Differential effects of 19-nor-1,25-(OH)\textsubscript{2}D\textsubscript{2} and 1\alpha\textsuperscript{-}hydroxyvitamin D\textsubscript{2} on calcium and phosphorus in normal and uremic rats

EDUARDO SLATOPOLSKY, MARIO COZZOLINO, and JANE L. FINCH

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

Differential effects of 19-nor-1,25-(OH)\textsubscript{2}D\textsubscript{2} and 1\alpha\textsuperscript{-}hydroxyvitamin D\textsubscript{2} on calcium and phosphorus in normal and uremic rats.

Background. Calcitriol, 1,25-(OH)\textsubscript{2}D\textsubscript{3} (1,25D), the most active metabolite of vitamin D, has been used in the treatment of secondary hyperparathyroidism (SH) because it controls parathyroid gland growth and suppresses parathyroid hormone (PTH) synthesis and secretion. Due to the calcemic and phosphatemic actions of 1,25D, two analogs with potentially less side effects, 19-nor-1,25-(OH)\textsubscript{2}D\textsubscript{2} (19-nor) and 1\alpha\textsuperscript{(OH)}D\textsubscript{2} (1\alphaD\textsubscript{2}) are currently being used in the treatment of SH.

Methods. This study compares the effects of these two analogs on calcium (Ca) and phosphorus (P) metabolism in normal, uremic, and parathyroidectomized (PTX) rats. Using doses of 50 to 250 ng of 19-nor or 1\alphaD\textsubscript{2}, experiments were conducted in normal and uremic rats.

Results. In uremic rats, 19-nor did not increase plasma Ca or P while 1\alphaD\textsubscript{2} caused a dose-dependent increase in both. In addition, while the Ca $\times$ P product remained unchanged in 19-nor-treated rats, it increased progressively with 1\alphaD\textsubscript{2} administration. In metabolic studies in normal rats treated with vehicle, 10 ng of 1,25D, 100 ng of 19-nor or 100 ng 1\alphaD\textsubscript{2}, intestinal calcium absorption and urinary calcium excretion were significantly higher in 1\alphaD\textsubscript{2}–treated rats compared to those receiving 19-nor. Similar results were seen for intestinal phosphorus absorption and urinary phosphorus excretion. Finally, the skeletal response to these two analogs was tested in PTX rats fed a calcium-deficient diet and treated daily with 100 ng of 19-nor or 1\alphaD\textsubscript{2}. The increase in plasma calcium in 1\alphaD\textsubscript{2}–treated rats was markedly higher than in those receiving 19-nor. Similar results were seen in plasma phosphorus when these studies were repeated using a phosphorus-deficient diet.

Conclusions. These studies demonstrate that when given in large doses to rats 19-nor is less calcemic and phosphatemic than 1\alphaD\textsubscript{2}. The lower Ca $\times$ P product in 19-nor-treated rats may be an important consideration in patient therapy. Further studies in patients are necessary to define the clinical applicability of these differences.

Key words: secondary hyperparathyroidism, PTH, uremia, calcitriol analogs, vitamin D, chronic renal failure, hemodialysis.

Received for publication October 8, 2001 and in revised form May 9, 2002
Accepted for publication May 13, 2002
© 2002 by the International Society of Nephrology
hyperparathyroidism [25, 26]. In contrast to 19-nor, this compound is a pro-hormone and must be activated by the liver by the addition of a hydroxyl group at carbon 25 before this vitamin D analog is active. The purpose of the present study was to compare, in normal and uremic rats, the calcemic and phosphatemic effects of these two vitamin D analogs, 19-nor and 1α,25D2.

METHODS

Effects of 19-nor-1,25-(OH)2D2 and 1α(OH)D2 on plasma calcium, phosphorus and parathyroid hormone in uremic rats

Renal insufficiency was induced in a group of 66 female Sprague-Dawley rats by 5/6 nephrectomy. This procedure involves the ligation of most of the branches of the left renal artery followed by right nephrectomy. The animals were divided into seven groups. Group 1 received vehicle and served as the uremic control group. Groups 2, 3, and 4 received 50, 100, or 250 ng of 19-nor, respectively, intraperitoneally three times a week for two weeks, and groups 5, 6, and 7 received, 50, 100, or 250 ng of 1αD2 intraperitoneally three times a week for two weeks. Six normal rats served as the normal control. At the end of the study the animals were euthanized and blood was obtained for total and ionized calcium, phosphorus, creatinine and parathyroid hormone. The rats were fed a rodent chow containing 0.9% calcium and 0.55% phosphorus.

