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 15. Requests for reprints should be addressed to: F. H. Adams, M.D., Division of Cardiology, Department of Pediatrics, University of California, School of Medicine, Center for the Health Sciences, Los Angeles, California 90024 (USA).
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Aldosterone newborn
diet weight
kidney

Plasma Aldosterone Concentrations during the Neonatal Period

M. C. RAUX-EURIN,^{1*} M. T. PHAM-HUU-TRUNG, D. MARREC, AND F. GIRARD

Laboratoire de Physiologie Endocrinienne Infantile, INSERM U 142, Hôpital Trousseau, Paris, France

Summary

The direct radioimmunoassay for plasma aldosterone (PA) set up in this laboratory has been reported elsewhere. Subjects were 115 normal full term newborns and infants. During the first week of life, there was a wide dispersion in the PA levels (<1-445, $n = 89$), but on the whole these levels were high (>6 ng/100 ml) and 35% were higher than those observed in children after stimulation (>48 ng/100 ml). Furthermore, there was a negative correlation between PA values and the day of sampling ($P < 0.01$). In older infants, PA values were lower and the ranges narrower. A highly significant negative correlation was found between Na:K ratios and PA levels. The mean geometrical value for PA levels was 53 ng/100 ml vs. 1.012 for Na:K mean ratio. When related to weight variations, PA values were randomly distributed. No correlation was found between PA and sodium intakes. The daily urinary excretion of tetrahydroaldosterone and 3-oxoconjugate of aldosterone were lower *per se*, but when related to surface area, were found to be roughly 3-fold those of control adult subjects. We conclude that in the newborn, both the production and excretion of aldosterone are different than values in the adult and that responses to the regulation factors mentioned above are decreased.

Speculation

The direct radioimmunoassay of PA facilitates the evaluation of this hormone during the neonatal period and infancy. The results obtained from plasma and urinary determinations of aldosterone provide evidence for a different pattern of both production and metabolism of aldosterone during these periods. An appreciation of these PA values and of their regulation is necessary in order to evaluate the significance of PA levels observed in pathologic cases.

It has previously been reported that PA levels are dramatically elevated during the neonatal period (3, 11) and infancy (5, 8). However, apart from this common point, the results obtained have been widely dispersed and all authors have found values overlapping those observed in the adult. We undertook the present study in order to obtain further information on PA levels, especially during the neonatal period, and to try and relate the results we obtained with a physiologic index of aldosterone activity or regulation.

METHODS

METHOD FOR MEASUREMENT OF PA

The direct radioimmunoassay set up in this laboratory has been reported elsewhere (11). One milliliter of plasma was extracted with 10 ml methylene chloride and the extract washed first with 1 ml of 0.1 M NaOH and then with 1 ml distilled water. Different aliquots of the extract, determined according to the expected aldosterone concentrations, were assayed without further purification with the aid of a highly specific antibody. The sensitivity of the assay was 1 ng/100 ml plasma. Some plasma samples from newborns were submitted to Sephadex LH20 chromatography as described by Murphy (9), using a methylene chloride-methanol (98:2) solvent.

URINARY METABOLITES OF ALDOSTERONE

These were assayed by radioimmunoassay after column chromatography.

SUBJECTS

The subjects were 115 normal full term newborns and infants. Blood samples were taken from the antecubital vein of the

resting infants between 9 and 11 AM, *i.e.*, 3–5 hr after the last intake of their usual food (either mother's milk or commercial milk). Daily weight and total sodium intake were recorded. Five of the newborns were sodium loaded with 1 M NaCl (3 mEq/kg/day) in addition to their normal formula.

Urine was collected from series of newborns. In 32 instances, specimens were collected over a period of a few hours with a view to determining urinary Na:K ratios. Ten infants were submitted to carefully controlled 24 hr urine collections in order to evaluate the excretion of tetrahydroaldosterone (THA) and of the acid-labile 3-oxoconjugate of aldosterone. Plasma sodium and potassium levels were determined in most cases. In addition, PA was measured in 30 children between the ages of 1 and 14 years and in 33 adult control subjects. Some of the children underwent a synthetic ACTH stimulation test (Synacthen, 0.25 mg i.m.). Informed consent was obtained from parents of infants and children and, in the case of adult control subjects, from the subjects themselves.

