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SECTION III
Simplified dosing regimens in children
A MODEL-BASED APPROACH FOR THE EVALUATION OF ONCE DAILY DOSING OF LAMIVUDINE IN HIV-INFECTED CHILDREN

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SUMMARY

Aim: Little attention has been paid to the effects of compliance and prescription practice on treatment outcome in HIV-infected children. In this context, an evaluation of the role of covariates on pharmacokinetics is required to establish the impact of differences in dosing regimen. Here we investigate whether a once daily dosing regimen of lamivudine provides comparable exposure to the currently approved paediatric regimen.

Methods: A hypothetical group of 180 patients between 3 months and 12 years old was used to evaluate the impact of body weight on systemic exposure to lamivudine. Simulation scenarios were evaluated using AUC and Cmax as parameters of interest. The analysis was performed using a population pharmacokinetic model previously implemented in NONMEM v.6.2.

Results: The simulations show that once daily dosing of lamivudine yields comparable exposure to historical values observed in children and adults, both for liquid and solid dosage forms. Simulated steady-state AUC_{0-24} and Cmax values after once daily doses ranged respectively from 9.95 mg•h/L and 1.9 mg/L for children lighter than 14 kg to 13.75 mg•h/L and 3.0 mg/L for children heavier than 30 kg. These values are comparable or higher than historical values observed after once daily dosing in children and adults.

Conclusions: Our findings illustrate how dosing regimens can be evaluated taking into account the effects of developmental growth on drug disposition. Most importantly, they suggest that the reduction in dosing frequency to once daily warrants safe, efficacious exposure, while representing an improvement in treatment acceptability and adherence.
6.1. INTRODUCTION

Historically prescription practice and patient compliance have not been considered as factors determining the successful use of antiretroviral drugs in HIV-infected children. Increasing evidence now shows that not only the availability of suitable paediatric dosage forms, but also dosing frequency can be an important determinant of compliance and consequently of treatment outcome (1). In fact, a significant correlation between lower pill burden and better virological outcome has been observed for antiretroviral drugs (2). In addition, numerous surveys of HIV patients in both the United States and Europe indicate that there is a strong preference for once daily dosing and compact therapy (3) and according to several studies once daily regimens are significantly better adhered to than other dosing regimens (4). It is well known that current combination antiretroviral therapy (cART) regimens require large numbers of pills or capsules to be taken several times per day and the overall pill burden may thus be too large to permit adherence for periods of many years. Differences in dosing regimen and/or dosing frequency may clearly constitute a burden for patients and in particular for younger children.

The availability of fixed-dose combinations and the possibility to administer all the drugs as once daily regimen may be very advantageous, with direct implications for adherence to therapy and for the overall treatment outcome (5,6,7). The use of a simple once daily cART regimen may therefore be a powerful solution to optimise treatment adherence and patient’s quality of life (8). Particularly in the paediatric field, there may be considerable benefits for both children and caregivers if dosing frequency can be reduced to once daily for all drugs in the regimen, allowing minimal interference with everyday school and home activities. Furthermore, one specific concern with older children is the stigma of taking medications during the day or having friends discover that they have an illness, so limiting the number of times a child has to take a medication can significantly improve not just compliance, but well-being.

Once daily dosing may provide the flexibility to maximise adherence according to individual circumstances – particularly in resource limited settings where most HIV-infected children live (9). For example, caregivers who are sellers in the market may find it hard to give drugs in the morning if they leave before the child is awake. Caregivers who work evenings may have to rely on others to administer evening doses. In addition, reducing administration frequency may significantly reduce medication error.

Lamivudine (3TC), a nucleoside reverse transcriptase inhibitor commonly administered in combination antiretroviral therapy to HIV-infected children (10), was initially administered twice daily in both adults and children. Lamivudine enters infected lymphocytes and is progressively phosphorylated by intracellular enzymes to the active moiety, lamivudine-5’ triphosphate, which acts as a chain terminator. The active intracellular lamivudine-triphosphate has a long half-life (16-19 hours) relative to the half-life of parent lamivudine in plasma (5-7 hours) (11). The long half-life of lamivudine-triphosphate coupled with intracellular pooling of precursor lamivudine-diphosphate supported the investigation of once daily dosing in adults. In fact, a once daily dose regimen was subsequently approved for adults based on clinical studies which showed equivalent antiviral activity (12) and equivalent area-under-the-curve \( \text{AUC}_{0-24} \) of plasma lamivudine and intracellular lamivudine-triphosphate (13) following once versus twice daily dosing of the same total daily dose. Even though a formal concentration-antiviral effect relationship is lacking due to the difficulties in routinely measuring the intracellular lamivudine-triphosphate concentrations, the plasma \( \text{AUC}_{0-24} \) of lamivudine can be considered the best plasma predictor of antiviral activity based on the mechanism of action and long half-life of the active moiety.

