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Drug Dosing in Adult and Paediatric Population in Developing Countries: Possible Pharmaceutical Misadventure (A Review)

[1]I.C. Maduka, [2]E.E. Neboh, [3]E.N. Shu and [4]E.J. Ikekpeazu
[1]Department of Chemical Pathology, University of Nigeria Teaching Hospital (UNTH), PMB 01129, Enugu, Nigeria
[2]Department of Chemical Pathology, College of Medicine, Enugu State University of Science and Technology (ESUT) G.R.A, Enugu State, Nigeria
[3]Department of Pharmacology and Therapeutics, College of Medicine, University of Nigeria, Enugu Campus (UNEC), Enugu State, Nigeria
[4]Department of Medical Biochemistry, College of Medicine, University of Nigeria Enugu Campus, (UNEC), Enugu State, Nigeria

Abstract: Drug dosage should be based on weight rather than age and this study aims at highlighting the problems of possible over-dosage or under-dosage where the weight of the patient is not considered before prescription is given, as is being practice by clinicians in most developed and developing countries. Drug dosing has always been a vital issue in drug administration over time. For instance, the paediatric clinician encounters several limitations of information in paediatric pharmacotherapy which includes small numbers on patients with rare disease, small size studies and huge inter-patient variability among this population. The physiology, pharmacokinetics and pharmacodynamics of medications are highly variable and there is need to simplify this variation as much as possible. Tailoring the therapy for children according to their developmental stage as well as chronological age, which include selecting the appropriate dosage regimen and age-specific ways to prevent medication errors and enhanced compliance of paediatric patients are both significant problems to be further addressed in paediatric therapy. The basic principles of management of severe falciparum malaria include, initiating treatment immediately; checking of the weight and blood sugar level of patient; choosing drug regimen and calculation of the drug dosage according to patient's body weight. Unfortunately, this is usually not done in most developing/ developed countries, during adult administration of artemisinin derivatives (orally), which might most likely lead to under dosage of most adult patients predisposing them to possible drug resistance development.

Key words: Antimalarial, administration, age-to-weight, body mass index, drug dosing, paediatric

INTRODUCTION

Although less than a quarter (25%) of currently available drugs carry an approved Food and Drug Administration (FDA) indication for use in Paediatric populations, more than three quarter of them have been used for patients younger than 18 years of age (Barradell and Fitton, 1995). The Paediatric clinician encounters several limitations of information in paediatric pharmacotherapy which includes small numbers on patients with rare disease, small size studies and huge inter-patient variability among this population (Bethell *et al*., 1997). Body size, proportion, organ development and function affect the pharmacokinetic behaviour of many drugs.

The physiology, pharmacokinetics and pharmacodynamics of medications are highly variable and to simplify this variation as much as possible, the age of the paediatric patient has been described by placing them into groups that describe trends in development and maturity. Age and weight are the two maturation end points used in clinical decisions for dosage calculation. With ages of paediatric patient ranging from 23-24 weeks gestation up to young adolescents, the diversity of the paediatric population presents a huge challenge to the neonatal clinician (Barradell and Fitton, 1995).

Pharmacokinetics (PK) studies of antiretroviral in children usually lag behind adult studies and usually licensed based on adult data. As a consequence, paediatricians are faced with a problem, given the unavailability of adequate dosing information and very little toxicity data (Bethell *et al*., 1997). Younger children especially were noted to have lower clearances, especially if Body Surface Area (BSA) was less than 1.2 m^2 (Barradell and Fitton, 1995). Underdosing a patient with antiretrovirals may foster development of genotypic

Corresponding Author: I.C. Maduka, Department of Chemical Pathology, University of Nigeria Teaching Hospital (UNTH), PMB 01129, Ituku-Ozalla, Enugu, Enugu State, Nigeria

resistance mutations, while overdosing could potentiate serious adverse effects.

