Thiocyanate Effect on Sodium Excretion in Normotensive and Hypertensive Subjects.* (19806)

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Although a half-century has passed since the introduction of thiocyanate into the treatment of hypertensive vascular disease, little is known about the mechanism of its depressor action. Effects on cell permeability(1), a parathyroid-like action upon the kidney(2), the production of changes in the adrenal cortex (3) and inhibition of amino-acid oxidation (3a) have been suggested. The recent finding of cyanide in the blood of animals and man following administration of thiocyanate (4) may indicate the operation of yet other mechanisms. In order to investigate the role of thiocyanate-induced sodium depletion as a possible factor in its hypotensive action, balance studies were undertaken before and during administration of this agent for short periods. For comparison, both normotensive and hypertensive subjects were included.

Methods. Following a control period of 6 or more days on a constant dietary and fluid intake, potassium or sodium† thiocyanate was given by mouth twice daily for 4 days to 16 patients with uncomplicated hypertensive vascular disease and to 26 normotensive subjects. With the exception of 9 members of the hypertensive group who were ambulatory hospital patients, all subjects carried on their customary activities, but took their meals, prepared by the metabolism ward dieticians, under supervision at the hospital throughout the study. Individuals with albuminuria, impaired urinary concentrating ability, diarrhea, fever, complicating respiratory or other infections were excluded from the study. Blood samples were drawn fasting, immediately before the first, and 12 hours following the fourth and eighth doses of thiocyanate. Peak serum thiocyanate concentrations ranged between 2.8 and 6.9 mg per 100 ml. In the normotensive group, the calculated daily sodium intake, constant in each subject, was varied between 75 and 233 mEq in different subjects with a mean of 139 mEq; corresponding values for the hypertensive series were, respectively 18, 227 and 138 mEq. The daily urinary sodium excretion was determined in all subjects, and the output of potassium, chloride and thiocyanate in most. Analysis of serum concentrations of sodium, potassium(5), chloride(6), bicarbonate(7) and thiocyanate(8) was made in a majority of the experiments. Urine volume and body weight were recorded daily, and whole blood cyanide concentrations(9) were measured in two hypertensive subjects.

Results. The average daily urinary excretions of sodium during the last 4 days of the control period and during the 4-day experimental period were compared. An increase over baseline values was observed in most normotensive and all hypertensive subjects, the mean change amounting to 16 and 26 mEq per day, respectively (Tables I and II). Among 26 normotensive subjects, the average daily urinary sodium output during thiocyanate administration exceeded the intake in seven. In contrast, all 16 hypertensive patients went into negative sodium balance during this period.

Small decreases in weight and increases in urine volume were generally observed. Chloride excretion roughly paralleled the sodium output; the urinary potassium remained essentially constant. Alterations in the levels of serum sodium, potassium, chloride bicarbonate and total protein appeared to be neither consistent nor significant. Whole blood cyanide concentrations in two hypertensive patients were 0.05 and 0.1 mg per 100

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† The sodium salt was given to 6 hypertensive patients. Appropriate corrections were made for the additional intake of sodium.

TABLE I.
Sodium Balance in Normotensive Subjects.

Subject	Sodium intake, mEq/24 hr	Avg 24 hr control urine sodium output, mEq/24 hr	Change in sodium output, mEq/24 hr
Group A—Low sodium intake			
1	81	68	—12
2	77	61	+12
3	79	49	+16
4	86	49	+43
5	83	63	— 3
6	83	60	+14
7	88	67	— 2
8	87	52	+21
9	75	52	+15
10	80	80	+ 2
11	83	60	+15
12	80	55	+18
13	90	57	+28
14	96	69	+29
15	79	55	+11
Group B—High sodium intake			
16	214	195	— 3
17	213	192	— 4
18	213	200	0
19	216	211	— 9
20	225	195	+46
21	215	217	+ 8
22	217	197	— 3
23	220	185	+29
24	189	150	+46
25	233	192	+60
26	223	186	+37
Mean values			
Group A	83	60	+14
" B	216	193	+19
" A+B	139	116	+16

ml at serum thiocyanate levels of 4.2 and 5.9 mg per 100 ml, respectively.

