Vitamin D metabolite requirements in dialysed children receiving recombinant human growth hormone

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Abstract

Background. The aim of the study was to assess the requirement of active vitamin D in dialysed children during treatment with recombinant human growth hormone (rhGH).

Methods. Twenty-six children (aged 5–15 years) were treated with rhGH for 6 months. The serum concentration of parathyroid hormone (PTH), alkaline phosphatase (AP), and calcium and phosphorus were measured in two groups of patients studied in the years 1994–1995 (group I) and 1995–1998 (group II) respectively. Group I received a constant dose of alfacalcidol that was sufficient to keep PTH below 200 pg/ml before rhGH treatment began. The serum PTH level was checked every 3 months. Alfacalcidol was administered to group II according to serum PTH levels checked on a monthly basis.

Results. In group I the PTH level increased after 3 and 6 months of rhGH treatment from mean level 73 ± 60; 155 ± 156 and 344 ± 249 pg/ml respectively; P < 0.05. AP activity increased after 6 months of treatment from 206 ± 99 to 325 ± 124 U/l respectively; P < 0.01. The calcium level decreased from baseline after 3 months of treatment from 2.36 ± 0.21 to 2.17 ± 0.12 mmol/l respectively; P < 0.05. In group II AP activity increased after 3 and 6 months of treatment from 272 ± 169 to 332 ± 192 and 404.9 ± 219.8 U/l respectively; P < 0.01. The mean level of phosphorus decreased after 6 months from 2.15 ± 0.28 to 1.70 ± 0.39 mmol/l respectively; P < 0.01. In group II the mean dose of alfacalcidol increased by 60.9%.

Conclusions. In children with end-stage renal failure, higher doses of vitamin D are needed during rhGH treatment. During rhGH treatment, frequent control of serum PTH level is necessary.

Keywords: alfacalcidol; alkaline phosphatase; children; end-stage renal failure; growth hormone; growth retardation; parathyroid hormone

Introduction

Growth retardation is one of the major problems in children with chronic renal failure (CRF). Treatment with recombinant human growth hormone (rhGH) improves growth velocity in these patients [1–5]. Data on the influence of growth hormone on bone metabolism in children with CRF are limited [5–7]. The question whether renal osteodystrophy, a typical consequence of CRF, increases the risk of occurrence or aggravation of calcium and active vitamin D metabolite deficiency during accelerated growth in response to growth hormone treatment remains unanswered.

The aim of the study was to determine changes in the requirement for vitamin D metabolites in dialysed children during the first 6 months of rhGH treatment.

Subjects and methods

Twenty-six dialysed children, 10 on haemodialysis (HD) and 16 on continuous ambulatory peritoneal dialysis (CAPD), were included in the study. Patients were divided into two groups according to different alfacalcidol dosage. Fourteen children (group I) aged 8.2–13.9 with a mean age of 11.2 years (seven on HD and seven on CAPD) were observed in 1994 and 1995. Twelve children (group II) aged 5–15 with a mean age of 10.9 years (nine on CAPD and three on HD) were observed from 1996 to 1998. Patients in group I received the same dose of alfacalcidol over the 6-month period of the study. This dose was established before rhGH treatment was begun and was sufficient to keep parathyroid hormone (PTH) serum level below 200 pg/ml. In patients belonging to group II, alfacalcidol doses were adjusted according to monthly serum PTH levels, in order to maintain PTH levels
below 200 pg/ml. Patients received alfacalcidol in daily oral doses except when PTH level increased to above 300 pg/ml. In these cases intermittent oral doses were given two or three times per week. Calcium carbonate was used in both groups as the only phosphate binder. In both groups it was adjusted every month to maintain a serum phosphorus level from 1.4 to 1.9 mmol/l. All of the patients were treated with rhGH at a dose of 1–1.1 IU/kg/week administered in six or seven subcutaneous injections per week.

All patients underwent transiliac bone biopsy following tetracycline labelling before rhGH treatment. Histomorphometric assessment according to the recommendations of the American Society of Bone and Mineral Research was performed [8].

