Peroperative PTH testing:

confirmation of successful surgical treatment of primary hyperparathyroidism

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Summary

Objective To study the reliability and applicability of a rapid parathormone (PTH) test as predictor of successful surgical treatment of primary hyperparathyroidism.

Design Prospective.

Method All 35 consecutive patients undergoing surgery for primary hyperparathyroidism in the University Medical Center Utrecht, The Netherlands, between August 1997 and August 1998, were tested just prior to surgery, and immediately following adenomectomy. The rapid PTH test consisted of a modification of the computerized immunometric detection by chemoluminescence.
The decrease of serum PTH as estimated with the rapid test was correlated with surgical findings as well as postoperative serum calcium levels. In the first 25 patients (group A) the reliability of the test was investigated. In the next 10 patients (group B) the PTH test results were allowed to have implications for surgical management, i.e. an insufficient (<50%) decrease of serum PTH following adenomectomy resulted in immediate re-exploration.

Results The 35 patients, 22 women and 13 men, had a median age of 58 years (range: 22-80). The results obtained with our rapid PTH test correlated fully with both conventional PTH measurement techniques and postoperative serum calcium levels. In group A 21/25 patients showed adequate (>50%) decrease of their serum PTH levels; the 4 patients without such decrease were the ones displaying persistent postoperative hypercalcemia. In group B 9/10 patients had adequate PTH decrease immediately following adenomectomy, while in one patient this was only attained after further exploration and excision of a second adenoma. No false-positive or false-negative measurements were encountered.

Conclusion The rapid PTH-test used is a reliable predictor of successful adenomectomy for primary hyperparathyroidism, also in minimally invasive surgery.

Introduction

The purpose of the surgical treatment of primary hyperparathyroidism is to normalize the calcium concentration in the serum. It is therefore necessary during the operation to locate and remove the hyperfunctioning parathyroid tissue. In the majority of the cases there is one adenoma; but two, three, or even four adenomas occur in about 15% of the patients. Because the serum calcium concentration from a successful operation decreases very slowly, one normally must wait until the next postoperative day in order to be certain the intended normalization indeed has occurred. In those cases where the serum calcium concentration has not decreased, or decreased enough, a second operation must be performed under less favorable conditions for both the patient as well as the surgeon.

The parathyroid hormone (PTH) has a half-life of less that five minutes [1], and should in theory be able to be used to determine during the operation if all of the hyperfunctioning tissue is removed. Until recently, reliable measurement of the PTH concentration in the laboratory was too labor-intensive and too time-consuming for this purpose. Now faster methods for the measurement of the PTH concentration have become available, and the ideal of having proof during the operation will be successful, is clearly in sight.

The usefulness of a recently developed, rapid PTH measurement was tested and correlated for operative and postoperative findings in 35 patients who were operated for primary hyperparathyroidism. At the same time the effects of this new approach for the following surgical strategy was studied.

Methods

All consecutive patients between August 1997 and September 1998 (13 months) who were candidates for surgical treatment of their primary hyperparathyroidism were eligible for the study. The diagnosis ‘primary hyperparathyroidism’ was formed based on a repeated increased concentration of calcium and parathormone in the serum. At the same time, according to protocol, a localizing diagnostic was performed using Doppler ultrasonography and spiral computed tomography examination of the neck. The results of this determined if a conventional, systematic neck exploration was performed, than if a direct removal of the adenoma in a minimally invasive way was sufficient. This direct exploration has as its disadvantage that not all the parathyroid tissue is identified nor can it be macroscopically

reviewed. For this limited procedure, just as with the conventional neck exploration, not identified diseased glands at imaging and exploration result in a persistent hypercalcemia.

At the beginning of the operation and eight minutes after the hyperfunctioning parathyroid tissue was removed, peripheral venous blood was drawn and a PTH measurement was done. In order to establish the reliability of the new measurement in the perioperative period, no surgical conclusions were drawn from the results of the PTH-values after resection in the first 25 patients (group A). In the following ten patients (group B) a decrease of PTH concentration of at least 50% was considered as evidence that all the hyperfunctioning tissue was removed. No decrease or a decrease of less than 50% was reason to immediately perform further neck exploration afterwards. If more adenomatous parathyroid tissue was found, a quick PTH-measurement was again done after its removal.

Measurement of parathormone

For the measuring of PTH a new modification of the automated immunometric (sandwich) measurement with chemoluminescence (Immulite, Diagnostic Products Corporation (DPC Holland), Apeldoorn) was utilized [2]. This measurement made use of two purified (cultured in goats) antibodies against, respectively, the first so-called N-terminal part (amino acids 1-34) and the last so-called C-terminal (amino acids 44-84) part of the PTH molecule. The C-terminal antibody is bound to a polystyrene bead and the N-terminal is recognized with the enzyme alkaline phosphatase, with which the chemiluminescence becomes activated after reaction with PTH. The measurement is directed towards the measuring of intact PTH; pieces of PTH show no cross-reaction in the assay.

