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Pharmacokinetics of Nevirapine in HIV Infected Children from Resource Limited Settings Using Fixed Dose Anti-retroviral Combinations

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: The pharmacokinetics of nevirapine in paediatric populations are important to consider for those receiving anti-retroviral treatment in resource limited settings. High rate of adherence is required to achieve therapeutic success with good record keeping system for monitoring and follow-ups.
Discussion: Children up to 2 years old have a higher rate of elimination for nevirapine compared to adult population and older children. Elimination rate in children less than 8 years are about twice those in adults. Prescriptions for the drug based on body surface area have been found to be too complex for use in resource limited settings and calculations based on weight bands are used. Though weight bands make drug administration easier the lower weight bands are likely to receive sub therapeutic doses when drug is administered especially when adult fixed dose combinations are used. Chewable paediatric tablets offer better pharmacokinetic profile compared to liquids or oral tablets, however availability of such dosage forms remains low. Solid dosage forms tend to give better nevirapine exposure when taken whole and not broken into halves or quarters as is the

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case in resource limited settings. Absorption and bioavailability of nevirapine may be affected by nutritional status when they is changes in fat/lean body mass ratio and physiological function due to malnutrition**.**

Conclusion: Effective antiretroviral treatment is limited by low availability of formulations for nevirapine only or fixed dose combinations for use in paediatric populations. Paediatric formulations are more accurate in achieving trough concentrations and sufficient nevirapine exposure. Adult tablets usually have to be broken in halves or quarters and this can affect the bioavailability of nevirapine and lead to sub therapeutic concentrations.

Keywords: Nevirapine; resource limited; fixed dose combinations; paediatric antiretroviral pharmacotherapy; non-nucleoside reverse transcriptase inhibitors.

1. INTRODUCTION

The increasing need for quality healthcare for paediatric HIV pharmacotherapy means increased access to antiretroviral dosage forms appropriate to target populations is necessary. While this is a desired goal that seen has seen many global initiatives been setup to spearhead the process of developing pharmaceuticals for paediatric market, little access to the formulations is still observed in resource limited settings. This has led to the use of adult tablet doses usually broken in half for children's therapy which may not give sufficient exposure for the antiretroviral. Malnutrition, lack of adherence and dosing based on weight bands also brings a challenge to achieving optimal pharmacokinetics with sub therapeutic concentrations often posing a risk to effective viral suppression. This review looks at the use of nevirapine in paediatrics and if a similar dilemma exists for the drug with good pharmacokinetic parameters in adult population when it is administered to paediatrics in resource limited settings.

Nevirapine is a first generation non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for antiretroviral therapy in adults and children aged 15 days or older [1,2]. The drug is associated with poor aqueous solubility but high permeability across membranes. Moderate to severe skin rashes frequently occur in patients taking the drug with a 21% incidence were reported for paediatric population in a clinical trial carried out by Boehringer Ingelheim® Pharmaceuticals [1]. These include Steven-Johnson syndrome, toxic epidermal necrolysis and other hypersensitivity skin reactions. It is recommended that dosage be first initiated as 150 mg/m^2 once daily for 14 days and monitor for skin rashes and the dose is only increased if the rash has resolved. Hepatic damage also occurs and as a result the drug is contraindicated for patients with hepatic impairment [1,2].

Nevirapine is a weak base showing increased solubility at acidic pH values. Stability tests carried on the paediatric suspension Viramune® show that the formulation can be stable for up to 18 months for the newly recapped oral suspension and 24 months with the old pulp board liner confirmed the physical and chemical stability of the oral suspension and the antimicrobial efficacy of the preservative [1,3]. The generic version from Cipla Nevimune® also showed stability for a period of 24 months when not stored at temperatures above 30℃ [2].

