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Preclinical Perspectives on Bisphosphonate Renal Safety

JEAN-JACQUES BODY,^a THOMAS PFISTER,^b FRIEDER BAUSS^c

^aInstitut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; ^bPre-clinical Research and Development, F. Hoffmann-La Roche Ltd., Basel, Switzerland; ^cRoche Diagnostics GmbH, Pharma Research Penzberg, Penzberg, Germany

Key Words. Bone metastases • Bisphosphonates • Ibandronate • Renal safety • Preclinical

ABSTRACT

Renal insufficiency is not rare in cancer patients who may receive nephrotoxic medications as antineoplastic agents or for comorbid conditions. Thus, the choice of a particular bisphosphonate for patients with metastatic bone disease should be based not only on efficacy but also on the risk for renal deterioration. Some i.v. bisphosphonates have been associated with occasional renal toxicity in the clinical setting. Preclinical studies have also shown that there may be considerable differences among bisphosphonate renal

safety profiles. Comparative studies show variations in the risk for histopathologic damage and the ability to cause cumulative toxicity during intermittent dosing. Reasons for the differences among bisphosphonates are not fully understood; however, research shows that they may be influenced by pharmacokinetic properties such as renal tissue half-life or protein binding and intracellular potency. Further preclinical analyses are needed to confirm and evaluate differences among bisphosphonates. *The Oncologist* 2005;10(suppl 1):3–7

INTRODUCTION

Bisphosphonates are widely used to treat skeletal complications of malignancy [1]. They target the underlying pathophysiology of metastatic bone disease by inhibiting osteoclast-mediated bone resorption [2]. The long-term renal safety of bisphosphonates in clinical practice is important because of the significant morbidity associated with bone metastases and renal dysfunction experienced by many patients as a result of their underlying disease or treatment [3, 4].

The majority of the bisphosphonate that reaches the systemic circulation is rapidly bound to bone (40%–60%) [5]. Skeletal uptake of bisphosphonates depends on bone turn-

over, and bisphosphonate is deposited in areas of bone formation and destruction [6]. The remainder of the bisphosphonate is not metabolized and is eliminated unchanged by the kidneys through glomerular filtration and active tubular excretion [7, 8]. High doses accompanied by high molar concentrations (maximum plasma concentration [C_{max}]) of some bisphosphonates have been shown to overload the renal elimination mechanism, and the retained compound can damage renal cells [9, 10]. In animals, proteinuria and proximal tubular necrosis have been linked to reduced renal excretion and consequently to high concentrations of bisphosphonates, that is, pamidronate (Aredia®; Novartis

Correspondence: Jean-Jacques Body, M.D., Ph.D., Institut Jules Bordet, Université Libre de Bruxelles, 1 Rue Héger-Bordet, 1000 Brussels, Belgium. Telephone: 32-2-541-3303; Fax: 32-2-541-3311; e-mail: jj.body@bordet.be Received August 1, 2005; accepted for publication August 29, 2005. ©AlphaMed Press 1083-7159/2005/\$12.00/0

Pharmaceuticals Corporation, East Hanover, NJ, <http://www.pharma.us.novartis.com>), 5 mg/kg, and clodronate (Bonefos®; Schering AG, Berlin, <http://www.schering.de>; and Ostac®, Loron®; F. Hoffmann-La Roche Ltd., Basel, Switzerland, <http://www.roche.com>) 200 mg/kg, in renal tubular cells [11–13]. However, the doses used in those studies were 5–20 times higher than clinical doses.