Currently lamivudine is labelled for twice daily administration in children based on clinical trials which demonstrated antiviral activity at doses yielding similar exposure to those observed in adults. Given the mechanism of action of lamivudine (14) the exposure-antiviral response to HIV infection is likely to be similar between children and adults. Therefore, a once daily dose regimen in children that can match the \( \text{AUC}_{0-24} \) of the approved twice daily regimen in children or the once or twice daily regimen in adults should demonstrate equivalent antiviral activity in children. To that purpose, several studies have been conducted to explore the pharmacokinetics and feasibility of once daily dosing in children (15, 16). Nevertheless, an integrated, model-based evaluation of the impact of developmental growth factors has not been performed for once daily dosing in children. It can be envisaged that the use of once daily dosing in children will allow alignment with the approval of once daily fixed-dose combination antiretroviral pills for the adult indication. The aim of this study is therefore to assess whether lamivudine pharmacokinetics after once daily dosing is comparable to lamivudine pharmacokinetics after twice daily administration to HIV-infected children between 3 months and 12 years old. The use of simulation scenarios is proposed as the basis for evidence synthesis on the suitability of this new regimen in children. Simulated pharmacokinetic profiles are characterised in a large hypothetic paediatric cohort to determine the dose rationale without the requirement for further enrolment of children into a clinical trial (17, 18).

The relevance of this type of model-based extrapolation exercise has been recently highlighted in the concept paper of the EMA (19). The document emphasises how extrapolations enable one “to extend information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.”
Once daily dosing of lamivudine in HIV-infected children

6.2. METHODS

Simulations were performed to compare the systemic exposure of lamivudine after once daily dosing to historical values in children and adults and to explore how differences in demographic covariates affect steady-state exposure. The hypothetical population was represented by children between 3 months and 12 years old. For the purposes of our analysis, children were split into various age groups, each with 5 patients with different body weight (n=180). The correlation between age and body weight was based on the WHO weight-for-age tables (20). Lamivudine total daily doses were determined according to the currently recommended dose and method of administration, as indicated in the latest Summary of Product Characteristics (21).

A one-compartment model with first order absorption and elimination processes previously developed and validated by our group was used to simulate the pharmacokinetic profiles (Chapter 3). The model was built using pharmacokinetic data in 77 HIV-infected children receiving lamivudine both as twice and once daily dosing regimens. Body weight was found to be exponentially correlated to clearance and volume of distribution. Given that formulation was not found to influence the pharmacokinetic parameters, the same model was used to predict lamivudine pharmacokinetics in children receiving tablets or solution.

The frequency and times for pharmacokinetic sampling were based on a serial sampling scheme to mimic current practice with regard to estimating AUC over the dosing interval. Concentration vs. time data was then integrated using the trapezoidal rule to ensure realistic estimates of variability, as observed in a typical non-compartmental analysis. The hypothetical experimental protocol is depicted in figure 1. Given that a significant concentration-effect relationship for lamivudine could not be found in the past, the adequacy of the simulated dosing regimens was assessed graphically by determining the fraction of the paediatric population reaching systemic exposure comparable to $AUC_{0-24}$ values previously observed in studies of adults on approved once and twice daily dosing regimens. Cmax values of the paediatric population were also compared to historical values of Cmax from previous clinical trials. Simulations were performed using NONMEM version 6.2. Results were graphically summarised using R 2.8.2.

Figure 1 Diagram depicting the hypothetical experimental protocol

6.3. RESULTS

Simulations were performed using a population pharmacokinetic model previously developed and validated by our group. The goodness of fit and visual predictive checks are shown in figure 2.

Based on the original parameter estimates, the distribution of the area under the curve ($AUC_{0-24}$) and peak concentration (Cmax) values associated with a once daily dosing regimen for lamivudine were evaluated in a hypothetical group of paediatric patients. In total, the simulated population consisted of 180 patients between 3 months and 12 years old, which represent a population with comparable demographic characteristics of HIV-infected children in a typical clinical setting. The demographic characteristics of the simulated population is summarised in Table 1. In table 2 the doses of lamivudine administered to the simulated population are depicted.
Table 1 Demographic characteristics of the simulated paediatric population

