REVIEW

Review of commonly used age-based weight estimates for paediatric drug dosing in relation to the pharmacokinetic properties of resuscitation drugs

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AIM:
To study which weight estimate calculation used in paediatric resuscitation results in optimal drug dosing; Advanced Paediatric and Life Support (APLS) or the UK Resuscitation Council age-based formula.

METHOD
Commonly used drugs used in paediatric resuscitation were selected and a literature search conducted for each drug's pharmacokinetic properties, concentrating on the volume of distribution (Vd).
Hydrophobic drugs have a higher Vd than hydrophilic drugs as they distribute preferentially to fat mass (FM). The larger the Vd, the higher the initial dose required to achieve therapeutic plasma concentrations.
Actual body weight (ABW) estimates are a good indicator of Vd for hydrophobic drugs as they correlate well with FM. Ideal body weight (IBW) estimates may be a better indicator of Vd for hydrophilic drugs, as they correlate better with lean body mass. This highlights potential variation between ABW and IBW, which may result in toxic or sub-therapeutic dosing.

RESULTS
The new APLS formulae give higher estimates of expected weight for a wider age range. This may be a more accurate reflection of ABW due to increasing prevalence of obesity in children. The UK Resuscitation Council's formula appears to result in a lower estimate of weight, which may relate more closely to IBW.

CONCLUSION
The main drugs used in paediatric resuscitation are hydrophilic, thus the APLS formulae may result in too much being given. Therefore the UK Resuscitation Council's single formula may be preferred. In addition, a single formula may minimize error in the context of a child of unknown weight requiring administration of emergency resuscitation drugs.

Introduction

Optimal therapeutic drug dosing is based on both the pharmacokinetic and pharmacodynamic properties of a drug and minimizes toxicity and avoids sub-therapeutic levels [1]. Optimal therapeutic drug dosing in children in a resuscitation setting is difficult for a number of reasons, one of the most significant being the ability to estimate the child's weight. An

estimation of weight is essential as currently, a vast majority of the dosing guidelines in the *BNF for Children* (BNFC) are standardized by weight [2].

Both age and length have been used to estimate weight to calculate the most appropriate dosages of drugs required in an emergency setting. The exact methods of estimation have evolved over the years but at present there are three well-recognized methods [3].

Estimation of actual body weight (ABW)

(a) Age-based formulae

The formulae commonly used are in accordance with the Advanced Paediatric Life Support (APLS) manual [4], where substituting the age of the child into a mathematical formula aids generation of an approximate weight for children aged 1–10 years. The formula below is still taught on the UK Resuscitation Council and European Resuscitation Council courses.

$$\text{Weight (kg)} = 2 \times (\text{age in years} + 4)$$

As of July 2011, the APLS guideline for weight estimation based on age has been altered to the following:

1–12 months	$(0.5 \times \text{age in months}) + 4$
1–5 years	$(2 \times \text{age in years}) + 8$
6–12 years	$(3 \times \text{age in years}) + 7$

(b) Measured 50th centile weight

Weight is referenced from growth chart data. It uses a table constructed using Child Growth Foundation data (their 'Girls and Boys Four-in-One Growth Charts'). The BNFC contains an adapted version of this table [2] and the UK World Health Organisation (WHO) growth charts 2009 contain data for the 50th centile of weight split by gender [5] (see Table 1). An obvious difference is observed between the three sets of data, which can be attributed to how the data was collected and the ages of the subjects. Regarding the Child Growth Foundation data, for each age from 'newborn' to 11 years a weight is given. The girl-boy weights in the table were calculated as an average of the 50th centile for a girl and the 50th centile for a boy. In contrast, the UK-WHO growth charts combine data from UK-90 [6] based upon serial measurements of height and weight from 0 to 23 years and WHO data based upon breastfed infants from 0 to 4 years. It is unclear

Table 1

Comparison of weight estimates using Child Growth Foundation Data, BNFC and UK WHO Growth Chart Data

