TEN YEARS' EXPERIENCE WITH THE USE OF THIAZIDES IN THE PREVENTION OF KIDNEY STONES

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In our first presentation to this Association in 1965 we described the effects of thiazides on calcium metabolism and reported preliminary results which indicated that thiazides might be useful in the prevention of non-infected calcium stones.[1] We have now extended our experience with thiazide prophylaxis of calcium stones to 197 patients followed for up to 11 years. These observations which have confirmed the efficacy of thiazides in stone prevention form the basis of today's presentation.

The striking hypocalciuric action of thiazides is well illustrated in Figure 1, which we showed in our previous presentation. This is a metabolic study in the first of our patients to receive thiazides for stone prophylaxis. He had passed at least 24 calcium oxalate stones over the previous 15 years and when referred to us he was passing 3–4 stones per year. During the ensuing 11 years on thiazides he has had no further stones. The study indicates that the administration of hydrochlorothiazide, 50 mg twice daily caused a striking reduction in urinary calcium excretion and that this effect was sustained, in contrast to the sodium chloride diuresis which lasted only 1 day and the enhanced urinary excretion of potassium which lasted only 8 days. There was also a modest increase in urinary magnesium which also tended to be sustained.

The hypocalciuric effect of thiazides occurs in nearly all normal subjects and in nearly all disease states with the possible exception of hypoparathyroidism although we have observed the effect in one patient with surgical hypoparathyroidism and in one patient with pseudohypoparathyroidism. The mean reduction in urine calcium excretion is 150 mg per day,[2] although the urine calcium may fall by as much as 400 mg/day and the maximum effect is usually evident by the second to sixth day of thiazide administration. The dose of hydrochlorothiazide required to produce a maximum effect is usually 100 mg per day; rarely a marked effect can be obtained with as little as 25 mg per day and occasionally as much

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This work is supported by grants from the Medical Research Council of Canada (MT681).

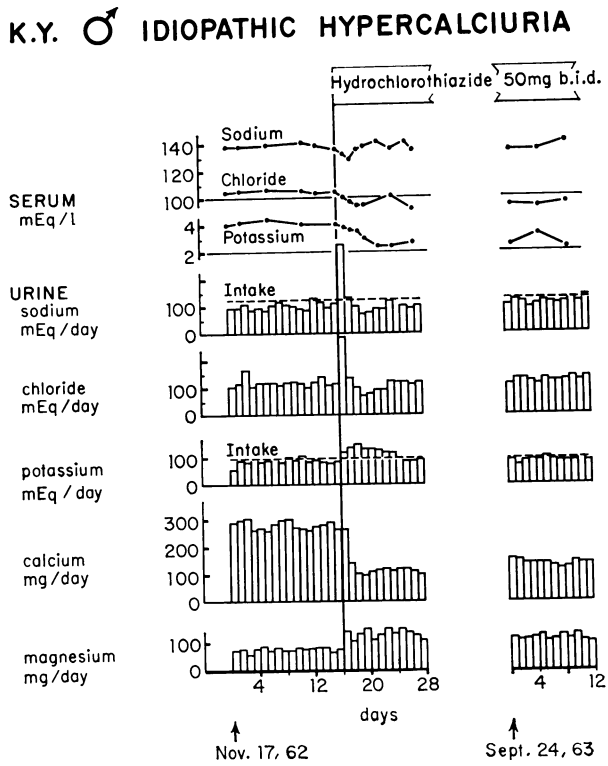

FIG. 1. Metabolic studies in Patient K.Y. with idiopathic hypercalciuria, the first of our patients to be given hydrochlorothiazide for the prevention of calcium stones. Hydrochlorothiazide produced only a temporary increase in urinary sodium, chloride and potassium excretion but there is a sustained reduction in urine calcium excretion and a sustained increase in urine magnesium excretion. See Fig. 2 for details of this patient's stone history.

