RENAL EXCRETION OF ELECTROLYTES IN PREMATURE INFANTS DURING ADMINISTRATION OF SODIUM SALTS OF UNREABSORBED ANIONS [1]

By HELEN McNAMARA and HENRY L. BARNETT

(From the Department of Pediatrics, The New York Hospital—Cornell Medical Center, New York, N. Y.)

(Submitted for publication November 24, 1953; accepted January 13, 1954)

The intravenous administration of fluids of high concentrations of sodium salts of anions not reabsorbed by the kidney tubules results, in normal adults (1–3) and children (4), in the excretion of the anions covered principally by sodium. However, in patients with nephrosis (1, 4–6) and in normal subjects given ACTH or cortisone (2, 3), potassium replaces sodium to a variable extent in covering these anions. In the normal dog, as in man, these unreabsorbed anions are excreted covered principally by sodium. However, experimentally decreasing glomerular filtration rate (GFR) acutely in the dog results to a large extent in the replacement of sodium by potassium when sodium salts of these anions are given (7, 8).

Several of these conditions under which sodium salts of unreabsorbed anions are excreted covered principally by potassium rather than by sodium obtain in the healthy premature infant. Thus, it has been observed that the premature infant does not excrete excess sodium as rapidly as the adult (9, 10) which may account for the greater tendency of the premature infant to become edematous. In addition, per unit surface area or per gram of kidney weight, GFR is lower in the premature infant than in the adult (11). For these reasons, it seemed of interest to observe the response of the premature infant to the administration of fluids of high concentrations of sodium salts of anions not reabsorbed by the kidney tubules. The results indicate that the premature infant, like the normal adult, excretes the unreabsorbed anions covered principally by sodium.

[1] This investigation was supported in part by research grants from The National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Public Health Service (A-389) and from The Playtex Park Research Institute.

PROCEDURE

Eight series of observations were made on eight premature infants ranging in age from 12 to 71 days, in weight from 1964 to 2212 Gm., and in surface area from 0.155 to 0.167 M^2. All observations were made in an air-conditioned metabolism unit in which temperature and humidity were maintained at 23° C. and 50 per cent, respectively, and technics previously described (12) were used for collecting blood and urine samples in premature infants.

The premature infants were receiving half-skimmed cow's milk formulas and were offered an additional 30 ml. of water following each of the last three feedings preceding the observations. The usual procedure was to collect urine for one or two control periods after which priming and sustaining infusions of inulin, sodium chloride, p-aminohippurate (PAH) and, in most instances, thiosulfate (S_2O_3) were given (see protocols for dosages and details of each observation). Blood samples were drawn after the control period, after an equilibration period of approximately one hour and at the completion of the observations.

Serum and urine were analyzed for inulin (13), PAH (14), S_2O_3[2] (15), sodium (16), potassium (16), chloride (17–19), bicarbonate (20), and phosphate (21); ammonium ion (22), titratable acid (titrated potentiometrically to pH 7.4), and pH were measured only in

[2] Because of the low GFR and TmPAH in the premature infant, it was not possible even at high concentrations in serum to achieve concentrations of either thiosulfate or PAH in urine comparable to those obtained in adults. For this reason, sodium salts of these two unreabsorbed anions were given together to subjects 3–7. The reported interference (23) in the measurement of thiosulfate by high concentrations of PAH in filtrates of blood was not observed. On the other hand, falsely high values of thiosulfate were found in urines containing high concentrations of PAH. This difficulty was overcome by using the indirect method for urine with the precaution of always providing an adequate excess of iodate. By employing this procedure, good recoveries of thiosulfate were obtained from urines containing concentrations of thiosulfate and PAH within the range of values encountered in these observations.

TABLE I

Protocols and data on effect of infusion of sodium salts of unreabsorbed anions on electrolyte excretion in premature infants

