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Research Article

POTENTIATION OF DIURETIC ACTION OF MERCUHYDRIN [1] BY AMMONIUM CHLORIDE [2]

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Potentiation of the diuretic action of mercurials by acidifying salts is well known (1–7). That the effect is synergistic and not merely additive was conclusively demonstrated by Ethridge, Myers and Fulton (8). The mechanism of this synergism is not well understood, and reports as to its nature are conflicting. Acidosis as the responsible factor has been emphasized by several investigators (1, 4, 8). This view also received support when it was noted that the administration of alkalinizing salts actually diminished the efficacy of mercurial diuretics (8). There are others, however, who observed potentiation of the mercurial effect persisting in the presence of a normal plasma acid-base balance in edematous patients receiving prolonged ammonium chloride administration (6, 7). Blumgart and associates reported a case in which the correction of a severe acidosis by alkali therapy restored responsiveness to a mercurial diuretic in a nephritic patient (9). Most recently, it has been noted that in dogs rendered acidotic by inhalation of 7% CO_2 there is no enhanced activity from the injection of a mercurial diuretic (10).

Since the one study of the combination of mercurials and ammonium chloride in normal individuals did not deal with effects on plasma acidity (11), it was considered of interest to determine whether any synergism would continue to exist after compensatory return of the plasma acid-base balance to normal. This normal balance can be achieved during prolonged administration of the salt to subjects in whom there is no disturbance in renal function or in fluid and electrolyte excretion. The mechanisms of this compensation have been investigated and thoroughly discussed elsewhere (12–14).

SUBJECTS AND MATERIALS

Twenty-four-hour urine volume and sodium, potassium, chloride and ammonia excretion were measured for a period of 80 consecutive days in five normal young adult male subjects. Fluid intake was allowed *ad lib*, but sodium chloride intake was held constant at 6 gms. per day. Arterialized venous blood samples (15) were drawn every seven days (three hours after the morning meal) and analyzed for pH, carbon dioxide content, sodium, potassium and chloride. Plasma bicarbonate was calculated from pH and carbon dioxide content by means of the Henderson-Hasselbach equation, using a pK of 6.1 for carbonic acid. Urine pH was also determined at the same time from a small specimen of urine voided directly into mineral oil. The chemical methods employed have been described in an earlier publication from this laboratory (16).

Each subject received an intramuscular injection of 2 ml. of Mercuhydrin at seven-day intervals throughout the 80-day period of study. The injections were given in the morning immediately following the withdrawal of the blood sample. After three control injections, ammonium chloride (uncoated tablets) was administered in a dosage of 2 gms. t.i.d. (with each meal) and continued for 30 days. The timing was such that mercurial injections were given on the days of maximum acidity and alkalinity of the plasma, respectively three days after starting and three days after stopping the ammonium chloride administration. A total of 11 mercurial injections were given to each subject during the 80-day period—three control, four during ammonium chloride administration, and four additional control injections.

RESULTS

The plasma and 24-hour urine electrolyte values for each day Mercuhydrin was given are tabulated in Tables I and II. It can be seen that the diuretic effect on water, sodium and chloride excretion is enhanced two-fold during the phase of ammonium chloride administration. Potassium excretion following mercurial injections during the two control periods (injection Nos. 1–3 and 8–11) did not differ from days on which no mercurial was given.

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TABLE I

Potentiation of mercurial diuresis maintained in presence of normal plasma acid-base balance achieved during prolonged NH_4Cl administration

