CLINICAL RESEARCH

Single dose versus daily intravenous aminohydroxypropylidene biphosphonate (APD) for the hypercalcaemia of malignancy

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Abstract

Thirty patients with hypercalcaemia and known malignant disease were randomly allocated to receive 60 mg 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) intravenously as a single dose or as consecutive daily doses of 30 mg (two days) or 15 mg (four days). The rate of infusion was the same for each regimen (7·5 mg/hour). Calcium concentrations fell in all patients and returned to normal in all but two. Relapse of hypercalcaemia occurred after a mean of 21 days in each group. Urinary calcium excretion fell in all groups and symptoms were greatly improved. After relapse patients were retreated with APD (30 mg as a single infusion) and normocalcaemia maintained by regular infusions at two to three week intervals.

APD given as a single 60 mg infusion over eight hours together with rehydration is recommended as the initial management of the hypercalcaemia of malignancy, followed by 30 mg APD roughly every two to three weeks to maintain normal or near normal serum calcium concentrations.

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Introduction

Hypercalcaemia is a common complication of malignant disease and may be expected to occur in 8-10% of cases. It is particularly common in squamous carcinoma of the bronchus and of the head and neck, in carcinoma of the breast and kidney, and in multiple myeloma.[1] Some tumours that frequently metastasise to bone, however, such as small cell carcinoma of the bronchus and carcinoma of the prostate, are rarely associated with this complication.

Conventional management of hypercalcaemia with rapid rehydration in combination with powerful natriuretic and calciuretic agents such as frusemide[2] is dangerous in the presence of compromised renal function. Corticosteroids are unreliable,[3] and mithramycin may cause liver damage and marrow toxicity. Calcitonin is only of short term benefit and rarely leads to normocalcaemia, as resistance develops after a few days. In addition, frequent administration of a high dose is necessary, often resulting in nausea, dizziness, and headaches.

The bisphosphonates (diphosphonates) are pyrophosphate analogues resistant to the effects of endogenous phosphatases. Of the three evaluated in this condition 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) is the most potent inhibitor of increased bone mineral mobilisation,[4] which is the main cause of the hypercalcaemia in most cases.

Bisphosphonates have been found to be better than more conventional forms of antihypercalcaemic treatment,[5,6] but the most appropriate dose and frequency of administration of APD to achieve and maintain normocalcaemia are unknown, though the efficacy of a single infusion has been described.[7] We report an evaluation of high dose (60 mg) APD given by infusion on one, two, or four days. In addition, we have determined the appropriate interval between maintenance infusions.

Patients and methods

With the approval of the local ethical committees we studied 30 patients with clinically established malignant disease and serum calcium concentrations (corrected for serum albumin) greater than 2·8 mmol/l. Informed consent was obtained in all cases.

Patients were randomly allocated to receive 60 mg APD (Ciba-Geigy Ltd,

Basle) in one of three regimens. Regimen A consisted of 60 mg APD given by intravenous infusion in 500 ml 0·9% saline over eight hours. Regimen B consisted of 30 mg APD given by intravenous infusion in 250 ml 0·9% saline over four hours on each of two consecutive days. Regimen C consisted of 15 mg APD given by intravenous infusion in 125 ml 0·9% saline over two hours on each of four consecutive days.

Biochemical analysis of serum sodium, potassium, creatinine, urea, calcium, albumin, phosphate, and magnesium concentrations was performed daily for the first week and thereafter at weekly intervals. Fasting urinary calcium, creatinine, and hydroxyproline values were measured on alternate days until day 6 and thereafter at weekly intervals. Urinary calcium excretion corrected for glomerular filtration rate[8] was calculated on each occasion. Patients' symptoms and general clinical state were recorded daily by nursing staff according to World Health Organisation scales for toxicity.[9]

Patients were entered into the study when they were considered by the referring physician to be adequately rehydrated (and often after other forms of hypocalcaemic treatment had failed). Specific chemotherapy was not altered or begun until normocalcaemia had been achieved. Retreatment with APD was given in some cases when the serum calcium concentration exceeded 2·65 mmol/l and thereafter at appropriate intervals for each patient.

Statistical comparison among the groups was by the Kruskal-Wallis non-parametric one way analysis of variance and of dynamic variables by using Friedman's non-parametric two way analysis of variance.

