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USE OF DIPHOSPHONATES IN POST-TRANSPLANT HYPERCALCAEMIA

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Summary

Nine patients with persistent post-transplant hypercalcaemia received 13 courses of diphosphonates. Clodronate (1.6g orally daily) or aminohexane diphosphonate (0.4–0.8g orally daily) given for four to 20 weeks suppressed bone turnover and significantly decreased serum calcium. These effects were maximal three months after the start of treatment and recurred when treatment was stopped. Diphosphonates may be a useful adjunct in the management of post-transplant hypercalcaemia and its associated bone disease.

Introduction

The incidence of persistent post-transplant hypercalcaemia ranges from 1 to 36% depending in part upon the diagnostic criteria used [1,2]. Its aetiology in most cases is related to pre-existing hyperparathyroidism, commonly associated with chronic renal failure, and the slow involution of parathyroid hyperplasia after transplantation. The complications of hyperparathyroidism include accelerated bone loss and those of hypercalcaemia. Of particular concern in transplant recipients are the adverse effects of hypercalcaemia on graft function, although hypercalcaemia is often considered to be benign.

The diphosphonates (bisphosphonates) are potent inhibitors of bone resorption [3]. Etidronate (ethane-1-hydroxy-1, 1-diphosphonate) is widely available for the treatment of Paget's disease, but its effects on hypercalcaemia are less marked than several newer anologues since the latter, in doses which effectively inhibit bone resorption, do not impair calcium entry into bone. Of these new diphosphonates the largest clinical experience has been acquired with clodronate (dichloromethylene diphosphonate) and we have previously shown this to be an effective short-term treatment of primary hyperparathyroidism [4]. We therefore investigated the therapeutic potential of clodronate and a less widely used diphosphonate, aminohexane diphosphonate (AHDP) in the tertiary hyperparathyroidism of transplant recipients.

Patients and methods

We studied 13 episodes of persistent post-transplant hypercalcaemia (serum calcium >2.65mmol/L for more than one month) in nine patients occurring between one day and six months after transplantation. All patients had stable graft function (creatinine <250μmol/L). Immunosuppressive therapy was either azathioprine (2.5mg/kg body weight) and prenisolone (0.15–0.5 mg/kg) (n=5), or Cyclosporin A (5–15 mg/kg) alone or with prednisolone (<15mg daily) (n=4). A rejection episode in two patients was treated with methyl prednisolone (1g daily for three days). None of the patients was taking vitamin D or its derivatives at any time after transplantation. Following their initial investigation, patients were given clodronate (1.6g daily) or AHDP (0.4–0.8g daily) by mouth for one to five months. Four patients were studied on two separate occasions with a time interval of 1–20 months between treatment courses.

Biochemical measurements were made at the start of treatment, at two weekly intervals during and monthly after stopping treatment. Serum measurements included creatinine, calcium (adjusted for fluctuations in albumin), phosphate and alkaline phosphatase (Technicon SMAC). Immunoassayable parathyroid hormone (iPTH) was measured using an anti-serum cross-reacting with the mid-molecule region of PTH. Urine was collected for two hours after an overnight fast for measurement of calcium, phosphorus, creatinine and peptide-bound hydroxyproline [4]. Calcium excretion was computed as the ratio of urinary calcium to urinary creatinine concentration which represents net calcium release from bone. The ratio of urinary hydroxyproline to urinary creatinine was used as an index of bone resorption [5].

The significance of differences between values before and during the 13 treatments was computed using the Wilcoxon rank sum test for paired data.

Results

All patients had features of hyperparathyroidism (Figure 1). In addition to hypercalcaemia and raised serum values of iPTH (>115pmol/L), patients had increased bone turnover as judged by high serum activity of alkaline phosphatase (>100IU/L) and increased urinary excretion of hydroxyproline (>30μmol/mmol cr). The mean fasting urinary excretion of calcium was increased (>0.3μmol/mmol cr), but not markedly so, and six patients had values within the normal range despite marked hypercalcaemia (3.03±SEM 0.13mmol/L). There was therefore some heterogeneity in the maintenance of hypercalcaemia: in nine hypercalcaemic episodes (69%) the increment in serum calcium was largely due to increased renal tubular reabsorption of calcium, whereas in the remainder this was mainly accounted for by increased calcium release from bone.

Treatment with clodronate or AHDP induced a significant fall in serum calcium in all patients but one, which was maximal after three months ($p<0.01$). There was no difference in response between clodronate and AHDP and the data from the 13 treatment courses were combined (Figure 1). The fall in serum was associated with a significant decrease in bone resorption as judged by urine

