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Evaluation of nevirapine dosing recommendations in HIV-infected children

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Nevirapine pharmacokinetics has been studied in adults and children. Subtherapeutic concentrations have been reported by several studies with current recommendations, especially in young children.

WHAT THIS STUDY ADDS

- This population pharmacokinetics analysis of nevirapine in human immunodeficiency virus-infected children provides new insights into the fate of this drug. The apparent clearance and apparent volume of distribution increased allometrically with bodyweight, whereas the relative bioavailability increased with postmenstrual age. Underexposure to nevirapine was found for the 3–10 kg bodyweight range, and dosing suggestions are provided.

AIMS

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor used for chronic human immunodeficiency virus infections in adults and children. The aims of this study were to investigate the population pharmacokinetics of NVP in children, establish factors that influence NVP pharmacokinetics and evaluate the current dosing recommendations.

METHODS

Concentrations were measured on a routine basis in 94 children aged from 2 months to 17 years. A total of 390 NVP plasma concentrations were retrospectively collected, and a population pharmacokinetic model was developed with Monolix 4.0.

RESULTS

Nevirapine pharmacokinetics was best described by a one-compartment model with first-order absorption and elimination. After standardization to a 70 kg adult using allometry, postmenstrual age had a significant effect on the bioavailability. Estimates of apparent clearance and volume of distribution were 3.9 l h^{-1} (70 kg)$^{-1}$ and 140 l (70 kg)$^{-1}$, respectively. Based on simulations of European Medicines Agency (EMA) and World Health Organization (WHO) dosing recommendations, the probability of observing minimal concentrations below the efficacy target of 3 mg l^{-1} is higher following the EMA recommendations than the WHO recommendations. However, NVP underdosing persists for the 3–6 and 6–10 kg weight ranges following the WHO recommendations.

CONCLUSIONS

It is suggested to increase doses to 75 and 100 mg twice daily for the 3–6 and 6–10 kg weight ranges, respectively, in order to obtain more than 95% of children with concentrations above 3 mg l^{-1}.

Introduction

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor used for chronic human immunodeficiency virus (HIV) infections in adults and children and in pregnant women for the prevention of mother-to-child transmission. Nevirapine has demonstrated a long-term suppression of viral replication in HIV-experienced and -naïve infected adults and children [1–4]. Several studies have also been conducted in newborns aged less than 6 months [5–8].

The current NVP dosing recommendations of the European Medicines Agency (EMA) at steady state are 7 mg kg^{-1} twice daily (BID) in children from 2 months to 8 years, 4 mg kg^{-1} BID for children older than 8 years and 200 mg BID for children weighing more than 50 kg (equivalent to the dosing recommendation based on the body surface area of 150 mg m^{-2} BID for children older than 15 days) [1, 2, 9, 10]. The total daily dose should not exceed 400 mg for any patient [1].

In adults, NVP is readily absorbed (>90%) after oral administration. The drug is highly lipophilic and is about 60% bound to plasma protein in the concentration range of 1–10 mg l^{-1}. This drug is extensively and primarily metabolized by the cytochrome P450 (CYP) isoenzymes 3A4 and 2B6 to several hydroxylated metabolites. The half-life at steady state (following auto-induction) is 25–30 h following a 200 or 400 mg daily regimen [1].

Patients taking NVP must be closely monitored for adverse events during the first 18 weeks of treatment and more specifically during the first 6 weeks; indeed, during this period the risk of severe hepatic failure or skin reactions is higher. However, skin rashes, Stevens–Johnson syndrome or hepatic events may occur at any time during treatment [1].

Nevirapine has a high interindividual variability in its pharmacokinetics and a low genetic barrier, i.e. development of resistance to the treatment appears with very few mutations of the virus. It is therefore important to ensure that sufficient minimal concentrations (C_{min}) are reached. It has been shown that minimal concentrations below 3 mg l^{-1} are associated with a higher risk of virological failure [11, 12]. Some studies have considered a minimal concentration above 8 mg l^{-1} as a target for toxicity [13, 14]; however, no relationships between toxicity and drug concentrations have been precisely defined. Since 2001, many clinical studies in children have reported subtherapeutic minimal concentrations of NVP < 3 mg l^{-1} following current EMA recommendations [11, 15]. Thus, more reliable fixed-dose combinations, according to bodyweight (BW), were recommended by the World Health Organization (WHO). These fixed-dose combinations including nevirapine, stavudine (d4T) and lamivudine (3TC), and are administrated twice daily with a higher NVP dose: Triomune Baby® (Cipla Ltd., Mumbai, India) for children weighing from 3 to 10 kg, Triomune Junior® for children from 10 to 30 kg and Triomune 30® for children and adolescents weighing more than 30 kg [16].