as 150 mg per day is required. This hypocalciuric effect is unique to the thiazide group of diuretics but is not exerted by diazoxide, the one member of the group which lacks a saliuretic action. This observation is compatible with the subsequent report by Suki[3] that the hypocalciuric action of thiazides is dependent upon contraction of extracellular fluid volume and can be blocked if volume contraction is prevented by salt and water administration. Presumably the hypocalciuric effect of thiazides can be attributed to proximal tubular reabsorption of sodium and of calcium secondarily, induced by contraction of extracellular fluid volume. The fact that other diuretics which also produce contraction of extracellular fluid volume do not possess a hypocalciuric effect is explained by the recent experiments of Dirks which demonstrate that thiazides block so-

dium reabsorption by the distal nephron without a concomitant increase in calcium excretion whereas this is not the case with other diuretics which he has studied.[4]

During the ten-year period 1962–72 we have started 197 patients with calcium stones on thiazides and have obtained adequate follow up data on all but 19 of them. Whenever possible, follow-up is accomplished by a return visit to the office at which time the patient is seen by myself or my associate, Dr. Cohanim. At these return visits serum and urine biochemistries are repeated and appropriate radiologic studies carried out. All biochemical determinations have been performed in our research laboratory. If return office visits cannot be arranged, follow up information has been obtained through direct communication with the patient and his referring physician.

The therapeutic regimen has been simple. In addition to the prescription of thiazides the patients have been asked to maintain a high fluid intake, which most of them had been doing prior to thiazide therapy. Milk and milk products have not been restricted except when the history indicates that these have been taken in excess. Dietary sodium chloride is not restricted unless there is difficulty in obtaining a satisfactory hypocalciuric effect with thiazides, which is only rarely the case. Potassium supplements have not been administered routinely although they are given if potassium deficiency appears to be a significant problem. Patients are cautioned that potassium deficiency may become a serious problem should a general anaesthetic or digitalis therapy be necessary at some future date or in the event of some other condition such as a gastrointestinal disturbance which causes significant potassium loss.

The results of thiazide administration for calcium stone prevention may be summarized as follows. Adequate follow up data have been obtained in all but 19 of our patients. Thiazides have been discontinued in 39 patients, for a variety of reasons which will be described later, but it is important to emphasize that in no instance has lack of effectiveness been the reason for discontinuing the drug. We have adequate follow up on 139 patients with calcium stones who have remained on thiazides. Stone progression, (i.e. formation of new stones or growth of stones present when treatment started) has occurred in only 8 patients with non-infected calcium stones who have adhered to the regimen. Even these 8 patients are greatly improved over their pre-treatment status and we know that at least 6 of them continue to take thiazides. There are an additional 7 patients in whom stone formation was arrested during thiazide therapy but whose condition progressed after they had temporarily stopped thiazides or reduced the dosage. These patients have subsequently resumed taking the full dose of the medication.