<table>
<thead>
<tr>
<th>Overall</th>
<th>&lt;14 kg</th>
<th>14-21 kg</th>
<th>21-30 kg</th>
<th>&gt;30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBJECTS</td>
<td>180</td>
<td>85</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>MEDIAN AGE (years)</td>
<td>3.5</td>
<td>0.91</td>
<td>4.5</td>
<td>8</td>
</tr>
<tr>
<td>MIN (years)</td>
<td>0.25</td>
<td>0.25</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>MAX (years)</td>
<td>12</td>
<td>3.5</td>
<td>7.5</td>
<td>11</td>
</tr>
<tr>
<td>MEDIAN WEIGHT (kg)</td>
<td>14.9</td>
<td>9.73</td>
<td>17.2</td>
<td>24.9</td>
</tr>
<tr>
<td>MIN (kg)</td>
<td>5.41</td>
<td>5.41</td>
<td>14.1</td>
<td>21.1</td>
</tr>
<tr>
<td>MAX (kg)</td>
<td>53.9</td>
<td>13.6</td>
<td>20.7</td>
<td>29.1</td>
</tr>
</tbody>
</table>

The simulation results are presented graphically in figures 3 and 4, which show the comparison between the simulated distributions of the secondary pharmacokinetic parameters [AUC$_{0-24}$ and Cmax] and historical data from previous clinical trials with lamivudine in children and adults (22, 23). For completeness, the pharmacokinetic parameters of lamivudine are presented in table 3. Box plots show that the predicted lamivudine exposure reached after once daily dosing was comparable or higher in every weight range than the exposure reached in historical trials where lamivudine was administered at approved once or twice daily doses to adults and twice daily doses to children. The predicted Cmax values on the once daily regimen exceeded those of the twice daily regimen in children; however, there was considerably overlap of the predicted Cmax values with those observed in adult subjects on the once daily regimen.

Table 2 Currently recommended doses of lamivudine in children

<table>
<thead>
<tr>
<th>Weight Band</th>
<th>Lamivudine Dose Regimen</th>
<th>Lamivudine Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14kg</td>
<td>Oral solution (4mg/kg) twice daily</td>
<td>8mg/kg/day</td>
</tr>
<tr>
<td>14 to 21kg</td>
<td>One-half tablet (75mg) twice daily</td>
<td>150mg</td>
</tr>
<tr>
<td>&gt;21 to &lt;30kg</td>
<td>One-half tablet (75mg) in the morning; One whole tablet (150mg) in the evening</td>
<td>225mg</td>
</tr>
<tr>
<td>30kg</td>
<td>One whole tablet (150mg) twice daily</td>
<td>300mg</td>
</tr>
</tbody>
</table>

Figure 3 Box plots showing the comparison between simulated distributions of lamivudine AUC$_{0-24}$ after once daily dosing and historical data from clinical trials. Box represents median, 25th and 75th percentiles, bars represent 10th and 90th percentiles. Simulated distributions (N= 500 replicate trials) are comparable or higher than historical data in each weight range.
Evidence synthesis by modelling and simulation

Undoubtedly, the use of once daily dosing of antiretroviral drugs in HIV-infected children may offer significant clinical advantages, especially in resource limited countries. There can be several benefits for both children and caregivers and adherence may be strongly maximised, with consequent improvements in treatment outcome.

Given that previous studies have shown similar pharmacokinetics between once and twice daily dosing and evidence on the preference of caregivers for once daily regimen, evidence synthesis rather than new evidence generation needs to be considered to support once daily dosing of lamivudine in HIV-infected children. We have used a model-based approach to evaluate whether differences exist in the pharmacokinetics of lamivudine after once daily dosing, as comparable to the achieved exposure after twice daily administration. Our results clearly show that simulation scenarios offer the possibility to evaluate the potential implications of changes in dosing regimen based on existing evidence in the adult population and limited experience in children.

It is unfortunate that historically population pharmacokinetic models have been used primarily as an alternative estimation method, with simulations being performed primarily as a diagnostic procedure during model validation, rather than as an evidence synthesis tool for subsequent decision making. Yet, evidence synthesis and in particular extrapolations are often used implicitly in many situations involving clinical or regulatory decisions, e.g. when extending conclusions from trial populations to the general populations. By applying a model-based approach, one can ensure explicit and systematic assessment of the assumptions, clinical implications and risks associated with the use of extrapolations.

Once daily dosing regimen: systemic exposure

Simulation scenarios show that lamivudine AUC\text{0-24} reached after once daily dosing are comparable to historical values in children on a twice daily regimen of lamivudine and adults receiving the approved once or twice daily lamivudine regimens. Figure 3 shows that the youngest group of children (between 0 and 14 kg) had quite a lower exposure compared to the older, heavier children. This fact, previously shown by Burger et al (24), could be partly explained by a slightly lower dose that the small children receive (as shown in table 3). Effectively, higher mg/kg doses are administered with the score tablet dosage regimens due to the pre-defined tablets strengths (either 75mg half tablet or 150mg whole tablet) and because of the weight band cut-offs selected to minimise under-dosing in heavier children. Therefore, lighter children in the same weight band receive doses that are substantially higher than the 8mg/kg/day when the solution is administered. There may also be some effect of the formulation, since these children receive solution and the heavy ones receive tablets, as shown in a recent study from Kasirye et al. (25)
Once daily dosing regimen: peak concentrations

