THIAZIDE DIURETICS IN RENAL HYPERCALCIURIA


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Summary

Forty-six renal hypercalciuric normocalcaemic patients were treated with hydrochlorothiazide (50mg/day) and amiloride (5mg/day), both to reduce new stone formation and to suppress parathyroid hyperfunction. A reduction of hypercalciuria and suppression of parathyroid hyperactivity were observed in 41 patients, while in the other five patients no evidence of parathyroid suppression was found and hypercalcaemia developed. Four of five patients underwent parathyroidectomy which was followed by a normalisation of biochemical signs of hyperparathyroidism.

These results suggest that the appearance of hypercalcaemia in renal hypercalciuric patients during hydrochlorothiazide/amiloride treatment may be of diagnostic value in unmasking pharmacologically non-suppressible normocalcaemic hyperparathyroidism.

Introduction

Idiopathic normocalcaemic hypercalciuria, which occurs in 30–40% of renal stone forming patients [1], is generally divided into four groups: 1. absorptive type, in which hypercalciuria is due to enhanced intestinal calcium absorption; 2. renal hypercalciuria (RH), caused by a primary defect in renal tubular reabsorption of Ca; 3. resorptive type or normocalcaemic hyperparathyroidism (HPTH) [2]; 4. renal tubular phosphate leak, leading to an increase of 1,25(OH)2D3 synthesis with consequent enhanced intestinal Ca absorption [3, 4].

While in absorptive hypercalciuria and in renal tubular phosphate leak parathyroid activity appears to be normal or suppressed, in renal and in resorptive hypercalciurias immunoreactive parathyroid hormone (iPTH) levels are often increased [5].

Reversibility of parathyroid hyperfunction [5] and reduction of frequency of stone recurrence [6] may be obtained in RH normocalcaemic patients after
chronic thiazide therapy. We report here the results of low dose hydrochlorothiazide (50mg/day) and amiloride (5mg/day) treatment in 46 stone forming renal hypercalciuric patients.

Patients and Methods

The diagnosis of RH in 46 adult patients was based on the following: fasting urinary Ca excretion (Ca$_E$) > 0.15mg/100ml of glomerular filtrate (GF) [7], serum Ca < 10.5mg/100ml and serum iPTH high or high-normal after adequate dietary preparation [2]. All patients had endogenous creatinine clearance > 80ml/min. Serum and urinary phosphate (P), Ca and creatinine levels were measured by standard methods; urinary hydroxyproline (OH-Proline) was measured by the method of Goverde et al [8] and serum iPTH by the method of Arnaud et al [9] using a C-terminal antibody. Cumulative Ca absorption rate was calculated according to the deconvolutional method [10]. Metabolic index was obtained by the least squares method from a log-log plot of $^{47}$Ca percentage variation against time [11]. After this metabolic evaluation low dose diuretic therapy (hydrochlorothiazide 50mg/day and amiloride 5mg/day) (HCTA) was started, Ca and P metabolism was reassessed monthly in all patients. Statistical evaluation was performed using Student’s t test and paired t test.

Results

The biochemical data of the 46 renal hypercalciuric stone forming patients are shown in Table I and compared with those of 40 normal subjects. The effects of HCTA administration on serum Ca and fasting urinary Ca$_E$ are shown in Figure 1: 41 patients showed a reduction of hypercalciuria and of stone recurrence [12] without change in serum Ca level. The other five patients had a transient reduction of hypercalciuria which later returned to pretreatment values; moreover in these patients a significant hypercalcaemia developed and progressively increased. After HCTA treatment was stopped, bone turnover studies were performed in these five patients as well as in RH and HPTH patients. These showed a higher activity than in normal subjects (P < 0.001) (Table II). RH patients showed a metabolic

