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Serum creatinine concentration, urinary creatinine excretion and creatinine clearance during the first 9 weeks in preterm infants with a birth weight below 1500 g

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Abstract Little is known about serum creatinine concentration, urinary creatinine excretion and creatinine clearance in preterm infants. The aim of the present study was to establish age related reference values for the first weeks of life in preterm infants with a birth weight < 1500 g. In addition, the possible influence of therapy with dexamethasone, spironolactone and catecholamines was investigated. In 34 patients, serum creatinine, urinary creatinine excretion and creatinine clearance were measured at weeks 1, 2, 3–4, 5–6 and 7–9 of life. Median birth weight was 1225 g (range 730–1495), mean gestational age 29 (range 26–34) weeks. Concentration of creatinine in serum and urine, urinary creatinine excretion per kilogram body weight and creatinine clearance showed a significant correlation with postnatal age. Thus age related reference values as proposed given in the present study are desirable. Median serum creatinine concentration decreased continuously within the first weeks of life: 97 (10–90th percentile: 69–141) in the 1st week, 70 (45–99) in the 2nd week, 57 (39–71) at week 3–4, 51 (42–62) at week 5–6 and 44 (39–48) µmol/l at week 7–9. Median creatinine output in µmol/kg body weight was 100 (10–90th percentile: 62–160) in the 1st week, 92 (65–120) in the 2nd week, 79 (52–122) at week 3–4, 89 (68–106) at week 5–6 and 86 (54–109) µmol/kg/d at week 7–9. Creatinine clearance increased significantly within the first weeks of life. Values were 12.5 (10–90 the percentile: 7–22) in the 1st week, 16 (10–28) in the 2nd week, 20 (11–34) at weeks 3–4, 23 (15–36) at weeks 5–6 and 29 (17–36) ml/min per 1.73 m^2 at weeks 7–9. Therapy with dexamethasone, spironolactone or catecholamines showed no influence on creatinine excretion. Creatinine clearance did not only depend on postnatal age but also on gestational age and on the necessity of mechanical ventilation. These findings indicate a reduced glomerular filtration rate in very immature and severely ill preterm infants.

Conclusion It might be necessary to lower dosage of renal excreted drugs in very immature and mechanically ventilated infants according to the creatinine clearance.

Key words Preterm infants · Serum creatinine · Creatinine excretion · Creatinine clearance · Reference values

Introduction

Little data are available concerning serum creatinine, creatinine excretion and creatinine clearance in preterm infants. Published studies are confined either to a small number of probands [3, 11, 13, 14] or are limited to the first days of life [8, 12]. In the present study parameters were measured regularly within the first 9 weeks of life. According to a standardized protocol, the possible influence of dexamethasone, spironolactone and catecholamines was evaluated.

Patients and methods

Studies were performed in preterm infants with a birth weight < 1500 g treated in the neonatal unit, Department of Paediatrics of the University of Kiel between August 1992 and May 1994. Patients with cardiac or renal malformations were excluded as were patients with clinical evidence of renal dysfunction. None of the children were treated with furosemide or chlorothiazide. In case of arterial hypotension, children were treated with catecholamines. Urine sampling was performed only in periods of stable fluid and mineral balance and normal blood pressure. Urine was collected in a plastic adhesive collection bag over a 24-h period. Loss of urine was controlled by weighing diapers. Whenever loss exceeded 15% of total collection volume, urine collection was considered inaccurate and was stopped. In 34 infants, a 24-h urine could be obtained during the 1st week (3–4 day), 2, 3–4, 5–6 and 7–9 weeks. Blood samples were taken during routine procedures within the collection periods. Whenever therapy with dexamethasone (0.1–0.5 mg/kg/d), spironolactone (3 mg/kg/d) or catecholamines (dopamine 2.5 µg/kg/min, dobutamine 7.5 µg/kg/min) was necessary, this was noted in the protocol.

Creatinine concentration in serum and urine was analysed immediately on the basis of a modified Jaffe reaction using a Hitachi 704 analyser. Creatinine clearance was related to a bodysurface of 1.73 m^2. Body surface was calculated from the normogram of Dubois and Dubois.