Hence the general objective of this review is to throw more light on the pharmaceutical misadventure which most developing countries practice via dosing by the term "adult" and not by the actual weight, as should be.

Ideal body weight for an adult: An adult is an individual who is above 21 years of age and has an average weight of 50-60 kg. In a study on body weight and disability among adults 45 years and older, self-reported Body Mass Index (BMI) (kilograms per meter square) was used to categorized participants into six BMI-defined groups (Okoro *et al*., 2004.) under weight (<18.5), normal weight (18.5 to <25), over weight (25 to <30), obese, class 1 (30 to <35); obese class 2 (35 to <40), and obese, class 3 (≥40) (Okoro *et al*., 2004), indicating the possibility of greater number of patients deviating from the normal weight group and also possible resistance arising as a result of underdose of such individuals.

Calculation of the male ideal weight (kg) is given by 50+2.3 x (height in inches - 60), while the female ideal weight is given by 45+2.3 x (height in inches - 60).

Artemisinin and derivatives: Artemisinin and its semi synthetic derivatives are potent, well-tolerated compounds that are used as first-line antimalarial therapy in many tropical countries (Barradell and Fitton, 1995; deVries and Dien, 1996). A number of studies have demonstrated the efficacy of artesunate in uncomplicated, severe (Hien *et al*., 1992a) and multi-drug resistant (Bunnag *et al*., 1996; Hien *et al*., 1992b) falciparum malaria, but no similar study has shown the possibility or error resulting from differences in weight of adult patients.

Since artesunate clears parasite more rapidly than quinine and may improve survival (Barradell and Fitton, 1995), intravenous (iv) artesunate has become an alternative to i.v quinine for the treatment of severe malaria in many countries (Looareesuwan *et al*., 1992). The pharmacokinetics and pharmacodynamics of artesunate and artemisinin derivatives have been assessed in patients with uncomplicated malaria (Bethell *et al*., 1997) and severe falciparum malaria (Looareesuwan *et al*., 1992) but yet no equivalent studies on the possibility of weight related error in adult dosage regimen of artesunate.

The drug regimen used for patients with complications remain empirical and do not differ significantly from those used for patients with milder malaria (deVries and Dien, 1996). Although neurotoxicity has yet to be demonstrated objectively in human receiving conventional doses of artemisinin drugs, residual concerns remain (Elias *et al*., 1999) which is one of the primary reasons for this review, also aimed at avoiding over dosage which might result from weight variation in adults and children.

ARTESUNATE AND AMODIAQUINE DOSAGE REGIMEN:(WEIGHT-FOR-AGE)

The world health organization /National centre for health statistics (WHO/NCHS) weight-for-age reference data are based on well nourished populations from developed countries and is suitable for comparing the nutritional status of different population (WHO,2006). This data set was standardized by age and sex, so that there was equal sex distribution in each 1 year age category, with the age distribution typical of a sub-saharan African population, and the convention of doubling the drug dose per age category was followed leading to the selection of first age groups.

These groups had an approximate doubling in median body weight : 0-1months (4.2 kg), 2-11 months (6.9 kg), 1-6 years (13.3 kg), 7-13 years (25.6 kg), and >14 years (58.0 kg) (WHO, 2006). Control programmes need simple dosing regimens, as complicated regimens carry the risk of dosing errors, the effects of which may out-weigh the intended advantages of greater accuracy (WHO, 2006).

Tablet containing 25 and 100 mg artesunate were chosen because these carried the lowest risk of overdosing; only 1 in 10,000 recipient would receive >10 mg/kg/day; 1 in 250 would receive >8 mg/kg/day and 1 in 1000 patient <2 mg/kg/day. The same reason applied to final choice of strength of the amodiaquine tablets, (WHO, 2006) (67.5 and 270 mg) resulting in only 83.4% of patients predicted to receive therapeutic dose of amodiaquine. The patients that received (<2 mg/kg) Artesunate also run the risk of developing resistant strains of plasmodium.

