Anaesthetists who deal with children have to scale their doses according to the patient’s size [1]. However, such scaling does not take account of age-related drug sensitivities, drug handling and drug toxicity. This presentation describes three methods of scaling for size and demonstrates their limitations as predictors of drug dosage in children.

SCALING FOR SIZE

This is sometimes called allometrics or allometric scaling (Gk. Alo- other, metron – measure). One of the first attempts at allometric scaling (with anything other than body weight) was the Surface Area Law, which asserts that physiological functions are comparable whatever the size of the organism when related to body surface area. The reasoning is that since most heat loss occurs through the skin, so metabolic rate and many physiological functions that depend on it will change in proportion to body surface area. In the surface area model metabolic rate varies with the weight to the power of 2/3, but we now know that a better approximation for metabolic processes is obtained by using an exponent of 3/4 as shown in figure 1 [2].

**Figure 1. Scaling: Why is animal size so important?**

Figure 1. Shows a log-log plot of metabolic rate against body weight in a variety of animals ranging from the mouse with a weight of a few grams to the elephant at over 5000 kg. The empirically derived line with a slope of 3/4 gives an excellent fit to the data.

In practice, three allometric models are used to predict paediatric doses from adult ones. The simplest (and least accurate) is the weight model, in which the dose for a paediatric patient is obtained by multiplying the adult dose by the weight of the patient divided by the adult weight. For example, using the weight model, the predicted dose of any drug in a 3 kg neonate would be equal to 3/70 x the adult dose. For the 3/4 power model, the calculation is similar except that we raise the fraction 3/70 to the power of 3/4; similarly for the 2/3 power model we raise this fraction to the power of 2/3. It will be demonstrated that when used to calculate paediatric doses, the weight model produces the smallest values, the 2/3 model produces the highest values and the 3/4 power model produces values intermediate between the other two.
SIZE AND DEVELOPMENTAL FACTORS AFFECTING PAEDIATRIC DOSES OF DRUGS

A major problem with using allometric models to predict paediatric doses from adult ones is that paediatric dosing not just a question of size, there are also a number of developmental factors which we must take into account. The latter are mainly concerned with immaturity of organ or enzyme systems, they affect the youngest patients, are drug specific and are not predictable by size models.

Size-related factors include cardiac output, fluid volumes, and tissue volumes. Developmental factors include protein binding of drugs, membrane permeability, hepatic and renal function, developmental changes in the number of receptors, the receptor type, the affinity of the receptor for drugs and the availability of natural legends. In general, the effects of size-related factors on drug dosage can be predicted by scaling methods while developmental factors cannot.

USE OF SIZE MODELS TO PREDICT PAEDIATRIC DOSES OF ANAESTHETIC DRUGS

This will be explored initially with reference to the variation in the ED50 dose of thiopental with age using the data of Westrin et al [3, 4]. In neonates the ED50 was found to be 3.5 mg/kg, but it increased rapidly after birth to peak at around 7 mg/kg in infants aged 1-6 months, and thereafter it declined throughout infancy and childhood (Figure 2). The decreased requirement in neonates compared with infants and children is thought to be due to reduced protein binding of thiopental while the increased requirements in infants and children compared with adults are thought to be due to their increased cardiac output, since this reduces the initial concentration of thiopental arriving at the brain.

FIGURE 2 VARIATION IN THE ED50 OF THIOPENTAL WITH AGE

Figure 2 shows that the variation in dose of thiopental with age follows a biphasic distribution indicating that at least two different processes are involved. Such curves cannot be modelled by a single mathematical function; hence it is impossible to predict the full range of paediatric doses from the adult value. It will be demonstrated that the dose requirements of thiopental in infants and children aged over 1 month can be predicted reasonably accurately from the adult value using a 3/4 power model. However, the same model massively overdoses neonates, who are sensitive to the effects of thiopental due to immature plasma protein binding, which cannot be predicted by size models. Similar overdosing of infants occurs when the 3/4 power model is used to predict the requirements of volatile anaesthetic agents and non-depolarising muscle relaxants [5-7]. However, succinylcholine is an exception to this rule, as dose requirements decline exponentially from birth to adulthood [8].

CONCLUSIONS

Doses of anaesthetic drugs in children aged over 1 year can be estimated reasonably accurately from the adult dose using a 3/4 power size model, which reflects changes in metabolic rate. Doses are much less predictable in infants aged less than 1 year due to immaturity of organs and enzyme systems. Reduced doses are frequently required in this age group.
REFERENCES