Results

Patient characteristics—Mean ages and serum calcium concentrations at presentation did not differ significantly among the three treatment groups (table I). Twelve patients had carcinoma of the bronchus, six multiple myeloma, five carcinoma of the breast, three carcinoma of the kidney, two carcinoma of the female genital tract, and in two the site of the primary tumour was unknown. Isotope bone scans were performed in 20 patients. In 10 (seven with bronchial carcinoma, two with female genital tumours, and one with carcinoma of the kidney) the scans were normal and the hypercalcaemia presumed to be due to tumour factors that mobilise calcium. (Isotope bone scans were not performed in patients with multiple myeloma.)

Effects on calcium—Serum calcium concentrations fell in all patients and became normal in all but two (one with carcinoma of unknown primary site and another with hypernephroma). No patient was completely resistant to APD. Figure 1 shows the effect of APD on serum calcium concentrations. There was no significant difference among the three regimens in their hypocalcaemic effects either in the rate of fall or in the nadir.

Serum magnesium—Hypomagnesaemia was present before the start of APD in 22 of the 27 patients in whom it was measured (mean 0·41 mmol/l; range 0·30-0·70 mmol/l). Mean serum magnesium concentration showed a progressive rise into the normal range in all patients after treatment.

Effects of urinary calcium excretion and hydroxyproline to creatinine ratio—Urinary calcium excretion fell into the normal range in all patients. There was no significant difference in the rate of fall among the three treatment groups (fig 2). No significant fall in the hydroxyproline to creatinine ratio was noted during the study.

Effect on symptoms—Table II shows the numbers of patients with symptoms and the severity of symptoms considered to be directly related to their hypercalcaemia at the time of admission and when calcium values had returned to normal (seven days). Gastrointestinal symptoms of nausea and vomiting, anorexia, and constipation had significantly improved with the return of calcium values to normal but APD appeared to have little detectable effect on neurological symptoms or on bone pain.

Tumour type and response in APD—As the falls in serum calcium concentration and urinary calcium excretion were similar in the three treatment groups, the data from those tumour types that occurred with the greatest frequency—namely, bronchial (12/30), myeloma (6/30), and breast (5/30)—were pooled. Comparison of the data again showed no difference in the initial level of hypercalcaemia or in the rate of response, though there was a tendency for multiple myeloma to be the most responsive (fig 3).

TABLE I—*Comparison of patients at start of treatment*

	Group A (n=10)	Group B (n=10)	Group C (n=10)
Mean age (years) (range)	61·2 (51-71)	62·4 (35-77)	64·4 (46-79)
Median serum calcium (mmol/l)*	3·31	3·26	3·14
Median calcium excretion (μmol/l glomerular filtration rate)†	155	184	133
Mean serum phosphate (mmol/l) (SD)	0·83 (0·26)	0·90 (0·34)	0·95 (0·20)
Mean serum creatinine (μmol/l) (SD)	95 (31)	120 (50)	164 (158)‡

*Calcium corrected for serum albumin.
†See text and ref 8.
‡Includes one patient with known chronic renal failure.