However, recent studies have shown that these increased NVP doses per weight could be insufficient to correct subtherapeutic C_{min} values in the bodyweight range 3–14 kg [13, 14, 17–20].

The aims of this study were as follows: (i) to investigate the population pharmacokinetics of NVP in children; (ii) to investigate the factors that influence NVP pharmacokinetics in this population; (iii) to compare NVP pharmacokinetic parameters with previous studies in children; and (iv) to evaluate the dosing recommendations in children.

Methods

Patients and treatment

Clinical data were collected retrospectively from the medical files of HIV-infected children and adolescents in five clinical centres. Blood samples were drawn at random time points using a therapeutic drug-monitoring methodology. Ethics committee approval and patient consent are not required in France in order to use therapeutic drug-monitoring data retrospectively. At each patient visit, time after the last dosing, BW, age and combined treatments were recorded. Nevirapine was administered as 7 mg kg^{-1} BID in children from 2 months to 8 years and 4 mg kg^{-1} BID for children older than 8 years. The pharmacokinetic study was performed after 15 days of treatment. All plasma samples were collected at steady state. The samples were not collected on the same occasion, the median (range) number of samples per patient was 3 (1–17) and the median (range) blood sampling time was 3.4 h (0.7–11.8).

Analytical method

Nevirapine was measured in a 100 µl plasma sample using a high-pressure liquid chromatography method (Beckman system GOLD®) with ultraviolet detection. Samples were extracted using *tert*-butyl methyl ether in the presence of 2-acetamidophenol as the internal standard. The separation was carried out on high-pressure liquid chromatography system with CLUZEAU column (250 mm × 3 mm, 5 µm) with a gradient of solvent A (0.87 g of pentane-1-sulfonic acid in 1 l of phosphate buffer) and solvent B (acetonitrile) as follows: 75% solvent A and 25% solvent B for 30 min.

The characteristics of the method were as follows: the calibration range was linear from 0.25 to 10 mg l^{-1}; the lower limit of quantification was 0.25 mg l^{-1}; the extraction yield was 88%; the reproducibility evaluated by the coefficient of variation was >93.6%; and the accuracy evaluated by the coefficient of variation was >96%. No analytical interference between the different antiretrovirals was noticed.

Modelling strategy and data analysis

Different structural models for NVP pharmacokinetics were investigated, i.e. one or two compartments with linear

elimination and first-order or zero-order absorption, with or without a lag time or a transit compartment for absorption. As nevirapine was given exclusively by oral route, clearance (*CL*) and volume of distribution (*V*) are apparent parameters, *V*/*F* and *CL*/*F*, where *F* is the unknown bioavailability fraction.

Data were analysed using the nonlinear mixed-effect modelling software program Monolix version 4.0 'http://www.lixoft.eu/' [21]. Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo procedure. The number of Markov Chain Monte Carlo chains was fixed to five for all estimations. Several error models (proportional, additive or mixed) were investigated to describe the residual variability (ε). The between-subject variabilities (η or BSVs) were assumed to be exponential. The objective function value (OFV) was used to test different hypotheses regarding the final model, covariate effect(s) on pharmacokinetic parameter(s), residual variability model (proportional *vs*. proportional plus additive error model), and structure of the variance–covariance matrix for the BSV parameters.

Continuous covariates (CO) were tested according to the following equation, using *CL* for example, $CL = \theta_{CL} \times \left(\frac{CO}{\text{median}(CO)} \right)^{\beta_{CO}^{CL}}$, where θ_{CL} is the typical value of clearance for a patient with the median covariate value and the power exponent β_{CO}^{CL} is the estimated influential factor. The main continuous covariates of interest in the population were age, postmenstrual age (PMA) and bodyweight. Parameter estimates were standardized for a mean standard BW using an allometric model. From allometric scaling theory the power exponents are typically 0.75 for clearance and one for volume of distribution [22].

