Key words: Cancer, Clodronate, Ibandronate, Glomerular injury, Renal complications, Zoledronic acid

comprehensive review

The Risk of Cumulative Renal Effects of Intravenous Bisphosphonates

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Abstract

Some level of renal dysfunction is common in patients with cancer. This could be a result of an age-related kidney function decrease, the underlying disease (eg, multiple myeloma), or the effects of nephrotoxic medications. Some intravenous (I.V.) bisphosphonates have been associated with occasional renal toxicity in the clinical setting. Therefore, the choice of an I.V. bisphosphonate should take into account the risk of renal deterioration. Preclinical studies also suggest that there might be considerable differences between the renal safety profiles of commonly used I.V. bisphosphonates. Variations in the risk of histopathologic damage and the ability to cause cumulative toxicity have been observed in comparative preclinical studies of I.V. bisphosphonates. The reasons for these apparent differences are not fully understood. Research shows that renal safety profiles might be influenced by pharmacokinetic properties, such as renal tissue half-life, protein binding, and intracellular potency. Preclinical analyses are warranted in order to confirm and evaluate these differences between bisphosphonates.

Introduction

As effective inhibitors of osteoclast-mediated bone resorption, bisphosphonates target the pathophysiology of metastatic bone disease.[1,2] The deterioration of renal function associated with the use of intravenous (I.V.) bisphosphonates in patients with metastatic bone disease has been widely reported and represents a significant safety issue. Although bisphosphonates share the kidney as the primary systemic target in animal toxicity studies, the renal effects caused by individual bisphosphonates are not uniform.[3] They differ with respect to dose relationship, structural target within the kidney, renal tissue half-life, and possibly intracellular mode of action. These differences translate into different renal safety profiles. For clinical use, the risk of nephrotoxicity has to be assessed separately for each bisphosphonate in specific clinical situations (according to dose, treatment regimen, target population, etc). The chemical structures of different bisphosphonates are shown in Figure 1.

For the majority of agents, 40%-60% of bisphosphonates reaching the systemic circulation is rapidly bound to bone.[4] The skeleton acts as a sink, explaining the rapid disappearance of bisphosphonates from the blood and why the apparent total plasma clearance is much higher than the renal clearance, which is actually similar to creatinine clearance.[5] Skeletal uptake is a function of the number of bone metastases and the degree of bone turnover.[6] The remaining

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Bisphosphonates and Renal Function