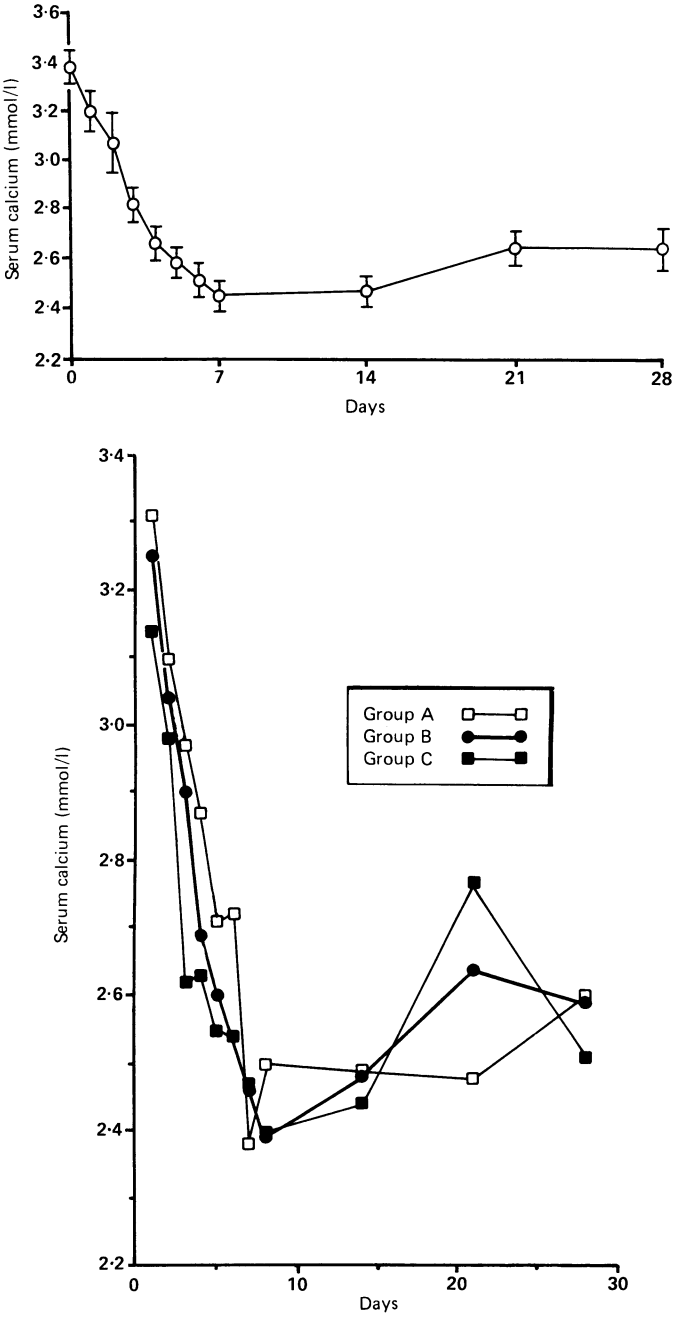

FIG 1—Effect of APD on serum calcium: top, all patients (mean, SEM); bottom, comparison among treatment groups (medians).

Side effects of treatment—All patients tolerated the various infusion regimens of APD well with no evidence of local thrombophlebitis. One patient reported xanthopsia beginning at the end of his second infusion of APD and lasting two hours, but this symptom did not return after two subsequent infusions. A transient and asymptomatic fever was noted in five patients, but in the context of malignant disease this was difficult to ascribe with certainty to the APD. Hypocalcaemia (serum calcium concentration corrected for albumin <2·1 mmol/l) occurred in four patients (three with multiple myeloma, one with carcinoma of the bronchus) but was asymptomatic and required no treatment. No patient developed further impairment of renal function during the study, and indeed the serum creatinine concentration fell in all groups (though not significantly).

Maintenance treatment—Eleven patients survived longer than one month after the onset of hypercalcaemia (five with carcinoma of the breast, three with multiple myeloma, one with uterine sarcoma, one with carcinoma of the bronchus, one with an unknown primary tumour). Despite alteration in

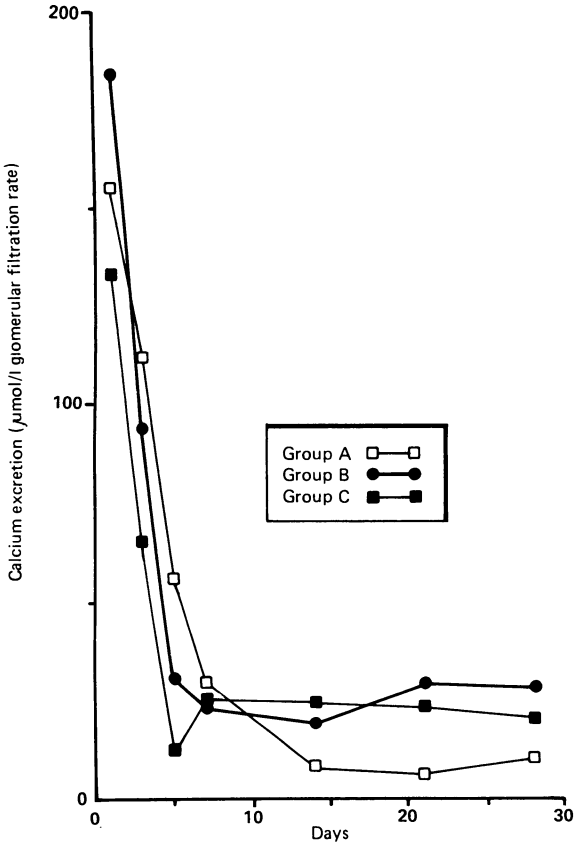

FIG 2—Effect of APD on median urinary calcium excretion in each group of patients.

