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EVALUATION OF RENAL RESPONSIVENESS TO EXOGENOUS PARATHYROID HORMONE ON THE FIRST AND THIRD DAYS OF LIFE*

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The renal proximal tubular responsiveness to parathyroid hormone (PTH) during the first days of life is controversial. It has been suggested that the neonate in the first week of life may have a depressed renal response to PTH stimulation and that this could be of importance in the pathogenesis of early hypocalcemia or hyperphosphatemia[1,2]. Other studies, however, have reported that neonates do appear to respond to exogenous or endogenous PTH stimulation with increasing cyclic adenosine monophosphate (c-AMP) and phosphate levels in the urine[3,4].

The present study investigates the development of renal responsiveness to exogenous PTH stimulation by determining the urinary c-AMP levels and tubular phosphate reabsorption (TPR) percentages in full term and premature infants on the first and third days of life.

Material and Methods

Six full term and six premature infants, all healthy, admitted to the intensive care nursery of the Hacettepe University Institute of Child Health, were included in the study. Males were selected so as to ensure more complete urine collections. Gestational ages of the premature infants ranged from 34 to 37 weeks and birthweights from 1750 to 2250 gm. The full term infants were fed breastmilk and the premature infants a formula*****

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***** SMA, s-26 Wyeth Laboratory-Collective Company (21 mEq/l phosphorus).

The first urine following birth was not used. Thereafter, timed urine specimens for measurement of c-AMP, phosphate and creatinine were collected. To initiate urine flow, an intravenous hydration of 20 ml/kg was given 60 to 120 minutes before parathyroid extract* (PTE) infusion (5 U/kg, 83 micro U/kg/min) in 5% glucose solution for one hour's duration[2]. After PTE infusion, the urine specimens were obtained over approximately a four-hour period. Blood was drawn by heel prick before and after PTE infusion to measure calcium (Ca), phosphate (P), creatinine (Cr) and protein. The same procedures were repeated on the third day of life.

Urine specimens were kept frozen at −20°C until analyzed. Blood specimens were centrifuged and analyzed immediately. Urinary c-AMP levels were determined according to the radioimmunoassay method[5,6] with the "cyclic AMP assay kit"**. The levels of serum calcium were measured by an atomic absorption spectrophotometer[7]. The Folin-Wu method was used for creatinine measurements[8], while phosporus was determined by the Frankel and Reitman method[8].

Data were analyzed by means of Student's t test.

Results

Tables I and II show the results (mean ± SEM) of measurements of tubular phosphate reabsorption, creatinine clearance, c-AMP, and serum phosphorus and calcium, before and after PTE infusion in full term and premature infants, respectively, on the first and third days of life.

Tubular phosphate reabsorption. The decreases in TPR percentages before PTE infusion from the first to the third day were insignificant for both groups ($p > 0.05$). Both the full term and premature infants responded to the PTE infusion, as can be seen from the decreasing TPR percentages. These decreases were statistically significant ($p < 0.05$) except for the full term infants' values on the first day ($p > 0.8$). In comparing the groups after PTE infusion, the premature infants showed lower TPR percentages than the full term infants on the first day ($p < 0.01$), while both groups registered the same drops in TPR percentages on the third day.

Creatinine clearance. Mean creatinine clearance (C_{cr}) values before PTE infusion increased in all infants from the first to the third day ($p > 0.1$ and $p > 0.05$). C_{cr} values in premature infants were significantly lower than in full term infants on both the first and third days ($p < 0.05$). On the first day, creatinine clearances were (mean ± SEM) 19.2 ± 3.8 ml/min/1.73 m^2 and 9.66 ± 1.46 ml/min/1.73 m^2 in full term and premature infants, respectively. On the third day, they were 28.8 ± 5.6 ml/min/1.73 m^2 and 14.93 ± 2.02 ml/min/1.73 m^2 in full term and premature

* Para-Thor-Mon "p-20", Eli Lilly Co., Indianapolis, Indiana, U.S.A.

** The Radiochemical Center, Amersham Buckinghamshire, England, Code No. TRK 432.

TABLE I

Renal Responsiveness to PTE Infusion in Full Term Infants on the First and Third Days of Life

(n = 6)

Day of life		TPR %	C_{cr} ml/min/1.73 m²	Serum phosphorus mg/dl	Serum calcium mg/dl	c-AMP picomol/min/kg
1st	Before PTE infusion	99.5 ± 0.15*	19.2 ± 3.8	8.1 ± 0.8	11.2 ± 0.6	31.38 ± 9.19
	After PTE infusion	98.3 ± 0.50	33.1 ± 4.5	6.3 ± 0.4	10.9 ± 0.3	115.30 ± 22.50
		$p > 0.8$	$p > 0.05$	$p < 0.05$	$p > 0.05$	$p < 0.01$
3rd	Before PTE infusion	96.4 ± 1.25	28.8 ± 5.6	8.0 ± 0.6	10.8 ± 0.8	52.14 ± 28.70
	After PTE infusion	87.3 ± 2.70	40.0 ± 8.9	7.1 ± 0.3	11.3 ± 0.9	170.25 ± 57.30
		$p < 0.05$	$p > 0.05$	$p < 0.05$	$p < 0.05$	$p > 0.05$

TPR = tubular phosphate reabsorption, C_{cr} = creatinine clearance, c-AMP = cyclic adenosine monophosphate.

* Results expressed as mean ± SEM.

