Primary hyperparathyroidism and thiazide diuretics

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Summary
Six patients receiving thiazide diuretics were referred for evaluation of mild to moderate hypercalcaemia (serum calcium 2.65–2.98 mmol/l). All patients were considered to be suffering from primary hyperparathyroidism. Withdrawal of the diuretic was followed by a reduction in the serum calcium, one patient becoming normocalcaemic.

The mechanisms responsible for these changes are discussed. In hypercalcaemic patients taking thiazides, it is recommended that the effects of withholding the diuretic should be observed before more radical measures are considered.

Introduction
Thiazide diuretics are widely used in clinical practice and their major effect on the promotion of the renal excretion of sodium is well known. Their effects on calcium metabolism appear to be less well appreciated. The renal excretion of calcium is consistently reduced by thiazide diuretics (Higgins et al., 1964); a less frequent response is hypercalcaemia.

The advent of multichannel autoanalysers into clinical practice has brought to light more and more patients with unsuspected hypercalcaemia (Heath, Hodgson and Kennedy, 1980). In the majority this is mild and the result of primary hyperparathyroidism. Six patients with hypercalcaemia are reported, 4 of whom were discovered on routine biochemical screening. All the patients were receiving thiazide diuretics withdrawal of which was accompanied by a fall in the serum calcium, one patient becoming normocalcaemic.

Patients and methods
The patients, 2 men and 4 women, were studied in a metabolic unit, and all had been referred from other clinicians for investigation of hypercalcaemia. The clinical details are shown in Table 1. The duration of thiazide therapy (bendrofluazide or hydrochlorothiazide) ranged from 6 months to 8 years.

Thiazide therapy was continued for ≥5 days, and was then withdrawn under close clinical supervision for ≥ 6 days. The patients were ambulant and allowed a free diet throughout the study.

Venous samples of blood were drawn at intervals for estimation of the serum concentrations of calcium, inorganic phosphate, creatinine, albumin and immuno-assayable parathyroid hormone (iPTH). Continuous 24-hr urine collections were made for determination of calcium, creatinine, phosphate and magnesium. The renal tubular reabsorption of phosphate expressed as the index of phosphate excretion (IPE) (after Nordin and Bulusu, 1968), and the urinary calcium excretion/l of glomerular filtrate (C_{\text{CaG}}) (after Nordin, Hodgkinson and Peacock, 1967), were derived from fasting serum and urine samples obtained between 8 and 11 a.m.

Serum and urine calcium, inorganic phosphate, creatinine and magnesium, serum iPTH and serum proteins and albumin were measured as previously described (Davies, Mawer and Adams, 1977). The serum calcium concentrations were corrected for changes in the serum albumin throughout the study (Leading Article, 1977).

Results
The mean serum concentrations of calcium, inorganic phosphate and iPTH when the patients were receiving the diuretic are shown in Table 1. All the patients were hypercalcaemic. One patient had hypophosphataemia, and 3 had decreased renal tubular reabsorption of phosphate. Serum iPTH was detectable in all, and greater than normal (>0.8 μg/l) in 4 patients. These collected findings indicate that all the patients had primary hyperparathyroidism.

Withdrawal of the diuretic was associated with an increase in the urinary calcium in all, and in 5
Primary hyperparathyroidism and thiazides

TABLE 1. Clinical details of the patients

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Presentation</th>
<th>Diuretic (duration)</th>
<th>Biochemistry on initial referral</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calcium (mmol/l)</td>
<td>Phosphate (mmol/l)</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>F</td>
<td>Abdominal pain, Hypertension</td>
<td>Hydrochlorothiazide (8 years)</td>
<td>2.73</td>
<td>0.97</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>F</td>
<td>Hypertension</td>
<td>Bendrofluazide (1 year)</td>
<td>2.78</td>
<td>0.81</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>M</td>
<td>Band keratopathy</td>
<td>Bendrofluazide (4 years)</td>
<td>2.85</td>
<td>0.81</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>F</td>
<td>Backache, Cerebral thrombosis</td>
<td>Bendrofluazide (6 months)</td>
<td>2.98</td>
<td>0.77</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>M</td>
<td>Renal stones, Hypertension</td>
<td>Bendrofluazide (11 months)</td>
<td>2.65</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>F</td>
<td>Osteoarthritis</td>
<td>Hydrochlorothiazide (2 years)</td>
<td>2.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Fig. 1. The response to thiazide withdrawal in Patient 4.

