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Concentration Changes in Urinary Electrolytes Produced by Mercurial Diuretics.* (19956)

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Mercurial diuretics usually produce an increase in sodium and chloride excretion by increasing the urine volume and by increasing the urinary electrolyte concentrations. Under certain conditions mercurials can decrease urinary sodium and chloride concentrations. An attempt will be made to define the conditions which determine these different changes in urinary electrolyte concentrations.

Methods. Both anesthetized and unanesthetized dogs were used. Anesthesia was produced by means of an intravenous injection of 30 mg of pentobarbital per kg and the depth of anesthesia was kept constant by infusing 0.3 to 0.4 mg of pentobarbital per kg per minute. The dogs received infusions of 3% glucose or 2% sodium chloride. The constant rate of infusion was varied between 1.8 and 17 cc per minute per m^2 of body surface. Para-aminohippurate (PAH) clearance at low plasma concentrations was considered to be the renal plasma flow (RPF) while inulin or creatinine clearance was used as an index of glomerular filtration. Sodium and potassium were determined in plasma and urine by means of an internal standard or a Beckman flame photometer. Chloride was determined by the method of Van Slyke and Hiller(1). In general, the methods used were essentially similar to those used in a previous study(2). The experiments on unanesthetized animals were conducted on trained female mongrel dogs weighing 18 to 22 kg. Isotonic saline infusions were given into a leg vein and blood specimens were obtained from an external jugular vein. Urine was collected by means of a self retaining soft rubber catheter. About one hour following the start of the saline infusion, 0.1 unit of pituitrin was injected intramuscularly and enough pituitrin was added to the infusion fluid to give a constant injection rate of about 200 milliunits per hour. After pituitrin had been injected for approximately one hour, 8 mg per kg of mersalyl was given together with glutathione or cysteine. The procedures and analytical methods used in these experiments were essentially the same as those described for the anesthetized group

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of animals. The mercurial diuretics used were mersalyl or Esidron acid.[*] Both substances were used without aminophylline and the acids were dissolved in isotonic saline by means of sodium hydroxide. In most instances the mercurials were given together with cysteine or glutathione in a 1:1 molar ratio(3,4). Three experiments were conducted on rats using essentially the same technic as described by Burn(5) for the assay of antidiuretic hormone. Water was given by a stomach tube (5 cc per 100 g of body weight) followed by the subcutaneous injection of 2 milliunits of pitressin per 100 g of body weight. Mersalyl and cysteine (1:1 molar ratio) were given intramuscularly in a dose of 1 or 3 mg per 100 g of body weight

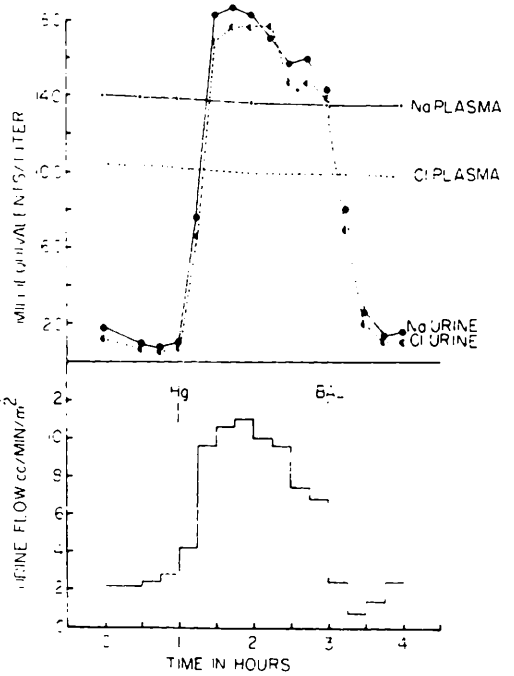

FIG. 1. Effect of mersalyl on urine flow and urinary sodium and chloride concentration during an infusion of .25% sodium chloride in 3% glucose. ♀ dog 14.3 kg, pentobarbital anesthesia, intrav. infusion of .25% sodium chloride in 3% glucose at a rate of 6.4 cc/min./m² body surface. At Hg inj. of 25 mg of mersalyl and cysteine (1:1 molar ratio) per kg. At BAL 10 mg of 2,3 dimercaptopropanol/kg intramusc.

