THE EFFECTS OF THIAZIDES IN IDIOPATHIC HYPERCALCIURIA

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TORONTO, CANADA

In 1959, Lamberg and Kuhlback[1] found that the administration of oral chlorothiazide and hydrochlorothiazide to normal subjects and to patients with congestive heart failure resulted in decreased urinary excretion of calcium. Since then there have been several reports confirming these findings in normal subjects and in various disease states.[2-5]

The purpose of our study was to investigate the effects of the benzothiadiazine diuretics in patients with renal lithiasis due to idiopathic hypercalciuria and to assess their therapeutic value in the prevention of further stone formation.

Idiopathic hypercalciuria has in the experience of ourselves and others[6] been the commonest metabolic abnormality found in patients with recurrent renal lithiasis. We arbitrarily define the condition as an excessive urinary excretion of calcium which is unaccounted for by any other underlying abnormality. When the dietary intake of calcium is normal (800–1000 mg./day) a urinary calcium excretion exceeding 300 mg./day in the male or 250 mg./day in the female is generally considered to constitute hypercalciuria.[6] In this disorder the serum calcium level is normal although serum phosphorus levels are sometimes low. The cause of the hypercalciuria is not clear. Absorption from the intestine appears to be increased.[7] In a few cases this overabsorption of calcium has been considered to be the primary cause of the disease[8] but in the majority it is felt to be secondary to a primary renal loss of calcium.[9, 10]

Methods

We have administered hydrochlorothiazide, in a dosage of 50 mg. twice daily, to 29 patients with idiopathic hypercalciuria and in 7 of these, complete metabolic balance studies were performed. All balance studies were done on the Farquharson Investigation Unit and biochemical determinations were done in a research laboratory. After the constant diets were begun an equilibration period of at least 8 and usually 12 days

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was allowed to elapse before the balance studies commenced. Chemical analysis of the diet was performed at the beginning and end of each study. Blood for all determinations was taken at 8 a.m. in the fasting state. Daily 24 hour urine collections were analyzed for creatinine, calcium, magnesium, phosphorus, citrate, sodium, potassium and chloride. In addition, at least once during each period a 24 hour urine collection was analyzed for pH, ammonia, titratable acid, and bicarbonate content. To minimize exposure to air, these specimens were collected with a funnel connected to tubing extending under a layer of paraffin oil. Stools were collected in 4 day periods. Chemical determinations were made by previously cited methods.[11]

Results

In all but 3 of the patients, hydrochlorothiazide resulted in a marked and sustained reduction in the urinary excretion of calcium. Results obtained in the patients who had complete balance studies are depicted in Figure 1. The mean urinary calcium excretion for the group is plotted during a 12 day control period and for the first 4 days of thiazide administration. Urinary calcium excretion fell by approximately 50% and the change is maximum by the third or fourth day of drug administra-

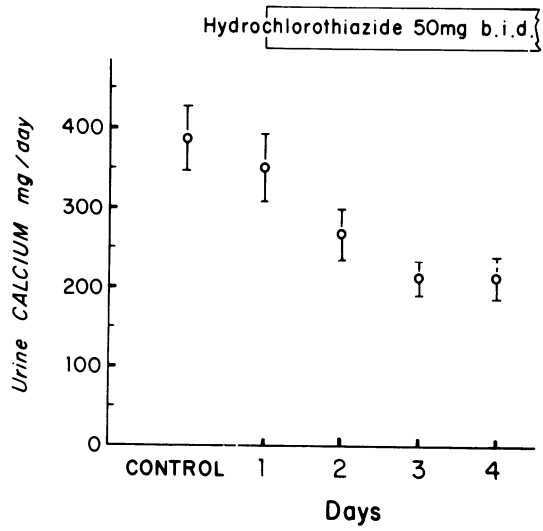

Fig. 1. The effect of hydrochlorothiazide on urinary calcium excretion in 7 patients with idiopathic hypercalciuria, taking a constant diet on the Clinical Investigation Unit. The mean urinary calcium excretion for all patients is shown during a 12-day control period and for the first 4 days of thiazide administration.

