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Intravenous 1,25(OH)$_2$ Vitamin D3 Therapy in Haemodialysis Patients: Evaluation of Direct and Calcium-Mediated Short-Term Effects on Serum Parathyroid Hormone Concentration

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Abstract. Eleven patients on chronic haemodialysis treatment thrice weekly received 1 μg 1,25(OH)$_2$D3 i.v. after each dialysis for 3 weeks. Phosphate binders were mainly $CaCO_3$, supplemented in a few patients by moderate amounts of $Al(OH)_3$. Ionised calcium was measured by ion-selective electrode, normal values being 1.28–1.42 mmol/l. PTH was estimated by an N-terminal-sensitive assay; normal values are <0.25 ng/ml. Results before and after 1,25(OH)$_2$D3 were: ionised calcium before haemodialysis, 1.19 ± 0.12 and 1.17 ± 0.14; ionised calcium after haemodialysis, 1.33 ± 0.07 and 1.30 ± 0.09; PTH before haemodialysis, 1.39 ± 0.71 and 1.38 ± 0.69; PTH after haemodialysis, 0.64 ± 0.22 and 0.60 ± 0.17; Phosphate before haemodialysis, 1.85 ± 0.48 and 2.18 ± 0.43 ($P < 0.05$). No change of PTH concentration and ionised calcium before and after haemodialysis treatment could be documented after i.v. 1,25(OH)$_2$D3 treatment. Mild and severe hyperparathyroidism were indistinguishable. Increased serum calcium concentrations therefore appear to be required for the suppression of PTH secretion by i.v. 1,25(OH)$_2$D3 therapy.

Key words: Haemodialysis; i.v. 1,25(OH)$_2$ vitamin D3; Serum parathyroid hormone

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Introduction

Excessive parathyroid hormone (PTH) secretion is an important cause of renal osteodystrophy [1]. Serum PTH concentrations are increased early in the course of renal disease and are linked initially to predominantly intracellular phosphate retention [2]. This is followed at later stages of the disease by an extracellular increase of inorganic phosphate [3]. Phosphate retention is related to reduced ionised calcium concentrations, suppressed synthesis of 1,25(OH)$_2$ vitamin D3 (1,25(OH)$_2$D3) and the expression of its receptors. All these factors participate in the aetiology of renal hyperparathyroidism [4].

Suppression of parathyroid hormone secretion in renal disease is related to elevated serum ionised calcium concentrations [5]. Normal serum PTH values, however, are difficult to reach and are usually only observed in hypercalcaemic patients [6]. This was true with calcium supplementation as well as with the peroral administration of vitamin D metabolites [7]. A new approach for the treatment of renal hyperparathyroidism was initiated by the group of Slatopolsky with the use of intravenously administered 1,25(OH)$_2$D3 [8]. The authors postulated that a more pronounced suppression of parathyroid hormone secretion was brought about with intravenous 1,25(OH)$_2$D3 than with its peroral administration [9].

The present study was carried out to differentiate between effects of intravenous 1,25(OH)$_2$D3 and the increase in serum ionised calcium before and during haemodialysis treatment. Low doses of intravenously

administrated $1,25(OH)_2D3$ did not change serum calcium values at the start of haemodialysis; treatment-related augmentation of ionised calcium suppressed PTH to the same extent before and after i.v. $1,25(OH)_2D3$.

Patients and Methods

The study was carried out in 11 patients on chronic haemodialysis, mean age 36.2 ± 14.2 (SD) years, treated thrice weekly for 2.5–3.5 h by means of high-flux polysulphone filters (Fresenius F60), using acetate dialysate with 1.5 mmol/l of calcium (Table 1). One microgram of $1,25(OH)_2D3$ (Abbott Company) was administered i.v. after each dialysis session for 3 weeks. Serum ionised calcium by ion-selective electrode (AVL company, CV = 0.7%), immunoreactive N-terminal parathyroid hormone (PTH) (CV = 14%) [10] and inorganic phosphorus (ammonium molybdate reaction, CV = 1.8%) were measured before and after i.v. $1,25(OH)_2D3$ treatment. Moreover, effects of individual haemodialysis treatments on the increase of the serum ionised calcium and the suppression of PTH were evaluated. All the patients were kept on calcium carbonate as a phosphate-binding agent, supplemented in some candidates with small doses of aluminium hydroxide. Mean serum aluminium values were increased 5-fold as compared to normal subjects, but distributed within the Gaussian distribution of the haemodialysis population. Statistical analysis was performed by Student's t-test for paired data.

