Acute effects of intravenous 1α-hydroxycholecalciferol on parathyroid hormone, osteocalcin and calcitriol in man

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The acute effects of a single intravenous injection of 2 μg of 1α-hydroxycholecalciferol (alfacalcidol) were studied for a 24-h period in six normal males (mean age 33 years), six women with primary hyperparathyroidism (mean age 72 years) and six women with established osteoporosis (mean age 63 years). In all three groups, serum calcitriol levels rose to a peak 2–3 h after administration of alfalcaldol. Basal levels were highest in the primary hyperparathyroidism group at (mean±SEM) 81±2 vs 62±12 (normal males) (p<0.05) and 56±5 pmol/l (osteoporosis) (p<0.01). Highest peak levels were found also in the primary hyperparathyroidism group at 150±15 vs 114±15 (normal males) (p<0.05) and 127±15 pmol/l (osteoporosis) (p<0.01). The rise in calcitriol was higher in the primary hyperparathyroidism group than either the normal males or osteoporotic patients (p<0.05).

No significant differences were evident in basal serum calcidiol concentrations among the three treatment groups. As might be expected, highest basal concentrations of parathyroid hormone (PTH), serum calcium and serum osteocalcin were noted in the primary hyperparathyroid group (PTH: 17.1±7.7 vs 1.9±0.5 (normal males) (p<0.01) and 2.1±0.3 pmol/l (osteoporosis) (p<0.01); calcium: 3.06±0.08 vs 2.50±0.02 (normal males) (p<0.01) and 2.43±0.02 mmol/l (osteoporosis) (p<0.01); osteocalcin: 1.10±0.08 vs 0.56±0.16 (normal males) (p<0.05) and 0.53±0.21 nmol/l (osteoporosis) (p<0.05). Following treatment with alfalcaldol, no significant change was observed in PTH, calcium or osteocalcin serum concentrations in any group. These results show that maximal conversion of alfalcaldol to calcitriol occurs within a few hours of administration of alfalcaldol in normal males and patients with primary hyperparathyroidism and osteoporosis. Whilst this may reflect differences in activity of the enzyme 25-hydroxylase among these groups, other explanations, such as differences in calcitriol clearance, cannot be excluded.

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In recent years calcitriol has been recognized increasingly as a key hormone in the control of PTH secretion (1). Conversely, PTH is also of major importance in the metabolism of calcitriol, with one of its principal actions being stimulation of the 1α-hydroxylase enzyme, which leads to increased conversion of calcidiol to the active metabolite of vitamin D₃, calcitriol (2).

Further evidence of the interactions between PTH and calcitriol comes from the fact that chronic oral administration of calcitriol has been used successfully to suppress excess PTH secretion in conditions such as chronic renal failure (3). However, the doses required are usually associated with the development of hypercalcaemia (4). It has been noted, however, that adequate PTH suppression can be achieved without this concomitant rise in serum calcium when either calcitriol or 1α-hydroxycholecalciferol (alfacalcidol) (which is metabolized quickly to calcitriol) is given intravenously rather than orally (5).

Administration of intravenous alfalcaldol is, therefore, a useful way of stimulating an acute rise in calcitriol, which would allow the acute effects of calcitriol upon other peptides to be studied.

In this study the acute effects of a single intravenous bolus of alfalcaldol upon the PTH/vitamin D axis are described in normal subjects and in patients with primary hyperparathyroidism and osteoporosis.