It has been suggested that the mechanism of bisphosphonate-induced renal toxicity is precipitated bisphosphonate aggregation or calcium complexes in the kidney [6, 14]. However, no corpuscular precipitations were reported during kidney histopathological analyses in animals [12, 15–20]. Therefore, it has been postulated that a more likely pathomechanism is that bisphosphonates induce cell death in renal cells in a manner similar to their apoptotic effects in osteoclasts and possibly even cancer cells [16, 17]. Nitrogen-containing bisphosphonates, such as zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation), alendronate (Fosamax®; Merck & Co., Inc., Whitehouse Station, NJ, <http://www.merck.com>), risedronate (Actonel®; Procter & Gamble Pharmaceuticals, Inc., Cincinnati, OH, <http://www.pgpharma.com>), and ibandronate (Bondronat®; F. Hoffmann-La Roche Ltd.), inhibit protein prenylation of small GTPases by blocking the mevalonate pathway, and the enzyme farnesyl pyrophosphate synthase in particular [21, 22]. Lipid prenylation anchors GTPases to intracellular membranes where they can interact in a variety of cellular processes, such as integrin signaling, endosomal trafficking, membrane ruffling, and apoptosis [21–26]. These common mechanisms of action might somehow also influence the renal safety of bisphosphonates.

Although all bisphosphonates have been shown to elicit some constrictive effects on the kidney in preclinical toxicity studies, their potentials to cause renal toxicity are not equal [27]. The present article reviews the preclinical data, outlining a rationale for the differences in bisphosphonate renal safety.

PRECLINICAL EVIDENCE FOR DIFFERING RENAL SAFETY PROFILES

Comparative preclinical studies have shown differences in the renal safety profiles of bisphosphonates. Pfister et al. [15] investigated the potential for subclinical renal damage following bisphosphonate treatment at clinically relevant levels. In that controlled, 25-week, preclinical study, groups of rats were given ibandronate (1 mg/kg) or zoledronic acid (1 mg/kg or 3 mg/kg) intermittently—with a between-dose interval of 3 weeks—or as a single dose by i.v. injection. Doses were selected experimentally because of their ability to produce minimally nephrotoxic subclinical effects in the animals.

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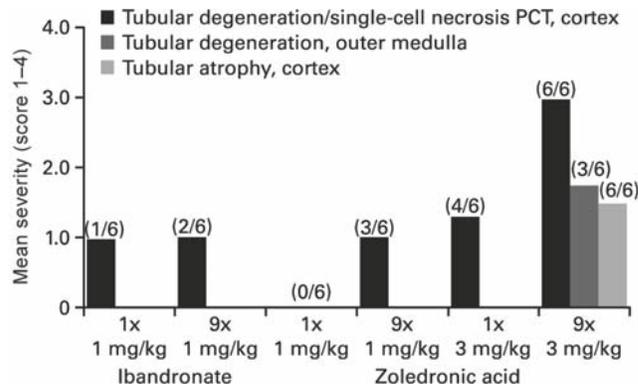


Figure 1. Histopathologic findings in the kidneys of rats after single or intermittent dosing of ibandronate or zoledronic acid [15]. Abbreviation: PCT, proximal convoluted tubules.

Both single and intermittent ibandronate dosing led to similar incidences of proximal tubular degeneration and single-cell necrosis. Histopathologic renal changes were similar in severity and incidence in rats receiving single or intermittent doses of ibandronate (Fig. 1). Intermittent dosing of zoledronic acid, however, induced a higher incidence and severity of renal damage than single dosing (Fig. 1). Accumulated renal damage also was observed for a lower intermittent dose of zoledronic acid (1 mg/kg) that did not produce histopathologic renal damage when given only once (Fig. 1). It was concluded that, unlike ibandronate, intermittently administered zoledronic acid was associated with a risk for causing accumulated renal damage over time in this rat model.

