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Validity of Endogenous Creatinine Clearance in Low Birthweight Infants

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Summary

Despite methodologic problems, endogenous creatinine clearance is commonly used as an estimation of glomerular filtration rate (GFR). Inulin clearance was compared to endogenous creatinine clearance in a group of low birthweight infants to establish the validity of the latter. Thirty-three low birthweight infants (birthweight mean = 1600 g, gestational age mean = 33 wk) were studied between 10 hr and 10 days of age to simultaneously measure GFR by inulin and endogenous creatinine clearances. Inulin and creatinine clearances correlated directly ($r = 0.738$, $P > 0.001$). The slope of the regression line suggested an overestimation of GFR (inulin clearance) by creatinine clearance at the low GFR range and an underestimation at the high GFR range. The data were divided into two groups by the median inulin clearance (12.5 ml/min/1.73m^2). The ratio of creatinine to inulin clearance was significantly higher in the low GFR group (1.28 ± 0.16 *vs.* 0.89 ± 0.04 SEM, $n = 19$, $P < 0.05$). There was no difference between the two groups in plasma creatinine, birthweight, gestational age, incidence of respiratory distress, or oxygen requirements at the time of the studies. Endogenous creatinine clearance represents a good estimation of GFR (inulin clearance) in low birthweight infants. However, at the low GFR range, it represents an overestimation and at the high GFR range, an underestimation.

Speculation

In low birthweight infants, tubular secretion of creatinine and plasma chromogens interfere with the accuracy of endogenous creatinine clearance. Tubular secretion of creatinine is probably of relatively greater importance at lower GFR's accounting for an overestimation of GFR by creatinine clearance. At higher GFR's, plasma chromogens are probably of more importance and account, in part, for the underestimation of GFR by creatinine clearance.

The validity of endogenous creatinine clearance as a measure of GFR in adults, children, and infants has long been the subject of discussions and investigations (1–3, 7, 8, 16). Despite methodologic and technical problems (11), it remains the most commonly used laboratory aid for the assessment of glomerular functions in clinical practice. In neonates, the problem is compounded by the presence of noncreatinine interfering substances such as chromogens, including bilirubin, which may raise the plasma creatinine levels, thus, giving falsely low endogenous creatinine clearances. The Jaffé reaction (6), a commonly used method for the determination of creatinine in biologic fluids, does not exclude these interfering substances (1, 2, 6, 11). Although falsely high plasma and urinary creatinine levels may counterbalance each other in the calculation of creatinine clearance, the correlation with true GFR has not been established in low birthweight infants. The purpose of this study was to establish the correlation between endogenous creatinine and inulin clearance as a measure of GFR in low birthweight infants.

MATERIALS AND METHODS

Thirty-three low birthweight infants (17 males and 16 females, 27 appropriate and 6 small for gestational age) were the subjects of this study. The mean gestational age was 33 wk (range 30–36 wk) and the mean birthweight was 1600 g (range 1040–2275 g). Gestational age was assessed in all infants by the Dubowitz scoring system (4). Thirty-eight studies were performed between 10 hr and 10 days of age. The mean study weight was 1530 g (range 840–2250 g). The study was approved by the institutional human use committee and parental consent was obtained in each case.

Inulin and creatinine clearances simultaneously were performed as follows: uncatheterized timed urine samples were collected on a specially designed neonatal urine collection bed; at the end of each collection, the bladder was creded to assure as complete emptying of the bladder as possible. After a timed discard urine specimen, an initial prime dose of inulin (50 mg/kg) was administered iv *via* a peripheral vein followed by a continuous infusion of inulin at a dose of 0.1 mg/kg/min using a calibrated infusion pump. Urine collection was continued until 2–6 accurately timed urine collections were obtained. The urine specimens were then pooled and creatinine and inulin concentrations were measured. Three-quarters of ml of whole blood was obtained by heel puncture, 45 min after the onset of the inulin infusion for plasma inulin (13) and creatinine. To minimize the quantity of the total whole blood drawn from these infants, one sample was taken for inulin; it has been previously shown that low birthweight infants reach a serum steady-state for inulin 45 min after the onset of the infusion (13). Serum bilirubin was measured in 26 studies (14). Plasma and urine creatinine and inulin were measured on plasma (19) and urine by a micromethod modified from Folin and Wu (6) and from Roe *et al.* (18), respectively. Bilirubin was measured by the Martinek method (14). Inulin and creatinine clearances were calculated by the conventional formulas. All clearances were expressed per 1.73m^2 of body surface area as calculated from a standard nomogram using body length and weight (17).