patients with a fall in the serum calcium. These responses were variable in their magnitude and timing; in one patient (no. 5) the serum calcium concentration fell to normal (2.53 mmol/l). The response to thiazide withdrawal is illustrated for patient 4 in Fig. 1. In this patient, the urinary calcium did not increase until the 4th day after the drug was stopped. In the other patients the urinary calcium excretion increased earlier and, in one patient, was discernible within 48 hr. This variation in response has been observed previously (Higgins et al., 1964). For this reason, the mean serum and urine values obtained during thiazide therapy have been compared with those during the 4th, 5th and 6th days off treatment (Table 2).

Withdrawal of thiazide was accompanied by a significant reduction in the mean serum concentration of calcium (mean change 0.12 mmol/l range 0 to 0.2 mmol/l) and in the urinary magnesium; and by significant increases in the mean urinary calcium excretion and creatinine clearance (Table 2). There was no significant change in the mean serum and urinary phosphate, iPE, CaE or the serum iPTH; and no relation was found between the serum iPTH and the changes in serum or urinary calcium.

No relation was found between the decrement in the serum calcium and the increment in the urinary calcium; in all but one of the patients the fall in the serum calcium was less than would be expected for the cumulative increase in the urinary calcium. This finding indicates that thiazide withdrawal caused an increased movement of calcium through the extracellular space, either through increased intestinal calcium absorption or increased bone resorption. That fasting CaE was unchanged may suggest that bone resorption was unaltered.

Discussion

Many studies have been made of the effects of thiazide diuretics on calcium metabolism. The most consistent response is a sustained reduction in the renal excretion of calcium, which is reversed when the drug is withdrawn (Higgins et al., 1964). Hypercalcaemia occurs less frequently. In most instances this is almost wholly explained through the effects
of haemoconcentration; for, when the effects of changes in the concentration of the serum proteins are taken into account, the total serum calcium 'corrects' to normal. This effect apart, thiazides do cause significant increases in the ultra-filtrable and ionized fractions of the serum calcium (Brickman, Massry and Coburn, 1972; Stote et al., 1972; Porter et al., 1978). This effect is seldom sufficient to cause hypercalcaemia in persons with normal parathyroid function. Patients with primary hyperparathyroidism behave differently, and show greater increases in the corrected serum calcium (Van der Sluy Veer, Birkenhager and Smeenk, 1966). This exaggerated response had been used to provoke hypercalcaemia as an aid to diagnosis in patients thought to have hyperparathyroidism with normal or equivocally raised serum calcium concentrations (Adams et al., 1970).

The findings of the present studies are in agreement with previous observations of Brickman et al. (1972). Withdrawal of the diuretic was associated with an increase in the urinary calcium, and a fall in the serum calcium. The patients reported here had primary hyperparathyroidism, and in one the serum calcium fell to normal when the diuretic was withdrawn.

The mechanisms responsible for thiazide-induced hypercalcaemia are not fully understood, but a major factor is the associated reduction in the renal excretion of calcium. This effect is partly attributable to a reduction in the filtered load of calcium (through decreases in the glomerular filtration rate), and partly to increased renal tubular reabsorption of calcium. Both effects can be abolished with sodium replacement (Brickman et al., 1972) and occur independently of parathyroid hormone (Porter et al., 1978).

Although there is good evidence that thiazide-induced hypercalcaemia is largely explained through the reduction in the renal excretion of calcium, extra-renal mechanisms play a part. Patients with advanced renal failure and minimal urinary outputs of calcium develop hypercalcaemia when given thiazides (Koppel et al., 1970). This observation suggests that under these conditions thiazides increase the losses of calcium from bone. The reported effects of thiazides on the intestinal absorption of calcium are conflicting (Ehrig, Harrison and Wilson, 1974), some studies showing no effect, some increased absorption and others, reduced absorption.

