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Research Article

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Effects of Disodium Dichloromethylene Diphosphonate on Hypercalcemia Produced by Bone Metastases

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ABSTRACT The aim of this study was to determine the ability of disodium dichloromethylene diphosphonate (Cl2MDP) to reduce the hypercalcemia secondary to skeletal metastases and induced by stimulation of bone resorption by malignant cells. Five patients with hypercalcemia due to bone metastases of breast or renal cancer were treated orally for 4 wk with 3,200 mg of Cl2MDP and 4 wk with a placebo in a double blind, crossover study. During the Cl2MDP period of administration four patients experienced a rapid and significant decrease in serum calcium and urinary calcium excretion together with an increase in alkaline phosphatase. In the remaining patient who developed a sudden paraplegia at the onset of the therapy followed by a marked increase in serum calcium levels and urinary calcium excretion, Cl2MDP was able to reverse this worsening of hypercalcemia or to reduce serum and urinary calcium to normal values. For all patients, urinary hydroxyproline excretion was unchanged during the Cl2MDP period when compared with the prestudy or placebo periods. From these results, and because of the rapid relapse of hypercalcemia during the placebo period or after withdrawal of the treatment, we can conclude that Cl2MDP is capable of reducing excessive mobilization of calcium resulting from bone metastases.

INTRODUCTION

In vitro studies using mouse calvaria have demonstrated that disodium dichloromethylene diphosphonate (Cl2MDP)[1] inhibits both parathyroid hormone-stimulated and unstimulated bone resorption (1, 2). Although Cl2MDP is the most potent inhibitor of bone resorption known, it depresses bone formation less than disodium ethane-1-hydroxy-1, 1 diphosphonate or 3-amino-1-hydroxy-propilidene-1, 1 diphosphonate as demonstrated by both in vitro and in vivo rat studies. Cl2MDP does not inhibit osteoid mineralization (3, 4). A recent study on Paget's disease of bone (5), suggests that Cl2MDP may be a potentially effective treatment for bone diseases characterized by an increased osteoclastic activity, because it induces a decrease in bone resorption without impairing bone mineralization. Osteolytic bone lesions from metastatic origin are mostly the result of the stimulation of bone resorption by malignant cells (6, 7). Therefore, we carried out a pilot study on the effects of Cl2MDP on the mobilization of calcium from bone in metastatic disease.

METHODS

The study was a double blind, placebo-controlled, crossover designed trial. It was approved by the local ethics committee.

Patients. Five patients were selected as having clinical, radiological, and bone scan evidence of skeletal metastases a hypercalcemia >2.75 mmol/liter and <3.75 mmol/liter, and a prognosis for survival of >2 mo. Sex and age of the patients and sites of the metastases are summarized in Figs. 1 and 2. Treatment with mithramycin, calcitonin, phosphorus, indomethacin, or corticosteroids at a dose>15 mg/d were excluded during the week preceding the initiation of Cl2MDP. In addition, patients demonstrating an increase in serum calcium>0.4 mmol/liter above the initial value were excluded from the double blind study and treated with Cl2MDP in an open protocol. During the study patients received chemotherapy and eventually cobalt therapy to the most painful lesions. The patients received 3,200 mg Cl2MDP/d for 4 wk divided into four equal oral doses, and a lactose-containing placebo for 4 wk given in the same manner. All patients were randomly assigned to begin the study with either Cl2MDP or placebo.

Clinical status was assessed and blood and urine assays performed twice a week. Blood was drawn for calcium (Ca), phosphorus (P), and alkaline phosphatase (AP). Immunoreactive serum parathyroid hormone levels (iPTH) were measured at the onset of the study and again at the end of the 4th and 8th wk. 24-h urine collections were made to measure urinary Ca and hydroxyproline (OHP) excretions.