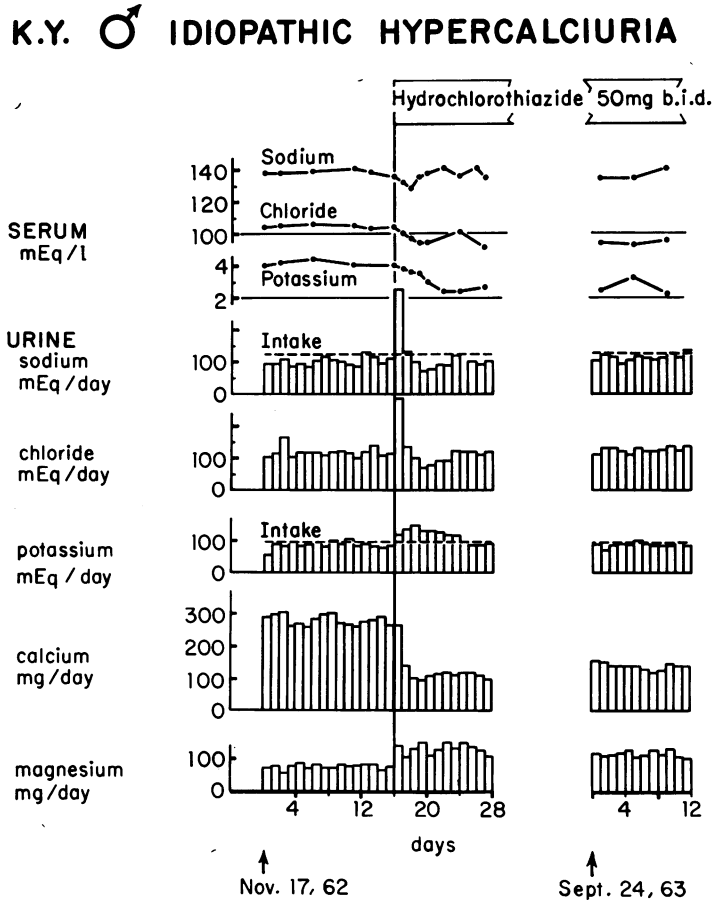

FIG. 2. Metabolic studies in patient K.Y.

tion. There is usually relatively little change in urinary calcium excretion during the first 24 hours.

Studies performed in the first patient in our series (K.Y.) are seen in Figure 2. In this patient urinary calcium excretion was initially around 450 mg./day but on constant diet fell to approximately 300 mg. per day. When hydrochlorothiazide was given, the expected increase in urinary sodium and chloride excretion occurred immediately but was of only 1 day's duration. Similarly there was the expected increase in urinary potassium, but this too was only temporary, and after 7 days the urinary excretion of potassium had returned to control levels. With urinary calcium excretion, on the other hand, the picture is entirely different. The maximum change has not occurred until the third day but in contrast to sodium, chloride and potassium the effect is sustained. This patient con-

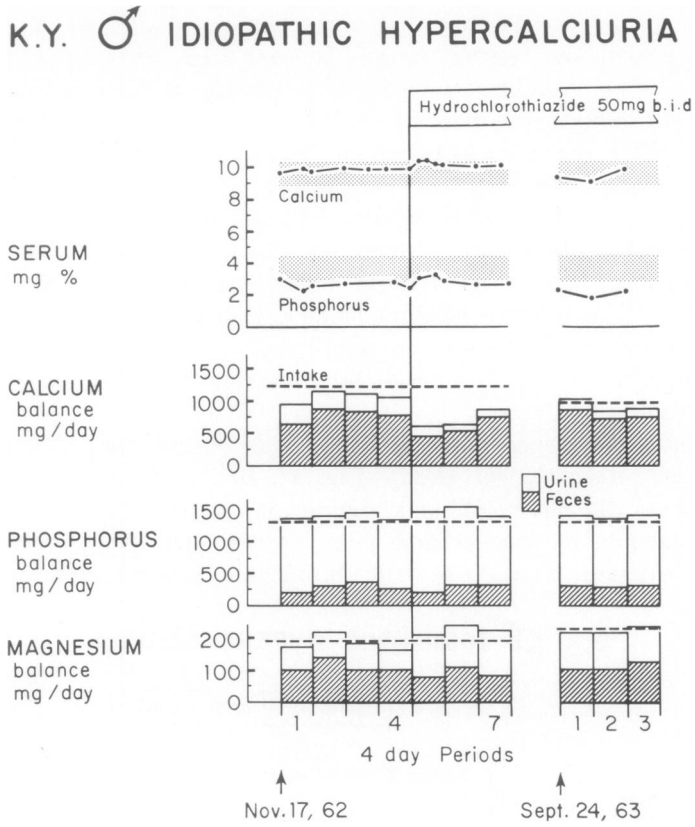

FIG. 3. Balance data in patient K.Y. The shaded areas show our normal ranges for serum chemistries.