Patients and methods

A single intravenous bolus of 2 μg (5 nmol) of alfalcaldol was given to six normal males (mean age 33 years, range 30–36), six women with primary hyperparathyroidism (PHPT) (mean age 72 years, range 65–78) and six women with established osteoporosis (mean age 63 years, range 52–70). The diagnosis of primary hyperparathyroidism was made on the basis of the presence of hypercalcaemia associated with either elevated or inappropriately detectable PTH. The diagnosis of osteoporosis was made on the basis of the presence of
at least one vertebral compression fracture on a dorso-
lumbar spinal X-ray associated with a bone density,
measured by dual-energy X-ray absorptiometry (DXA,
Lunar DPX), of at least one standard deviation below
that of age-matched controls. All studies commenced at
09.00 h, with the subject fasting, and blood was drawn
through an indwelling peripheral intravenous cannula
at time zero, just before administration of alfalcaldiol
and at 1, 2, 3, 5, 8, 12 and 24 h. All subjects were
ambulant during the day, took usual meals at 09.00,
12.00 and 1700 h and went to sleep at midnight.
Measurement of serum calcium, albumin and alkaline
phosphatase was made by standard methods at each
time point. Intact PTH(1–84) was measured by a two-
site immunoradiometric assay (6) and calcidiol and
calcitriol were measured using a modification of the
method of Reinhardt et al. (7). The vitamin D metabolites
to be measured were extracted from serum and separat-
ed from other metabolites by the use of high-perfor-
mance liquid chromatography (HPLC). The purified
calcidiol and calcitriol then were quantitated using
competitive protein binding assays with charcoal sepa-
ration. Serum osteocalcin was measured by radioimmu-
noassay (Incastar Ltd., Wokingham, UK). Serum calcium
concentrations were adjusted for the prevailing albumin
concentration as described previously (8).

Statistical comparison within each given treatment
group was carried out using Sheffe's test for multiple
simultaneous comparisons, while one-way analysis
of variance was used to assess differences between the
groups. Comparison between the baseline parameters in
all three groups was carried out using a Mann–Whitney
U-test.

Informed consent was obtained for all subjects and
this study was approved by our local hospital ethical
committee.

Results
In each group, calcitriol levels rose to a peak 2–3 h after
administration of alfalcaldiol (Fig. 1). Thereafter, levels
fell slowly, although mean values tended to remain
above baseline even at 24 h. As might be expected, basal
calcitriol concentrations were highest in the PHPT
group (Table 1). Highest peak levels also were found in
the PHPT group at (mean ± SEM) 150 ± 15 vs 114 ± 15
(normal males) (p < 0.01) and 127 ± 15 pmol/l (osteop-
porosis) (p < 0.05). One-way analysis of variance
showed that the rise in calcitriol was greater in the PHPT
patients than in the normal males and osteoporotic
patients (F = 4.1, df = 1/64, p < 0.05). No statistically
significant difference in the calcitriol response was
evident between the normal males and the osteoporotic patients. Furthermore, no differences were noted in the basal serum concentrations of calcidiol among the three groups (Table 1).

As shown in Table 1, basal serum concentrations of PTH, calcium and osteocalcin were highest in the PHPT group. Following administration of intravenous alfalcacidol, however, no significant changes were observed in any of these parameters in any of the three groups over the 24-h follow-up period. Serum alkaline phosphatase concentrations tended to be higher in the PHPT group, although this was not statistically significant. Similarly, after administration of intravenous alfalcacidol, no change in alkaline phosphatase concentration was observed in any of the groups over the follow-up period.

Discussion

This study illustrates the changes that occur in serum calcitriol concentrations after a single intravenous injection of alfalcacidol. In all treatment groups, peak concentrations of calcitriol were found between 2 and 3 h after intravenous alfalcacidol.

Prolonged courses of intravenous calcitriol or alfalcacidol therapy have been shown to suppress successfully the excess PTH secretion associated with chronic renal failure without the development of concomitant hypercalcemia (5). Where alfalcacidol is used, 25-hydroxylation must first take place for the formation of calcitriol (9). It is believed generally that this metabolic step is not regulated stringently in human liver cells (10). However, some degree of regulation does take place because the relative increases in calcidiol concentration in the face of large intakes of vitamin D$_3$ are small (11). In this present study, basal serum calcidiol concentrations were similar in all three groups. This would suggest that the greater increase in calcitriol levels seen in the PHPT patients was not due to differences in the basal concentrations of calcidiol.

The results in this present study are similar to those described by Papapoulos et al. (12) in a group of patients with chronic renal failure on regular haemodialysis. In that study, the response of calcitriol to intravenous alfalcacidol appeared to be linear in the dose range 1–4 μg. Papapoulos et al. (12) also found that serum calcitriol concentrations remained significantly elevated for a prolonged period—returning to normal only after 1 week. Mawer et al. (13) described similar changes in serum calcitriol concentrations after the oral administration of calcitriol. While peak changes in calcitriol have been shown to occur within 15 min of the intravenous administration of calcitriol (14), the slower time to peak calcitriol concentrations in this study presumably reflects the time required for hepatic 25-hydroxylation to take place.