The chemical and pharmacokinetic properties of NVP are advantageous as it can be formulated as a heat stable liquid preparation, and its bioavailability is not affected by food intake. Nevirapine can exist in two pseudo polymorphic forms, anhydrous and hemihydrates [2,4]. The anhydrous form has been used for the development of the oral tablet due to its higher intrinsic aqueous solubility (90 µg/ml at 25℃).

2. PHARMACOKINETICS OF NEVIRAPINE

Like other NNRTIs nevirapine is used in combination with other antiretroviral agents classified as protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), fusion inhibitors (FIs), CCR5 antagonists and intergrase strand transfer inhibitors (INSTIs) [5,6,7]. Paediatric dosing of nevirapine is based on body surface area or weight bands according to the WHO and local treatment guidelines for resource limited settings [7,8,9]. Nevirapine in combination with two NRTIs is recommended for first line treatment of HIV positive children 24 months old and above or in infants below 24 months without previous exposure to the drug during prevention of mother-to-child transmission (PMTCT) programmer of HIV [6,7].

In resource limited settings availability of appropriate dosage forms for paediatrics may be low and adult doses may be divided for use in

children [10]. Bioavailability and plasma levels of nevirapine have to be maintained high for sufficient viral suppression. In these settings pill burdens, lack of paediatric formulations, sub-optimal adherence, malnutrition and patients genomics may all affect the effectiveness of nevirapine and ability to achieve steady state plasma levels [6,5,10]. Adverse drug reactions like skin rashes and occurrence of viral resistance also affect the use of the NNRTI. Nevirapine is given with an induction dose for 2 weeks once daily then maintenance dose twice daily [7,11].

Patients receiving NNRTIs are required to have a higher rate of adherence in comparison to those receiving other antiretrovirals drugs like the PIs. Resource limited settings may also have poor records for patient's age and adherence. Sub therapeutic concentrations have been reported by several studies with current recommendations, especially in young children. The apparent clearance and apparent volume of distribution increased allometrically with bodyweight, whereas the relative bioavailability increased with postmenstrual age [9,12].

Nevirapine is readily absorbed after oral doses and absorption is not affected by food or antacids, with 90% or more bioavailability been achieved [13]. Nevirapine tablets and oral suspension are comparably bioavailable and interchangeable at doses up to 200 mg. Peak plasma concentrations occur 4 hours after a single dose [13,14]. Nevirapine is about 60% bound to plasma proteins. Concentrations in the cerebral spinal fluid are about 45% of those in plasma. The drug undergoes extensive metabolised by hepatic microsomal enzymes, principally by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, to several hydroxylated metabolites [13,15]. The CYP3A4 enzyme is major inducer of nevirapine metabolism and is found in the hepatic and gastric cells [13]. Auto induction of these enzymes results in a 1.5- to 2-fold increase in apparent oral clearance after 2 to 4 weeks at usual dosage, and a decrease in terminal half-life from 45 hours to 25to 30 hours over the same period [13,5]. Nevirapine is mainly excreted in the urine as glucuronide conjugates of the hydroxylated metabolites.

Herbal supplements as food or allopathic medicines can stimulate production of CYP3A4 enzyme within the liver and gastric cells. This leads to decrease in efficacy of nevirapine which results in therapeutic failure and reduced virological response of HIV to nevirapine when herbal supplements are co-administered with other drugs and herbs like St. John's wort (*Hypericum perforatum*) [1,4].

Metabolic activity changes also occur in the digestive system, renal and metabolic systems in HIV positive patient. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when co-administered with nevirapine. In general it decreases plasma levels of protease inhibitors [16,15,5].

In children, nevirapine elimination accelerates during the first years of life, reaching a maximum at around 2 years of age, followed by a gradual decline during the rest of childhood; values in children under 8 years area about twice those in adults [13,17].