Results (Fig. 1)

Before treatment with $1,25(OH)_2D3$, the serum ionised calcium values amounted to 1.19 ± 0.12 mmol/l (normal 1.28–1.42 mmol/l, mean ± 2 SD). During individual haemodialysis treatments, serum ionised calcium was increased to 1.33 ± 0.7 mmol/l. Corresponding values, after 3 weeks of i.v. $1,25(OH)_2D3$ treatment were 1.17 ± 0.14 mmol/l and 1.30 ± 0.09 mmol/l respectively. N-terminal PTH concentrations were 1.39 ± 0.71 ng/ml and 0.64 ± 0.22 ng/ml before and after dialysis prior to $1,25(OH)_2D3$ treatment (normal < 0.25 ng/ml). After 3 weeks i.v. $1,25(OH)_2D3$ PTH amounted to 1.38 ± 0.69 ng/ml before and 0.60 ± 0.17 ng/ml after haemodialysis. Serum phosphorus concentrations amounted to 1.85 ± 0.48 mmol/l (normal 0.7–1.6 mmol/l) before $1,25(OH)_2D3$ treatment. After $1,25(OH)_2D3$ the values were slightly increased to 2.18 ± 0.43 mmol/l ($P < 0.05$). On correlation analysis the decrease of PTH was related to the increase of serum ionised calcium during haemodialysis before as well as after $1,25(OH)_2D3$ treatment (Fig. 2).

Discussion

Increased serum ionised calcium concentrations are known to suppress PTH secretion [1]. In chronic renal insufficiency with and without dialysis treatment, near normal PTH values have only been observed during hypercalcaemia. This observation was related by Brown and others to an increased set point for PTH secretion in hyperplastic parathyroid glands [11–13]. Besides calcium supplementation, peroral vitamin D and its metabolites reduced serum PTH in concert with increased calcium values. Reduced serum PTH values were anticipated from in-vitro results, revealing suppression of mRNA values encoding for pre-pro-PTH by $1,25(OH)_2D3$ independent of ambient calcium concentrations [11,12]. Several other groups showed suppression of PTH by $1,25(OH)_2D3$ in vitro [14–16].

In contrast, direct suppression of the PTH secretion by $1,25(OH)_2D3$ is questionable in vivo and has not been universally demonstrated [7]. With peroral vitamin D metabolites a direct suppression of PTH secretion could not be dissociated from concomitantly increased serum calcium concentrations. An alternative arose when $1,25(OH)_2D3$ administered intravenously was claimed to suppress PTH secretion directly [8]. The mechanism was thought to be increased sensitivity to calcium-induced suppression of PTH secretion [9]. In these studies calcium was increased within minutes of i.v. $1,25(OH)_2D3$ administration and almost simultaneously, PTH decreased. The two variables, increased serum concentrations of $1,25(OH)_2D3$ and calcium, have not been clearly separated. None the less, increased serum calcium values in concert with or due to i.v. $1,25(OH)_2D3$ are effective in reducing serum PTH.

With the present study a potential direct suppression of PTH secretion by i.v. $1,25(OH)_2D3$ in the absence of increased ionised calcium concentration was investigated. Moreover, reduction of serum PTH levels as a consequence of haemodialysis treatment increasing serum calcium concentrations was confirmed [9]. Serum ionised calcium concentrations before the start of haemodialysis were stable and in a slightly hypocalaemic range; 1 μg $1,25(OH)_2D3$ administered three times weekly by the i.v. route for 3 weeks did not alter mean serum PTH values in our patients. Moreover, grouping of the patients with great and small initial PTH values did not affect our conclusions. The quantity of phosphate binders administered was left unchanged. As a result of the treatment with $1,25(OH)_2D3$ serum inorganic phosphorus values were slightly elevated ($P < 0.05$). This observation reveals a

Table 1. Patients' characteristics and biochemical data before i.v. 1,25(OH)$_2$D3 treatment

Patient	Age	Sex	Diagnosis	Duration of renal insufficiency (years)	Duration of dialysis therapy (months)	Ionised serum calcium (mmol/l)	Serum alkaline phosphatase (U/l)	Serum inorganic phosphate (mmol/l)	N-terminal PTH (ng/ml)
1	21	m	Rapidly progressive GN	01.0	13	1.25	49	2.07	0.33
2	33	f	Reflux nephropathy	05.0	36	0.91	76	2.02	2.42
3	30	f	Unknown origin	03.0	16	1.24	102	2.11	0.97
4	30	f	Lupus nephritis	02.5	16	1.11	45	2.02	1.27
5	24	m	Urethral valves	13.0	14	1.09	118	1.35	1.99
6	63	m	Analgesic nephropathy	10.0	02	1.20	89	1.69	2.33
7	21	m	Adult polycystic disease	08.0	39	1.20	100	0.99	1.11
8	53	m	Adult polycystic disease	01.0	14	1.21	54	1.59	2.00
9	48	f	Glomerulonephritis	16.0	23	1.35	105	1.53	0.79
10	28	f	Mesangial proliferative GN	06.0	11	1.25	61	2.39	1.50
11	47	m	Diabetic nephropathy	04.0	24	1.33	34	2.64	0.63
			Normal values			1.28–1.42	30–115	0.7–1.16	<0.25

