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Case Presentation

Alendronate-Induced Nephropathy

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Abstract

Background: Alendronate is considered a safe drug with respect to kidney function when used per manufacturer recommendations.

Objective: To describe reported cases of nephrotoxicity associated with alendronate.

Methods: Pubmed search of English literature up to January 14, 2022. Search terms include alendronate, bisphosphonates, proteinuria, renal failure, adverse effects. Pertinent case reports, reviews, and guidelines of professional organizations are included.

Results: Review of literature revealed 7 patients who developed nephrotoxicity likely due to alendronate therapy for osteoporosis. In 5 patients, kidney function was normal before starting alendronate. Five patients presented with nephrotic syndrome and had focal segmental glomerulosclerosis (FSGS) on renal biopsy. Collapsing FSGS was specifically demonstrated in 2 patients. Nephrotoxicity was diagnosed as early as 2 weeks and up to 3 years after starting alendronate. No clear predisposing factors or patient demographic characteristics could be outlined in association with this adverse effect. In addition to discontinuation of alendronate, treatment consisted of glucocorticoids followed by angiotensin-converting enzyme inhibitors and diuretics. In 4 of the 7 patients, renal function did not return to normal and 3 subjects required hemodialysis.

Conclusions: Physicians should be aware that alendronate may be uncommonly associated with nephrotoxicity. Checking protein in urine 2 weeks after starting alendronate and periodically thereafter may help early diagnosis of this serious adverse effect.

Key words: alendronate, nephrotoxicity, bisphosphonates, safety.

Introduction

Alendronate is an oral bisphosphonate widely used worldwide for prevention and treatment of osteoporosis [1]. Following a single intravenous dose of alendronate, approximately 50% of the drug is excreted in urine [2]. The manufacturer does not recommend the use of alendronate in subjects with creatinine clearance <35 ml/min due to lack of experience with this agent in renal failure [2]. Indeed, alendronate may be regarded as a safe drug with respect to renal function provided that it is administered according to manufacturer recommendations. In a large retrospective study from Taiwan (n=5,046), Hsu et al [3] compared renal outcomes between postmenopausal women with osteoporosis initiating alendronate versus denosumab using propensity score matching. Over 5 years, these authors found a slower decline in renal function in patients treated with alendronate compared with denosumab [3].

However, there are few reports in the literature showing that alendronate may be associated with FSGS, specifically the collapsing variant of FSGF. The latter is an aggressive form of FSGS characterized by severe nephrotic syndrome that rapidly progresses to acute renal failure [4, 5]. Collapsing FSGS was previously reported as uncommon adverse effects of intravenous bisphosphonates, namely pamidronate and zoledronic acid [6, 7]. The main purpose of this article is to describe the characteristics of previously reported cases of alendronate-induced nephrotoxicity, and to draw attention of physicians to this uncommon but serious adverse effect.

Characteristics of patients

Review of literature unraveled 7 patients who presented with nephrotoxicity in association with alendronate therapy for osteoporosis between 1997 and 2015 [8-14] (table1). The age range was 36-79 years. Among the 7 cases reported, 4 were women. One patient had already a diagnosis of FSGS before starting alendronate [11], and another patient had pre-existing chronic kidney disease [10]. Meanwhile, except for osteoporosis, two patients: a 36-year-old man and 55 year-year old woman, had no co-morbidities [12, 13] (table 1). Inspection of table 1 shows that it is difficult to find specific predisposing factors for alendronate-induced nephrotoxicity. In fact, it seems that any age, gender,

or race, might be predisposed irrespective of co-morbid conditions (table 1).