3. PHYSIOLOGICAL DEVELOPMENT AND MALNUTRITION IN CHILDREN

Development and maturation of organ systems involved in absorption, metabolism, and elimination of ARV drugs produce significant changes in the pharmacokinetics and pharmacodynamics (PD) of ART throughout childhood [6,11]. Faster clearance of ARV drugs by children compared to adults requires significantly higher per weight or body surface area dosing of ARV drugs in younger children in order to achieve similar systemic ARV exposures [11,14]. In addition to the developmental changes in the PK of ARV drugs, multiple factors such as nutritional status and co-morbidities have the potential to influence the PK and PD of ART in children [17,3,10].

In resource-limited settings significant number of cases anemia, decreased weight and delayed growth among HIV-infected children represent common challenges to ART. Concomitant illnesses, such as hepatitis, malabsorption and diarrhea, have the potential to alter absorption of ARV drugs. Metabolic and endocrine abnormalities associated with malnutrition have the potential to influence the volume of distribution and the total body clearance of lipophilic ARV drugs [10,11].

Children on ART developing TB and other chronic illnesses present a challenge in treatment selection because a high risk of drug-drug interactions occurring limit choice of drugs to be used for ART intervention [13,18,19]. The development of the paediatric ART dosing

guidelines has been instrumental in promoting safe and effective use of ART in children but data on the developmental changes in the ARV PK/PD are still limited in children [9,11,20].

Therapeutic drug monitoring (TDM) of ARV drugs needs to be considered in paediatric patients with drug-drug interactions and ART failure, especially where adherence failure had not been established. The use of the PK data in combination with viral resistance may provide grounds for a successful individualized dosing of ARV drugs in children and adolescents [13,21]. Compared to older children, neonates and young infants have delayed absorption, reduced liver metabolism and renal elimination of drugs. Rapid changes in renal function occur in the first days of life, making the dosing of ARV in neonates a challenging task [22,6,11].

4. BARRIERS TO EFFECTIVE ART EXPOSURE IN CHILDREN

Dosage recommendations of antiretroviral drugs in children may be based on weight or surface area. Prescriptions based on surface area are complex and prone to error. In recognition of this the WHO HIV Working Group produced standardized dosing tables for the use of fractions of FDC tablets in children [20,12,9]. Recommended doses aimed for an 'optimal' dose for weight bands determined by calculating surface area values from median heights for weight of international growth charts [9]. The Malawian national ART guidelines for children are adapted from these standardized tables.

Even with availability of the paediatric formulations of the ARV drugs, serious challenges to an efficient paediatric ART remain across the countries and continents [20]. Among those are specific paediatric adherence barriers such as palatability and high dosing volumes of the liquid ARV formulations, pill swallowing capacity of the child, dispensability of the paediatric ARV preparations, bioavailability of the FDC ARV components, parental and child behavior modification skills, disclosure or HIV status, handling and delivery of pediatric ART to the caregivers, and, most importantly, caregiver's experience and capacity to administer ART to younger patients and to serve as a supplier of ART, encouragement and support for older children [20,23,24].

For the treatment of HIV infection in infants, children, and adolescents nevirapine is given orally with other antiretroviral drugs. The following doses by bodyweight have been suggested according to age:

- From 15 days to 8 years: 4 mg/kg once daily for 14 days and then, if no rash is present, 7 mg/kg twice daily.
- 8 to 16 years: 4 mg/kg once daily for 14 days then 4 mg/kg twice daily thereafter

Alternatively, the dose may be calculated according to body-surface; an oral dose of 150 mg/m^2 once daily for two weeks is given followed by 150 mg/m^2 twice daily thereafter. A total dose of 400 mg daily should not be exceeded [13,19,11].

The weight-adjusted oral clearance of NVP is higher in younger children than in older children or adults. The initial FDA pediatric dosing of 7 mg/kg twice daily in children less than 8 years of age was thus reduced to 4 mg/kg for children 8 years of age or older. Subsequently, an alternative dosing recommendation of150 mg/m^2 twice daily was approved by the FDA [9].