Age-related change functions for pharmacokinetic parameters have been described previously [23]. The effect of PMA on the relative bioavailability was investigated following the Hill equation, $F = F_{\text{adult}} \times \frac{\text{PMA}}{\text{PMA} + \text{PMA}_{50}}$, where F_{adult} is the reference bioavailability in adults, fixed to one and PMA_{50} is the PMA corresponding to $F = 0.5$.

Binary covariates were tested according to the equation, $CL = \theta_{CL} \times (\beta_{CO}^{CL})^{CO}$, where CO = 0 is for the reference θ_{CL} value and CO = 1 for the *CL* value in the presence of the covariate. The main binary covariates of interest in the population were sex and antiretroviral treatment. A covariate was finally retained if it met the following conditions: (i) its effect was biologically plausible; (ii) a reduction in OFV value was observed; and (iii) it produced a reduction in the variability of the pharmacokinetic parameter, assessed by the associated intersubject variability. Graphical evaluation of the goodness of fit was mainly assessed by observed *vs*. predicted concentrations (PRED-DV) and weighted residuals *vs*. time and/or weighted residuals *vs*. PRED.

The final population model was mainly evaluated by the normalized prediction distribution errors (npde) metrics [24] and the prediction-corrected visual predictive check [25]. Diagnostic graphics and distribution statistics were obtained using RfN (link on http://wfn.sourceforge.net) via the R program [26].

Individual Bayesian estimates of the pharmacokinetic parameters were used to calculate the individual area under the concentration–time curve from time zero to 12 h (AUC_{0-12}) and the C_{min} of NVP.

Dose simulations

Using the final population model, the probability of obtaining the target C_{min} between 3 and 8 mg l^{-1} in 94 000 children (1000 simulations of our 94 children) was calculated for different twice-daily doses (50, 75, 100, 125, 150, 175 and 200 mg) in 13 bodyweight groups (3–6, 6–10, 10–15, 15–20, 20–25, 25–30, 30–35, 35–40, 40–45, 45–50, 50–55, 55–60 and >60 kg). Simulations were also performed in order to determine the percentage of patients below the efficacy target following the EMA and WHO dosing recommendations.

- The EMA dosing recommendations are currently 7 mg kg^{-1} BID for children more than 2 months to 8 years and 4 mg kg^{-1} BID for children older than 8 years [2].
- the WHO dosing recommendations are 50 mg BID (3–6 kg), 75 mg BID (6–10 kg), 100 mg BID (10–14 kg), 125 mg BID (14–20 kg), 150 mg BID (20–25 kg) and 200 mg BID above 25 kg [16].

Results

Demographic data

The median [95% confidence interval (CI)] follow-up duration of therapeutic drug monitoring for the 94 children (50 girls and 44 boys) was 12.5 months (range 0–93 months), and 390 NVP concentrations were available for pharmacokinetic evaluation. The pharmacokinetic study was performed after 15 days of treatment, in children older than 2 months. At baseline, the median (95% CI) age was 6.3 years (10 months to 14 years), the median (95% CI) bodyweight was 20 kg (3–64 kg) and the median (95% CI) NVP dose was 100 mg (21–200 mg) twice daily.

Population pharmacokinetics

Three concentrations were below the linit of quantification and were treated as left-censored data by the program. A one-compartment model with first-order absorption and elimination described the data adequately. The absorption constant could not be estimated adequately (no sample between 0 and 1 h after drug intake) and was finally fixed

Table 1

Population pharmacokinetic parameters of nevirapine in 94 children (aged 2 months to 17 years)

	Parameter	RSE (%)
Structural model		
K_a (h^{-1})	0.4	—
V/F (l (70 kg)$^{-1}$)*	140	39
CL/F (l h^{-1} (70 kg)$^{-1}$)*	3.93	5
θPMA_{50} (years)	0.55	36
Statistical model		
BSV *CL/F*	0.33	10
$\sigma_{proportional}$	0.30	4