Figure 1

Chemical Structures of Bisphosphonates

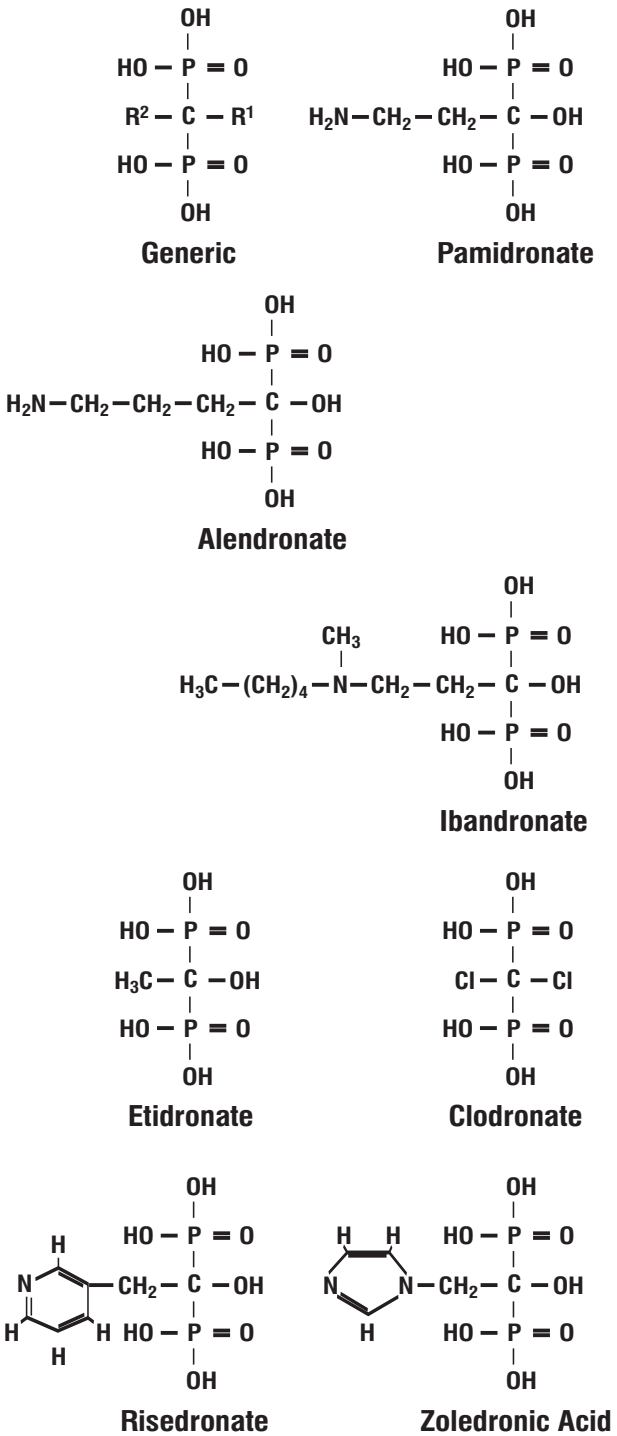
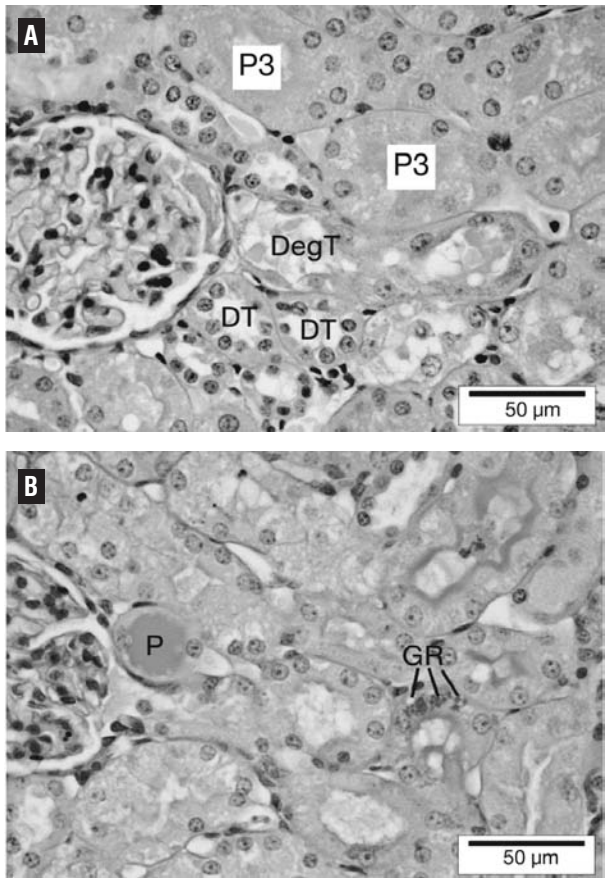


Figure 2

Kidney Sections After Bisphosphonate Dosing[35,36]



Kidney sections after (**A**) a single dose of ibandronate (3 mg/kg) showing degenerative PCT changes, intact distal tubules, and P3 sections; (**B**) a 10-mg/kg dose of zoledronic acid showing degeneration of the PCT, cytoplasmic granules, and intraluminal proteinaceous material.

unbound bisphosphonate is eliminated, unchanged through the kidneys by filtration and by active tubular secretion.[7,8] High molar concentrations of some bisphosphonates after large doses and/or rapid administration have been shown to overload the mechanism for renal elimination, and the remaining compound can damage renal cells. For example, the net renal secretion and high concentration of bisphosphonates in tubular cells were linked to proteinuria and proximal tubular necrosis after a 5-mg/kg[9] parenteral dose of pamidronate and a 200-mg/kg dose of clodronate (doses 5- to 20-times higher than clinical doses in humans).[10,11]

Acute renal toxicity has been reported after treatment with overdoses of rapidly infused non–nitrogen-containing bisphosphonates (etidronate and clodronate).[12,13] Highly potent nitrogen-containing bisphosphonates have been shown to be effec-

tive at lower molar concentrations of the drug.[14,15] However, deteriorated renal function in patients with metastatic bone disease has been linked to high doses and recommended clinical doses of pamidronate and zoledronic acid.[16-25]