A comparison of dosing using weight bands relating to body surface area would reflect as follows:

Table 1. Recommended dosing weight bands for nevirapine [9]

Weight range (kg)	Induction dose (160-200 mg/m^2/dose once daily)		Maintenance dose (160-200 mg/m^2/dose twice daily)	
	10 mg/mL suspension	200 mg tablet	10 mg/mL suspension	200 mg tablet
5 – 5.9	6 mL	-	6 mL	-
6 – 6.9	7 mL	-	7 mL	-
7 – 7.9	8 mL	-	8 mL	-
8 – 8.9	9 mL	-	9 mL	-
9 – 9.9	9 mL	Half a tablet	9 mL	Half a tablet
10 – 10.9	10 mL	Half a tablet	10 mL	Half a tablet

Children in resource-poor settings are under-represented in antiretroviral therapy (ART) programmes. Effective treatment programmes are hindered by cost of treatment, accessibility and availability of appropriate paediatric antiretroviral drug formulations [9,25,26]. The approach of providing divided doses from antiretroviral tablets for adult fixed dose as a treatment option for HIV positive paediatric population based on WHO dosing weight bands is commonly used in different countries. This includes combination of 30 mg of stavudine, 150 mg of lamivudine and 200 mg of nevirapine (Triomune 30) which is administered to children. The main challenge to using this approach is that the proportions of drugs in divided adult formulations may not be appropriate for children [27,21].

5. DISCUSSION

5.1 Formulation Types and Weight Bands

Data on pharmacokinetics of nevirapine based fixed dose combinations was analyzed and reviewed. In the study carried out by Soumya Swaminathan et al. [24] in India the type of formulation used did not affect the peak or trough plasma concentrations. In the 94subjects under study the fixed dose combination was taken as a whole tablet or broken in half either asd4T 6 mg: 3TC30 mg: NVP50 mg or d4T10 mg: 3TC40 mg: NVP70 mg and d4T 30 mg: 3TC150 mg: NVP 200 mg. The fixed dose combination with 70 mg nevirapine had a lower than recommended dose according to body surface area but this did not affect peak or trough concentrations. Nevirapine was administered according to body surface area and a range of doses were available for the tablet dosage forms used in the study [24].Where a wide range of paediatric formulations are available achieving optimal plasma peak and trough levels is more achievable for nevirapine.

A study done by Goenke Poerksen et. al. [21] in Malawi with 78 children the fixed dose combinations of Triomune 30 (containing 30 mg d4T, 200 mg NVP and 150 mg 3TC) and Triomune 40 containing 40 mg of d4T and similar concentrations of NVP and 3TC were administered. Dosing was carried out according to weight bands (<5, 5-<8, 8-<12, 12-<14, 14-<19, 19-<26, 26-<30 and ≥30 kg), which were chosen according to the Malawian paediatric national ART guidelines which are different to other dosing weight bands that have been recommended in other ART guidelines [21,8,7,9]. It was observed that children taking Triomune 30 doses between one-quarter tablet once daily and one-half tablet twice daily were significantly more likely to have a sub therapeutic NVP concentration. This was observable especially in the first 3 weight bands where higher risk of under dosing existed especially when weight bands are used with smaller subjects receiving higher concentration than bigger subject including those with stunted growth or body wasting that could be under dosed [21].

WHO recommended weight band dosing is wider than FDA recommended bands. Under dosing in lower weight bands might have also been caused malabsorption of the drug, drug-drug interactions or poor adherence however other studies done in Malawi and Zambia have consistently observed that the major driver of NVP exposure in very young children receiving fractions of adult Triomune® formulations is the drug dose suggesting that splitting of adult formulations results in under dosing of NVP [21,28]. The effect of crushing the tablets or of being unequally divided when cutting unscored tablets might have an additional effect on the administered dose [21,29].

