Acute change in parathyroid function in primary hyperparathyroidism following ultrasonically guided ethanol injection into solitary parathyroid adenomas

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Ultrasonically guided percutaneous injection of 96% ethanol into solitary parathyroid tumours in patients with primary hyperparathyroidism may be used as an alternative to surgery in selected patients. Contrary to surgical parathyroidectomy, the acute changes in parathyroid function following ultrasound-guided chemical parathyroidectomy have never been described. Seven consecutive and highly selected patients with primary hyperparathyroidism were treated with ultrasonically guided injection of ethanol (96%) into solitary and biopsy-verified parathyroid tumours. Basic treatment included a maximum of three injections separated by intervals of 24 h. In six of the seven patients normal serum values of ionized calcium were achieved within 36–120 h (median 36 h) and normal serum values of intact parathyroid hormone within 6–78 h (median 24 h). Three patients received two injections and three patients three injections. One patient remained hypercalcaemic in spite of three injections. Subsequent surgery showed the patient to have two parathyroid adenomas, of which only one had been detected ultrasonically. The present study has demonstrated a fast normalization of parathyroid function following two to three ethanol injections into solitary parathyroid tumours in selected patients with primary hyperparathyroidism.

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The conventional treatment of patients with primary hyperparathyroidism is neck surgery and removal of the diseased parathyroid tissue. In experienced hands the cure rate is high (about 95%) and postoperative complications are few (1). Not all patients are suitable for surgery, either due to concomitant diseases contraindicating surgery or due to an unacceptable risk of postoperative morbidity (2–5). In addition, some patients may refuse surgery.

Ultrasonically guided percutaneous ethanol (96%) injection has been shown to inactivate hyperactive parathyroid tumours in patients with primary hyperparathyroidism (6, 7). We now use this treatment as an alternative to surgery in selected patients (8). The course of decline in serum concentrations of calcium and parathyroid hormone (PTH) during surgical intervention and in the early postoperative period have been well documented (9–12).

The aim of the present study was to investigate and describe the course of normalization of parathyroid function in a consecutive group of patients with primary hyperparathyroidism treated with ultrasonically guided chemical parathyroidectomy and to compare this with the well-known course after surgery.

Material and methods

Seven consecutive patients (females) with biochemically proven primary hyperparathyroidism were referred for treatment. Table 1 details the clinical data. Serum concentrations of ionized calcium and PTH of each individual patient are indicated in Fig. 1. All patients had ultrasound visualization and biopsy verification of a single parathyroid tumour according to principles described previously (13, 14). Three patients (nos 1, 2 and 6) refused surgery (Table 1). In another three patients (nos. 3–5) a prompt lowering of serum-ionized calcium was indicated, due to acute and severe hypercalcaemic symptoms, which included a condition of mental confusion, fatigue, dehydration, anorexia and weight loss. These patients were initially treated with saline infusions in combination with loop diuretics. In spite of this, their symptoms and hypercalcaemia persisted. Patient no. 4 was treated additionally with intravenous infusion of bisphosphonate, with only a temporary reduction in serum calcium values. Furthermore, patient no. 3 suffered from a severe cardiac disease, precluding surgical intervention. Patient no. 5 was followed as an outpatient for 2 years because she had mild primary
hyperparathyroidism. She was offered neck surgery several times but refused and was subsequently admitted in hypercalcaemic crisis. The last patient (no. 7) had a cardiac arrest about 1 month prior to admission. She suffered from severe cardiac disease, ruling out the possibility of surgical treatment in general anaesthesia. Instead, she was treated repeatedly with bisphosphonate infusions, resulting in only short-lived improvements of serum calcium values.

Ultrasound examinations were performed with a 7-MHz sector scanner (B & K Medical, Denmark) mounted with a needle-steering device for precise placement of needles.

