Can we use 99mTc-MIBI in functional studies of the parathyroid gland?

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Abstract. The usefulness of technetium-99m-sestamibi (99mTc-MIBI) in patients with secondary hyperparathyroidism on haemodialysis was assessed. We studied 33 patients with parathyroid scintigraphy with i.v. (99mTc-MIBI). Static images in a scintillation camera were taken at 15 and 120 min after the injection. With P × Ca < 80, we performed an inhibition test with calcitriol i.v. 2 μg, three times a week, for 2 weeks. The MIBI study and assessment of intact parathyroid hormone (iPTH) were performed before (baseline study) and after inhibition. A ‘focal positive study’ corresponded to one or more areas of abnormal hypercaptation in relation to surrounding thyroid tissue seen in early images and persisting in later images, and a ‘negative study’ did not correspond to the previous image. In the baseline study, iPTH in the positive MIBI group was significantly greater than in the negative group. Eight positive MIBI patients had a bone biopsy; six corresponded to severe osteitis fibrosa and two to mild osteitis fibrosa. In the negative MIBI group, four of the six patients who had bone biopsy had mild forms of osteitis fibrosa (Fisher = 0.03); the other two had low turnover forms. A positive inhibition test was defined when the basal uptake disappeared after calcitriol administration. In these patients, we observed a significant decrease of iPTH, not observed in the negative inhibition test. In 10 patients who had been parathyroidectomized, those with a positive basal MIBI result had a nodular parathyroid hyperplasia. We conclude that a scintigraphic parathyroid study with 99mTc-MIBI showed a good correlation with functional parathyroid status. With the same inhibition test, only some glands were inhibited, suggesting that this could be the expression of different vitamin D receptor densities in inhibited glands and/or a different kind of proliferation in those glands. This test would be of value in functional studies when a therapeutic decision must be made.

Key words: chronic renal failure; haemodialysis; 99mTc-MIBI parathyroid scintigraphy; parathyroid hyperplasia; secondary hyperparathyroidism

Introduction

The understanding of pathogenic mechanisms in secondary hyperparathyroidism has progressed in recent years [1–3]. Radiisotopic techniques, like other imaging procedures, have been useful for the detection of parathyroid glands [4]. The most commonly used radioisotopic method is double subtraction with T1201 and Tc99 or I123 [5]. The usefulness of a cationic complex of isoalkilonitriles of technetium (99mTc-MIBI) has been described, mainly in primary tumours. These compounds penetrate within the intracellular and intramitochondrial spaces, depending on the respective membrane potential difference. Hence they will be taken up by cells in a phase of activity and they have been used as tumour markers. Uptake by benign tumours is not the rule, but primary parathyroid adenomas have shown a good incorporation of the radiomarker [5].

The aim of this study was to evaluate the usefulness of 99mTc-MIBI in the diagnosis of secondary hyperparathyroidism in uraemic patients and to determine if there is any relationship between the functional status and the intensity of uptake by means of an inhibition test.

Patients and methods

We studied 33 patients with secondary hyperparathyroidism on chronic haemodialysis, 19 women and 14 men with a mean age of 54 ± 13 years and a mean time on haemodialysis of 67 ± 37 months. In all patients, we performed a parathyroid study with i.v. 99mTc-MIBI, 20 mCi per 70 kg of body weight (baseline study). Static images in a scintillation camera (SOPHA Computer DSX) were taken at 15 and 120 min after the injection [6]. When the calcium phosphorus product was < 80 we performed an inhibition test. We administered i.v. calcitriol, 2 μg after haemodialysis during 2
weeks, measuring calcium and phosphorus at days 5 and 10, and afterwards we repeated the scintigraphic study. Intact parathyroid hormone (iPTH) was determined simultaneously with the basal study and with the study after calcitriol.

We defined a ‘focal positive study’ when we observed one or more clearly defined areas of abnormal uptake in relation to the surrounding tissue, placed in the thyroid area, visible in early images and persisting on late images (washout); and the study was ‘negative’ when it did not correspond to the previous situation [6].

Calcium, phosphorus and alkaline phosphatase were determined by standard methods. iPTH was measured by immunoradiometric assay (IRMA) (ELSA-PTH, CIS BIO International Laboratory, France) (normal values: 8–76 pg/ml).

A statistical analysis was performed using the Student’s t-test and $\chi^2$. A $P$ value < 0.05 was considered significant. The results are shown as $x \pm SD$.

**Results**

From 33 basal studies, 22 were positive, with one or more glands taking up the radiotracer, and 11 were negative. In one of the positive studies the image was located in the mediastinum, with a negative image in the neck. Fifteen patients had a concomitant sonography; in eight of them there was coincidence of images in both techniques.

