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Bisphosphonate pretreatment attenuates hungry bone syndrome postoperatively in subjects with primary hyperparathyroidism

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Abstract Primary hyperparathyroidism is characterized by hypercalcemia with loss of bone mass. After parathyroidectomy, hypocalcemia may develop in some patients due to unregulated bone mineralization. Preoperative administration of bisphosphonates, potent inhibitors of osteoclast activity, may prevent postoperative hypocalcemia after parathyroidectomy. We retrospectively reviewed medical records to investigate the effect of bisphosphonate pretreatment on serum calcium level changes after parathyroidectomy. Twenty-three patients with a diagnosis of primary hyperparathyroidism underwent parathyroidectomy between April 1997 and August 2002. Clinical and laboratory data were collected before and after the operation. These patients were divided into two groups; those showing hungry bone syndrome ($n = 9$) and those not ($n = 14$). None of the 9 patients with hungry bone syndrome had received bisphosphonate pretreatment. Of the 14 patients without hungry bone syndrome, 6 had received bisphosphonate pretreatment ($P < 0.05$). Furthermore, preoperative calcium concentration was not related to the occurrence of hypocalcemia in those without bisphosphonate pretreatment. In conclusion, administration of bisphosphonates in primary hyperparathyroidism can prevent the occurrence of hungry bone syndrome after parathyroidectomy.

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Introduction

Primary hyperparathyroidism can induce hypercalcemia and loss of bone mass by increasing osteoclastic bone resorption [1]. Generally, parathyroidectomy is suggested as the treatment of choice, especially in patients with symptomatic hypercalcemia [2]. Hypocalcemia after operation, the so-called hungry bone syndrome (HBS), is sometimes found in these patients [3–5]. The mechanisms for the hypocalcemia that occurs after parathyroidectomy are not completely clear, but studies have suggested aggressive calcium uptake by bone postoperatively as a possible cause [6]. Bisphosphonates have a potent effect on the inhibition of osteoclastic bone resorption and are widely used in the treatment of osteoporosis and hypercalcemia [7,8]. Previously, the only study to show that the administration of a bisphosphonate prevented postoperative hypocalcemia following parathyroidectomy was a case report of a 62-year-old woman who received palmidronate [9]. In this retrospective study, we analyzed the effect of preoperative administration of bisphosphonates on postoperative hypocalcemia in patients with primary hyperparathyroidism.

Subjects and methods

Hospital records of patients with hyperparathyroidism who underwent parathyroidectomy surgery between April 1997 and August 2002 were reviewed. Exclusion criteria were: (1) age less than 20 or more than 80 years, (2) history of chronic renal failure, and (3) hyperphosphatemia during hypocalcemia.

Table 1. Clinical characteristics of all study subjects

No.	Sex	Age (years)	Before operation					After operation		
			Bisphosphonate	Ca (BO) (mg/dl)	Alk-P (U/l)	BUN (mg/dl)	I-PTH (pg/ml)	I-PTH (pg/ml)	Ca (nadir) (mg/dl)	No. of days to Ca nadir[a]
1	F	78	Intravenous clodronate 300 mg/day for 1 day and oral clodronate 1600 mg/day for 3 days	11.1	285	14	256	13.7	9.0	1
2	F	56	Intravenous clodronate 300 mg/day for 15 days	11.6	196	19	270	12.6	9.0	2
3	M	50	Intravenous clodronate 300 mg/day for 2 days and oral clodronate 1600 mg/day for 7 days	12.0		19	199	5.63	9.7	6
4	F	29	Intravenous pamidronate 60 mg/day for 1 day	11.8	318	23.4	832	28.8	9.2	6
5	F	73	Oral clodronate 1200 mg/day for 17 days	15.4		37.8	270	9.6	10.2	7
6	F	59	Oral clodronate 1600 mg/day for 13 days	11.5	97	36	132	1.8	8.6	3
7	F	67		13.3		30.5	197	1.0	8.0	4
8	M	75		13.2	94	18	257	13.9	9.4	6
9	F	38		13.0	330	21.4	209	4.85	6.8	2
10	F	19		13.0		17	983	23	7.9	2
11	F	35		12.7	45	26	247	31	9.3	1
12	F	73		12.3		16.3	449	17.9	8.3	4
13	F	48		11.8	149	15	304	29	8.6	1
14	M	70		11.8		31	240	18.4	8.5	2
15	F	57		11.6		16	203	30.0	9.0	1
16	F	60		11.5		13	122	28	9	1
17	F	40		11.5	122	12.5	102	3.14	8.2	1
18	F	52		11.4	214	9.6	207	27.8	8.6	2
19	F	68		11.3		22.4	140	56	7.6	0
20	F	57		11.2	317	17.1	175	1.0	7.5	3
21	F	76		10.7	121	27.5	784	15.5	9.6	1
22	F	77		10.2		12.1	121	32.3	8.4	1
23	F	62		10.0	222	30.4	221	1.0	6.2	5

