Immunometric Assays of Parathyrin in the Diagnosis of Hypercalcemic Individuals

The application of immunometric assays to the measurement of parathyrin (PTH) has provided the sensitivity and specificity required to measure the intact, circulating, biologically active form of the molecule, PTH 1–84. These assays have been an important advance in permitting study of the regulation of PTH secretion in response to rapid changes of mineral ions, in disorders of altered skeletal activity such as hyperparathyroidism, and in understanding the recovery of remaining parathyroid gland function after parathyroid adenectomy. Nonetheless, a paramount question remains: Do these assays offer advantages to the clinician for the diagnosis of hypercalcemic individuals?

Malignancy and hyperparathyroidism account for >90% of all cases of hypercalcemia. Hypercalcemia associated with malignancy is the most common cause of hypercalcemia in hospitalized patients (1), whereas the majority of ambulatory patients will have hyperparathyroidism, which is increasingly being recognized as a consequence of biochemical screening of asymptomatic individuals.

In this issue of *Clinical Chemistry*, Endres et al. (2) provide us with a study comparing a mid-molecule assay (recognizing PTH 44–68) with two immunometric assays, an immunchemoluminimetric assay (Magic Lite PTH; Ciba Corning Diagnostics, Stoughton, MA) and an immunoradiometric assay (IRMA) (Allegro Intact PTH; Nichols Institute Diagnostics, San Juan Capistrano, CA) in the diagnosis of hypercalcemic disorders and hypoparathyroidism. The mid-molecule assay principally identifies biologically inactive mid- and carboxyl-terminal fragments that are either derived from the metabolism of PTH 1–84 or secreted by the parathyroid gland.

Their data clearly confirm what has been published in other reports (3–7) on immunometric PTH assays, namely, that these assays can virtually completely separate individuals with hyperparathyroidism from those with malignancy or other non-parathyroid-induced hypercalcemic states. The USC/Los Angeles County Medical Center study population included 29 patients with hyperparathyroidism, 12 of whom had surgically confirmed disease and four of whom had coexistent malignancy. In the IRMA, 73% of hyperparathyroid patients had PTH values >65 ng/L, whereas 97% of hyperparathyroid patients had above-normal serum values of PTH 1–84 in the immunochemilumimetric assay. In contrast, all hyperparathyroid patients had above-normal serum concentrations of PTH in the mid-molecule assay.

There are several possible explanations for these findings. There was an excellent correlation between the two immunometric assays ($r = 0.978$), and the only real difference in the results obtained with these assays was that 65 ng/L was considered to be the upper limit of normal in the IRMA vs 55 ng/L in the immunochemilumimetric assay. Patients with hyperparathyroidism and coexistent malignancy, who were initially thought to have hypercalcemia of malignancy, had PTH concentrations in the high normal range or only slightly above normal, suggesting that osteoclastic bone resorption with release of calcium from the skeleton may have partially suppressed above-normal concentrations of PTH in serum.

The recently described peptide, parathyrin-related protein (PTHrP), is responsible for hypercalcemia-complicating epidermoid cancers, including renal and lung carcinoma. PTHrP has amino-terminal homology with human PTH (eight of the first 13 amino acids are identical) and binds to a common PTH/PTHrP receptor on bone and kidney target tissue (8). PTH and PTHrP amino acid sequences diverge considerably beyond amino acid position 13, and antisera used in mid-molecule PTH assays, in carboxyl-terminal PTH assays, and as the capture antibody in immunometric assays do not recognize PTHrP.

PTH secretion has been shown to be pulsatile (9), and measurements of the intact hormone, which has a half-life of minutes, may represent sampling from a trough. The relatively increased concentrations of mid- and carboxyl-terminal fragments, with their longer half-lives, are a direct result of the metabolism of increased amounts of intact PTH secreted in hyperparathyroidism. Furthermore, PTH fragments secreted by the adenomatous or hyperplastic parathyroid tissue probably contribute further to increased mid- and carboxyl PTH fragments.

Immunometric assays for PTH 1–84 have been available for three years and have become widely applied in the diagnosis of hypercalcemic patients. Discussion of PTH assays at the recently convened NIH consensus conference on asymptomatic hyperparathyroidism (October 29–31, 1990, in Bethesda, MD) yielded an overall agreement that these immunometric assays measure above-normal concentrations of PTH in 90% of hyperparathyroid patients, whereas the remaining 10% of patients have serum PTH 1–84 near the upper limit of normal. Dr. John Bilezikian, of Columbia University College of Physicians and Surgeons, presenting data from a longitudinal natural history study of >100 patients with asymptomatic hyperparathyroidism, reported serum concentrations of PTH 1–84 by IRMA to be above normal in 92% of the patients. Our own experience with the IRMA at the Massachusetts General Hospital is that above-normal PTH concentrations in serum are found in 90% of patients who are operated on for primary hyperparathyroidism.

A hormone assay must be interpreted in light of its
clinical correlation data: in this case, the ranges found for normal subjects, hyperparathyroid patients, cancer patients with hypercalcemia, and the other diseases that account for the remaining 5% of hypercalcemic individuals.

Most often, patients with hypercalcemia of malignancy have symptoms attributable to the underlying malignancy, and the hypercalcemia is of recent onset. The greatest failing of mid-molecule assays is that they give above-normal values for PTH in 20–25% of patients with hypercalcemia associated with malignancy (10, 11); at times, therefore, they may mislead the clinician to consider hyperparathyroidism and subject a patient to unwarranted parathyroid surgery. It is our hope that the advent of immunometric assays for PTH, in conjunction with clinical judgment, will permit reliable discrimination between hypercalcemia associated with malignancy and that of hyperparathyroidism.

References

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