DIRECT FEED-BACK REGULATION OF PTH-SECRETION BY 1,25-DIHYDROXYVITAMIN D₃ IN RENAL FAILURE: A CONTROLLED TRIAL

S Madsen, K Ølgaard, J Ladefoged
Rigshospitalet, Copenhagen, Denmark

Summary

To elucidate whether the kidney hormone 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) regulates the secretion of parathyroid hormone (PTH) by direct feed-back, 10 patients with acute oliguric tubulo-interstitial nephropathy were investigated. Serum ionised calcium (Ca++) was kept constant and subnormal by continuous peritoneal dialysis with low Ca++ dialysis fluid. In the control period (24h) PTH was found to be constantly increased. In the treatment period (30h) 1,25(OH)₂D₃ was injected i.v. every 6 hours. A significant suppression of PTH-levels was observed after a lag-period of 12–18h during stable low Ca++. In the control group PTH remained constantly increased throughout the trial. The data suggest that 1,25(OH)₂D₃ regulates PTH-secretion in humans with normal parathyroid glands by direct feed-back.

Introduction

The kidney hormone 1,25(OH)₂D₃ has been recognised as an important biologically active metabolite of vitamin D and the effect of 1,25(OH)₂D₃ on the target organs gut, bone and kidney has been extensively studied in recent years. Multiple factors have been shown to influence the biosynthesis of 1,25(OH)₂D₃ in the kidney and among these the stimulation of the 1-alpha-hydroxylation of 25(OH)D₃ by PTH has been firmly established [1]. Theoretically one could expect a direct feed-back loop between 1,25(OH)₂D₃ and PTH secretion, as otherwise these two calcemic hormones could perpetuate each others secretion and result in hypercalcaemia. However, increasing levels of Ca++ directly inhibit the secretion of PTH and thereby the renal activation of vitamin D. Thus, this long loop via Ca++ might be the only mechanism operating in the system.

Three sets of information suggest that vitamin D may have important biological effects on the parathyroid gland. Firstly, it has been shown that the parathyroids in the chick selectively localise 1,25(OH)₂D₃ [2]. Secondly, cytoplasmic receptors and nuclear binding of 1,25(OH)₂D₃ have been demonstrated in the
parathyroids of the chick and the pig [3,4]. Thirdly, it has been found that simultaneous administration of 1,25(OH)$_2$D$_3$ and 24,25(OH)$_2$D$_3$ mediate a marked reduction of gland weight in chicks [5].

From animal experiments conflicting results on a possible PTH-suppressive effect of 1,25(OH)$_2$D$_3$ have been reported, while only few conclusive studies have been performed in man.

The present study was carried out in patients with normal parathyroid glands during conditions where disturbing effects of changes in Ca$^{++}$ levels during the trial could be neglected.

Material and methods

Ten patients, 3 females and 7 males, with acute oliguric tubulo-interstitial nephropathy (so-called shock kidney) were investigated. No patient had a urinary output exceeding 150ml/24h during the study and the duration of uraemia (blood urea > 20mmol/L) did not exceed 6 days when the study was initiated. Five of the patients with a mean age of 52 years (range 22–70) received 1,25(OH)$_2$D$_3$, while 5 of the patients with a mean age of 49 years (range 28–75) served as a control group.

The shock kidney patients were continuously peritoneally dialysed without equilibration time by a low-calcium (0.80mmol Ca$^{++}$/L) dialysis fluid. To achieve a steady-state the patients were dialysed for 4 hours before the study was initiated. After a 24 hours control period, 1,25(OH)$_2$D$_3$ was injected i.v. in a dose of 250 nanograms every 6 hours to the 1,25(OH)$_2$D$_3$ group, while the control group received no injections. The study was continued for at least 54 hours. Every 6 hours venous blood was drawn from an indwelling catheter and analysed for Ca$^{++}$ [6] and PTH [7]. No patient developed clinical symptoms or signs of hypocalcaemia during the trial.

Results

The mean values (± SEM) for serum Ca$^{++}$ and PTH at 0, 6, 12, 18, 24, 30, 36, 42, 48 and 54 hours for the 1,25(OH)$_2$D$_3$ group and the control group are shown in Table I.

Ca$^{++}$ remained constantly low in both groups and, in particular, no rise in Ca$^{++}$ took place after administration of 1,25(OH)$_2$D$_3$. No significant difference in Ca$^{++}$ existed between the two groups.