		CONTROL			NH_4Cl 113 mEq/day				CONTROL			
Mercurial Injection No.[a]		1	2	3	4	5	6	7	8	9	10	11
Subj. Bo.	pH[b]	7.40	7.41	7.40	7.33	7.35	7.38	7.40	7.43	7.39	7.39	7.40
	HCO_3^-[c]	27	28	25	19	27	28	27	29	26	27	27
	Na^+[c]	136	136	134	134	136	134	137	138	138	137	139
	Vol.[d]	1380	1680	1550	2400	2400	2790	2820	1230	1570	1370	1700
Subj. Cu.	pH	7.41	7.41	7.40	7.31	7.36	7.37	7.39	7.43	7.39	7.40	7.40
	HCO_3^-	29	27	26	21	25	27	26	30	27	26	26
	Na^+	140	136	135	138	137	137	140	142	141	130	141
	Vol.	1560	2600	1700	3600	3320	3360	3550	2250	1900	2600	2520
Subj. La.	pH	7.40	7.41	7.41	7.32	7.40	7.41	7.41	7.44	7.41	7.41	7.40
	HCO_3^-	24	25	24	17	24	24	23	29	25	25	26
	Na^+	140	137	137	136	135	135	137	138	137	136	137
	Vol.	2850	2970	2570	4080	3810	3650	3650	3000	2100	2480	2280
Subj. Ni.	pH	7.40	7.40	7.39	7.32	7.36	7.38	7.39	7.43	7.39	7.41	7.40
	HCO_3^-	27	24	24	20	24	26	26	30	26	25	25
	Na^+	142	138	138	137	137	137	138	138	141	140	141
	Vol.	1200	1380	1170	2100	3000	2100	2700	970	1200	1100	1140
Subj. Wr.	pH	7.41	7.41	7.40	7.33	7.35	7.37	7.40	7.44	7.40	7.40	7.39
	HCO_3^-	27	25	27	19	23	26	26	30	26	26	26
	Na^+	140	137	138	137	137	136	139	139	140	139	139
	Vol.	1160	1180	1350	2850	3040	3220	3310	1420	1300	1480	1100

[a] 7 days interval between injections. Nos. 4 and 8 respectively 3 days after starting and 3 days after stopping NH_4Cl.
[b] Plasma pH.
[c] Plasma values in mEq/L.
[d] Urine volume in ml/24 hours.

TABLE II

Effect of mercurial diuretic on electrolyte excretion during prolonged NH_4Cl administration*

		CONTROL			NH_4Cl 113 mEq/day				CONTROL			
Mercurial Injection No.		1	2	3	4	5	6	7	8	9	10	11
Subj. Bo.	Na^+	206	184	189	266	252	258	302	180	172	184	192
	NH_4^+	24	40	20	85	87	79	80	33	36	35	40
	Cl^-	202	184	199	365	358	366	413	170	211	197	208
	K^+	42	48	53	66	76	76	84	53	59	46	55
Subj. Cu.	Na^+	144	190	130	302	268	252	334	125	102	153	140
	NH_4^+	23	35	30	110	98	96	94	37	30	42	45
	Cl^-	172	188	143	440	400	370	460	130	118	184	141
	K^+	42	51	53	73	73	66	82	48	50	48	49
Subj. La.	Na^+	300	302	270	430	395	350	364	359	228	277	267
	NH_4^+	16	18	22	90	90	92	99	29	37	19	21
	Cl^-	328	319	309	540	500	450	491	387	236	281	294
	K^+	95	99	95	119	95	95	109	61	96	88	111
Subj. Ni.	Na^+	162	152	182	212	289	208	320	132	149	121	166
	NH_4^+	26	37	24	82	85	87	86	29	24	30	32
	Cl^-	171	175	177	328	449	325	435	150	162	145	172
	K^+	79	54	57	82	116	92	97	60	84	64	56
Subj. Wr.	Na^+	228	212	227	413	354	377	440	260	262	252	241
	NH_4^+	24	28	29	83	85	104	98	26	29	32	33
	Cl^-	241	222	249	519	500	540	554	264	252	276	245
	K^+	39	45	49	70	82	86	91	35	62	50	40

* All values in mEq/24 hours. This table is constructed identically to Table 1.

The slight increase during the period ammonium chloride was given (injection Nos. 4–7) was compensated for by decreased excretion on the day following diuresis, and there was no change detected in any of the weekly plasma levels.

It is apparent from the data shown in Tables I and II that the potentiating effect persists despite return of the plasma acid-base balance to normal. The degree of potentiation observed when there was no acidosis present (injection No. 7) was equal to that during the most acidotic period (injection No. 4). Plasma chloride, not tabulated, in every instance reciprocated the changes in plasma bicarbonate. There was no significant change in plasma sodium at any time during the period of study. Retention of sodium and chloride occurred for two to three days following each diuretic day, and was most marked during the period of potentiated injections. This is shown in Figures 1 and 2 in which complete data on water, sodium and ammonia excretion from two representative subjects have been charted. It can also be seen that ammonia excretion was unaltered by the mercurial injections.