Age	Average UK weight (kg)		UK WHO growth chart 0–4 years	
	Child Growth Foundation data	BNFC	Girls	Boys
Newborn	3.5	3.5	3.5	3.75
3 months	6	6.1	5.75	6.4
6 months	7.8	7.6	7.25	7.9
9 months	8.9	—	8.25	8.9
12 months	9.8	9	9	9.7
18 months	11.1	—	10.2	10.9
2 years	12.2	—	11.5	12.1
3 years	14.4	14	13.9	14.2
4 years	16.4	—	16	16.2
5 years	18.5	18.0	—	—
6 years	20.6	—	—	—
7 years	23.0	23.0	—	—
8 years	25.8	—	—	—
9 years	28.6	—	—	—
10 years	31.8	32.0	—	—
11 years	35.3	—	—	—

which set of weights is the most accurate, hence reducing the safety of its use in clinical practice.

(c) Tape-based measurements for weight

A Broselow tape is a colour-coded system that helps clinicians decide the dose of medication to administer; for each height an estimate of weight is given. The data is referenced from the National Health and Nutrition Examination Survey (NHANES) carried out by the Centers for Disease Control and Prevention in the United States. It includes height and weight measurements for children 0–18 years old [7]. According to a recent prospective study, by Sandell and Charman, looking at the safety of using age-based estimates when resuscitating children, they report that both Broselow tape length-based and measured 50th centile age-based weights outperformed the Resuscitation Council's mathematical formulae [3].

Due to issues of impracticality, such as trapped limbs, immobility and agitated patients [3], and 'discontinuous pattern of change seen throughout infancy and early childhood' [8], this method is not recommended for use in clinical practice.

Body composition

However, whichever method of weight estimation is used, and irrespective of the fact that correct weights may be ascertained, no indication is given of body composition. The body is composed of four compartments; fat, water, protein and mineral. Fat is often referred to as the fat mass (FM); and water, protein and mineral is often referred to as the fat free mass (FFM), which together form the two compartment model [9]. FFM is sometimes referred to as lean body mass (LBM). It should be noted that LBM and FFM are not directly equivalent, but the difference as a percentage of ABW is usually less than 3–5% [10]. Hence, for the purpose of this review, it will be assumed they are equal.

Body composition alters with age, and also within age groups. This is important because although two children may have the same weight estimation, they may have substantially different proportions of fat mass and lean body mass [11]. A number of pharmacokinetic variables, based on body composition, can affect drug efficacy. These include the method of administration, rate of absorption, volume of distribution, metabolism and excretion [12].

Pharmacokinetic properties of the drugs used in paediatric resuscitation

Volume of distribution is deemed the most important pharmacokinetic factor affecting the ability to give a dose of drug within the correct therapeutic range. The other pharmacokinetic factors, including absorption, metabolism and excretion, do not alter the plasma levels to as great an extent, as discussed below.

In terms of absorption, the problems of varying gastric emptying rates, gastric pH and GI bacterial flora [13] are mainly overcome in resuscitation circumstances as the majority of drugs are given intravenously, thus bypassing these mechanisms. Hence the 'bioavailability of parenterally administered drugs usually is considered to be 1' [14]. Other drug delivery methods include via the intramuscular (IM) or preterm neonates (PR) route. The IM route is not usually a problem, assuming it is given in the same location, and only in preterm neonates is it problematic

as absorption is variable because they have a small percentage of body weight that is skeletal muscle or fat in comparison to older infants, children and adults. (Preterm neonates have been excluded from this discussion as neither of the age-based estimations of weight account for babies born preterm.) Further, in neonates, blood flow in muscles varies in the first 2–3 weeks of life [15]. This can either increase or decrease the absorption of the drug, but is not dependent on body composition. PR absorption in terms of rate and extent is dependent upon retention and rectal venous drainage. This has considerable inter-individual variation, which is not dependent on age or weight [15].

The plasma protein binding of various drugs is less in the neonate compared to infants and children because of lower total plasma protein concentration and lower drug–protein binding capacities [16]. As the pharmacological action of a drug is attributed to its unbound form of the drug, increased free concentrations can lead to toxicity [13]. There is no definitive evidence to suggest that this is a factor relating to body composition or weight.