tinued to take the hydrochlorothiazide and repeat balance studies were performed 1 year later at which time urinary calcium was still diminished. There is also a sustained increase in urinary magnesium which precedes the calcium change, usually being apparent on the first day of thiazide administration.

A fall in serum potassium occurred in all patients, usually to below normal levels. Not shown in Figure 2 is the rise in plasma bicarbonate to the upper range of normal or in some cases to above normal. There was generally a slight rise in blood pH as well.

The serum calcium level generally rises slightly (Fig. 3) to the upper range of normal or to slightly above normal but this effect is only temporary, lasting 2 or 3 days. In our balance charts total intake is indicated by the interrupted line, the top of each bar indicates total excretion. Fecal excretion is shown by the cross hatched portion of the

bar and urinary excretion by the open portion of the bar. The shaded areas designate our normal ranges. In each case, balance studies were preceded by an equilibration period of 8–12 days on the constant diet. In the control periods, this patient (K.Y.) was in slightly positive calcium balance. With the administration of hydrochlorothiazide, not only did urinary calcium fall, but there was also a sharp drop in fecal calcium resulting in strongly positive calcium balance. However, this fall in fecal calcium appears to be only temporary and at the time of restudy the following year, this patient was no longer retaining significant amounts of calcium. The positive calcium balance is not accompanied by phosphorus retention. There was no significant change in fecal magnesium but magnesium balance became slightly negative due to the rise in urinary magnesium.

We have done repeat balance studies during prolonged thiazide therapy in one other patient (B.K.—Fig. 4). In this patient, thiazide administration did not result in a significant change in fecal calcium although calcium balance became more positive due to the reduction in urinary calcium. There was still significant calcium retention at the

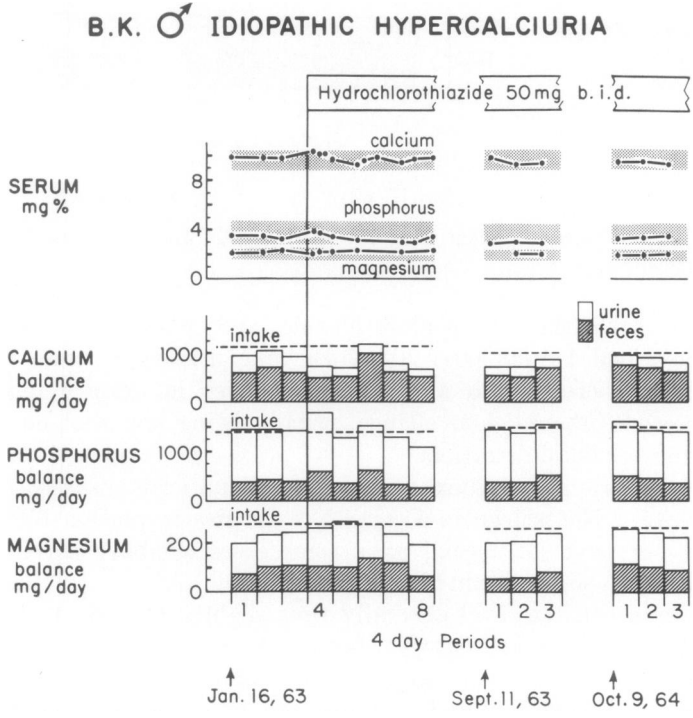

FIG. 4. Balance data in patient B.K.

TABLE 1

Ca^{47} Studies in Patient E.H.

	Control (2 μc Ca^{47} I.V. Nov. 25, 64)	Hydrochlorothiazide (2 μc Ca^{47} I.V. Dec. 7, 64)
Whole body count (after 12 days)	46% dose	54% dose
Total urine tracer (0–12 days)	38.3% dose	29.2% dose
Total stool tracer (0–12 days)	8.4% dose	6.3% dose
Endogenous fecal calcium	125 mg/day	66 mg/day
Bone accretion rate	874 mg/day	864 mg/day

time of the second study 9 months later, but at the time of the third study 21 months later, fecal calcium had risen and the calcium balance was much less positive.