Analytical methods. Total serum and urinary Ca were

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[1] *Abbreviations used in this paper*: AP, alkaline phosphatase; Cl2MDP, disodium dichloromethylene diphosphonate; iPTH, immunoreactive serum parathyroid hormone; OHP, hydroxyproline.

measured by a complexometric method (Corning calcium analyzer 940, Corning Medical, Corning Glass Works, Medfield, Mass.) (8). The normal adult range is 2.45±0.07 mmol/liter for serum Ca and 0.4±0.05 mmol/mmol creatinine per d for urinary Ca. Serum P was performed by a colorimetric method (9), normal adult range: 1.15±0.15 mmol/liter. Total urinary OHP was assayed by the method of Kivirikko et al. (10), the normal upper limit for this method is <29 μmol/mmol of creatinine per d. Serum iPTH was performed by radioimmunoassay using a guinea pig antibody (GP6) capable of recognizing the carboxy terminal end of PTH; the normal adult range is 250±134 pg bovine PTH/ml (11).

Statistical analyses. Data were analyzed by the *t* test and least-squares linear regression (12).

RESULTS

The changes in serum Ca are shown in Figs. 1 and 2 that represent respectively, patients who received Cl2MDP first (Nos. 1, 4, 5) and those who received placebo first (Nos. 2, 3). Four patients (Nos. 1, 2, 4, 5) began to show a rapid decrease in serum Ca, the lowest value being reached within 7–10 d of Cl2MDP therapy. In patients 4 and 5 the reduction in hypercalcemia was not prolonged with a rapid relapse of hypercalcemia after withdrawal of Cl2MDP. A progressive worsening in patient 5 with serum Ca >3.75 mmol led to discontinuation of the study during the placebo period.

Patient 3 developed a sudden paraplegia 2 d after the onset of Cl2MDP therapy. This was followed by a marked increase of serum Ca and urine Ca. Cl2MDP therapy was not interrupted and the decrease in serum Ca was rapid and acute; at the end of the 4th wk of treatment serum Ca was under the lower normal value, at 2.12 mmol.

When we compared the mean values of serum Ca

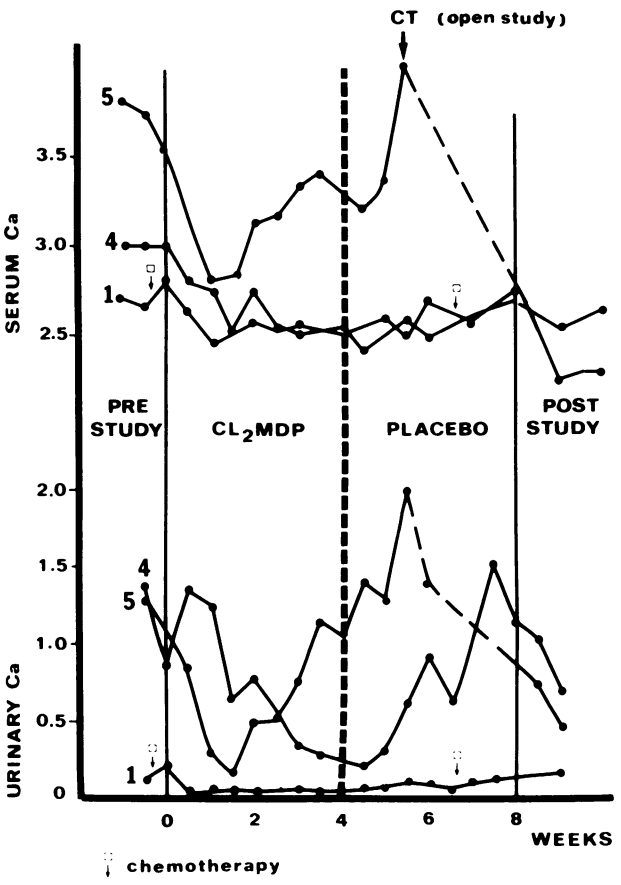

FIGURE 1 Total serum calcium (millimoles per liter) and 24 h urinary calcium (millimoles per millimoles creatinine per day) excretion during the prestudy period, Cl2MDP period, placebo period, and poststudy period in three patients: 1, male, 50 yr old, renal carcinoma; 4, female, 74 yr old, breast carcinoma, and 5, female, 72 year old, breast carcinoma.