Statistic calculations were made with the software SPSS-PC (Chicago, Illinois USA). Values for creatinine concentration, amount and clearance were non-normally distributed, therefore expressed as 10th, 50th and 90th percentile. Univariate variance analysis was determined for the factor postnatal age and urinary creatinine amount and concentration, serum creatinine concentration and creatinine clearance. The multivariate variance analysis (MANOVA) was performed to investigate the influence of gestational age, birth weight, mechanical ventilation, catecholamines, spironolactone and dexamethasone. Baseline differences between two groups were evaluated by the Mann-Whitney-U-test. *P*-values of less than 0.05 were considered to indicate statistical significance.

Results

Serum creatinine concentration

Median creatinine concentration in serum decreased continously and significantly (univariate analysis) within the first weeks of life from 97 µmol/l to 44 µmol/l ($P < 0.001$). Dispersion (10th-90th percentile) decreased from 69–141 µmol/l to 39–48 µml/l. Age-related data are given in Table 1. Multivariate analysis showed also a significant influence of gestational age on serum creatinine concentration. Mechanical ventilation, application of dexamethasone, spironolactone or catecholamines as well as birth weight were without influence on the serum creatinine concentration. Serum concentration did not correlate with diuresis.

Table 1 Plasma creatinine concentration (µmol/l). Our own data and values obtained from the literature. Values are given as median and range or mean and standard deviation

Authors	Gestational age	Postnatal age	*n*	Concentration
Stonestreet und Oh [14]	26–36 weeks	1.–10. day	13	114 (70–158)
		32.–94. day	13	53 ± 4
Gordjani et al. [8]	28–32 weeks	4.– 5. day	7	60 (54–86)
		8.–10. day	5	73 (65–86)
	33–37 weeks	4.– 5. day	13	63 (60–70)
		8.–10. day	6	53 (50–60)
Brion et al. [5]	25–28 weeks	1. week	10	123 ± 70
		2.–8.week	26	79 ± 44
		> 8. week	9	35 ± 18
	29–34 weeks	1. week	27	79 ± 26
		2.–8. week	27	62 ± 26
		> 8. week	1	31
Feldman et Guignard [7]	30–40 weeks	6.–30. day	34	35 (12–62)
Present study	26–34 weeks	1. week	34	97 (69–141)[a]
		2. week	34	70 (45–99)[a]
		3.–4. week	34	57 (39–71)[a]
		5.–6. week	34	51 (42–62)[a]
		7.–9. week	34	44 (39–48)[a]

[a] 10th–90th percentile

Table 2 Influence of gestational age, birth weight, mechanical ventilation, catecholamines, spironolactone and dexamethasone on creatinine in serum and urine. Results of multivariate variance analysis (MANOVA); *P*-values

	Birth weight	Gestational age	Mechanical ventilation	Catecholamines	Spironolactone	Dexamethasone	Age
Serum creatinine concentration	0.52	0.04	0.12	0.12	0.47	0.24	0.00
Creatinine amount in urine	0.34	0.94	0.41	0.98	0.67	0.50	0.08
Creatinine clearance	0.38	0.00	0.01	0.05	0.51	0.10	0.00

Table 3 Creatinine clearance (ml/min per 1.73 m^2). Our own data and values obtained from the literature. Values are given as median and range or mean and standard deviation (*RDS* respiratory distress syndrome)

Authors	Gestational age	Postnatal age	*n*	Creatinine clearance
Gordjani et al. [8]	28–32 weeks	4– 5 days	12	10.7 (9.4–15.3)
		8–10 days	7	14.2 (12.1–28.7)
	33–37 weeks	4– 5 days	13	20.6 (14.4–31.6)
		8–10 days	4	33.3 (23.1–43.4)
Siegel und Oh [13]	< 30 weeks	2. day	7	5.0 (2–10)
	30–33 weeks	2. day	13	9.0 (5–12)
	34–35 weeks	2. day	8	13 (6–28)
Ross et al. [11]	28–33 weeks	1.–61. day	13	14.7 ± 0.9 (ohne RDS)
	28–33 weeks	1.–61. day	9	7.5 ± 2.6 (mit RDS)
Aperia et al. [3]	32–34 weeks	4.–6. day	8	24.1 ± 1.7
		3–5. week	6	37.0 ± 3.7
Brion et al. [5]	25–28 weeks	1. week	10	11.0 ± 5.4
		2.–8.week	26	15.5 ± 6.2
		> 8. week	9	47.4 ± 21.5
	29–34 weeks	1. week	27	15.3 ± 5.6
		2.–8. week	27	28.7 ± 13.8
		> 8. week	1	51.4
Our data	26–34 weeks	1. week	34	12.5 (7–22)[a]
		2. week	34	15.7 (10–28)[a]
		3.–4. week	34	19.7 (11–34)[a]
		5.–6. week	34	23.3 (15–36)[a]
		7.–9. week	34	28.7 (17–36)[a]