Drug metabolism occurs predominantly in the liver, although the kidneys, intestines, lungs and skin may be involved [17]. Of the factors affecting hepatic metabolism, it is enzyme activity and blood flow that are relatively lower in children compared to adults. Elimination of drugs by the kidneys is dependent on glomerular filtration rate (GFR), tubular secretion and reabsorption. Both the hepatic and renal factors affecting metabolism and elimination depend on age rather than weight.

All the drugs selected for this study are used in paediatric resuscitation including CPR, hypertensive emergencies, anaphylaxis, seizures, infection, acute asthma and cerebral oedema.

Aim

The aim of this study is to determine which weight estimate calculation used in paediatric resuscitation results in optimal drug dosing: the calculations comprising the three new Advanced Paediatric and Life Support (APLS) age-based formulae or the UK Resuscitation Council age-based formula. Further, the study compares estimates of actual body weight and ideal body weight and their use in accurate drug dosing in children in a paediatric resuscitation setting.

Method

Drugs commonly used in paediatric resuscitation were selected and a literature search conducted for each drug's pharmacokinetic properties, concentrating on the volume of distribution derived from its hydrophilic and hydrophobic properties and their relationship to body composition (see Table 2). The primary medical search engines used were the Ovid MEDLINE (1948–December 2012) and EMBASE (1974–December 2012) databases. Phrases including 'volume of distribution', 'pharmacokinetic', 'pharmacodynamics', 'hydrophilic', 'hydrophobic', 'paediatric', 'APLS', 'resuscitation', 'age' and 'weight' were used in combination to achieve variation in search results. Estimates of actual

Table 2

Comparison of the pharmacokinetic properties of drugs used in paediatric resuscitation [13–15, 19, 21]

Hydrophilic	Ampiphilic	Hydrophobic
Adrenaline	Amiodarone	Atropine
Sodium Bicarbonate		Verapamil
Calcium Gluconate		Lidocaine
Isoprenaline		Diazepam
Flecanide		Midazolam
Adenosine		Lorazepam
Salbutamol		Phenytoin
Magnesium Sulphate		Thiopentone
Aminophylline		Benzyl Penicillin
Ceftriaxone		Paracetamol
Sodium Nitroprusside		Prednisolone
Morphine		Hydrocortisone
Suxamethonium		Dexamethasone
Chlorpheniramine		Ketamine
Mannitol		Furosemide
Labetalol		Epoprostenol
Digoxin		

body weight (ABW) and ideal body weight (IBW) were compared, and ABW estimates were calculated using both UK Resuscitation Council and APLS formulae.

Results

The new APLS formulae give higher estimates of expected weight for a wider age range. This may be a more accurate reflection of ABW than the UK Resuscitation Council estimate, owing to an increasing prevalence of obesity in children. The UK Resuscitation Council's formula appears to result in a lower estimate of weight, which may relate more closely to IBW than ABW (see Table 3).

The APLS formulae therefore would be most appropriate for use with hydrophobic drugs whilst the UK Resuscitation Council formula would be most appropriate for use with hydrophilic drugs.

Discussion

Volume of distribution of drugs, a major factor in drug efficacy, is dependent on the pharmacokinetic relationship of the proportion of body water and proportion of body fat [13]. The body, as described in the two compartment model is comprised of fat mass and lean body mass [9] as described previously. An age-based estimate of weight does not give any indication of either of these.

Hydrophilic drugs preferentially distribute to body water; the extracellular fluid which consists of plasma and the interstitial fluid. Hydrophilic drugs, therefore, have a smaller volume of distribution than hydrophobic drugs, which distribute preferentially to fat tissue or freely between lean and fat tissue [18]. The smaller the volume of distribution, the lower the dose of drug required to achieve adequate plasma concentrations.

Hydrophilic

The actual volume of distribution is dependent upon the amount of body water. Total body water in a term neonate is approximately 75%, decreasing to 60% (25% extracellular and 35% intracellular) by one year of age and only by 12–13 years of age does it reach adult values of around 60% (20% extracellular, 40% intracellular) [12]. Thus neonates will have a larger volume of distribution in comparison to older infants and children and will require higher doses of hydrophilic drugs.

