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Effect of reducing the paediatric stavudine dose by half: A physiologically-based pharmacokinetic model

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ABSTRACT

Owing to significant dose-related toxicity, the adult stavudine dose was reduced in 2007. The paediatric dose, however, has not been reduced. Although the intended paediatric dose is 1 mg/kg twice daily (b.i.d.), the current weight-band dosing approach results in a mean actual dose of 1.23 ± 0.47 mg/kg. Both efficacy and mitochondrial toxicity depend on the concentration of the intracellular metabolite stavudine triphosphate (d4T-TP). We simulated the effect of reducing the paediatric dose to 0.5 mg/kg. A physiologically-based pharmacokinetic model consisting of 13 tissue compartments plus a full ADAM model was used to describe the elimination of stavudine. The volume of distribution at steady-state and apparent oral clearance were simulated and the resulting AUC profile was compared with literature data in adult and paediatric populations. A biochemical reaction model was utilised to simulate intracellular d4T-TP levels for both the standard and proposed reduced paediatric doses. Simulated and observed exposure after oral dosing showed adequate agreement. Mean steady-state d4T-TP for 1.23 mg/kg b.i.d. was 27.9 (90% CI 27.0–28.9) fmol/10^6 cells, 25% higher than that achieved by the 40 mg adult dose. The 0.5 mg/kg dose resulted in d4T-TP of 13.2 (12.7–13.7) fmol/10^6 cells, slightly higher than the adult dose of 20 mg b.i.d. [11.5 (11.2–11.9) fmol/10^6 cells], which has excellent antiviral efficacy and substantially less toxicity. Current paediatric dosing may result in even higher d4T-TP than the original 40 mg adult dose. Halving the paediatric dose would significantly reduce the risk of mitochondrial toxicity without compromising antiviral efficacy.

1. Introduction

The current standard paediatric dose of stavudine is 1 mg/kg twice daily (b.i.d.); however, the current weight-band dosing approach results in a mean actual dose of 1.23 ± 0.47 mg/kg b.i.d. At the current dose, stavudine is associated with progressive fat metabolism defects including lipoatrophy, lipohypertrophy, dyslipidaemia and insulin resistance. Lipoatrophy, a very slowly progressive disfiguring loss of fat in the face and limbs, may begin after as little as 6–9 months of therapy and eventually appears in up to 36% of children [1]. This stigmatising condition has become the hallmark of human immunodeficiency virus (HIV) infection and often leads to reduced adherence to antiretroviral therapy (ART). Lipohypertrophy, which involves abnormal fat accumulation in the breasts, abdomen and nape of the neck, is less common before puberty [2]. Dyslipidaemia and insulin resistance have both been associated with early atherosclerosis-like vascular abnormalities in children [3]. One option to manage toxicity is to switch to another antiretroviral medication, however for children in the developing world the options are limited. The anaemia-inducing effect of zidovudine limits its usefulness, especially in sub-Saharan Africa where malaria- and malnutrition-related anaemia is already common and is strongly associated with poor neurocognitive outcomes in adult life [4]. Abacavir has very few real adverse effects but is expensive and may have reduced efficacy in patients with high viral loads, making it less suitable as an initiation drug [5]. Tenofovir is avoided in children owing to concerns about its renal and bone toxicities, which may be more pronounced in growing children than in adults [6,7]. In contrast, stavudine is potently effective, cheap and remarkably safe in the short-term (first 6 months of therapy), particularly in settings where routine monitoring for acute adverse drug effects is limited. Logistically, the paediatric liquid formulation

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of stavudine is a dry powder requiring reconstitution with a specific volume (202 mL) of distilled water. The resulting liquid must be transported in a cooler box and requires refrigeration at 4 °C to maintain stability for 1 month. In the rural setting where refrigeration is a rare commodity, the adult formulation is often used in an off-label manner wherein caregivers who do not have access to a refrigerator are instructed to disperse the contents of an adult capsule in 5 mL of water and then withdraw the required fraction using a syringe. The accuracy and bioavailability of this 'opened capsule' administration method for stavudine have been validated [8]. In contrast to abacavir, the stavudine adult capsule formulation has a well-established supply chain throughout Africa and is stable at room temperature (<25 °C) for at least 2 years. Thus, stavudine remains a commonly used ART drug for children in the developing world.

The frequency and severity of stavudine-related lipoatrophy and dyslipidaemia are strongly dependent on the dose and duration of use. The likelihood of developing this mitochondrial toxicity appears to be directly linked to the intracellular concentration of stavudine's phosphorylated intracellular metabolite, stavudine triphosphate (d4T-TP) [9]. The in vitro 50% inhibitory concentration (IC_{50}) of d4T-TP against HIV-1 is between 0.009 μM and 6 μM, depending on the phenotypic and genotypic resistance to nucleoside reverse transcriptase inhibitors [10]. The d4T-TP concentration required to inhibit half-maximum human mitochondrial DNA polymerase γ activity, which is responsible for synthesis of proviral DNA, was ca. 0.05 μM [11]. The current standard adult dose of 30 mg b.i.d. achieves a median intracellular d4T-TP concentration in the mid range of the IC_{50} values (ca. 2–3 μM) [12], yet produces an excellent virological response. As a result, several strategies of dose reduction have been hypothesised [12–14].