Observation number	Subject	Period	Elapsed time	Urine flow	Inulin clearance	Urine										Blood						
						Na	K	NH_4	TA	PAH	S_2O_3	Cl	HPO_4	HCO_3	pH	Na	K	PAH	S_2O_3	Cl	HPO_4	HCO_3
			min.	*ml./min.*	*ml./min.*	*μEq./min.*										*mEq./L.*						
			0													142.4	6.2	0		109.8	3.8	27.8
1	P. E.	1	15–83	0.10		1.4	6.0	2.1	2.1	0		3.2	6.8	0.2	5.4							
	6-24-52			Priming infusion = 4.0 ml. of 10% inulin and 2.5 ml. of 20% PAH																		
	Age: 16 days		91–306	Sustaining infusion = 0.5 Gm. inulin, 0.7 Gm. PAH and 15.4 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																		
	Wt.: 2031 Gm.		159															65.4				
	SA: 0.156 M^2	2	163–253	0.16	3.3	23.7	6.0	1.7	4.2	12.6		14.9	6.0	0.1	5.5							
		3	253–303	0.27	4.0	40.6	6.9	1.7	2.1	13.7		29.7	4.7	0.4	5.5							
			306													147.0	4.6	48.4		111.8	4.4	23.6
			0													146.0	6.6	0		110.2	4.1	26.2
			15–86	0.11		1.9	7.4	2.8	2.7	0		4.9	6.9	0.3								
2	K. R.			Priming infusion = 4.0 ml. of 10% inulin and 2.5 ml. of 20% PAH																		
	7-22-52	1	89–215	Sustaining infusion = 0.5 Gm. inulin, 0.7 Gm. PAH and 15.4 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																		
	Age: 71 days		134												6.0			54.8				
	Wt.: 2002 Gm.	2	136–177	0.35	6.0	48.2	17.1	2.2	2.7	22.1		35.2	8.5	3.7	5.8							
	SA: 0.155 M^2	3	177–194	0.92	7.2	122.1	19.6	2.3	1.4	24.0		89.8	12.1	13.4	6.8							
		4	194–211	0.79	7.1	100.9	15.0	2.5	1.6	23.6		79.6	9.2	11.7								
			215													141.4	5.9	58.2		112.4	4.6	26.0
		1	0–32	0.14		4.1	8.1			0	0	5.6	8.3					0			5.3	
			46–81	Priming infusion = 4.2 ml. of 10% inulin. Sustaining infusion = 0.5 Gm. inulin and 16.0 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																		
3	P. A.		81–177	Priming infusion = 4.2 ml. of 10% $Na_2S_2O_3$ and 2.6 ml. of 20% PAH																		
	9-16-52			Sustaining infusion = 0.5 Gm. inulin, 0.5 Gm. $Na_2S_2O_3$ and 14.6 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																		
	Age: 24 days		114															38.6	29.0		4.3	
	Wt.: 2075 Gm.	2	118–140	0.19	4.4	32.2	13.9			15.0	15.9	10.1	8.9									
	SA: 0.159 M^2	3	140–156	0.29	4.3	43.1	15.1			15.7	19.7	17.8	10.4									
		4	156–173	0.31	3.7	44.6	12.5			14.1	17.8	19.6	9.1									
			177															48.7	27.3		3.8	
		1	0–14	0.68		6.2	9.9			0	0	7.2	7.8									
		2	14–27	0.65		4.3	8.7			0	0	5.9	7.3									
			45															0	0	98.7		
4	R. O.			Priming infusion = 4.0 ml. of 10% inulin, 4.0 ml. of 10% $Na_2S_2O_3$ and 2.5 ml. of 20% PAH																		
	3-8-53		76–219	Sustaining infusion = 0.5 Gm. inulin, 0.5 Gm. $Na_2S_2O_3$, 0.7 Gm. PAH and 14.6 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																		
	Age: 22 days		149															55.6	31.1	105.7	3.6	
	Wt.: 2097 Gm.	3	153–175	0.25	4.8	39.6	12.3			21.3	16.7	8.6	8.6									
	SA: 0.160 M^2	4	175–193	0.43	5.7	75.8	14.5			22.9	17.9	27.7	11.0									
		5	193–212	0.57	5.5	73.2	11.0			21.8	16.9	27.1	9.9									
			219															50.8	28.2	106.6	3.6	

