Population pharmacokinetic models for lamivudine and nevirapine for measuring adherence using therapeutic drug monitoring

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INTRODUCTION AND AIM

Adherence to combined antiretroviral (ARV) therapy (cART) is a predictor of suppression of HIV replication, disease progression and death.1 Methods used to measure cART adherence include medication event monitoring systems, self report, clinical review, questionnaires, diaries, therapeutic drug monitoring (ARV TDM), pill count and pharmacy refill data.2 ARV TDM may improve patient outcome due to the clinical consequences of therapeutic failure, marked interindividual variability in ARV plasma concentrations, and data supporting concentration/response relationships.3 Unlike non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs) are not considered suitable candidates for ARV TDM. The NRTI lamivudine (3TC) is the active moiety and is only weakly correlated with parent plasma concentrations.4 However, due to long half-lives of NNRTIs, it may be difficult to evaluate cART adherence using NNRTI steady-state concentrations (Fig. 1).

The NRTI lamivudine (3TC) has suitable pharmacokinetic (PK) properties (\(t_{1/2} = 0.9\) h [SD 0.41 h], half-life = 8.41 h [SD 1.46 h]) to assess dosing history up to 36 hours post-dose. Additionally, 3TC pharmacokinetics is unaltered by concomitant anti-tuberculosis treatment, a common opportunistic infection in our population.

Routine blood sampling at ARV-outpatient clinics is seldom pre-dose/trough concentrations and acceptable minimum single time-point concentration data during the whole 12-hour NVP and 3TC dosing intervals were unavailable. The aim of the analyses was to use a population modeling approach to obtain concentration "cut-off" values (e.g. the lower limit of the 95% prediction intervals) for NVP and 3TC concentrations to assess adherence to cART.

METHODS

Population PK models for 3TC and NVP were developed using rich and sparse data obtained from three pharmacokinetic studies (Table 1). One compartment models with first-order absorption and elimination were fitted to log-transformed concentration-time data. Typical population values for PK parameters, and interindividual and residual variability were obtained using the FOCE INTER estimation method in NONMEM VI. Interindividual variability (IV) was modeled as an exponential variance model or slope-intercept variance models were used to describe the residual variability. Xpose 4 was used to visualize the data. Models were selected by comparing the NONMEM objective function value, goodness-of-fit plots and scientific plausibility. The non-parametric bootstrap and visual predictive check (VPC) were used to evaluate the final models. Rich and sparse data were analyzed separately, simultaneously (combined) and using rich data as prior information for sparse data analysis (prior using the TNPPI functionality in NONMEM VI).

RESULTS

Mean (relative standard error [RSE]) population parameter estimates are provided in Table 2 (NVP) and Table 3 (3TC) for sparse data and inadequate to reliably estimate population parameters. However, there were no marked differences in parameters between rich and sparse patient data and a combined analysis of sparse and rich data (CL/F = 2.52 L/h [4.7% RSE]; V/F 115 L [14%]; \(t_{1/2} = 3.21\) h [41%]) on an analysis of sparse data with prior from rich data (CL/F = 2.52 L/h [4.56% RSE]; V/F 104 L [8.8%]; \(t_{1/2} = 2.69\) h [35%]) gave similar population parameter estimates. For 3TC, higher CL/F and ka in HIV than patients were indicated in both the combined analysis and when using the prior functionality. Once this was accounted for, the different analyses provided similar parameter estimates: combined analysis (CL/F = 14.6 L/h [3.6%]; V/F 86 L [2.4%]; \(t_{1/2} = 1.52\) h [18.0%]), prior (CL/F = 14.3 L/h [2.5%]; V/F 86 L [2.5%]; \(t_{1/2} = 1.80\) h [2.0%]).

The VPC lower limit of the 95% confidence interval (2.5th percentile real data integrated with simulated data with 95% confidence interval for the simulated data) for the final models are plotted in Fig. 2A (3TC) and 2B (NVP).

CONCLUSION

Population pharmacokinetic models for 3TC and NVP were developed from rich and sparse data. Combined analyses and sequential rich-sparse analyses using the prior functionality led to the same model decisions and very similar parameter estimates. The minimum cut-off values to assess adherence will be evaluated in ongoing cART adherence studies.

REFERENCES