During the study period, fluid and electrolyte therapy proceeded as determined by the primary physicians caring for the infants. At the time of study, all infants were receiving iv fluids and 26 infants were also receiving oral feedings. The mean fluid intake was 125 ml/kg/24 hr (range 59–210 ml/kg/24 hr).

For statistical analysis, the unpaired Student t test was used and the slope of the regression line was compared to an ideal slope of 1, by the formula $t = 1 - b/SEb$, b = slope, SEb = SE of the slope, respectively.

RESULTS

As shown in Figure 1, inulin and creatinine clearances correlated directly ($r = 0.738$, $P < 0.001$) with the regression equation: $y = 3.78 + 0.66x$. However, the slope was significantly less than the ideal slope of 1 ($t = 3.88$, $P < 0.001$). In fact, the slope of the regression line suggested a trend of overestimation of GFR (inulin clearance) by creatinine clearance at the low GFR range and underestimation of the GFR at the high GFR range. To statisti-

cally validate this impression, we have arbitrarily divided the data into two groups: those with high or low inulin clearances, *i.e.*, greater or less than 12.5 ml/min/1.73m^2, (the demarcating value of 12.5 ml/min/1.73m^2 is the median of all results).

As seen in Table 1, the ratio of creatinine to inulin clearance was significantly greater in the low GFR group (1.28 ± 0.16 *vs.* 0.89 ± 0.04 M ± SEM, $n = 19$, $P < 0.05$), and there was no significant difference between the two groups in plasma creatinine, birthweight, gestational age, incidence of respiratory distress, and oxygen requirement at the time the studies were performed. Linear regression analysis showed no correlation between birthweight and gestational age with the ratio Ccr/Cin, respectively. Likewise, there was no correlation between total plasma creatinine and the Ccr/Cin ratio or inulin clearance, respectively.

The mean serum bilirubin concentration was 7.6 ± 0.4 mg/dl (M ± SEM, $n = 26$) and did not correlate with either plasma creatinine or creatinine clearance.

DISCUSSION

Several reports have demonstrated a close approximation of creatinine clearance to GFR as measured by inulin at normal levels of glomerular filtration. However, at reduced GFR levels, creatinine clearance overestimates GFR (1, 2, 8, 16), presumably due to the tubular secretion of creatinine in these subjects in whom the reduced glomerular functions were secondary to renal pathology. In our study, the correlation between inulin and creatinine clearances in low birthweight infants was significant; however, the regression line suggested a trend of overestimation of GFR by creatinine clearance at low GFR's when compared with those at higher values of GFR. The slope of this regression line was significantly different from 1. This difference was emphasized when the creatinine inulin clearance ratio (C_{cr}/C_{in}) of those with lower GFR's was compared with those with higher GFR's. C_{cr}/C_{in} ratio should be unity (1.0) if the estimation by creatinine clearance is equal to inulin clearance (GFR); a greater ratio would indicate overestimation and a smaller ratio would indicate an underestimation of GFR by C_{cr}. The accuracy of endogenous creatinine clearance as an estimate of GFR is altered by the presence of noncreatinine chromogens (11) and by tubular secretion of creatinine in infants with both ranges of GFR's.