The modification holds that a shorter incubation time is used than until now has been described: the original measurement has a reaction time of 60 minutes, while the modification is incubated for 30 minutes. The measurement is tolerant for serum as well as ethylene diamintetra-acetate (EDTA). In practice EDTA-plasma is worked with since the plasma and cells being separated from each other directly after the blood is drawn. After being received by the laboratory and centrifuged for four minutes, the assay is begun, which proceeds further automatically in the Immulite, which is made ready for the PTH-measurement in advance. After approximately 45 minutes the results are available after calculation with the attached microcomputer. The sensitivity of the shortened assay ($\sim$ 0.1 pmol/L), is practically identical to the original; the variation between measurements amounts to 5.3% at 4.8 pmol/L, 3.0% at 34.4 pmol/L, and 3.3% at 90 pmol/L (each time $n = 10$). The correlation between the long and the short method were determined in more than 100 samples; the correlation coefficient amounted to 0.992 at a gradient of 0.986, which says that the results were absolutely comparable.

Results

The study was performed with 35 patients with primary hyperparathyroidism. It involved 22 women and 13 men with a median age of 58 years (range: 22-80). The median serum concentrations of calcium and parathormone were, respectively, 2.75 mmol/L (ranges: 2.51-3.81; normal: 2.20-2.60), and 13.3 pmol/L (ranges: 2.3-148.0; normal for normocalcemia: <8 pmol/L). In 26 patients (group A, 19; group B, 7) a minimally invasive operation was performed. The other 9 patients (group A, 6; group B, 3) underwent a conventional neck exploration.

Group A (reliability of the assay)

Of the 25 patients from this group, 21 became normocalcemic after the operation (**Table 1**). The perioperatively measured decrease of the PTH serum concentration with these patients was, with a median decrease of 82%, unmistakable.
With the four patients who still showed hypercalcemia after the operation, the perioperatively measured PTH values showed no (two patients) or an insufficient decrease (15% and 30%). Of these four patients, two underwent in the meantime repeat surgery; at that a second parathyroid adenomas was found, after which this was removed and microscopically confirmed. Upon this the perioperative PTH concentration decreased significantly then and normocalcemia existed after the operation. The two other patients with persistent hypercalcemia are still waiting to be reoperated.

Group B (applicability of the assay)

This group consisted of 10 patients (**Table 2**). In 9 a significant decrease of the serum PTH concentration (median decrease: 87%) was determined during the operation. In one patient the PTH concentration barely decreased after resection of one adenoma (from 9.4 to 7.3 pmol/L). Further exploration followed immediately, by which a second adenoma was found and removed, followed with a significant decrease of the PTH concentration (from 7.3 to 1.2 pmol/L). All ten patients were normocalcemic after exploration.

In total was thus 33 times (30 times during primary exploration, 3 times during further exploration) perioperatively a significant decrease of the serum PTH concentration established and in all these 33 cases normocalcemia later existed, as proof of a successful exploration. In four cases (during the 'reliability study') the operation was ended, while no or only a limited decrease of the serum PTH concentrations was ascertained, which was followed by persistent hypercalcemia. There were in this patient group, therefore, no false-negative and no false-positive results found.

Table 1 Serum parathormone concentrations measured before and after resection of hyperfunctioning parathyroid tissue in 25 patients with primary hyperparathyroidism (Group A, reliability study).

	perioperative					postoperative
	serum PTH concentration in pmol/L			serum calcium concentration in mmol/L		normocalcemia
patient	preresection	postresection	decrease (%)	preresection	postresection	
1	14.0	1.4	90	2.75	2.27	yes
2	14.0	3.1	78	2.92	2.50	yes
3	8.5	0.9	89	2.66	2.18	yes
4	53.0	4.8	91	3.02	2.28	yes
5	11.4	0.1	99	2.68	1.97	yes
6	61.0	4.4	93	3.16	2.24	yes
7	12.3	2.3	81	2.75	2.11	yes
8	17.0	2.9	83	2.70	2.30	yes
9	12.0	1.0	92	2.59	1.94	yes
10	13.3	13.5	0	2.78	2.73	no *
11	27.3	2.4	91	3.01	2.18	yes
12	11.7	1.2	90	2.51	2.10	yes
13	21.0	14.2	33	2.81	2.71	no#
14	6.2	1.4	78	2.60	2.07	yes
15	25.8	1.9	93	2.87	2.35	yes
16	28.2	2.2	92	2.64	2.25	yes
17	13.9	11.9	14	2.79	2.71	no *
18	2.3	0.1	94	2.70	2.16	yes
19	11.3	0.9	92	2.63	2.25	yes
20	34.5	9.6	72	3.02	1.95	yes
10 b *	12.3	2.0	84	2.76	2.11	yes
21	4.1	2.0	52	2.70	2.20	yes
17 b *	11.5	1.3	89	2.72	2.39	yes
22	6.4	0.9	86	2.65	2.01	yes
23	15.0	4.2	72	2.94	2.40	yes
24	109.0	20.0	82	2.72	2.05	yes
25	4.6	4.5	0	2.90	2.65	no#

* reexploration is executed.

reexploration will be executed.