| TABLE I. Biochemical data in renal hypercalciuric (RH) patients compared with normal subjects |
|-----------------------------------------------|-----------------------------------------------|----------------|
| parameter                        | RH 46 patients | Normal subjects 40 patients | p     |
| Serum Ca mg/100ml               | 9.55 ± 0.45   | 9.52 ± 0.35                | NS    |
| Fasting Ca$_E$mg/100 ml GF       | 0.20 ± 0.04   | 0.07 ± 0.03                | < 0.001|
| Tm PO$_4$/GFmg/100ml             | 2.31 ± 0.49   | 3.21 ± 0.22                | < 0.001|
| Serum i-PTH ng/ml               | 1.44 ± 0.81   | 0.77 ± 0.47                | < 0.001|
| Urinary OH-Proline mg/m²/24hr    | 40.9 ± 27.2   | 14.0 ± 6.10                | < 0.001|

Values are mean ± SD

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Figure 1. Effects of hydrochlorothiazide (50mg/day) and amiloride (5mg/day) (HCTA) administration on serum Calcium and fasting urinary Calcium excretion (Ca_F) in 46 renal hypercalciuric patients. PTX = parathyroidectomy

TABLE II. Bone turnover studies in patients with renal hypercalciuria, hydrochlorothiazide-amiloride (HCTA) induced hypercalcaemia, hypercalcaemic hyperparathyroidism and normal subjects

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Cumulative Ca absorption rate (% of administered) (dose)</th>
<th>Metabolic Index</th>
<th>Exchangeable Ca pool (L/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal hypercalciuria</td>
<td>8</td>
<td>64.8 ± 21.2*</td>
<td>0.38 ± 0.12*†</td>
<td>106 ± 17*†</td>
</tr>
<tr>
<td>HCTA induced hypercalcaemia</td>
<td>5</td>
<td>78.6 ± 23.2*</td>
<td>0.50 ± 0.05*</td>
<td>152 ± 44*</td>
</tr>
<tr>
<td>Hypercalcaemic hyperparathyroidism</td>
<td>3</td>
<td>93.4 ± 5.6*</td>
<td>0.50 ± 0.04*</td>
<td>185 ± 49*</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>40</td>
<td>38.1 ± 7.2</td>
<td>0.20 ± 0.05</td>
<td>65 ± 15</td>
</tr>
</tbody>
</table>

Values are mean ± SD
* Differs from normal subjects, P < 0.001
† Differs from patients with HCTA induced hypercalcaemia, P < 0.05

index, exchangeable Ca pool and intestinal Ca absorption rates lower than in patients with HCTA-induced hypercalcaemia, but, due to the small number of patients, the differences were barely significant (Table II).

Four of five patients with thiazide induced hypercalcaemia underwent para-
thyroidectomy (PTX) (Figure 1). Three months after surgery a significant improvement (P < 0.001) in the biochemical signs of hyperparathyroidism was observed when compared with preoperative values: serum Ca 9.3 ± 0.4 versus 11.8 ± 0.7, fasting CaF 0.07 ± 0.01 versus 0.21 ± 0.02, Tm PO4/GF 3.0 ± 0.3 versus 1.4 ± 0.1 and iPTH 0.8 ± 0.4 versus 2.1 ±0.5.

Discussion

Several diagnostic approaches have been proposed to separate renal hypercalciuria with mild secondary hyperparathyroidism from a resorptive hypercalciuria due to autonomous HPTH. Adams et al [13] employed phosphate deprivation, but since hypophosphataemia may stimulate 1,25(OH)2D3 synthesis [3, 4], the reliability of this test is uncertain. Muldowney et al [14] suggested that an increased serum ionised Ca is a good marker of autonomous HPTH but commercially available apparatus for measuring serum ionised Ca is expensive and complex, while calculations of ionised Ca from total serum Ca are inaccurate [15, 16]. More recently Broadus and Thier [17] suggested an oral Ca tolerance test: patients with RH displayed a minimal calcaemic response and a minimal but appropriate suppression in urinary cyclic adenosine-monophosphate (cAMP), while patients with primary HPTH displayed hypercalcaemia with a clearly inappropriate reduction in nephrogenous cAMP. However these results have been obtained in a small number of patients and require confirmation.