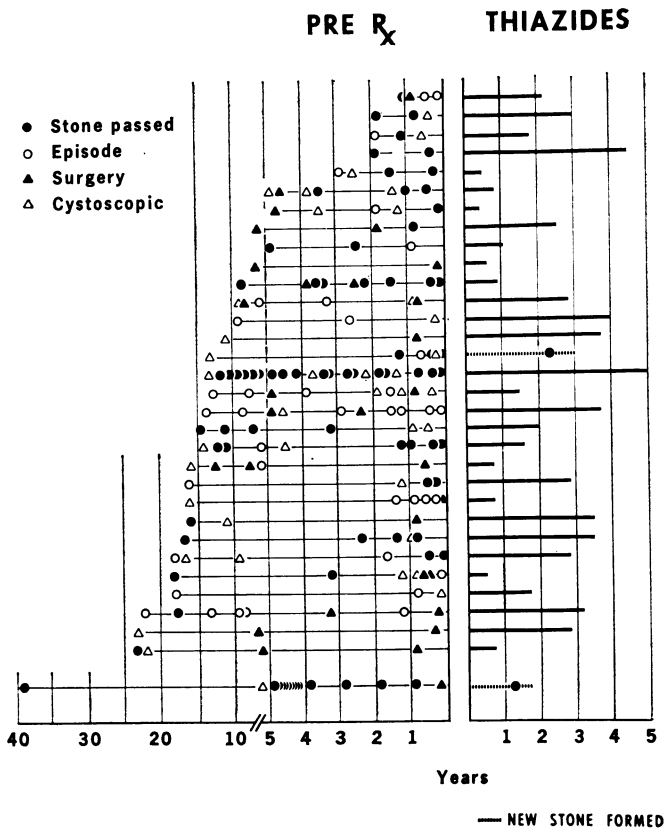

FIG. 2. A graphic outline of the stone histories (up to November 1967) of all 32 patients taking thiazides for stone prevention who had no radiographic evidence of stones when treatment was initiated. Each horizontal line depicts the clinical course of a patient before and during thiazide administration. New stone formation occurred in only 2 of the thiazide treated patients. The patient shown on this chart to have the longest period of treatment (5 years) is K.Y. (see Fig. 1) who has now been stone free for 11 years on thiazides.

At the present time therefore it appears that 80% of patients who are started on thiazides will remain on long term therapy and that in 90–95% of them thiazides effectively arrest stone formation. It should also be mentioned here that our treatment group includes approximately 10 patients with rapidly progressing struvite stones associated with intractable or recurrent urinary tract infection. Although we have the impression that thiazides are a useful adjunct to treatment in some of these patients definite evidence of stone growth occurred in 4 of them.

The detailed stone history of some of our thiazide treated patients is

depicted graphically in Figure 2, which was prepared in 1967 when we had been using thiazides for stone prevention for five years. At that time there were approximately 75 patients in our series—in approximately one half of them (37) no stones were evident radiologically when treatment began, so that any events occurring during thiazide treatment were presumed to represent new stone formation. New stone formation occurred in only two of the 37 patients during the treatment period.

Although the efficacy of thiazides in stone prevention is presumably related in large part to the hypocalciuric effect of these drugs we have been interested in examining other possible contributory mechanisms. The increase in urine magnesium previously referred to may be of significance since the magnesium ion is known to block the calcification of rachitic rat cartilage in vitro[5] and enhances the solubility of calcium oxalate in simple solutions.[6] Twenty-four hour urine volumes in our thiazide treated patients have not been significantly greater than control values. Dr. Thomas informs me that the urinary excretion of pyrophosphate, another calcification inhibitor, or of the unidentified inhibitor which Dr. Howard and he have been studying for many years, is not increased by thiazides.[7] It is of considerable theoretical interest that thiazides are effective despite the fact that they sometimes cause a considerable reduction in urine citrate excretion.[8]

We have recently been interested in the effect of thiazides on urinary zinc excretion, stimulated by Thomas' observations that zinc can block the in vitro calcification of an organic matrix particularly where the magnesium ion is also present in the system.[9] We have now studied urinary excretion of zinc before and during thiazide administration in 41 patients and have now followed some of these patients for as long as 3 years during thiazide therapy.[10] Thiazides result in a marked increase in urine zinc excretion (Fig. 3) and this effect appears to be sustained indefinitely as demonstrated in Figure 4 on which are plotted all the urine zinc determinations which we have performed on our patients during the course of thiazide therapy.

Special reference should be made to the effects of thiazides on serum calcium levels since there appears to be some confusion on this subject in the current literature. We have measured total serum calcium and ultrafiltrable calcium before and during thiazide therapy at the time of all follow up visits. Thiazides frequently produce an initial elevation of total serum calcium of approximately 0.5 mg%. This is transient, usually lasting less than one week and is due to hemoconcentration—the level of calcium in the serum ultrafiltrate does not change during this period. Rarely a slight elevation of total serum calcium due to hemoconcentration persists during chronic thiazide therapy—these cases can be recognized by finding