Reference	Patient and co-morbidity	Dose and duration of alendronate	Renal pathology	Treatment	Outcome
Zagornik et al [8]	57 year-old woman with multiple myeloma	10 mg/d for 1 month	Acute renal failure. Renal biopsy was not performed.	Only stopping alendronate	Renal function normalized after 3 doses of chemotherapy
Pena et al [9]	74-year-old-woman with chronic lymphocytic anemia	2 weeks (dose not reported)	Acute granulomatous interstitial nephritis leading to acute renal failure	Prednisone and transient hemodialysis for 6 weeks	Partial recovery of kidney function
Pascual et al [10]	48-year-old African-American man liver transplant recipient with CKD*	35 mg/week (duration not specified).	Collapsing FSGS**	Losartan and enalapril	Serum creatinine increased from 3.3 to 4.0 mg/dl and proteinuria persisted
Miura et al [11]	61-year-old Japanese man with pre-existing FSGS**	2 weeks (dose not reported)	FSGS**	Prednisolone and 6 cycles of hemodialysis.	Serum creatinine and urinary protein normalized after 40 days.
Prikis et al [12]	55-year-old Caucasian woman	10 mg/d for 3 years followed by 70 mg/week for 4 years.	FSGS**	Prednisone and lisinopril	Partial remission after 6 weeks
Yilmaz et al [13]	36-year-old man	4 months (dose not reported)	FSGS** could not be ruled out	Diuretics.	Proteinuria disappeared after 40 days.
Garimella et al [14]	79-year-old woman with hypertension	70 mg/week chronically (duration not specified)	Collapsing FSGS**	Prednisone for 16 weeks.	Renal failure progressed and patient started twice weekly hemodialysis.

Abbreviations: *CKD: chronic kidney disease, **FSGS: focal segmental glomerulosclerosis

Table 1. *Cases of alendronate-induced nephropathy*

It should be emphasized that the first patient with multiple myeloma reported by Zazgornick et al [8] had vomiting 2 weeks after starting alendronate. Thus, dehydration secondary to vomiting might be a precipitating factor for acute renal failure in this patient.

Clinical presentation

In 2 patients reported as brief "letters to the Editor", physical exam findings were not reported [8,12]. In the patient described by de la Vega et al [9] who presented with laboratory abnormalities of acute renal failure, physical exam was unremarkable except for basal crackles on lung auscultation. Meanwhile, all remaining cases presented with generalized anasarca due to severe nephrotic syndrome (generalized edema, gross proteinuria, hypoalbuminemia, hyperlipidemia) [10,11,13, 14].

Renal Pathology

Six of the 7 patients underwent renal biopsy [9-14]. The renal pathology of the case reported by de la Vega et al [9] was described as acute granulomatous interstitial nephritis. In the 5 remaining patients, kidney biopsy findings were consistent with FSGS including 2 cases being specified as collapsing FSGS (table 1) [10,14]. The hallmark pathological feature of collapsing FSGS is marked wrinkling and "collapse" of the glomerular basement membranes associated with hypertrophy and hyperplasia of overlying podocytes [6].

Treatment and outcome

In all patients, alendronate was suspected as the culprit for acute renal injury and was discontinued. Treatment consisted of glucocorticoids for 6-16 weeks in 4 patients [9, 11, 12, 14] (table 1), angiotensin-converting enzyme inhibitors in 2 patients [10,12], and only diuretics in one patient [13]. Regarding the outcome, only 2 patients fully recovered, with disappearance of proteinuria after 40 days [11, 13]. In another patient, kidney function recovered after unknown duration following 3 pulse doses of chemotherapy given for her multiple myeloma [8]. This chemotherapy consisted of dexamethasone, vincristine, and doxorubicin

[8]. However, the 4 remaining patients had either partial recovery [9,12] or worsening of kidney function [10]. Moreover, 3 patients progressed to end-stage renal disease that required either transient or permanent hemodialysis [9, 11,14].

Mechanisms

The mechanisms of alendronate induced nephrotoxicity are unclear. It is possible that alendronate causes toxic effect in podocytes. The latter represent an important barrier to protein loss in the renal glomeruli, and injury of podocytes results in marked proteinuria [15]. Indeed, podocyte injury was the mechanism by which pamidronate induced its nephrotoxic effects [6]. Garimella et al [14] hypothesized that alendronate might cause injury of podocytes in kidneys similar to its toxic effects on osteoclasts in bones because of similar cytoskeletal structure between podocytes and osteoclasts. This hypothesis is interesting and requires further investigation.

Conclusions

Seven cases of alendronate-induced nephrotoxicity were described. This number is likely under-reported given the widespread use of alendronate. Nephrotoxicity may occur shortly (as early as 2 weeks) or years after alendronate use. Men and women of any age are equally affected. No clear predisposing factors could be identified for such toxic renal effect. Unfortunately, in most cases, nephrotoxicity can lead to acute renal failure which may not be fully reversible. Physicians should be aware of this uncommon but serious adverse effect of alendronate. Since proteinuria is an early sign of alendronate-associated nephrotoxicity, it may prudent to check urine protein 2 weeks after starting alendronate and then periodically every 6 months.

Conflict of interest

The authors have no conflict of interest to declare.

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