SHORT COMMUNICATION

The effect of renal function on changes in circulating concentrations of 1,25-dihydroxycholecalciferol after an oral dose

S. E. PAPAPOULOS, T. L. CLEMENS, L. M. SANDLER, L. J. FRAHER, J. WINER AND J. L. H. O’RIORDAN
Department of Medicine, The Middlesex Hospital, London

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Summary

1. 1,25-Dihydroxycholecalciferol [1,25-(OH)₂D₃] was administered orally to four normal subjects and six patients with chronic renal failure not on dialysis. The serum concentration of 1,25-(OH)₂D₃ was measured by radioimmunoassay in both groups from samples taken before, and at regular intervals up to 48 h after, the oral dose.

2. The plasma half-time for the disappearance of the administered 1,25-(OH)₂D₃ was estimated by determining the time for a 50% reduction from the peak increment of the sterol. In normal subjects the calculated value ranged from 5 to 8 h compared with 18 to 44 h in uraemic patients.

3. It appears from our studies that in uraemic subjects there is impaired ability to metabolize or excrete 1,25-(OH)₂D₃.

Key words: 1,25-dihydroxycholecalciferol, kidney, radioimmunoassay, uraemia.

Abbreviation: 1,25-(OH)₂D₃, 1,25-dihydroxycholecalciferol.

Introduction

1,25-Dihydroxycholecalciferol [1,25-(OH)₂D₃] is now frequently used in the treatment of various disorders of mineral metabolism such as renal disease where there is a failure of endogenous production of the hormone [1]. Study of the pharmacokinetics of exogenously administered 1,25-(OH)₂D₃ in man is therefore important. It has become possible to measure the serum concentration of 1,25-(OH)₂D₃ and, therefore, to study its absorption and clearance from the circulation. In the study reported here, the changes in serum concentrations of 1,25-(OH)₂D₃ after an oral dose of synthetic 1,25-(OH)₂D₃ were determined in normal subjects and in patients with severe chronic renal failure.

Methods

Measurement of 1,25-(OH)₂D₃

1,25-(OH)₂D₃ was measured by radioimmunoassay [2] with the following modifications. Serum (5 ml) was extracted with an equal volume of cyclohexane/ethyl acetate (1:1, v/v). Extracts were purified by Sephadex LH20 followed by high pressure liquid chromatography (HPLC). 1,25-(OH)₂D₃ fractions were assayed with antisera 02282 at a final dilution of 1:100000 in a phosphate buffer (KH₂PO₄, 70 mmol; pH 6.0). The tracer used was [23,24-³H]-1,25-(OH)₂D₃ with a specific radioactivity of 70–110 Ci/mmol (Amersham International). The sensitivity of the assay was 10 fmol/tube, resulting in a detection limit of 19 pmol/l when 5 ml of serum was extracted. The normal range of the assay is 53–142 pmol/l (n = 34).

Administration of 1,25-(OH)₂D₃

Four normal male subjects aged between 25 and 32 years, and six patients with chronic renal
disease who were not on dialysis, were studied. The uraemic group had a creatinine clearance ranging from 9 to 27 ml/min. In each case the study was started at 11:00 hours by collection of a control blood sample. Fifteen minutes later another control blood sample was taken (time 0) and, immediately thereafter, 1,25-(OH)₂D₃ (four capsules containing 0.5 µg each) was administered. Blood samples were collected at intervals for 24 h and in some cases up to 48 h afterwards. The sera were deep-frozen until assay. Samples from each individual were extracted, chromatographed and assayed together.

Statistical analysis was made with the Wilcoxon rank sum test.

Results

The increase in circulating concentrations of 1,25-dihydroxycholecalciferol achieved in four normal and six uraemic subjects after an oral dose of 2 µg is illustrated in Fig. 1. In the normal individuals the pattern was characterized by rapid absorption, with 1,25-(OH)₂D₃ concentrations reaching a peak at between 1 and 7 h. The range in the peak increment over basal values was 123–257 pmol/l and the absolute peak concentration achieved was between 235 and 351 pmol/l. Thereafter, concentrations fell progressively and were 12–26 pmol/l above basal values at 24 h.

