DETERIORATION OF RENAL FUNCTION IN NON-DIALYTIC URAEMICS CAUSED BY 1α(OH)D₃ WHICH WAS NOT ATTRIBUTABLE TO HYPERCALCAEMIA

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Summary

Ten patients with renal failure not on dialysis were subjected to our study to evaluate the effect of 1α(OH)D₃ on calcium metabolism and its influence on renal function.

The results suggest the possibility that 1α(OH)D₃ might be effective in bone disease due to secondary hyperparathyroidism. On the other hand, 1α(OH)D₃ depressed creatinine clearance without any increase of Ca, Ca x P product or PRA.

1α(OH)D₃ is to be prescribed to patients not on dialysis only with careful attention to the dosage and the duration, and frequent observation of renal function is necessary.

Introduction

It is widely acknowledged that bones are often affected in patients with chronic renal failure even before dialysis becomes necessary [1,2]. Recently it has been confirmed many times [3–5] that 1α-hydroxy-cholecalciferol (1α(OH)D₃) is very effective in the treatment of the renal osteodystrophy seen in dialysis patients. Naturally, it is expected that 1α(OH)D₃ might be effective in non-dialysed patients for prevention of such bone disease.

The present study is based on our observations of non-dialysed patients to whom 1α(OH)D₃ was administered for a relatively short period. Our attention was focused on how the medication would influence their calcium metabolism and renal function.

Patients and method

Patients were selected from out-patients who showed values of more than 1000 pg/ml immunoreactive parathyroid hormone (iPTH) by N-terminal assay. Ten patients (2f, 8m) with non-dialysed uraemia were studied. The average age was 43.
Aetiological disease of renal failure was chronic glomerulonephritis in all. Their creatinine clearance (Ccr) ranged from 7.9 to 27.0; the average 14.4 ± 1.9ml/min. Medication was given after obtaining the informed consent of patients. The dosage of 1α(OH)D₃ (Teijin Pharmaceutical Co Ltd) was 1μg/day. The serum phosphorus (P) was controlled at a level under 6.0mg/100ml before the start of the study by the administration of aluminum hydroxide. The dosage was not changed throughout the period of 1α(OH)D₃ administration.

Serum and urinary Ca, P, Mg and alkaline phosphatase (Al-P) were determined with OCPC, Fiske-Subbarow, xyldyl blue and Bessey-Lowry methods respectively, by using the Sequential Multiple Autoanalyser with Computer (SMAC, Technicon Co Ltd). The serum and urinary electrolyte compositions were measured every other week.

The method of Ccr measurement was one-hour endogenous creatinine clearance, modified from Van Slyke [6]. The stability of this method was well confirmed. Ccr was determined every other week.

The serum iPTH was measured by radioimmunoassay using bovine N-terminal (1-34) antibody. The serum 25-hydroxy-cholecalciferol (25(OH)D) (normal range: 10–55ng/ml) and 24,25-dihydroxy-cholecalciferol (24,25(OH)₂D₃) (normal range: 0.8–4.9ng/ml) determined by competitive protein binding assay [7]. The serum 1,25-dihydroxy-cholecalciferol (1,25(OH)₂D₃) (normal range: 18–52 pg/ml) was measured by radioreceptor assay using chick cytosol [8]. The plasma renin activity (PRA) was measured by a modified method of Haber's [9]. The values after one-hour supine rest (before loading) and after an intravenous injection of 40mg furosemide followed by one-hour in a standing position (after loading) were obtained.

The measurements of iPTH, Vit D metabolites and PRA were done before the medication and at the second week or later after the start of the medication.

All the measured values were shown in Mean ± SEM. Statistical analyses were done using Student's t test.

Results

25(OH)D changed from the premedication value of 19.7 ± 3.0 to 16.1 ± 3.5ng/ml after medication, and 24,25(OH)₂D₃, from 1.2 ± 0.3 to 1.5 ± 0.4ng/ml, where no significant changes were observed. On the other hand, 1,25(OH)₂D₃ values changed from 8.3 ± 1.5 to 28.8 ±3.8pg/ml (p < 0.001), showing a rise in all.

Serum Ca, P and Ca x P product did not change significantly during the medication period (Figure 1). It is noteworthy that the Ca value did not rise. The highest Ca value during the period was 10.0mg/100ml, which is in the normal range. The serum Mg and albumin values, not shown in the figures, equally did not show any significant change. The Al-P value did rise significantly in the second week of medication, but it gradually lowered.

Administration of 1α(OH)D₃ decreased the iPTH values in all cases.