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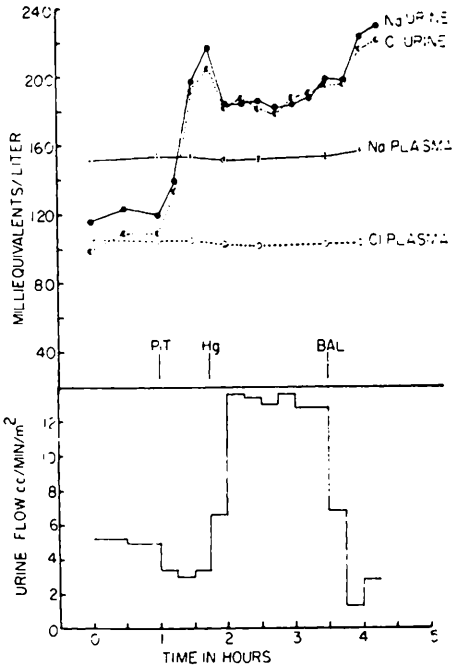

FIG. 2. Mersalyl diuresis during a pituitrin infusion. ♀ dog 14.8 kg, unanesthetized; infusion of .86% sodium chloride at 7 cc/min./m² body surface. At Pit.: start i.v. infusion of pituitrin 10 milliunits/kg/hr. At Hg: intrav. inj. of 30 mg of mersalyl and cysteine (1:1 molar ratio)/kg. BAL: 8 mg of 2,3 dimercaptopropanol/kg intrav.

15 to 20 minutes before the administration of the water and pitressin. The time required for the excretion of 50% of the water load was calculated and was used an an index of activity.

Results. The results were essentially the same in the anesthetized and unanesthetized animals. Mersalyl and Esidron acid were shown to have similar qualitative and quantitative actions on urinary flow and electrolyte excretion(2) and in the present study most of the experiments were conducted with mersalyl.

Mercurial effects during the infusion of hypotonic saline. The infusion of 3% glucose or hypotonic saline (0.2% NaCl in 3% glucose) resulted in low urinary electrolyte concentrations, minimal values being attained within 2 to 3 hours after the start of the infusion. The mercurial produced an increase in urine flow and an increase in the urinary sodium and chloride concentration. This increase in sodium and chloride concentration approached and in some instances even ex-

TABLE I. Effect of an Injection of Mersalyl into the Left Renal Artery on Urine Flow and Electrolyte Excretion. Male dog 23 kg, pentobarbital anesthesia, I.V., infusion of 3.8 cc/min. of a 3% glucose solution. 30 mg of mersalyl was injected into the left renal artery. Determinations were made on separate kidneys.

Time, min.	Urine flow, cc/min.		Glomerular filtration, cc/min.		Plasma sodium, mM/l	Urinary Na, conc., mM/l		Na excretion, microequiv./min.	
	Right	Left	Right	Left		Right	Left	Right	Left
0– 30	.17	.16	22.8	25.3	126	9	7	1.53	1.12
30– 50	.68	.80	21.5	25.8	128	1.5	1.5	1.02	1.20
50– 52				Mersalyl 30 mg into left renal artery					
50– 70	.70	.80	28.2	31.1	127	.90	.94	.63	.75
70– 85	.17	2.43	27.5	23.7	126.5	17.8	152	3.03	369.4
85–100	.27	2	29.2	28.2	127	3.1	144	.83	288
100–115	.25	1.13	30.7	26	128	2.6	124	.65	140
115–130	.17	.48	25.7	30.5	125	4.1	123	.69	59.4
130–145	.20	.23	26.3	31	122	6.1	93	1.22	21.4
145–160	.25	.30	29.5	28.2	124	4.2	85	1.05	25.5

TABLE II. Action of Mersalyl on Urinary Sodium and Chloride Concentration and Excretion during a Hypertonic Saline Infusion. Male dog 12.3 kg, pentobarbital anesthesia. Infusion of 2% sodium chloride intravenously, at a rate of 12.5 cc/m² body surface/min. All values are based on one m² of body area.