[a] 10th–90th percentile

Urinary creatinine excretion

Median creatinine concentration in urine was 1.1 (10th–90th percentile: 0.6–2.0) in the 1st week, 0.9 (0.4–1.5) in the 2nd week, 0.9 (0.4–1.4) at week 3–4, 1.1 (0.8–1.2) at week 5–6 and 1.1 (0.6–1.3) mmol/l at week 7–9. Within all different collection periods, diuresis showed a significant negative correlation with creatinine concentration in urine (*r*-values between –0.40 and –0.75).

Age-dependent differences of urinary creatinine excretion expressed per kilogram of body weight were significant ($P < 0.001$) in the univariate variance analysis but no uniform trend was registered. Median creatinine output in µmol/kg body weight was 100 (10th–90th percentile: 62–160) in the 1st week, 92 (65–120) in the 2nd week, 79 (52–122) at week 3–4, 89 (68–106) at week 5–6 and 86 (54–109) µmol/kg per day at week 7–9. In a multivariate setting, gestational age, birth weight, need for mechanical ventilation or therapy with dexamethasone, spironolactone or catacholamines and postnatal age showed no influence on the creatinine excetion per kilogram body weight (Table 2). Diuresis did not correlate with creatinine excretion per kilogram body weight.

Creatinine clearance

Creatinine clearance increased steadily during the first 9 weeks of life and showed a statistically significant age-dependency ($P < 0.001$). Age-related values are given in Table 3. Therapy with dexamethasone, spironolactone or catecholamines was without influence on the creatinine clearance. Diuresis was not correlated to creatinine clearance. In the multivariate analysis, creatinine clearance was significantly dependent on postnatal age, gestational age and mechanical ventilation (Table 2). In the 1st and 2nd weeks of life, creatinine clearance depended on gestational age and the need for mechanical ventilation: me-

dian clearance was significantly lower in infants with an gestational age ≤28 weeks (n = 15) than in those whose gestational age was > 28 weeks (n = 19) (1st week: 10 vs 14.5 ml/min per 1.73 m^2, 2nd week: 13 vs 18 ml/min per 1.73 m^2; U-Test $P < 0{,}05$). In the same period creatinine clearance was higher in non-ventilated than in ventilated infants (U-Test $P < 0.05$). Median clearance in the 1st week was 14.5 versus 11; 2nd week 18 versus 13 ml/min per 1.73 m^2).

Discussion

The investigated parameters of creatinine excretion were significantly age-dependent. This held true in a multivariate analysis, considering gestational age, birth weight and therapy with dexamethasone, spironolactone or catecholamines (Table 2). Therefore it appears appropriate to refer to age-related reference values, as proposed in this study. We are well aware of the fact that reference values should be obtained in healthy probands. However, preterm infants with a birth weight < 1500 g can not be considered as healthy. Therefore care was taken to exclude pathological features unrelated to immaturity. Patients with renal or cardiac malformation were excluded as were patients with other evidence for renal dysfunction. Sampling was only performed in patients with normal blood pressure and stable mineral and fluid balance.

Serum creatinine concentration

Serum creatinine concentration is increased during the 1st days of life. Values did not depend on gestational age, but are strongly related to maternal serum creatinine concentration [8]. With increasing postnatal age serum creatinine concentration decreases. This decrement is positively correlated with gestational age and is thought to reflect maturation of glomerular filtration [8]. In mature newborns a median creatinine concentration of 35 µmol/l was found after 5 [7] respectively 10 [8] days of life. In the present study, investigating preterm infants with a birth weight < 1500 g, decrement was much slower, the median serum creatinine concentration in the 7–9th week of life was 44 µmol/l.