Another study compared the acute nephrotoxic effects of ibandronate, zoledronic acid, and clodronate [16]. Both ibandronate and zoledronic acid were given as a single i.v. dose over a range of 1–20 mg/kg and 1–10 mg/kg, respectively. Clodronate was administered as a control since renal damage has been described for two intraperitoneal injections of 200 mg/kg during a single day [28]. Blood and urinary biochemistry and kidney histopathology analyses were performed on the first and fourth days after bisphosphonate dosing. Tubular degeneration was observed only on the fourth day after dosing with 1–20 mg/kg of i.v. ibandronate, 3–10 mg/kg of i.v. zoledronic acid, or 200-mg/kg twice-daily intraperitoneal clodronate. Characteristic findings were degeneration and single-cell necrosis of the proximal convoluted tubules, although there were qualitative differences among bisphosphonates in the localization, type, and severity of lesions. The dose–effect relationship was stronger with zoledronic acid than with ibandronate. Granular deposits in the lumen of distal tubules occurred only with zoledronic acid at the highest dose tested (10 mg/kg). The clinical relevance of these

findings needs to be clarified, even if similar histological changes have been described recently in patients treated with intermittent zoledronic acid [20].

Other preclinical studies add to the weight of evidence supporting the renal safety of ibandronate. The effect of ibandronate on bone was investigated in rats with normal versus moderately impaired renal function induced by two-thirds nephrectomy [29]. Intermittent ibandronate prevented the reductions in bone mass, changes in bone structure, and reduced bone turnover in these partly nephrectomized rats without further deterioration of renal function.

The impact of urinary diversion using several types of intestinal segments on the bone metabolism of growing rats with renal insufficiency was examined by Brkovic et al. [30]. Uremic rats underwent enterocystoplasty using stomach, ileum, or colon. An additional group with colic augmentation received ibandronate. All groups undergoing subtotal nephrectomy by removing five-sixths of the renal mass had a decreased endogenous creatinine clearance of approximately 30%. Ibandronate (10 µg/kg per day for 12 weeks) prevented relative decreases in bone mineral density of the tibia and femur that occurred following ileocystoplasty without causing further deterioration of renal function.

PATIENT BIOPSIES

The potential deleterious effects of bisphosphonate treatment on the kidney have been demonstrated by renal biopsies. Pamidronate-induced renal toxicity is characterized by collapsing focal segmented glomerulosclerosis [19, 31, 32]. High-dose pamidronate, however, was shown on one occasion to induce acute tubular necrosis, probably resulting from pre-existing renal impairment [17]. Renal toxicity characterized by acute tubular necrosis is more often seen with zoledronic acid. This potential toxicity was well demonstrated in six patients with multiple myeloma or Paget's disease who had received i.v. zoledronic acid, 4 mg monthly over 15 minutes [20]. Renal biopsy revealed acute tubular necrosis characterized by tubular cell degeneration, loss of brush border, and apoptosis. No biopsy exhibited the pattern of collapsing focal segmented glomerulosclerosis observed with pamidronate nephrotoxicity. In this report, acute tubular necrosis with zoledronic acid occurred after a mean duration of 4.7 months (range, 3–9 months), in agreement with the cumulative renal toxicity described in rats [15]. There also have been clinical reports of renal failure occurring with zoledronic acid after just one dose [33]. It is, however, unclear whether the patients received previous bisphosphonate therapy or had pre-existing renal impairment that may have contributed to the cumulative toxic effects of zoledronic acid. There are two possible mechanisms by which

zoledronic acid could elicit nephrotoxic effects: (a) an acute mechanism that damages renal cells, and (b) a progressive but potentially reversible increase in serum creatinine levels. It is not known whether reports of acute tubular necrosis result from a previously unseen or unconsidered increase in serum creatinine.

RATIONALE FOR RENAL SAFETY DIFFERENCES

Preclinical and clinical studies suggest that the renal safety profiles of bisphosphonates differ [15–17, 19, 20, 29–32, 34]. Several factors may explain these differences (Table 1). Clinical evidence for differences is discussed elsewhere [35].

