

cannabis smoking when prescribing drugs to such patients.

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SHOULD CLEARANCE BE NORMALISED TO BODY SURFACE OR TO LEAN BODY MASS?

In 1928, McIntosh, Möller & Van Slyke concluded that urea clearance values in children (8 children aged 3 to 12 years), when normalised to 1.73 m² body surface area (BSA), fell within the range of clearances observed in normal adults (60–100 ml min⁻¹ 1.73 m² BSA). Normalisation of renal, hepatic or body clearance values to 1.73 m² BSA have since become a standard method.

As part of a study in which we examined the feasibility of a method for the estimation of serum half-lives of drugs from creatinine clearance, we were unable to confirm these findings. When the means of 11347 creatinine clearances (CCr) of 5146 normal subjects (68 publications, reference list available from the authors on request) were plotted as a function of age (Figure 1), the CCr of children (1 to 30 days, 8 to 18 years) did not fall within the CCr (35–110 ml min⁻¹ 1.73 m² BSA) observed in normal adults. It can also be seen that a unique normal clearance range for all ages, which was the original aim of McIntosh *et al.* (1928) is not realistic. According to the patient's age, 60 ml min⁻¹ 1.73 m² BSA should be regarded one time as a normal renal function, another time as a decreased or sometimes even as an increased renal function.

In our study, we looked for a normalisation of a clearance in order to obtain for a same clearance value, a same drug half-life, independent of the age of the subject. When CCr was expressed in ml/min or in

ml min⁻¹ 1.73 m² BSA, quite different half-lives for gentamicin (Nunnery & Riley, 1969; McCracken & Jones, 1970; McCracken, Chrane & Thomas, 1971; McCracken, 1972; Matzetti, Konca, Panero & Orzalezi, 1973; Paisley, Smith & Smith, 1973; Simon, Schmitt, Malerczyk & Arkenau, 1973; Siber, Echeverria, Smith, Paisley & Smith, 1975) were observed in several age groups compared to half-lives in adults with the same CCr (Table 1). Similar data can be presented for other drugs e.g. amikacin, ampicillin, carbencillin, cefazolin, tobramycin, etc. This is not surprising as CCr in ml min⁻¹ or in ml min⁻¹ 1.73 m² BSA is not related to the distribution volume (V_d) of the drug. However, the package insert of many drugs still recommends CCr in ml min⁻¹ as a guide for drug dosage adjustments in renal impairment. Sometimes these inserts do not even mention that the guidelines should only be used in adults. In fact, until this paper, no dosage rules were available for neonates and children with renal dysfunction. The more the individual V_d differs from the mean V_d for adults, the more absurd calculated drug half-lives or dosage guidelines will be obtained. Only when clearance is normalised to a standard V_d, will similar drug half-lives in adults and children correspond with identical clearances. For example in the case of CCr, the V_d of creatinine is equal to the total free body water (Dominguez, 1950). Furthermore, the latter is a constant part of 72% (± 1%) of

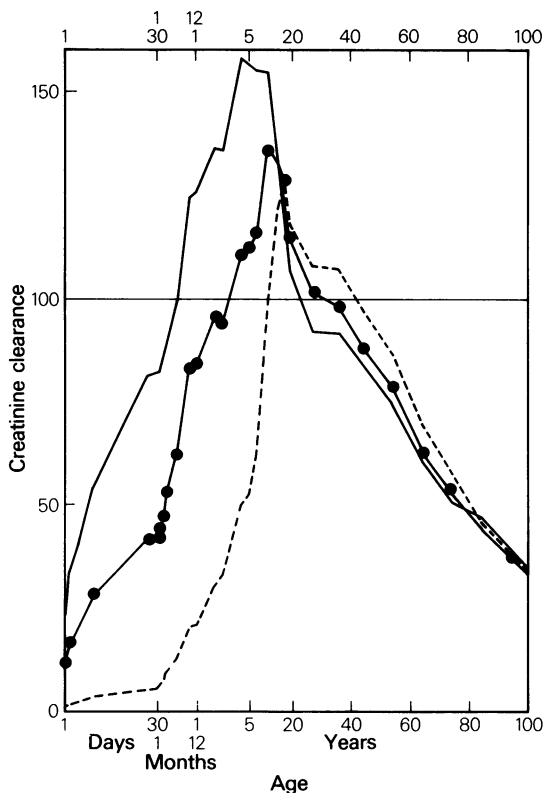


Figure 1 Creatinine clearance and different normalisations in function of age. LBM = lean body mass. BSA = body surface area. — ml min⁻¹ 50 kg⁻¹ LBM. ●—● ml min⁻¹ 1.73 m⁻² BSA. - - - ml min⁻¹.

the lean body mass (LBM = total body weight minus body fat), independent of the extent of obesity and independent of the age of the subject (Behnke, 1963). A normalisation to 50 kg LBM was chosen, because 50 kg LBM is about the mean LBM for a male of 25 years.