Urinary pH in all subjects was between 4.5 and 5.0 during the administration of ammonium chloride. In four instances, this represented a drop of about one pH unit from control values. In Subject Ni. urine pH, low to begin with, did not drop further upon administration of the salt. Urinary titratable acidity was not determined; but it is possible that it was increased during this period since, in terms of the chloride ingested as ammonium chloride, ammonia synthesis by the kidney was

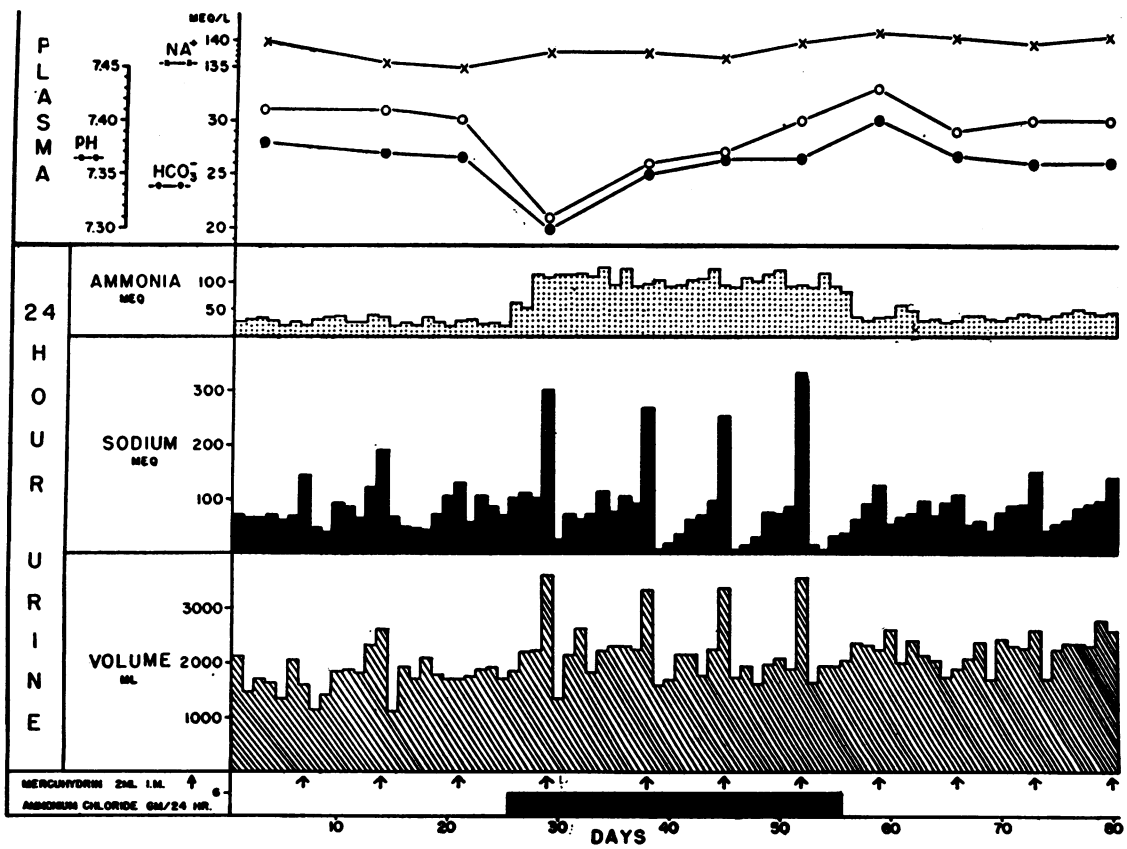

FIG. 1. SUBJECT CU.