Medication, type of bisphosphonate that the patient received; Ca (BO), calcium level before operation; Alk-P, alkaline phosphatase; BUN, blood urea nitrogen; I-PTH intact parathyroid hormone; Ca (nadir), minimal plasma concentration of calcium after operation

[a] Number of day(s) after operation when nadir calcium occurred

Preoperative plasma concentrations of all patients' calcium (normal range, 8.5–10.6 mg/dl), urea nitrogen (normal range, 5–25 mg/dl), alkaline phosphatase (normal range, 50–190 U/l), and intact parathyroid hormone (I-PTH; normal range, 12–72 pg/ml) were recorded. I-PTH and serial calcium concentrations were collected postoperatively. Hungry bone syndrome (HBS) was defined by a postoperative calcium level of less than 8.5 mg/dl [3]. The study was approved by the institutional review board committee.

Values for all descriptive data are expressed as means ± SEM. The χ^2 method was used to assess differences based on sex, the number of patients with bisphosphonate pretreatment, and the occurrence of HBS. For differences among three study groups, the nonparametric Kruskal-Wallis test was. The nonparametric Mann-Whitney *U*-test was used to compare the plasma concentrations of calcium, urea nitrogen, alkaline phosphatase and I-PTH between the bisphosphonate group and the nonbisphosphonate group. Statistical analyses were conducted with SPSS 10.0 (Chicago, IL, USA).

Results

A total of 23 subjects with primary hyperparathyroidism were enrolled in the study. The clinical characteristics of the study subjects are shown in Table 1. The patients were classified into two groups: in the HBS group, there were 9 patients who experienced HBS after parathyroidectomy; in the non-HBS group, there were 14 patients who did not develop HBS after parathyroidectomy. There were no significant differences in sex and age between these two groups (Table 2). The lowest postoperative plasma calcium concentrations were significantly lower in the HBS group than in the non-HBS group (7.7 ± 0.2 vs 9.1 ± 0.1 mg/dl; $P < 0.001$). None of the 9 patients in the HBS group had received bisphosphonate treatment before parathyroidectomy, but 6 of the 14 patients in the non-HBS group had received bisphosphonate pretreatment ($P < 0.05$). There were no significant differences in admission plasma concentrations of calcium (11.8 ± 0.4 vs 12.0 ± 0.3; $P = 0.658$), alkaline phosphatase (248 ± 48 vs 169 ± 31 U/l; $P = 0.123$), blood urea

Table 2. Clinical and laboratory analyses of patients before parathyroidectomy (grouped by occurrence of hungry bone syndrome)

	HBS	Non-HBS	*P*
No.	9	14	
Sex (M/F)	0/9	3/11	0.253
Age (years)	56 ± 6	58 ± 4	0.900
Serum calcium before operation (mg/dl)	11.8 ± 0.4	12.0 ± 0.3	0.658
I-PTH (pg/ml)	289 ± 93	309 ± 58	0.186
Alkaline phosphatase (U/l)	248 ± 48	169 ± 31	0.123
Blood urea nitrogen (mg/dl)	20 ± 2	21 ± 3	0.831
Bisphosphonate pretreatment (no. of persons)	0	6	0.048*

* $P < 0.05$

Table 3. Clinical and laboratory analyses of patients before parathyroidectomy (grouped by bisphosphonate pretreatment and preoperative calcium concentrations)

	Bisphosphonate pretreatment	No bisphosphonate pretreatment		
		Severe hypercalcemia	Mild hypercalcemia	*P*
No.	6	6	11	
Sex (M/F)	1/5	1/5	1/10	0.902
Age (years)	58 ± 7	51 ± 10	61 ± 3	0.726
Calcium before operation (mg/dl)[a]	12.2 ± 0.6	12.9 ± 0.1	11.2 ± 0.2	0.002*
I-PTH (pg/ml)	327 ± 103	390 ± 124	238 ± 58	0.155
Alkaline phosphatase (U/l)	224 ± 50	156 ± 88	191 ± 31	0.662
Blood urea nitrogen (mg/dl)	26 ± 5	21 ± 2	18 ± 2	0.125
Occurrence of HBS (no. of persons)	0	4	5	0.051
Nadir calcium (mg/dl)	9.3 ± 0.2	8.3 ± 0.4	8.3 ± 0.3	0.058
No. of days to Ca nadir[b]	4 ± 1	3 ± 1	2 ± 0	0.038*

* $P < 0.05$

HBS, hungry bone syndrome; Nadir calcium, minimal plasma concentration of calcium after operation

[a] Severe hypercalcemia group $P = 0.001$, compared with mild hypercalcemia group

[b] Bisphosphonate group $P = 0.025$, compared with mild hypercalcemia group

nitrogen (20 ± 2 vs 21 ± 3 mg/dl; $P = 0.831$), or I-PTH (289 ± 93 vs 309 ± 58 pg/ml; $P = 0.186$).