Take two children aged 6 years old: their ABW may be different, but the proportion of body water is likely to be similar (Figure 1). Hence the volume of distribution should be the same for both children, indicating that they require the same loading dose of hydrophilic drug. Using the UK Resuscitation Council formula the age-based weight estimate would be 20 kg, whereas using the APLS formulae it would be 25 kg. This would mean the child given the hydrophilic drug dosed according to the APLS formulae would receive a higher dose, which may result in potential toxicity.

For drugs with a narrow therapeutic range (e.g. Digoxin, Aminophylline and Flecanide), there is only a small difference in dosage between sub-therapeutic levels and toxicity [15].

Hydrophobic

Hydrophobic (lipophilic) drugs have a larger volume of distribution than hydrophilic drugs and thus require higher dosage levels to achieve therapeutic plasma concentrations [12]. The volume of distribution is dependent on the amount of body fat. On average, a full-term neonate has 12–16% body fat which increases to 20–25% by one year of age. This age range, however, is not accounted for in the age-based estimates of weight. In adults, body fat accounts for approximately 18% of body weight [19, 20]. Thus, due to higher proportion of fat, the volume of distribution for hydrophobic drugs will be higher in children than neonates.

Take two children aged 6 years old: their age-based weight estimate according to the UK Resuscitation Council formula would be 20 kg and according to the APLS formulae would be 25 kg. Fat mass in children may vary significantly. If one child had a higher proportion of fat, the drug given would have a higher volume of distribution. The higher the volume of distribution, the higher the loading dose required to achieve therapeutic plasma concentrations. Thus the child given a dose of hydrophobic drug based on the UK Resuscitation Council formula may potentially receive a sub-therapeutic dose.

For example, Phenytoin, used in status epilepticus, has a loading dose of 18 mg/kg for all ages. A child with a higher than average proportion of body fat and hence a high volume of distribution could receive a sub-therapeutic dose, whilst a child with much lower than average proportion of body fat could potentially receive a toxic dose despite their age-based weight estimate being the same, calculated by either formula. The possibility of

Table 3

Comparison of weight estimates using the UK Resuscitation Council formula and the APLS formulae

Age	UK Resuscitation Council Weight (kg) = 2 × (age in years + 4) (For ages 1–10 years)	APLS formulae 1–12 months weight (kg) = (0.5 × age in months) + 4 1–5 years weight (kg) = (2 × age in years) + 8 6–12 years weight (kg) = (3 × age in years) + 7 (For ages 1 month–12 year)
1 months	—	4.5
6 months	—	7
11 months	—	9.5
1 years	10	10
2 years	12	12
3 years	14	14
4 years	16	16
5 years	18	18
6 years	20	25
7 years	22	28
8 years	24	31
9 years	26	34
10 years	28	37
11 years	—	40
12 years	—	43

toxicity is further exacerbated by the fact that Phenytoin displays zero-order kinetics within the therapeutic range of plasma concentrations [21]. Zero-order kinetics is a 'state at which the rate of an enzyme reaction is independent of the concentration of the substrate' [22]. Hence a small increase in the dose may lead to a large change in plasma concentrations if the metabolism is saturated. Knowledge of the volume of distribution can aid dosing to achieve appropriate plasma concentrations and minimize toxicity. Further difficulty is encountered as the time taken for hydrophobic drugs to distribute from water to fat compartments differs between drugs depending on the degree of lipophilicity [23]. Hence it is not always possible to increase the dose without causing toxicity, and titration in small increments may be required.

For many drugs differences in the volume of distribution will affect the plasma concentration. However, as the therapeutic range is large, this will not lead to toxic or sub-therapeutic doses. Similar to hydrophilic drugs, those with a narrow therapeutic range are more likely to be affected by differences in fat mass and lean body mass.

Actual body weight vs ideal body weight

All age-based estimates of weight used currently estimate actual body weight. Actual body weight represents fat mass plus lean body mass. An alternative is to estimate ideal body weight which represents lean body mass (Figure 1).

The attention paid to body composition is of increasing importance, as, in accordance with the Health Survey for England in 2006, the proportion of obese boys and girls aged 2–15 years

was 17% and 15%, respectively [24]. It has been found that obese children have excesses in whole body fat mass, lean body mass and bone mineral content. The excess in fat mass is the greatest and tends to account for 30–50% of weight [9].