Time, min.	Urine flow, cc/min.	GFR, cc/min.	Plasma Na, mM/l	Urinary Na conc., mM/l	Na excreted, mM/min.	Plasma Cl, mM/l	Urinary Cl conc., mM/l	Cl excreted, mM/min.
0– 20	14	123	161.3	198.5	2.78	125	185	2.59
20– 40	13.4	125	165.8	232	3.10	129	222	2.97
			Mersalyl with cysteine, 25 mg/kg i.v.					
40– 60	11.28	98.3	165	233.7	2.64	129	229	2.58
60– 80	10.93	97	165.3	224.2	2.45	129	221	2.42
80– 90	17.5	102.6	169.4	206	3.61	134	204	3.57
90–100	22.2	100.9	171.9	204	4.53	136	201	4.46
100–110	22.8	98.3	174.9	215	4.90	139	213	4.86
110–120	19	87.8	173.7	210	4	139	210	3.99
			BAL, 5 mg/kg i.v.					
120–140	10	73.4	183.6	215	2.14	150	214	2.14
140–160	6	91.6	181.8	235.6	1.40	149	232	1.39
160–180	9.8	99.5	182	236.8	2.32	149	232	2.27

ceeded that of plasma (Fig. 1). This overshoot was more commonly seen with chloride than with sodium probably because plasma chloride was lower than the plasma sodium concentration. In 4 of our experiments urinary sodium concentration exceeded that of plasma by 20 to 40 milliequivalents following the mercurial injection. In 5 successful experiments the mercurial was injected into the left renal artery and produced a unilateral diuresis(6). In 2 of these experiments the injection of 20 mg of mersalyl into the left renal artery resulted in a unilateral diuresis and increase in sodium concentration which exceeded that of the plasma by about 25-30 milliequivalents (Table I).

Mercurial effects during the infusion of hypertonic saline. Two per cent sodium chloride was infused into 5 anesthetized dogs. In 3 of these the urinary sodium and chloride concentration was above that of plasma by about 50 to 70 milliequivalents. The injection of the mercurial resulted in a reduction of the urinary sodium concentration; however, the mercurial induced volume changes resulted in a net increase in sodium and chloride excretion. In all 3 instances the urinary sodium and chloride concentration after the mercurial

TABLE III. Action of Mersalyl on Pitressin Antidiuresis in the Rat. All animals received 50 cc/kg of distilled water by mouth. Pitressin was given subcutaneously while mersalyl with cysteine (1:1 molar ratio) was given intramuscularly. Each group consisted of 3 rats weighing 200 to 265 g, 3 experiments were conducted.

	50% excretion time in min.	Avg
Control	75, 68, 70	71
Mersalyl, 10 mg/kg	60, 63, 68	64
" 30 "	67, 70, 59	66
Pitressin, 20 m units/kg	143, 132, 137	137
Mersalyl, 10 mg/kg + pitressin, 20 m units/kg	135, 129, 135	133
Mersalyl, 30 mg + pitressin, 20 m units/kg	125, 135, 130	130

remained well above that of plasma (Table II).

Mercurial effects during pituitrin infusion. Four anesthetized and 3 unanesthetized dogs were infused with isotonic saline at a rate of about 7 to 15 cc per minute per m^2 of body surface. After an adequate control period pituitrin was added to the infusion field. In both the anesthetized and unanesthetized dogs, the pituitrin effects were variable. Pituitrin antidiuresis was observed in 3 dogs of this series (Fig. 2) and in the remaining dogs, pituitrin increased urine flow. However, pituitrin, regardless of the urine volume response, always increased the concentration of sodium and chloride ions in the urine and in 3 instances it raised the concentration of these ions appreciably above those of plasma sodium and chloride concentrations. The administration of a mercurial after pituitrin increased urine flow and the net sodium and chloride excretion in every one of our experiments. In those experiments in which urinary sodium and chloride concentrations were above those of plasma, the mercurial produced a significant reduction in the urinary concentration of these ions. However, following the mercurial the urine was still hypertonic to plasma as regards sodium and chloride (Fig. 2).