Abbreviations are as follows: F, bioavailability; BSV, between-subject variability estimates; *CL/F*, apparent elimination clearance; K_a, absorption rate constant; RSE, relative standard error; σ, residual variability estimates; θPMA_{50}, PMA corresponding to *F* = 0.5; and *V/F*, apparent central volume of distribution. *The typical parameters refer to a patient weighing 70 kg according to the following allometric scaling model: [typical value] = [typical parameter] × (bodyweight/70)^{PWR}, where PWR = 0.75 for the *CL* term and PWR = 1 for the *V* term. $CL/F = 3.93 \times (\text{bodyweight}/70)^{0.75}/[\text{PMA}/(\text{PMA}_{50} + \text{PMA})]$. $V/F = 140 \times (\text{bodyweight}/70)^{1}/[\text{PMA}/(\text{PMA}_{50} + \text{PMA})]$.

to 0.4 h^{-1} [27]. Between-subject variability could be estimated only for apparent clearance. The proportional model for the residual variability ensured a good agreement between observed and predicted values. Bodyweight was included in the model, using a one and a three-quarters allometric scaling for *V/F* and *CL/F*, respectively. These parameters were normalized for a 70 kg BW adult and decreased the objective function value by 66 units and the *CL/F* BSV from 0.47 to 0.34. The effect of PMA on the bioavailability was statistically significant, decreasing the objective function value by 8.2 units and the BSV on *CL/F* to 0.33. The effects of sex and other co-medications were also evaluated on the *CL/F* parameter, but no significant relationship appeared. The final model was then:

$$CL\,(\text{l h}^{-1}\,(70\,\text{kg})^{-1}) = \theta_{CL} \times \left(\frac{\text{BW}}{70}\right)^{0.75} \times \frac{\text{PMA} + \text{PMA}_{50}}{\text{PMA}}$$

$$V\,(\text{l}\,(70\,\text{kg})^{-1}) = \theta_{V} \times \left(\frac{\text{BW}}{70}\right)^{1} \times \frac{\text{PMA} + \text{PMA}_{50}}{\text{PMA}}$$

Table 1 summarizes the final population pharmacokinetic estimates, including the relative standard errors. All parameters were well estimated regarding the relative standard error values of the estimates. The empirical Bayesian estimate of η-shrinkage on *CL/F* was 0.02. Final model performance was appreciated by comparing population predicted and individual predicted with observed plasma concentrations and population weighted residuals *vs.* predicted concentrations for nevirapine (Figure 1).

The prediction-corrected visual predictive check shows that the 5th, 50th and 95th percentiles of observed data are well included within the 90% CI of the 5th, 50th and 95th simulated percentiles (Figure 2). The mean and variance of the npde metrics were not significantly different from 0 ($P = 0.13$) and 1 ($P = 0.17$) and their distribution was not different from a normal one ($P = 0.23$; global adjusted *P*-value, $P = 0.39$). Table 2 summarizes values of AUC_{0-12} and C_{min} obtained from the present study and from previous studies in children.

Figure 3 displays the median NVP C_{min} values as a function of bodyweight derived from 1000 simulations of the final model following the EMA or WHO dosing recommendations. Figure 3A shows that the EMA dosing recommendations lead to subtherapeutic C_{min} values for children weighing less than 10 kg (14 children). As shown in Table 3 and Figure 3B, the WHO recommendations seem to correct this subtherapeutic dosage in part, because more than 71% of patients were above the efficacy target; however, the youngest children were still underexposed. Simulations of doses of 75 and 100 mg for the bodyweight ranges 3–6 and 6–10 kg, respectively, lead to C_{min} values above the efficacy target in 96 and 97% of cases, respectively (Table 3).