In 2007, a meta-analysis by Hill et al. showed that a reduced adult dose of either 20 mg or 30 mg b.i.d. significantly lowers the frequency of delayed toxicity (lipoatrophy, dyslipidaemia, lactic acidosis, peripheral neuropathy) while maintaining excellent antiviral efficacy [13]. In response, the World Health Organization (WHO) recommended that the adult dose be reduced to 30 mg b.i.d. [15]. The paediatric dose, however, has not yet been reduced. Up to now, there has been resistance to reducing the paediatric dose, with antagonists citing a lack of evidence showing that antiviral efficacy will be maintained at the lower dose. A substantial reduction in the standard paediatric dose is likely to drastically reduce the frequency and severity of lipoatrophy, dyslipidaemia and insulin resistance, allowing continued safe use of this highly effective, logistically simple, widely available and remarkably cheap ART drug.

2. Methods

2.1. Physiologically-based pharmacokinetic (PBPK) approach

The approach taken in this study utilises a 'bottom-up' approach that combines physicochemical properties, intrinsic clearance and physiological system information to describe the population of interest with PBPK models [16]. A typical organ compartment depicted in Fig. 1 can be solved mathematically by mass balance on each compartment. Assuming perfusion-limited kinetics, Eq. (1) is the mass balance equation for a compartment *j*, representing a generic organ, except for the lung.

$$\frac{V_{\text{tis}}\,dC_{\text{tis}}}{dt} = Q_{\text{tis}}\left(C_{b,a} - \frac{C_{\text{tis}}}{K_p/K_{\text{B:P}}}\right) - R \quad (1)$$

where Q_{tis} is the blood flow for the tissue compartment, K_p is the tissue-to-plasma partition coefficient, $K_{\text{B:P}}$ is the blood–plasma partition coefficient, subscript b represents blood and tis represents

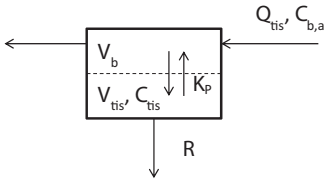

Fig. 1. A representative organ of the body, representing blood flow and tissue perfusion. V_b, Volume of blood; $C_{b,a}$, drug concentration in the arterial blood; V_{tis}, tissue volume; C_{tis}, drug concentration in the tissue; K_P, tissue-to-plasma partition coefficient; *R*, elimination process; Q_{tis}, blood flow for the tissue compartment.

tissue, C_{tis} is the drug concentration in the tissue, $C_{b,a}$ is the drug concentration in the arterial blood and V_{tis} is the tissue volume. For a non-eliminating tissue, *R* is negligible. For an eliminating tissue, *R* can be defined by $\text{CL}_{\text{int,u}}\left(\left(C_{\text{tis}} \times f_{\text{up}}\right)/K_p\right)$, where $\text{CL}_{\text{int,u}}$ represents the unbound intrinsic clearance of the tissue and f_{up} represents the fraction unbound in plasma.

Assuming that the lung is not an eliminating organ, the kinetics of the drug in the lung compartment can be described by:

$$\frac{V_{\text{lu}}\,dC_{\text{lu}}}{dt} = Q_{\text{lu}}\left(C_{b,v} - \frac{C_{\text{lu}}}{K_p/K_{\text{B:P}}}\right) \quad (2)$$

where V_{lu}, Q_{lu} and C_{lu} are the volume, blood flow and drug concentrations in the lung, and $C_{b,v}$ represents the drug concentration in venous blood.

The mass balance equation for the venous blood is as follows:

$$\frac{V_{b,v}\,dC_{b,v}}{dt} = \sum_i Q_{t,i}\left(\frac{C_{t,i}}{K_p/K_{\text{B:P}}}\right) - Q_{\text{lu}}C_{b,v} \quad (3)$$

where *i* represents the various organs that are connected to the venous blood compartment except the lung, and $V_{b,v}$ is the volume of the venous blood.

For the arterial blood, the kinetics is defined by:

$$\frac{V_{b,a}\,dC_{b,a}}{dt} = Q_{\text{lu}}\left(\frac{C_{\text{lu}}}{K_p/K_{\text{B:P}}} - C_{b,a}\right) \quad (4)$$

where $V_{b,a}$ is the volume of the arterial blood.

2.2. Model development and qualification

The PBPK model for stavudine utilises a perfusion-limited clearance consisting of 13 compartments representing various organs, as shown in Fig. 2, in the full advanced dissolution, absorption and metabolism (ADAM) PBPK model in Simcyp v. 14 (Simcyp Ltd., Sheffield, UK). The physicochemical properties of stavudine were obtained from publicly available information and the pharmacokinetic parameters from published scientific literature, as listed in Table 1. The full PBPK model uses the predicted volume of distribution values for stavudine, which was based on the method by Rodgers and Rowland [17].

The resulting exposure parameter, the area under the concentration–time curve (AUC), was compared with the literature values from in vivo studies [8,18–21]. The model qualification was measured by the slope (β) of the regression line:

$$\text{predicted}\ \ \text{AUC}_{0-\infty} = \alpha + \beta(\text{observed}\ \ \text{AUC}_{0-\infty}) + \varepsilon \quad (5)$$

The intercept (α) was set to 0. The error term (ε) was used to account for interstudy variation. The PBPK model of stavudine redistribution and elimination in adults is qualified if the two-sided 90% confidence interval (CI) of the slope of the regression line for the predicted mean $\text{AUC}_{0-\infty}$ lies within 0.8 and 1.25 of the literature-reported geometric mean $\text{AUC}_{0-\infty}$ at various doses.

The formulation was assumed to be a solution as the drug is often administered using the open-capsule method to paediatric

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