The values of serum creatinine concentration in the present study (Table 1) are in agreement with data given in the literature. However, little precise data are available: previous studies on the serum creatinine concentration in preterm infants did not provide age-related values [5, 7, 14] or were confined to the first 10 days of life [8]. Other groups published values as mean with standard deviation [5, 14]. As the study of Gordjani et al. [8] and our own data show, serum creatinine concentration in premature infants is not normally distributed. Therefore such an statistical approach is not appropriate for giving reference values.

Urinary creatinine excretion

As expected, creatinine concentration in urine was negatively correlated with diuresis, indicating a relatively constant urinary creatinine amount. Therefore the excretion of other substances can be related to urinary creatinine concentration. Comparable data in the literature are not available.

Creatinine excretion per kilogram body weight as investigated in the present study was in accordance with the findings of Al Dahan et al. [2]. The authors investigated the urinary creatinine concentration in 84 samples of 60 mature or premature infants aged between 3 and 68 days. The median urinary creatinine amount was 90 µmol/kg per day and 95% percentile range: 45–180 µmol/kg per day. However, these data were not differentiated according to age. In aggreement with our data, these authors found no significant relation between urinary creatinine excretion and gestational age. Suphten [15] found a creatinine excretion of 71.2 ± 9.5 µmol/kg per day in 15 premature infants with a gestational age of 26–33 weeks during the first 2 weeks of life. Because of non-normal distribution our data are given as percentiles. Thus, comparison with Suphten's data is not possible.

Creatinine clearance

Urinary creatinine is entirely filtrated, glomerular secretion or resorption is not of considerable influence. Therefore, creatinine clearance can be used to estimate glomerular filtration [8]. This also applies for preterm infants. Comparing creatinine clearance and inulin clearance, Aperia et al. [3] and Brion et al. [5] found a significant correlation between both methods used as indices of glomerular filtration. Glomerular filtration showed a positive correlation with both gestational and postnatal age [3, 10, 16]. This correlation was confirmed by the present study in preterm infants with a birth weight below 1500 g during the first 9 weeks of life.

Postnatally, creatinine clearance increases in term-born as well as in preterm born infants [1, 3–6, 8–10]. In term-born infants this increase is faster than in premature infants [3, 8–10]. This difference might be due to a smaller number and to immaturity of glomeruli in preterm infants [3, 10].

The results of the present study are in agreement with previously published data of the literature (Table 3). Only Aperia et al. [3] found a higher clearance, which might be due to the higher gestational age of their study group compared to ours.

In none of the previous studies, the number of probands per age group exceeded constantly 10 [1, 3, 8, 11, 13]. Others do not provide age-related values [5, 11] or include only the first 10 days of life [6, 8]. We feel that such studies, as well as those providing mean values with standard deviation [3, 5, 11] may not be appropriate to provide reference values for the first weeks of life in preterm infants although values are non-normally distributed [8, present study].

Multivarariate variance analysis showed a significant influence of mechanical ventilation on creatinine clearance especially in the first 2 weeks of life. This can hardly be explained by the effects of mechanical ventilation itself. More probably, the need for mechanical ventilation indicates that these infants are more severely ill than others. A decreased creatinine clearance in ventilated compared to non-ventilated preterm infants has been reported by Ross et al. [11]. These findings might indicate a reduced glomerular filtration rate in severely ill preterm infants. Thus it might be useful, to take the decreased creatinine clearance of ventilated preterm infants in account, when applying drugs excreted by the kidney.

Application of dexamethasone, spironolactone or dopamine and/or dobutamine did not alter the parameters of creatinine excretion indicating a stable glomerular filtration rate. As dopamine and dobutamine were used to treat arterial hypotension and urine sampling was only performed during periods of stable bood pressure, these findings indicate that treatment was sufficient to ascertain unchanged renal function.

For individually adapted parenteral nutrition und drug therapy of premature infants, renal function should be assessed accurately and easily. The present study shows that age has a major influence on the parameters of creatinine excretion. Due to age-related changes of serum creatinine concentration and creatinine clearance, pointing towards a long-lasting maturational process of the glomerular filtration, age specific reference values as provided by this study, are mandantory. In mechanically ventilated preterm infants, the glomerular filtration rate is reduced. In these children, it might be useful to access the actual glomerular filtration rate when applying drugs excreted by the kidney.

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