TABLE II

Renal Responsiveness to PTE Infusion in Premature Infants on the First and Third Days of Life

(n = 6)

Day of life		TPR %	C_{cr} ml/min/1.73 m^2	Serum phosphorus mg/dl	Serum calcium mg/dl	c-AMP picomol/min/kg
1st	Before PTE infusion	97.9 ± 1.01*	9.66 ± 1.46	7.2 ± 0.45	10.38 ± 0.70	29.6 ± 14.66
	After PTE infusion	92.9 ± 1.11	29.38 ± 5.95	6.35 ± 0.41	10.67 ± 0.62	137.2 ± 28.19
		$p < 0.05$	$p < 0.05$	$p < 0.05$	$p > 0.05$	$p < 0.01$
3rd	Before PTE infusion	94.5 ± 2.17	14.93 ± 2.02	8.0 ± 0.87	9.92 ± 0.62	29.2 ± 14.67
	After PTE infusion	74.8 ± 5.95	39.15 ± 6.06	7.25 ± 0.53	11.0 ± 0.95	193.1 ± 99.9
		$p < 0.05$	$p < 0.01$	$p > 0.05$	$p > 0.05$	$p > 0.10$

TPR = tubular phosphate reabsorption, C_{cr} = creatinine clearance, c-AMP = cyclic adenosine monophosphate.

* Results expressed as mean ± SEM.

infants, respectively. After PTE infusion, mean C_{cr} values in the premature infants rose significantly on both the first and third days of life ($p < 0.05$ and $p < 0.01$) but did not change significantly in the full term infants ($p > 0.05$).

Urinary cyclic AMP. The mean urinary c-AMP levels (picomol/min/kg) of the full term and premature infants rose after PTE infusion on both the first and third days. The first day responses were found to be statistically significant in both groups ($p < 0.01$), while the third day responses were insignificant ($p > 0.05$ and $p > 0.1$). When the third day results were documented individually, the changes in the urinary c-AMP levels of both groups following PTE infusion varied widely, and the standard deviations were high. The differences between first day and third day mean values were not significant either before or after PTE infusion ($p > 0.5$). There was no difference between mean values in the two groups of infants ($p > 0.8$).

Serum phosphorus. The mean serum phosphorus levels (mg/dl) in the full term infants decreased significantly after PTE infusion on both the first and the third day (Table I, $p < 0.05$). In the premature infants, the changes in serum phosphorus after PTE were significant on the first day (Table II, $p < 0.05$) but not on the third day ($p > 0.05$).

Serum calcium. Both groups of infants had normal calcium levels before PTE infusion and normal serum protein levels for gestational age. There were no significant changes in mean serum calcium levels after PTE infusion ($p > 0.05$) except for the full term infants on the third day, where the mean serum calcium level rose to 11.3 ± 0.9 from 10.8 ± 0.8 (Table I, $p < 0.05$).

Discussion

During intrauterine life, glomerular development prevails over tubular development, and medullary development precedes and exceeds cortical development[9]. In early postnatal life, glomerular filtration rates are low, as a result of relatively impermeable basement membranes, high intrarenal vascular resistance, and low net driving force for filtration. However, since proportionally, tubular transport capacity is even lower, a state of glomerulotubular imbalance, characterized by glomerular preponderance, exists during infancy. This is expressed in a limited capacity of the nephrons to handle the filtrated load, which results in urinary loss of substances such as phosphate[9].

It has been reported that early neonatal hyperphosphatemia is caused by a low glomerular filtration rate (GFR), the relative unresponsiveness of tubular epithelium to PTH, and the limited secretory capacity of the neonate's parathyroid gland[2,10-11]. This finding is also reflected in the present study, which shows low GFR in the premature and full term infants on the first and third days of life (Tables I, II).

The drops in the TPR percentages before PTE infusion from the first to the third day were insignificant for both full term and premature infants. This result shows that neonatal parathyroid activity is still limited on the third day and/or that the renal tubular functions are immature.

All infants responded to PTE infusion by decreasing TPR percentages (Tables I, II). After PTE infusion, the changes in the TPR percentages for the two groups were significant on the third day of life ($p < 0.05$). The renal tubular responsiveness probably played a major role in this result, since the TPR percentages before PTE infusion did not drop significantly from the first to the third day. On the first day, the prematures showed lower TPR percentages after PTE than the full term infants ($p < 0.01$). This discrepancy between the two groups may be related to the greater maturity of the tubular functions of the full term infants.

The serum phosphate levels on the third day were as high for the full term infants as for the prematures. This finding may be due to the fact that premature infants were fed on a formula high in phosphorus as well as to the limited renal function of the prematures.

In all the infants, increases in the urinary c-AMP excretion before PTE infusion from the first to the third day were insignificant. This result may be due both to the immature renal tubular function and the limited endogenous parathyroid hormone activity of the increased plasma-borne urinary c-AMP[12].

PTH acts by stimulating the particulate membrane enzyme adenyl-cyclase in both kidney proximal tubules[13;14]. The increases in the urinary excretion of c-AMP after PTE in our cases directly reflect the effect of PTH on the renal tubules[14]. All infants in this study responded to PTE infusion with an increase in urinary excretion of c-AMP. Although the urinary c-AMP response to PTH in both groups was significant on the first day, on the third day it was not. This result could be related to the wide range of individual measurements of urinary c-AMP.

In conclusion, the decreases in the TPR percentages in all infants after PTE infusion show that low PTH activity, in addition to low GFR, could be responsible for the hyperphosphatemia observed in the first days of life. This study suggests the presence of "transient hypoparathyroidism" in the early neonatal period.

Summary

Renal responsiveness to PTE infusion was investigated by determining the urinary c-AMP and tubular phosphate reabsorption percentages in six full term and six premature male infants on the first and third days of life. The decreases in the TPR percentages in all infants after PTE infusion show that low PTH activity, in addition to low GFR, could be responsible for the hyperphosphatemia observed in the first days of life. Although the individual responses varied widely, the infants responded to PTE infusion with an increase in urinary excretion of c-AMP.

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