There were no significant differences regarding age, time on haemodialysis, calcium, phosphorus and alkaline phosphatases between negative and positive groups. The iPTH was significantly greater in the positive than in negative group ($P < 0.0001$) (Table 1).

Fourteen patients had a bone biopsy; 12 of them showed osteitis fibrosa and the others an osteomalacia and a mixed form both with aluminium. In the two last patients, the MIBI was negative.

Ten patients had been parathyroidectomized; nine had a positive basal study and nodular hyperplasia on parathyroid histology. On the contrary, a negative MIBI corresponded to a diffuse hyperplasia.

In four patients with a positive basal study, the inhibition test was positive (parathyroid uptake disappeared after calcitriol administration) (Figures 1–3). In these patients, iPTH changed from $1722 \pm 908$ to $530 \pm 258$ pg/ml ($P = 0.002$) after calcitriol administration. In patients with a negative inhibition test

![Fig. 1. Parathyroid scintigraphy with 99mTc-MIBI. Basal study showing three images in the neck (positive study).](image)

![Fig. 2. The same patient as in Figure 1 after i.v. calcitriol administration (one gland has disappeared) (positive inhibition test).](image)

**Discussion**

Much progress has been made in recent years regarding morphological studies of the parathyroid glands (ultrasound, computer tomography, magnetic resonance and scintigraphy with 201T1-99Tc) [4]. The scintigraphy of parathyroid glands with Tc99-alkilisonitrile allows a morphological study including the localization of ectopic glands. This tracer penetrates into cells with high metabolic activity, such as malignant and adenomatous cells [7]. There is little information about the uptake of MIBI by hyperplastic parathyroid cells.

**Table 1. Clinical and humoral data**

<table>
<thead>
<tr>
<th></th>
<th>Positive MIBI</th>
<th>Negative MIBI</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 12</td>
<td>53 ± 17</td>
<td>N.S.</td>
</tr>
<tr>
<td>Time on dialysis</td>
<td>75 ± 50</td>
<td>67 ± 44</td>
<td>N.S.</td>
</tr>
<tr>
<td>Ca (mg/dl)</td>
<td>9.78 ± 1.32</td>
<td>9.02 ± 1.26</td>
<td>N.S.</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>6.67 ± 1.65</td>
<td>6.98 ± 2.22</td>
<td>N.S.</td>
</tr>
<tr>
<td>AP/N</td>
<td>2.25 ± 1.77</td>
<td>1.83 ± 1.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>1153 ± 608</td>
<td>464 ± 329</td>
<td>&lt;0.0001</td>
</tr>
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AP, alkaline phosphatase; n, normal.
Functional parathyroid scintigraphy with 99mTc-MIBI

In our study, the 99mTc-MIBI scintigraphy showed a relationship to functional parathyroid status. According to our results, the 99mTc-MIBI scintigraphy was useful for completing the functional study of secondary hyperparathyroidism in patients on hemodialysis. As we can see, positive studies corresponded to increased concentrations of iPTH, more severe forms of osteitis fibrosa on bone histology and nodular hyperplasia of the parathyroid gland. This could indicate a different degree of severity of hyperparathyroidism in positive MIBI glands.

This fact could be related to a greater uptake by cells with high metabolic activity, which could explain the greater uptake of radiotracer by them. Other authors have observed a large negative intracellular potential in high activity cells [8,9].

Piwnica-Worms et al. have demonstrated an inverse relationship between cell membrane expression of P-glycoprotein and 99mTc-MIBI uptake [8]. Other authors have pointed to a different expression of P-glycoprotein in the cell membrane of normal, hypoplastic and tumoral cells which could also offer an explanation for the different uptake of the radiotracer [10].

Fukuda et al. have demonstrated a different density of vitamin D receptors in nodular and hyperplastic parathyroid tissue [11], and recent work has shown different numbers of calcium sensors on the surface of adenomatous and nodular hyperparathyroid tissue [12]. This could also be an explanation of the different uptake patterns of the radiotracer in the MIBI study, as has been mentioned by other authors [13].

Searching for an indirect demonstration of this phenomenon we performed, as shown, an inhibition test with vitamin D. Our results showed the possibility of inhibiting certain glands, and this fact corresponded to lesser severity in the clinical status. The patients who had a positive inhibition test had less severe forms of hyperparathyroidism as measured by iPTH. It is possible that nodular tissue, corresponding to severe forms of hyperparathyroidism and to a monoclonal parathyroid growth [14–16], had a lower number of vitamin D receptors and could not be inhibited by the test [17].

We conclude that this test would be of value in functional studies when a therapeutic decision must be made. It is probable that it will allow the selection of patients for medical treatment, surgical removal or even percutaneous ethanol injection [18], according to the results of the inhibition test; and perhaps it might be useful for the study of recurrent hyperparathyroidism after parathyroidectomy.

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References