Transient Renal tubular dysfunction following Zoledronic Acid treatment

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Abstract

Drug induced transient tubular dysfunction is often encountered in clinical practice. Zoledronic acid is one of the potent nitrogen containing bisphosphonates used in the management of postmenopausal osteoporosis commonly. Zoledronic acid induced transient tubular dysfunction (TTD) has rarely been reported. A 73 years old female with recent history of intravenous zoledronic acid administration for postmenopausal osteoporosis, presented with altered sensorium and with hyponatremia, hypokalemia, hypochloridaemia. She was treated conservatively and patient improved. TTD could be a rare clinical presentation following administration of zoledronic acid with paucity of documentation in medical literature.

Keywords: Zoledronic acid, Transient tubular dysfunction, Postmenopausal osteoporosis

How to cite this article: Gnanadeepan T, Mayilananthi K, et al (2020): Transient renal tubular dysfunction following zoledronic acid treatment, Ann Trop Med & Public Health; 23(S23): SP232323. DOI: http://doi.org/10.36295/ASRO.2020.232355

Introduction

Zoledronic acid is a potent bisphosphonate commonly used in the management of postmenopausal osteoporosis, hypercalcaemia of malignancy and osteolytic bone diseases. Bisphosphonates inhibit osteoclastic bone resorption by getting attached to hydroxyapatite binding sites on bony surfaces, especially surfaces undergoing active resorption. They predominantly improve the bone mineral density in the lumbar spine and the femoral neck.¹

Zoledronic acid is rapidly processed through kidneys after intravenous infusion and hence it is contraindicated in patients with severe renal impairment (creatinine clearance of less than 35 ml/min). The nephrotoxicity is both dose and infusion-time dependent.

The common adverse effects of zoledronic acid include fatigue, anemia and flu like symptoms. The other rare adverse effects include osteonecrosis of jaw, ocular complications, electrolyte abnormalities (such as hypocalcemia, hyponatremia, hypophosphatemia, hypomagnesemia), atrial fibrillation and renal dysfunction.

Acute tubular necrosis is the most common form of renal toxicity seen following zoledronic acid that can manifest as transient tubular dysfunction. However, no case of zoledronic acid induced TTD has been reported yet, to the best of our knowledge.

**Case report**

A 73 year old female with no comorbid illnesses, presented to the emergency department with disorientation for 2 days. She did not have loss of consciousness, convulsions, headache, diarrhoea, vomiting or fever. She reported a history of urinary incontinence. On examination, the patient was drowsy, but responded to voice and had a Glasgow Coma Scale score of 11/15 (E3M5V4). She had signs of mild dehydration with tachycardia. The neurological examination revealed normal deep tendon reflexes with a bilaterally flexor plantar response. She did not have neck stiffness. The examination of other systems was normal.

The patient had received an intravenous infusion of 5mg zoledronic acid for postmenopausal osteoporosis 3 days ago. There was no history of consumption of any other allopathic or native medicines. The laboratory tests revealed normal blood counts, normal blood sugars and Thyroid function tests, altered renal parameters, metabolic alkalosis, hyponatremia, hypochloridaemia, hypokalemia, hypocalcemia and low serum osmolality with a normal urine osmolality. There were elevated levels of urine spot sodium, potassium and chloride with no proteinuria, hematuria, casts or pus cells. The laboratory parameters of the patient are displayed in the table. Brain and abdomen imaging were normal.

2 weeks prior to presentation, the patient had a routine annual checkup and was diagnosed to have osteoporosis. Her routine evaluation including electrolytes was found to be normal. The calcium and vitamin D levels done prior to intravenous zoledronic acid treatment were normal.

**Discussion:**

Drug induced renal dysfunction is a common problem encountered by the treating physicians. It often produces a diagnostic dilemma as some of these manifestations mimic features of renal diseases related to the primary disorder for which the drug is prescribed.

Bisphosphonates, are generally safe to use, they occasionally produce undesired effects. These include multiple forms of nephrotoxicity, osteonecrosis of the mandible, hypocalcemia, post infusion pyrexia and flu like symptoms. Renal disease induced by these drugs, though uncommon, is noteworthy. These include collapsing focal segmental glomerulosclerosis, Fanconi syndrome and nephrotic syndrome. Bisphosphonates are internalized by the
tubular cells and may impair cell energetics by incorporation into ATP analogues with resultant inhibition of ATP dependent metabolic pathways as well as loss of brush border in the tubules. All these can lead elevation of renal parameters, acquired Fanconi syndrome and electrolyte disturbances\(^3\).

Zoledronic acid is prone to produce acute tubular dysfunction, as the drug is predominantly excreted unchanged via the kidneys. The postulated mechanisms of tubular toxicity and necrosis involve cellular effects similar to the effects documented in the osteoclast\(^3\).

In this patient, hyponatremia, hypokalemia and hypochloridaemia were reported following zoledronic acid treatment and the possible mechanism for this dys electrolytemia is a transient defect in the Na-K-2Cl cotransporter present in the thick ascending limb of Loop of Henle. Renal function universally improves after discontinuation of the drug, which can be restarted later using a longer infusion time (over 30 to 60 minutes for zoledronic acid\(^5\).

This patient was treated with intravenous normal saline, 3% NaCl solution, potassium chloride syrup, and calcium infusion. The patient’s condition improved gradually and her sensorium became normal within 48 hours. She was discharged after 5 days with a normal serum electrolyte level. On follow up after 6 months, the patient had normal electrolyte and renal profile, and there were no episodes of altered sensorium or clinical evidence of neurological dysfunction.

**Conclusion:**

Zoledronic acid is one of the commonly used drugs in the treatment of postmenopausal osteoporosis. Dyselectrolytemia following zoledronic acid is a significant adverse effect, albeit rare. Hence, we suggest mandatory evaluation of serum electrolytes before and after administration of zoledronic acid, especially when administered to elderly women above the age of 60, for the treatment of osteoporosis. This subset of patients must be observed with caution, as the adverse effects may be fatal.

**References:**

1. Jack DeRuiter and Randall Clark Bisphosphonates: Calcium Antiresorptive AgentsDrs DeRuiter and Clark, Endocrine Module, Spring 2002


4. Abrahamsen, Bo\(^ab\) Bisphosphonate adverse effects, lessons from large databases, Current Opinion in Rheumatology: July 2010 - Volume 22 - Issue 4 - p 404-409 doi: 10.1097/BOR.0b013e32833ad677

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<th>Parameters</th>
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<th>Day 1</th>
<th>Day 3</th>
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Table – Laboratory parameters