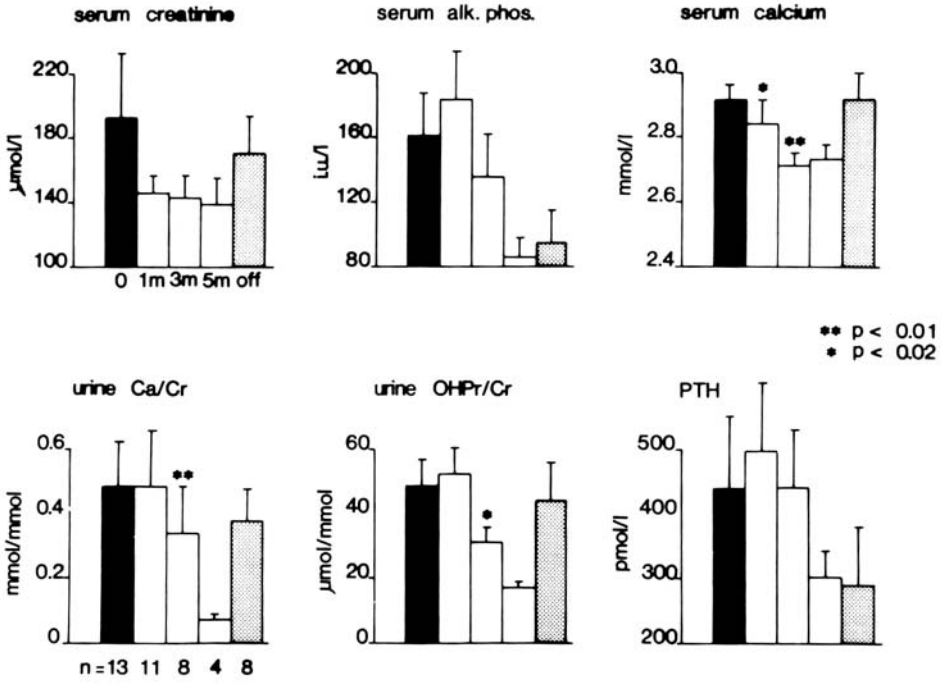

Figure 1. Serum and urine measurements (mean±SEM) in 13 hypercalcaemic episodes before, during (1, 3 and 5 months) and after treatment with diphosphonates. Asterisks denote significance of difference from initial values

hydroxyproline excretion and net calcium release from bone (fasting calcium excretion), values for which consistently decreased to normal. Serum alkaline phosphatase also decreased but fell after the decrease in hydroxyproline. Serum iPTH levels rose transiently at one month but, contrary to expectation, fell gradually thereafter. Serum creatinine also decreased though this did not reach statistical significance. No side effects of treatment were observed.

In order to determine whether these reponses were due to diphosphonate treatment or due to the natural history of hypercalcaemia, we studied the effects of stopping treatment in eight episodes. Hypercalcaemia and increased urinary calcium and hydroxyproline excretion recurred within four weeks of stopping treatment (Figure 1) suggesting a specific effect of the diphosphonates on increased bone resorption.

Discussion

In the absence of vitamin D toxicity, persistent transplant hypercalcaemia is usually attributable to hyperparathyroidism which may persist for many years after adequate graft function is established [2]. The expected effects of hyperparathyroidism include increased bone turnover and hypercalcaemia due mainly

to increased renal tubular reabsorption of calcium [5]. Even though hypercalcaemia is due to high renal tubular reabsorption of calcium, if bone turnover is increased (as was invariably found in our patients) it might be expected that the inhibition of bone resorption would decrease the calcium released from bone and cause a fall in serum calcium. This sequence of events was noted in our patients treated with clodronate or AHDP.

Despite the apparent efficacy of diphosphonates, their potential as a treatment for hypercalcaemia is limited by two additional factors. Firstly, increased renal tubular reabsorption of calcium would not be expected to decrease during diphosphonate treatment. This appeared to be so in our patients since, although urinary calcium and hydroxyproline excretion decreased to normal, mean serum calcium values fell only to the upper end of the normal range and normal values were attained in only two patients. These findings are similar to our earlier observations in primary hyperparathyroidism [4], but contrast with those in myeloma where serum calcium commonly falls to entirely normal values [6]. Secondly, inhibition of bone resorption was followed by a later decrease in bone formation. The subsequent decrease in bone formation therefore would decrease calcium entry from the extracellular fluid into the skeleton and attenuate the hypocalcaemic response. Our patients were not studied for sufficiently long to document this, but it is notable that serum alkaline phosphatase had decreased markedly in the four patients studied for five months. These considerations suggest that diphosphonates might provide an effective long-term treatment for the increased bone turnover found in these patients, although a less adequate long-term treatment for hypercalcaemia.

Notwithstanding these potential limitations in the long-term management of hypercalcaemia, the hypocalcaemic action of diphosphonates may be used to evaluate the role if any of hypercalcaemia on renal function. Following the start of treatment the mean values of serum creatinine fell, although this did not reach statistical significance. Nevertheless, in several individuals there was a marked decrease in serum creatinine which increased when treatment stopped. This suggests that in a minority, hypercalcaemia contributed to impaired graft function. The treatment may therefore provide a method of assessing the contribution of hypercalcaemia to graft function, and aid decisions as to the advisability of parathyroidectomy.

We were surprised to note that mean values for iPTH decreased during treatment. It is possible that this reflected the spontaneous regression of hyperparathyroidism during treatment, or a change in the peripheral metabolism of iPTH with improved renal function. Against this latter possibility is the observation that iPTH remained suppressed despite the increase in serum creatinine after stopping treatment.

We conclude that both clodronate and AHDP are effective agents in decreasing bone turnover in hyperparathyroid bone disease associated with transplantation. This action in turn decreases serum calcium values although normal values are rarely attained. The diphosphonates clearly have potential in the treatment of both bone disease and hypercalcaemia, and longer term studies on a larger number of patients would be of interest.

Acknowledgments

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