chemotherapy, hypercalcaemia returned in two patients with carcinoma of the breast, and these were maintained normocalcaemic thereafter by an infusion of 30 mg APD every three weeks. In the patients with multiple myeloma hypercalcaemia recurred after six months of chemotherapy in one (again responsive to APD), and another was maintained normocalcaemic initially by monthly infusions and as the disease progressed by infusions of 30 mg APD every three weeks. The patient with uterine sarcoma remained normocalcaemic for four months with infusions of APD every three weeks but then became hypercalcaemic again. Control was regained with 60 mg APD. The patient with carcinoma of the bronchus had two further infusions of APD 30 mg and remained normocalcaemic to his death. The patient with the unknown primary tumour was alive and asymptomatic with a corrected calcium concentration of 2·85 mmol/l seven months after initial presentation receiving infusions of 30 mg APD every two weeks.

Discussion

This study has shown that a single dose of 60 mg APD given over eight hours as an intravenous infusion was effective in restoring normocalcaemia in 28 (93%) of 30 patients with hypercalcaemia and malignant disease. The drug was free of serious side effects and well tolerated. There was no significant difference in response among the three dosage regimens.

Bisphosphonates interact with bone mineral in such a way as to inhibit osteoclast function, though their precise mode of action remains unknown. These agents are poorly absorbed from the gut and in the absence of a reliable assay their pharmacokinetics are ill understood. In the setting of hypercalcaemia the patients are frequently extremely nauseated and already receiving intravenous fluids and therefore oral administration in the acute phase has little to offer.

The mechanisms of hypercalcaemia differ with different tumours. Many factors influence the renal handling of calcium during hypercalcaemia. In the dehydrated state there is a tendency for the kidneys to conserve calcium (no matter how inappropriate), as the renal mechanisms for conserving sodium and calcium are closely linked. In addition, with the falling glomerular filtration rate and the direct toxicity of hypercalcaemia on renal tubules elimination of calcium is impaired. More recently it has been shown that the parathyroid hormone receptors within the renal tubules are maximally stimulated in many patients with the hypercalcaemia of malignancy.[10] Indeed, the abnormal renal reabsorption of calcium in the patients in this study was evident from the persistently low calcium excretion (fig 2) even in the face of recurring hypercalcaemia. None the less, the most important mechanism initially must be increased bone resorption sufficient to overcome the normal renal mechanisms for maintaining normocalcaemia. This hypothesis is supported by the fact that those patients with a high incidence of the humoral hypercalcaemia of malignancy (in which tumour stimulation of renal calcium reabsorption would be expected to be maximal—for example, in bronchial carcinoma) responded equally well to APD as did patients who would be expected to have "activated" osteoclasts and therefore a high rate of bone resorption (breast cancer, myeloma).

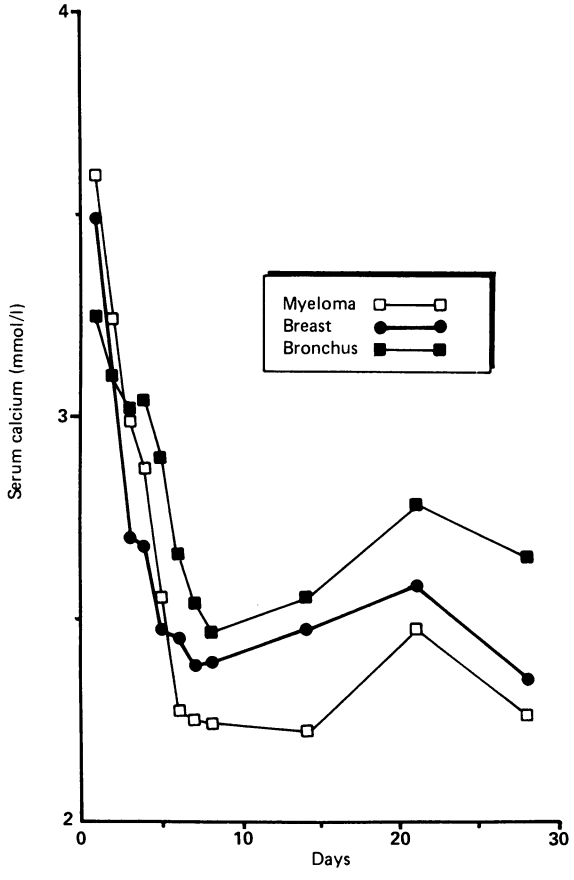

FIG 3—Effect of tumour type on response of serum calcium (median) to APD.

