

Preoperative intravenous ibandronate for treating severe hypercalcemia associated with primary hyperparathyroidism: an effective and low cost

Zafer Pekkolay¹, Faruk Kılınç², Hikmet Soylu¹, Belma Balsak¹, Mehmet Güven¹, Şadiye Altun Tuzcu³, Alpaslan Kemal Tuzcu¹

¹Dicle University School of Medicine Adult Endocrinology Department, Sur, Diyarbakır, Turkey - E-mail: drpekkolay@gmail.com; ²Firat University School of Medicine Adult Endocrinology Department, Elazığ, Turkey; ³Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

Summary. Primary hyperparathyroidism (PHPT) is a prevalent mineral metabolism disorder usually caused by a single parathyroid adenoma. Although PHPT is the most frequent cause of hypercalcemia, severe hypercalcemia cases are rarely encountered. Severe hypercalcemia results in fatal complications unless immediately treated; moreover, it causes delays in surgery for PHPT, the primary treatment. Some patients admitted because of hypercalcemia require intravenous bisphosphonate treatment. Aimed to investigate the efficacy of intravenous ibandronate, which is a relatively cheap drug than other intravenous bisphosphonates, in the preoperative treatment of symptomatic hypercalcemia in patients with PHPT. Also, there are some difference in the total cost of treatment for patients treated with ibandronate and zoledronate. The medical records of patients operated at Dicle University Department of General Surgery between 2010 and 2017 due to PHPT were retrospectively evaluated. Patients who were admitted because of hypercalcemia associated with parathyroid adenoma and underwent minimally invasive surgery subsequent to the lowering of calcium levels via preoperative intravenous ibandronate and zoledronate were included. Totally, 20 of 167 patients received a preoperative bisphosphonate due to hypercalcemia associated with PHPT. Seven patients treated with zoledronate only. Thirteen were treated with ibandronate only. There was no difference in hypercalcemia correction between the groups. Percentage of patients with hypocalcemia was less in the ibandronate group. The hypocalcaemic period was shorter in patients receiving ibandronate. Cost of hospital stay in patients receiving ibandronate is cheaper than zoledronate (780±462 USD versus 1765±1537 USD). Ibandronate use reduces the cost of hypercalcemia treatment by 55% in comparison with zoledronic acid. Intravenous ibandronate for treating severe hypercalcemia associated with PHPT is an effective and relatively cheap drug.

Key words: hyperparathyroidism, hypercalcemia, ibandronate

Introduction

Primary hyperparathyroidism (PHPT) is a common mineral metabolism disorder caused by excessive secretion of parathyroid hormone (PTH) from a parathyroid adenoma. Typically, biochemical outcomes of autonomously active parathyroid tissue are persistently elevated levels of PTH despite the presence of hypercalcemia (1).

Although PHPT is the most frequent cause of hypercalcemia in patients presenting to polyclinics, it is rarely the reason for patients who are hospitalized due to hypercalcemia. Severe hypercalcemia results in fatal complications unless immediately treated; moreover, it causes delays in undergoing surgery for PHPT, which is the primary treatment (2-4).

Severe hypercalcemia is one of the indications to perform surgery for treating PHPT (5). During sur-

gical preparation, intravenous fluids and furosemide are administered. In most patients hospitalized due to severe hypercalcemia, intravenous bisphosphonate treatment is required. Bisphosphonates reduce calcium levels by inhibiting osteoclastic activity (6). In case of severe hypercalcemia, zoledronate is frequently used due to its high efficacy. Ibandronate has been used and demonstrated to be efficient for treating hypercalcemia of malignancy (7, 8).

In the present study, we aimed to investigate the efficacy of intravenous ibandronate, which is a cheaper drug than other intravenous bisphosphonates, in the preoperative treatment of severe hypercalcemia in patients with PHPT. Also, is there any difference in the total cost of treatment for patients treated with ibandronate and zoledronate?