The dose of ethanol (96%) was estimated individually, depending on the intraglandular dissemination. The maximum dose was calculated to half of the volume of the parathyroid tumour (half of the product of length, width and depth). A maximum of three treatments separated by short intervals of 24 h were planned. Treatments were stopped whenever serum concentrations of ionized calcium had normalized or if complications occurred. The patients were followed with blood tests 6, 12 and 24 h after each ethanol injection.

Serum-ionized calcium was measured at pH 7.4 using an ionized calcium analyser (Radiometer, Copenhagen, Denmark) (normal reference values 1.15–1.35 mmol/l). Determination of serum PTH was performed as intact PTH (1–84) (Allegro intact PTH kit, Nichols Institute, San Juan Capistrano, C A, USA) (normal reference values 1.04–5.21 pmol/l).

Informed consent was obtained from all patients.

Results

The number of treatments given to each individual patient and the individual course of serum values of ionized calcium and PTH after treatment are indicated in Fig. 1.

In six patients (nos 1–5 and 7) normalization of serum-ionized calcium was achieved within 36–120 h (median 36 h) following initial treatment. Normal serum PTH values were achieved within 6–78 h (median 24 h). Normalization of serum PTH was observed before normalization of serum-ionized calcium. An increase in serum PTH values could generally be noted following normalization of serum-ionized calcium concentrations.

One patient (no. 6) remained hypercalcaemic after three ethanol injections. Following this the patient—in spite of initial refusal—accepted neck surgery. Two parathyroid adenomas were found, of which only one had been detected ultrasonically. Postoperatively the parathyroid function normalized.

In patient no. 4 the interval between the first and second treatment was extended from 24 to 48 h. A large parathyroid tumour was found (5.2 ml) and a more cautious approach was decided owing to the large amount of ethanol calculated to inactivate the tumour, hereby possibly explaining the delayed normalization of parathyroid function.

In patient no. 5 the clinical condition improved in parallel with the normalization of ionized calcium. However, 48 h after initial treatment the patient began to bleed diffusely from the upper and lower gastrointestinal tract. She underwent operation and a bleeding duodenal ulcer with penetration to the pancreas was found. One week later recurrence of gastrointestinal bleeding occurred and the patient died. The serum values of ionized calcium were found to be normal.

Follow-up disclosed two more patients who have died 1 month (no. 3) and 3 months (no. 4) after treatment. Both patients were hospitalized at the time of death and blood tests did not show recurrence of hypercalcaemia. Patient no. 3 died of her cardiac disease. Patient no. 4 became mentally improved following treatment. However, about 1 month later the patient developed anaemia and anorexia. She resisted further investigations. Two days prior to her death the serum value of ionized calcium was 1.25 mmol/l and the serum value of intact PTH(1–84) was 4.8 pmol/l. The remaining patients have been followed from 1 to 14 months and they are still normocalcaemic.

Patient no. 7 developed suggillations around the puncture site, which required no treatment. No other complications associated with the ethanol injections were observed.

Discussion

Previous studies have documented the possibility of ultrasonically guided percutaneous ethanol treatment of