In an animal model, zoledronic acid, but not ibandronate, was demonstrated to be linked to cumulative renal toxicity [15]. A short renal tissue half-life may avert such accumulation by producing lower steady-state concentrations in renal cells. In that model, ibandronate had a terminal renal tissue half-life of 24 days [5], which may explain the absence of toxicity when using a standard clinical 3- to 4-weekly dosing interval [15], whereas the longer comparative renal tissue half-life of zoledronic acid (150–200 days) [36] might not allow enough time for repair of renal damage.

In the same animal model, it was also shown that the factor between the lowest lethal dose and renal lowest observed effect level may also be relevant when considering a rationale for renal safety differences among bisphosphonates. This factor has been shown to indicate the safety margin between the first signs of renal toxicity and a dose that can cause lethal renal damage [15]. The factor between the lowest lethal dose and renal lowest observed effect level is larger for ibandronate (25) than for zoledronic acid (3.3). This difference may indicate that ibandronate has a broader renal safety margin and is less likely to cause renal damage

Table 1. Preclinical data on bisphosphonates suggest that renal safety profiles differ [15, 35]

| | Ibandronate | Zoledronic acid |
|---|--|---|
| Protein binding | 87% | 56% |
| Renal tissue half-life | 24 days | 150–200 days |
| Factor between lowest lethal dose and renal LOEL | 25 | 3.3 |
| Renal toxicity | No cumulative toxicity at 3-weekly dosing interval | Cumulative toxicity at 3-weekly dosing interval |

Abbreviation: LOEL, lowest observed effect level.

when doses are increased [15]. In the clinical setting, phase II studies showed that intensive ibandronate dosing, 4 mg infused over four consecutive days [37] and 6 mg infused over three consecutive days as a loading dose followed by intermittent dosing every 3–4 weeks [38, 39], relieves moderate-to-severe metastatic bone pain without adverse renal effects.

Because bisphosphonates cause renal toxicity through their intracellular effects on renal tubular cells, their intracellular potencies and renal tissue kinetics are likely to be important when considering differences among renal safety profiles. The lower the intracellular concentration of a bisphosphonate needed for inhibition of osteoclasts, the lower the expected effects in other cells, including renal tubular cells. Consequently, the influx of bisphosphonate into the target cells, intracellular transport, and rate of elimination from the cell should be key determinants of bisphosphonate renal safety. This is supported by investigations in which the cellular influx of alendronate did not vary with dose, whereas a saturable transport system eliminated the drug from the cell [9]. Thus, dose and C_{max} will affect the intracellular concentration of the bisphosphonate and, consequently, increase the risk for cellular damage.

Protein binding also may be important for the renal safety of a bisphosphonate, but it is the least understood factor. Generally, since only non-protein-bound bisphosphonate can enter tubule cells, a high level of protein binding may reduce the intracellular disposition, and thus the risk of cumulative renal damage, by reducing or delaying the pas-

sage into renal cells. On the other hand, if dissociation of the drug-protein complex is very rapid, tubular secretion may not be significantly limited by protein binding. Ibandronate has a higher level of protein binding (87%) than zoledronic acid (56%), pamidronate (54%), and clodronate (36%). The relevance of different protein binding in the clinical setting is, however, unclear and requires further examination.

CONCLUSIONS

Preclinical studies have demonstrated distinct differences among bisphosphonates in the risk for histopathologic renal damage and the potential to cause cumulative toxicity over time [15, 16]. The precise reasons for these differences among bisphosphonates are not completely understood, yet available data indicate that they may be influenced by pharmacokinetic properties such as renal tissue half-life or protein binding and intracellular potency.

Clinical data appear to confirm these preclinical findings and suggest that the risk for renal toxicity is not the same for all bisphosphonates. Reports of renal failure with the clinical use of zoledronic acid contrast with data for ibandronate that suggest its renal safety is comparable with that of placebo [34]. Further investigation is necessary to compare the renal safety profiles of the agents in more detail.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Dr. Body has acted as a consultant and performed contract work for Hoffmann-La Roche.

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