Hyperparathyroidism was diagnosed when osteoid volume to bone volume (OV/BV) was >3%, bone formation rate to tissue volume referent (BFR/Tv) >600 mm²/mm³/day and mineralization lag time (MIt) was <25 days. Osteomalacia was diagnosed when OV/BV >11% and BFR/Tv <400 mm²/mm³/day. Mixed lesion was diagnosed when OV/BV >11%, BFR/Tv >400 mm²/mm³/day, and MIt was >25 days. Adynamic bone disease was diagnosed when OV/BV <11% and BFR/Tv <210 mm²/mm³/day. Normal bone histology (NB) was indicated when OV/BV was 2–11% and BFR/Tv was 210–600 mm²/mm³/day. Osteoporosis (OP) was characterized by significant lowering of trabecular bone volume without excessive quantity of osteoid and a BFR/Tv below 210 mm²/mm³/day.

In group I the serum concentrations of intact PTH were measured at baseline and every 3 months, and alkaline phosphatase activity (AP), calcium, and phosphorus were determined monthly during rhGH treatment. In group II, the serum levels of PTH, AP activity, calcium, and phosphorus were measured monthly. The results are shown in 3-month intervals for both groups. Serum PTH level was determined by immunoradiometric method (INCSTAR Co., Rochester, Minnesota; laboratory reference value 10–55 pg/ml), AP activity was determined by the kinetic method (laboratory reference value 100–280 U/l), and serum levels of calcium and phosphorus were determined by routine laboratory methods.

Statistics

Statistical analysis was performed using Student’s t-test, Wilcoxon’s test, and Fisher’s test. A value of P<0.05 was considered to be statistically significant. Results are given as mean ± SD.

Results

The results of bone biopsies before rhGH treatment in group I revealed adynamic bone disease in five patients, hyperparathyroidism in three, normal bone histology in four, mixed lesion in one, and osteoporosis in one patient. The results in group II were: adynamic bone disease in three patients, hyperparathyroidism in four, normal bone histology in three, mixed lesion in one, and osteomalacia in one patient. No significant differences in the prevalence of particular types of renal osteodystrophy in either group were found.

Mean values of serum PTH, calcium, phosphorus concentrations, and AP activity in both groups are shown in Table 1. There were no significant differences in biochemical parameters between patients treated with HD and CAPD. However, after analysing all HD patients from groups I and II together and all CAPD patients from group I and II together, we observed significant differences in AP activity during treatment compared with results obtained before treatment. Mean values in the HD group before treatment and at 3 and 6 months were 206±118 U/l, 247.8±108 U/l and 370±201.6 U/l respectively. The differences between: before treatment versus 3 months, before treatment versus 6 months and 3 months versus 6 months of treatment were all significant. Mean values in the CAPD group before treatment and at 3 and 6 months were 255.9±148.8 U/l, 319.1±163.2 U/l and 357.2±164.7 U/l respectively. The differences between: before treatment versus 3 months, before treatment versus 6 months and 3 months versus 6 months of treatment were all significant. There was no significant difference in the mean dose of alfacalcidol at the start of rhGH treatment between groups I and II (0.076±0.03 and 0.092±0.021 µg/kg/week respectively). After 6 months of treatment, the dose in group II significantly increased to 0.148±0.05 µg/kg/week (P<0.01).

In all patients, an increase in growth velocity was observed. In group I, the mean value of growth velocity before rhGH treatment was 1.1±0.8 cm per 6 months and during treatment, it was 3.79±1.11 cm per 6 months (P<0.05). In group II, the mean value of growth velocity before rhGH treatment was 1.08±1.17 cm per 6 months, and during treatment it was 4.49±1.65 cm per 6 months (P<0.05). There was no significant difference between groups before and during rhGH treatment. The mean value of growth velocity per 6 months in patients with adynamic bone disease was 4.5 cm, and it was 5.5 cm, 4.1 cm, 3.9 cm and 4.4 cm in hyperparathyroidism, normal bone histology, mixed lesion and osteomalacia respectively. There was no significant difference between growth velocity in patients with different types of renal osteodystrophy.

Discussion

Many factors influence calcium-phosphorus homeostasis and bone metabolism, e.g. PTH, vitamin D metabolites, and growth hormone. Growth hormone directly, or through insulin-like growth factor (IGF-1), has a stimulatory effect on osteoblasts and osteoclasts [9]. In patients with ESRD, decreased tissue or cell response to growth hormone and decreased synthesis of vitamin D metabolites was noted. Calcitriol is a very important factor for normal mineralization of bone tissue [10]. Because of the differing densities of vitamin D receptors, which depend on hyperparathyroidism type, polymorphism of the receptor gene, and decreased relation of calcitriol to the receptors, the dose of vitamin D necessary to maintain the PTH level below 200 pg/ml is different in each patient with end-stage renal disease.

