Urinary creatinine excretion in the newborn

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SUMMARY We measured the excretion rate of endogenous creatinine in 84 24-hour urine collections obtained from 60 term and preterm newborn infants between the 3rd and the 68th postnatal day, at postconceptional ages 28–42 weeks. The rate was positively correlated with weight, height, and postconceptional age but not with postnatal age; the strongest correlation was that with weight. When the rate was factored by weight it was constant across the range of values studied, with a median and logarithmic mean value of 90 $\mu\text{mol/kg/day}$ (10 mg/kg/day) and a range (2 log SD) of 45–180 $\mu\text{mol/kg/day}$ (5–20 mg/kg/day).

In 1913, Myers and Fine showed that the urinary excretion rate of creatinine was directly proportional to total body creatine content.¹ Shortly afterward Bürger reasoned that, as virtually all the creatine in the body is located in muscle, and as the creatine concentration in muscle is constant, the urinary excretion rate of creatinine must be proportional to muscle mass.² Measurement of the urinary excretion rate of creatinine has been used extensively in recent years in the assessment of nutritional state,^{3,4} and it has been used as a yardstick against which to measure the normal excretion rates of other metabolites: the ratio of the urinary concentration of any substance *x* to that of creatinine ($U_x:U_{cr}$) provides a measure of the excretion rate of *x* which avoids the need for a timed urine collection, provided that the excretion rate of creatinine is known. Normal ranges for the urinary excretion rate of creatinine are available for infants and children after the neonatal period, as well as for adults,⁵ but there is only one published study of the rate in premature babies in the first few days of life.⁶ In the present report we present the results of measure-

ments of the urinary excretion rate of creatinine in a large group of well preterm and term infants.

Patients and methods

Altogether 84 24-hour urine collections were obtained from 60 infants, birth weight 800–4200 g, gestational age 27–40 weeks, and postnatal ages ranging from 3–68 days (table 1). Gestational age was estimated by a combination of menstrual history, ultrasound evaluation, and the clinical criteria of Dubowitz *et al.*⁷ All the infants were in good condition at the time of study; none required mechanical ventilation or other major procedures and there was no evidence of any abnormality of renal function. Urine was collected by the method of Tarlow.⁸ Adhesive plastic bags were carefully applied to the skin after painting with compound tincture of benzoin, which both protects the skin and improves adhesion. Care was taken to efface skin creases. A plastic tube was inserted into a hole in a dependent corner of the bag, the joint being sealed with epoxy glue. The other end of the tube was

Table 1 *Characteristics of infants studied*

	No of observations*	Mean (SD)	Range
Postnatal age (days)	84	12.3 (12.0)	2–68
Postconceptional age (days)†	84	238 (23)	198–290
Weight (g)	84	1750 (660)	910–4200
Length (cm)	83	42.4 (4.5)	34–56.5

*A reliable length measurement was not obtained for one study.

†Postconceptional age was calculated as the sum of gestational age and postnatal age on the day of study.

connected to a collecting flask, the interior of which was kept at a slightly negative pressure relative to atmospheric by means of a Roberts pump. This ensured that the bag itself was empty almost all the time. Voiding was observed at the beginning and end of each collection period. The babies were inspected frequently for evidence of leakage, which was easily detected because of the system used; only complete collections were included in the study. Creatinine was estimated in urine by a kinetic (reaction rate) modification of the alkaline picrate

method.⁹ The results were analysed by correlation and linear regression.

The study was approved by the ethical committee of Guy's Hospital and the United Medical and Dental Schools of Guy's and St Thomas's Hospitals.

Results

The pooled, interassay coefficient of variation of the laboratory method for creatinine estimation was 2.6%. Histograms of the distribution of values for

Fig 1 Histograms showing the frequency distribution of urinary creatinine excretion expressed in $\mu\text{mol/day}$ (upper panel, left) and in $\mu\text{mol/kg/day}$ (lower panel, left). The right hand panels show the distribution of the natural logarithm ($\log_e$) of the data shown in the left hand panels.