Materials and Methods

The medical records of all patients who were operated at Dicle University School of Medicine, Department of General Surgery, between 2010 and 2017 due to PHPT were retrospectively evaluated. Patients who were admitted to the hospital due to hypercalcemia associated with parathyroid adenoma and underwent minimally invasive surgery after the lowering of calcium levels because of preoperative intravenous ibandronate and zoledronate were included. A total of 20 patients were included in the study. In our laboratory, the PTH measurement method is chemiluminescent (Roche Cobas E601) and the normal calcium range is 8.4-10.2 mg/dl. Preoperative calcium, phosphorous, and PTH levels were recorded. The duration for calcium levels to normalize after ibandronate/zoledronate treatment were recorded. The cost of hospital stay for each patient was recorded in both groups. Postoperative calcium, phosphorous, and PTH levels were assessed. All patients underwent minimally invasive surgery. The pathology reports of all patients reported the presence of adenoma. One patient had cystic parathyroid adenoma. Patients who took ibandronate/zoledronate due to hypercalcemia associated with PHPT but who were not operated, patients who used bisphosphonates other than ibandronate/zoledronate to treat hypercalcemia, and patients who were

treated with hemodialysis and/or calcitonin along with ibandronate/zoledronate were excluded. Our treatment scale for hypercalcemic PHPT: calcium 10.4-12 mg/dl fluid and diuretic, 12-14 mg/dl + bisphosphonates, >14 mg/dl + calcitonin, altered consciousness, cardiac effects + hemodialysis.

From hospitalization to excretion to the hospital, we have set up the cost calculations for PHPT treatment.

Calcium normalization time was calculated as (day) when calcium was ≤ 12 mg/dl after the patient was given bisphosphonate.

Statistical analyses were performed by using SPSS software, version 22. Non-parametrical variables were assessed using Wilcoxon signed-rank test. A p-value of <0.05 was considered statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local ethics committee has approved this study (Dicle University 198/2017).

Results

Totally, 20 of 167 patients (11.9%) who were operated underwent preoperative bisphosphonate treatment due to severe hypercalcemia associated with PHPT. Among them, 7 (29.1%) (five female and two male) were treated with zoledronate only, 13 (54.2%) were treated with ibandronate only. Among these 13 patients, seven were female and six were male. The mean age of the patients was 56 ± 18 (range, 18-89) years (62 ± 19 ibandronate group/ 57 ± 17 zoledronate group). All patients were of Caucasian origin and exhibited significant hypercalcemia symptoms. The mean calcium level in patients before ibandronate treatment was 14.31 ± 0.92 mg/dL, and the mean duration of calcium regulation after ibandronate treatment was 3.3 ± 1 (range, 2-5) days. Mean calcium levels after ibandronate treatment was 10.19 ± 0.89 mg/dl ($p=0.001$); mean preoperative PTH levels were 585.69 ± 389.95 pg/ml, and mean postoperative PTH levels were 44.13 ± 43.15 pg/ml ($p=0.001$) The mean calcium level in patients before zoledronate

treatment was 14.6 ± 0.96 mg/dl, and the mean duration of calcium regulation after zoledronate treatment was 2.43 ± 0.78 (range, 1-3) days. Mean calcium levels after zoledronate treatment was 11.02 ± 1.18 mg/dl ($p=0.01$); mean preoperative PTH levels were 1351 ± 580 pg/ml, and mean postoperative PTH levels were 28.86 ± 1.58 pg/ml ($p=0.01$) (Table 1). There was no difference in hypercalcemia correction between the groups. The hypocalcaemic period was shorter in patients receiving ibandronate. Percentage of patients with hypocalcemia was less in the ibandronate group (23% versus 71%). Three patients (23%) had postoperative hypocalcemia in ibandronate groups, and five patients (71%) in zoledronate groups. Cost of hospital stay in patients receiving ibandronate is cheaper than zoledronate (780 ± 462 USD versus 1765 ± 1537 USD). Ibandronate use reduces the cost of hypercalcemia treatment by 55%.