Discussion. The observation that thiocyanate administration may be accompanied by a sodium diuresis suggests the possibility that the depressor action of this agent may result, at least in part, from its production of salt depletion. In the hypertensive group, the increase over baseline values of the mean sodium excretion during thiocyanate therapy is highly significant ($P < 0.0001$). It is almost as significant in the normotensive series ($P < 0.0001$), although the difference between the mean changes in the two groups is not ($P = 0.06$). The latter statistics reflect the fact that the average response of the normotensive group is disproportionately increased by the small number of subjects in whom the sodium diuresis greatly exceeds the mean value. The question is therefore raised again whether these "hyperreactors" are in reality in a "pre-hypertensive" stage(10).

The mechanism by which thiocyanate produces a sodium diuresis is not clear, but certain hypotheses can be made. Increases in urine volume during thiocyanate administration to rabbits(11,12) and man (8) were mentioned in early reports. More recent observations have shown a greater increase in urinary chloride concentrations in dogs given thiocyanate than in those receiving other ions in the lyotropic series(13). In view of the conversion of thiocyanate to cyanide *in vivo*, another possible mechanism for the observed diuresis is suggested by the finding that cyanide in small doses is a powerful diuretic in dogs(14). Carbonic anhydrase, an enzyme present in the kidney, is inhibited by thiocyanate as well as cyanide(15); inhibition of this enzyme is accompanied by increased urinary base excretion(16-18). Because of the general belief that thiocyanate is stable, it is of considerable interest that this ion yields measurable amounts of cyanide rapidly *in vitro* in the presence of erythrocytes(19).

The hypotensive action of sodium depletion in hypertensive vascular disease is widely ac-

TABLE II.
Sodium Balance in Hypertensive Subjects.

Subject	Sodium intake, mEq/24 hr	Avg 24 hr control urine sodium output, mEq/24 hr	Change in sodium output, mEq/24 hr
Group A—Low sodium intake			
1	92	84	+13
2	97	100	+15
3	90	82	+12
4	92	75	+20
5	88	83	+14
6	18	16	+22
7	90	84	+ 7
8	87	50	+44
Group B—High sodium intake			
9	182	154	+57
10	207	163	+63
11	132	108	+32
12	219	205	+27
13	225	206	+25
14	225	218	+24
15	227	255	+20
16	132	122	+25
Mean values			
Group A	82	72	+18
" B	194	179	+34
" A+B	138	126	+26

cepted. In the light of the data presented, it is conceivable that the depressor action of thiocyanate may be mediated by this mechanism either directly or as a sequel to its conversion to cyanide. A direct effect of thiocyanate or cyanide on the vascular system, however, cannot be excluded. In either case, it is apparent that the influence of derived cyanide throughout the body as well as upon the kidney must be included in any consideration of the mechanism of action of thiocyanate in hypertensive disease.

Summary. A small but highly significant sodium diuresis accompanied short-term thiocyanate administration to uncomplicated hypertensive subjects on constant dietary regimens. Although slight but insignificant differences were observed between the mean responses of normotensives as compared to hypertensives, it was suggested that the similarity was attributable to the presence of a few hyperreactive and perhaps "pre-hypertensive" individuals in the normotensive series. The conversion of thiocyanate to cyanide *in vivo* was confirmed. Thiocyanate-induced sodium depletion was suggested as a possible factor in the depressor action of this agent, mediated either directly or through derived cyanide.

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Effect of Ether on Certain Coxsackie Viruses.* (19807)

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Soon after the discovery of the Coxsackie viruses by Dalldorf and his associates(1), numerous similarities between these agents and the poliomyelitis viruses were noted(2). It has been emphasized that both are hardy viruses, highly resistant to physical and chemical agents; a notable similarity being their resistance to diethyl ether.

In other studies(3,4) we have been concerned with the *in vitro* effect of diethyl ether on a number of viral agents. Because of the accumulating evidence that the individual members of the Coxsackie family of viruses

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