Early onset acute tubular necrosis following single infusion of zoledronate

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Summary
Zoledronate is a highly potent bisphosphonate widely used in the treatment of postmenopausal osteoporosis. We report the first occurrence of toxic acute tubular necrosis (ATN) following treatment with zoledronate in a patient with osteoporosis. A 63-year-old Caucasian female with rheumatoid arthritis on anti-immune agents received a single dose of zoledronic acid (reclast) for worsening osteoporosis. Twelve days later, she developed renal failure with a rise in serum creatinine from a baseline level of 1.1 mg/dL to 5.5 mg/dL. Renal biopsy showed toxic ATN. Zoledronate was discontinued and the patient had subsequent gradual improvement in renal function with final serum creatinine of 1.8 mg/dL at 1 month of follow up. Careful monitoring of serum creatinine and awareness of the potential nephrotoxicity may avert the development of acute renal failure in osteoporosis patients treated with this agent.

KEY WORDS: zoledronate; toxic ATN; renal failure.

Introduction
Zoledronate is a highly potent nitrogen-containing intravenous bisphosphonate that is in widespread use for the treatment of hypercalcemia of malignancy, bone metastases and Paget's disease of bone. At lower doses, it is used to decrease bone resorption in patients receiving antiresorptive therapy. Few reports have described a toxic form of acute tubular necrosis (ATN) in cancer patients receiving zoledronate. Herein, we report the occurrence of toxic ATN following treatment with a single zoledronate infusion in a patient with osteoporosis.

Case
A 63-year-old Caucasian female was hospitalized with acute renal failure. She had a long-standing history of seropositive nodular erosive rheumatoid arthritis, for which she had been on multiple immunosuppressive drugs and biologics in the past. Other medical diagnoses included osteoarthritis, osteoporosis, deep venous thrombosis, antiphospholipid syndrome, 30-pack-year history of smoking, and depression. Her surgical history was significant for total abdominal hysterectomy for squamous cell carcinoma of the cervix, left donor nephrectomy, and L5 laminectomy, foraminotomy, medial facetectomy for right synovial cyst. Medications included low-dose prednisone, methotrexate, tofacitinib (xeljanz, Pfizer), bupropion, and coumadin. She had no history of severe renal, hepatic, or pulmonary disease. She was allergic to penicillin and sulfa drugs. She denied any nonsteroidal anti-inflammatory drug use.

She had been well until approximately 1 week before this admission, when she started experiencing malaise, anorexia, nausea and mild confusion. Twelve days prior to hospitalization, she received a single dose of zoledronic acid (reclast, Novartis) for worsening osteoporosis at the dose of 5 mg intravenously diluted in 100 cc of normal saline and infused over 30 minutes. On examination, blood pressure was 134/82 with a heart rate of 78. The patient was alert, and oriented only to place and person. The remainder of the examination was normal. Her most recent serum creatinines were 1.1 mg/dL (3 months ago) and 5.5 (current). Urinalysis showed 2+ protein, specific gravity of 1.015, with no blood, nitrites, or bacteria. Urine protein creatinine ratio was 0.348 (reference range, <0.165).

Due to the close temporal relationship between zoledronate administration and the onset of renal failure, zoledronate was di-

Table 1 - Summary of clinical and laboratory features.

| Age (years) | 63 |
| Gender | Female |
| Race | C |
| Baseline serum creatinine (mg/dL) | 1.1 |
| At admission | |
| Serum creatinine (mg/dL) | 5.5 |
| BUN (mg/dL) | 57 |
| Calcium (mg/dL) | 9.2 |
| Albumin (g/dL) | 3.5 |
| Hemoglobin (g/dL) | 10.5 |
| UPC | 0.348 |
| Zoledronic acid | |
| Duration of therapy (days) | 12 |
| Dose (mg) | 5 |
| Infusion time (minutes) | 30 |
| Length of follow-up (months) | 1 |
| Last serum creatinine (mg/dL) | 1.8 |

BUN: Blood urea nitrogen
UPC: Random urinary protein to creatinine ratio
C: Caucasian
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Figure 1 - Histologic evaluation of the kidneys shows renal cortex parenchyma with extensive necrosis and desquamation of proximal tubular epithelial cells (arrows) consistent with acute tubular necrosis. The glomeruli are unremarkable. Significant interstitial inflammation is not identified for an interstitial nephritis. (Hematoxylin and Eosin, 20x).

Figure 2 - Histologic evaluation of the renal medulla parenchyma shows collecting duct lumens filled with necrotic proximal tubular epithelial cells and tubular casts (arrow). (Hematoxylin and Eosin, 20x).

