Format: Abstract

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1alpha(OH)D3 One-alpha-hydroxy-cholecalciferol--an active vitamin D analog. Clinical studies on prophylaxis and treatment of secondary hyperparathyroidism in uremic patients on chronic dialysis.

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Abstract

Chronic uremia is characterized by decreased levels of plasma 1,25(OH)2D3 due to decreased renal 1-hydroxylase activity and by decreased renal phosphate excretion. The consequence is an increased synthesis and secretion of parathyroid hormone--secondary hyperparathyroidism--due to the low levels of plasma calcium, low levels of plasma 1,25(OH)2D3 and high levels of phosphate. The association between renal bone disease and chronic renal failure is well described. Epidemiological studies have indicated that an association also exists between secondary hyperparathyroidism and increased mortality and cardiovascular calcifications in chronic uremic patients. Treatment of secondary hyperparathyroidism in chronic uremia focuses on avoiding hyperphosphatemia by the use of oral phosphate binders, which bind phosphate in the intestine and a concomitant substitution by a 1 alpha-hydroxylated vitamin D analog in order to compensate for the reduced renal hydroxylation. Additional treatment with aluminum containing phosphate binders to overcome phosphate absorption and retention was initiated already in the 1960s and used extensively until aluminum toxicity was disclosed in the mid-1980s. Instead calcium carbonate and calcium acetate were used as phosphate binders. Until recently, the most commonly used active vitamin D drug was either the natural 1,25(OH)2D3, or the 1 alpha-hydroxylated analog, 1alpha(OH)D3 which after 25-hydroxylation in the liver is converted to 1,25(OH)2D3. 1alpha(OH)D3 was produced by LEO Pharma in 1973. The two vitamin D analogs were used in different geographical areas: In Europe 1alpha(OH)D3 was mainly used, while 1,25(OH)2D3 was mainly used in the USA. 1,25(OH)2D3 increases the intestinal absorption of calcium and improves skeletal abnormalities. The combined treatment with calcium containing phosphate binders and active vitamin D induces an increase in plasma Ca 2+ and hypercalcemia became a clinical problem. Subsequently therefore, dialysis fluid with a reduced calcium concentration ("low-calcium") was introduced. In 1981 Madsen et al. [148] demonstrated for the first time a direct suppressive effect of intravenous 1,25(OH)2D3 on plasma PTH in acutely uremic patients. In 1984, Slatopolsky et al. [74] demonstrated that intravenous 1,25(OH)2D3 induces a marked suppression of plasma PTH with no increase in plasma Ca 2+ in chronic uremic patients. In the middle of the 1980s, 1alpha(OH)D3 became available not only as an oral, but also as an intravenous formulation. The main purpose of the present studies was to increase the knowledge of the action and effects of different treatment