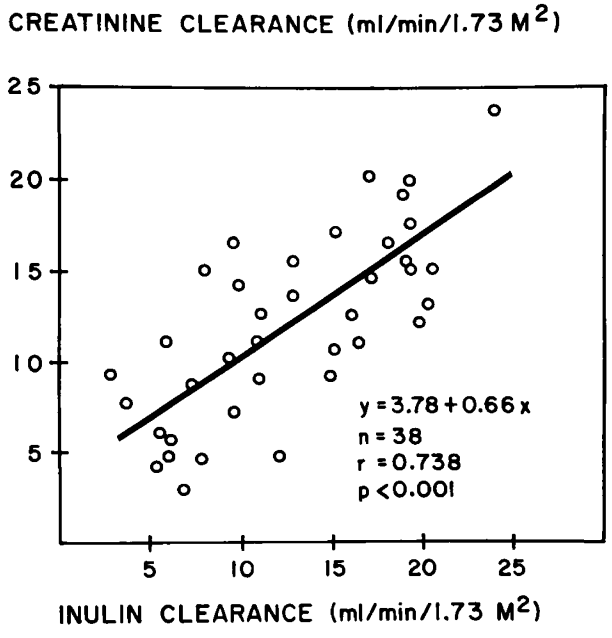

Fig. 1. Relationship between inulin and creatinine clearance in low birthweight infants.

Table 1. *Relationship of high and low GFR's (C_{in}) to validity of creatinine clearance*

Parameters	Inulin clearance (ml/min/1.73m^2) ≤12.5 (19)	≥12.6 (19)
Creatinine clearance / Inulin clearance	1.28 ± 0.16	0.89 ± 0.04[1]
Plasma creatinine (mg/dl)	1.20 ± 0.063	1.10 ± 0.052
Birthweight (kg)	1.509 ± 0.070	1.691 ± 0.078
Gestation (wk)	32.0 ± 0.36	33.0 ± 0.43
RDS		
Yes	6	7
No	12	8
O_2 required during study	0.23 ± 0.01	0.23 ± 0.01

[1] $P < 0.05$ (unpaired t test).

In infants with lower GFR's, C_{cr} overestimated GFR. The reason for this overestimation is very likely due to secretion of creatinine *via* the tubules. The C_{cr}/C_{in} ratio was 1.28, which is considerably higher than the ratio reported for children with GFR's less than 20 ml/min/1.73m^2 (1). This ratio is particularly high, as it is a minimum estimate of tubular creatinine secretion, because these infants also have noncreatinine plasma chromogens (11). Low birthweight infants have an increased extracellular fluid volume (ECF) (5). An increased extracellular fluid space alters many tubular functions (9, 10, 15). It is possible that an increased ECF may likewise effect tubular creatinine secretion. Because ECF was not determined, this possibility remains speculative. Whether this markedly increased tubular secretion of creatinine is on the basis of developmental immaturity or renal pathologic lesions is not known.

Although GFR's in the infants with relatively higher clearances are significantly lower than those seen in older children, creatinine clearance underestimated GFR ($C_{cr}/C_I < 1.00$ or 0.89 in our series). This ratio is below that reported for older children (1). Although both tubular creatinine secretion and plasma chromogens (11, 19) are probably present in this group, tubular secretion of creatinine must be significantly lower permitting plasma chromogens to be of relatively more importance and consequently causing the underestimation of GFR by C_{cr}.

There is a variability in the GFR's reported here. The infants studied were between 10 hr and 10 days of life. In low birthweight infants, a low GFR has been reported in the first 24 hr with a significant increase during the first 3 days of life (12).

In our series, no correlation was found between serum bilirubin, plasma creatinine, and creatinine clearance. True creatinine and bilirubin are independent variables, although both may contribute to the total chromogen concentration. The level of bilirubin seen here and the sample size were not of sufficient magnitude to significantly alter the total creatinine concentration.

CONCLUSION

GFR's were measured simultaneously by inulin and endogenous creatinine clearance in 33 low birthweight infants. Endogenous creatinine clearance represents a good estimation of GFR (inulin clearance) in these infants. Tubular secretion of creatinine and the presence of noncreatinine chromogens in the plasma are probably the two factors that interfere with the accuracy of this measurement in infants.

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