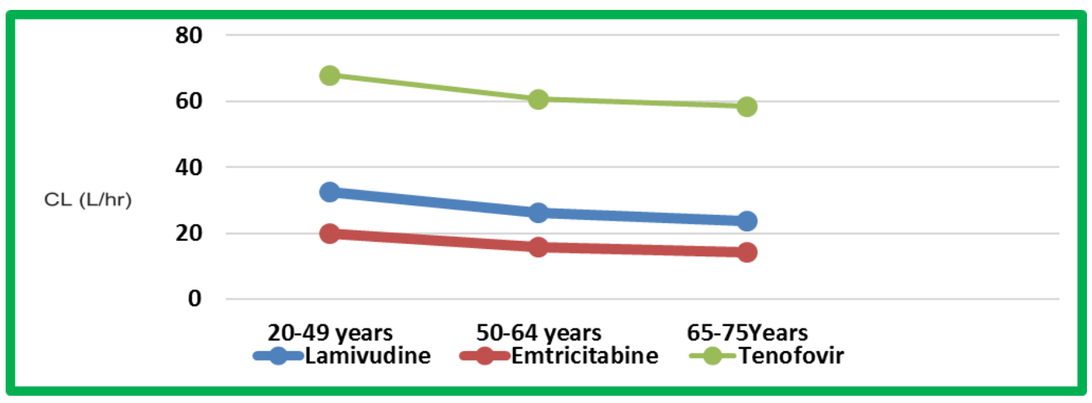

Figure 3: Predicted mean CLpo with age

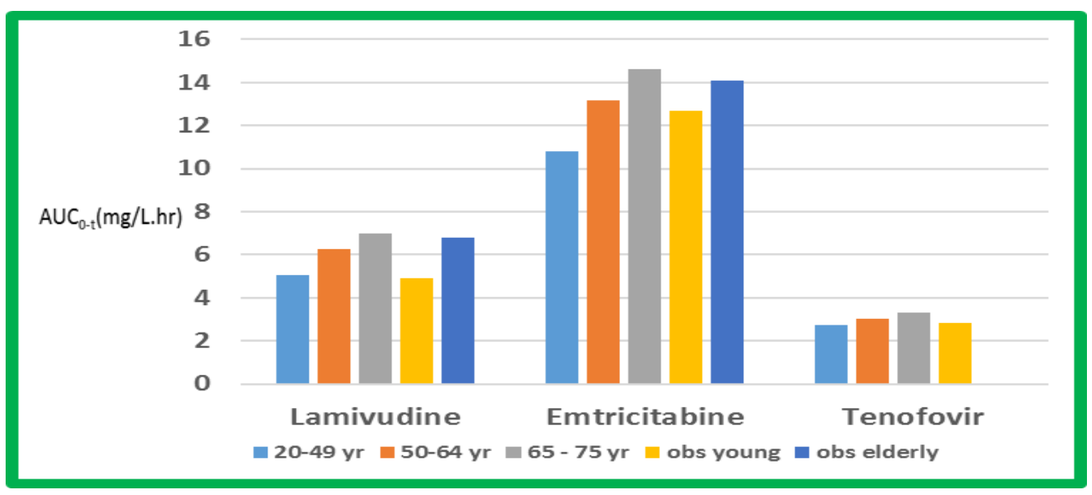

Figure 4: Predicted and Observed (Obs)[2-6] mean AUC with age

Conclusions

- The PBPK models recovered the clinical data in older subjects acceptably.
- Exposure to the three drugs increased with an increase in age.
- Although the % increases in AUC do not appear to be major, elderly patients on standard doses of these drugs require careful monitoring for toxicity This suggests that some of the elderly patients may require a reduction in dose.

References

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