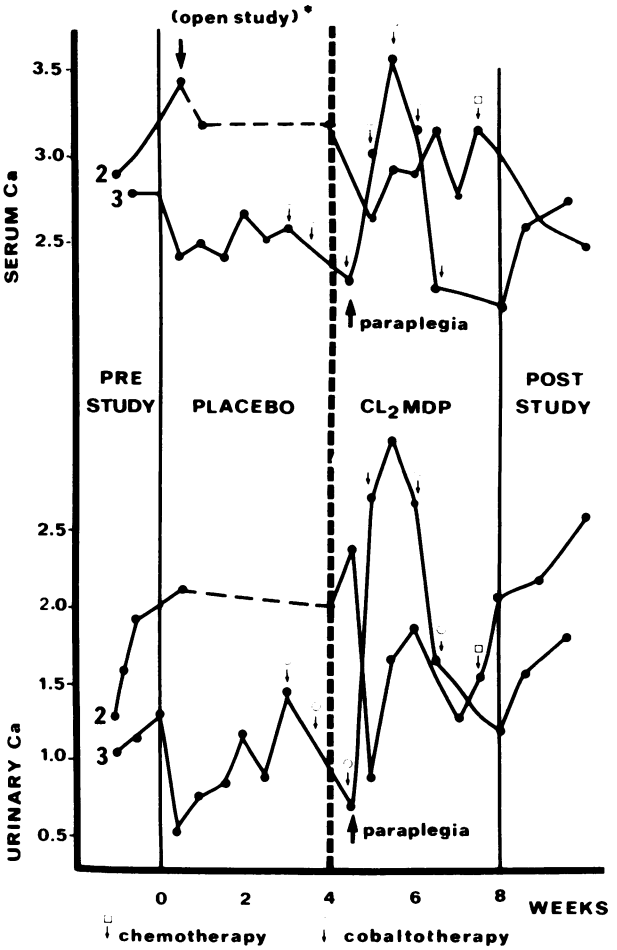

FIGURE 2 Total serum calcium (millimoles per liter) and 24 h urinary calcium (millimoles per millimoles creatinine per day) excretion during the prestudy period, placebo period, Cl2MDP period, and poststudy period in two patients: 2, male, 42 yr old, breast carcinoma,* in this case, because of an increase of serum Ca >0.4 mmol/liter the patient was excluded from the blind protocol and treated with Cl2MDP in an open study; and 3, female, 55 yr old, breast carcinoma.

TABLE I

Changes in Serum Ca, Urine Ca, and OHP during the Prestudy, Cl2MDP, and Placebo Period

	Patient	Prestudy	Cl2MDP	P*	Placebo	P‡
		n§ = 3	n§ = 8		n§ = 8	
Serum Ca, *mmol/liter*	1	2.75±0.05	2.52±0.06	<0.01	2.65±0.09	<0.01
	4	3.0±0.02	2.57±0.09	<0.01	2.65±0.20	NS
	5	3.77±0.08	3.15±0.22	<0.01	3.62±0.28	<0.01
Urine Ca, *mmol per mmol creatinine per day*	1	0.20±0.03	0.04±0.08	<0.001	0.08±0.02	<0.01
	4	1.13±0.35	0.69±0.42	<0.001	0.85±0.45	NS
	5	1.14±0.20	0.65±0.35	<0.01	1.38±0.32	<0.01
Urine OHP, *μmmol per mmol creatinine per day*	1	28±9	18±5	<0.01	22±10	NS
	4	55±11	59±21	NS	75±30	NS
	5	66±15	60±23	NS	67±17	NS

Values are expressed as the mean (±SD) of all determinations during the period indicated.

* *P*, comparison between pre-study and Cl2MDP values.

‡ *P*, comparison between Cl2MDP and placebo values.

§ *n* = number of determinations.

during the prestudy and Cl2MDP periods (Tables I and II) we found a significant decrease in serum Ca during Cl2MDP administration in all but one patient (3, with paraplegia). For two patients (1 and 4) receiving placebo after Cl2MDP, serum Ca values during the placebo period remained lower than the prestudy values. The changes in urine Ca were similar to that in serum Ca (Figs. 1 and 2) and the mean values of urine Ca were significantly lower during the Cl2MDP period than during the prestudy period for all patients. In two (1 and 4) this effect was maintained during the placebo period (Tables I and II). On the contrary, serum P did not change during the three periods.