Fig. 1 also depicts the increase in circulating 1,25-(OH)₂D₃ in six uraemic subjects after a 2 µg oral dose. In three of these subjects, the basal concentration was undetectable (<19 pmol/l) and, in the remainder, it was at the limit of detection. 1,25-(OH)₂D₃ appeared rapidly in serum from uraemic patients after the dose, with the pattern for absorption being similar to that observed in normal subjects. Absolute peak concentrations of 108–212 pmol/l were reached 3–7 h after administration of the sterol. However, in contrast with the rapid disappearance of 1,25-(OH)₂D₃ from the blood of normal subjects, the clearance in uraemic patients was delayed. At 24 h the concentration was from 60 to 91 pmol/l above basal.

The half-time of the disappearance of orally administered 1,25-(OH)₂D₃ from the circulation was estimated by determining the time taken for a 50% reduction from peak increment of the sterol. By this evaluation, the calculated half-times for normal subjects ranged from 5 to 8 h and half-times for the uraemic patients were from 18 to 44 h. The peak increment in 1,25-(OH)₂D₃ after the oral dose did not differ significantly between the normal subjects and the patients with chronic renal failure. However, the value at 24 h

![Fig. 1](image-url)
was significantly greater in the patients with impaired renal function \( (P < 0.01) \).

**Discussion**

The increasing use of synthetic 1,25-(OH)\(_2\)D\(_3\) in the treatment of various disorders of mineral metabolism has prompted the study of the fate of exogenously administered 1,25-(OH)\(_2\)D\(_3\) in man. Radioimmunoassay of serum concentration of 1,25-(OH)\(_2\)D\(_3\) in normal subjects after oral administration of 2 \( \mu \)g of synthetic steroid demonstrated that it was rapidly absorbed from the circulation with peak concentrations achieved within 1–7 h. In normal subjects, clearance of 1,25-(OH)\(_2\)D\(_3\) was also rapid with a half-time of 5–8 h.

It should be noted that determination of the half-time of the reduction of peak increment in 1,25-(OH)\(_2\)D\(_3\) may, in part, be a reflection of the distribution phase as well as the terminal or clearance phase of the steroid. Kumar *et al.* [3] have shown in rats that there is an enterohepatic circulation of 1,25-(OH)\(_2\)D\(_3\) and that when the steroid was given intravenously some appeared in the bile, much of it in a more polar form. It was not possible to saturate this pathway and there is no evidence that this is altered in uraemia.

Our estimations of the half-time of disappearance of radioimmunoassayable 1,25-(OH)\(_2\)D\(_3\) agree well with findings of both Mawer and colleagues [4] and Gray and co-workers [5], who studied the clearance of radiolabelled 1,25-(OH)\(_2\)D\(_3\) in healthy adults. In addition, other preliminary studies [6, 7] have shown that serum concentrations of 1,25-(OH)\(_2\)D\(_3\) in normal subjects given the steroid by mouth follow a pattern similar to that seen in the healthy subjects reported here.

Although the increase in circulating 1,25-(OH)\(_2\)D\(_3\) in uraemic patients was similar to that observed in normal subjects, the disappearance of the steroid from their circulation was clearly delayed. It might be argued that the deficiency in 1,25-(OH)\(_2\)D\(_3\) in uraemic patients before treatment could have affected the distribution of the exogenous steroid, thus in part accounting for the observed delayed clearance. However, for comparison, we studied a patient with untreated hypoparathyroidism who had unmeasurable concentrations of 1,25-(OH)\(_2\)D\(_3\) before the oral dose and the pattern seen was similar to that in healthy subjects. In this patient, the 1,25-(OH)\(_2\)D\(_3\) concentration rose from 24 pmol/l to reach a peak of 240 pmol/l by 7 h and fell to an undetectable concentration by 24 h.

1,25-(OH)\(_2\)D\(_3\) is further metabolized, for example, to 1,24,25-trihydroxy-vitamin D [8] and to calcitriol, which has a carboxylic acid group in the side chain at position C-23. Although the full role of the kidney in the further metabolism of 1,25-(OH)\(_2\)D\(_3\), remains to be established, it would seem possible from the studies presented here that this organ is not only the site of synthesis of 1,25-(OH)\(_2\)D\(_3\), but may also be important in the metabolism of the sterol and its removal from the circulation. In addition, delayed clearance of 1,25-(OH)\(_2\)D\(_3\) used in the treatment of renal osteodystrophy may be a factor in the development of hypercalcaemia in uraemic patients and necessitate a reduction in the dosage required.

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**References**


