Communications

Chloride:Phosphate Ratio with Hypercalcemia Secondary to Thiazide Administration

Frank H. Lawler, MD, and Henry P. Janssen, MD
Johnson City, Tennessee, and Linton, North Dakota

Hypercalcemia may be an important sign of underlying systemic disease. Included in the differential diagnosis are disease entities that must be carefully distinguished.[1-4] The chloride:phosphate ratio has been advocated as an initial screening determination in the differentiation between primary hyperparathyroidism and other causes of hypercalcemia, such as malignancy.[5-7] The ratio, however, has had varied acceptance in the literature.[1,3]

Another cause of hypercalcemia is the administration of thiazide diuretics.[4,8,9] The inclusion of this cause in a differential diagnosis is important because it is easily treatable, generally self-limited,[10] and may allow avoidance of a costly diagnostic evaluation. A case is described in which the chloride:phosphate ratio erroneously indicated a diagnosis of hyperparathyroidism, when the hypercalcemia was actually due to a thiazide diuretic.

From the Department of Family Practice, East Tennessee State University, Johnson City, Tennessee, and the Linton Medical Center, Linton, North Dakota. Requests for reprints should be addressed to Dr. Frank H. Lawler, Department of Family Practice, East Tennessee State University, Johnson City, TN 37614.

Case Report

A 66-year-old white woman under treatment for hypertension with a thiazide triamterene diuretic (Dyazide) presented with complaints of weakness, lethargy, and mild abdominal pain. She had been discharged from the hospital ten days previously after treatment for Pseudomonas pneumonia. Laboratory studies during that admission revealed the following: calcium, 11.6 mg/100 mL; inorganic phosphate, 0.9 mg/100 mL; chloride, 92 mEq/L; and urine containing phosphate crystals (2+). These findings were initially attributed to dehydration, but re-examination in the clinic showed persistent hypercalcemia and hypophosphatemia.

Physical examination showed a toxic appearing elderly woman who was very weak. The thyroid gland was nonpalpable. No abnormalities were otherwise noted. Laboratory investigation demonstrated a calcium level of 11.9 mg/100 mL; phosphate, 2.1 mg/mL; and uric acid, 13.4 mg/100 mL. The patient was admitted for evaluation and therapy. Technetium thyroid scan showed no abnormalities. Radiologic examination of the hands failed to show subperiosteal resorption. An intra-

0094-3509/83/010153-02$00.50

venous pyelogram was normal. Therapy with intravenous saline, corticosteroids, and furosemide (Lasix) returned the calcium to normal level in two days. The phosphate level remained low at 1.9 mg/100 mL. Because of the elevated calcium and an initial chloride:phosphate ratio of greater than 100 (92/0.9), a tentative diagnosis of parathyroid adenoma was made, and arrangements were begun for exploratory surgery pending results of a parathormone assay. Return of the assay showed a level of 53 mEq (normal range, 20 to 70). The patient was subsequently re-evaluated, and a diagnosis of hypercalcemia, hypophosphatemia, and hyperuricemia secondary to antihypertensive medication was made. When the thiazide medication was discontinued, the serum calcium, phosphorus, and uric acid returned to normal levels. With removal of the etiologic agent, laboratory values returned to normal. The patient was switched to furosemide for control of her blood pressure, and follow-up calcium levels two and five months later remained in the normal range.

Comment

Hypercalcemia is a known side effect of thiazide diuretics.[8-10] Generally the effect is transient, and calcium levels, while high, are not alarming. Other effects of thiazide diuretics include hyperuricemia and hypokalemia.[8,10] The patient exhibited rather profound hyperuricemia, in addition to sustained hypophosphatemia, contributing to the initial error in diagnosis. Mahomadi et al[10] measured serum phosphate levels in patients on thiazide diuretics and did not note a similar effect. The patient also did not exhibit hyperchloridemia, which is common in hyperparathyroid patients.[6,7]

The chloride:phosphate ratio has been advocated as a clinical screen for primary hyperparathyroidism in hypercalcemic patients.[5,7] Advocates note a good distinction between primary hyperparathyroidism and other causes of hypercalcemia, with a ratio of greater than 33 to 1 suggestive of primary parathyroid disease. Other investigators have found the ratio of no or limited value as a screening test.[1,3,6] Lafferty[6] has found that the absolute value of serum chloride is a more specific test in hypercalcemia. Several authors describe appropriate methods of evaluating the hypercalcemic patient in an efficient and thorough manner,[2-4,6] and emphasize use of laboratory tests such as chloride, phosphate, and calcium levels to indicate pursuit of a diagnosis from the extensive differential, including neoplasia, primary parathyroid disease, and other less common causes.

Summary

The chloride:phosphate ratio is of only limited value in aiding the clinician in the differential diagnosis of hypercalcemia. The use of thiazide diuretics may cause hypercalcemia with a chloride:phosphate ratio said to be consistent with a diagnosis of primary hyperparathyroidism. Parathormone assay remains the "gold standard" for definitive diagnosis of hyperparathyroidism.

References

1. Fisken RA, Heath DA, Somers S, Bold AM: Hypercalcemia in hospital patients. Clinical and diagnostic aspects. Lancet 1:202, 1981
2. Reynolds LR, Flueck JA: Evaluation of the hypercalcemia patient. Am Fam Physician 23:105, 1981
3. Wong ET, Freier EF: The differential diagnosis of hypercalcemia: An algorithm for more effective use of laboratory tests. JAMA 247:75, 1982
4. Zawada ET, Lee DBN, Kleeman CR: Causes of hypercalcemia. Postgrad Med 66:91, 1979
5. Broulik PD, Pacovsky V: The chloride-phosphate ratio as the screening test for primary hyperparathyroidism. Horm Metab Res 11:577, 1979
6. Lafferty FW: Primary hyperparathyroidism: Changing clinical spectrum, prevalence of hypertension, and discriminant analysis of laboratory tests. Arch Intern Med 141: 1761, 1981
7. Palmer FJ, Nelson JC, Bacchus H: The chloride-phosphate ratio in hypercalcemia. Ann Intern Med 80:200, 1974
8. Hollifield JW: Biochemical consequences of diuretic therapy in hypertension. J Tenn Med Assoc 71:757, 1978
9. Zerwakh JE, Pak CYC: Selective effects of thiazide therapy on serum 1,25-dihydroxyvitamin D and intestinal calcium absorption in renal and absorptive hypercalciurias. Metabolism 29:13, 1980
10. Mahomadi M, Bivins L, Becker KL: Effect of thiazides on serum calcium. Clin Pharmacol Ther 26:390, 1979