TABLE II—*Effect of APD on symptoms of WHO grade 2* or worse*

Symptom	Group A		Group B		Group C	
	Day 0	Day 7	Day 0	Day 7	Day 0	Day 7
Constipation	10	1†	8	1†	8	1†
Anorexia	6	1†	8	1†	9	2†
Nausea and vomiting	4	0†	7	0†	5	1†
Thirst	8	0†	9	0†	8	1†
Neuromuscular	4	3‡	6	3‡	6	5‡
Bone pain	5	3‡	5	4‡	5	3‡

*Moderate, severe, or intractable (see ref 9).
†Significantly different from day 0 ($p<0·0001$).
‡Not significantly different from day 0.

Though the urinary hydroxyproline to creatinine ratio has been proposed as a useful indicator of bone breakdown in malignancy,[11] we found no significant fall in this variable in patients whose rate of bone mineral resorption had clearly been decreased. The explanation is possibly that tissue other than bone continues to be broken down at a greatly increased rate, masking any fall produced from the decreased bone turnover.

Of additional interest was the finding of quite profound hypomagnesaemia in some patients (as low as 0·3 mmol/l). This may simply result from an inability of the renal tubules to differentiate between divalent cations as the filtration of calcium increases. Though no patient had symptoms directly related to hypomagnesaemia, its role in the neuromuscular symptoms in concert with hypercalcaemia warrants further investigation.

All patients obtained much relief of their distressing symptoms, and in a setting which is often preterminal the value of an effective agent which is free of side effects is self evident. We therefore now use APD 60 mg as a single infusion over eight hours along with adequate saline rehydration as the sole initial management of the hypercalcaemia of malignancy and give further APD when hypercalcaemia recurs or at regular intervals of three weeks to maintain normocalcaemia. Evidently other factors including the response to chemotherapy determine the eventual outcome.

We are grateful to the many nursing staff whose help was invaluable; to the departments of chemical pathology at Hope Hospital, Christie Hospital, and Manchester Royal Infirmary; to Mr R Swindell, of the department of medical statistics, Christie Hospital; and to Ciba-Geigy Ltd for providing APD and financial support.

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Raised plasma intact parathyroid hormone concentrations in young people with mildly raised blood pressure

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Abstract

To study the role of parathyroid gland activity in early primary hypertension plasma concentrations of intact parathyroid hormone were measured in 90 untreated young subjects, aged 16-29, with stable mildly raised blood pressure and in 40 normotensive control subjects selected from the same population in Zoetermeer, The Netherlands. Intact parathyroid hormone concentration was significantly higher in the hypertensive than the normotensive group (2·34 (SE 0·11) pmol/l *v* 1·47 (0·13) pmol/l, respectively; difference 0·87 pmol/l; 95% confidence interval 0·55 to 1·21; $p<0·0001$). Serum total calcium concentration was 2·36 (0·01) mmol/l in the hypertensive group and 2·42 (0·01) mmol/l in the normotensive group (difference 0·06 mmol/l; 95% confidence interval 0·02 to 0·09; $p=0·02$). Urinary calcium excretion over 24 hours did not differ significantly between the two groups (4·17 (0·28) mmol/24 h in the hypertensive group and 3·89 (0·39) mmol/24 h in the normotensive group; difference 0·28 mmol/24 h; 95% confidence interval −0·66 to 1·22). In the hypertensive group both systolic and diastolic blood pressures increased slightly though significantly with intact parathyroid hormone concentrations. No obvious associations between serum calcium concentration and blood pressure were observed.

These findings support the view that enhanced activity of the parathyroid gland may play a part in the early stage of primary hypertension.

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Introduction

An association between activity of the parathyroid gland and blood pressure was first suggested by Hellstrom *et al,* who reported an increased prevalence of hypertension in primary hyperparathyroidism.[1] Furthermore, the prevalence of hyperparathyroidism in subjects with primary hypertension is considerably higher than that in the general population.[2] The raised blood pressure seems not to be secondary to renal damage resulting from hypercalcaemia in hyperparathyroidism,[3,4] and whether blood pressure falls after parathyroidectomy in patients with primary hyperparathyroidism is still uncertain.[4,5]

Two studies have shown increased concentrations of circulating total immunoreactive parathyroid hormone in middle aged patients with hypertension,[6,7] and preliminary findings suggest that concentrations of circulating intact parathyroid hormone (1-84) may be raised in younger subjects with hypertension.[8] In addition, oral calcium supplementation seems to lower blood pressure in subjects with mild hypertension who have higher than average serum intact