regimes with 1alpha(OH)D3, and thereby to improve the prophylaxis and treatment of secondary hyperparathyroidism in uremic patients on chronic dialysis. 168 patients on chronic dialysis treatment and six healthy volunteers were included in the seven studies included in this thesis. The first part of the studies, focused on short- (12 weeks) and long-term (103 weeks) effects of intravenous 1alpha(OH)D3 on plasma PTH and plasma Ca 2+ in relation to the doses of 1alpha(OH)D3 given. Further, it was examined whether the marked suppression of plasma PTH induced by 300 days of intermittent intravenous treatment with 1alpha(OH)D3, could be maintained when the administration was changed from intravenous to the oral route for 16 further weeks and then shifted back to intravenous administration for another 16 weeks. The second part focused on long-term effects (88 weeks in hemodialysis patients and 52 weeks in CAPD patients) of a treatment modality combining 1alpha(OH)D3, and CaCO3 as phosphate binders instead of aluminum containing compounds and a decreased calcium concentration in the dialysis fluid to 1.25 mmol/l in an attempt to avoid development of hypercalcemia. The third part focused upon the pharmacokinetic differences between intravenous and oral administration of 1,25(OH)2D3 and 1alpha(OH)D3 and upon the acute effects of different doses of the two compounds on the plasma levels of PTH, Ca 2+ and phosphate. Plasma PTH is a biochemical parameter most often used for the diagnosis and monitoring of bone disease in patients with chronic uremia. The level of plasma PTH measures depends on the assay used. More specific assays measuring only whole PTH 1-84 without co-measuring large C-terminal fragments have been developed. In this thesis, five different assays were used - one "N-terminal", one "C-terminal", two "Intact" and one "Whole" PTH assay. Each sample was analyzed by 1-3 different assays. Based on the results of my studies [1-7], it is concluded that: 1a. Intravenous administration of 1alpha(OH)D3 induces a marked suppression of plasma PTH without causing serious side-effects in patients on chronic hemodialysis. It is possible to prevent hypercalcemia by closely monitoring plasma Ca 2+ levels and by adjusting the dose of 1alpha(OH)D3 accordingly. 1b. Long-term intermittent intravenous treatment with 1alpha(OH)D3 was effective in suppressing plasma levels of Intact PTH. 1c. When plasma intact PTH was suppressed to a stable level by intravenous 1alpha(OH)D3 the suppression could be maintained by intermittent oral 1alpha(OH)D3 therapy. It was not examined whether a similar degree of suppression of severe secondary hyperparathyroidism could be induced by intermittent oral 1alpha(OH)D3 treatment alone. The responses following chronic intravenous or oral administration of 1alpha(OH)D3 on circulating levels of intact PTH and N- and C-terminal PTH fragments did not reveal any significant differences between the two routes of administration on the actions on the parathyroid glands. 2a. The combination of "low-calcium" hemodialysis fluid (1.25 mmol/l), CaCO3 as a phosphate binder, and intermittent intravenous 1alpha(OH)D3 prevented development of secondary hyperparathyroidism in uremic patients with normal PTH at the initiation of the study and induced a long-term suppression of PTH in patients with secondary hyperparathyroidism. No clinical or biochemical indications of development of adynamic bone disease were observed. Intravenous administration of 1alpha(OH)D3 prevented a decrease of BMC in the lumbar spine and femoral neck of hemodialysis patients both with normal and with elevated PTH levels. It was possible to use larger doses of CaCO3 and to reduce, but not exclude, the use of aluminum-containing phosphate binders in combination with intravenous administration of 1alpha(OH)D3. A decrease of plasma Ca 2+ was induced during dialysis, and special care had to be taken on the compliance of the patients as to the use of CaCO3

binders in order not to aggravate secondary hyperparathyroidism. 2b. In patients on CAPD, the use of low-calcium dialysis (1.25 mmol/l) made it possible to use larger doses of CaCO3 phosphate binders and to reduce, but not exclude, the use of aluminium containing phosphate binder in combination with oral pulses of 1alpha(OH)D3. A negative calcium balance was induced, and it is therefore recommended that a reduction of the calcium concentration in the dialysis fluid is only used in patients under strict control. 3a. The metabolic clearance rate of 1,25(OH)2D3 was 57% lower in uremic patients than in normal subjects ($p < 0.03$). The bioavailability of 1,25(OH)2D3 in both normal subjects and uremic patients was markedly lower following administration of 1alpha(OH)D3 both intravenously and orally than after administration of oral 1,25(OH)2D3. Despite lower plasma 1,25(OH)2D3 levels after administration of 1alpha(OH)D3 than after 1,25(OH)2D3, no significant difference was observed in the PTH suppressive effect in uremic patients of 4 mug intravenously of either of the two vitamin D analogs. 3b. A single intravenous high dose of 10 mug of 1alpha(OH)D3 or 1,25(OH)2D3 significantly suppressed plasma PTH. The acute suppressive effect of 1,25(OH)2D3 was three times greater than that of 1alpha(OH)D3.The increase in plasma Ca 2+ after intravenous administration of 10 mug 1,25(OH)2D3 was significantly higher than that of 1alpha(OH)D3. Due to the simultaneous effect on plasma Ca 2+ observed it was not possible to decide whether 1alpha(OH)D3 has a direct effect per se on the parathyroid glands or not. The study further did not give any further knowledge about the possible therapeutic equivalence of long-term treatment with 1alpha(OH)D3 or 1,25(OH)2D3. The PTH responses to acute administration of the 1alpha(OH)D3 and 1,25(OH)2D3 analogs were in principle the same when measured by one "whole" PTH and two "intact" PTH assays, namely mainly in a parallel shift of the PTH response curve. In this study on chronic uremic patients circulating levels of large C-terminal PTH fragments were not affected by differences in plasma Ca 2+ concentration or by the intravenous administration of 1alpha(OH)D3 or 1,25(OH)2D3. There is now a general agreement on the importance of carefully controlling plasma phosphate, normalize and avoid increases of plasma Ca 2+, and not to oversuppress PTH during treatment. Focus today is on the potential deleterious role of calcium overloading in the development of vascular calcifications in uremic patients. There is an urgent need for a development of an algorithm for the use of phosphate binders and vitamin D supplementation in combination with calcimimetics focusing upon long term morbidity and mortality in uremic patients.

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