However, the peak admission plasma calcium concentration was higher in patients who received bisphosphonates (13.5 ± 0.6 vs 11.9 ± 0.2; $P = 0.030$). In order to determine the effect of preoperative calcium concentrations on the development of HBS postoperatively, the 6 patients with higher preoperative calcium concentrations, defined as the severe hypercalcemia group, were selected from the 17 patients without bisphosphonate treatment. The peak admission calcium concentrations were not significantly different between the 6 patients with bisphosphonate treatment, defined as the bisphosphonate group, and 6 patients in the severe hypercalcemia group (13.5 ± 0.6 vs 12.9 ± 0.1 mg/dl; $P = 0.630$). After bisphosphonate treatment, the serum calcium concentrations in the bisphosphonate group were marginally reduced before operation (13.5 ± 0.6 vs 12.2 ± 0.6 mg/dl; $P = 0.068$). The posttreatment calcium levels were still not significantly different from those in the severe hypercalcemia group ($P > 0.05$). The other 11 patients, defined as the mild hypercalcemia group, had a lower preoperative calcium concentration (11.2 ± 0.2 mg/dl) than the patients in the severe hypercalcemia group ($P = 0.001$). There were no differences in sex ($P = 0.902$), age ($P = 0.726$), alkaline phosphatase ($P = 0.662$), or blood urea nitrogen ($P = 0.125$) between these three groups (Table 3). No HBS was found in the patients in the bisphosphonate group, but four episodes of HBS were found in the severe hypercalcemia group and five episodes of HBS were found in the mild hypercalcemia group. There were no differences in the occurrence of HBS between the severe hypercalcemia group and the mild hypercalcemia group ($P = 0.620$). Neither the nadir calcium concentration (8.3 ± 0.4, and 8.3 ± 0.3 mg/dl; $P > 0.05$) nor the number of days after the operation when hypocalcemia (nadir calcium) occurred (3 ± 1 and 2 ± 0 days; $P > 0.05$) were different between these two groups.

Discussion

The effect of a high PTH concentration is to induce generalized demineralization of bone and increase fracture risk [1,10–12]. Parathyroidectomy is an effective treatment for primary hyperparathyroidism. Medical treatment with bisphosphonates is a choice for hypercalcemia before operation, but sometimes bisphosphonates are administered when hypercalcemia is resistant to other management, such as forced diuresis [13,14]. Hypocalcemia is a common complication of parathyroidectomy, with more than 50% of subjects in previous studies showing hypocalcemia, with the lowest serum calcium level usually found around the

third postoperative day [4,15]. Bisphosphonates can suppress the osteoclastic bone resorption during high serum concentrations of I-PTH before parathyroidectomy [16]. The prevention of hungry bone syndrome (HBS) by bisphosphonates in our study may have resulted from the mitigation of sequential aggressive calcium reuptake after parathyroidectomy.

In our study subjects, the bisphosphonates were administered to patients with a higher calcium concentration before operation. Therefore, we divided patients with hypercalcemia without bisphosphonate pretreatment into groups with severe hypercalcemia and mild hypercalcemia. However, there was no difference in the occurrence of HBS between these two groups. A similar result, no correlation between the occurrence of HBS and preoperative calcium concentration, was found by logistic regression analysis ($P = 0.607$). In accordance with our finding, Mittendorf et al. [15] also demonstrated that postoperative hypocalcemia was not related to preoperative calcium concentration. Therefore, prevention of HBS is important in both severe hypercalcemia and mild hypercalcemia. The preoperative administration of bisphosphonates is probably necessary in all patients with hypercalcemia.

Both oral and intravenous administration of bisphosphonates is effective for the inhibition of bone resorption during hyperparathyroidism, but the dosage and duration of treatment are important factors [16–18]. The purpose of bisphosphonate administration is to decrease the calcium level during hypercalcemia, and most of the patients received bisphosphonates for only several days [13,19]. In a case report, Kumar and Ralston [9] demonstrated that the 2-day administration of intravenous bisphosphonates prevented the postoperative development of HBS. In our study, the dosage of bisphosphonates was not controlled. Furthermore, calcium or/and vitamin D were replaced after the occurrence of hypocalcemia. We cannot state that the significant difference between the bisphosphonate and non-bisphosphonate groups in the number of days after operation at which the nadir calcium occurred was related to the effects of the bisphosphonates, because varying dosages of calcium (and vitamin D) were administered to the subjects after the hypocalcemia occurred. Further, prospective, research, using a larger patient population is required to establish the dose effect of the preoperative administration of bisphosphonates.

The decline of bone resorption during the period of administration of bisphosphonates in subjects with hyperparathyroidism and those with HBS can be demonstrated by biochemical bone markers and bone mineral density [20,21]. In our study, however, the clinical practice did not include these assessments. Whether alterations of biochemical bone markers and bone mineral density after bisphosphonate treatment are associated with the prevention of HBS will be an interesting issue for further short- and longterm follow-up studies [22,23].

In conclusion, preoperative administration of bisphosphonates in subjects with primary hyperparathyroidism attenuates the severity of hypocalcemia after parathyroidectomy. Further study to determine routine preoperative treatment with bisphosphonates, and the dose effect, is encouraged.

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