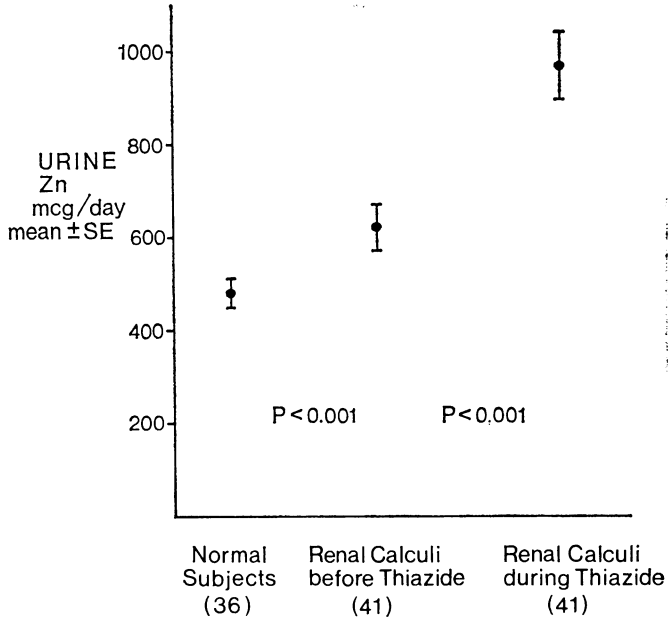

FIG. 3. Urine zinc excretion in normal subjects and in 41 stone patients before and during hydrochlorothiazide administration. Urine zinc excretion is doubled by hydrochlorothiazide.

a perfectly normal ultrafiltrable calcium. In our experience true hypercalcemia (i.e. elevation of ultrafiltrable calcium as well as total calcium) has occurred in only 3 of our patients during thiazide therapy and these have all had an underlying disturbance of calcium metabolism. Two of these patients have subsequently had parathyroid adenomas removed and one had sarcoidosis. It should also be stressed that thiazides do not increase the risk of uric acid stones since the total excretion of uric acid in the urine is not increased by these agents.

As previously indicated thiazides have been discontinued in 39 patients for whom it was initially prescribed. In two patients this was done shortly after starting the drug when it was evident that no significant hypocalciuric effect was obtained. In the remainder, the drug was stopped after varying periods of time (up to 7½ years) on treatment. The development of intolerable side effects was the reason for discontinuing therapy in 20 patients, or approximately 10% of those for whom the drug was initially prescribed. In the remaining 19 patients the reasons for discontinuing thiazides were as follows: in 9 patients the drug was discontinued by the patient or by the family physician for no apparent good reason; in 5 patients the drug was discontinued by the patient or by the family doctor

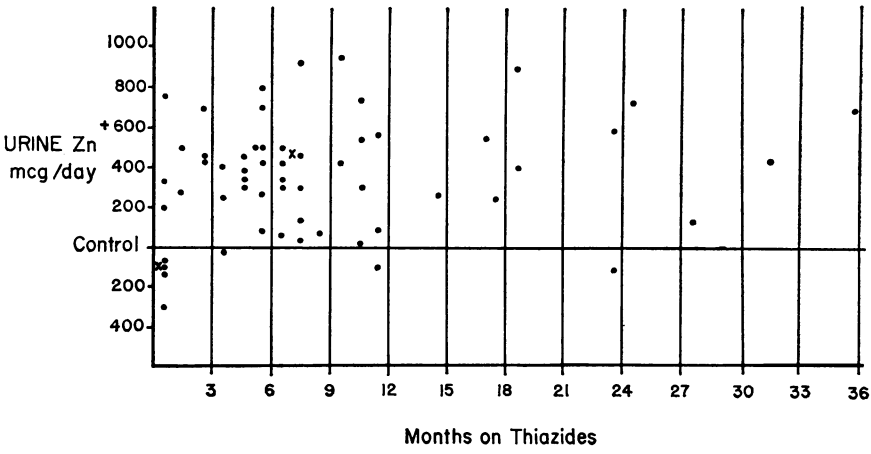

FIG. 4. Urinary zinc excretion during follow up visits of patients taking thiazides. "X" denotes patient on Hydrochlorothiazide 150 mg per day. Each plotted value is the difference between the determination obtained during thiazide therapy and the pre-treatment determination for that patient.

because it was thought to be no longer needed. In 1 patient who developed true hypercalcemia while on therapy, thiazides were discontinued after a parathyroid adenoma was removed. In one patient it became apparent during treatment that the patient had serious psychiatric problems and that most of his stone episodes were factitious. One patient has died of a myocardial infarction.

