

# Acute delirium in an elderly woman following zoledronate administration

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Received: 11-12-2013

Revised: 01-02-2014

Accepted: 07-02-2014

## ABSTRACT

Zoledronate is a third-generation bisphosphonate having distinctive profile of high potency as well as prolonged duration of action. Intravenous zoledronate is the recently approved bisphosphonate for the treatment of osteoporosis and has an attractive once-yearly regimen for the treatment of osteoporosis. Here we report, for the first time, a case of acute delirium following zoledronate administration for osteoporosis. An 86-year-old female patient presented to orthopedics out-patient department (OPD) with complaints of pain and unable to bear weight on left thigh with history of fall from bed 2 months back. She was diagnosed as fracture neck of femur with severe osteoporosis and treated conservatively. She was given zoledronate IV 5 mg infusion over 30 min. After 10-12 h of zoledronate infusion, patient became confused, disorientated, and agitated. A septic work-up was negative. Electrolyte disturbances were excluded with normal sodium, potassium, calcium, and magnesium levels. Computed tomography of the brain was unremarkable. A metabolic cause could not be found for the change in her mental state. Patient was referred to medicine department where she was diagnosed as drug-induced acute delirium probably due to zoledronate. Patient was advised injections haloperidol and torsemide. In the following 48 h, her confusion got cleared and mental status was improved. According to the Naranjo's scale, the effect of zoledronate in our patient was scored 6 indicating a probable likelihood of causing delirium. It was a probable cause of acute delirium according to World Health Organization (WHO) causality scale.

**Key words:** Delirium, Naranjo probability scale, osteoporosis, zoledronate

## INTRODUCTION

Zoledronate belongs to third generation bisphosphonates, and is an analog of pyrophosphate. They have strong affinity for bone, especially which are undergoing remodeling. These are

the major class of drugs used for the treatment of diseases undergoing excessive osteoclast-mediated bone resorption, such as osteoporosis, Paget's disease, hypercalcemia, and tumor-induced osteolysis.<sup>[1]</sup> Zoledronate has distinctive profile of high potency as well as prolonged duration of action. It is 10,000 times more potent than first-generation agents like etidronate.<sup>[2]</sup> It is the only bisphosphonate that has been developed exclusively for IV use.<sup>[3]</sup> Oral bisphosphonates are associated with poor compliance to therapy due to gastrointestinal adverse effects like heartburn, esophageal irritation or esophagitis, abdominal pain, diarrhea, very low intestinal absorption, and complex dosing regimen.<sup>[1]</sup> Intravenous bisphosphonates address these limitations through infrequent injectable dosing that assures 100% bioavailability.

Access this article online	
Quick Response Code:	Website: <a href="http://www.jpharmacol.com">www.jpharmacol.com</a>
	DOI: 10.4103/0976-500X.136115

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Due to these factors, intravenous zoledronate is being increasingly used for various conditions. Intravenous zoledronate is the recently approved bisphosphonate for the treatment of osteoporosis and has an attractive once-yearly regimen for the treatment of osteoporosis. It has become a part of standard therapy in the treatment of multiple myeloma, hypercalcemia of malignancy, bone metastases of various solid tumors such as breast, prostate, and lung.<sup>[4]</sup> Few cases of central nervous system (CNS) side effects like confusion, anxiety have been reported during clinical trials of zoledronate but all of them have been reported in patients treated for hypercalcemia of malignancy, which itself is associated with various risk factors for delirium.<sup>[5]</sup> Here we report, for the first time, a case of acute delirium following zoledronate administration for osteoporosis.

## CASE REPORT

A 86-year-old female patient presented to orthopedics outpatient department (OPD) with complaints of pain and inability to bear weight on left thigh following history of fall from bed 2 months back. She was diagnosed as fracture neck of femur and was admitted for further treatment. There was no past history of diabetes, hypertension, psychiatric illness, dementia, alcoholism, epilepsy, chronic medication, and no family of psychiatric diseases. Physical examination revealed that the patient was having blood pressure of 160/90 mmHg and complete neurological examination including mental state was normal. Routine investigations such as complete blood count, electrolytes, liver, and renal function tests were within normal limits. The X-ray left hip joint showed fracture neck of femur with severe osteoporosis.