Discussion

Severe hypercalcemia is a rare disorder accounting for 2-5% of patients with PHPT. Severe hypercalcemia is an emergency medical condition and may be life threatening. Therefore, it should be immediately treated (9-11). As severe hypercalcemia is usually associated with a single parathyroid adenoma, surgery is the primary treatment. Patients are usually operated following the regulation of calcium levels with intrave-

nous bisphosphonates. Bisphosphonates reduce surgical complications associated with hypercalcemia and shorten preoperative period (12, 13).

In our series of 13 patients, we successfully treated severe hypercalcemia using 3 mg of intravenous ibandronate, and the patients were operated and cured. In a literature review, we did not find data on ibandronate use for treating hyperparathyroidism with severe hypercalcemia.

There are some studies in the literature covering few cases of hyperparathyroidism with severe hypercalcemia, which is a rare medical condition. The study with the most cases was a series by Sarfati et al. that included 59 patients (4, 14, 15).

Phitayakorn et al. normalized preoperative calcium levels by administering pamidronate to six patients and zoledronate to one patient (12).

Starker et al. treated eight patients with bisphosphonate and preoperatively achieved normocalcemia. However, the bisphosphonates used were not specified (13).

Lv et al. administered zoledronate to nine patients due to hypercalcemia associated with PHPT and observed significant reduction in calcium levels (16).

We observed that ibandronate, which is cheaper than other bisphosphonates, is effective.

Our study showed that ibandronate was non-inferiority to zoledronate for treatment PHPT hypercalcemia.

Table 1. Characteristic of patients groups

	Ibandronate group n =13	Zoledronate group n=7	P value
Age (year)	62±19	57±17	N.S
Sex (female/male)	7/6	5/2	N.S
Calcium (mg/dl) before treatment	14.3±0.92	14.6±0.96	N.S
Calcium (mg/dl) after treatment	10.19±0.89	11.02±1.18	N.S
PTH (pg/ml)before surgery	585±398.95	1351±580	N.S
PTH (pg/ml)after surgery	44±43.15	28.86±1.58	N.S
Post-bisphosphonate hypocalcemia (yes/n)	3/13 (23%)	5/7 (71%)	
Calcium <12 mg/dl (day)	3,3±1 (2-5)	2,48±0,78 (1-3)	
Hospital stay cost (USD)	780±462	1765±1537	

N.S: Non significance

In PHPT, the total hospital cost of patients receiving ibandronate for hypercalcemia was lower than in zoledronate

Cost of hospital stay in patients receiving ibandronate is cheaper than in zoledronate (780±462 USD versus 1765±1537 USD). Ibandronate use reduces the cost of hypercalcemia treatment by 55%.

One of the undesired outcomes of effective bisphosphonates is the occurrence of hypocalcemia after treatment. Corsello et al. reported hypocalcemia over a three-month period in a patient they followed up after zoledronic acid treatment (17). In our study, we observed a lower rate of hypocalcemia in patients treated with ibandronate. It was thought to be due to shorter duration of action of ibandronate. In our study, the mean duration of calcium regulation after ibandronate treatment was 3.31±1.03 (range, 2-5) days.

In hypercalcemia of malignancy, zoledronate, which is highly effective, may be preferred. We believe that ibandronate is a reliable alternative for treating hypercalcemia associated with hyperparathyroidism.

The retrospective nature of our study and the low number of patients are the limitations of our study. Double-blind prospective studies that include larger number of patients are required.

To conclude, although hypercalcemic crisis associated with hyperparathyroidism is rare, it is a life-threatening condition. Intravenous ibandronate may be an effective and relatively cheap drug in the surgical preparation and treatment of patients with hypercalcemic crisis associated with PHPT. Ibandronate use reduces the cost of hypercalcemia treatment by 55% in comparison with zoledronic acid.

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Correspondence:

Zafer Pekkolay, MD, Asst. Prof
Dicle University School of Medicine
Adult Endocrinology Department,
Kitlibil Mahallesi, 21280 Sur, Diyarbakır/Turkey
Tel. +90 4122088001-4175
E-mail: drpekkolay@gmail.com