The proportion of patients predicted to receive therapeutic doses for various tablet strengths of amodiaquine and artesunate using the five default age categories are shown in Table 1. Artesunate tablets containing between 25 and 30 mg (paediatric strength) and between 100 and 120 mg (adult strength) would each result in 99.9% of patients receiving doses within the range 2-10 mg/kg/day. Thus these were associated with the lowest risk of overdosing and were chosen as therapeutic dose (deVries and Dien, 1996)

Multiplying the median weight for each category by the currently recommended doses of 10 mg/kg/day for amodiaquine and 4 mg/kg/day for artesunate, gives the optimal tablet strength. Dosing accuracy was defined as the proportion of individuals [using Malaria-Weighted Anthropometric Reference (MWAR) data set] who were predicted to receive a dose within the therapeutic ranges when dose was based on age using the default age categories described (WHO, 2006).

Table 1: The overall proportion of patients predicted to receive dosage within and outside the defined therapeutic doses of amodiaquine and artesunate using different tablet strengths for both drugs and anthropometric data from sub-saharan Africa

Amodiaquine tablets strength (mg)		Therapeutic dose 7.5-15 mg/kg/day		
Paediatric tablets	Adult tablets	Below (%)	Within (%)	Above (%)
62.5	250	17.6	77.4	5.1
65	260	13.5	79.9	6.6
67.5	270	10.0	81.9	8.2
70	280	8.4	81.1	10.5
72.5	290	5.5	81.8	12.7
75	300	4.1	81.3	14.6
77.5	310	3.4	78.8	17.9
Artesunate tablets strength (mg)		Therapeutic dose 2-10 mg/kg/day		
Paediatric tablets	Adult tablets	Below (%)	Within (%)	Above (%)
20	80	4.1	95.9	0
22.5	90	1.7	98.3	0
25	100	0.1	99.9	0.01
27.5	110	0.06	99.9	0.03
30	120	<0.01	99.9	0.1
32.5	130	<0.01	99.5	0.5
35	140	0	99.0	1.0

For artesunate, dosing accuracy was very insensitive to changes in age cut-off points, in contrast to that of amodiaquine. Models run with 8 mg/kg as the upper cut-off points for artesunate provided the same age cut-off points as the models that used 10 mg/kg/day as the upper threshold (data not shown) (WHO, 2006).

Nevertheless, an evaluation of the tolerability of this fixed artesunate and amodiaquine combination will be necessary in further clinical trials and when deployed widely, by pharmacovigilance (WHO, 2006).

CONCLUSION

The pharmacokinetics of artesunate and dihydroartemisinin are not influence by the severity of the malaria infection (Hien *et al*., 1992b).

Tailoring the therapy for children according to their developmental stage as well as chronological age, which include selecting the appropriate dosage regimen and age-specific ways to prevent medication errors and enhanced compliance of paediatric patients are both significant problems to be further addressed in paediatric therapy (Angus *et al*., 2002). This is usually taken care of by high specificity of age and weight consideration in paediatric dosage regimen, unlike that of adults. The great need to prevent pharmaceutical misadventures in paediatric patients presents opportunities for scientists to participate in the provision of pharmaceutical care for paediatrics (Bunnag *et al*., 1996). Thus paediatric clinicians must always adhere.

The basic principles of management of severe falciparum malaria include, initiating treatment immediately; checking of the weight and blood sugar level of patient; choosing drug regimen and calculation of the drug dosage according to patient's body weight (Anonymous, 2002). This unfortunately is usually not done in most developing countries, during adult administration of artemisinin derivatives (orally), which might most likely lead to under dosage of most adult patients predisposing them to possible drug resistance development.

RECOMMENDATION

Drug dosage should be based on weight rather than age as is being practice in most developed and developing countries. Also clinicians and drug companies should desist from using the term "adult" in dosing procedures to avoid the problems of possible over dosage or under dosage where the weight of the patient is not considered before prescription is given.

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