Of the seven patients in whom metabolic balance studies were done, B.K. was the only one in whom thiazide administration was not followed by reduced fecal calcium. In the other patients fecal calcium fell from 10% to 46%. In one patient (E.H.) whose fecal calcium fell by 44% by conventional balance techniques, Ca^{47} was injected intravenously during the control period and again during the period of drug administration (Table 1). The recovery of the administered tracer dose in the stools during the 12 days following the injection was considerably less in the treatment period as compared to the control period. The calculated endogenous fecal calcium in this patient was 125 mg./day in the control period as compared to 66 mg./day in the treatment period.

We are aware of only 2 reports in the literature dealing with the effects of the benzothiazides on fecal calcium excretion. Lichtwitz and his associates[2] report balance studies on 9 patients given hydroflumethiazide (100 mg./day). Fecal calcium was reported as rising in 6 patients and falling in 3. However, in this study there is no reference to equilibration periods on diet, diets were not analyzed, the control period was of only two days' duration and the treatment period lasted for only an additional 3–5 days.

Nassim and Higgins[5] performed balance studies in 7 patients given bendroflumethiazide (5.0 to 7.5 mg./day). Their studies were begun after an equilibration period of 3 to 4 days on a diet constant in calcium and phosphorus content, and extended throughout control periods of 12 to 18 days and treatment periods of 6 to 24 days. In 5 of their patients, fecal calcium changed by 5% or less whereas in the other two patients fecal calcium increased by 17% and 18%. We are unable to account

for the discrepancy between our findings and those of Nassim and Higgins, although it should be pointed out that the dose of hydroflumethiazide which they used is equivalent to only ½ to ¾ the dose of hydrochlorothiazide used in our experiments.

We have studied a number of drugs in the benzothiadiazine group including chlorothiazide, hydrochlorothiazide, bendroflumethiazide and polythiazide and have found that all affect urinary calcium excretion in a similar manner. Chlorthalidone which is a phthalimidine rather than a benzothiazide derivative of the sulfonamide group has a similar action. Neither spironolactone nor triamterene lower urinary calcium excretion.

The mechanism by which the thiazides lower urinary calcium excretion is of considerable fundamental importance. Walser pointed out that the natriuresis induced by mercurial diuretics and acetazoleamide is accompanied by a simultaneous increase in urinary calcium excretion and suggested that the transport of these ions in the kidney is related, with a common transport mechanism possibly being involved.[12] Walser also noted that the diuretics of the benzothiadiazine class have the opposite effect but offered no explanation for this.[13]

The reduction in calcium clearance induced by the thiazides could be due to a fall in the filtered calcium load resulting either from diminished glomerular filtration rates, or from increased protein binding of plasma calcium. In our experiments no significant change in the ultrafilterability of plasma calcium resulted from thiazide administration. Although in most experiments a decrease in endogenous creatinine clearance sufficient to account for the reduction in urinary calcium was observed, these changes were evident and often most marked on the first day of thiazide administration at a time when little change in urinary calcium had as yet occurred. Moreover, reduced filtered loads would not account for the rise in urinary magnesium which must be attributed to decreased tubular reabsorption of filtered magnesium since there was no significant change in the magnesium concentration of the plasma ultrafiltrate. Since calcium and magnesium are thought to share a common tubular transport mechanism[14] it seems likely that there is altered tubular handling of calcium as well. The decrease in fecal calcium observed in some of our patients also suggests that thiazides may have a general effect upon calcium transport.

