insulin resistance in patients with non-insulin-dependent diabetes mellitus been ascribed to abnormal islet cell products or circulating insulin antagonists. In most cases it is thought to be caused by a combination of a decreased number of receptors and a postreceptor defect. The rationale for the present study was that, although the sequence of postreceptor events is not clear, a drug able to inhibit postreceptor degradation might promote the metabolic effects of insulin and overcome, at least in part, the insulin resistance. There is some precedence for this approach, as Blazar *et al* showed a dramatic decrease in the insulin resistance of a patient with insulin dependent diabetes mellitus after treatment with chloroquine.⁸

In the control group administration of chloroquine had negligible effects on glucose homeostasis and plasma insulin and C peptide concentrations. This supports the findings of Philips *et al*, who showed that, unlike quinine, which can produce severe hypoglycaemia, infusion of chloroquine and other synthetic antimalarial drugs has no appreciable effect on plasma glucose and insulin concentrations.⁹ The diabetic patients in this study experienced significant changes in glucose tolerance after treatment with chloroquine, the largest changes occurring in those who showed the greatest glucose intolerance before treatment. These changes represent a median decrease of 8.9% (range 0.4% to 12.1%) in the glucose intolerance of this group of patients.

The improvement in glucose tolerance in the patients with non-insulin-dependent diabetes mellitus was reflected by a significant increase in plasma insulin concentration during the glucose tolerance test. The fact that the C peptide concentrations did not show a similar increase argues against increased output of insulin as a mode of action of the chloroquine. The insulin assay used in this study also detects proinsulin, and the raised values may therefore reflect increased circulatory proinsulin. This would imply that chloroquine had interfered with the proteolytic conversion of proinsulin to insulin in the Golgi apparatus of the islet cells and would be expected to have a deleterious effect on glucose homeostasis rather than the beneficial effect shown here.

Although the glucose tolerance improved significantly on glucose challenge, there was no apparent change in the basal fasting glucose

concentration. This may be connected with the short duration of the treatment with chloroquine and is now being investigated. Whether or not the effect of chloroquine is hepatic or peripheral cannot be determined from this study; inhibition of intraligandosomal breakdown is certainly a possible mechanism.

Interestingly, in the controls and the one diabetic patient with near normal glucose tolerance chloroquine had negligible effects on glucose tolerance. This suggests that in non-diabetic subjects the normal homeostatic mechanisms responsible for insulin-glucose regulation may compensate for perturbations in the insulin concentrations that may be caused by chloroquine and thus prevent the onset of hypoglycaemia.

The results of this study suggest that treatment of non-insulin-dependent diabetes mellitus with chloroquine or suitable analogues may provide a means of diabetic control that does not entail stimulation of pancreatic insulin production. In particular, our results suggest that chloroquine may be useful in diminishing postprandial hyperglycaemia in obese patients with non-insulin-dependent diabetes mellitus.

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Effect of single high dose infusions of aminohydroxypropylidene diphosphonate on hypercalcaemia caused by cancer

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Abstract

Single intravenous infusions of 30 mg aminohydroxypropylidene diphosphonate were given to 16 patients who had malignant hypercalcaemia to assess host tolerance and the effect on serum calcium concentration. Ten of these patients also received intravenous rehydration or corticosteroids, or both. The serum calcium concentrations decreased significantly after treatment with aminohydroxypropylidene diphosphonate. Ten patients became normocalcaemic (normal range, adjusted for serum

albumin, 2.25-2.75 mmol/l), two became hypocalcaemic, three showed decreases in serum calcium concentrations of more than 0.75 mmol/l, and one showed a decrease of more than 0.55 mmol/l. Only one patient had a minimum concentration greater than 2.77 mmol/l. Aminohydroxypropylidene diphosphonate was effective in metastatic and non-metastatic hypercalcaemia, and its hypocalcaemic effect was prolonged in some cases. There were no appreciable side effects.

Single high dose infusions of aminohydroxypropylidene diphosphonate could replace conventional daily lower dose infusions, but the optimum frequency of high dose infusions remains to be determined.

Introduction

Hypercalcaemia associated with malignancy was the most common type of hypercalcaemia identified in a large hospital survey.¹ The treatment of hypercalcaemia associated with malignancy may be

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difficult, and there is no universally effective and specific calcium lowering agent.

Recently, encouraging results have been shown for the diphosphonates, including aminohydroxypropylidene diphosphonate.² Intravenous aminohydroxypropylidene diphosphonate is effective, when compared with volume repletion,³ mithramycin, corticosteroids, and calcitonin,⁴ at treating hypercalcaemia caused by cancer. It has previously been given by daily intravenous infusion, doses ranging from 1.75 mg to 30 mg, and most patients have been given 15 mg daily over several days.³⁻⁴ Ralston *et al* found that serum calcium concentrations decreased considerably two days after the start of daily infusions of aminohydroxypropylidene diphosphonate, but about half of their patients remained mildly hypercalcaemic.⁴

Intravenous infusion of 15 mg aminohydroxypropylidene diphosphonate with intravenous saline and salmon calcitonin daily for six days has been effective in reducing serum calcium concentrations in eight patients suffering from hypercalcaemia associated with cancer.⁵ Our previous work⁶ led us to examine aminohydroxypropylidene diphosphonate given as a single high dose bolus to determine if this could replace daily lower dose intravenous infusions to treat malignant hypercalcaemia.