Patient was put on traction and treated conservatively with oral aceclofenac 100 mg bd for pain and atenolol 25 mg and amlodipine 5 mg od for hypertension. On 6<sup>th</sup> day of admission, her BP returned to 122/70 mmHg with normal electrolytes and renal function test. She was given zoledronate IV 5 mg infusion over 30 min. Infusion was uneventful except when the patient complained of mild flu-like symptoms, which was controlled with oral aceclofenac 100 mg, and no additional treatment was given. After 10-12 h of zoledronate infusion, patient became confused, disorientated, and agitated. She had no idea of place, time of day, or the city, although she was fully orientated in the morning. She had difficulty in understanding instructions and her speech became incoherent.

Over the next 3-4 h, her confusion and disorientation progressed with misidentification of hospital staff as well as inability to recognize family members. She stated that everyone was trying to harm her and refused treatment. She was sleepless, agitated, tried to get out of bed and pulled off IV catheter. Her BP was 130/80 mmHg and was afebrile. No focal neurological

abnormalities were noted. A septic work-up was negative. Serum electrolyte levels were within normal limits with potassium 4.1 mEq/L, sodium 140 mEq/L, calcium 8.8 mg/dL, and magnesium 1.8 mEq/L. Her urine output decreased to 500 ml/24 h but renal function parameters increased but were within normal limits; serum creatinine 1.1 mg/dL and blood urea 35 mg/dL. She was hemodynamically stable. Findings of the computed tomography (CT) scan of the brain were unremarkable. A metabolic cause could not be found for the change in her mental state. Patient was referred to medicine department where she was diagnosed as drug-induced acute delirium probably due to zoledronate. Patient was advised injections haloperidol and torsemide. In the following 48 h, her mental state improved, confusion cleared and started to identifying her relatives.

## DISCUSSION

Delirium is an acute onset disturbance in consciousness associated with altered cognition that cannot be usually related with preexisting or newer onset dementia.<sup>[6]</sup> Delirium develops within hours to days over a short period of time. It is characterized by distractibility, reduced awareness of the surroundings, inability to focus, and altered cognition. It is usually associated with metabolic disturbances, infections, drug intoxications, cerebral insufficiency, or trauma to the head, especially in the elderly and rarely after administration of drugs. It is associated with high mortality and morbidity and its outcome mainly depends upon early identification of cause with correcting or eliminating the cause. So it is important to identify the drugs causing delirium. In this case, the sequence of the development of the behavioral change after infusion of zoledronate and absence of any evidence of other possible causes, strongly suggest that zoledronate may have played a part in the development of the delirium. According to the Naranjo probability scale the effect of zoledronate in our patient was scored 6 indicating a probable likelihood of causing delirium and also it was a probable cause of acute delirium according to World Health Organization (WHO) causality scale.<sup>[7]</sup>

Atenolol and amlodipine are also reported to cause acute delirium but in this case they can be easily ruled out as these drugs were started 6 days before infusion of zoledronic acid and were continued after infusion.<sup>[8,9]</sup> There was no recurrence of delirium with continued use of atenolol and amlodipine. For ethical reasons, we did not reexpose the patient to zoledronate. Central nervous system (CNS) side effects like confusion, anxiety have been reported during clinical trials of zoledronate but all of them have been reported in patients treated for hypercalcemia of malignancy, which itself is associated with various risk factors for delirium. The exact mechanism for zoledronate-induced acute delirium is

not known. Physicians and surgeons should be aware that zoledronate, which is increasingly used for osteoporosis may cause delirium, especially in the elderly population. Proper psychiatric history and mental evaluation should be done before initiating zoledronate treatment so as to avoid delirium-associated complications.

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**How to cite this article:** Nasiruddin M, Fayazuddin Mohd, Zahid M, Iftekhar S. Acute delirium in an elderly woman following zoledronate administration. *J Pharmacol Pharmacother* 2014;5:217-9.

**Source of Support:** Nil, **Conflict of Interest:** None declared.

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