RESULTS

During the first week of life, there was a wide dispersion in the PA levels (Fig. 1). Four values (4%) fell within the range of nonstimulated children (*i.e.*, <6 ng/100 ml), but on the whole, these levels were high and 35% were even higher than those observed in children after Synacthen stimulation (*i.e.*, over 48 ng/100 ml) (Table 1). Furthermore, there was a negative correlation between PA values and the day of sampling. Conversely, the PA values were lower and the ranges narrower in the following age groups: 6 days–3 months and 4–12 months (Table 1). The 1–14-year-old children had PA levels similar to those of adults. All plasma sodium and potassium levels were within the normal range. Additional studies concerning the values observed in the 0–6-day-old group were carried out as follows.

Fig. 1. Plasma aldosterone values in terms of the day of sampling. (The regression analysis was undertaken on logarithmically transformed plasma aldosterone values which were taken as the dependent variable.)

Table 1. Plasma aldosterone levels (nanograms per 100 ml) observed in various age groups

Age	n	Range	Geo-metrical mean	95% confidence limit	P
Birth–6 days	89	<1–445	55.34	5.65–542	<0.001
7 days–3 months	19	6–128	22.04	3.40–143	
4–12 months	7	3–10	6.06	2.81–13.01	<0.01
1–14 years	27	<1–6	1.80	0.63–5.12	<0.001
Adults	33	<1–3.8	1.63	0.57–4.59	
1–14 years (after short acting Synacthen (0.25 mg i.m.))	26	6–48	14.70	3.76–56.7	NS [†]

[†] Nonsignificant.

Fig. 2. Correlation between plasma aldosterone levels and urinary Na:K ratio. (Regression analysis was undertaken on logarithmically transformed data.)

SEPHADEX LH20 CHROMATOGRAPHY

Some of the plasma samples with high PA levels were pooled and submitted to Sephadex LH20 chromatography. Only one peak of immunoreactive steroid was obtained and this corresponded perfectly with the elution pattern of tritiated aldosterone.

URINARY NA:K RATIOS (FIG. 2)

The 32 infants whose urinary specimens were collected had PA levels ranging from 3–200 ng/100 ml. A highly significant negative correlation was found between NA:K ratios and these PA levels. The mean geometrical value for those PA levels was 53 ng/100 ml vs. 1.012 for NA:K mean ratio.

VARIATIONS IN WEIGHT

In the first 3–5 days of life the percentage of weight loss in relation to birth weight was between 3% and 12%, and this was followed by a normal weight increase. In spite of the progressive decrease in PA levels as the babies grew, these values were randomly distributed when related to weight variations (Fig. 3).

SODIUM INTAKE

Sodium intake was evaluated for 20 breast-fed (<0.3 mEq/kg/day), 17 bottle-fed (0.6–1.3 mEq/kg/day), and 5 sodium-loaded

Fig. 3. Daily aldosterone values as a function of weight variations.

Fig. 4. Daily aldosterone values as a function of sodium intake.

(3-4.4, mEq/kg/day) infants aged 2-6 days. No correlation was found between PA and sodium intake (Fig. 4).

MEASUREMENT OF DAILY URINARY EXCRETION OF THA AND 3-OXOCONJUGATE OF ALDOSTERONE (TABLE 2)

These values were low, *per se*, but when related to the surface area, they were found to be roughly 3-fold those of control adult subjects. A correlation was found between the newborn's urinary excretion of THA and the acid-labile conjugate of aldosterone ($r = 0.75$) with a mean THA to 3-oxoconjugate ratio of 2.4. There was, however, no correlation between these urinary metabolites and either the urinary Na:K ratios or the PA levels.

DISCUSSION

Several questions concerning the PA levels observed in the newborn arise, not only from our data, but also from those of other authors.

Table 2. *Urinary metabolites of aldosterone*¹

Exp.	Age, days	THA, $\mu\text{g}/24\text{ h}$	3 OXO, $\mu\text{g}/24\text{ hr}$	THA:3-OXO	Urinary Na:K	PA, ng/100 ml
1	1	4.5	1.5	3	0.26	75
2	1	10.9	4.4	2.5	0.33	130
3	1	1.6	0.7	2.3	0.22	44
4	1	11.5	3.7	3.1	0.34	60
5	2	3.1	2.2	1.4	0.27	95
6	2	0.10	4.4	2.3	1.05	45
7	3	14.8	7.1	2.1	0.2	100
8	3	3.9	1.8	2.2	0.06	98
9	3	6.5	2.3	2.8	0.7	75
10	3	4.5	2.5	1.8	0.86	51
Adults ²		20-50	6-10			<1-3.8

¹ THA: tetrahydroaldosterone; 3-OXO: 3-oxoconjugate; PA: plasma aldosterone.

