High-dose alfalcacidol improves anaemia in patients on haemodialysis

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Abstract

Background. Alfalcacidol is efficient for treating secondary hyperparathyroidism in patients on maintenance haemodialysis (HD). Little is known about the direct impact of high-dose alfalcacidol on anaemia in end-stage renal failure. We therefore carried out a prospective study over 18 months to examine the direct effect of high-dose alfalcacidol on erythropoiesis in erythropoietin (rHuEpo)-dependent anaemic patients on HD for more than 6 months with moderate hyperparathyroidism.

Study design. Twelve patients received oral alfalcacidol at a dosage of 6–7 mg per week and calcium carbonate during the first 12 months, calcium carbonate without alfalcacidol during the next 3 months, and again alfalcacidol and calcium carbonate during the last 3 months. Criteria for selection were haemoglobin <10 g/dl, iPTH >250 pg/ml, transferrin saturation (TS) >25%, S-ferritin >300 mg/l, and S-aluminium <40 mg/l.

Results. Haemoglobin (Hb) and reticulocyte counts increased during the first phase, decreased and returned to a baseline prior to starting vitamin D treatment in the second phase, and again increased when alfalcacidol was reintroduced, whereas iPTH decreased during the first 3 months of the first phase and then remained stable, as did S-calcium, which increased during the first 3 months and then remained constant. S-phosphate increased during the first and third phases, and decreased during the second phase. Two patients during the first phase and one patient during the third phase presented hypercalcaemia; requiring a temporary discontinuation of alfalcacidol.

Conclusion. High-dose alfalcacidol is efficient in anaemic patients with moderate hyperparathyroidism on maintenance HD and has a direct effect on erythropoietic cells regardless of serum calcium and iPTH levels.

Key words: high-dose alfalcacidol; anaemia; haemodialysis; moderate hyperparathyroidism

Introduction

Anaemia is one of the more constant clinical features in patients on maintenance haemodialysis (HD). The aetiology of anaemia in these patients is multifactorial. The major factors seem to be inappropriate low serum erythropoietin, functional iron deficiency, dialysis insufficiency, aluminium overload, and secondary hyperparathyroidism (HPT) [1–9].

High-dose calcitriol, the active form of vitamin D, is widely used in haematological disorders [10–11] and HPT treatment [12–14]. Furthermore, in vitro and other studies indicate that bone marrow erythropoietic cells have specific receptors for calcitriol, and calcitriol induces proliferation and maturation of stem cells [4–6,10,11]. The present study was designed for evaluation of direct effect of high-dose alfalcacidol on anaemia without recombinant human erythropoietin (rHuEpo) throughout the study in anaemic patients on HD with moderate HPT, who were, 1 month before, under rHuEpo, for 18 months of follow-up.

Subjects and methods

Patients

Twelve patients, from a total population of 200 patients in six haemodialysis units, on maintenance HD for at least 6 months and without rHuEpo therapy or calcitriol for at least 1 month before the study, iPTH >250 pg/ml (normal 55) and haemoglobin concentration (Hb) <10 g/dl were selected. They were eight males and four females, with a mean age 59 ± 14 years. The mean duration of HD was 134 ± 179 months. There were seven patients with the diagnosis of chronic glomerulonephritis, two had chronic tubulointerstitial nephritis, and three were of unknown aetiology. We excluded all patients with iron, folate or vitamin B12 deficiency, serum aluminium exceeding 40 mg/l, active bleeding lesions, active untreated infection, malignancies or other causes of inflammation, and also patients with medications that affect erythropoiesis or bone homeostasis such as angiotensin-converting enzyme inhibitors, aluminium compounds, or corticosteroid therapy.

Dialysis programme

All patients underwent dialysis three times a week, utilizing bicarbonate-buffered dialysate with calcium (1.5 mmol/l) and
Kt/V 1.19 ± S-aluminium (mS-albumin (g/l) 38.17 ±

**Table 1. Mean (± SD) S-albumin, S-aluminium, and dialysis parameters**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-albumin (g/l)</td>
<td>38.17 ± 1.47</td>
<td>38.42 ± 1.31</td>
<td>38.16 ± 1.46</td>
<td>39.41 ± 1.30</td>
<td>38.25 ± 1.10</td>
<td>39.75 ± 1.14</td>
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<tr>
<td>S-aluminium (mg/l)</td>
<td>20.8 ± 8.2</td>
<td>13.2 ± 5.2</td>
<td>14.3 ± 2.3</td>
<td>14.3 ± 1.2</td>
<td>15.3 ± 2.1</td>
<td>15.7 ± 5.5</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.19 ± 0.07</td>
<td>1.22 ± 0.08</td>
<td>1.21 ± 0.10</td>
<td>1.2 ± 0.06</td>
<td>1.2 ± 0.08</td>
<td>1.19 ± 0.08</td>
</tr>
<tr>
<td>Protein catabolism rate (g/kg/day)</td>
<td>1.13 ± 0.08</td>
<td>1.14 ± 0.08</td>
<td>1.17 ± 0.08</td>
<td>1.13 ± 0.08</td>
<td>1.11 ± 0.07</td>
<td>1.13 ± 0.06</td>
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**Study design**

The study, which was for 18 months, was subdivided into three phases:

The first phase was the first 12 months during which all patients were treated with alfacalcidol and calcium carbonate. The second phase was the next 3 months, during which all patients were treated with calcium carbonate without alfacalcidol for maintaining constant serum calcium and iPTH levels. The third phase was the last 3 months, during which all patients were treated with alfacalcidol and calcium carbonate.

The dose of alfacalcidol was decreased or increased weekly to maintain serum calcium above 2.2 mmol/l and below 3 mmol/l and serum phosphorus below 2.5 mmol/l; as was calcium carbonate which was given as phosphate chelator exclusively.