Table 2 Correlation coefficients and regression statistics for the relation between 24 hour creatinine excretion and weight, length, postconceptional age, and postnatal age based on the linear regression equation $y=a+bx$

Dependant variable y	Independent variable x	Correlation coefficient (r)	p Value	Intercept a	Slope b
Urinary creatinine excretion ($\mu\text{mol/day}$)	Weight (g)	0.72	<0.0001	2.02	0.09595
Urinary creatinine excretion (mg/day)	Weight (g)	0.72	<0.0001	0.23	0.01085
Urinary creatinine excretion ($\mu\text{mol/day}$)	Length (cm)	0.67	<0.0001	-381	12.98
Urinary creatinine excretion (mg/day)	Length (cm)	0.67	<0.0001	-43.1	1.47
Urinary creatinine excretion ($\mu\text{mol/day}$)	Postconceptional age (days)	0.69	<0.0001	-465	2.66
Urinary creatinine excretion (mg/day)	Postconceptional age (days)	0.69	<0.0001	-52.7	0.30
Urinary creatinine excretion ($\mu\text{mol/day}$)	Postnatal age (days)	0.001	>0.99	—	—

the urinary excretion rate of creatinine both uncorrected ($\mu\text{mol}/\text{day}$) and corrected for body weight ($\mu\text{mol}/\text{kg}/\text{day}$) are shown in fig 1 (before and after logarithmic transformation). Frequency distribution analysis showed obvious deviation from normality in the arithmetic plots of both variables, while the logarithmic plot gave a good approximation to normality; the median and logarithmic mean values were identical. The urinary excretion rate of creatinine ($\mu\text{mol}/\text{day}$) was positively and highly significantly correlated with weight ($r=0.72$, $p<0.0001$), length ($r=0.67$, $p<0.0001$), and postconceptional age (the sum of gestational and postnatal age, $r=0.69$, $p<0.0001$) but not with postnatal age ($r=0.001$, $p=\text{NS}$) (table 2, figs 2–5). In contrast, the excretion rate of creatinine factored by body weight ($\mu\text{mol}/\text{kg}/\text{day}$) did not correlate with weight ($r=0.11$, $p=\text{NS}$), height ($r=0.17$, $p=\text{NS}$), postconceptional age ($r=0.19$, $p=\text{NS}$), or postnatal age ($r=-0.07$, $p=\text{NS}$); the plot against postconcep-

Fig 2 The regression of the urinary excretion of creatinine on weight. The regression and correlation statistics are given in table 2.

Fig 3 The regression of the urinary excretion of creatinine on length. The regression and correlation statistics are given in table 2.

tional age is representative (fig 6). Over the range of data studied, the median (and logarithmic mean) value for 24-hour creatinine excretion was $90.4 \mu\text{mol}/\text{kg}/\text{day}$ with a normal range, defined as 2 logarithmic SD, of $45.4\text{--}179.5 \mu\text{mol}/\text{kg}/\text{day}$ ($10.2 \text{ mg}/\text{kg}/\text{day}$, range $5.1\text{--}20.3$).

Fig 4 The regression of the urinary excretion of creatinine on postconceptional age. The regression and correlation statistics are given in table 2.

Fig 5 Urinary excretion of creatinine plotted against postnatal age. There was no significant relation between the two variables (see table 2).

Fig 6 Urinary excretion of creatinine expressed per kg body weight, plotted against postconceptional age. No significant relation was found ($r=0.19$, $p=\text{NS}$).

Discussion

Urinary creatinine is derived from muscle creatine.¹⁰ Virtually all the body creatine is located in skeletal muscle and about 2% of this store is converted to creatinine daily and subsequently excreted in the urine.¹¹ In a steady state the excretion rate of creatinine must equal its production rate; it follows that the urinary excretion rate of creatinine is proportional to muscle mass. The urinary excretion rate of creatinine has been used in anthropometric studies as an indirect index of muscle mass since 1938,¹² and subsequent investigators have confirmed that it declines in malnourished children¹³ and, with some limitations, that the creatinine-height index provides a measure of the degree of protein depletion or repletion in children in hospital.³ The validity of the urinary excretion rate of creatinine in the measurement of muscle mass is the subject of a recent review.⁴ It is therefore useful to know the limits of its normal range, in relation both to the investigation of body composition and in order that the excretion rate of other substances may be standardised to it.