Both the basal concentration and the absolute increase in calcitriol were significantly higher in the PHPT group. As all three groups received the same dose of alfalcacidol, this would suggest that the activity of hepatic 25-hydroxylase is increased in patients with primary hyperparathyroidism. However, contrary to the experience of Silverberg et al. (15), there was no evidence of impairment of calcitriol formation in those patients with osteoporosis. This study, however, cannot exclude other explanations for the changes in calcitriol observed in the PHPT patients, such as impaired calcitriol metabolism or clearance.

The activity of the 1α-hydroxylase enzyme has been shown to decline with increasing age (16); however, similar age effects on the 25-hydroxylase enzyme would not explain the changes seen in this study. The greatest rise in calcitriol (and therefore, presumably, the greatest 25-hydroxylase activity) was seen in the PHPT patients, who were also the oldest.

No significant changes were noted in intact PTH concentrations in this present study. Llach et al. (17) similarly failed to demonstrate any changes in immuno-reactive PTH concentrations after the acute administrati-
tion of 2.7 μg of oral calcitriol. The reasons for this apparent lack of effect on PTH secretion remain unclear, particularly since Chertow et al. (18) showed that, in vitro, calcitriol inhibits the release of PTH from parathyroid slices within 2 h. This work was carried out in the rat and certainly species differences may, at least in part, explain this discrepancy.

Intravenous alfalcacidol and calcitriol are being used increasingly to treat the secondary hyperparathyroidism associated with chronic renal failure (5, 12, 19, 20). These studies have been carried out generally over weeks or months and are associated with significant PTH suppression, usually without concomitant hypercalcaemia. This may be due either to a direct effect of vitamin D in suppressing PTH synthesis (21) or an alteration to the set point for serum calcium, such that PTH is suppressed at a lower serum calcium concentration than pretreatment (5).

No significant rise in serum calcium was noted in any of the three groups studied. In fact, the mean serum calcium concentration tended to fall in the normal subjects in the initial 12 h after administration of alfalcacidol (data not shown). This was noted also by Llach et al. (17), where again this change was transient and not statistically significant.

In addition to suppressing PTH synthesis, an increase in the concentration of calcitriol is known to stimulate osteoblastic production of osteocalcin (22). In this study, basal levels of osteocalcin were higher in the patients with PHP, in keeping with their increased bone turnover. By contrast, as has been described previously (23), osteocalcin levels in the osteoporotic patients were no different from normal. The acute administration of intravenous alfalcacidol, however, was not associated with any increase in osteocalcin concentrations in any of the three groups studied. As is the case with PTH, this may be because calcitriol is likely to exert its effect on osteocalcin by stimulating peptide synthesis rather than secretion. Duda et al. (24) demonstrated significant increases in osteocalcin in both normal and osteoporotic postmenopausal women after oral administration of 2 μg of calcitriol daily. In that study, however, increases were first described between days 1 and 3. No comment was made on changes within 24 h. Similar results were noted by Gram et al. (25) where against 2 μg of calcitriol was given orally, in that case to normal males. This led to significant increases in osteocalcin after 1 week; however, again no measurements were made within the initial 24-h period. Duda et al. (24) also noted that while osteocalcin levels increased, serum alkaline phosphatase concentrations did not change. The reason for this discrepancy between alkaline phosphatase and osteocalcin was not apparent.

In conclusion, this study describes for the first time the changes in serum calcitriol concentrations that occur in normal subjects and patients with primary hyperparathyroidism and osteoporosis after a single intravenous injection of alfalcacidol. These results might suggest that liver 25-hydroxylase activity is increased in primary hyperparathyroidism. Furthermore, calcitriol does not appear to alter serum PTH concentrations in the acute situation. Similarly calcitriol does not appear to have an acute effect on stimulating a rise in serum osteocalcin concentrations. These results would suggest that the changes of PTH suppression and osteocalcin stimulation seen in longer term studies occur via changes in hormone synthesis rather than secretion.

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References


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