Metabolic studies in normal rats

Blood was drawn from the tail of 28 normal female Sprague-Dawley rats weighing 225 to 250 grams for the determination of plasma calcium and phosphorus. The animals were then divided into four groups and placed in group housing, and treatment was begun. The rats received daily injections of (1) vehicle (100 μL propylene glycol), (2) 10 ng of 1,25-(OH)2D3, (3) 100 ng of 19-nor, or (4) 100 ng of 1αD2 for 14 days, and were given free access to deionized water and normal rodent chow containing 0.90% calcium and 0.55% phosphorus. We chose the same dose of 19-nor and 1αD2 for comparison. The dose of 1,25-(OH)2D3 was derived from previous studies. On the last four days of treatment the rats were placed in metabolic cages. Twenty-four hour urine and feces were collected and daily dietary intake monitored. Results are taken from the mean of the last three days of treatment. At the end of the study, rats were euthanized and blood was taken for the measurement of ionized calcium, total calcium and phosphorus. The urine was acidified and each 24-hour urine sample was analyzed for calcium and phosphorus. Urinary excretion is expressed as total calcium or phosphorus excreted in mg per 24 hours. Feces for each 24-hour period were dried in a drying oven at 100°C and ashed overnight in a Lab Heat muffle oven (Blue M Corporation, Blue Island, IL, USA). The ash was dissolved in concentrated hydrochloric acid and analyzed for calcium and phosphorus. Prior to the study, the diet also was analyzed for calcium and phosphorus using the same method. The net amount of intestinal calcium or phosphorus absorbed was expressed as the percent of ingested calcium or phosphorus not appearing in the feces.

Calcemic response to 19-nor-1,25-(OH)2D2 and 1α(OH)D2 in parathyroidectomized rats

Normal parathyroidectomized (PTX) rats were used in this study to eliminate the effects of 19-nor and 1αD2 on PTH synthesis and secretion, and to provide a wider range of calcium levels in which to evaluate these two compounds. Parathyroid glands were removed microsurgically from a group of 15 female Sprague-Dawley rats weighing 225 to 250 grams. Rats were fasted overnight and blood was drawn to confirm parathyroidectomy. Only animals with a plasma total calcium less than 7 mg/dL were used in this study. A diet deficient in calcium was used to eliminate the contribution of intestinal absorption to plasma calcium levels. Parathyroidectomized rats were fed a diet containing 0.02% calcium and 0.35% phosphorus and received daily intraperitoneal injections of vehicle (propylene glycol), or 100 ng of 19-nor or 1αD2 for a period of 35 days. Blood was obtained from the tail every two to three days for the first 11 days and then at days 18 and 35 for plasma calcium determinations.

Phosphatemic response to 19-nor-1,25-(OH)2D2 and 1α(OH)D2 in parathyroidectomized rats

Studies were performed as described in the last section of this article, except that in this study a group of 23 PTX rats were fed a phosphorus deficient diet (0.02% phosphorus, 0.5% calcium). In addition, the rats received daily intraperitoneal injections of vehicle (propylene glycol) or 200 ng of 19-nor or 1αD2 for a period of 10 days. Blood samples were obtained from the tail as previously described on days 0, 2, 4, 6, 8, and 11 for plasma phosphorus determinations.

Analytical determinations

Total calcium was measured using an atomic absorption spectrophotometer (model 1100B; Perkin-Elmer, Norwalk, CT, USA). Ionized calcium was measured using an ionized specific-calcium electrode (model ICA-1; Radioneter, Copenhagen, Denmark). Plasma creatinine, blood urea nitrogen (BUN) and phosphorus were determined by autoanalyzer (Mira Plus; COBAS, Branchburg, NJ, USA). Intact PTH was measured using an immunoradiometric assay specific for rat PTH (Immutopics, San Clemente, CA, USA).