Discussion

Nevirapine concentrations were satisfactorily described by a one-compartment model with linear absorption and elimination, including the effects of bodyweight on *CL/F* and *V/F* and PMA on the relative bioavailability. The following observations support the model used: (i) the pharmacokinetic parameters were standardized for a 70 kg bodyweight adult and the apparent clearance estimate was 3.9 l h^{-1} (70 kg)$^{-1}$, close to previously published values in adults [28, 29]; (ii) NVP half-life and $AUC_{0-12\,h}$ following a 200 mg BID NVP dosage were, respectively, around 25 h and 51 mg h l^{-1}, results similar to other estimates in adults [28, 30, 31]; and (iii) the mean apparent clearance estimate in our population ($CL/F = 1.7$ l h^{-1}) was also in agreement with the previous paediatric population study (1.9 l h^{-1}) of Nikanjam *et al.*, which also found an age effect after allometric scaling of the apparent parameters [32]. In the present study, the effect of PMA was significant on the basis of a decrease in the OFV, although there was no substantial reduction in the corresponding BSV; however, this effect was retained in the model for the following reasons: (i) it improved the diagnostic plots; (ii) it allowed prediction of the adult values; and (iii) it was also reported by another group [32]. The effect of PMA on the bioavailability of NVP in children showed that at 210 weeks of life (4 years), 90% of the adult value was reached.

Based on EMA and WHO dosing recommendations, the probability of observing concentrations below the target of 3 mg l^{-1} is higher following the EMA than the WHO dosing recommendations. Indeed, following the WHO dosing recommendations the probability of observing concentrations below the efficacy target was less than 6%

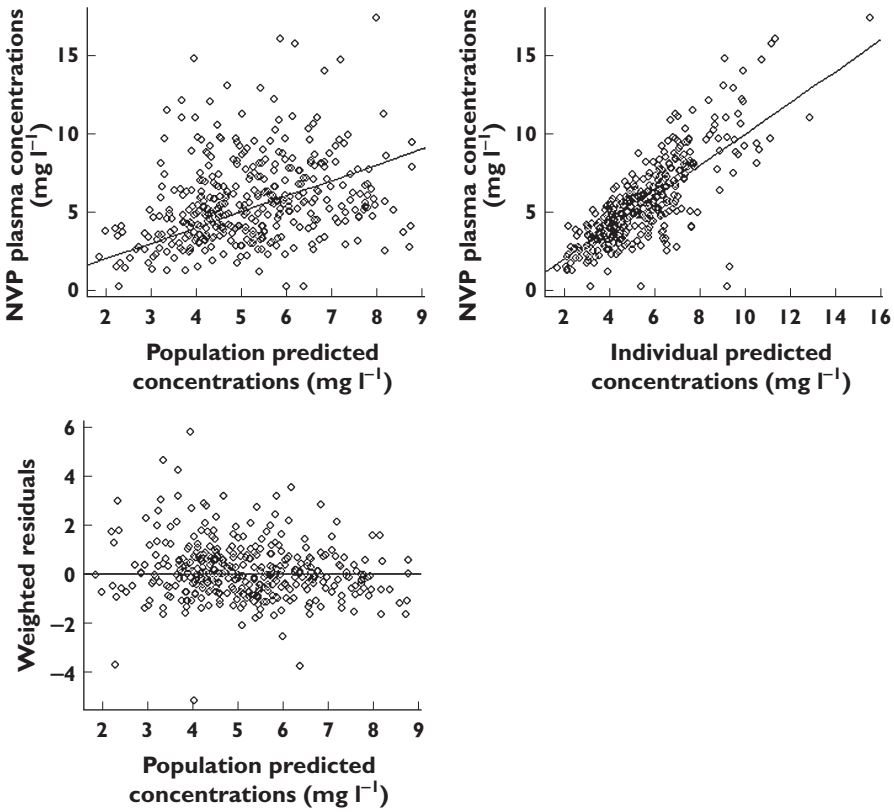

Figure 1

Observed nevirapine (NVP) concentrations *vs.* population predicted NVP concentrations (top left), observed NVP concentrations *vs.* individual predicted NVP concentrations (top right), and population weighted residuals *vs.* population predicted NVP concentrations (bottom left)