The exact mechanism of bisphosphonate-induced renal toxicity is unknown. One hypothesis suggests that precipitation of bisphosphonate aggregates or complexes in the kidney might contribute to renal toxicity.[26,27] Alternatively, it was proposed that the same intracellular effects described for osteoclasts could also cause renal cellular injury, leading to apoptosis.[22] Newer nitrogen-containing bisphosphonates, such as zoledronic acid, alendronate, risedronate, and ibandronate, inhibit the mevalonate pathway through the farnesyl pyrophosphate synthetase required for protein prenylation of small guanosine triphosphatases (GTPases).[28,29] Lipid prenyl groups anchor the GTPases in cell membranes and ensure their correct interaction and function in a variety of cellular processes (integrin signaling, endosomal trafficking, membrane ruffling, and apoptosis).[28,30-33] These common mechanisms of action might somehow influence the interaction between bisphosphonates and the kidney.

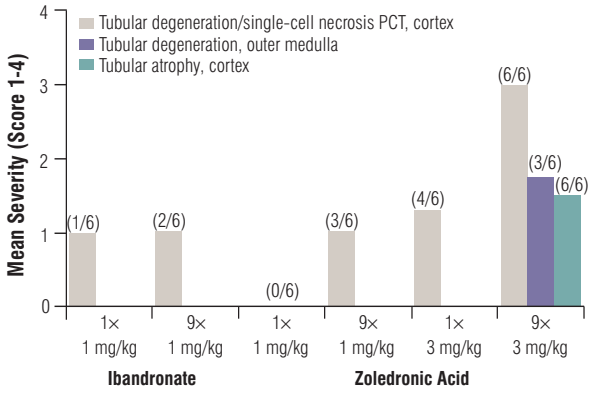
Nephrotoxic hypotheses that focus on class effects of bisphosphonates exclude different renal effects in animal models or patients with metastatic bone disease, regardless of the drug, yet preclinical and histopathologic evidence suggest that the effect of individual bisphosphonates on the kidney varies.

Site of Renal Damage

Histopathologic studies in clinically relevant rat models can identify and categorize subclinical renal damage that might otherwise be undetected using conventional measures of renal functioning, such as serum creatinine.[34-36] Research showed tubular degeneration on day 4, when the acute nephrotoxicity of ibandronate (1-20 mg/kg in a single I.V. injection), zoledronic acid (3-10 mg/kg in a single I.V. injection), and clodronate (200-mg/kg twice-daily intraperitoneal injections) were compared in rats.[35,36] The severity of degenerative changes in the proximal convoluted tubule (PCT) was dose-dependent for ibandronate and zoledronic acid. However, the dose-effect relationship was stronger for zoledronic acid than ibandronate. Acute treatment with bisphosphonates was well tolerated with a 10-mg/kg dose of ibandronate and a 3-mg/kg dose of zoledronic acid. The absence of drug precipitation in the kidney, even at the highest doses, suggested that the tubular damage might be caused by the interaction of bisphosphonates with PCT epithelial cells, which might have the same molecular targets as osteoclasts. Although degeneration and single-cell necrosis of the PCT were characteristic common findings, there were qualitative differences in localization and type of lesion between bisphosphonates (Figure 2).[35,36] Lesions induced by ibandronate and clodronate were locally restricted to the P1 and P2 segments of the PCT; zoledronic acid also induced changes in the outer medulla, P3 segments of the tubules, and distal tubules at the highest dose (10 mg/kg).

Figure 3

Histopathologic Findings in the Kidney After Single or Intermittent Dosing of Ibandronate or Zoledronic Acid[34]



Reproduced with permission from Pfister et al. The effects of minimally nephrotoxic doses of ibandronate and zoledronic acid following single and intermittent infusion in rats. Toxicology 2003; 191:159-167.