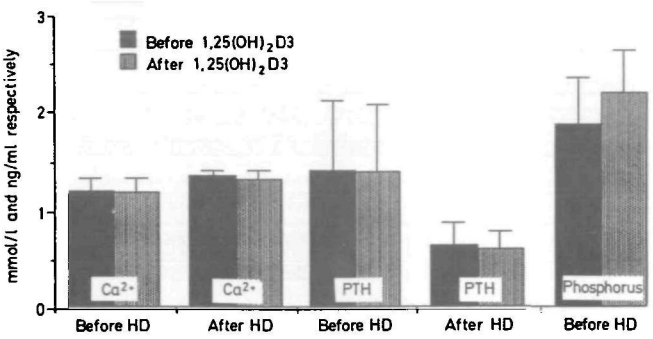

Fig. 1. Serum ionised calcium, PTH and phosphorus before and after i.v. 1,25(OH)$_2$D3. Effects of haemodialysis treatment.

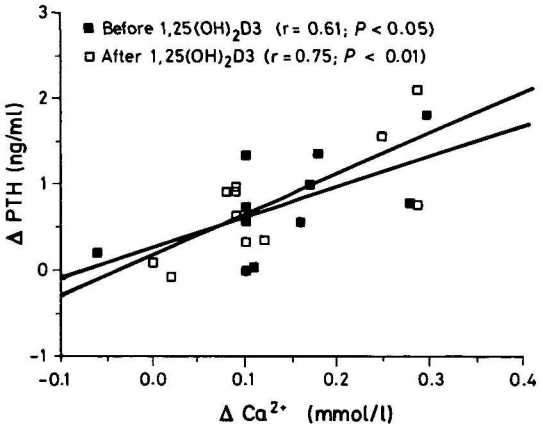

Fig. 2. Correlation between changes in ionised serum calcium and PTH during haemodialysis treatment before and after 1,25(OH)$_2$D3.

biological effect of the 1,25(OH)$_2$D3 administered and perhaps can be considered as a contribution to the lack of suppressive effect of i.v. administered 1,25(OH)$_2$D3 on PTH, as recently suggested by Slatopolsky et al [17]. In contrast to this opinion Brandi et al [18] showed a suppression of PTH with i.v. 1-α-hydroxyvitamin D3 despite a marked increase of serum phosphorus; the suppression of PTH, however, was accompanied by a marked increase in the serum calcium concentration.

The 1,25(OH)$_2$D3 dose used was taken from published data which showed suppression of PTH in some patients [8]. This was accentuated during prolonged treatment with increasing doses of 1,25(OH)$_2$D3 concomitant with an increase of the serum ionised calcium concentrations. More prolonged treatment with 1 μg of 1,25(OH)$_2$D3 as used in the present study might suppress PTH secretion in the absence of increased serum calcium concentrations. Serum ionised calcium was always elevated during haemodialysis treatment, and PTH reduced accordingly. Here also, the values were indistinguishable before and after 1,25(OH)$_2$D3 treatment. With a larger dose of 1,25(OH)$_2$D3 during a prolonged treatment time and while decreasing the dialysate calcium to 2.5 mEq/l,

Dunlay et al [19] showed an effect on PTH without a significant increase in serum calcium concentration. The sigmoidal shape relation between PTH and haemodialysis-induced hypo- and hypercalcaemia was displaced, showing a smaller PTH stimulation at low serum calcium concentrations after $1,25(OH)_2D3$; pre- and post-treatment relations, however, were only marginally affected. With a long-term intermittent treatment by i.v. calcitriol inducing an increase of the serum calcium concentration, an amelioration of osteitis fibrosa in dialysis patients was recently demonstrated by bone histomorphometry [20].

In conclusion, short-term i.v. administration of $1,25(OH)_2D3$ in slightly hypocalcaemic haemodialysis patients did not reduce serum PTH concentrations. Suppression of serum PTH by haemodialysis-induced increases of the ionised serum calcium concentrations was the same before and after i.v. $1,25(OH)_2D3$ treatment. These data might suggest a synergistic effect of $1,25(OH)_2D3$ and the increase in serum ionised calcium concentration for the suppression of serum PTH concentrations in haemodialysis patients.

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