Intraoperative monitoring of intact PTH during surgery for primary hyperparathyroidism

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Intraoperaives Monitoring der intakten PTH-Sekretion bei Eingriffen wegen primärem Hyperparathyreoidismus

Abstract. The intraoperative differential diagnosis between adenoma and hyperplasia during surgery for primary hyperparathyroidism (pHPT) is sometimes difficult. Several methods have been proposed to aid the surgeon in deciding on the amount of parathyroid tissue to be resected. We examined the use of intraoperative monitoring of intact PTH in 47 patients operated upon for pHPT. The highly sensitive assay for intact PTH was modified to permit a total turn-around time from gland excision to obtained result of about 60 min. The correlation (r) between the results of the modified and the conventional method, which requires 24 h of incubation, was 0.98. At 15 min after removal of the parathyroid adenoma the levels of intact PTH had decreased by [mean (SD)] 85 (11)%. A decrease of 63% in intact PTH in patients with parathyroid adenoma predicted with 95% confidence the 4 patients with primary hyperplasia as not having parathyroid adenoma. We conclude that intraoperative measurement of intact PTH could be a valuable adjunct to surgical skill, especially for reoperative parathyroid surgery.

Zusammenfassung. Die intraoperative Differentialdiagnose zwischen Adenom und Hyperplasie bereitet bei Eingriffen wegen primärem Hyperparathyreoidismus (pHPT) gelegentlich Schwierigkeiten. Es wurden verschiedene Methoden vorgeschlagen, nach denen der Chirurg entscheiden kann, wieviel parathyreoides Gewebe zu resezieren ist. Wir untersuchten bei 47 Patienten, die wegen pHPT operiert wurden, die Anwendung des intraoperativen Monitoring der intakten PTH-Sekretion. Der entsprechende hochsensitive PTH-Assay wurde modifiziert, damit ein komplettes Resultat von der Exzision an über 60 min zu erzielen war. Die Korrelation r zwischen den Ergebnissen nach modifizierter und konventioneller Methode (die eine 24-h-Inkubation erfordert) betrug 0.98. Die intakte PTH-Sekretion verringerte sich 15 min nach Entfernung des parathyreoiden Adenoms um 85 (11)% [Mittelwert (SD)]. Die Patienten mit parathyreoidem Adenom wiesen eine PTH-Verringerung von 63% auf; dies ließ bei den 4 Patienten mit primärer Hyperplasie zu 95% zuverlässig erkennen, daß sie kein parathyreoides Adenom hatten. Wir folgern daraus, daß die intraoperative Messung der PTH-Sekretion ein wichtiges chirurgisches Hilfsmittel (insbesondere bei Reoperationen) sein kann.

Schlüsselwörter: Primärer Hyperparathyreoidismus – Chirurgie – PTH (Parathormon)

It is important for the endocrine surgeon to distinguish between parathyroid adenoma and hyperplasia as the cause of primary hyperparathyroidism (pHPT) during surgery, since the amount of parathyroid tissue to be removed depends on the diagnosis. The intraoperative differential diagnosis between unilateral and multiglandular disease is presently based mainly on the macroscopic appearance of the parathyroid glands [1, 2]. To help the surgeon, several additional tools have been introduced, including the use of frozen section for examination of the excised parathyroid glands with intracellular fat staining [2–4], intraoperative density or floating test [5] and assessment of parathyroid activity, i.e., urinary cAMP [6–8] and ionized calcium [9]. Except for intraoperative histology with fat staining, which is very much favoured by surgical centres dedicated to the concept of unilateral neck exploration [10–12], none of the above methods has gained widespread acceptance. Nevertheless, the decline in excretion of urinary cAMP after surgical removal of a parathyroid adenoma suggests that secretion of PTH is suppressed in the remaining normal-sized glands [6–8], and consequently the serum levels of intact PTH can also
be expected to fall after adenomectomy. Since the introduction of highly sensitive assays for intact PTH, such a decline has also been shown in several studies [13–17]. Thus, after adenomectomy serum levels of intact PTH have been found to decline to less than 40% of baseline values at 15 min after excision of the parathyroid adenoma [13], and a difference in decline of intact PTH has been demonstrated between patients with pHPT resulting from parathyroid adenoma and those with pHPT resulting from hyperplasia [16, 18, 19]. Conventional assays for intact PTH require a long-term incubation (usually 24 h), which precludes their use as an intraoperative aid to the surgeon. However, the development of sensitive assays for intact PTH with short incubation time might be of great practical advantage [13, 20, 21]. In this study we describe our experience with intraoperative measurement of intact PTH during surgery for pHPT.