Table 1. Blood chemistries in normal and uremic rats

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Cr mg/dL</th>
<th>T Ca mg/dL</th>
<th>I Ca mg/dL</th>
<th>P mg/dL</th>
<th>PTH pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6</td>
<td>0.78 ± 0.05</td>
<td>8.96 ± 0.08</td>
<td>4.46 ± 0.07</td>
<td>5.77 ± 0.29</td>
<td>50.3 ± 13.2</td>
</tr>
<tr>
<td>Uremic control</td>
<td>9</td>
<td>1.16 ± 0.04</td>
<td>9.02 ± 0.13</td>
<td>4.62 ± 0.13</td>
<td>7.48 ± 0.93</td>
<td>185.4 ± 114.8</td>
</tr>
<tr>
<td>U+19-nor (50 ng)</td>
<td>10</td>
<td>1.33 ± 0.05</td>
<td>9.23 ± 0.09</td>
<td>4.61 ± 0.08</td>
<td>6.47 ± 0.65</td>
<td>76.3 ± 16.6</td>
</tr>
<tr>
<td>U+19-nor (100 ng)</td>
<td>10</td>
<td>1.28 ± 0.03</td>
<td>9.30 ± 0.12</td>
<td>4.57 ± 0.08</td>
<td>5.24 ± 0.24</td>
<td>58.2 ± 9.4</td>
</tr>
<tr>
<td>U+19-nor (250 ng)</td>
<td>10</td>
<td>1.17 ± 0.06</td>
<td>9.51 ± 0.12</td>
<td>4.63 ± 0.05</td>
<td>6.72 ± 0.70</td>
<td>54.6 ± 14.0</td>
</tr>
<tr>
<td>U+1α-D2 (50 ng)</td>
<td>9</td>
<td>1.50 ± 0.20</td>
<td>9.79 ± 0.17</td>
<td>4.76 ± 0.08</td>
<td>6.62 ± 0.71</td>
<td>138.9 ± 44.1</td>
</tr>
<tr>
<td>U+1α-D2 (100 ng)</td>
<td>9</td>
<td>1.44 ± 0.06</td>
<td>11.87 ± 0.20</td>
<td>5.46 ± 0.09</td>
<td>7.94 ± 0.31</td>
<td>&lt;2</td>
</tr>
<tr>
<td>U+1α-D2 (250 ng)</td>
<td>9</td>
<td>1.81 ± 0.08</td>
<td>12.10 ± 0.20</td>
<td>5.34 ± 0.16</td>
<td>9.54 ± 0.51</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

*P < 0.05 from uremic control

**P < 0.01 from uremic control

Material and reagents

1αD2 was provided by Dr. Hector DeLuca (Madison, WI, USA), 1,25-(OH)2D3 was supplied by Dr. Milan Uskokovic (Hoffman LaRoche, Nutley, NJ, USA) and 19-nor-1,25-(OH)2D2 was provided by Abbott Pharmaceuticals (Abbott Park, IL, USA). We greatly appreciate their generosity. Normal rodent chow was manufactured by Ralston Purina Inc., (#5001; St. Louis, MO, USA) and the calcium-and phosphorus-deficient diets were purchased from Dyets Inc. (Bethlehem, PA, USA).

Statistical analysis

All results are expressed as mean ± SEM. One way analysis of variance (ANOVA) was used for comparison between groups and non-paired t test was used to compare normal rats with each uremic group.

RESULTS

Effects of 19-nor-1, 25-(OH)2D2 and 1α(OH)D2 in uremic rats

Table 1 shows the effects of two weeks of treatment with 19-nor or 1αD2 on plasma creatinine, ionized calcium, phosphorus and PTH in the uremic rats. The administration of 19-nor (50, 100, or 250 ng) did not increase ionized calcium or phosphorus. On the other hand, the administration of the same dose of 1αD2 produced a dose dependent increase in both blood chemistries.

The administration of 50 ng of 19-nor suppressed the increase in PTH seen in uremic rats treated with vehicle alone (19-nor, 76.3 ± 16.0 pg/mL versus uremic control, 185 ± 115 pg/mL). The same dose of 1αD2, however, did not significantly suppress the increase in PTH (138.9 ± 41.1 pg/mL). The PTH level in rats treated with the 50 ng dose of 19-nor was significantly lower than that of rats treated with the 50 ng dose of 1αD2 (P < 0.01). In addition, PTH levels in rats treated with 100 ng or 250 ng of 19-nor (100 ng, 58.2 ± 9.4 pg/mL; 250 ng, 54.6 ± 14.0 pg/mL) were not different from those of normal rats (50.3 ± 13.2 pg/mL). Although complete suppression of PTH (<2 pg/mL) was seen in rats treated with 100 and 250 ng of 1αD2, this was accompanied by a marked increase in plasma-ionized calcium (1αD2 100 ng, 5.46 ± 0.09 mg/dL and 1αD2 250 ng, 5.34 ± 0.16 mg/dL vs. uremic control, 4.62 ± 0.13 mg/dL, P < 0.001).

