Calcium-Carbonate-Induced Calciphylaxis

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Dear Sir,

Control of hyperphosphatemia is thought to be central to prevent secondary hyperparathyroidism and renal osteodystrophy [1]. Aluminum-containing phosphate binders have been widely used for this purpose with success [2], but recently, gastrointestinal absorption of aluminum has been recognized to result in aluminum intoxication as manifested by osteomalacia, encephalopathy, proximal myopathy, and microcytic anemia [3]. Therefore, several nonaluminum-containing phosphate binders have been used with discordant results. Calcium carbonate represents a safe and effective alternative treatment, although its clinical use has been limited by its propensity to cause hypercalcemia and some digestive discomfort [4].

We report a patient treated with high doses of calcium carbonate as phosphate binder, who developed a reversible calciphylaxis after calcium carbonate withdrawal. To our knowledge, it represents a nondescribed side effect of calcium carbonate as phosphate binder in hemodialyzed patients.

Case Report

An 83-year-old woman with chronic renal failure of unknown etiology was on maintenance hemodialysis from June 1983. A moderate secondary hyperparathyroidism (PTHn: 70 ng/ml) was controlled with aluminum hydroxide as phosphate binder and vitamin D3.

Because the patient was included in a study to evaluate efficacy and safety of calcium carbonate in hemodialyzed patients, aluminum hydroxide was replaced by calcium carbonate and vitamin D supplementantation was withdrawn in December 1986.

During the next 6 months, treatment with calcium carbonate was effective for calcium and phosphorus control, but PTHn increased progressively. In July 1987, the patient developed progressive weakness with bad tolerance to hemodialysis, and high plasma levels of

Fig. 1. Relationship between phosphorus, calcium, and plasma PTHn levels and the phosphate binder treatment.

phosphorus (13 mg/dl) and calcium (11.3 mg/dl) were present (fig. 1). The patient was admitted to our hospital because of extremely painful violaceous skin lesions with necrotic centers on both calves, resembling cutaneous vasculitis. A skin biopsy specimen showed necrosis of the dermis and epidermis with narrowing and occlusion of arteries and arterioles, caused either by intimal fibrosis associated with mural calcification, or by massive calcification alone. Also, traces of

calcium were evident in the subcutaneous interstitium. Calcium carbonate was stopped, aluminum hydroxide and vitamin D supplementation were resumed. Daily hemodialysis, calcium heparin, and nifedipine as vasodilator were also introduced. Rapidly, plasma calcium and phosphorus levels normalized the pain in the legs decreased and the ulcerative lesions tended to cicatrize. The presence of soft-tissue calcifications underlying the ulcerations were detected by X-ray films and a ^{99m}Tc revealed pyrophosphate scintigraphy of the legs. A muscle biopsy revealed the presence of calcifications in medium and large arteries and ischemic myolysis.

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Six months after the development of calciphylaxis, the patient remains in good health with her legs completely healed.

Discussion

Soft-tissue and vascular calcifications commonly occur in uremic patients; however, the calcium deposits in the blood vessels are only occasionally associated with vascular insufficiency and/or ischemic changes which lead to gangrene or necrosis [5]. In 1962, Selye [6] described a process of soft-tissue calcification and necrosis that could be produced in rats when an appropriate biochemical milieu was created prior to challenge with a variety of precipitating agents the 'systemic calcifying factors' (vitamin D₂, D₃, calcium salts, bovine parathyroid hormone), which he termed 'calciphylaxis'. Afterwards, several reports have pointed to the similarity between these experimental lesions and the phenomena described occasionally in uremic patients with ischemic ulcers and vascular calcifications [7, 8]. The three factors contributing to the appropriate milieu for induced calciphylaxis are renal failure, hyperparathyroidism, and high plasma phosphorus level. Other factors, including serum calcium level, vitamin D therapy, corticosteroids, and immunosuppressive agents could contribute to the appearance of this syndrome [7]. In our patient the milieu was optimal for the calciphylaxis syndrome, and calcium carbonate may have triggered it. This side effect could represent a limiting factor to the use of calcium carbonate as phosphate binder, especially in patients with secondary hyperparathyroidism.

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