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Effect of Frusemide on Calcium Excretion

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Summary: After giving oral frusemide (Lasix) to 14 normal volunteers significant hypercalciuria occurred in all of them. This could not be accounted for by any change in glomerular filtration rate, but was possibly due to decreased tubular reabsorption.

Introduction

Previous workers have described an effect of thiazide diuretics on calcium excretion and have suggested the possibility of the use of the thiazides in the therapy of idiopathic hypercalciuria. Duarte (1967) has shown an increased clearance of ultrafilterable calcium in dogs infused with frusemide (Lasix)—an effect contrary to that found with the thiazides. Hänze and Seyberth (1967) also confirmed this in normal subjects with intravenously administered frusemide, ethacrynic acid, and oral triamterene. In view of these conflicting reports on such an important issue we have undertaken the study of the effects of frusemide on the urinary excretion of calcium in normal subjects following oral administration of the drug.

Materials and Methods

Fourteen members of the staff volunteered for the trial. Urine was collected over an eight-hour period, from 9 a.m. to 5 p.m., on two consecutive working days. Blood samples were taken in the middle of the collection period with the usual precautions required for calcium estimation. Frusemide 80 mg. was given at 9 a.m. on the second collection day. There was no restriction on diet or fluid intake in the two periods of study.

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Serum and urinary creatinine were estimated by using the Jaffe reaction as modified for the autoanalyser, and osmolalities were measured on the advanced osmometer by use of freezing-point depression. Serum and urine calciums were estimated by an automated fluorometric method described by Martin and Baird (1965); urine calciums were also estimated by the atomic absorption spectrophotometric method of Willis (1960).

Results

The Chart gives the results of urinary calcium determinations carried out on the 28 specimens by the two methods mentioned. The correlation coefficient was 0.9916.

The results of the calcium estimations are shown in the Table. The calcium excretion per 100 ml. of glomerular filtrate is calculated by the formula suggested by Nordin, Hodgkinson, and Peacock (1967) as follows:

$$\text{Calcium mg./100 ml. glomerular filtrate} = \frac{\text{urine calcium} \times \text{plasma creatinine}}{\text{urine creatinine}}$$

when all concentrations are expressed as mg./100 ml. The results presented show a highly significant increase in calcium excretion after an oral dose of frusemide in normal volunteers.

Results of Calcium Estimations

Subject No.	Total 8-hr. Urinary Calcium (mg.)		Calcium/100 ml. G.F. (mg.)		Calcium/mg. Creatinine (mg.)		*Change in G.F.R. (ml./min.)
	Control	Frusemide	Control	Frusemide	Control	Frusemide	
1	58	212	0.014	0.374	0.095	0.34	-19
2	51.2	126	0.062	0.162	0.062	0.171	-8
3	67.8	140	0.104	0.218	0.087	0.181	-14
4	69	155	0.118	0.327	0.112	0.297	-22
5	47.2	109	0.139	0.273	0.132	0.248	+9
6	57.2	116	0.107	0.266	0.086	0.217	-20
7	122	153	0.196	0.35	0.188	0.21	-9
8	52	118	0.076	0.24	0.095	0.31	-27
9	91.5	171	0.16	0.25	0.178	0.28	+8
10	45	114	0.06	0.28	0.067	0.28	-71
11	25	132	0.058	0.34	0.043	0.24	-11
12	40	169	0.082	0.32	0.109	0.39	+9
13	32	149	0.049	0.25	0.049	0.23	-4
14	31.5	110	0.058	0.23	0.053	0.18	-20
Mean	56.5	140.4	0.098	0.277	0.097	0.255	-14.2
S.E.M.	6.85	7.95	0.013	0.016	0.012	0.017	
P	<0.001		<0.001		<0.001		

* - Indicates decrease in glomerular filtration rate and + an increase.

Urine volume during the control period was 57 ml./hour (S.E.M. 6.5 ml.) and total solute excreted 356 mOsm (S.E.M. 27.4 mOsm). After the diuretic frusemide the urine voided increased to 277 ml./hour (S.E.M. 18.5 ml.) and the total solute excreted was 630 mOsm (S.E.M. 30.5 mOsm).

Discussion

The anthranilic acid derivative frusemide has been investigated by several workers and its potency as a diuretic has been well documented.

The filtered load of calcium is the concentration of calcium in the plasma water (ultrafilterable calcium) multiplied by the glomerular filtration rate. Ultrafilterable calcium was not measured in our subjects, as there is no readily available method which is reproducible, reliable, and accurate and which is suitable for a routine laboratory. However, total serum calcium measured by an automated fluorometric method showed no significant difference in all our subjects during the two periods of study: control 9.8 mg./100 ml., S.E. 0.13; frusemide 9.5 mg./100 ml., S.E. 0.13. Furthermore, variation in the rates of glomerular filtration, both individual and in this instance frusemide-induced, is overcome by relating calcium output to a fixed volume of glomerular filtrate—that is, 100 ml. About 98 to 99% of the filtered calcium is reabsorbed and a slight reduction in tubular reabsorption of calcium would produce a marked increase in calcium excretion.

It has been shown that a water diuresis *per se* has no appreciable effect on the rate of excretion of calcium in the urine (Wolf and Ball, 1950), but Epstein (1960) suggested that

the non-specific effect of solute diuresis in decreasing calcium reabsorption would be a factor in evaluating the influence of diuretics on calcium excretion. In our series the amount of solutes excreted expressed as milliosmoles is greater over the period of frusemide-induced diuresis.

Lamberg and Kuhlback (1959) reported a marked reduction in urinary calcium after the administration of chlorothiazide and suggested that the hypocalciuria was induced by an increase in tubular reabsorption of calcium. Suki, Schwetmann, Rector, and Seldin (1967) noted that increasing sodium excretion by saline infusion results in increased calcium excretion, whereas the thiazide diuretics caused a decrease in calcium excretion despite a sodium diuresis. They suggested that the diuresis caused by the distal tubular action of the thiazide diuretics led to a shrinkage of extracellular fluid volume and stimulated proximal tubular reabsorption of calcium.

Duarte (1967), reporting studies on mongrel dogs, showed that both frusemide and ethacrynic acid intravenously administered caused an immediate and significant increase in renal clearance of ultrafilterable calcium and magnesium. Phosphate clearance was increased slightly after frusemide but was unaffected by ethacrynic acid. He also showed that repletion of water and electrolyte loss during frusemide diuresis enhanced calcium and magnesium excretion. He concluded that frusemide and ethacrynic acid have an "action blocking the tubular reabsorption of calcium and magnesium." Hänze and Seyberth (1967) also noted similar findings in normal subjects and felt that there might be an active tubular secretion of these cations.

In this study the massive diuresis induced by oral frusemide on our normal subjects would have tended to produce a contraction of the extracellular volume, and hence, by the argument of Suki *et al.* (1967), a decreased calcium excretion. The results shown agree with the findings of Duarte (1967) and of Hänze and Seyberth (1967), and a decreased tubular reabsorption of calcium is suggested as the mechanism of the increased calcium excretion observed.

It is interesting to speculate whether prolonged therapy with frusemide for hypercalcaemia in malignancy or myelomatosis will lower serum calcium as a result of the calcium diuresis.

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