Table 2 Serum parathormone concentrations measured before and after resection of hyperfunctioning parathyroid tissue in 10 patients with primary hyperparathyroidism (Group B, reliability study).

	perioperative					postoperative
	serum PTH concentration in pmol/L			serum calcium concentration in mmol/L		normocalcemia
patient	preresection	postresection	decrease (%)	preresection	postresection	
1	8.3	1.5	82	2.75	1.94	yes
2	16.4	1.6	90	2.66	2.28	yes
3	8.7	1.4	84	2.60	2.14	yes
4	9.4	7.3 (1.2)	32 (84)	2.75	(2.13)	yes
5	148.0	11.3	92	2.90	1.95	yes
6	12.0	2.5	79	3.01	2.15	yes
7	10.0	3.9	61	2.80	2.10	yes
8	11.1	1.0	91	2.79	2.05	yes
9	35.1	4.7	87	2.90	2.10	yes
10	61.5	11.4	82	3.80	2.55	yes

Numbers between parentheses are values after reoperation and resection of a second adenoma.

Discussion

The results of our investigation showed that perioperative PTH-measurements can be of good use in determining the completeness of resection of hyperfunctioning parathyroid tissue and with that to predict the chance of success of the operative treatment of primary hyperparathyroidism.
This finding agrees with the recently published experiences of a group Swedish investigators [3]. Going by the definition that the PTH concentration should be decreased by at least 50% five minutes after resection and at least 60% 15 minutes after resection in order to be able to predict a positive result, they found a sensitivity of 86% by the 5 minute and 97% by the 15-minute definition. The specificity was 100%. The development of a rapid, but especially reliable PTH-assay brings a number of not to be undermined advantages with it. In the first place the patient can be placed in a prospect of greater certainty. Furthermore, a decrease in the number of non-successful explorations can be expected along with the accompanying complications of parathyroid surgery, which are seen mainly in repeat operations. The decrease of the necessity for repeat operations, and with it the decrease of supplementary examination and the number of hospital admittances will above all be cost-efficient. Finally, the development and applicability of the rapid PTH-assay can be seen as a definite step towards wide application of the direct, minimally invasive treatment of primary hyperparathyroidism.

Until now most experts saw as the golden standard the bilateral, systematic exploration of the neck in which all the four parathyroid glands are identified and inspected [4]. Not unjustly, incidentally, because with such a conventional neck exploration is the change of success in experienced hands high, 95 to 97%; that can not be said until now of less extensive explorations, of which the unilateral is the most applied. Now that a rapid PTH-assay is available to assure the success of the surgery, there is no hindrance standing in the way of ample application in the less invasive approach. One of those is the technique with which we, owing to the developments in radiology, such as echodoppler and spiral computed tomography examination, recently achieved very promising results [5]. It is then also to be expected that the indication for operative treatment of primary hyperparathyroidism will be more ample than suggested before [6].

Next to the rapid PTH-assay used by us are special 'kits' obtainable for some time which are so quick that the total time needed between collection of blood on the one side and the result of the PTH measurement on the other side amounts to only a quarter of an hour [7]. The high costs associated with this method however seem to matter when weighed against the time that is saved. It is true that we must wait 45 minutes for the results after collection of the blood samples using our method,

but the (expensive) procedure at the operation rooms do not have to be impeded by that. The practical solution that we found for that, and that is in the meantime being routinely applied with success, is the following;
The patient with primary hyperparathyroidism is one of the first to be operated in the daily schedule. When the surgeon feels that all the hyperfunctioning parathyroid tissue is removed, a blood sample is taken to check the PTH measurement and the operation is ended. After that the patient, such as usually is done, goes to the recovery room. There he/she stays in any case until the result of the PTH measurement is known. In the majority of cases (in this group 30 of the 35 patients) the PTH concentration provides immediately the assurance of a successful operation and the patient, as soon as it is anesthesiologically responsible, can be returned to the nursing ward. The patient, by whom an insufficient decrease was determined, went then from the recovery room back to the operation room, where the neck exploration was continued. The extra burden for the patient stays thus limited and our experiences teaches in the meantime that patients choose by far this design over the uncertainty that is characteristic to the conventional course of things.

In summary, it seems from this study with a rapid perioperative PTH assay that this method can reliable predict the result of the operation and that it must be possible, by a consistent application to reduce the number of unsuccessful explorations for primary hyperparathyroidism to practically none, even when less invasive approaches become applied.

References

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