By comparison, the same dose of 19-nor (100 ng) suppressed the increase in PTH seen in the uremic control group by almost 70% (58.2 ± 9.4 pg/mL) but did not increase plasma ionized calcium (4.57 ± 0.08 mg/dL) or phosphorus (5.24 ± 0.24 mg/dL).

Examination of the Ca × P product (Fig. 1) revealed that none of the doses of 19-nor increased this parameter above that seen in the uremic control group (control, 67.2 ± 7.9; 19-nor 50 ng, 59.6 ± 5.9; 19-nor 100 mg, 48.7 ± 2.3; 19-nor 250 mg, 64.3 ± 7.2 mg2/dL2). In contrast, both the 100 ng and 250 ng doses of 1αD2 caused a marked increased in the Ca × P product (100 ng, 94.6 ± 4.8 mg2/dL2/
The intestinal absorption of calcium increased from 4.46 ± 0.39 mg/24 h in control rats to 17.9 ± 1.36 mg/24 h (P < 0.01) after treatment with 1,25-(OH)D3, while 19-nor induced a more modest increase in urinary calcium excretion (10.5 ± 1.25 mg/24 h, P < 0.05). In contrast to 19-nor, administration of 1αD2 increased urinary calcium excretion to 21.9 ± 2.5 mg/24 h (P < 0.01). The urinary calcium in 1αD2-treated rats was similar to that seen in 1,25-(OH)D3-treated rats. The urinary calcium excretion in 19-nor-treated rats, however, was significantly less than that seen with either 1,25-(OH)D3 (P < 0.01) or 1αD2 treatment (P < 0.01). Figure 5 shows that 24-hour urinary phosphorus increased from 5.37 ± 1.14 mg/24 h in the control group to 20.7 ± 2.4 mg/24 h (P < 0.01) with 1,25-(OH)D3 treatment, to 24.7 ± 2.7 mg/24 h (P < 0.01) in rats receiving 1αD2, but only to 10.9 ± 1.21 mg/24 h (NS) in
the 19-nor treated rats. As with urinary calcium, the increase in urinary phosphorus was not different between 1,25D and 1αD2 treated rats, but both of these groups had greater urinary P excretion compared to 19-nor (P < 0.01 and P < 0.001, respectively). Plasma total calcium was higher in the 1αD2-treated group compared to 19-nor-treated rats (10.9 ± 0.19 vs 10.1 ± 0.07 mg/dL). Plasma ionized Ca and phosphorus were similar in both groups (date, not shown).

Calcemic and phosphatemic responses of normal PTX rats to 19-nor and 1αD2

The calcemic and phosphatemic effects of 19-nor and 1αD2 were compared in PTX rats treated daily with either compound. After 35 days, total plasma calcium had increased from 5.33 ± 0.30 to 8.29 ± 0.32 mg/dL in 19-nor-treated rats while 1αD2 induced a greater response, increasing plasma calcium from 5.35 ± 0.38 to 10.1 ± 0.15 mg/dL over the same time period (Fig. 6). The increase in plasma calcium was significantly greater in 1αD2 treated rats than in those receiving 19-nor (P < 0.001). Plasma calcium in vehicle-treated rats remained unchanged during the course of the study.

The phosphatemic response to 19-nor and 1αD2 is shown in Figure 7. As expected, serum phosphorus initially increased after PTX from 7.14 ± 0.39 to 10.7 ± 0.29 mg/dL. Thereafter the rats were fed a phosphate deficient diet and started on 200 ng daily of 19-nor or 1αD2. By the eleventh day of treatment serum phosphorus increased from 4.93 ± 0.20 mg/dL in control rats to 5.66 ± 0.25 mg/dL with 19-nor treatment, but to 8.61 ± 0.59 mg/dL with 1αD2 administration (P < 0.01).

DISCUSSION

Chronic renal failure (CRF) is characterized by changes in mineral homeostasis, with secondary hyperparathyroidism (SH) appearing even in the early stages of renal insufficiency leading to the development of renal osteodystrophy [27–29]. Thus, controlling SH has been a primary goal in the treatment patients with CRF.