The hypercalcaemic response to short term thiazide administration has been advocated for detecting non-suppressible normocalcaemic hyperparathyroidism in some experimental [18] and clinical reports [3,19,20]. However, in some of the patients in these studies hypercalcaemia disappeared after a few days in spite of continued administration of the diuretic [20]. Since an early and transient hypercalcaemia may occur in normal subjects [18] and in renal hypercalciuric patients [3] receiving thiazide therapy, a longer period of treatment is advisable to separate suppressible from autonomous normocalcaemic hyperparathyroidism.

In our experience prolonged administration of hydrochlorothiazide (50mg/day) and amiloride (5mg/day) was actually accompanied by a significant reduction of hypercalciuria and by normalisation of biochemical signs of HPTH in 41 patients. In these patients only moderate fluctuations of serum Ca levels, within the normal range, were observed. The other five patients had a transient reduction of hypercalciuria that returned to pretreatment values after three or more months. Moreover, a significant hypercalcaemia developed, progressively increased and was not reversed to normal by HCTA withdrawal.

The different behaviour of serum Ca between the two groups of patients suggests that homeostatic mechanisms were normal and able to compensate for thiazide-induced hypercalcaemia in the first group. The hypercalcaemic response to thiazide in the other five patients would indicate a failure of the compensatory mechanism, probably due to autonomous hyperparathyroidism [20].

The results of increased bone turnover observed in the latter patients, after thiazide withdrawal, seem to confirm a more significant parathyroid hyperactivity than in RH patients, although this investigation cannot clearly separate the two groups.
Four of five patients were submitted to neck exploration and in all cases a parathyroid adenoma was found and removed. The operation was followed by normalisation of biochemical signs of HPTH.

We conclude that prolonged low doses hydrochlorothiazide and amiloride administration in RSF patients, may reduce hypercalciuria and stone formation in renal hypercalciuric patients and may be an easy and economical method of unmasking normocalcaemic non-suppressible hyperparathyroidism in non-responder patients.

References


Open Discussion

MALLUCHE (Los Angeles) This study confirms previous results published by Parfitt and other investigators. Let me add some information on the mechanism of thiazide-induced serum calcium elevation. Studies done in our laboratory showed that thiazides increase the number of osteocytes per unit volume bone. This might explain, at least in part, the effect on serum calcium seen with thiazide-treatment.

CANTALUPPI Maybe thiazide diuretics act in such a way, but probably in the forty-one patients that responded to thiazide treatment there was a real correction of the hyperparathyroidism—probably because thiazide corrected the underlying defect in renal handling of calcium.
OREOPOULOS (Toronto) I do not know what amiloride is. In our clinic we have never seen this response, and I wonder if amiloride is responsible for this?

CANTALUPPI Amiloride is a diuretic of the distal nephron. It is not responsible for this effect.

OREOPOULOS How can you separate these two effects?

CANTALUPPI Studies using amiloride alone clearly showed no reduction in calcium excretion.

OREOPOULOS So can you explain why you gave both?

CANTALUPPI We gave both in order to spare potassium, and avoid thiazide-induced hypokalaemia.

OREOPOULOS My other question was whether some of these patients would be picked up as hypercalcaemic if you measured the ionic calcium. The total calcium may be normal by the ionic elevated. I wonder whether in these five patients the ionic calcium was measured.

CANTALUPPI I perfectly agree with you. But I have just commented about the difficulty in determining ionised calcium by commercially available apparatus.

OREOPOULOS Was the ionised calcium elevated in these five patients?

CANTALUPPI We have not measured it.

BIJVOET (Chairman) Well Dr Cantaluppi, not many of us measure the ionised calcium, because the method is still very impractical, so I can understand why you did not measure it.