Twenty-four-hour excretion of ammonia, sodium, and water is plotted in the lower part of the figure; plasma pH, sodium, and bicarbonate concentrations in the upper part. Note enhanced effect of Mercuhydrin injections (indicated by the arrows) on sodium and water excretion during the entire period of ammonium chloride administration, irrespective of changes in plasma pH and bicarbonate. Decreased excretion of sodium on the days following mercurial diuresis is also evident.

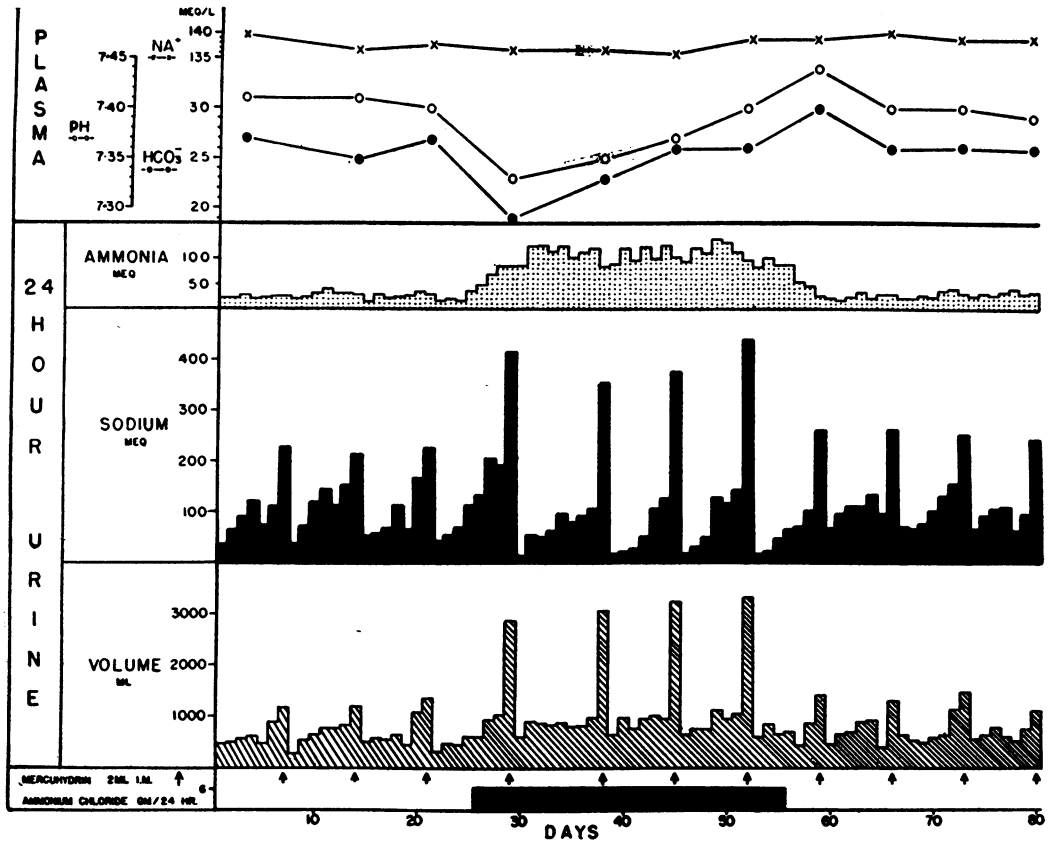

FIG. 2. SUBJECT WR.

This figure is otherwise identical to Figure 1.

consistently less than intake in all five subjects (Table II). It is also possible that increases in unmeasured calcium and magnesium excretion occurred, or that there was incomplete absorption of the ammonium chloride tablets in the intestinal tract. Either of these situations could well account for this slight deficit.

It should also be noted that at the time of the alkalosis which followed discontinuance of ammonium chloride (injection No. 8) there was no inhibition of the mercurial effect. Sodium and chloride output was equal to, and in one instance (Subject La.) greater than, that on other control days.