The vast majority of patients receiving thiazides have normal parathyroid function, and very few of them develop overt hypercalcaemia. This is predictable and explicable in terms of normal serum calcium homeostasis, and its relation to parathyroid function. Non-parathyroid-induced increases in the serum calcium cause a reduction in parathyroid secretion with a consequent fall in the renal tubular reabsorption of calcium, calcium release from bone and possibly intestinal calcium absorption (through decreased renal production of 1,25 dihydroxycholecalciferol). These effects cause a net fall in the entry of calcium into the extra-cellular space and, within limits, they offset the tendency to hypercalcaemia. Thiazides promote the entry of calcium into the extracellular space. It may be predicted that patients with normal parathyroid function will show a reduction in serum iPTH when given thiazides; there is some evidence that this occurs (Stote et al., 1972). In contrast, patients with primary hyperparathyroidism, and hence autonomous parathyroid function, may be expected to show no reduction in serum iPTH with thiazides, and hypercalcaemia is to be expected. The findings in the present study support this conclusion; thiazides had no effect on the serum iPTH.

An increasing number of patients are now discovered to have hypercalcaemia through the 'routine' biochemical analysis of serum by multichannel autoanalysers. In the great majority the serum calcium is marginally or moderately increased, and often causes no symptoms or complications. These patients commonly have primary hyperparathyroidism. Four of the patients described were found to have hypercalcaemia on routine serum biochemical analysis, and were considered to have primary hyperparathyroidism. The further management of these asymptomatic patients has to be decided on clinical grounds, and many appear to be manageable.

Table 2. The effects of thiazide administration and withdrawal. Mean values (± s.e. mean)

<table>
<thead>
<tr>
<th>Thiazide</th>
<th>Serum Ca (mmol/l)</th>
<th>Serum P (mmol/l)</th>
<th>iPTH (µg/l)</th>
<th>24-hr urine Ca (mmol)</th>
<th>Mg (mmol)</th>
<th>P (mmol)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Ca (µmol/l) glomerular filtrate</th>
<th>Index of phosphate excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>2-8 (0-045)</td>
<td>0-85 (0-031)</td>
<td>1-05 (0-19)</td>
<td>5-96 (1-26)</td>
<td>3-36 (0-26)</td>
<td>21-85 (1-5)</td>
<td>67-3 (6-76)</td>
<td>53-5 (7-73)</td>
<td>0-56 (0-08)</td>
</tr>
<tr>
<td>Absent</td>
<td>2-68 (0-036)</td>
<td>0-78 (0-022)</td>
<td>1-04 (0-16)</td>
<td>8-33 (1-47)</td>
<td>2-70 (0-22)</td>
<td>21-87 (1-78)</td>
<td>75-1 (7-83)</td>
<td>57-5 (5-75)</td>
<td>0-56 (0-11)</td>
</tr>
<tr>
<td>P*</td>
<td>&lt;0-01 n.s.</td>
<td>&lt;0-01 n.s.</td>
<td>&lt;0-05 n.s.</td>
<td>&lt;0-05 n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* = Paired t test; n.s. = not significant.
conservatively. In the authors’ experience the raised serum calcium tends to remain stable over many years, and to cause no problems. Nonetheless, in some asymptomatic patients, the decision to explore the neck or not can be difficult to make; and is sometimes arbitrary. The authors are guided by the age of the patient, the degree of hypercalcaemia and the urinary output of calcium. The decision may be clarified, in patients receiving a thiazide diuretic, by observing their response to withdrawal of the drug. When this is possible, the serum calcium may be restored to normal, or at least to a level which is acceptable for a conservative approach.

Acknowledgments
This work was supported in part by a programme grant from the Medical Research Council to Professor S. W. Stanbury. We thank Dr G. A. Lumb for PTH assay.

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doi: 10.1136/pgmj.57.664.80

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