Hence obesity in any age group will increase the volume of distribution of hydrophobic drugs, owing to increases in fat mass [13]. It has been suggested that, for hydrophobic drugs, there is a good correlation between volume of distribution and total body weight (TBW). Hence ABW can be used as it reflects this [25, 26].

The volume of distribution of hydrophilic drugs is dependent on lean body mass as it is a close reflection of body water. Estimation of lean body mass in an emergency setting is near impossible owing to the complexity of the formula and variables involved.

Cheymol suggests that for use of relatively hydrophilic drugs, doses should be calculated based on IBW as it reflects lean body mass [25]. In a paediatric population, the most common method of calculating IBW is to use body mass index (BMI) [27], the formula for which is:

$$BMI = weight/height^2$$

Hence, by knowing the average BMI associated with a given age and sex, IBW could be calculated by measuring height. However, this has its own pitfalls as mentioned previously, such as immobility and agitated patients, as well as variation in respect to age and sex [28, 29]. Despite impracticality, IBW would be useful if a simple method of estimation could be developed, as
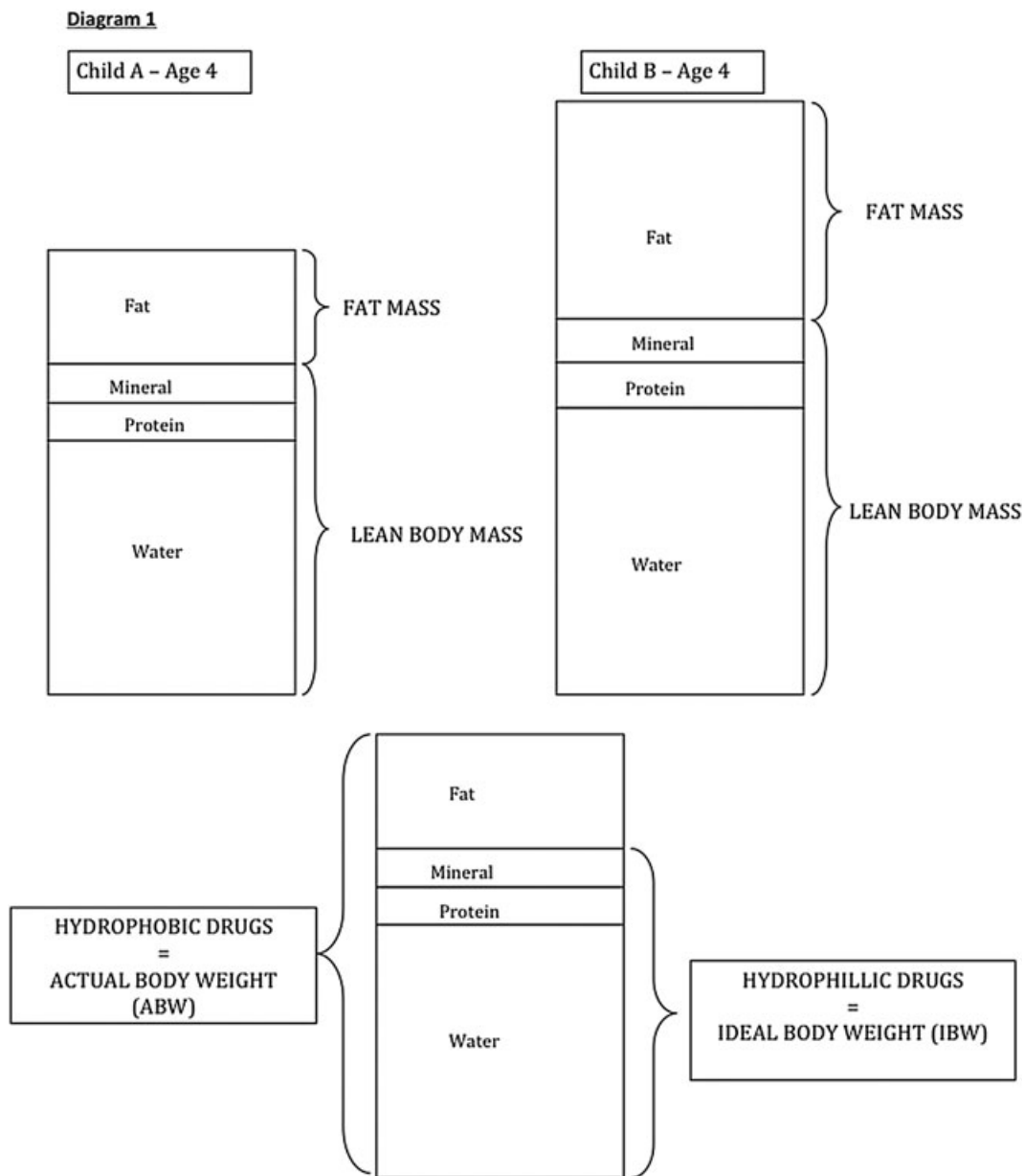
Diagram 1