Analysis of renal tissue from patients after bisphosphonate-related acute renal toxicity has also shown pathologic differences between the effects of zoledronic acid and pamidronate. Several publications report collapsing glomerulonephritis (a form of focal segmental glomerulosclerosis) during pamidronate therapy, particularly at high doses (> 90 mg and ≥ 360 mg per month).[21,22,25,37-39] Renal complications after zoledronic acid have been shown in patients receiving the recommended 4-mg dose once a month.[23,40] All patients in cohort 6 reported by Markowitz et al were diagnosed with acute tubular necrosis without glomerular injury.[23]

Accumulative Renal Effects

Preclinical evidence suggests the renal safety of single bisphosphonate doses does not necessarily predict long-term effects of repeated-interval doses. In a controlled 25-week study, Pfister and colleagues investigated the risk of subclinical renal damage potentially accumulating to clinically relevant levels after intermittent dosing of ibandronate and zoledronic acid in rats.[34] To mimic hypothetically occurring subclinical renal effects in patients, minimally nephrotoxic doses (MND; ie, those that were high enough to induce subclinical renal damage after a single I.V. administration) for both bisphosphonates were used. Initial dose-selection experiments showed that the MND for ibandronate and zoledronic acid in

rats were 1 mg/kg and 3 mg/kg, respectively (a 1-mg/kg dose of zoledronic acid was also tested to allow equivalent dose comparisons with ibandronate when both agents were given intermittently). In addition to single-dose administration, doses were given at a clinically relevant between-dose interval of 3 weeks for 6 months (a total of 9 administrations), and nephrotoxicity was assessed by serum biochemistry, urinalysis, and kidney histopathology.

The results showed minimal renal damage during single or intermittent dosing of ibandronate (1 mg/kg); and histopathologic renal changes were similar in severity and incidence between ibandronate groups. In contrast, degeneration and single-cell necroses of the PCT were observed after intermittent dosing of a 1-mg/kg dose of zoledronic acid, whereas a single I.V. injection showed minimal PCT damage. Intermittent 3-mg/kg dosing of zoledronic acid resulted in a greater severity and incidence of PCT findings compared with a single dose. Besides the PCT damage demonstrated with a single dose, repeated administration of a 3-mg/kg dose of zoledronic acid produced additional renal damage to the outer medulla and tubular atrophy of the cortex (Figure 3).[34]

Investigators concluded that zoledronic acid had a higher risk of causing accumulated renal damage over time than ibandronate in this rat model. The results indicate that dosing every 3 weeks provided sufficient time for repair of possible subclinical renal damage for ibandronate but apparently not for zoledronic acid. Because the risk of cumulative renal effects is most likely related to residual tissue concentration (the amount of bisphosphonate remaining in the kidney from the previous doses), the absence of toxic accumulation with ibandronate might be explained by its shorter renal tissue half-life (24 days) versus zoledronic acid (150-200 days).[4,41,42] Standard dosing of an I.V. 6-mg dose of ibandronate every 3 to 4 weeks for 96 weeks had a renal safety profile comparable with placebo in phase III trials of patients with breast cancer and bone metastases.[43-45]

Dose-Effect Relationship

The ratio between the lowest lethal dose of ibandronate (25 mg/kg), zoledronic acid (10 mg/kg), and their MND (1 mg/kg and 3 mg/kg, respectively) was 25 for ibandronate but only 3.3 for zoledronic acid in the rat model of single I.V. bisphosphonate dosing.[34,42] Data suggest the therapeutic window of ibandronate (the range between lowest effective dose and highest dose that can be used without causing renal toxicity) is particularly broad. In addition, ibandronate loading doses (4-mg infused dose on 4 consecutive days, with a 16-mg total dose or 6-mg infused dose on 3 consecutive days, with an 18-mg total dose followed by intermittent dosing every 3 to 4 weeks) have been used in pilot studies to treat moderate-to-severe metastatic bone pain without adverse renal effects.[46-48] The results, however, must be confirmed in randomized, controlled studies. Phase III trials of loading-dose ibandronate followed by oral or I.V. standard dosing for patients with metastatic bone pain (comparator: standard zoledronic acid dosing) are planned.

Renal Tissue Kinetics

The mechanism of nephrotoxicity caused by bisphosphonates is related to intracellular effects in tubular cells. Differences in renal tissue kinetics are therefore key determinants of differences in clinical renal safety profiles between bisphosphonates. This includes the influx of bisphosphonate into the target cells, their persistence and intracellular transport, as well as the elimination rate from the cell (this defines the renal tissue half-life discussed earlier). Uptake and secretion from renal cells appear to be rate-determining and are controlled by unknown transport mechanisms that are selective for bisphosphonates.[49-52] Kino et al showed that when the plasma concentration increases, cellular influx of alendronate remains almost constant, whereas secretion from the cell is almost completely saturated.[49] This suggests that dose and peak plasma concentration affect the intracellular concentration of bisphosphonates and consequently the risk of cellular damage. This is most likely the reason why nephrotoxicity is not an issue for oral bisphosphonates, which are absorbed relatively slowly and are therefore administered as high daily doses compared with the lower monthly doses of I.V. bisphosphonates.