As anticipated from drugs showing linear pharmacokinetics, the reduction in dosing frequency resulted in an increase in median Cmax by approximately two-fold. Figure 4 shows that the maximum peak concentration reached after once daily dosing is much higher compared to twice daily administration. Once daily administration of lamivudine to HIV-infected children also results in higher Cmax than the historical values observed in adults and children during previous clinical trials in which twice daily dosing has been used. 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 (28), the predicted increase in Cmax after once daily administration is unlikely to result in a higher risk of adverse events. Again Cmax values appear to be slightly lower for children lighter than 14 kg. However the simulated maximum peak concentration in this group of children is comparable with reference Cmax values in adults receiving once daily dosing and higher than reference Cmax values in children receiving lamivudine twice daily and in adults receiving lamivudine twice daily.

Clearly one of the major concerns about once daily administration of antiretroviral drugs is the higher risk of viral failure. In adults it has been shown that once daily lamivudine in combination with zidovudine and efavirenz would provide comparable treatment outcome as twice daily lamivudine (12). It has also been shown that didanosine, another NRTI with similar pharmacokinetic properties as lamivudine, allows for once daily administration without increased risk of viral failure (29–31). Regarding the increased risk of drug resistance, previous studies demonstrated that once daily dosing of antiretrovirals is strongly correlated to increased patient adherence to therapy. Given that high levels of adherence may avoid development of resistance, the use of once daily dosing regimen is not expected to increase the probability of virus mutations and drug resistance.

**Limitations**

One of the main limitations in our study was that lamivudine plasma pharmacokinetics can only be considered as a limited marker of drug exposure as it is the intracellular lamivudine triphosphate metabolite that becomes pharmacologically active. However, no alternative is available due to the requirements for adequate sampling of intracellular concentrations of nucleoside transcriptase inhibitor triphosphate, which is logistically and technically difficult. This is further complicated by the volume of blood required for the bioanalysis of intracellular lamivudine triphosphate concentrations, which makes serial evaluations impractical for paediatric patients. Instead, we have made explicit assumptions about the use of plasma concentrations, namely that equilibrium between plasma and intracellular concentrations is rapidly reached and drug distribution into cells is driven by a first order process, without the risk of saturation occurring within the range of concentrations observed after once or twice daily dosing.

**Conclusions**

In conclusion, the possibility of evaluating the implication of different dosing regimens using a model-based approach shows one of the various applications of virtual clinical trials in paediatric clinical pharmacology research. Our findings strongly suggest that when the same total daily lamivudine dose is administered, the reduction in dosing frequency to once daily does not represent a potential risk of under- or over-dosing in the paediatric population. Taking into account the evidence regarding acceptability and adherence in previous paediatric and adult HIV trials, the current results provides evidence for an alternative, once daily dosing regimen, with the advantages of improved adherence and consequently efficacy and clinical outcome for children, particularly in resource limited settings.

### Table 3. Summary of the pharmacokinetic parameters of the simulated population. Values are presented as geometric mean (95% CI) except for dose which is presented as median (range)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OVERALL</th>
<th>&lt; 14 kg</th>
<th>14-21 kg</th>
<th>21-30 kg</th>
<th>&gt; 30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>8.51 (5.55-10.66)</td>
<td>8.45 (7.84-9.25)</td>
<td>8.72 (7.21-10.61)</td>
<td>9.01 (7.75-10.66)</td>
<td>8.34 (5.55-9.91)</td>
</tr>
<tr>
<td>AUC_{0-24} (mg•h/L)</td>
<td>11.26 (10.70-11.86)</td>
<td>9.65 (9.01-10.36)</td>
<td>11.83 (10.51-13.26)</td>
<td>13.47 (11.84-15.37)</td>
<td>13.68 (12.01-15.52)</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>2.25 (2.14-2.362)</td>
<td>1.87 (1.75-2.01)</td>
<td>2.38 (2.13-2.66)</td>
<td>2.79 (2.50-3.14)</td>
<td>2.87 (2.53-3.22)</td>
</tr>
<tr>
<td>CL/F / (L/h/kg)</td>
<td>0.96 (0.91-1.020)</td>
<td>1.12 (1.04-1.211)</td>
<td>0.93 (0.83-1.060)</td>
<td>0.84 (0.74-0.950)</td>
<td>0.74 (0.65-0.850)</td>
</tr>
</tbody>
</table>
Once daily dosing of lamivudine in HIV-infected children

References


23. GlaxoSmithKline Document Number RM2000/00258/00. Study ID EPV10001. An Open-Label, Randomized, Two-way Crossover Study to Compare the Steady-State Pharmacokinetics of Lamivudine and Lamivudine Triphosphate Following Lamivudine 300mg Once Daily Versus EPIVI.