We have no good explanation for the delay in reduction of urinary calcium after thiazides are administered. It is possible that the action is in fact immediate but that it is prevented from taking place by the initial sodium diuresis. As yet we have not put this hypothesis to the test. Another possibility is that the reduction in urinary calcium is not a direct effect but that it occurs indirectly in response to other changes

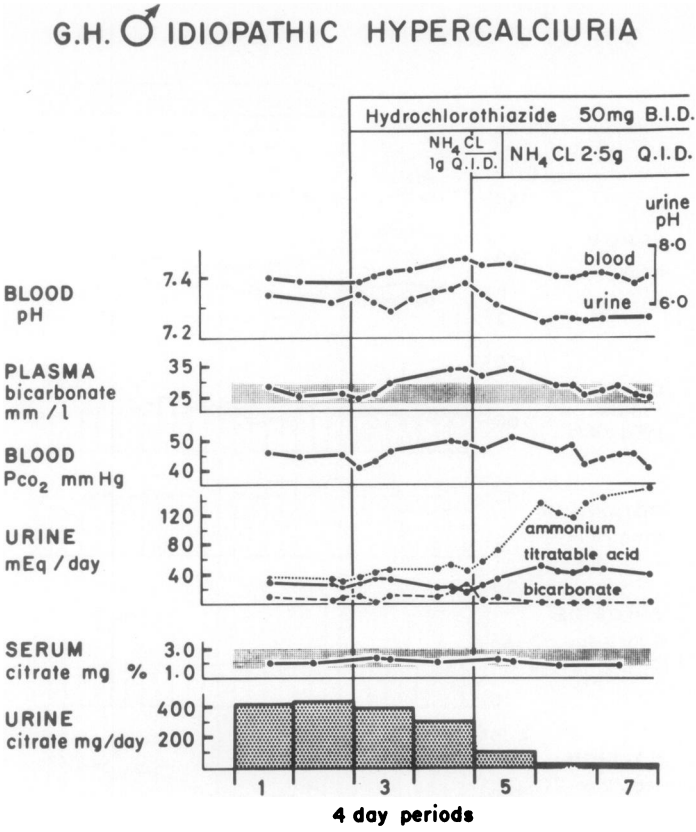

FIG. 5. Patient G.H. Acid-base changes resulting from hydrochlorothiazide administration (periods 3 and 4) and hydrochlorothiazide plus ammonium chloride (periods 5–7).

produced by thiazides. I should like to describe briefly two experiments pertaining to this possibility.

In patient G.H. (Fig. 5) we have corrected the mild thiazide induced extracellular alkalosis by administering sufficient ammonium chloride to restore blood pH and plasma bicarbonate to control levels. However, the intracellular acidosis due to the potassium deficiency has probably been aggravated as shown by the rise in urinary ammonia and fall in urine pH and citrate. With ammonium chloride, urinary calcium excretion increased considerably but the increase in urinary magnesium induced by thiazides was maintained (Fig. 6). Ammonium chloride also produced a rise in fecal calcium, and calcium balance, which had become significantly positive initially as a result of thiazide administration once more became negative (Fig. 7).

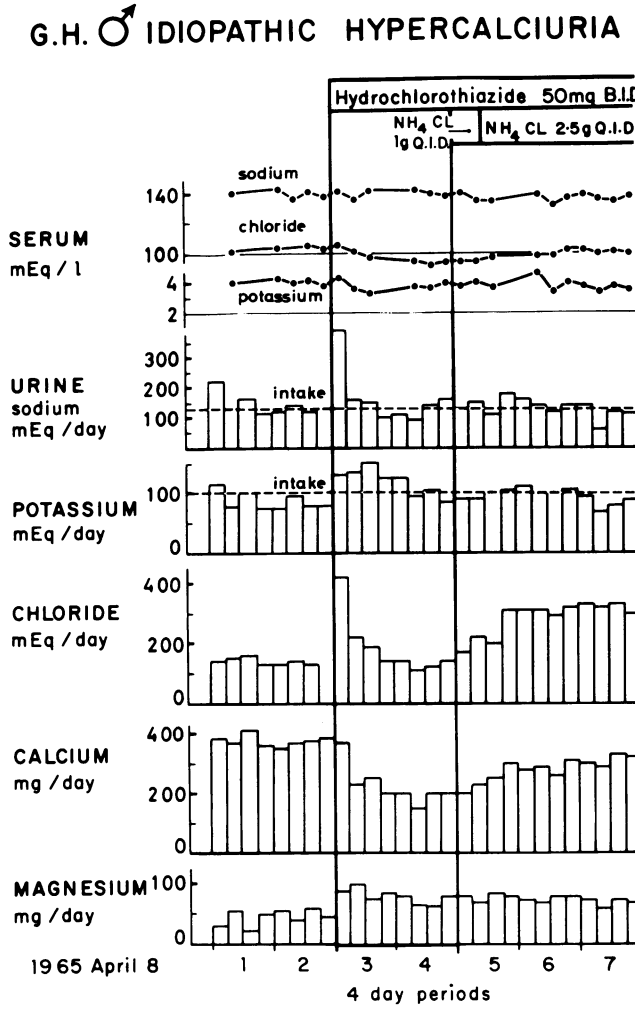

FIG. 6. Patient G.H. Changes in serum and urinary electrolytes produced by hydrochlorothiazide (periods 3 and 4) and hydrochlorothiazide + ammonium chloride (periods 5–7).