Patients and methods

Sixteen adult patients who had malignant hypercalcaemia, comprising five women with breast cancer and 11 men with other cancers, were treated. All but three had evidence of bone metastases in skeletal radiographs and isotope skeletal scans. The median age of the patients was 59 (range 31 to 70). Two patients had previously received treatment for hypercalcaemia: one had received intravenous rehydration, frusemide, and corticosteroids and the other intravenous rehydration, frusemide, and calcitonin. Despite these treatments both remained biochemically and symptomatically hypercalcaemic.

Aminohydroxypropylidene diphosphonate 30 mg in 500 ml normal saline was infused intravenously over two hours. Ten patients were also given other potentially hypocalcaemic treatment. Intravenous rehydration with three or more litres of normal saline daily was given to nine patients; of these, four were randomised to receive corticosteroids as well (table). In addition, one patient received corticosteroids alone.

Biochemical measurements were made with an autoanalyser (Technicon). The serum calcium concentrations were corrected for serum albumin using serum albumin concentrations measured simultaneously with serum calcium.⁷ The paired Wilcoxon test was used for statistical analysis.

After the early effects of aminohydroxypropylidene diphosphonate had been determined some patients started or changed specific anticancer treatments—for example, radiotherapy, hormone treatment, cytotoxic chemotherapy, or a combination of these.

Results

Serum calcium concentrations decreased significantly ($p < 0.001$) in all patients after treatment with aminohydroxypropylidene diphosphonate when pretreatment concentrations were compared with the lowest concentrations after treatment (table). Normal calcium concentrations were restored in 10 patients, including four of the six who received only treatment with aminohydroxypropylidene diphosphonate, and hypocalcaemia occurred in two. Calcium concentrations decreased to just above the normal range (2.76, 2.76, and 2.77 mmol/l; normal range 2.25–2.75 mmol/l) in a further three patients. One of two patients resistant to previous treatment became normocalcaemic after treatment with aminohydroxypropylidene diphosphonate. Of the four patients not achieving normal calcium concentrations, one showed a decrease of more than 0.55 mmol/l, three showed decreases of more than 0.75 mmol/l, and only one patient had a minimum serum calcium concentration greater than 2.77 mmol/l after treatment with aminohydroxypropylidene diphosphonate. Serum calcium concentrations fell below the normal range in two patients but returned to normal in 24 hours without any clinical signs of hypocalcaemia being observed.

The time taken to reach normal or minimum serum calcium concentrations was one to nine days after treatment with aminohydroxypropylidene diphosphonate. Individual serum calcium concentrations plotted against time generally indicated a decline in concentrations up to eight days after treatment (figure). Two patients (13%) achieved normal or minimum concentrations within one day and four patients (the modal group) on the third day; by the fourth day after treatment eight patients (50%) had achieved normal or minimum concentrations.

Serum calcium concentrations after a single intravenous infusion of 30 mg aminohydroxypropylidene diphosphonate in four patients remaining hypercalcaemic (top), 10 patients who achieved normocalcaemia (middle), and two patients who briefly became hypocalcaemic (bottom).

Despite initial decreases of more than 0.75 mmol/l in their serum calcium concentrations two patients became appreciably hypercalcaemic again on day 13. Recurrent hypercalcaemia was detected at 10, 11, 13, 55, and 69 days' follow up in five patients who became normocalcaemic after the first infusion of aminohydroxypropylidene diphosphonate. Worsening hypercalcaemia (> 3.0 mmol/l) was detected at 13, 24, and 47 days in three patients who did not achieve normocalcaemia after the first infusion. Five patients were retreated with 30 mg aminohydroxypropylidene diphosphonate in a two hour intravenous infusion, and decreases in serum calcium concentrations of 0.29–1.03 mmol/l occurred, but only one patient achieved normal calcium concentrations.

