Diagnostic Applications of Calcitonin Immunoassay*

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ABSTRACT

The radioimmunoassay for calcitonin has become an important clinical procedure for the diagnosis of medullary thyroid carcinoma. Most patients with this thyroid tumor have elevated basal levels of the hormone which can establish the presence of the malignancy. In some patients, provocative tests of calcitonin secretion are necessary for definitive diagnosis. In addition to establishing the diagnosis, the calcitonin assay can be used to define the extent of the disease and to evaluate therapeutic procedures. This assay may also be useful in the diagnosis of other calcitonin-producing tumors.

Introduction

Medullary thyroid carcinoma is a distinct form of thyroid tumor which can occur in either a familial or sporadic pattern.10,12,13,14 In familial cases, this tumor can be associated with a form of multiple endocrine adenomatosis, MEA Type II.15 This tumor is a neoplasm of the calcitonin-secreting, parafollicular cells of the thyroid gland.17 Consequently, the measurement of calcitonin in the peripheral blood of patients by radioimmunoassay can serve as a diagnostic test for the presence of this tumor.1,2,5,6,13,16

Diagnosis of Medullary Thyroid Carcinoma

Most patients with medullary thyroid carcinoma have basal plasma levels of calcitonin that are clearly elevated and, therefore, diagnostic of the presence of tumor.3,6 Thus, this relatively simple immunoassay determination can establish the diagnosis of this tumor with virtual certainty.4 In fact, elevated plasma levels of calcitonin may be present early in the course of this tumor so that elevated concentrations of the hormone occur before there is clinical evidence of the presence of the malignancy.11 However, a significant percentage, perhaps 25 percent, of patients with this tumor do not have basal levels of calcitonin which are clearly diagnostic.4 In these people, provocative tests of calcitonin secretion are necessary to establish the presence of the malignancy.

Provocative Tests of Calcitonin Secretion

Three types of agents have been used for provocative tests of calcitonin secretion. One of the earliest substances shown to
stimulate the secretion of calcitonin by medullary thyroid carcinoma was glucagon. Although glucagon did stimulate calcitonin secretion in some patients with this tumor, its effect has been too variable to serve as the basis for a reliable provocative test. In addition, glucagon can stimulate catecholamine release, a potentially dangerous effect in patients with medullary thyroid carcinoma since they have such a relatively high incidence of pheochromocytomas.

Gastrin has been shown recently to be a stimulus for calcitonin secretion in patients with medullary thyroid carcinoma. Its effect appears to be consistent and its administration relatively easy. Although promising, more experience with gastrin will be necessary in order to establish its reliability as a provocative test in patients with this form of tumor. In addition, gastrin is still an investigative drug and not widely available.

The most reliable provocative test for calcitonin secretion in patients with medullary thyroid carcinoma is calcium infusion. When infused at a rate of approximately five mgs per kilogram per hr for two to four hours, calcium consistently stimulates calcitonin secretion in patients with medullary thyroid carcinoma. Furthermore, it has been shown that calcium infusion can stimulate calcitonin from non-diagnostic to diagnostic levels in patients with this tumor. Despite its reliability, standard calcium infusion has several drawbacks. The procedure takes several hours during which a large dose of parenteral calcium is given. Plasma calcium levels often rise several milligrams during the procedure, and nausea and vomiting have been reported at the end of such an infusion.

Because of the reliability of calcium as a provocative test for calcitonin secretion, the effect of a shorter and more convenient calcium infusion procedure has been evaluated in patients with medullary thyroid carcinoma. In this method, 150 mg of calcium is given over a 10-minute period and plasma samples are collected for calcitonin measurement at 0, 15, 30 and 60 minutes. Our preliminary application of this procedure has demonstrated that it is a reliable stimulus to calcitonin secretion in patients with medullary thyroid carcinoma. Plasma calcitonin rose significantly as early as 15 minutes and generally remained elevated throughout the sampling time. The most consistent increase in plasma calcitonin took place in the 30 min sample. Plasma calcium levels rose less than one mg and the procedure was well tolerated.

These results suggest that a 10-minute calcium infusion, which is less hazardous and more convenient than the two to four hour calcium infusion, may be useful as a provocative test for the diagnosis of medullary thyroid carcinoma. However, until the...
effect of such shorter calcium infusions can be fully evaluated, a standard calcium infusion should be used in those patients in whom there is clinical justification for such a procedure, such as a family history for medullary thyroid carcinoma or the presence of certain associated features such as pheochromocytomas, neuromas or hyper-parathyroidism.

Other Applications of the Calcitonin Immunoassay

In addition to its usefulness as a diagnostic procedure for the presence of medullary thyroid carcinoma, the measurement of calcitonin has several other clinical applications in patients with this form of tumor. Plasma samples collected at selective venous catheterization can be assayed for calcitonin. This procedure may be useful in documenting the extent of tumor involvement and demonstrating the presence of metastatic disease. Furthermore, serial measurements of calcitonin can be made in patients during treatment, usually surgical, for this tumor. In this way, the effectiveness of the treatment procedure in removing the malignant tissue can be evaluated.

In addition to being a sero-marker for the presence of medullary thyroid carcinoma, it has recently become apparent that calcitonin may signal the presence of other forms of malignant tumors. Some of these tumors may have the same embryological origin, neural crest, as the calcitonin-secreting cells of the thyroid gland. However, the abnormal secretion of calcitonin may be a characteristic that is even more widespread among malignant tissues.

References