**Absolute reticulocyte counts (Figure 2)**

Reticulocyte counts increased during the first phase and reached a maximum at 12 months (P < 0.005 vs before), decreased abruptly during the second phase (P < 0.005 vs 12 months), and re-increased during the third phase (P < 0.005 vs 15 months).

**Serum iPTH, calcium and phosphorus levels (Figure 1)**

There were a decrease in iPTH levels and an increment in S-calcium during the first 3 months (P < 0.005 vs before) and a progressive stabilization in iPTH and S-calcium levels during the next 15 months (n.s.).

Two patients during the first phase and one during the third phase presented hypercalcaemia, necessitating a temporary discontinuation of alfacalcidol and calcium carbonate for 2 weeks. The mean serum phosphorus levels, which were statistically higher under alfacalcidol (P < 0.005), were within the low normal range in the second phase because of alfacalcidol discontinuation, increase in calcium carbonate dosage, sustained S-PTH secretion, and normal phosphorus intake.

**Iron status, S-aluminium and S-albumin levels**

Iron status, which was assessed by TS and serum ferritin, was constant throughout the study (Figure 2). S-ferritin, which was higher during the second and third phases, but remained statistically insignificant (n.s. vs before). TS was >25% throughout the study. S-aluminium levels were <40 mg/l during the study period (Table 1). Aluminium compounds were avoided in all patients selected, since a form of low turnover osteodystrophy and anaemia was noted with oral aluminium exposure [9,12,13].

Nutritional state, which was assessed by S-albumin, was good throughout the study; as were dialysis parameters (Table 1).
Fig. 1. Mean concentration of haemoglobin, iPTH, S-calcium, S-phosphate and mean weekly dosage of alfacalcidol

Fig. 2. Mean absolute reticulocyte counts, transferrin saturation and S-ferritin
Alfacalcidol and calcium carbonate doses

The dose of alfacalcidol was temporarily reduced in a few cases from 7 to 3 or 4 mg weekly because of high serum calcium or high phosphorus levels. In absolute values, the mean alfacalcidol dose was 6.1 ± 1.5 mg per week during the first phase and 5.8 ± 1.2 mg per week during the third phase; the mean calcium carbonate dose was 8.2 ± 2.3 g daily during the first phase, 10.1 ± 2.4 g daily during the second phase, and 7.1 ± 3.5 g daily during the last phase.

Iron intravenous substitution and need for transfusions

Intravenous iron, which was exclusively used, was indicated when TS was <25% and/or S-ferritin <500 mg/l.

The mean individual intravenous ferric hydroxide polymaltose dose was 400 ± 60 mg/month, 333 ± 49 mg/month before and during the study respectively. No patients were transfused throughout the study.

Discussion

The present study clearly shows the positive impact of high-dose alfacalcidol on anaemia and moderate secondary hyperparathyroidism in HD patients with a good iron status and efficacious dialysis parameters. Previous studies in myeloplastic anaemia [10,11] and in anaemia with end-stage renal failure on HD or peritoneal dialysis [4–6] found improvement of anaemia with high-dose alfacalcidol.

iPTH, which has a direct inhibitory effect on erythropoiesis, increases bone marrow fibrosis, decreases erythrocyte survival, interferes with Epo production and is a resistance factor in rHuEpo therapy, is one of the mechanisms suggested [4–8], but in our study iPTH decreased during the first 3 months of the first phase and then remained stable throughout the study, while Hb increased during the first phase, decreased and returned to a baseline prior to starting vitamin D treatment in the second phase, and increased again when alfacalcidol was re-introduced (Figure 1). We cannot thus consider iPTH suppression as the only factor resulting in an improvement of anaemia.

In vitro studies indicate that the culture medium calcium concentration improves the response of bone marrow erythropoietic cells to rHuEpo [6], but in our study S-calcium was increased during the study period, whereas Hb dropped during the second phase; suggesting that S-calcium is not the main factor explaining the improvement of anaemia.

In fact there are few reports [4–6,10,11] concerning the direct effect of calcitriol on erythropoiesis with or without renal failure, but our study clearly documents that alfacalcidol in a high dose has a positive effect, independently of S-PTH and S-calcium, on anaemia in HD populations; however, the mechanism of its action remains to be elucidated.

Functional iron deficiency and aluminium overload were carefully avoided in this trial by displacing TS towards more than 25%, S-ferritin >500 mg/l, parenteral administration of iron salt during HD sessions, and calcium carbonate as exclusive phosphate chelator [3].

In agreement with other studies [4], the selection of high-dose oral alfacalcidol engenders much inconvenience: (i) an important rise in S-calcium (2 patients in the first phase and 1 patient in the last phase), (ii) a substantial increase in S-phosphate, explaining the negative effect of alfacalcidol on long-term iPTH levels, which were not reduced to the normal range except in four patients within the high normal range and one patient within the low normal range, (iii) an induction of adynamic bone disease, an important subject of debate, in patients within the low range iPTH concentrations without aluminium intake [12,13], and (iv) an increase in the Ca×P ion products, a propensity toward soft-tissue calcification.

In the second phase a higher S-calcium compared to normal (as evidenced by a higher set point) and a lower S-phosphate were required to sustain iPTH secretion.

We acknowledge that the number of subjects selected was small in this study and lacked a control group, but our selection criteria and study design were rigorous in order to use all patients as their own controls and to obtain a rational conclusion from our results. We conclude that high-dose alfacalcidol is efficient in anaemic patients with moderate HPT on maintenance HD, and has a direct effect on erythropoiesis, but its adverse effects of vitamin D must be taken into consideration. Further studies are necessary to confirm these results.

References

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Received for publication: 6.5.96
Accepted in revised form: 1.11.96