ONCE DAILY DOSING OF LAMIVUDINE IN HIV-INFECTED CHILDREN

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Introduction

- The use of antiretroviral (ARV) drugs in children requires careful considerations regarding dosing frequency and patient compliance.
- There may be considerable benefits for both children and caregivers if dosing frequency can be reduced to once daily for all drugs in the ARV regimen.
- The aim of this investigation was to assess whether systemic exposure to lamivudine (3TC) following a once daily dosing regimen is comparable to twice daily dosing.

Methods

A one-compartment pharmacokinetic model with body weight as covariate on clearance and volume of distribution was used to characterise drug exposure in HIV-children from 3 months to 12 years old.

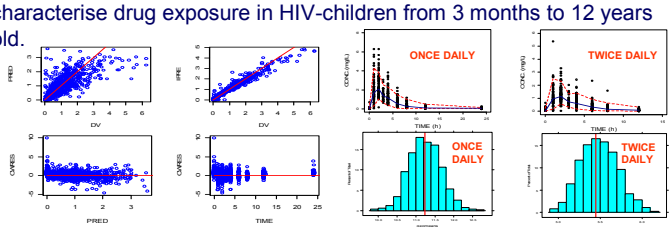

Figure 1: Population PK Model validation. Diagnostic plots showing predicted and observed data according to a one compartment model with first order elimination and first order absorption. Poster presentation at the "6th International Symposium on Measurement and Kinetics of In Vivo Drug Effects" in Noordwijkerhout, the Netherlands (April 2010).

Simulations were performed in NONMEM v6.1 taking into account the WHO weight-for-age tables as reference for the correlation between age and body weight. The simulated population consisted of 180 patients. 3TC was administered twice daily according to the currently recommended dosing algorithm, as indicated in the latest SPC. QD administration assumed same total daily dose given once daily. Systemic exposure was assessed in terms of secondary PK parameters: area under the plasma concentration-time curve (AUC) and predicted peak concentration (Cmax).

Table 1: Latest Summary of Product Characteristics of lamivudine

Weight Range	Dose Regimen	Total Daily Dose
<14kg	Oral solution (4mg/kg) BID	8mg/kg/day
14 to 21kg	One-half tablet (75mg) BID	150mg
>21 to <30kg	One-half tablet (75mg) in the morning One whole tablet (150mg) in the evening	225mg
≥30kg	One whole tablet (150mg) BID	300mg

Table 2: Demographic characteristics of the simulated paediatric population

	Overall	< 14 Kg	14-21 Kg	21-30 Kg	> 30 Kg
Subjects	180	85	34	31	30
Med. Age	3.5	0.91	4.5	8	10.5
Med. weight	14.9	9.73	17.2	24.9	35.9

Results

The AUC after once daily dosing in HIV-infected children between 3 months and 12 years old is comparable to historical values in children on a twice daily regimen of lamivudine as well as to the exposure in adults receiving lamivudine once or twice daily.

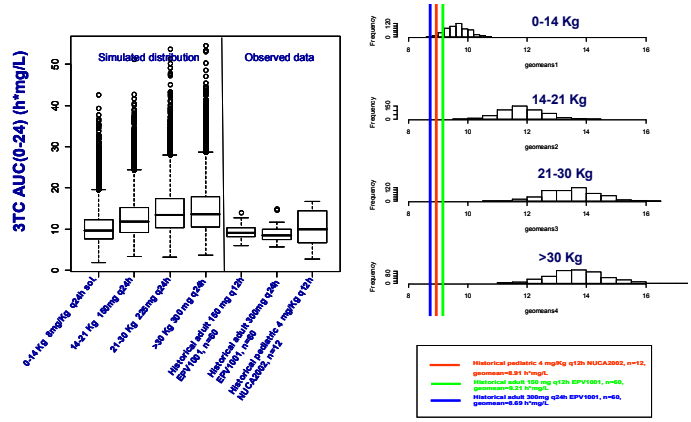

Figure 2: Boxplots show the comparison between simulated distributions of lamivudine AUC (0-24) after once daily dosing and historical data from clinical trials. Histograms show the simulated distributions of lamivudine AUC (0-24) values after once daily dosing for each weight range. Simulated distribution represent 180 paediatric patients (N=500 replicate trials).

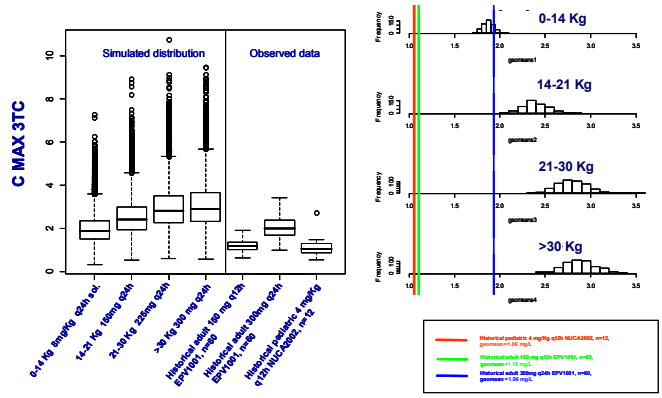

Figure 3: Boxplots show the comparison between simulated distributions of lamivudine Cmax after once daily dosing and historical data from clinical trials. Histograms show the simulated distributions of lamivudine Cmax values after once daily dosing for each weight range. Simulated distribution represent 180 paediatric patients (N=500 replicate trials).

Given that once daily lamivudine was approved for use in adults based on good safety and efficacy and the positive tolerability and safety profile of once daily lamivudine was observed in small studies of children (Bergshoeff, 2005; PENTA-15, In Press; Musiime, 2009), the predicted increase in Cmax after once daily administration is unlikely to result in a higher risk of adverse events.

Conclusions

The use of 3TC according to a once daily dosing regimen provides appropriate exposure to children aged from 3 months to 12 years. Our findings suggest that the reduction in the dosing frequency to once daily does not lead to under dosing in this paediatric population. Furthermore, these results illustrate how modelling and simulation can be used to integrated existing data and address relevant clinical questions in paediatric drug development.

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