Patients and methods

Patients. The decline of intact PTH was measured in 47 patients with hyperparathyroidism, 35 women and 12 men with a mean age of 64 (SD 13) years. The mean (SD) preoperative level of serum calcium was 2.81 (0.25) mmol/l and the mean (SD) serum level of intact PTH was 14.9 (26.6) pmol/l.

Surgery. Patient with pHPT were subjected to unilateral surgical neck exploration: when a parathyroid adenoma was found it was removed, together with excision or biopsy of the ipsilateral normalized gland, and sent for histology. Bilateral exploration was performed in cases of hyperplasia, with excision of 3–3.5 parathyroid glands. Once the first macroscopically enlarged gland was found a sample for intact PTH was drawn from a peripheral vein. Special care was taken not to manipulate the gland before clamping of the vascular pedicle. After excision of the enlarged gland, sampling was performed after 5 (n = 34) and 15 min (n = 47).

Histology. Parathyroid adenoma was diagnosed when an enlarged parathyroid gland exhibited a remnant of normal glandular tissue outside its capsule and/or a variation and enlargement in nuclear size together with decreased cytoplasmic fat, and the ipsilateral gland was normal in weight and histology. Hyperplasia was diagnosed when two or more glands show increased glandular and parenchymal cell weight, together with decreased fat cell content and reduced and pathologic arrangement of cytoplasmic fat of the parenchymal cells [22].

Analysis. Serum levels of intact PTH were measured using the N-tact PTH assay (Incat, Stillwater, Minn., USA). In this assay, two polyclonal antibodies were used. One antibody was a 125I-labelled goat antibody directed to PTH[1–34], The other antibody was a goat antibody directed to PTH[39–84], which was bound to a solid phase. The sensitivity of this assay is 0.13 pmol/l and the reference range in a normal population 1.0–5.0 pmol/l. To shorten the time needed for analysis, the assay was modified as previously described [21]. Briefly, the volume of both the tracer and the sample is doubled, and incubation is done with shaking (300 Hz) and at 37°C for 30 min. The within-assay variation between 0.8 and 10 pmol/l is <4% for the conventional method and <8% for the rapid method. The results obtained by the conventional and rapid methods differ by a factor of two. This is probably due to matrix differences in the standard and samples, with a slower reaction rate in standards, since the stability of PTH in both standards and samples at 37°C was excellent and did not differ. The correlation between the methods is 0.98.

Serum calcium was measured with an autoanalyzer (Kodak Ektachem 700x R-C).

Statistics. The results were expressed as mean (SD). Correlation between biochemical variables was assessed by using linear regression analysis. A probability level for random difference of P<0.05 was considered significant.

Results

In 43 patients a single parathyroid adenoma with a mean weight of 1.03 (1.51) g was found, whereas 4 patients had primary hyperplasia. All patients had normal or low serum levels of calcium at follow-up after a minimum of 8 weeks.

After excision of a parathyroid adenoma intact PTH decreased rapidly. The decline in levels of intact PTH was 65 (20)% at 5 min and 85 (11)% at 15 min (Fig. 1). No significant correlation was found between the decline of intact PTH at 15 min and baseline serum levels of calcium (r = 0.12; P < 0.45), intact PTH (r = 0.10; P < 0.54) or the weight of the excised parathyroid adenoma (r = 0.07; P < 0.66). In contrast, a more sluggish decline of intact PTH was seen in the 4 patients with hyperplasia, with a mean decrease of intact PTH by 37 (9)% at 15 min. Calculating the decline of intact PTH at 15 min after gland removal revealed that a decrease in intact PTH by more than 63% of the baseline value predicted with 95% confidence the 4 patients with primary hyperplasia as not having a parathyroid adenoma (Fig. 2). It was also found that intact PTH did not decrease after excision of normal parathyroid tissue (Fig. 3).

Discussion

With the introduction of highly sensitive assays for intact PTH, measurement of PTH has become possible without interference by a "noise" of inactive fragments. The half-life of the intact PTH has thereby been calculated to approximately 5 min [23]. In our study, a rapid decrease of intact PTH was found after excision of a parathyroid adenoma, confirming that the function of the normalized parathyroid glands left in situ is suppressed. This