TABLE I—*Continued*

Observation number	Subject	Period	Elapsed time	Urine flow	Inulin clearance	Urine										Blood						
						Na	K	NH_4	TA	PAH	S_2O_3	Cl	HPO_4	HCO_3	pH	Na	K	PAH	S_2O_3	Cl	HPO_4	HCO_3
			min.	*ml./min.*	*ml./min.*	*μEq./min.*										*mEq./L.*						
5	S. A. 4-28-53 Age: 33 days Wt.: 2159 Gm. SA: 0.164 M^2	1	0–16	0.14		4.9	5.7			0	0	6.3	5.0									
		2	16–32	0.34		8.7	10.3			0	0	10.4	10.1									
			35													136.6	6.3			110.8		
			78–175	Priming infusion = 4.4 ml. of 10% inulin, 5.5 ml. of 10% $Na_2S_2O_3$ and 2.8 ml. of 20% PAH Sustaining infusion = 0.5 Gm. inulin, 0.63 Gm. $Na_2S_2O_3$, 0.75 Gm. PAH and 14.4 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																	
			141													142.0	5.8	57.5	43.3			
		3	144–162	0.31	5.2	51.5	19.0			19.3	23.8	12.4	11.2									
		4	162–177	0.43	5.4	78.2	15.8			17.2	23.2	30.7	11.8									
			178													145.4	5.3	48.3	40.5	115.7		
6	B. R. 5-12-53 Age: 12 days Wt.: 2171 Gm. SA: 0.165 M^2	1	0–16	0.24		4.1	6.0					7.2	5.6									
		2	16–30	0.45		5.5	5.9					8.0	4.9									
			34													137.8	5.6					
			43–229	Priming infusion = 4.4 ml. of 10% inulin, 5.5 ml. of 10% $Na_2S_2O_3$ and 2.8 ml. of 20% PAH Sustaining infusion = 0.5 Gm. inulin, 0.63 Gm. $Na_2S_2O_3$, 0.75 Gm. PAH and 14.4 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																	
			105													143.0		64.0	46.1			
		3	109–139	0.21	4.8	48.0	7.8			20.4	23.7	10.7	9.7									
		4	139–169	0.23	4.9	51.7	8.7			19.2	22.8	11.0	10.5									
			171													142.4	4.7	54.8	40.7			
7	P. U. 5-19-53 Age: 34 days Wt.: 1964 Gm. SA: 0.152 M^2	1	0–44	0.17		2.3	8.3	0.9	1.9	0	0	5.0	3.6	0.5	6.1							
			49													141.1	5.4		0	103.3	3.9	25.9
			55–208	Priming infusion = 3.9 ml. of 10% inulin, 4.9 ml. of 10% $Na_2S_2O_3$ and 2.4 ml. of 20% PAH Sustaining infusion = 0.5 Gm. inulin, 0.63 Gm. $Na_2S_2O_3$, 0.75 Gm. PAH and 14.4 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																	
			127													146.2		59.6	42.8	106.1		
		2	124–154	0.19	4.4	37.8	14.7	1.3	5.2	17.3	21.0	5.3	7.6	0.3	5.0							
		3	154–180	0.30	5.0	56.3	15.0	1.3	3.8	17.9	22.7	14.7	9.6	1.0	6.1							
		4	180–206	0.27	4.2	50.3	13.5	1.3	3.3	15.7	19.5	13.6	9.4	0.9	6.0							
			208													145.6	4.7	53.6	38.2	108.0	3.7	25.9
8	M. A. 12-2-52 Age: 13 days Wt.: 2212 Gm. SA: 0.167 M^2	1	0–20	0.49		10.8	15.1	1.3	2.5			14.8	7.3	1.5	6.5							
			22														6.2					29.5
			22–167	Sustaining infusion = 0.4 Gm. inulin and 16.0 mEq. NaCl per 100 ml., given at 0.5 ml. per min.																		
		2	82–139	0.18	3.6	7.0	6.4	2.3	3.7			9.4	5.6	0.3	5.2							
			114													142.6						26.3
		3	139–166	0.30	4.7	24.7	8.1	2.0	2.9			26.8	6.4	0.7	6.0							
			164																	105.6		27.1

urine. As indicated in the protocols, not all of these measurements were made in each observation.

GFR was estimated in each observation from the clearance of inulin (C_{IN}) during two or three urine collection periods following equilibration. Rates of excretion of electrolytes were calculated as microequivalents (μEq.) per min. Because of variation in the duration of the periods, mean values were calculated by weighting each value by the duration of the period.

RESULTS

The results of a typical observation are shown graphically in Figure 1 and protocols for each of the eight observations are given in Table I. Values for C_{IN} in this group of premature infants ranged from 3.6 to 6.5 with a mean of 4.8 ml. per min. Per 1.73 M^2, these values represent a range from 32 to 59 per cent of the adult mean value and are similar to those previously reported (9). The administration of sodium salts of PAH and S_2O_3 altered the renal excretion of electrolytes as follows:

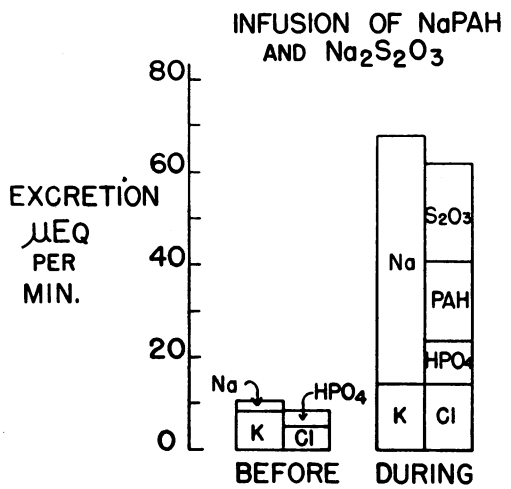

FIG. 1. EFFECT OF INFUSION OF UNREABSORBED ANIONS ON ELECTROLYTE EXCRETION IN A PREMATURE INFANT (SUBJECT P. U.)

Effect on sodium and potassium excretion

In each of the five observations (3–7) where sodium salts of PAH and S_2O_3 were given, there was an increase during the infusion in the absolute rates of excretion of sodium and potassium. However, the increase in rate of excretion of potassium was not even sufficient to cover the increased rate of excretion of chloride and phosphate which made up only 39 per cent of the total measured [8] anions excreted during the infusion. The major fraction (mean: 61 per cent) of the total measured anions excreted during the infusions consisted of PAH and S_2O_3 and the increase in the absolute rate of excretion of sodium was more than sufficient to cover these unreabsorbed anions. Thus, during the control periods the per cent of anions (calculated as the sum of Cl and HPO_4) covered by sodium ranged from 30 to 43 per cent and by potassium from 46 to 97 per cent. During infusions of PAH and S_2O_3, the per cent of anions (calculated as the sum of Cl, HPO_4, PAH, and S_2O_3) covered by sodium ranged from 68 to 87 per cent and by potassium from 13 to 25 per cent. The per cent of anions covered by sodium increased from a mean value of 35 per cent during the control periods to 80 per cent during the infusions while the per cent covered by potassium decreased from 63 to 21 per cent.

In the one observation (Subject 8) in which only sodium chloride was given, the changes in the per cent of anions covered by sodium and potassium were in the same direction as those which occurred during the infusion of PAH and S_2O_3. However, as expected, the magnitude of the changes was smaller.

Effect on other electrolytes

The rate of excretion of chloride increased in each observation. Although the rate of excretion of phosphate during PAH administration did increase over the control value in six of seven observations, in only one instance was the increase greater than two-fold.[4] Where measured, there were no marked and consistent changes in pH of the urine or in the rates of excretion of ammonia (NH_4), titratable acid (TA) or bicarbonate (HCO_3).

[8] During infusions of thiosulfate, sulfate (24) which is excreted at a high rate, was not measured.

[4] West and Rapoport (25) have reported 2.3 to 16-fold increases in the rate of excretion of phosphate following injections of PAH. However, their observations were made immediately after the injection of single large doses of PAH whereas here measurements were made during a continuous infusion and after a priming dose and equilibration period.

DISCUSSION

The mechanism by which, under certain conditions, the renal excretion of unreabsorbed anions (given as sodium salts) is covered principally by potassium rather than sodium is not clear. The present observations show that, in spite of a low GFR, the premature infant, apparently unlike the dog with an equivalent reduction in GFR induced acutely, excretes these anions covered almost wholly by sodium. Available data suggest that excretion of PAH and S_2O_3 covered principally by sodium is not due to any specific limitation in rates of potassium excretion in the premature infant. The highest rate of potassium excretion observed in these infants was 19.6 μEq. per min. representing 45 per cent of the rate of filtration of potassium. Under other conditions in a similar group of premature infants, Tudvad, McNamara, and Barnett (26) observed rates of potassium excretion as high as 34 and 36 μEq. per min., the former representing a value of 172 per cent of the rate of filtration.

SUMMARY

In the premature infant, as in the adult, the administration of sodium salts of the unreabsorbed anions, PAH and S_2O_3, results in the renal excretion of the anions covered principally by sodium.