The reason for normalisation of LBM is further illustrated in Figure 2. Take a person A and a person B with a V_d of creatinine of 100 and 40 l respectively. The kidney can be represented by a filter retaining all creatinine. The CCr is then equal to the filtration rate. When the two persons have the same CCr (40 ml min⁻¹) and assuming no new creatinine is added to the system, all creatinine will be cleared four times as fast in person A as in person B. Indeed, the half-life of creatinine will be

$$\begin{aligned} (10.000 \text{ ml} \times 0.693)/(40 \text{ ml min}^{-1}) &= 173.25 \text{ min in person A} \\ (40.000 \text{ ml} \times 0.693)/(40 \text{ ml min}^{-1}) &= 693 \text{ min in person B.} \end{aligned}$$

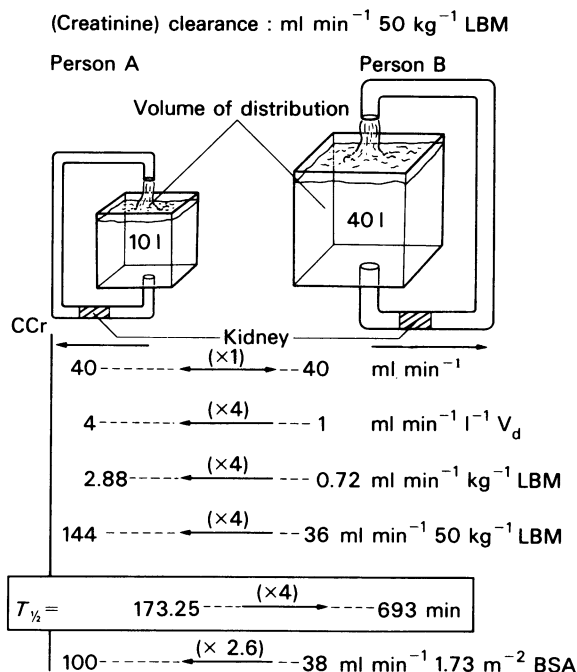


Figure 2 Illustrative example. V_d = volume of distribution, LBM = lean body mass, BSA = body surface area. Figures in brackets refer to multifold differences.

The same is true for drugs mainly distributed in the total free body water or in the extracellular water which is about 45% (\pm 5%) of the total free body water. The V_d of most drugs will be therefore four times as small in person A as in person B. This means that the half-lives of these drugs will be four times smaller in person A than in person B, although the two persons have the same CCr (40 ml min⁻¹). Person A can be a child of 4 years old, with a body weight of 16.5 kg, a height of 103 cm, an LBM of 14 kg, a BSA of 0.69 m² and a normal renal function (CCr = 100 ml min⁻¹ 1.73 m⁻² BSA). Person B can be a man of 25 years with a body weight of 69 kg, a height of 174 cm, an LBM of 56 kg, a BSA of 1.82 m² and an impaired renal function (CCr = 38 ml min⁻¹ 1.73 m⁻² BSA). With the normalisation of CCr to BSA a 2.6 fold difference in CCr between A and B is found when it should be a four fold difference. This can be explained by the fact that V_d and the total free body water do not correlate linearly with the BSA. During a man's life, the total free body water increases by a factor 20 (from 2 to 40 l), while the BSA increases by a factor 8 (from 0.21 to 1.73 m²). Only when CCr is normalised to 50 kg LBM can a same CCr result in a same drug half-life, independent of the age and LBM of the subject.

Table 1 Comparison of gentamicin half-life in children and adults for same creatinine clearances

Age group	Mean creatinine clearance in children ⁽¹⁾	Mean gentamicin half-life in children ⁽²⁾	Corresponding gentamicin half-life in adults for a same creatinine clearance ⁽³⁾
1-7 days	1.5 - 3 ml min ⁻¹	5.2 h	66.6 - 46.7 h
	12 - 24 ml min ⁻¹ 1.73 m ⁻²		16.1 - 9.8 h
	25 - 48 ml min ⁻¹ 50 kg ⁻¹ LBM		8.7 - 4.7 h
3-14 days	2.5 - 4 ml min ⁻¹	4.9 h	58.3 - 39.0 h
	19 - 31 ml min ⁻¹ 1.73 m ⁻²		11.9 - 6.9 h
	38 - 59 ml min ⁻¹ 50 kg ⁻¹ LBM		6.0 - 3.7 h
14-30 days	4 - 5 ml min ⁻¹	3.2 h	39.0 - 31.3 h
	31 - 42 ml min ⁻¹ 1.73 m ⁻²		6.9 - 5.4 h
	59 - 82 ml min ⁻¹ 50 kg ⁻¹ LBM		3.7 - 2.8 h
1-6 months	5 - 13 ml min ⁻¹	3.0 h	31.3 - 14.7 h
	42 - 62 ml min ⁻¹ 1.73 m ⁻²		5.4 - 3.7 h
	82 - 98 ml min ⁻¹ 50 kg ⁻¹ LBM		2.8 - 2.3 h
2 months-2 years	6.5 - 28 ml min ⁻¹	2.5 h	23.5 - 7.8 h
	44 - 92 ml min ⁻¹ 1.73 m ⁻²		4.9 - 2.5 h
	82 - 133 ml min ⁻¹ 50 kg ⁻¹ LBM		2.7 - 1.7 h
1-5 years	21 - 53 ml min ⁻¹	1.8 h	10.2 - 4.3 h
	84 - 112 ml min ⁻¹ 1.73 m ⁻²		2.8 - 2.1 h
	126 - 157 ml min ⁻¹ 50 kg ⁻¹ LBM		1.8 - 1.5 h
5-10 years	53 - 88 ml min ⁻¹	1.3 h	4.3 - 2.6 h
	112 - 130 ml min ⁻¹ 1.73 m ⁻²		2.1 - 1.8 h
	157 - 153 ml min ⁻¹ 50 kg ⁻¹ LBM		1.5 - 1.5 h