The protein-binding rate of bisphosphonates is another factor that might influence the propensity of bisphosphonates to cause renal damage. Because only non–protein-bound bisphosphonates can be taken up by the tubule cells, a high level of protein binding might limit or at least delay the entry and reduce the risk of accumulative renal damage. The protein-binding rate of ibandronate in patients is approximately 85% compared with 22% for zoledronic acid.[53,54] The intracellular bisphosphonate is eliminated by the active tubular secretion. The relevance of protein binding in the clinical setting remains highly speculative however, and further investigation is required.

Having a relatively long renal tissue half-life might help explain why some patients develop renal dysfunction when treated with the recommended zoledronic acid dosing regimen of 4-mg infusions every 3 to 4 weeks.[17-20,55,56] Although the incidence of renal adverse events was not significantly different from pamidronate or placebo in clinical trials, retrospective analyses of patient safety data show a nonnegligible incidence of renal toxicity with zoledronic acid that has justified the current recommendations to adjust zoledronic acid dose according to creatinine clearance.[40,57,58] Because the link between histologic damage and clinical outcome in patients is unclear (ie, minimal tubular damage could remain undiagnosed), further examination through kidney biopsy would help determine the extent and cause of

Table 1

Preclinical Renal Safety Data for Ibandronate and Zoledronic Acid[4,34-36,41,53,54]

Study	Safety Characteristic	Ibandronate	Zoledronic Acid
Bauss et al[4,41] CDER[53,54]	Renal $t_{1/2}$	24 Days	150-200 Days
CDER[53,54]	Serum protein binding (humans)	85%	22%
Pfister et al[35,36]	Lowest lethal dose	25 mg/kg	10 mg/kg
	Minimal nephrotoxic dose	1 mg/kg	3 mg/kg
	LLD-MND ratio	25	3.3
	Histopathologic effects of a single intravenous injection	Degeneration and single-cell necrosis in P1 and P2 segments of the PCT (1-20 mg/kg).	Degeneration and single-cell necrosis in P1, P2, and P3 segments of the PCT, outer medulla (3-10 mg/kg), and distal tubules (10 mg/kg).
Pfister et al[34]	Histopathologic effects of repeated intermittent dosing*	Minimal PCT degeneration similar in incidence and severity to single dosing. Slight-to-moderate hypertrophy and hyperplasia of the medulla.	Slight-to-marked PCT degeneration. Minimal-to-moderate outer medulla degeneration. Minimal-to-slight tubular atrophy with thickened basement membrane. Marked-to-massive hypertrophy and hyperplasia of the medulla.
	Biochemical effects of repeated intermittent dosing	Biochemical parameters were similar to untreated controls.	Significantly decreased creatinine clearance; significantly increased serum creatinine, urinary GST-α and lactate dehydrogenase (1 mg/kg and 3 mg/kg). Significantly increased urinary protein and serum urea (3 mg/kg).

*Every 3 weeks for 6 months with MND.
Abbreviations: GST-α = glutathione S-transferase–α; LLD = lowest lethal dose

any adverse renal effects. However, this is quite an aggressive procedure likely to be performed only in patients developing severe renal dysfunction. It is unknown whether monitoring proteinuria, microalbuminuria, and/or the excretion of tubular renal enzymes could help predict and thus possibly avoid future renal dysfunction.

Conclusion

Clinical evidence suggests that renal safety can complicate I.V. bisphosphonate therapy for metastatic bone disease. Human data are sparse, but preclinical data show differences between bisphosphonates in risk of histopathologic renal damage and toxicity accumulation over time (Table 1).[4,34-36,41,42,53,54] In particular, preclinical findings support empirical clinical observations suggesting that zoledronic acid has a greater potential for renal toxicity than ibandronate. This validates the recommendations that zoledronic acid dosing should be adjusted according to creatinine clearance. Although the exact mechanisms responsible for the differences in nephrotoxic potential are unclear, variations inherent in the renal structures affected by therapy and pharmacokinetic properties of bisphosphonates, such as renal tissue half-life and protein binding, might be contributing factors. For this reason, additional preclinical studies are needed in order to thoroughly investigate the renal effects of bisphosphonate therapy.

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