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Parathyroid hormone therapy for hypoparathyroidism

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Hypoparathyroidism is a disease characterized by hypocalcemia and insufficient parathyroid hormone (PTH). It is a rare disorder that has been given an orphan disease designation in the United States and European Union. Hypoparathyroidism is the only endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved therapy. Conventional therapy includes calcium and active vitamin D supplementation, often in large doses. Although serum calcium can be controlled with conventional therapy, it can be a challenge and, moreover, does not address other aspects of the disease, such as abnormal skeletal features and reduced quality of life. This review focuses on PTH replacement therapy in hypoparathyroidism, utilizing the full-length molecule PTH(1-84) as well as the fully active but truncated form PTH(1-34). PTH therapy addresses some aspects of the disease not ameliorated with conventional therapy.

Introduction

Hypoparathyroidism is a disease characterized by hypocalcemia and insufficient parathyroid hormone (PTH). Many patients also demonstrate hyperphosphatemia and hypercalciuria. The acute

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clinical manifestations relate to symptoms of hypocalcemia and neuromuscular irritability, including muscle cramps and paresthesias. Life-threatening heart arrhythmias, laryngospasm and seizures can occur. Long-term complications include nephrocalcinosis, nephrolithiasis or renal failure; soft-tissue calcifications in the basal ganglia, other brain compartments, or the vasculature itself; neurocognitive complaints and reduced quality of life; and abnormally low bone turnover [1–4]. While patients with hypoparathyroidism often have bone mineral density values higher than healthy controls, there is some evidence that vertebral fracture risk may be increased [5], although overall fracture risk may be similar to age-matched controls [6].

Hypoparathyroidism is rare, with an estimated 59,000 individuals in the United States suffering from the disorder [7]. It has been given an orphan disease designation by the United States Food and Drug Administration and the European Commission. The most common cause is inadvertent removal or irreversible damage to the parathyroid glands during thyroid or other neck surgery [1]. Other causes include autoimmune disease and rare genetic disorders such as DiGeorge syndrome, familial isolated hypoparathyroidism, autoimmune polyglandular syndrome type 1 and autosomal dominant hypocalcemia [8,9]. Severe magnesium deficiency is the only reversible cause of hypocalcemia with low PTH concentrations through impairment of PTH release and PTH resistance [1].

Hypoparathyroidism is the only endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved therapy. This review focuses on the use of PTH treatment in hypoparathyroidism, in the form of the full-length molecule PTH(1-84) as well as the fully active but truncated form PTH(1-34).

Treatment of hypoparathyroidism

There are no formal guidelines to assist in management decisions for patients with hypoparathyroidism. Intravenous calcium may be necessary in the acute setting. Conventional therapy in the outpatient setting includes calcium and active vitamin D supplementation, often in large doses. Maintaining serum calcium within an acceptable range must be balanced against the development of hypercalciuria and the presence of hyperphosphatemia. Serum calcium often fluctuates in hypoparathyroid patients on conventional therapy, requiring adjustments in the supplementation regimen. Thiazide diuretics may be a useful adjunct in the setting of significant hypercalciuria [1].

While Fuller-Albright first considered the use of a parathyroid extract in hypoparathyroid subjects in 1929 [10], this research was abandoned for many years until the past several decades when PTH became available as a potential therapeutic agent. The theoretical advantages of PTH over conventional therapy in the management of hypoparathyroidism include: a reduction in the amounts of calcium and vitamin D requirements, reduction in urinary calcium, improvement in quality of life, reduction in ectopic soft tissue calcification, and improvement in abnormal bone remodeling dynamics. PTH has been investigated as a therapy for hypoparathyroidism in the form of the full-length molecule PTH(1-84) [11–14] as well as the fully active but truncated form PTH(1-34) [15–18]. Both formulations are administered as a subcutaneous injection. In the studies investigating PTH(1-34), the dose of PTH was titrated to achieve independence from active vitamin D therapy. The pharmacokinetics of PTH(1-34) are relatively short, requiring multiple injections per day. In the studies investigating PTH(1-84), PTH was used as an add-on to standard therapy. The pharmacokinetics of PTH(1-84) are relatively long, with once daily or every other day injections possible. The long-term studies investigating PTH(1-34) and PTH(1-84) therapy of hypoparathyroidism are summarized in Table 1.

Effects of PTH therapy on supplementation requirements and serum calcium

In the studies of PTH(1-34), the drug was titrated to maintain serum calcium in the intended low-normal range off active vitamin D therapy. The studies investigating PTH(1-84) have used either fixed doses or doses titrated to maintain biochemistries. All studies have demonstrated that serum calcium was maintained in the setting of a reduction or elimination of calcium and active vitamin D supplementation [11–18].

The pivotal trial of PTH(1-84) therapy is the REPLACE trial [14], a multicenter study of 134 subjects randomized to PTH(1-84) ($n = 90$) or placebo ($n = 44$). Subjects were initially treated with PTH(1-84) at