(1) obtained from 2057 children with normal renal function (68 publications)

(2) obtained from 120 children with normal renal function (8 publications)

(3) calculated for adults according to Dettli (1977)

Densitometric or even skinfold methods for the determination of the LBM are too complex for routine use in clinical practice. Because of the practicality and the good correlation with the skinfold technique, we suggest that the LBM in neonates, children, and adults should be calculated using the following formula, which is based upon the work of James (1976):

males:

$$\text{LBM} = 1.10 \times \text{weight} - 128 \times (\text{weight}^2/\text{height}^2)$$

females:

$$\text{LBM} = 1.07 \times \text{weight} - 148 \times (\text{weight}^2/\text{height}^2)$$

LBM = lean body mass in kg

Weight in kg

Height in cm

Using CCr in ml min⁻¹ per 50 kg LBM, the existing dosage regimen based upon CCr can not only be extended to children and neonates, but can also be

improved for adults, especially when the LBM of a subject differs greatly from 50 kg.

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A NEUROENDOCRINE APPROACH TO BENZODIAZEPINE TOLERANCE AND DEPENDENCE

Tolerance to the subjective effects of benzodiazepines is well-recognized clinically: most patients reporting initial drowsiness find it wanes over a few days. Normal subjects given a single dose of a long-acting benzodiazepine report progressively fewer subjective effects of drowsiness over the next few hours despite plasma concentrations of the drug hardly diminishing (Greenblatt & Shader, 1979). Tolerance also develops rapidly to the characteristic electroencephalographic effects, such as increase in fastwave activity and decrease in auditory evoked responses (Lader, Baker & Curry, 1980). Animal work shows that the benzodiazepine-induced depression of active social interaction wears off after a few days (Vellucci & File, 1979). Further support for a non-pharmacokinetic tolerance comes from case studies of acute overdosage (Greenblatt, Woo, Allen, Orsulak & Shader, 1978). Finally, there is cross-tolerance between the benzodiazepines and barbiturates and alcohol.

It is well-known that excessive doses of benzodiazepine over prolonged periods of time can lead to physical dependence and a characteristic withdrawal syndrome (Hollister, Motzenbecker & Degan, 1961; Fruensgaard, 1976; Preskorn & Denner, 1977). In such documented cases, the patients have escalated the dose thus giving a clear indication of tolerance and of probable physical dependence. We have withdrawn patients from high- and low-dose, long-term benzodiazepine treatment and all have experienced some form of withdrawal reaction. More importantly, the changes on withdrawal of normal doses were indistinguishable from those on withdrawal of high doses, both in quality and quantity (Hallstrom & Lader, 1981). It would, therefore, seem that physical

dependence on benzodiazepines does not necessarily lead to escalation of dosage and, hence, it would be useful to look for a biological marker of tissue tolerance to these drugs.

We investigated this possibility using a neuroendocrine strategy. The intravenous injection of 10 mg diazepam is a potent stimulus to the secretion of growth hormone (GH) (Syvalahti & Kanto, 1979). These authors found that after an intravenous administration of 10 mg diazepam to ten, drug-free, healthy volunteers, the content of serum GH rose significantly from 7.5 ± 0.9 ng/ml to 17.1 ± 3.8 ng/ml in 15 min ($P < 0.05$) and to 19.6 ± 2.9 ng/ml in 30 min ($P < 0.01$) before returning to pre-test levels at 120 min. The GH response probably involves the stimulation of GABA-ergic mechanisms as a similar GH response follows the administration of other GABA-mimetic drugs such as γ -hydroxybutyric acid (Takahara, Yunoki, Yakushiji, Yamauchi, Yamane & Ofuji, 1977), γ -amino β -hydroxybutyric acid (Fioretti, Melis, Paoletti, Parodo, Caminiti, Corsini & Martini, 1978), muscimol (Tamminga, Neophytides, Chase & Frohman, 1978), and baclofen (Koulu, Lammintausta & Dahlström, 1979).

We measured GH responses to diazepam in patients who had received diazepam in normal therapeutic doses (15-30 mg/day) for at least 1 year (range 4-12 years). All patients were admitted to a metabolic ward for the study. All were male and their age range was 32-38 years. Their psychiatric diagnoses were of anxiety neurosis and/or personality disorder and none were alcoholic or took other drugs. Following an overnight fast and the insertion of an intravenous cannula, patients were infused intravenously with diazepam (10 mg/75 kg body weight) over 3 min.