In a study done in Thailand by Vanprapar et al. [30] a total of 35 children were enrolled with 18 receiving a chewable paediatric fixed dose combination tablet of 3TC:NVP and D4T while 17 subjects received liquid formulation of 3TC:NVP and D4T.Dosing was done according to the following weight bands (≥6–8 kg,>8–16 kg,>16–23 kg,>23–30 kg). Generally lower exposure to NVP was observed in the lower weight band for both the liquid formulation and chewable tablet. Smaller children can have a larger body surface area relative to body weight when compared with older children/adults, the weight band dosing of NVP could inadvertently be lower when converting the dose to mg/m^2 [12,30]. Even though a high rate of adherence was achieved in the study >97% seven subjects from the group using chewable tablets had sub therapeutic concentration of nevirapine ranging between 1.4 and 2.9 µg/mL. In the group receiving liquid formulation 4 have inadequate nevirapine exposure with plasma concentration range between 1.6 and 2.7 µg/mL. Nevirapine exposure proved to be therapeutically adequate in a chewable tablet dosage form compared to the liquids [30,6].

Chewable tablet dosage form also give the advantage of having a less variable bioavailability profile compared to the liquid dosage form and absorption of active drug from

site leading away from the hepatic circulation. However with standard treatment guidelines the weight bands would require breaking of tablet into halves or quarters which affect its release profile and taste masking effect of the dosage form [30,31].

5.2 Effect of Malnutrition

In countries where inadequate food security is experienced in paediatric populations' drug pharmacokinetics can be affected because of inadequate physiological development in a child. Malnutrition compounded or symptom of HIV/AIDS can make antiretroviral therapy ineffective. Pathophysiological alterations to the body due to malnutrition lead to change in nutrition transport, mucosal and villous atrophy, modification of permeability of the intestinal mucosa, and altered activity of small-intestine enzymes could be a reason for drug absorption disturbances [20,23].

Changes in fat/lean body mass ratio also affect drug distribution and calculations based on weight bands might not accurately give the required dose for administration. The patients may also have decreased drug protein binding capacity [17]. Reduced plasma protein, mainly albumin, causes an increase in the free drug concentration and subsequently augments the drug's toxicity. Additionally, liver dysfunction in malnutrition is the main reason for the altered metabolism of drugs and impaired renal function, especially in dehydration, significantly influences drug excretion [17,6,22].

A study done in Uganda comparing pharmacokinetic data of malnourished children compared to those form rich resource countries showed higher NVP exposure was experienced in children in resource limited settings than those receiving adequate nutrition [32]. Though the observation was interesting and different from EFV another NNRTI the researchers did not qualify the type of condition that the malnourished children experienced, whether they was stunted growth, body wasting or change in fat/lean body mass.

However a study by Soumya Swaminathanet et al. [24] showed that undernourished and stunted children experienced lower NVP concentrations 2 hours after administration compared to those who are not stunted. Children with stunted growth may experience less NVP exposure due to larger body surface area compared to the recommended weight band for dosing [24]. Potential for subtherapeutic concentrations of NVP existed in those that were stunted, under 3 years old and had CYP2B6 GG or GT genotype for hepatocytes.

6. CONCLUSION

Effective ART is limited by low availability of formulations for NVP only or fixed dose combinations for use in paediatric populations. Paediatric formulations are more accurate in achieving trough concentrations and sufficient NVP exposure. Adult tablets usually have to be broken in halves or quarters and this can affect the bioavailability of NVP and lead to sub therapeutic concentrations. Considering the dynamics of body surface area and weight band dosing improved availability of paediatric formulations will lead to improved pharmacokinetics and for NVP based therapy. Lower weight bands especially those with stunted growth require higher concentration of NVP dose for exposure as the weight band dosing of NVP could inadvertently be lower when converting the dose to mg/m^2. While malnutrition leads to lower NVP exposure in resource limited settings the effects are relevant when there is reduce physiological function and stunted growth that affect drug bioavailability. The presence of CYP2B6 GG or GT genotypes has the potential of resulting in sub therapeutic concentrations for NVP through hepatic first pass effect thereby reducing effective therapy. Formulation of paediatric products avoiding or by passing first pass effect would help to improve therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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