Except in patient 1, who had only one metastatic localization, all patients had elevated pretreatment urine OHP consistent with increased bone resorption. During treatment with Cl2MDP this excretion was not significantly changed (Table I).

In addition, we noted a progressive increase in serum AP during Cl2MDP therapy (Table III) and the

TABLE II

Changes in Serum Ca, Urine Ca, and OHP during the Prestudy or Placebo Period and the Cl2MDP Period

	Patient	Prestudy or placebo	Cl2MDP	P
Serum Ca, *mmol/liter*	2	3.30±0.21 n* = 6	2.15±0.18 n* = 8	<0.001
	3	2.80±0.08 n* = 10	2.72±0.44 n* = 8	NS
Urine Ca, *mmol per mmol creatinine per day*	2	2.20±0.25 n* = 6	1.58±0.30 n* = 8	<0.05
	3	1.12±0.35 n* = 10	1.93±0.90 n* = 8	NS
Urine OHP, *μmol per mmol creatinine per day*	2	67±9 n* = 6	82±21 n* = 8	NS
	3	139±72 n* = 10	161±60 n* = 8	NS

Values are expressed as the mean (±SD) of all determinations during the period indicated.

* *n* = number of determinations.

TABLE III
Changes in AP (Bodansky units/dl) during Prestudy, Cl2MDP, and Placebo Period

Patient	Prestudy	Cl2MDP	Placebo	r*	P
1	2.1±0.1 n‡ = 3	1.9±0.6 n‡ = 8	2.7±0.4 n‡ = 8	0.47	0.05
2	6.8±0.3 n‡ = 6	9.3±1.4 n‡ = 8		0.71	<0.01
3	23.1±2.1 n‡ = 10	23.9±2.7 n‡ = 8 (paraplegia)		0.25	NS
4	4.7±0.3 n‡ = 3	9.4±1.7 n‡ = 8	15.6±3.6 n‡ = 8	0.85	<0.001
5	6.4±0.3 n‡ = 3	8.8±1.5 n‡ = 8	9.5±0.3 n‡ = 8	0.66	<0.01

Values are expressed as the mean (±SD) of all determinations during the period indicated.
* r = correlation coefficient between AP values and time during the study.
‡ n = number of determinations.

following placebo period. There was no change in iPTH levels and no adverse clinical side effects, such as gastrointestinal intolerance or fever, were observed.

DISCUSSION

In four patients Cl2MDP therapy lowered hypercalcemia and hypercalciuria resulting from metastatic bone disease. Patient 3 developed paraplegia and increased hypercalcemia and hypercalciuria upon bedrest while he was receiving cobalt therapy but the decrease of serum and urinary Ca resulted from Cl2MDP therapy and not from improvement of the disease. We did not observe a simultaneous decrease in urinary OHP although the effect of Cl2MDP would be theoretically related to a reduction of an increased bone resorption. The maximal effect was observed within 7–10 d but persisted throughout the Cl2MDP period only in the two patients with the less extensive disease. Serum Ca and urinary Ca rose again after withdrawal of Cl2MDP.

These results are in agreement with those noted by Van Breukelen et al. (13) with 3-amino-1-hydroxypropilidene-1,1 diphosphonate for the treatment of hypercalcemia from bone metastases but in this study the concurrent effects of chemotherapy were not determined and by Siris et al. (14) with Cl2MDP for the treatment of skeletal mobilization of Ca in multiple myeloma. Siris et al. (14) nevertheless found a reduction in OHP excretion but this decrease was much smaller than that in Ca excretion and the duration of Cl2MDP therapy was longer in this study (8 wk).

From these results and those obtained in the treatment of Paget's disease (5) we can conclude that Cl2MDP given orally is effective in reducing osteolytic bone destruction due to increased resorption. This reduction in osteoclastic activity is possibly accompanied by a transitory increase in bone formation as reflected by the increased AP. In the management of hypercalcemia of malignancy it remains necessary to better define the effective doses and eventually their adjustment according to the magnitude of hypercalcemia. The duration of treatment and the best route of administration, the drug being potentially more effective when used intravenously, must be determined. However, Cl2MDP appears as an effective drug for the treatment of disorders associated with excessive bone resorption and probably for the preventive extension of osteolytic metastases.

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