Action of 1,25-Dihydroxycholecalciferol in Normal and Uraemic Man

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It is now recognised that cholecalciferol (Vitamin D₃) undergoes two obligatory hydroxylations, first in the liver to 25-hydroxycholecalciferol (Ponchon et al, 1969) and next in the kidney (Fraser & Kodicek, 1970) to 1,25-dihydroxycholecalciferol (1,25 DHCC), the probable active form (Myrtle & Norman, 1970), before exerting biological action. Since the kidney is the only organ capable of producing 1,25 DHCC, derangements in calcium homeostasis in uraemia have been attributed, at least in part, to deficient production of the active hormone. In a preliminary report from this laboratory, it has been shown that 1,25 DHCC augmented the intestinal absorption of radiocalcium and increased serum calcium in three uraemic patients receiving 2.7μg/day (Brickman et al, 1972). In the present report, observations of the effectiveness of 1,25 DHCC are extended over a wider range of dosage and in both normal man and in patients with advanced renal failure.

MATERIALS AND METHODS

Studies were carried out in normal adult hospital and laboratory workers and in patients with advanced renal failure (creatinine clearance 0 to 24 ml/min, mean 9.5 ml/min). Measurements included serum and urinary calcium and phosphorus, intestinal absorption of radiocalcium (⁴⁷Ca), and complete metabolic balance studies, four in normal subjects and six in uraemic patients. Plasma levels of parathyroid hormone (iPTH) were measured by radioimmunoassay. Methods employed are described elsewhere (Coburn et al, 1973; Kopple & Coburn, 1973).

The 1, 25 DHCC was prepared precisely as described elsewhere (Norman & Wong, 1972); it was given in a single daily oral dose of 0.027, 0.14, 0.68 and 2.7 μg (molar equivalents to 1, 5, 25, and 100 IU, respectively, of cholecalciferol (vitamin D₃)). The duration of treatment was 7 to 16 days.
RESULTS

In both normal subjects and patients with uraemia, intestinal absorption of calcium was increased by 1, 25 DHCC. In both groups there was a significant relationship between the increment in $^{47}$Ca absorbed and the log dose of 1, 25 DHCC given (Figure 1). A dose of 0.14 µg/day caused a significant increase in calcium absorption in the normal subjects, but this quantity was without effect in the uraemic patients who required 0.68 µg/day for an effect. The actual fractions of radiocalcium absorbed in the two groups before and after 7 days of treatment are shown in Figure 2. Before treatment, intestinal absorption of $^{47}$Ca was significantly lower in the uraemic patients; however, after treatment with 0.14, 0.68 and 2.7 µg in normal subjects and 0.68 and 2.7 µg/day in the patients with chronic renal failure, the mean values for the two groups were the same. These results are contrasted to
increases in mean absorption from $0.17 \pm 0.015$ to $0.19 \pm 0.19$ and from $0.25 \pm 0.012$ to $0.28 \pm 0.016$ in uraemic patients and normal subjects, respectively, after seven days of treatment with cholecalciferol (vitamin D$_3$) 40,000 IU (1 mg)/day (Coburn et al, 1973). In many instances, intestinal absorption increased to values well above the normal range (Figure 3) to levels observed only in patients with conditions characterised by hyperabsorption of calcium.

With increased intestinal absorption of calcium during treatment with 1, 25 DHCC serum calcium concentrations also rose. The increment was greater in the patients with renal disease ($1.68 \pm 0.48$ mg/100ml) than in the normal subjects ($0.26 \pm 0.08$ mg/100ml). In one instance, treatment with 1, 25 DHCC was useful in the management of severe hypocalcaemia after subtotal parathyroidectomy (Figure 4). An example of the changes in serum and urinary calcium, and phosphorus and plasma iPTH levels in a patient receiving two separate doses is shown in Figure 5. With the increase in serum calcium levels, serum iPTH fell towards normal. There was no consistent change in serum phosphorus level during treatment in the uraemic patients.

The results of metabolic balance studies in the uraemic patients are summarised in Figure 6. During treatment with amounts of 1, 25 DHCC that
Figure 3. The values for intestinal absorption of $^{47}$Ca in uraemic patients before and after treatment with 1, 25 DHCC. Results are shown in relation to each individual's previous habitual daily dietary intake of calcium. The interrupted lines encompass the entire limit of normal while the curved line includes all observations in 96 patients with advanced renal failure (Coburn et al, 1973). Results in 3 patients have been previously reported (Brickman et al, 1972).

Figure 4. Effect of 1, 25 DHCC on serum calcium and phosphorus in a uraemic patient, under treatment with regular haemodialysis, who had undergone subtotal parathyroidectomy five weeks earlier. The patient continued to receive ergocalciferol (vitamin D$_2$) 5 mg/day and supplemental dietary calcium during the entire period.
increased $^{47}$Ca absorption, faecal calcium and phosphorus fell with a tendency toward positive balances for calcium and phosphorus. In the normal subjects, an increase in urinary calcium equivalent to the decrease in faecal calcium resulted in no change in overall calcium balance.

**DISCUSSION**

These results provide ample confirmation of a previous communication from our laboratory (Brickman et al., 1972), which showed that 2.7 μg/day of 1,25 DHCC was able to overcome the 'vitamin D-resistance' of uraemia. The results show that very small quantities are able to produce greater effects in normal man than are produced by much larger quantities of calciferol (Bauer & Marble, 1932; Chu et al., 1941). These results indicate that
the production of 1, 25 DHCC from its precursors must be carefully controlled, observations which underscore the view that 1, 25 DHCC is, in reality, a renal hormone and not a 'vitamin'.

The finding that an amount of 1, 25 DHCC that has no measurable action in uraemic patients but is effective in normals is consistent with the view that uraemia itself may directly impair intestinal calcium transport, independent of the reduction in renal mass. These observations are in agreement with studies in experimental animals (Baerg et al, 1970; Wong et al, 1972) and patients (Coburn et al, 1973) with uraemia. On the other hand, the demonstration that very small amounts of 1, 25 DHCC are capable of restoring intestinal absorption of calcium to normal are consistent with observations of Mawer et al (1973) and Schaefer et al (1972) that the renal production of this hormone is impaired in chronic renal failure. The present study also points to possible eventual therapeutic usefulness of 1, 25 DHCC in clinical
medicine. Obviously, long-term trials of therapy will be needed. It is felt that the greater calcaemic response to 1,25 DHCC observed in the uraemic patients is almost certainly due to high circulating levels of parathyroid hormone in these patients.

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