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Table 1. Clinical data in seven patients with primary hyperparathyroidism treated with ultrasonically guided ethanol injection.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Main clinical manifestations</th>
<th>Associated disease</th>
<th>Cause for selection</th>
<th>Size (cm) and volume (ml) of Parathyroid tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>Asymptomatic</td>
<td>Breast carcinoma</td>
<td>Refusal of surgery</td>
<td>1.3 × 1.1 × 0.7 (0.5)</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>Mental depression</td>
<td>Non-toxic goitre</td>
<td>Refusal of surgery</td>
<td>1.5 × 0.7 × 0.7 (0.4)</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>Acute hypercalcaemic symptoms</td>
<td>Cardiac disease</td>
<td>Severe hypercalcaemia</td>
<td>0.9 × 0.5 × 0.7 (0.2)</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>Acute hypercalcaemic symptoms</td>
<td>–</td>
<td>Severe hypercalcaemia</td>
<td>2.6 × 2.0 × 2.0 (5.2)</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>Acute hypercalcaemic symptoms</td>
<td>–</td>
<td>Severe hypercalcaemia</td>
<td>2.0 × 2.0 × 1.0 (2.0)</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>Confusion, mental depression, dehydration</td>
<td>Cardiac disease</td>
<td>Refusal of surgery</td>
<td>1.2 × 1.0 × 1.0 (0.6)</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>Dementia, mental depression</td>
<td>Cardiac disease</td>
<td>High surgical risk</td>
<td>2.3 × 1.0 × 1.0 (1.2)</td>
</tr>
</tbody>
</table>
Fig. 1. The decline in serum concentrations of ionized calcium (○) and intact PTH (●) following percutaneous ethanol injections (arrows) into solitary parathyroid tumours in seven patients with primary hyperparathyroidism. Dotted horizontal lines indicate upper limit (1.35 mmol/l) of normal values of serum-ionized calcium. Full horizontal lines indicate upper limit (5.21 pmol/l) of normal values of serum intact PTH.

The decline in serum concentrations of ionized calcium (○) and intact PTH (●) following percutaneous ethanol injections (arrows) into solitary parathyroid tumours in seven patients with primary hyperparathyroidism. Dotted horizontal lines indicate upper limit (1.35 mmol/l) of normal values of serum-ionized calcium. Full horizontal lines indicate upper limit (5.21 pmol/l) of normal values of serum intact PTH.

parathyroid tumours in patients with primary hyperparathyroidism (6–8, 15). The intervals between treatments should be short, avoiding intraglandular injections into fibrotic tissue. It was suggested that the treatment should be reserved only for patients not fit for surgery (8, 15).

In experienced hands parathyroid surgery is usually safe, with a high cure rate. Therefore, we have decided only to offer percutaneous treatment to patients with solitary parathyroid tumours and only after a careful evaluation and in agreement with the surgical and endocrinological departments (8). Thus, patients admit-
t ed for percutaneous treatment are few and limited to patients with a high surgical risk, older and fragile patients, patients with severe concomitant diseases and patients who refuse surgery. So far, no studies have reported on the more acute changes of the serum concentrations of ionized calcium and PTH during the period of percutaneous treatment and in the immediate post-treatment period.

Following ethanol therapy, a more rapid decline in serum concentrations of PTH as compared to ionized calcium could be observed. The half-life of the biologically active intact PTH is approximately 5 min (12). Close follow-up after parathyroid resection has shown a rapid decline in serum intact PTH, reaching a nadir 1–3 h after completion of surgery (9, 10, 12). In contrast, the fall in serum concentration of ionized calcium is much slower, remaining high throughout the duration of surgery and reaching its nadir at about 20 h after parathyroid resection (10–12). The secondary increase in serum PTH levels is probably stimulated by the reduction in serum levels of ionized calcium. Similar observations have been reported following parathyroid resections (10, 12).

Patients with severe hypercalcaemic symptoms may be in a life-threatening condition. These patients should receive prompt calcium-lowering treatment. Standard treatment with saline infusions in combination with loop diuretics may be insufficient to lower the serum calcium. The calcium-lowering effects of calcitonin or the recently introduced bisphosphonates are short-lived (16, 17) and treatment with mithramycin involves a risk of serious side-effects (16). Additionally, none of these drugs can cure the patient.

Previous studies have shown ultrasonically guided ethanol injection to be useful in selected patients with primary hyperparathyroidism where there are major contraindications or opposition to surgical treatment, resulting in a long-term condition of normocalcaemia or mild hyperparathyroidism (8, 18). The present study has demonstrated the possibility of a rapid lowering of serum concentrations of ionized calcium and PTH following two or three ethanol injections into solitary parathyroid tumours. In case no obvious biochemical improvement is seen after at least three injections, as seen in patient no. 6, we recommend that further treatment attempts should be stopped because multiglandular parathyroid disease is suspected.

References