Symptomatic hypocalcaemia after the administration of bisphosphonates

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Summary
The bisphosphonates are widely and very safely used both for the prevention and the management of metastatic bone disease in tumoral processes. In spite of this, its use if not free of complications, of which hypocalcaemia, which is usually light, is one of the most frequent. There are various factors which increase the risk of this occurring, some of which are not yet well known, but which should be taken into account in all patients before the administration of these drugs to avoid serious cases of symptomatic hypocalcaemia.

Key words: bisphosphonates, zoledronic acid, prostate carcinoma, bone metastasis, hypocalcaemia.
Introduction
The bisphosphonates have a well-established role in the management of tumoral hypercalcemia and other skeletal complications of neoplasms. Their usually good levels of tolerance may make us forget that on occasion they have serious secondary effects. It should be of interest, therefore, for us to communicate the case of a patient recently treated in our centre, as a warning in this matter.

Clinical case.
A 74 year old male with a history of post-traumatic epileptic crisis, in treatment with phenytoin and phenobarbitol; high digestive haemorrhage secondary to duodenal ulcer and carcinoma of the prostate with bone affectation, as well as urethrovessical and ganglion carcinoma, in treatment with bicalutamide and leuproreline for the past four months. Admitted due to pain and increased diameter of the right inferior member, which was related to compression of the iliac vessels by lytic metastases in the right iliac bone, extending into the soft tissues. Also present were multiple osteoblast metastases. Notable among the complementary tests were anaemia of chronic disease (Hb, 10.8 g/dl), a moderate deterioration in renal function (urea, 81 mg/dl; creatinine, 1.6 mg/dl) alkaline phosphatase, 1,150 U/l (normal, 129 U/l) and calcium at the lower limit for normality (8.1 mg/dl; normal: 8.4-10.4 mg/dl), with albumin of 3.7 g/dl and corrected calcium of 8.4 mg/ml.

As part of the palliative treatment, and with the aim of reducing the tumoral affectation of the bone and the osteoporosis derived from the hormonal blockage, local radiotherapy was administered as well as a dose of 4 mg of zoledronic acid by short intravenous infusion. Five days later, he began to feel a sensation of “numbness” in both arms. Notable from the physical examination was a positive Trouseau sign after 1 minute. The total calcemia was 4.8 mg/dl, and of ionic blood calcium 2.7 mg/dl (normal: 4.6-5.4 mg/dl). In the ECG there was a prolongation of QT (0.48 sec). The magnesium and phosphatemia were normal (2.3 mg/dl and 2.7 mg/dl respectively). The concentration of 25 (OH) vitamin D was very low (7 ng/ml; normal: 20-60 ng/ml) and the parathormone (PTH) was raised (526 pg/ml; normal 0-65 pg/ml).

Treatment was initiated with endovenous calcium and vitamin D derivatives (calcifiedol 266 µg/24h and calcitriol 2 µg/24h), with which the tetanic manifestations disappeared after 48 hours. At the time of discharge, six days later, the calcemia was 7.9 mg/dl. Outpatient treatment was continued with calcium and vitamin D supplements at the same dose as during the admission, and it was decided to suspend indefinitely the treatment with zoledronic acid. A month later the calcemia was 7.9 mg/dl.

The bisphosphonates inhibit bone resorption and, apart from their use in osteoporosis, have a well-established role in the prevention and management of skeletal complications of neoplasms. Due to its potency and ease of administration zoledronic acid is the bisphosphonate most frequently used. In general, its tolerance is good, with the most frequent non-specific manifestations being pseudo-flu.

Hypocalcemia is another frequent secondary effect. In recent clinical trials hypocalcemia has been observed in approximately 5-10% of patients treated with zoledronate. However, it is light and without clinical repercussions. Thus, in the series of Zuradelli, 48% of patients with hypocalcemia had levels of calcium of between 8 and 8.5 mg/dl; 40% between 7 and 8 mg/dl; 11% between 6 and 7 mg/dl and only 1% had calceemia lower than 6 mg/dl. Symptomatic cases are fortunately rare, given the tendency of hypocalcemia provoked by the inhibition of bone resorption induced by the bisphosphonates to be compensated for by an increase in the secretion of PTH, which reduces the renal elimination of calcium and increases its intestinal absorption through the stimulation of the renal hydroxylation of vitamin D. Cited also among those factors which increase the risk of developing serious hypocalcemia, have been the previous existence of hypocalcemia, various disorders which tend to impede this compensatory response, such as renal insufficiency, hypomagnesemia, vitamin D deficiency, hypoparathyroidism and treatment with loop diuretics, which increase calciurias. Our patient had a number of these risk factors, including the deterioration of renal function and vitamin D deficiency, as well as treatment concomitant with anti-epileptics, which, unfortunately, were not corrected before the administration of the bisphosphonate. Whether on not the risk of hypocalcemia is higher in those patients with osteoblast metastasis is open to discussion. In principle, this would be expected, given their greater tendency to deposit calcium in the skeleton and the frequency with which these patients have spontaneous hypocalcemia. In fact, some studies have even found a lower frequency of hypocalcemia after the administration of zoledronic acid in patients with prostate cancer.

In order to limit the risk of hypocalcemia, all the aforementioned factors should be discounted, for which reason an earlier analytical determination of vitamin D, PTH, phosphatemia, magnesemia, and calcemia, and the correction of any alterations before initiating treatment with bisphosphonates would be recommended. In the case of vitamin D deficit, high doses may be used (for example, 10,000-20,000 U/day) over 2-4 weeks, since vitamin D and calcium supplements in “physiological” doses are not always efficacious, which is not surprising, given that at this dose vitamin D may take months to normalise. In any case, bisphosphonates should be avoided in patients with earlier hypocalcemia, hypoparathyroidism or renal insufficiency with creatinine clearance lower than 30 ml/min (except in the case of tumoral hypercalcemia).

In short, zoledronic acid and other powerful bisphosphonates are useful in the treatment of skeletal complications of neoplasms. However,
although they are usually well tolerated, they are not free of potentially serious secondary effects. Therefore, clinicians should be scrupulous in identifying and dealing with those factors which may increase their toxicity prior to their administration, which is rarely urgent. The case which we present is a warning of the consequences which may result if this is not carried out.

**Bibliography**