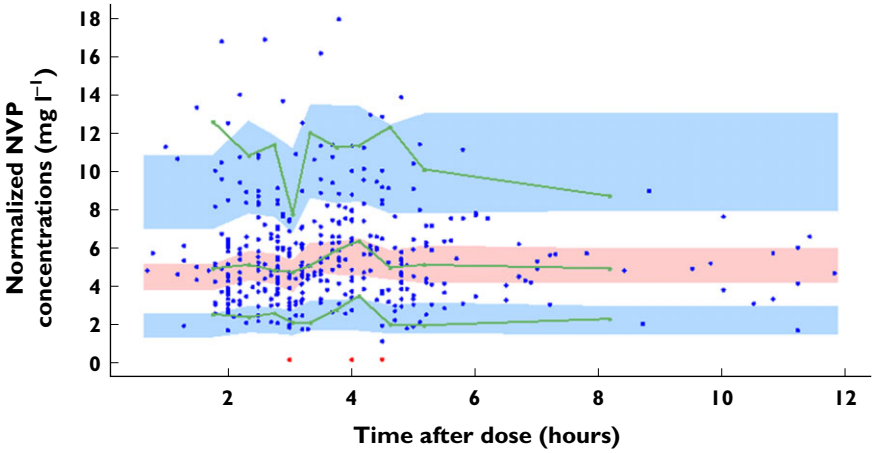

Figure 2

Prediction-corrected visual predictive check for nevirapine (NVP) concentrations *vs.* time (in hours). The green lines show the 5th, 50th and 95th percentiles of observed data; the areas represent the 90% confidence interval around the simulated percentiles; and the red dots correspond to values below the limit of quantification

for patients weighing more than 10 kg; however, the probabilities were 19 and 11% in the 3–6 and 6–10 kg weight ranges, respectively. Thus, the WHO dosing recommendations appeared to be sufficient only for patients weighing more than 10 kg, which is in agreement with recent studies [13, 19, 20]. Fillekes *et al.* have conducted a study in 15 children from 3 to 6 kg treated with Triomune Baby® and concluded that 27% of them had subtherapeutic NVP

Table 2

Comparison of nevirapine-derived pharmacokinetic parameters between our study and previous studies of children

Parameter [median (range)]	Present study	Previous paediatric studies Chokephaibulkit *et al.* [34]	Pollock *et al.* [14]
Number of children	94	34	25
Age (years)	7.2 (0.17–17.5)	8.4 (3–15)	6.3 (0.8–16)
Bodyweight (kg)	21 (2.9–67)	— (4–40)	15.9 (6.3–38.9)
Daily dose	200 (40–400) mg	328 (244–435) mg m^{-2}	250 (100–400) mg
CL ($l\ h^{-1}\ kg^{-1}$)	0.08 (0.03–0.14)	0.08 (0.02–0.16)	0.1 (0.03–0.18)
AUC_{0-12} ($mg\ h^{-1}\ l^{-1}$)	65.3 (25–191)	78.4 (50–307)	79.9 (44–146)
C_{min} ($mg^{-1}\ l^{-1}$)	4.3 (1.3–14.2)	5.98 (2.57–24.4)	5.9 (2.3–9.1)

Abbreviations are as follows: *CL*, clearance; AUC_{0-12}, area under the concentration-time curve from 0 to 12 h; C_{min}, minimal concentration.