Child A – Age 4

Child B – Age 4

Diagram 1. Diagram to illustrate the differences between Fat Mass and Fat Free Mass.

Figure 1

Differences between fat mass and fat free mass.

it more accurately represents body composition and therefore volume of distribution for hydrophilic drugs. Hence a more accurate drug dose could be given to minimize the likelihood of toxicity or sub-therapeutic doses.

Overall, ABW estimates are a good indicator of volume of distribution for hydrophobic drugs, as they correlate well with FM. IBW estimates may be a better indicator of volume of distribution than ABW for hydrophilic drugs, as they correlate better with lean body mass. According to the European Resuscitation Council, the main drugs used in paediatric CPR are Adrenaline, Amiodarone, Atropine, Magnesium, Calcium and Sodium Bicarbonate [30, 31]. All, with the exception of Atropine, are hydrophilic. However, it is important to note

that all of the above formulae are estimates, hence it is vital that one looks at the child to ensure the estimated weight from the calculation is a rough match prior to drug dosage calculations. This practical point will help avoid mistakes when using the formula for children who are very over- or underweight for their age.

Limitations

Although the effect of body composition on volume of distribution was explored, we recognize that other pharmacokinetic properties must also be addressed. Some evidence shows an

allometric correlation between weight and metabolism and clearance of drugs. However, other evidence shows this does not take into account changes in enzyme and organ function that occur with age [32, 33]. Thus further work is required to see the effect of these pharmacokinetic factors, whether age or weight has more of an effect, and whether as a result the formulae need to be adjusted accordingly.

It must also be noted that pharmacodynamics properties can also affect drug concentration and effect. This was identified as an area of limited evidence and hence a potential source for further research.

Lastly, neither the APLS nor the UK Resuscitation Council formulae take into account variation in weight according to sex. This is likely because there is limited data looking at whether there is a significant weight difference according to sex and whether this weight difference is a result of differences in fat mass. This is a further area that could be explored in the future.

Conclusion

The gold standard in current practice, if time and circumstance permits, is to weigh the child in order to calculate the doses of resuscitation drugs. Often this is not the case and age-based formulae are used to calculate actual body weight, despite the fact that simple and practical difficulty arises as a result of varying pharmacokinetic properties of drugs and varying body compositions of patients for a given weight. The two factors lead to difficulty in ensuring that the therapeutic dose of the drug is achieved.

The main drugs used in paediatric resuscitation are hydrophilic, thus the APLS formulae may result in too high a dose being given. Therefore the UK Resuscitation Council's single formula may be preferred. In addition, the single formula is simple and easy to remember so may minimize error in the context of a child of unknown weight that requires administration of emergency resuscitation drugs.

Suggestions for improvement include hydrophobic drugs dosed dependent on actual body weight, and hydrophilic drugs dosed according to ideal body weight. This indicates that in the resuscitation setting, the drug dose should be found using the most accurate method of calculation given the pharmacokinetic properties of the drug. Hence, the method of calculation should be drug-dependent rather than a 'one fits all' approach, although it is recognized that this can be difficult in practice. More detailed research is required into methods and accuracy of IBW calculation in children.

Although the effect of body composition on volume of distribution was explored, more work is required into the effect on other pharmacokinetic properties. Furthermore, there is no substantial evidence yet as to the effects of pharmacodynamics parameters. These are possible areas for further research.

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