We found that the urinary excretion rate of creatinine was positively correlated with weight, height, and postconceptional age but not to post-natal age. As might be expected, the correlation with weight was the strongest, but the three relations were remarkably similar, reflecting the association of these three developmental parameters with each other. Thus far, our findings are similar to those of Sutphen⁶ but there are two important differences: firstly, the relation between weight and excretion rate was constant in our study at all weights and maturities examined. This is shown by the fact that the intercept (a) of the regression equation relating the urinary excretion rate of creatinine to weight is not significantly different from zero (table 2, fig 2), and (b) by the complete lack of any significant relation between height, weight, or postconceptional age and urinary excretion rate of creatinine factored by body weight (fig 6). In contrast, Sutphen predicted an output of 7.22 mg/kg (64 μ mol/kg) at a birth weight of 700 g and 8.37 mg/kg (74 μ mol/kg) at 1500 g; however, in the same paper he states that the standard error of the estimate of the urinary excretion rate of creatinine from weight was 1.26 mg (11.1 μ mol). Thus these two estimates were separated by less than one standard error, even though lying close to the extreme values for weight examined in that study, and the difference cannot be regarded as even approaching significance. We studied a much larger sample across a considerably wider range of weight and maturity, which would be expected to make any such change with age or size

more, rather than less, apparent and we conclude that infants of weight 900–4200 g and postconceptional age 198–290 days may be regarded as belonging to a single population with respect to excretion rate factored by weight.

The second difference between our results and those of Sutphen lies in the normal range of values found. As with most biologically derived data exhibiting a wide range of dispersion of values about the mean, our results conform more closely to a logarithmic than to an arithmetic distribution, the latter being significantly skewed to the right (fig 1). The urinary excretion rate of creatinine expressed per kg of body weight approximates well to a logarithmic distribution in that (a) the median value and the logarithmic mean coincide, and (b) the SD and 2 SD points cut the distribution curve symmetrically, with three observations falling outside each end of the 2 SD range. The best representation of the 'average' value, therefore, is the logarithmic (geometric) mean and the best representation of the normal range of dispersion of values the 2 (log) SD range, being roughly equivalent to the 3rd and 97th percentiles. Thus our mean value is 90 μ mol/kg/day with a range of 45–180 (10 mg/kg/day, range 5–20). This is considerably different from Sutphen's average value of 71 μ mol/kg/day (8.06 mg/kg/day); indeed, his maximum observed value was 84 μ mol/kg/day (9.5 mg/kg/day), which is below our mean. The difference is not the consequence of the different ways the data were handled, as our arithmetic mean (SD) is even higher at 95.7 (33.3) μ mol/kg/day (10.8 (3.8) mg/kg/day). Nor can it be due to the fact that our infants were, on average, studied at a somewhat greater postnatal age than Sutphen's, as there was no correlation between the urinary excretion rate of creatinine and postnatal age, contrary to the suggestion of Sertel and Scopes.¹⁴ Differences in laboratory methodology are unlikely to be responsible as both studies used minor modifications of the Jaffe reaction, which is reliable at creatinine concentrations found in urine (although not necessarily in plasma at low concentrations). One possible explanation for the discrepancy lies in the fact that Sutphen seems to have factored by birth weight, while we used actual weight on the day of the study. The average age at the time of study in Sutphen's investigation was 7 days, when the babies were probably appreciably below birth weight, which would introduce an error as a consequence of dividing by a weight greater than that which actually obtained at the time. In a recently published study of glomerular filtration rate in newborn infants, Brion *et al* incidentally included some pooled data on the urinary excretion rate of creatinine¹⁵: the overall mean value obtained

from 202 term and premature babies (calculated from data presented in their table 1) was 101 $\mu\text{mol/kg/day}$ (11.4 mg/kg/day), a value almost identical to the arithmetic mean of our own observations. Furthermore, in that study as in ours, there was little change in the excretion rate with age in either term or premature subjects.

We conclude that the urinary excretion rate of creatinine in preterm infants is positively correlated with weight, length, and postconceptional age, but is not influenced by postnatal age within the range of values studied. The normal range is 45–180 $\mu\text{mol/kg/day}$ (5–20 mg/kg/day) with an average (logarithmic mean) value of 90 $\mu\text{mol/kg/day}$ (10 mg/kg/day).

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