The PTH concentrations were increased (2–3 times upper normal limit) in the control period (0–24h) and the PTH values did not differ significantly in the two groups. A suppression of PTH took place in all 5 patients during 1,25 (OH)$_2$D$_3$ treatment. At 54 hours, 30 hours after the first injection of 1,25(OH)$_2$D$_3$, the PTH values were reduced to 57.4% of the mean pre-treatment values (p < 0.01) and likewise at 42 hours (18 hours after the first vitamin D injection) the difference between the two groups was significant (p < 0.01, Fisher's exact test). In the control group PTH values remained constantly increased throughout the trial. The mean changes of Ca$^{++}$ and PTH are shown in Figure 1 and the individual course of each patient is shown in Figure 2.
TABLE I. Ca\textsuperscript{++} and i-PTH (mean ± SEM) during low-calcium peritoneal dialysis. The patients in the 1,25(OH)\textsubscript{2}D\textsubscript{3} group received 0.25μg 1,25(OH)\textsubscript{2}D\textsubscript{3} i.v. at 24, 30, 36, 42, 48 and 54 hours.

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**Figure 1. Ca\textsuperscript{++} and i-PTH (mean ± SEM) during low-calcium peritoneal dialysis. The arrows indicate i.v. injection of 0.25μg 1,25(OH)\textsubscript{2}D\textsubscript{3}. The normal range of Ca\textsuperscript{++} and i-PTH is indicated by the hatched areas.**

Upper panel: 1,25(OH)\textsubscript{2}D\textsubscript{3} group. Lower panel: Control group.
Figure 2. Individual course of Ca++ and i-PTH during continuous low-calcium peritoneal dialysis in 5 patients receiving 1,25(OH)₂D₃ 0.25μg i.v. (the arrows, upper panel) and in 5 control patients (lower panel)

Discussion

The best possible way to study a supposed suppressive effect of 1,25(OH)₂D₃ on PTH-secretion would be a situation where PTH-secretion is increased. In primary hyperparathyroidism administration of 1,25(OH)₂D₃ may be hazardous and in secondary hyperparathyroidism PTH secretion may only be partially suppressable. Thus, we chose to investigate patients with acute renal failure. These patients are supposed to have normal parathyroid glands. Our data show that it is possible to induce moderate secondary hyperparathyroidism in these patients by low-
calcium dialysis. Moreover, the experimental design made it possible to study the effect of 1,25(OH)₂D₃ during conditions where Ca²⁺ was maintained stable.

The PTH assay used here primarily detects the COOH-terminal fragment of the PTH molecule [8]. Due to reduced metabolic turnover of COOH-terminal fragments in the uremic state, rapid alterations in PTH secretion may not be detectable by this procedure. The lag-period which was observed before PTH levels decreased after 1,25(OH)₂D₃ administration may partly be explained by this phenomenon. Since the control group maintained constantly increased levels of PTH throughout the trial, removal of PTH fragments by the dialysis procedure cannot explain the suppression of PTH levels observed in the treatment group.

It should be considered whether the amounts of 1,25(OH)₂D₃ given in the present study are pharmacological rather than physiological. The administered dose (1µg/24h) is supposed closely to represent the quantity produced per day and seems therefore within the physiological range. The route of administration is of minor importance as several data [9,10] indicate that the biological effects of 1,25(OH)₂D₃ are nearly identical with both i.v. and oral administration of the compound.

The presented data, which suggest that 1,25(OH)₂D₃ has a direct suppressive effect on PTH secretion, are in good agreement with the observations by Chertow et al [11], who found a 43% decrease in PTH-levels 4h after administration of 1,25(OH)₂D₃ to the rat. Several investigations, including that of Llach et al [12] are at variance with our data. Llach et al studied the acute effect of 1,25(OH)₂D₃ administration to normal subjects and found no inhibitory effect on PTH secretion. The reason for this apparent discrepancy may, apart from differences in experimental design, be that modulation of PTH secretion by vitamin D can only be detected when baseline secretion of PTH is increased.

The mechanism by which 1,25(OH)₂D₃ may modulate PTH secretion was not clarified by the present study. Apart from a direct effect on the parathyroids, the possibility exists that the alteration in PTH secretion could occur as a result of some indirect effect of 1,25(OH)₂D₃. The present study has served to clarify that such an effect is not mediated via changes in serum ionised calcium.

References

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Open Discussion

KOKOT (Katowice, Poland) Did you determine the concentration of $1,25(\text{OH})_2\text{D}_3$ in blood?

MADSEN We have not measured the concentration of $1,25$. We have no method for this at present.

KOKOT Do you expect that giving about $1\mu g$ of this active metabolite will give an unphysiological level in blood?

MADSEN No, as I said the amount given was about $1\mu g$/day which is about the range normally produced per day, so I think the level might be quite in the physiological range.