TEACHING EDITORIAL

Hypercalcemia: Differential Diagnosis Aided by Measurement of Calciotrophic Hormones

Hypercalcemia is detected more frequently now through increased use of multiphasic screening of patients' sera (*1–3*). Although the physician faces the complex differential diagnosis after hypercalcemia is confirmed, direct measurements of the appropriate hormones may be used to confirm their clinical decisions rather than the less specific and sensitive tests of previous decades (*4,5*). In this issue of the *Journal,* Morita and associates (*6*) demonstrate the utility of the simultaneous measurement of plasma immunoreactive parathyroid hormone (iPTH), immunoreactive calcitonin (iCT), and 25-hydrobyvitamin D (25-OH-D).

The authors present data from patients with diseases commonly associated with hypercalcemia and Table 1 summarizes their major results as a diagnostic scheme. Most importantly, the direct measurements used allowed diagnostic separation of 88% of their patients. Results from three of 24 patients did not meet the criteria of the scheme; although after further analysis or study two of these may have been categorized within the scheme. Discriminant analysis of iPTH and calcium values as performed by Arnaud et al. (vide infra) might correctly identify the occasional patient with primary hyperparathyroidism and "normal" iPTH, and extraction of more tissue might reveal the patient with hepatoma to have ectopic hyperparathyroidism (*7*). Finally, a patient with myeloma and a probable calcium-binding protein is exceedingly rare—only one case has been reported to date (*8,9*).

The authors' iPTH results are consistent with previous reports. Measurement of fasting iPTH in the morning is ideal to separate normal subjects from those with primary hyperparathyroidism. In normal subjects, Arnaud et al. (*10*) have demonstrated a negative correlation between calcium and iPTH over the normal range of serum calcium values, and this makes physiological sense. When endogenous demands for calcium are high, serum calcium drops, and this increases iPTH secretion and bone resorption with resultant normalization of serum calcium. Conversely, if serum calcium concentration increases within the normal range, iPTH secretion decreases. In contrast to normal subjects, hypercalcemic patients with primary hyperparathyroidism had a positive correlation between calcium and iPTH; i.e., for a given calcium concentration, iPTH values were far too high. To achieve complete separation of normals from patients with nearly occult parathyroid disease, this laboratory has occasionally used calcium-induced iPTH suppression (*11,12*).

In patients without renal failure who have hypercalcemia associated with excessive intake of vitamins D and A or absorbable calcium products, sarcoidosis, or thiazide administration, iPTH is generally low or normal. The exact mechanism for thiazide-induced hypercalcemia is not known, and some patients in whom it occurs have mild primary hyperparathyroidism.

Ectopic hyperparathyroidism or pseudohyperparathyroidism results from synthesis and secretion of PTH by nonparathyroid malignancies with no apparent skeletal metastasis (*14*). First suggested by Albright (*15*) and subsequently documented by measurement of iPTH in tumors and sera of affected patients (*16,17*), the syndrome is difficult to distinguish biochemically from primary hyperparathyroidism. Measurement of iPTH was initially considered valueless for differentiating ectopic from primary hyperparathyroidism because patients with either disease had high iPTH values (*18*). This problem is apparent in Fig. 3 of the article by Morita et al.; iPTH values are high in both primary and ectopic hyperparathyroid patients. Fortunately, it is possible to separate these groups with radioimmunoassay measurements in radioimmunoassays that detect carboxyl-terminal fragments of parathyroid hormone in circulation. Riggs, Benson, Arnaud and co-workers (*19–21*) have separated more than 90% of such

patients by observing lower iPTH values in patients with ectopic as contrasted with primary hyperparathyroidism but who have comparable degrees of hypercalcemia.

In human hypercalcemia a possible compensatory homeostatic role of calcitonin is often considered because iCT increases in response to acute hypercalcemia, and administration of exogenous calcitonin may cause hypocalcemia. Regardless of whether CT secretion is compensatory, measurements of iCT appear to improve differential diagnosis of hypercalcemic patients. In hypercalcemia caused by hyperparathyroidism, a majority of laboratories report normal or low iCT values (*22–25*), although some differ (*26,27*). The low or normal values in patients with primary hyperparathyroidism aid in their separation from those with cancer (Table 1). Two precautions are in order. Most patients with primary hyperparathyroidism associated with multiple endocrine neoplasia, 2a (medullary carcinoma of the thyroid gland, pheochromocytoma, and hyperparathyroidism) will have high iCT (*28*); and although hypercalcitoninemia is common in patients with some advanced malignancies, particularly in lung and breast not all will have high iCT values, even if hypercalcemic (*29–31*). In cancer patients, both ectopic and thyroidal secretion of iCT have been reported.

Complete agreement with or absolute reproduction of the results of Morita et al. are not to be expected from all laboratories for two reasons: a) the variety of techniques used to measure the hormones, and b) the immunochemical heterogeneity or circulating parathyroid hormone and calcitonin. The latter concept, first described by Berson and Yalow (*32*), is based on observations that human plasma or sera contain multiple circulating forms of iPTH and iCT and that the assays used to measure these hormones have different specificities for the various forms of iPTH or iCT. Those interested in detailed discussions of these phenomena are referred to the publications of Arnaud and his associates (*33,34*) for parathyroid hormone and to those of Singer and Habener, Sizemore and Heath, Snider and associates, and Goltzman and Tischler (*35–38*) for calcitonin. Numerous referral laboratories now perform these hormone measurements, and many have good information regarding the specificities and usefulness of their assays. Referring physicians are advised to discuss their cases with the laboratory to maximize patient benefits and to minimize inappropriate use of the tests.

Now that measurements of the calciotrophic hormones are "coming of age in clinical medicine" (*33*), what do they do for us? Will they supplant clinical judgment, diminish the use of indirect tests, or increase cost-effectiveness? It is clear they will not replace clinical judgment—physicians almost intuitively know when to search for malignancies; thiazide- and vitamin D-induced hypercalcemia may be identified by history alone and withdrawal of the drug advised. Specialists have already discontinued the use of many nonspecific indirect tests (*4,5*), and this trend should spread. As it continues and as calciotrophic hormone measurement decreases the frequency of incorrect diagnosis and unwarranted cervical exploration, our cost-effectiveness will improve.

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TABLE 1

Hormone	Malignancies with bone metastasis	Malignancies with ectopic hyperparathyroidism	Primary hyperparathyroidism	Excessive intake of vitamin D_2
iPTH	L,N	H	H	N
iCT	H	H	L,N	N
25-OH-D	L,N	L,N	N	H

L = low; N = normal; H = high.

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