In the last experiment, we attempted to correct the thiazide induced hypokalemia in patient E.H. by infusing 80 mEq. potassium chloride daily. (Fig. 8). Despite the fact that serum potassium levels remained slightly below normal (3.4 mEq./l.), our balance studies showed that enough of the infused potassium was retained to correct entirely the potassium deficit produced by the thiazides. The potassium infusions resulted in a slight rise in urinary calcium but no significant change in

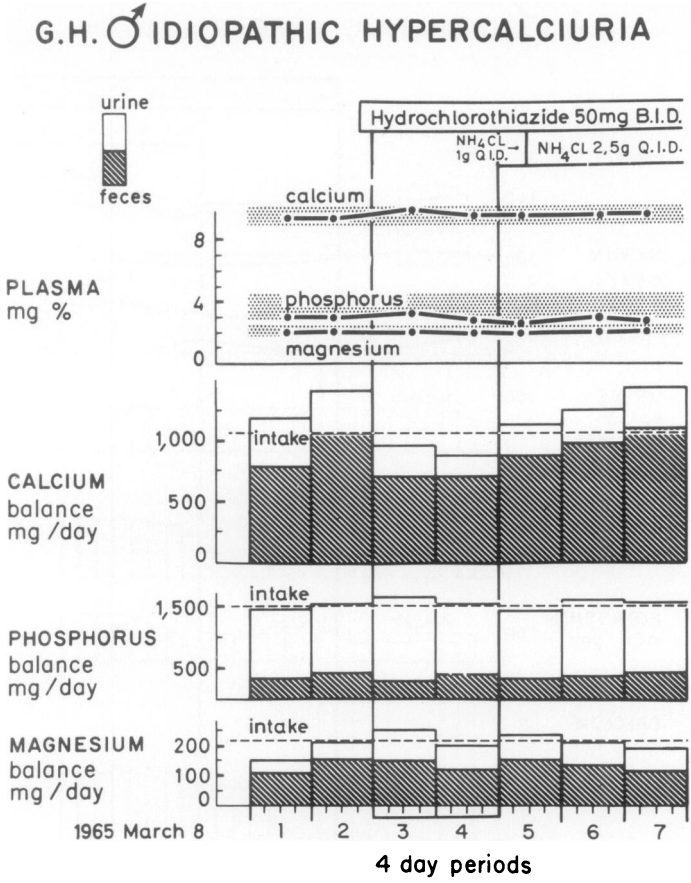

FIG. 7. Patient G.H. Balance data during control periods (1 & 2), hydrochlorothiazide administration (periods 3 and 4) and hydrochlorothiazide + ammonium chloride administration (periods 5–7).

urinary magnesium. The changes in calcium balance are, however, rather striking (Fig. 9). The calcium balance which was negative in the control periods became strongly positive in the thiazide periods due to a fall in both urinary and fecal calcium. With the potassium chloride infusions, there was a sharp rise in fecal calcium and calcium balance once more became negative.

The last two experiments, although of considerable interest, are by no means conclusive with regard to the mechanism by which thiazides affect calcium and magnesium metabolism. We would, therefore, prefer to withhold any interpretation until further information is available.