REFERENCES

1. Burnett, C. H., Burrows, B. A., and Commons, R. R., The lack of correlation between glomerular filtration rate, and serum electrolyte concentration changes, urinary electrolyte excretion, or edema formation following sodium loads in subjects with normal kidneys, glomerulonephritis, and the nephrotic syndrome. J. Clin. Invest., 1949, **28**, 773.
2. Burnett, C. H., The actions of ACTH and cortisone on renal function in man *in* Renal Function. Transactions of the Second Conference, October 19–20, 1950, edited by Bradley, S. E., New York, Josiah Macy Jr. Foundation, 1951, p. 106.
3. Ingbar, S. H., Kass, E. H., Burnett, C. H., Relman, A. S., Burrows, B. A., and Sisson, J. H., The effects of ACTH and cortisone on the renal tubular transport of uric acid, phosphorus, and electrolytes in patients with normal renal and adrenal function. J. Lab. & Clin. Med., 1951, **38**, 533.
4. Metcoff, J., and Wallace, W. M., The nephrotic syndrome in children: response to intravenous sodium loads. J. Clin. Invest., 1950, **29**, 835.
5. Metcoff, J., Rance, C. P., and Nakasone, N., Observations on renal mechanisms for sodium and potassium excretion in ACTH-induced diuresis of nephrotic edema. J. Clin. Invest., 1951, **30**, 661.
6. Metcoff, J., The Nephrotic Syndrome 1951. Third Annual Conference on The Nephrotic Syndrome, edited by Metcoff, J., New York, The National Nephrosis Foundation, Inc., 1953, p. 37.
7. Lauson, H. D., Fourth Annual Conference on The Nephrotic Syndrome 1952, edited by Metcoff, J., New York, The National Nephrosis Foundation, Inc., 1953, p. 85 (mimeographed).
8. Lauson, H. D., and Thompson, D. D., Effects of decrease in glomerular filtration rate on cation excretion during loading with nonreabsorbable anions. Federation Proc., 1953, **12**, 83.
9. Gordon, H. H., Levine, S. Z., Wheatley, M. A., and Marples, E., Respiratory metabolism in infancy and in childhood. XX. The nitrogen metabolism in premature infants—comparative studies of human milk and cow's milk. Am. J. Dis. Child., 1937, **54**, 1030.
10. Dean, R. F. A., and McCance, R. A., The renal responses of infants and adults to the administration of hypertonic solutions of sodium chloride and urea. J. Physiol., 1949, **109**, 81.
11. Barnett, H. L., and Vesterdal, J., The physiologic and clinical significance of immaturity of kidney function in young infants. J. Pediat., 1953, **42**, 99.
12. Barnett, H. L., Hare, K., McNamara, H., and Hare, R., Measurement of glomerular filtration rate in premature infants. J. Clin. Invest., 1948, **27**, 691.
13. Schreiner, G. E., Determination of inulin by means of resorcinol. Proc. Soc. Exper. Biol. & Med., 1950, **74**, 117.
14. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M., The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Invest., 1945, **24**, 388.
15. Newman, E. V., Gilman, A., and Philips, F. S., The renal clearance of thiosulfate in man. Bull. Johns Hopkins Hosp., 1946, **79**, 229.
16. Fox, C. L., Jr., Stable internal standard flame photometer, for potassium and sodium analyses. Anal. Chem., 1951, **23**, 137.
17. Van Slyke, D. D., and Hiller, A., Application of Sendroy's iodometric chloride titration to protein-containing fluids. J. Biol. Chem., 1947, **167**, 107.
18. Van Slyke, D. D., Nomogram for correction of low urine chloride values determined by the silver iodate reaction. J. Biol. Chem., 1947, **171**, 467.
19. Schales, O., and Schales, S. S., A simple and accurate method for the determination of chloride in biological fluids. J. Biol. Chem., 1941, **140**, 879.
20. Van Slyke, D. D., and Neill, J. M., The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. J. Biol. Chem., 1924, **61**, 523.

21. Fiske, C. H., and Subbarow, Y., The colorimetric determination of phosphorus. J. Biol. Chem., 1925, **66**, 375.

22. Conway, E. J., Microdiffusion Analysis and Volumetric Error, 3rd revised ed., London, C. Lockwood, 1950, p. 95.

23. Elliott, S. R., II, and Scott, H. W., Jr., Effect of para-aminohippuric acid on sodium thiosulfate determinations in renal clearance studies. Bull. Johns Hopkins Hosp., 1948, **83**, 213.

24. Theis, F. V., and Freeland, M. R., Thromboangütis obliterans. Treatment with sodium tetrathionate and sodium thiosulfate. Arch. Surg., 1940, **40**, 190.

25. West, C. D., and Rapoport, S., Urinary excretion of phosphate following the injection of sodium p-aminohippurate. Proc. Soc. Exper. Biol. & Med., 1949, **71**, 322.

26. Tudvad, F., McNamara, H., and Barnett, H. L., Renal response of premature infants to administration of bicarbonate and potassium. Pediatrics, 1954, **13**, 4.