The 1,25-(OH)2D3 analog, 19-nor-1,25-(OH)2D2 is currently being used in the treatment of SH because it retains the ability of the parent compound to effectively...
suppress PTH, but produces significantly less hypercalcemia and hyperphosphatemia, providing a larger therapeutic window in which to treat patients. In a 12-week multi-center clinical trial, Martin et al reported a 60% decrease in serum PTH in hemodialysis patients receiving 19-nor compared to those receiving placebo [30]. In their study, mean serum calcium increased slightly in 19-nor-treated patients, although the difference was not statistically significant. While 19-nor and 1,25D were not directly compared, the results of Martin et al have led to widespread use of 19-nor for SH in patients on hemodialysis.

Recently another vitamin D analog, 1α(OH)D₂ (1αD₂) also has been used for the treatment of SH. Comparative studies between oral and IV administration of 1αD₂ in patients with CRF indicate that both modes of treatment suppress PTH, although the degree of hypercalcemia and hyperphosphatemia is greater with the oral preparation [26]. Since to our knowledge no studies have compared the efficacy of 19-nor and 1αD₂ in treating SH, we compared the effect of these two compounds on plasma calcium, phosphorus and PTH in uremic rats and on intestinal Ca and P absorption and bone resorption in normal and PTX rats.

We first compared the ability of these two analogs to suppress PTH in uremic rats. 19-nor suppressed PTH and without changes in serum ionized Ca or P, while 1αD₂ suppressed PTH only at doses where a marked increase in serum Ca and P occurred. However, it is possible that on intermediate doses of 1αD₂, that is, 75 ng, could suppress serum PTH with little effect on serum calcium. Earlier in vitro studies from our laboratory showed that 19-nor can suppress PTH secretion in cultured bovine parathyroid cells with the same potency as 1,25-(OH)₂D₃ [23]. Although 19-nor is hypercalcemic at very high doses, it was also shown to suppress PTH levels in uremic rats at doses that did not affect serum Ca or P levels [23, 24].

To further evaluate the higher calcemic response by 1αD₂, we assessed the effects of the two compounds on intestinal calcium absorption and bone mineral mobilization. Previous studies from our laboratory comparing 1,25-(OH)₂D₃ and 19-nor showed 19-nor to be about 10 times less effective than 1,25(OH)₂D₃ both in increasing intestinal Ca and P absorption [31] and in mobilizing Ca and P from bone [32]. Our current study repeated these earlier studies comparing 19-nor and 1αD₂. In metabolic studies 19-nor was significantly less potent in increasing both intestinal Ca and P absorption than 1αD₂. In addition, there was significantly less urinary Ca and P excretion with the 19-nor treatment. For bone resorption studies, PTX rats treated with either analog were fed diets deficient in either Ca or P. This was done to eliminate any contribution of intestinal Ca or P absorption to serum Ca or P, allowing for an indirect measurement of bone resorption of Ca and P by these two analogs. These studies also showed 1αD₂ to be more potent than 19-nor in mobilizing Ca and P from bone at equivalent doses.

While little is known about the mechanism of action of 1αD₂, it is not surprising that it would have more potent calcemic and phosphatemic properties than 19-nor. Unlike 19-nor, 1αD₂ is a pro-hormone and first must be activated. This activation occurs in the liver by the addition of a hydroxyl group at carbon 25 producing the active compound 1,25-(OH)₂D₃. 1,25(OH)₂D₃ has been shown to have the same potency as 1,25-(OH)₂D₃ in stimulating intestinal calcium transport and bone mineral mobilization [33, 34]. In addition, a recently published study using the mouse bone marrow culture model compared the bone resorbing activities of 1,25-(OH)₂D₃, 1,25-(OH)₂D₃, and 19-nor(OH)₂D₃ [35]. In that study, 1,25-(OH)₂D₃ and 1,25-(OH)₂D₃ had the same activity while the bone-resorbing activity of 19-nor(OH)₂D₃ was 70% less. Since osteoblasts and not osteoclasts express the vitamin D receptor (VDR), it was thought that there must be some factor(s) responsible for communication between these two cell types triggering osteoclastic bone resorption. Recent studies have identified this protein as osteoprotegerin ligand (OPGL or RANKL) [36–38]. Holiday et al found that 19-nor, although seemingly as potent as 1,25-(OH)₂D₃ in osteoclast recruitment, was less active in osteoclast activation [35]. The comparative effect of 19-nor on RANKL production is not known, but recently Lacey et al found that a higher concentration of OPGL is required for osteoclast activation than for osteoclast recruitment [36]. One possible explanation for the decreased osteoclast activity of 19-nor is that 19-nor may induce RANKL to levels high enough for the recruitment of osteoclasts but not for their activation. This hypothesis requires further experimental confirmation.