Figure 2 shows changes of serum urea nitrogen (SUN), creatinine (Creat.) and Ccr during the period of 1α(OH)D₃ administration and after termination. After the termination, values for these three did not show significant differences. However, during the administration, SUN and Creat. significantly increased at the 4th
Figure 1. Changes of serum Ca, P, Al-P, Ca x P product and iPTH levels during 1α(OH)D₃ administration to non-dialysed uraemics
Figure 2. Percent changes of serum urea nitrogen (SUN), creatinine, creatinine clearance (Ccr) during administration of 1α(OH)D₃ and after termination of the medication.

As to the Ccr changes, differences between 'During Administration' and 'After Termination' are significant (p < 0.05) up to 10 weeks.

week and thereafter, while Ccr began to decrease significantly at the second week and later.

Table I lists the urinary excretion of Ca, P and PRA values before and during the medication. None of the values changed significantly during 1α(OH)D₃ administration.
TABLE I. Urinary excretion of Ca and P, and plasma renin activity (PRA) before and during administration of 1α(OH)D₃

<table>
<thead>
<tr>
<th></th>
<th>UCaV</th>
<th>UPiV</th>
<th>PRA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(mg/hr)</td>
<td>(mg/hr)</td>
<td>(ng/ml/hr) Before Loading</td>
</tr>
<tr>
<td><strong>Before Medication</strong></td>
<td>1.4 ± 0.4</td>
<td>20.4 ± 1.4</td>
<td>2.57 ± 0.66</td>
</tr>
<tr>
<td><strong>During Medication</strong></td>
<td>1.1 ± 0.3</td>
<td>21.3 ± 1.8</td>
<td>3.39 ± 0.73</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

(M ± SEM)

Discussion

The absorption of 1α(OH)D₃ was confirmed by the rise of serum 1,25(OH)₂D₃ in all cases.

The serum Ca values of our patients did not show any significant change in contrast to the rise of Ca values observed in patients on haemodialysis [10–12].

The reason for this difference may be that non-dialysed patients are maintained on low protein diets which are apt to contain low calcium. As a matter of fact, the protein intake of the patients in the present study was in the range of 0.5 to 0.7g/kg body weight/day on the average.

It is impressive that the changes of Al-P value were similar to those of dialysis patients. The temporary Al-P rise might be due to transient bone resorption because of the direct action of 1α(OH)D₃ on bone, rather than its action in increasing intestinal Ca absorption.

In view of the fact that iPTH fell, 1α(OH)D₃ can be regarded as effective in the prevention or treatment of renal osteodystrophy, particularly the type due to secondary hyperparathyroidism. However, a decrease of Cr caused by administration of 1α(OH)D₃ was observed in this study.

Some reports have previously suggested that administration of active Vit D metabolites causes decline of renal function [10–13]. According to the past reports, in all cases a rise in serum Ca follows the medication. Our study was on the contrary.

As to why active Vit D administration depresses renal function, the mechanism has not yet been clearly elucidated. Some suggestions are given: firstly, Ca salt depositions in renal tissue might be contributory because of the rise of Ca x P product. Secondly, acceleration of blood coagulation might have been induced because of the rise of serum Ca. Thirdly, renal vasospasm is induced by the rise
of plasma renin activity. In our experience, hypercalcaemia was not observed in any of the patients and factors such as Ca x P product and PRA did not change significantly.

Therefore, we cannot help considering that 1α(OH)D₃ dosage has some direct influence on the kidney as Dr Parfitt [13] has suggested before.

We would like to advise that if 1α(OH)D₃ is to be prescribed to non-dialysed patients under any conditions, all careful attention is necessary in determining the dosage and the period of administration. It should be used only with careful and frequent observations of renal function.

Acknowledgments

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Open Discussion

LINS (Stockholm) You gave in your paper three possible explanations for the deterioration of renal function during treatment with 1α(OH)vitamin D₃. I have another one. We have studied patients with hypercalcaemia and especially the effect of PTH on renal function. We have found that in patients with hypercalcaemia and high PTH levels the renal function is rather stable but in patients with low or undetectable PTH levels as in sarcoidosis, the hypercalcaemia affects renal function much more. We have obtained the same results in experimental studies in dogs. My question is: What do you think about the effect of low PTH levels on renal function, especially the renal blood flow?

YOSHIYAMA I think PTH has direct effects on the renal function. I agree the possibility with you but I have no evidence.
PART XVII

Guest Lecture  METABOLIC ALTERATIONS CAUSED BY URAEMIA

Chairman:  J Bergström