Although our experience indicates that the use of thiazides is an extremely effective means of preventing non-infected calcium stones, the precise indications for this form of treatment still require definition. Treatment with thiazides has the advantage of being effective, cheap and convenient but carries with it a significant incidence of side effects. Furthermore an alternative form of prevention of calcium stones with oral phosphate has been used successfully by our President Dr. Howard and by Dr. Thomas.[11, 12] It is our present practice to prescribe thiazides for selected patients with non-infected calcium stones who have had multiple recurrences or in whom there is evidence of a recent increase in size of stones present in the urinary tract. We have also found that thiazides arrest stone formation in patients with medullary sponge kidneys. The use of thiazides is not restricted to patients with hypercalciuria since the regimen has also been found to be quite effective in those who have normal urinary calcium excretion. If patients cannot tolerate thiazides because of side effects it is our present practice to prescribe oral phosphate supplements instead. We believe that further studies are needed with both

types of treatment before the precise role of each in stone prevention regimens is clearly defined. In the meantime however we suggest that thiazides should be the drug of first choice when calcium stones are associated with hypertension, an association which occurred in 34 of our patients. Another situation in which thiazides appear to possess an advantage is the patient with suspected hyperparathyroidism; in such instances the diagnosis might become clearly evident during thiazide administration whereas phosphate therapy would tend to mask this disorder.

Summary

Hydrochlorothiazide has been administered for the prevention of calcium stones to 197 patients during the years 1962–1972. The drug has been discontinued in 20% of patients and in one half of these the development of intolerable side effects was the reason for stopping the drug. Follow up has been inadequate in a further 10% of patients, leaving 139 patients, or approximately 70%, on long term treatment who have been adequately followed. Stone formation has been completely arrested in all but 8 patients with non-infected calcium stones.

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DISCUSSION

DR. HERBERT LANGFORD (Jackson): One comment and one question: The comment is so tangential that it may even miss, but we have been doing a study, getting 24 hour urine in a community-based study of blood pressure in black females. Two weeks ago I got an excited call from our statistical-epidemiological conferees. I had asked them to break down the urine excretion of the hypertensives who were on therapy and those who weren't on therapy. They called with much excitement. Those who listed that they were taking hypotensive therapy were putting out about half as much calcium as the others. The question growing from that: have you other studies concerning calcium absorption, in these people, and also incidently have you studied sodium excretion, because while the calcium data was so clear we didn't have to bother with the t test, but there was a suggestion that the sodium excretion of those chronically taking the thiazides might be slightly increased as if they were sodium deprived and increased their sodium in-take?

DR. YENDT: I am glad your treated hypertensive patients had less calcium in the urine because as we all know, thiazides are the mainstay of treatment in that group. Your question with regard to calcium absorption: We have done some studies and there are some studies reported in the literature. In the acute studies, some of our patients had a reduction in fecal calcium as well as urinary calcium initially for a few months, so that they went into strongly positive calcium balance. In two of those patients, we brought them back a year later for study at which time their GI mechanism presumably had adapted because their fecal calcium had risen. So that they were now absorbing less calcium and they were back into zero calcium balance. So despite the fact that the urine calcium drops and stays down in these people, on the basis of those two studies, it does not appear that they go on retaining calcium forever. Those are the only two long-term studies I know about. The data with regard to the short-term studies are contradictory because none of the others reported at that time showed that the fecal calcium diminished initially with thiazide therapy so our data is a little different from the other reports in the literature.

On the basis of talking to our patients, I suspect that what you say is true—that many of them do in fact increase their salt intake on thiazides. I am afraid that we don't have that particular point analyzed at this time.

DR. SAMUEL P. ASPER (Baltimore): Dr. Yendt, since passing a kidney stone is such a painful episode, I am sure your patients are most grateful to you for the success of your treatment. In those two patients who did pass stones, were you able to capture those stones and carry out a chemical analysis of them and compare the result with that of the stones analyzed prior to therapy?

DR. YENDT: First of all, I should say that only 2 had passed new stones in 1967, but as of 1973, 8 of the total group have had some evidence of progression. We have analyzed stones after they have been on thiazides and have found no significant difference in them.