² Normal sodium intake.

IS THE ASSAYED STEROID REALLY ALDOSTERONE?

There is a good deal of experimental evidence that the steroid we assayed is indeed aldosterone. The specificity of the direct assay has been previously tested and no cross-reaction was found with the usual circulating steroids (11). Furthermore, the results obtained after chromatography of some of the plasma samples from newborns were in total agreement with those of the direct assay.

HAVE THESE SCATTERED ALDOSTERONE LEVELS SOME PHYSIOLOGICAL SIGNIFICANCE?

Urinary Na:K ratios are assumed to be a function of the renal tubular response to aldosterone (13). We were able to relate urinary Na:K ratios obtained from newborns to their PA levels. However, it should be noted that the urinary Na:K ratios were also widely dispersed and that the lowest Na:K ratios, which should correspond with some state of hyperaldosteronism, were obtained in association with very high PA values (ranging from 30-200 ng/100 ml). These findings might reflect a relative insensitivity of the newborn's kidney to aldosterone. This has been

previously assumed by Greenberg *et al.* (7), who used aldosterone perfusions. Unfortunately, no aldosterone measurements were performed in the course of these studies.

IN VIEW OF THE WIDE DISPERSION, CAN PA VALUES BE RELATED TO FACTORS WHICH USUALLY INTERFERE WITH ALDOSTERONE REGULATION?

We investigated two physiologic events which occur in the newborn, *i.e.*, the variations in weight and the wide range of sodium intake which occur whether newborns are breast fed or bottle fed.

Neonatal decrease in weight is due to losses of both intracellular and extracellular water. Furthermore, an important decrease of body chlorides in newborns has been described (4). Our data indicated no relationship between these observations and PA levels. A decrease in urinary excretion of aldosterone at the time of maximum weight loss has been reported (1), but this study was done in premature infants whose sodium and volume regulations are known to be different from those of full term newborns (2). Acute blood volume change in the course of exchange transfusions was not found to induce PA changes in full term newborns (6).

No significantly different aldosterone levels were demonstrated in three distinct categories of newborns (breast fed, bottle fed, or sodium loaded), whose sodium intake covered a range from 0.3–4.5 mEq/kg/day.

Similar indications were reported by Siegel *et al.* (12), who found no correlation between the PA levels and the sodium intake of normal preterm, full term, or small for gestational age infants whose sodium intakes were within the same range as those administered in this study. These authors, however, found a weak correlation in infants with the respiratory distress syndrome who were given parenteral loads of sodium (2–8 mEq/kg/day of NaHCO_3).

IS THERE AN ALDOSTERONE METABOLISM PECULIAR TO THE NEONATAL PERIOD?

From our data, there is evidence that both the important metabolic pathways of aldosterone are active in newborns and, as previously reported (10), that the ratio of urinary THA to 3-oxoconjugate is similar to that in the adult. Furthermore, the urinary excretion of the 3-oxoconjugate of aldosterone has been shown to correlate perfectly with the aldosterone secretion rate in infants (14). The triated aldosterone excreted in urine as 3-oxoconjugate was found to be 6–15% of the administered dose (14). Therefore, the excretion of aldosterone metabolites appears to be low in even those newborns whose PA levels were 30–80-fold those of adults. In the absence of available data concerning accurate measurements of the metabolic clearance rate of aldosterone in newborns, this may be considered an indirect argument for a slower rate of metabolism of aldosterone during this period.

CONCLUSION

During the first week of life, PA levels are generally very high but values are widely dispersed. A relative insensitivity of the renal tubule may be involved since low urinary Na:K ratios are accompanied by considerably elevated PA levels. A decrease in the metabolic clearance rate is also possible. We conclude that, in the newborn, both the production and excretion of aldosterone are quantitatively different from those in the adult, and that responses to regulatory factors mentioned above, *i.e.*, variations in volume or sodium intake, are decreased.

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18. Requests for reprints should be addressed to: M. C. Raux-Eurin, M.D., Hôpital Trousseau, 26, Av. du Docteur Arnold Netter, 75012 Paris (France).
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