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Thiazides in the Prophylactic Treatment of Recurrent Idiopathic Kidney Stones

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In a double-blind prospective clinical study patients with at least two verified episodes of urolithiasis, but stone-free at the time of inclusion in the study, were subjected to prophylactic treatment with either bendroflumethiazide (2.5 mg) + 573 mg potassium chloride 3 times a day, or placebo. The material included a total of 22 patients, all males, aged 20–49 years. We found a clear tendency to reduced stone formation in the group treated with the active drug ($P < 0.1$). Calcium excretion was reduced by 25–50% in 7 of 12 patients treated with thiazide.

In 1970, Yendt et al. [1] reported their findings on the reduction of kidney stone attacks in patients with recurrent kidney stones treated with thiazide diuretics. Earlier, others have published data indicating a reduction of urinary calcium excretion in patients treated with thiazides [2, 3, 4]. During the last few decades the syndrome of recurrent idiopathic kidney stones has been on the increase in the Western industrialized countries [5]. Since the publication of Yendt et al. in 1970, thiazide diuretics have been widely used as prophylactic treatment of recurrent idiopathic kidney stones.

The study of Yendt and his coworkers was based upon data from uncontrolled clinical studies. In 1975, at the Department of Urology, Copenhagen Country Hospital, Glostrup, it was decided to undertake a prospective double-blind controlled study with the objective of evaluating the effect of thiazides in the prophylactic treatment of recurrent idiopathic kidney stones.

Material

Included in the material were males aged 20–49 years, admitted to the Department with previously verified renal/ureteric stones and with at least one episode verified by X-ray or by spontaneous passing of a stone. The patients were included in the project at a time when they were stone-free, if they fulfilled the criteria, and after having been informed of the project and its purpose.

Excluded were patients with hypercalcaemia and other known metabolic disorders that might cause stones. Patients with diabetes mellitus were excluded, too, so were patients with obstructions of the urinary tract, neurogenic bladder

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disease, previous thiazide treatment or present diseases, for which treatment with thiazide would be indicated. Also excluded were patients with social, language or other problems making communication difficult.

The patients who fulfilled the criteria were included consecutively in the project from October 1975 till November 1980.

The study was originally planned to include 60 patients, but because of the strict criteria for inclusion, the project lasted unexpectedly long, and because of changes in the departmental structure it had to be terminated after the inclusion of 27 patients.

Method

The patients were allocated at random to either a thiazide group or a placebo group according to the allocation schedule drawn up prior to the study.

The tablets, which were to be taken 3 times daily, contained placebo or active drug. The latter contained 2.5 mg of bendroflumethiazide (Centyl) + 573 mg of potassium chloride. The patients' own physicians were instructed not to prescribe diuretics without informing the Department. The patients should also continue with their usual food, but were instructed not to use excess salt.

Before the treatment commenced the following examinations were made: Se-calcium, Se-protein, Se-electrolytes, Se-urate and fasting blood sugar. Urinary calcium and creatinine excretion during a 24-hour period were also measured. Calcium excretion was calculated in relation to creatinine excretion at each examination. The urine was also examined for cystine. The patients' weight, height and BP were registered.

The patients were controlled after the start of the treatment with blood tests every 3rd month, urine analysis every 6th month, and urography every year. They were questioned about possible stone symptoms and side effects at every control. The treatment lasted two years. The patients were advised to report if they had stone symptoms and had passed stones. In such cases urography was carried out and passed stones were analyzed.

In cases of verified stone recurrence the code was broken, and the study, treatment and control terminated. The patient then followed the normal routine of the Department, and the placebo-treated patient was offered active treatment.

Results

A total of 27 patients were included in the study; of these five were excluded, one because of hypertension, which needed treatment, and four were lost to follow-up. Of the remaining 22, twelve were allocated to treatment with the active drug (group A) and ten to placebo treatment (group B).