The optimal dose of vitamin D necessary to maintain
Vitamin D in dialysed children treated with rhGH

Table 1. Mean values of serum parathyroid hormone (PTH), alkaline phosphatase (AP), calcium, and phosphorus before and during rhGH treatment

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 14)</th>
<th></th>
<th>Group II (n = 12)</th>
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<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After 3 months of treatment</td>
<td>After 6 months of treatment</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>73.3 ± 60.1</td>
<td>155.3 ± 156.5*</td>
<td>344.6 ± 249.5*</td>
</tr>
<tr>
<td>AP (IU/l)</td>
<td>206.1 ± 99.5</td>
<td>256.6 ± 83.1</td>
<td>325.6 ± 124.6**</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.36 ± 0.21</td>
<td>2.17 ± 0.12*</td>
<td>2.26 ± 0.23</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.87 ± 0.32</td>
<td>2.2 ± 0.83</td>
<td>1.99 ± 0.73</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*P < 0.05 vs before treatment; **P < 0.01 vs before treatment; #P < 0.05 group I vs group II.

the PTH level below 200 pg/ml in children with end-stage renal failure who are treated with rhGH is unclear. After 6 months of rhGH treatment, there was a significant rise in the serum PTH level in the patients in group I, i.e. those whose alfalcaldol dose before treatment was sufficient to maintain the PTH level below 200 pg/ml and was unchanged during treatment. This was accompanied by a decrease in serum calcium levels after 3 months of rhGH treatment. In group II, in which the alfalcaldol dose was adjusted monthly to maintain the PTH levels below 200 pg/ml, it was necessary to increase the alfalcaldol dose by about 60%. It seems that accelerated growth during growth hormone treatment leads to an increased demand for calcium and active vitamin D metabolites. This points to the necessity of frequent control of PTH, calcium and phosphorus levels and an appropriate adjustment of the alfalcaldol and calcium carbonate doses.

The initial dose of vitamin D in children undergoing rhGH treatment is difficult to establish. Determining the type of renal osteodystrophy by bone biopsy may be helpful in choosing the initial dose of active vitamin D metabolite in particular cases. Nonetheless, even the diagnosis of adynamic bone disease in a biopsy taken before starting rhGH treatment and subsequent rapid growth does not justify withdrawal of active vitamin D supplementation. Intensive growth occurs even in these cases, leading to an elevated demand for calcium and active vitamin D metabolites.

The AP activity increased in the majority of patients during rhGH therapy. Increased AP activity during rhGH treatment of children with CRF, both those dialysed and those managed conservatively, has also been found by other authors [2,3,11]. The high AP activity observed in most of our patients is probably a consequence not only of high PTH serum concentration but also of activation of osteoblasts by growth hormone. In a multicentre study, no significant changes in the AP activity and calcium and phosphorus serum levels were found after 2 years of rhGH treatment compared to a control group [1]. In our study, the mean value of serum phosphorus did not increase during the observation period. Fine's study of 11 patients revealed a significant rise in the serum phosphorus concentration [11]. The same was found by Hansen et al. [12] in adult patients with growth hormone deficiency. In our investigations, serum phosphorus levels decreased in patients who received high alfalcaldol doses. This was probably caused by an increase in the amount of calcium carbonate ingested by group II children, whose initial serum concentrations were higher than those in group I patients. It is difficult to analyse these findings because absorption of phosphorus is influenced by alfalcaldol, calcium carbonate doses, and also by the amount of phosphorus in the diet. The heterogeneity of skeletal lesions in the population studied makes it more difficult to interpret the biochemical findings. According to Joffe et al. [13], it is not possible to evaluate precisely the osteodystrophy type on the basis of non-invasive examinations.

In our 6-month study, there was no difference in growth hormone effects between patients with different types of renal osteodystrophy treated with growth hormone. In a 1-year observation period of children with end-stage renal disease not treated with growth hormone, Kuizon et al. noted significantly diminished growth in children with adynamic bone [14]. There is not enough data in the literature to evaluate the importance of the type of renal osteodystrophy for the growth velocity in children with end-stage renal disease treated with growth hormone.

Conclusions

(i) An increase in the requirements of calcium and active metabolites of vitamin D was observed during rhGH therapy in children with CRF. (ii) According to dynamic changes in PTH serum level during rhGH therapy, frequent control is necessary in order to keep PTH serum concentration below 200 pg/ml.

References

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