Before treatment seven patients had increased serum urea concentrations,

Diagnoses, serum calcium concentrations before and after treatment with aminohydroxypropylidene diphosphonate, and concomitant treatments

Case No	Primary site diagnosis	Serum calcium concentration (mmol/l) before treatment	Minimum serum calcium concentration (mmol/l) after treatment	No of days taken to reach normal or minimum concentration	Concomitant treatment	
					Intravenous rehydration	Corticosteroids
1	Adenocarcinoma of unknown primary site	2.92	2.08	1	Yes	Yes
2	Large cell anaplastic lung cancer	3.48	2.18	3	Yes	Yes
3	Breast cancer	3.23	2.29	7	No	No
4	Squamous lung cancer	3.48	2.31	1	No	No
5	Bladder cancer	3.12	2.30	3	Yes	No
6	Breast cancer	3.97	3.10	2	Yes	No
7	Breast cancer	2.84	2.61	3	Yes	No
8	Small cell lung cancer	3.47	2.35	5	No	No
9	Squamous tongue cancer	3.16	2.61	5	Yes	Yes
10	Squamous lung cancer	3.62	2.76	9	No	No
11	Breast cancer	3.18	2.36	3	Yes	No
12	Breast cancer	3.37	2.56	6	No	No
13	Squamous lung cancer	3.35	2.77	6	Yes	Yes
14	Large cell anaplastic lung cancer	3.37	2.45	6	No	Yes
15	Squamous lung cancer	3.58	2.59	8	Yes	No
16	Squamous lung cancer	3.55	2.76	4	No	No

five of whom also had increased serum creatinine concentrations. After treatment the creatinine concentration in one and urea concentrations in three remained marginally abnormal. Transient fevers within one day of treatment occurred in three patients, but other side effects were not detected. The correction of hypercalcaemia was associated with an improvement in hypercalcaemic symptoms.

Discussion

Single infusions of 30 mg aminohydroxypropylidene diphosphonate were not appreciably toxic and were effective alone or when used in combination with other treatments in most patients with malignant hypercalcaemia. Only one patient remained moderately hypercalcaemic, despite a substantial decrease in serum calcium concentrations. A possible confounding factor in interpreting our results was the treatment with corticosteroids in five patients, but corticosteroids probably have a negligible effect on hypercalcaemia caused by solid tumours.⁸

The time in our study taken to reach normal or minimum serum calcium concentrations, whichever was earlier, was similar to that taken in studies that used daily lower dose infusions of aminohydroxypropylidene diphosphonate.^{3,4} This contrasts with the rapid early decrease in calcium concentrations seen when a combination of a calcitonin and aminohydroxypropylidene diphosphonate is used.⁵

Though intravenous rehydration is desirable because of the renal effects of hypercalcaemia,⁹ it is valuable to be able to correct hypercalcaemia with a single two hour intravenous infusion of 30 mg aminohydroxypropylidene diphosphonate. Thus this treatment could be effective and convenient for ambulatory patients who have mild to moderate asymptomatic hypercalcaemia and who are not dehydrated. Intravenous rehydration should remain the first step of treatment for patients who have symptomatic hypercalcaemia or more than moderate biochemical hypercalcaemia.

Our results suggest that single high dose infusions of aminohydroxypropylidene diphosphonate could replace conventional daily lower dose infusions. This would lessen the risk of thrombophlebitis at the infusion site⁴ and be advantageous in terms of cost. The optimum frequency of treatment with high doses of aminohydroxypropylidene diphosphonate is uncertain and needs further study.

A critical determinant of long term normocalcaemia is the control of cancer with specific anticancer treatment, but for patients whose cancers cannot be controlled a high dose infusion of aminohydroxypropylidene diphosphonate every week or alternate week may help to control distressing hypercalcaemia.

Aminohydroxypropylidene diphosphonate for intravenous use was supplied by Ciba-Geigy Pharmaceuticals.

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100 YEARS AGO

Hydrophobia during the past few weeks of abnormally hot weather, says an Odessa correspondent, appears to have become epidemic. "Our Pasteurian Hospital here," he adds, "is overwhelmed with cases. The operating room is crowded during six hours every day, with continuously succeeding batches of patients from every quarter. Within the last ten days, besides local cases, there have arrived for treatment here forty-seven patients, twenty from Kieff bitten by rabid dogs, fifteen from Podolia bitten by a rabid wolf, and twelve Montenegrins also suffering from mad wolf bites. There are seven Turkish cases under treatment, and 120 others from various neighbouring districts. Each patient is inoculated twice a day for ten, and in some cases for twenty, consecutive days, so that Dr. Gamalea and his two lady assistants have just now their hands full. The authorities here seem to have taken alarm at the

extraordinary increase of rabies, and are taking measures for the destruction day after day of the stray dogs in different quarters of the city." Within twenty-four hours of writing, the correspondent learns that three deaths have occurred among the patients in the bacteriological station there; the victims being a man and two boys who formed part of a contingent of fourteen Caucasians bitten by a rabid she-wolf. The deceased lad is said to have been under treatment for nineteen days, and to have been inoculated thirty-eight times. Dr. Gamalea would not guarantee the efficacy of the Pasteur system in the cure of wolf-bitten patients unless they were in his hands not later than three days after being bitten. This was of course impossible in the case of the deceased Caucasians, who could not reach the Odessa station within a week. (*British Medical Journal* 1887;ii:524.)