DISCUSSION

It is apparent that the synergistic effect of ammonium chloride on the diuretic action of Mercuhydrin is independent of the pH and bicarbonate concentration of the plasma. The data support the view (10) that acidosis *per se* is not the decisive factor. By the same token, an alteration of the anion pattern of the extracellular fluid, *i.e.* an increase in the plasma concentration of chloride at the expense of bicarbonate (10, 17), is equally unlikely inasmuch as the potentiation continued in the presence of subsequent normal bicarbonate and chloride concentrations. Moreover, no diminution beyond the control effect occurred when the subjects were alkalotic. It is possible, of course, that increases in total body chloride occurred and might account for the observed results. Against this is the observed potentiation of mercurial diuresis in edematous patients receiving cation exchange resins (18). These resins produce a deficit of fixed base in the extracellular fluid, and thereby cause an acidosis which when compensated is characterized by either normal or increased plasma chloride concentrations (18, 19). In any event, however, it is extremely unlikely that increases in total body chloride content occur under these conditions.

Furthermore, it has been shown that the administration of potassium chloride does not enhance the diuretic effect of certain organic mercurials (8). This has been confirmed by administering potassium chloride in amounts of 113 meq. per day to subject Wr. under conditions identical to those described earlier for the study of the effect of ammonium chloride. Ingestion of the potassium salt was begun four days following mercurial injection No. 11 (Table II) and continued for three weeks. The average 24-hour excretion rates of water, sodium and chloride for the control injections (Nos. 8–11) were 1,325 ml., 253 meq., and 259 meq., respectively (calculated from Tables I and II). The average excretion rates for these same substances during potassium chloride administration (three mercurial injections at weekly intervals) were 1,330 ml. water, 218 meq. sodium, and 341 meq. chloride. Plasma electrolyte pattern and acid-base concentration during this latter period did not differ from that of the control period. The increase in chloride excretion was covered by an equal amount of potassium. These observations demonstrate the absence of any enhancing effect of potassium chloride on the excretion of water and sodium following mercurial injections in the normal human subject.

The potentiating effect on sodium excretion cannot be accounted for on the basis of mercurial inhibition of ammonia synthesis since the 24-hour output on the days of mercurial administration did not differ from that on non-mercurial days. Moreover, during the two control periods, endogenous ammonia excretion was similarly unaltered.

Increased acidity of the urine with resulting increase in the concentration of ionized mercury within the tubular cell is a possibility that must be considered. It has been postulated that organic mercurials act by liberating mercury ions (20). The general acceptance of this concept has led to the view that the potentiating effect of acidifying salts is due to an increase in the dissociation of mercury from its organic complex although there is no real evidence to support such an idea. Actually, *in vitro* studies indicate that at least 40% of some organic mercurials would have to be ionized in order to account for their effects on this basis (21). Moreover, in experiments on the isolated rabbit kidney cortex, it has been shown that altering the pH of the medium has no effect on the degree of inhibitory action of Mercuhydrin on certain transport mechanisms (22). In order to implicate urine acidity as affecting the degree of dissociation of organic mercury, the assumption must be made that the mercury ion enters the tubular cell by reabsorption from the glomerular filtrate, and not directly from the blood stream in the course of secretion. If the latter were the case, persistence of the potentiating effect in the presence of normal plasma acid-base concentrations would be difficult to explain on the basis of an increase in the dissociation of the organic mercurial. In view of these considerations, and from the evidence that in one subject there was no change in urinary pH during the period of potentiation, there is little support for the concept that a change in the ionization of Mercuhydrin could account for the observed enhancement.

Small rises in filtration rate, undetectable by present clearance techniques, could conceivably be of significance. It has been shown that raising (23), or lowering (24), glomerular filtration rate profoundly alters the renal response to mercurial diuretics. A corollary to this, however, is that tubular function as regards absolute sodium and chloride reabsorption remains constant. This would seem to be a very unlikely occurrence.

The most reasonable hypothesis would therefore appear to be that some as yet undefined alteration in the metabolism of the tubular cells is an influencing factor. Whether this leads to the accumulation of a greater concentration of Mercuhydrin within the cell, or whether in some manner the equilibrium reaction between the mercurial and the susceptible enzyme is shifted towards the formation of a more stable complex is, of course, purely speculative.

SUMMARY

Data have been presented showing that in normal subjects potentiation of a mercurial diuretic by ammonium chloride administration is not dependent on any alteration in plasma acid-base balance.

The possible nature of this mechanism has been discussed.

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