DR. THOMAS A. WARTHIN (Boston): You comment that the stones are calcium oxalate in identity. Those of us who dabble in disorders of the gastrointestinal tract, have been interested in the high occurrence of stones, calcium monooxalate that occur in patients with Crohn's disease. These individuals have been studied. There are a lot of conflicting investigations, but, in general, they seem to have normal urinary calcium and a hyperoxyluria. Does thiazide therapy alter this urinary oxalate?

DR. YENDT: Well, there is one report in the literature by a man named Glazenburg.* It's in a Netherland's publication—that, in fact, reports a rather striking reduction in urinary oxalate excretion on thiazides. We have urinary oxalate data on 39 patients before and during thiazide administration which did not confirm the striking reduction reported in that other paper although there is significant difference in the mean urinary oxalate between the control data and the treatment data, but it certainly is not very impressive at the present time. The 39 patients studied by us did not have hyperoxaluria secondary to ileal disease. We have subsequently studied one such patient in whom there has been a striking reduction in urinary oxalate excretion during thiazide administration. That is as much as I can say at the moment.

DR. HENRY T. RICKETTS (Chicago): I wanted to know about the nature of the side effects that you had. Were they anything unusual beyond hyperglycemia and uric acid?

DR. YENDT: I think there are the usual thiazide side effects that we are all acquainted with in the treatment of hypertensive patients. I get the impression that perhaps the normotensive stone patient is a little more sensitive to thiazides than the hypertensive patient, but that is purely a clinical impression and I couldn't back that up, but the side effects are the same.

DR. JOHN EAGER HOWARD (Baltimore): Why did you stop the drug in most of them? Because he started to fall down from hypokalemia, vomited, got gout or what?

DR. YENDT: Dr. Howard has been doing this to me for years. The reason for stopping the drug, Dr. Howard, was on the slides. In 19 patients we stopped the drug because of side effects. Ten per cent of all treated patients.

DR. HOWARD: What were the side effects?

DR. YENDT: The commonest side effect in our patients was a feeling of weakness, fatigue and sleepiness. I'm not convinced that all those side effects were due to potassium deficiency and that is why I didn't say yes they were due to hypokalemia.

DR. RICHARD B. HORNICK (Baltimore): You were very careful to point out that your patients were non-infected who had these stones. There has been a series of papers recently, concerning experimental pyelonephritis in mice, in which there has been an evaluation of various diuretics as specific agents to treat the infected kidneys. It would appear that thiazides were very effective in these animals in clearing the bacteria. I wonder if you have tried thiazides in patients with infection and who have stones?

DR. YENDT: Yes, approximately 10 of our treated group had either recurrent or intractable urinary tract infections associated with struvite stones. In some of those patients we were unsuccessful in eradicating the infection even on thiazides, and certainly on the basis of that small experience, I would not be able to confirm or otherwise this experimental observation that I did not know about. It is very interesting.

DR. WILLIAM C. THOMAS, JR. (Gainesville): We do the opposite of what you do. We give phosphates. If they don't work we give thiazides. Perhaps thiazides are less effective in Florida than in Ontario. Could there be some difference in the stone content in the two areas? We also do not find the low magnesium excretion which is sometimes seen in patients with stones in Kingston.

DR. YENDT: First of all, in reply, I should say that I think it is very important that we are treating stone patients differently for the reason which I tried to

* GLAZENBURG, J. The effect of hydrochlorthiazide on the renal excretion of oxalic acid and on the formation of oxalate stones in the urinary tract. *Arch. Chir. Neerland* **23**: 217, 1971.

emphasize in my presentation. The precise indications for all types of therapy still require clarification. I think we should be going at it in different ways as long as those different ways seem to make sense.

I just can't answer the remaining questions that Dr. Thomas puts forward. I think there may well be a difference in his patients from our patients. With regard to the magnesium question particularly, we're worried not only that our stone patients may be different but we are worried that even our normal subjects may be different. In Kingston we find that the mean urinary magnesium excretion in normal subjects is about 78 milligrams per day, which is lower than any value that I can find in the literature. This may indicate that perhaps we are living in an area where the population at large might have an increased susceptibility to stones. We should all keep this in mind in studying stone formation, that we may, in fact, be studying different types of patients in different areas.