If the mineral constituents of the urine are of any importance at all

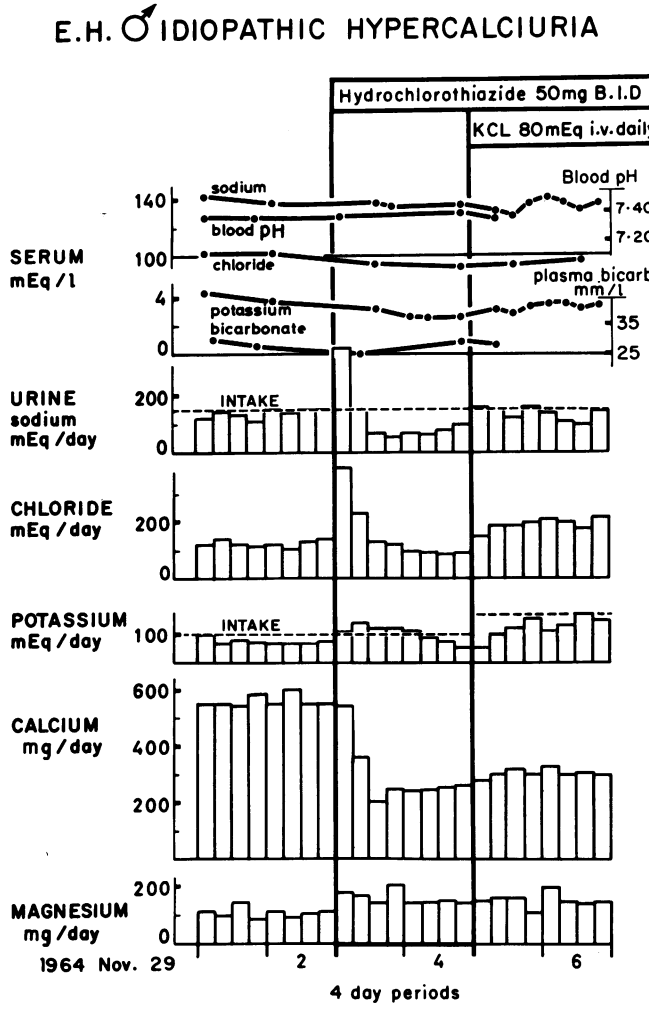

FIG. 8. Metabolic studies in patient E.H.

in the causation of renal lithiasis, then in theory the administration of thiazides to patients with idiopathic hypercalciuria should be a useful prophylactic measure. Not only the decrease in urinary calcium but also the increase in urinary magnesium should prove to be beneficial.[15] We do not feel that our experience is large enough to warrant drawing conclusions at this time. However, our preliminary results are sufficiently encouraging to warrant further therapeutic trials. Our 29 patients are all on long term therapy. They are receiving no other treatment except a copious fluid intake—which most had been taking previously. The first

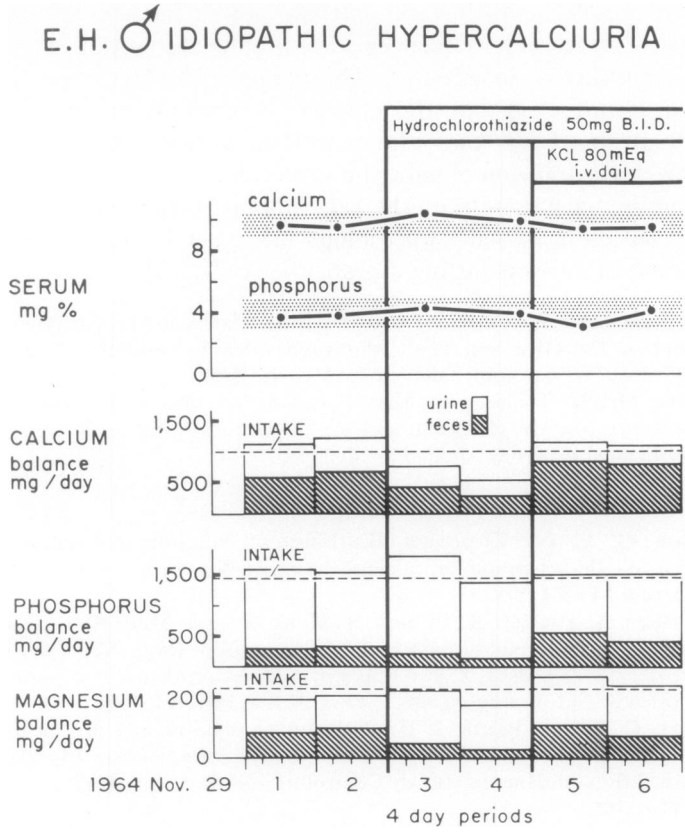

FIG. 9. Balance data in patient E.H.

patient (K.Y.) who had a total of 18 stones and was experiencing renal colic and passing calculi every 3 months for 2 years prior to the administration of hydrochlorothiazide has been entirely free of symptoms and stones during the 3 years which have elasped since treatment was begun. Three of the 29 patients have each had a bout of renal colic while taking hydrochlorothiazide but in two of these, this probably resulted from small stones which were present when treatment was begun.