Pituitrin antidiuresis and mersalyl in rats. In these experiments 10 mg and 30 mg of salyrgan with cysteine per kg were given intramuscularly followed by the oral test dose of water and the subcutaneous injection of pitressin. It can be seen from Table III that the mercurial in either dose decreased slightly the 50% excretion time of the water load. Pitressin alone produced a marked increase in the excretion time while pitressin and the mercurial given together had about the same effect as pitressin alone. The effects of the mercurials on urinary potassium excretion were variable. As has been described by Mudge *et al.*(7), mercurials increased net potassium excretion when urinary potassium was low and decreased it when it was high. However, under all conditions of the present experiments urinary potassium concentration was decreased by the mercurial.

Discussion. The results clearly indicate that the mercurial does not block the ability of the kidney to produce a hypertonic urine as regards sodium and chloride nor does it block the antidiuretic effect of pitressin. These findings are in agreement with those of Weston *et al.*(8) and Pitts *et al.*(9). It must be concluded that the mercurials do not interfere with those renal tubular mechanisms involved in the production of a hypertonic urine nor do they impair the ability of the tubules to respond to pitressin. In contrast the mercurial diuretics counteract the effects of the salt retaining adrenal cortical hormones(10). A possible mechanism of the mercurial diuretics suggested by Mudge, Foulks, and Gilman(11), and Weston *et al.* (8) could be the inhibition of proximal tubular reabsorption of water, sodium and chloride. In this part of the tubule, the reabsorption of fluid and salt has been postulated to be isosmotic to glomerular filtrate. The inhibition of this reabsorptive mechanism would thus result in the addition to the control urine of electrolytes equivalent in amounts to those present in glomerular filtrate. Thus if the urine is hypotonic to plasma as regards sodium and chloride, the addition of glomerular filtrate should increase the above urinary electrolyte concentrations. On the other hand, if the control urinary sodium and chloride concentration is hypertonic to plasma the addition of glomerular filtrate should decrease the urinary sodium and chloride concentrations. If this hypothesis is correct, urinary

sodium and chloride concentrations after the mercurial should not exceed those of plasma. However, we have demonstrated that the urinary sodium concentration can increase to levels significantly higher than those of plasma (Fig. 1). A possible cause for this overshoot phenomenon could be the release of antidiuretic hormone by the mercurial and the additive effects of these 2 substances could explain this overshoot phenomenon. Pack (12) and Kuschinsky(13) have shown that following the injection of mercury into rats the concentration of oxytocic and antidiuretic principles of the pituitary gland are reduced. If the release of antidiuretic hormone were the cause of the overshoot shown in Fig. 1 this overshoot should not occur if a unilateral diuresis is produced by injecting the mercurial into one renal artery. This overshoot can occur under the above experimental conditions and it must be concluded that this phenomenon is due to some direct action of the mercurial on the kidney. Another possible explanation could be that the mercurial sensitized the kidney to circulating antidiuretic principle. The experiments on rats reported here do not support this explanation (Table III). The above findings make it rather difficult to explain the effects of mercurials as being on either the proximal or distal convoluted tubule. The possibility of more than one site of renal action of mercurials must be considered.

Summary. 1. The mercurial diuretics increase sodium and chloride concentration in the urine when these ions are hypotonic to plasma. The mercurial induced increase in the urinary sodium and chloride concentrations can exceed those of plasma by a significant amount. 2. When urinary sodium and chloride concentrations are above those of plasma the mercurials reduce the concentration of these ions significantly. The ability of the kidney to produce hypertonic urine is not inhibited by mercurial diuretics. 3. Pituitrin induced antidiuresis and hypertonicity of the urine are not abolished by maximally effective doses of mercurial diuretics.

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Mating Types in *Stylonychia putrina*. (19957)

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Although conjugation in ciliated Protozoa was long extensively studied, especially by Maupas(1), mating types were first discovered by Sonneborn(2). It is now known that mating types exist in *Paramecium aurelia*(2,3), *P. bursaria*(4-6), *P. caudatum*(7-11), *P. multimicronucleatum*(11), *P. trichium*(12), *P. calkinsi*(12-14), and *Euplotes patella*(15). In several of these species, a number of varieties have been recognized, each with its distinctive mating types; and the number of interbreeding mating types within a variety