Zoledronate is widely used in the treatment of postmenopausal osteoporosis, and increasingly used in male osteoporosis and glucocorticoid-induced osteoporosis. In a large trial enrolling 7765 postmenopausal women with osteoporosis, once yearly 5 mg of zoledronate (infused over 15 minutes) for three consecutive years reduced the risk of vertebral (70%) and hip (41%) fractures, increased bone mineral density, and reduced markers of bone turnover as compared with placebo (1).

Similar to other nitrogen-containing bisphosphonates, zoledronate diminishes bone resorption by acting both extracellularly as calcium chelators and intracellularly within osteoclasts (2). Following intravenous administration of zoledronate, approximately 50% of the dose is rapidly incorporated into the bone, retained for long durations and re-cycled back into the circulation, and may later reaccumulates in bone. Most of the remainder is not metabolized, do not interact with or affect cytochrome P450 activity, and is excreted unchanged by the kidneys by glomerular filtration (3).

In patients with oncologic conditions, renal deterioration progressing to renal failure and dialysis was reported with intravenous zoledronate. In 2003, the Food and Drug Administration Adverse Event Reporting System identified 72 cases of renal failure associated with zoledronate including 42 patients with multiple myeloma and 22 with solid tumors (4). Renal failure developed after an average of 56 days of zoledronic acid use, following a mean of 2.4 doses. Eighteen patients (25%) received only one dose of zoledronic acid and had renal failure after an average of 11 days. Risk factors for renal deterioration were advanced cancer, previous bisphosphonate use, and exposure to nonsteroidal anti-inflammatory drugs. Of the 72 patients, 27 required dialysis and 18 died. At registered doses for osteoporosis, zoledronate shows little risk of renal adverse events in patients with creatinine clearances > 30 ml/min. In the phase 3 Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial, there was no increased risk of renal side effects with zoledronate compared to placebo over the course of 3 years (1). Another study found that transient changes in renal function can occur following an annual zoledronic acid infusion but, in the long term, renal function was not different from control patients (5).

Recently, the FDA sent out a newsletter to physicians reporting on 24 cases of acute renal failure reported postmarketing with intravenous zoledronic acid in the osteoporosis population (6). Over half of the patients (14/24) had underlying medical conditions (e.g., diabetes mellitus, congestive heart failure, chronic kidney disease) that may have contributed to their risk of renal impairment or acute renal failure; or had concurrent exposure to known nephrotoxic medications (e.g., NSAIDs). Fifty-four percent of the patients (13/24) had documented transient increases in serum creatinine following drug infusion (median increase in serum creatinine was 4 mg/dL).

Renal biopsy findings were not provided in any of the clinical trials and government reporting systems that have documented zoledronate nephrotoxicity. Case reports and clinical series have described a toxic form of ATN in patients treated with zoledronate (7, 8). A recent paper presented evidence that zoledronate is internalized by renal tubular cells via the process of fluid phase endocytosis. The resulting intracellular accumulation of zoledronate may act as an epithelial toxin inducing tubular cytotoxicity (9). The majority of cases of zoledronate associated toxic ATN reported to date had multiple myeloma or other cancers and received varying types of chemotherapy. The initial report included five patients with multiple myeloma and one with Paget’s disease. In all patients, zoledronate was administered at a dose of 4 mg intravenously monthly, infused over at least 15 minutes, and the duration of therapy was mean 4.7 months (range, 3 to 9 months). All patients developed renal failure with a mean serum creatinine of 3.4 mg/dL and only subnephrotic proteinuria. Renal biopsy revealed toxic ATN. Discontinuation of zoledronate led to improvement in renal function; with a mean serum creatinine of 2.3 mg/dL at a mean follow up of 3.2 months (7).

In contrast, our patient received zoledronate for osteoporosis and developed toxic ATN in the course of active treatment with immunosuppressives for rheumatoid arthritis. Furthermore, despite receiving intravenous zoledronate at the recommended low dose...
of 5 mg with slow infusion rate (30 min), this patient developed acute kidney injury only 12 days post-first dose. It is important to emphasize that this patient was not taking nonsteroidal anti-inflammatory drugs; however, she was treated with tofacitinib and methotrexate, both could possibly adversely affect kidney function.

Conclusion

We report the first association of toxic ATN with zoledronate in a patient with osteoporosis. Careful monitoring of serum creatinine and awareness of the potential nephrotoxicity may avert the development of acute renal failure in osteoporosis patients treated with this agent.

Funding sources

None.

Conflict of interest

None to report.

References