In *group A*, median age of the patients was 37 years (31–48 years); at the first stone episode it was 32 years (22–41 years). The median time from the first

stone episode to inclusion in the study was 4.5 years (1–14 years). The number of stone episodes prior to inclusion was 3 (2 to 9).

In *group B*, median age of the patients was 43 years (37–49 years); at the first stone episode it was 28 years (22–44 years). The median time from the first stone episode until inclusion in the study was 7 years (2–20 years). The number of stone episodes prior to inclusion was 3 (2–15).

The number of operations prior to inclusion in the study was identical in the two groups.

The removed or passed stones were all calcium/oxalate/phosphorus stones. No patients in *group A* experienced recurrence, while in group B four patients (40%) had verified recurrence during the treatment period (passed stones or positive stones demonstrated on X-rays) ($P < 0.1$). Urinary calcium excretion over a 24-hour period in comparison with creatinine clearance showed in *group A* a reduction of 25–50% in seven of the twelve patients. In *group B* no reduction was greater than 20% in the treatment period. Four patients treated with the active drug experienced recurrence within 2 years after termination of the study. Three re-started thiazide treatment and were free of symptoms during an observation period of 1 to 4 years.

In the placebo group, apart from the four who had recurrence during the study, there were another two who experienced recurrence within 2 years after the discontinuance of treatment. One patient in the placebo group had 15 stone attacks prior to the start of the study and after further stone formations, while receiving placebo treatment, the code was broken and he received treatment with the active drug. He has since then been free of recurrences over a 4-year period. Similarly, the three remaining patients in the placebo group who formed stones during the study had the code broken and were subsequently treated with the active drug. They have since remained symptom-free (1–3 years).

Side effects were few. One patient had transient diarrhoea. One patient complained of reduced potency which disappeared when the treatment was terminated at the end of the study. None discontinued treatment because of side effects. All the patients were normotensive at the start of the study, and no reduction of BP was observed in the thiazide group.

Discussion

Although we have not found a significant difference at the 95% level between the two groups in this study, we observed a clear tendency showing that thiazides have a prophylactic effect on stone recurrence in males with recurrent idiopathic renal/ureteric concrements ($P < 0.1$).

Greater significance is hardly possible in a material of this size. The two groups are comparable as to median age and number of stone recurrence. The age at the first episode is slightly lower in the placebo group, which should show a tendency to more frequent stone formation, but this is counterbalanced by a

genuinely lower frequency of stone formation in this group prior to the inclusion in the study; an average of 3 attacks in 6 years compared with 3 in 4.5 years in the thiazide group. The expected recurrence in the two groups should thus be the same.

In several uncontrolled clinical investigations [1, 6, 7, 8], a reduction of recurrence frequency of urinary tract concrements during thiazide treatment has been found. In a preliminary report [9], which is the only published, prospective, controlled and double-blind study, Brocks et al. have found that there was the same reduction in the formation of stones in the placebo group and the thiazide group. In this study the frequency of stone formation per patient-year in the two groups prior to and during the study has been calculated.

In view of the few severe cases of stones, we do not think that this method of calculation will give a reliable picture of the recurrence frequency in a study of this size over a period of 2 years. Therefore, we have chosen to compare the frequency of recurrence between the two identical groups.

The finding of a reduction in the 24-hour urinary calcium excretion of 25–50% in seven out of twelve patients [2, 3, 4, 7] is in agreement with other communications and may be one of the causes of the effect of thiazide treatment, but is hardly the whole explanation. Others have found that thiazides reduce oxalate excretion after treatment for some time and increase zinc excretion and maybe also magnesium [8] in the urine. This could be of help in reducing the formation of calcium concrement in the urine.

Conclusion

From this work we may conclude that thiazides apparently have a favourable effect as a prophylactic treatment of recurrent idiopathic urinary tract concrements in males, and reduce the amount of calcium excreted in the urine in the majority of those treated.

We consider it valuable to initiate a larger prospective controlled study with the purpose of confirming our results. This could be done as multi-centre studies and possibly with modifications of the strict criteria for inclusion of patients. The side effects are few and transient.

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