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Treatment with Clodronate in Patients with Hypercalcemia Secondary to Malignancy

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ABSTRACT

Dichloromethylen bisphosphonate (clodronate, Cl_2MDP) is a synthetic analogue to pyrophosphate, which inhibits increased bone resorption. This drug was given to 12 patients with hypercalcemia secondary to advanced malignant disease. Clodronate in a daily dose of 1.6 to 3.2 g generally caused a return of the serum calcium values to normal within 5-10 days with a concomitant improvement of symptoms related to the hypercalcemia. Side effects were few. Thus, clodronate appears to be a valuable adjunct for the medical management of patients with malignancy-associated hypercalcemia.

INTRODUCTION

Several malignant disorders release humoral factors that cause hypercalcemia, mainly through an increased bone resorption (6). Calcitonin is the only generally available medical therapy. While this treatment has proven valuable in the case of an acute hypercalcemic crisis its long-term usefulness is limited since the duration of action is generally only a few days (4, 6). Moreover, calcitonin must still be administered parenterally and is therefore not suitable for treatment of ambulatory patients.

During recent years developments of synthetic pyrophosphate analogues, bisphosphonates, have provided new possibilities for treatment of malignancy-associated hypercalcemia (8). Among these compounds clodronate (di-chloromethylene bisphosphonate, Cl_2MDP) has turned out to be the most effective (8). However, there are still only few studies concerning its clinical use and most patients have only been followed for short periods of time (4).

In the present report we describe some clinical aspects of treatment with clodronate in an unselected group of patients with hypercalcemia secondary to malignancy.

MATERIAL AND METHODS

The investigation was conducted at Gävle County Hospital. At this hospital serum calcium measurements are routinely performed as part of a multi-channel automated procedure. This study therefore comprises consecutive patients with malignancy associated hypercalcemia. The first five of them were given a daily amount of 1.6 g clodronate divided into 2 doses. If normocalcemia had not been obtained after 7 days the dose was doubled. When serum calcium was reduced to below 2.80 mmol/l individual titration of the optimal maintenance dose was carried out. Since it was found, after treating five such consecutive patients, that 5-10 days of treatment were required to achieve normocalcemia and that the capsules with clodronate were difficult to swallow, the inclusion criteria were changed so that only patients who were supposed to survive for at least one week and had no problems with feeding were included in the study. Furthermore, the initial dose was increased to 3.2 g/daily in the patients where initial serum calcium was above 3.0 mmol/l.

The clinical symptoms that possibly could be related to the hypercalcemia were evaluated before initiation of treatment and thereafter when serum calcium had normalized. Symptoms such as anorexia, fatigue and malaise were regarded as general symptoms while muscle tiredness and mental confusion were considered to be specific.

Serum calcium (normal range 2.20-2.60 mmol/l), adjusted for serum albumin, and creatinine concentrations were measured in the multianalyser used in hospital clinical practice (SMAC, Technicon, U.S.A.). Treatment results were evaluated by Student's paired t-test.

RESULTS

Details of the individual patients are given in Table 1. Apart from patient no 1, who only received the lower dose of clodronate, a clinically relevant reduction of serum calcium was achieved within 5-10 days of treatment. Only one patient (no 11) did not respond to oral therapy with the higher dose, but she displayed a prompt response when clodronate was given intravenously (5 mg/kg BW/day divided into two doses). In the remaining

patients the initial serum calcium value was 3.29 ± 0.45 mmol/l which declined to 2.62 ± 0.14 mmol/l within 10 days ($p<0.001$). There were no significant changes of the serum creatinine or alkaline phosphatase concentrations during treatment.

In four patients (nos 3, 5, 7, 12) the dose of clodronate could be reduced when normal serum calcium values were achieved. In three of them normocalcemia was maintained with a daily dose of 800-1600 mg while the remaining patient (no 5) recurred with hypercalcemia already after 2 days on a lower dose. When the dose again was increased serum calcium levels normalized.

Two of the patients (no 6 and 10) only lived for five days after initiation of the therapy. They were already at the beginning of treatment in the terminal stage of their disease.

There was no apparent effect of treatment regarding the general symptoms of anorexia, fatigue and malaise when serum calcium was normalized. However, mental confusion seen in three patients (nos 5, 7, 11) disappeared when normocalcemia was achieved. Pronounced muscle tiredness seen in one patient (no 3) also disappeared when she became normocalcemic.

No subjective side effects of the capsules were reported apart from difficulties in swallowing. The patient who received intravenous clodronate developed a myocardial infarction on the third treatment day when serum calcium had fallen from 3.67 to 2.87 mmol/l. This diagnosis was substantiated both by a characteristic, moderate, increase of ASAT (from 0.23 to 0.80 μkat/l, normal <0.7) and by the development of a small Q-wave over the anterior wall on ECG. The patient, who had no previous history of heart symptoms recovered uneventfully.

TABLE 1. Patient material, serum calcium values and effects of clodronate treatment.

No	Sex	Age	Diagnosis	Anticancer therapy during trial	Initial serum calcium (mmol/l)	Dose of clodronate (g)	Clinical symptoms probably related to hypercalcemia	Serum calcium on treatment	Days of therapy	Regress of symptoms with normocalcemia
1	M	68	Bronchial cancer	No	3.30	1.6	Muscle tiredness	3.33	11	Unclear
2	M	71	Bronchial cancer	No	3.03	1.6-3.2	Anorexia, fatigue	2.72	14	No
3	F	54	Mammary cancer	Yes	2.92	3.2-2.4	Muscle tiredness	2.45	28	Yes
4	F	39	Mammary cancer	Yes	2.79	1.6	None	2.57	98	-
5	M	76	Bronchial cancer	No	3.15	3.2-1.6-3.2	Mental confusion	2.60	42	Yes
6	M	75	Pancreatic cancer	No	3.81	3.1	Very bad general condition	2.65	5	No
7	M	79	Bronchial cancer	No	3.08	3.2-0.8	Mental confusion	2.50	27	Yes
8	M	70	Bronchial cancer	No	2.98	1.6	None	2.45	11	-
9	M	60	Myeloma	Yes	3.25	1.6	Muscle tiredness	2.65	20	No
10	F	65	Unknown primary tumor with liver metastasis	No	3.85	1.6	Very bad general condition	2.75	5	No
11	F	56	Bronchial cancer	No	3.67	3.2-4.8-i.v.	Mental confusion	2.87	14	Yes
12	F	64	Kidney neoplasm	No	4.07	6.4-1.6	None	2.87	11	-

DISCUSSION

All patients in the present study who received an adequate dose of clodronate responded with a significant reduction of serum calcium levels. These findings are in good agreement to previous reports (1-7). Subjective symptoms, probably related to hypercalcemia, such as mental confusion and muscle weakness were also considerably diminished when the serum calcium levels were normalized. There were no common side effects to the oral treatment, except for local irritation of the mouth and difficulties in swallowing the capsules in some patients.

Taken together with previous experience (4) the findings in the present study demonstrate that oral clodronate provides an efficient therapy for hypercalcemia associated with malignancy which can fairly easily be administered also to ambulatory patients, providing long-term maintenance of normocalcemia with improved quality of life.

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