Our current study compares equal doses of 19-nor (OH)₂D₃ and 1α(OH)D₂. It is likely that even though 19-nor(OH)₂D₃ is less calcemic than 1α(OH)D₂, serum levels of active hormone are higher in the 19-nor (OH)₂D₃-treated group than in rats receiving 1αD₂, since 1α(OH)D₂ must first be converted to 1,25-(OH)₂D₃. The rate of conversion of 1αD₂ to 1,25-(OH)₂D₃ is not known, but is probably similar to the rate of conversion of 1α(OH)D₂ to 1,25-(OH)₂D₃, since the liver enzyme responsible for this conversion, cytochrome P450, appears not to differentiate between 1α(OH)D₂ and 1α(OH)D₃ [39].

In standard bioassays 1α(OH)D₂ has been shown to be as effective as 1α(OH)D₃ but is 5- to 15-fold less toxic than 1α(OH)D₃ in vivo [40, 41]. Studies by Horst, Koszewski and Reinhardt give possible insight into the difference in toxicity between vitamin D₃ and vitamin D₂ [42]. Under physiological conditions they showed that the predominant monohydroxylated form of vitamins D₃ and D₂ is 25-(OH)D₃, but that in vitamin D₂-treated rats approximately 20% is 24-(OH)D₃. In contrast, when the...
same dose of vitamin D₃ was given, 24-(OH)D₂ could not be detected. 24-(OH)D₂ has two fold less affinity for the VDR and is less toxic than 25-(OH)D₃ [39]. In addition, Mawer et al demonstrated that vitamin D₂ and not vitamin D₃ can be converted to 1,24-(OH)₂D₃ [43]. This metabolite has potent cell differentiating activity, but lower calcemic activity than either 1,25-(OH)₂D₂ or 1,25-(OH)₂D₃. It has been proposed that 1αD₂ may be 24-hydroxylated in target cells to produce an active metabolite, 1,24-(OH)₂D₃, which is less toxic. This hypothesis remains to be tested.

There also is evidence in the literature that vitamin D analogs can bind differently than 1,25-(OH)₂D₃ to the VDR producing a conformational change in the VDR molecule that favors the selective recruitment of nuclear transcriptional co-activators resulting in a variable degree of VDR-mediated transcription [44–47]. The binding of 19-nor and 1,25-(OH)₂D₃, the active metabolite of 1αD₃, to the VDR could result in the recruitment of different co-activators.

Our current studies in uremic animals treated with 19-nor or 1αD₃ demonstrate that 1αD₃ also produces a marked increase in the Ca × P product at doses where 19-nor has no effect. Cardiovascular problems, including vascular calcification, are the most frequent cause of death in patients with CRF [48, 49]. Traditionally a Ca × P product of 75 mg²/dL² has been the target in treating patients with CRF. Recently, however, studies reveal that patients with a Ca × P product above 55 to 60 mg²/dL² tend to have vascular calcification while those below do not [50–52]. Thus, the recommended Ca × P product has been substantially lowered [53]. Our studies show that the effect of 19-nor on the Ca × P product is markedly less than that of 1αD₃, which could have significant biological consequences.

In summary, we demonstrate significant differences in calcium and phosphate metabolism in normal and uremic rats receiving 1,25-(OH)₂D₃, 19-nor 1,25-(OH)₂D₃ and 1α(OH)D₂. The current study aimed to determine the difference between the two vitamin D analogs. It seems from the results obtained in normal and PTX rats that there is a significant difference in the absorptive and resorptive properties of these two analogs. In these rats, 1αD₃ has a greater effect at the level of both the skeleton and intestinal tract when compared with 19-nor. Similar effects were observed in uremic animals with increased levels of parathyroid hormone. Although both compounds were effective in suppressing PTH, 1αD₃ induced significant increases in the Ca × P product. If the differential metabolic effects of 19-nor and 1αD₃ were mirrored in humans, the effects likely would be clinically significant. Further studies in patients are necessary to define these differences.

ACKNOWLEDGMENTS

This study was supported in part by a Washington University grant, Research in Renal Diseases, and by Abbott Pharmaceuticals.

Reprint requests to Eduardo Slatopolsky, M.D., Renal Division, Box 8126, Department of Internal Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110, USA

E-mail: eslatopo@im.wustl.edu

REFERENCES