SUMMARY

The administration of hydrochlorothiazide to 29 patients with idiopathic hypercalciuria was followed in most instances by a marked reduction in the urinary excretion of calcium. The maximum effect was not achieved until the second or third day of thiazide administration but was then sustained. Metabolic studies done in 7 patients showed that

there was usually a fall in fecal calcium as well but this effect appeared to be only temporary. Thiazides also produce a sustained rise in the urinary excretion of magnesium. The manner in which these effects are produced is not clear but the changes in calcium metabolism can be partially reversed by the administration of ammonium chloride by mouth or by the infusion of potassium chloride.

The preliminary results of thiazide administration to prevent further stone formation in patients with idiopathic hypercalciuria are sufficiently encouraging to warrant further therapeutic trials.

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DISCUSSION

DR. FRANCIS C. WOOD (Philadelphia): Mr. President, is it proper for a member to ask another member to answer a question about the paper that has come up this morning?

DR. HOWARD, do chlorothiazides change evil to good urine?

DR. JOHN EAGER HOWARD (Baltimore): This is an interesting question. I do not know anything about it.

DR. YENDT: Dr. Wood, I have asked Dr. Howard to find this out, but I have not been able to succeed in having him do it as yet. Perhaps your question will stimulate him to do so.

DR. LEWIS DEXTER (Boston): Have you utilized thiazides in patients with osteoporosis?

DR. YENDT: We have not, sir. When Lichtwitz reported his results in 1961 in the French literature, he had administered thiazides to patients with osteoporosis and found the same reduction in urinary calcium, but I have seen no reports concerning the long-term effects of thiazides in osteoporosis.

DR. THOMAS C. CHALMERS (Boston): I would like to ask two questions. Is the effect on urinary calcium excretion the same percentagewise in normals as it is in patients with hypercalciuria? Second, you mentioned the need for further trials of therapy, and I think it is important to emphasize that with any new therapy such as this the long-term side effects may be as great as the advantages. The usual response to a fervent request for a controlled study in a situation like this is that we do not see enough patients. The fact that you have already seen 29 patients suggests that you should be able to find out whether in the long run the administration of chlorothiazides prevents renal stones. Using the patient as his own control in a temporal study is fraught with all sorts of dangers due to other aspects of the therapy.

DR. YENDT: The answer to your first question is yes, the percentage fall in urinary calcium in idiopathic hypercalciuria is the same as in normal people roughly. I certainly agree with your comments with regard to interpretation. It is, I think, very difficult to draw conclusions with regard to a treatment for kidney stones. However these unusual patients who seem to have been getting stones several times a year for several years and then abruptly cease to have stones with a certain treatment, tend to impress one. The other patients are less impressive.

DR. WILLIAM PARSON (Charlottesville): It was my impression that associated with the long-term positive calcium balance you did not have positive phosphorus balance. Where did the calcium go? Did you measure nitrogen balance?

DR. YENDT: The positive calcium balance induced by thiazides was not accompanied by phosphorus retention. This is disturbing not only in our studies but also in balance studies reported by others. For example, in most reports dealing with high calcium intakes in patients with osteoporosis, significant retention of phosphorus is not seen, despite the fact that the calcium balance may be strongly positive. By some, such calcium "retention" has been attributed entirely to experimental error

inherent in measuring fecal calcium when the dietary intake of calcium is high. Personally, I am not convinced that this is so, although at the moment I have no good explanation for the retention of calcium without phosphorus. We have not done nitrogen balances.

DR. HENRY T. RICKETTS (Chicago): I wonder whether you studied uric acid excretion in these patients in view of the fact that thiazides do have an influence on uric acid metabolism in some individuals. Do these particular individuals demonstrate any such effect?

DR. YENDT: I was afraid someone would ask me that question. We did uric acid studies in the urine and in serum and, of course, the serum uric acids have risen, some of them. In the initial acute experiments we were not impressed by great changes in urinary uric acid excretion, and for that reason we have not analyzed our uric acid data with care and I hesitate to say anything more about it at this time.