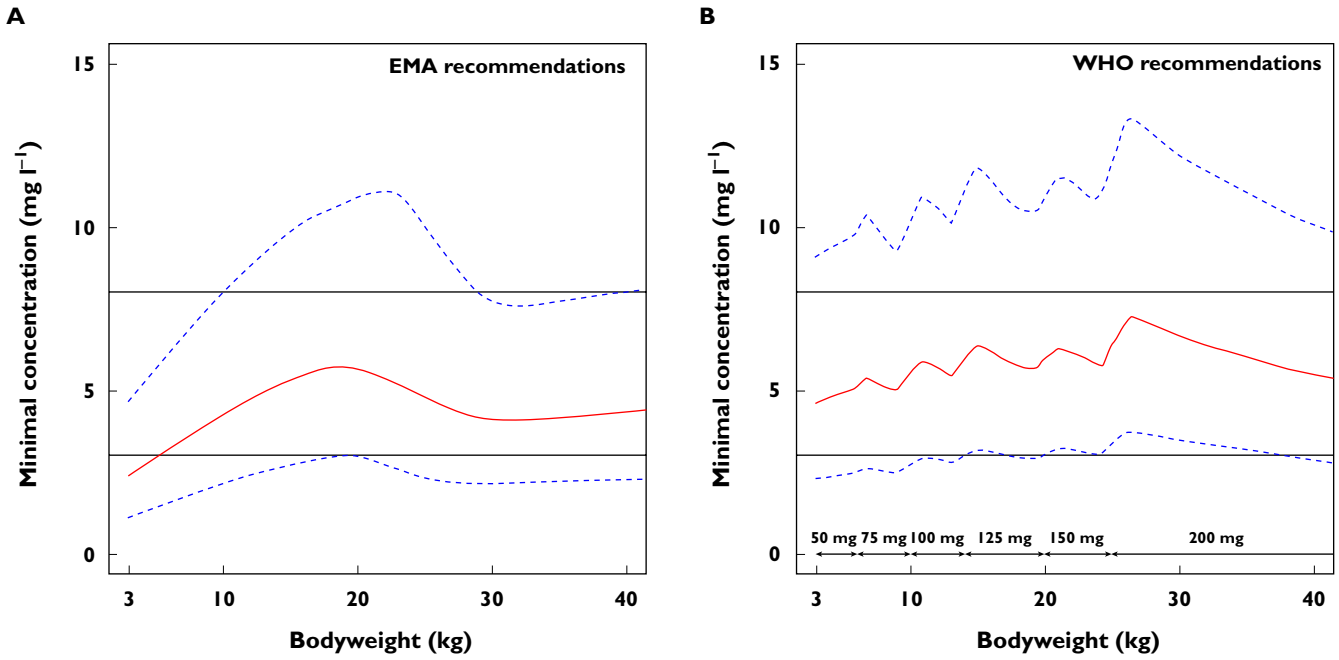

Figure 3

Calculated nevirapine (NVP) minimal concentrations (continuous line) and 90% confidence intervals (dashed lines) *vs.* bodyweight in children, following the European Medicines Agency (EMA) dosing recommendations (A) and the World Health Organization (WHO) dosing recommendations (B). The horizontal continuous lines represent the minimal concentration targets for efficacy (3 mg l^{-1}) and toxicity (8 mg l^{-1}), respectively

levels. This percentage was higher in children aged less than 5 months [20].

In order to avoid subtherapeutic dosage, which could lead to virological failure, higher dosing recommendations are suggested in the youngest children; 75 mg BID for the 3–6 kg weight range and 100 mg BID for the 6–10 kg group were simulated. These dose simulations resulted in 96 and 97% of patients with C_{min} values above 3 mg l^{-1}, whereas 34% (3–6 kg) and 33% (6–10 kg) were above 8 mg l^{-1}, which has been considered as a potential toxic level [13, 14, 33]. However, this toxicity threshold has not been properly defined because no significant relationship between high NVP concentrations and the occurrence of toxicity has been demonstrated either in adult or in pediatric patients. Poerksen *et al.* have conducted a study with 74 HIV-infected children treated with split Triomune 30® tablets and reported that 39% had C_{min} values above 8 mg l^{-1} without clinical signs of drug toxicity [13]. The balance between efficacy and toxicity for the youngest children from 3 to 10 kg suggests higher dosing recommendations; however, some caution must be exercised to avoid toxicity.

In conclusion, the WHO dosing recommendations seem appropriate in children weighing more than 10 kg, but doses could be increased to 75 and 100 mg BID in the 3–6 and 6–10 kg weight ranges, respectively, to obtain more than 95% of children with a minimal concentration

Table 3

Percentage of patients with minimal concentrations below, above or within the therapeutic interval (3–8 mg l^{-1}) following EMA dosing recommendations, WHO dosing recommendations or simulations of the present study

Weight band	Recommendation	<3 mg l^{-1} (%)	In the range (%)	>8 mg l^{-1} (%)
3–6 kg	EMA, 7 mg kg^{-1} BID	57	42	1
	WHO, 50 mg BID	19	73	8
	Simulation, 75 mg BID	4	62	34
6–10 kg	EMA, 7 mg kg^{-1} BID	27	70	3
	WHO, 75 mg BID	11	71	18
	Simulation, 100 mg BID	3	64	33

Abbreviations are as follows: BID, twice daily; EMA, European Medicines Agency; and WHO, World Health Organization.

above 3 mg l^{-1}. These suggestions should be confirmed prospectively.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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