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Nephrotoxicity of ibandronate and zoledronate in Wistar rats with normal renal function and after unilateral nephrectomy

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ABSTRACT

A previous animal study compared the nephrotoxic effect of ibandronate (IBN) and zoledronate (ZOL), but interpretation of these study results was limited because of the model of minimal nephrotoxic dosage with a dosage ratio of 1:3. The present study investigated the nephrotoxicity of ibandronate and zoledronate in a 1.5:1 dose ratio, as used in clinical practice and compared the nephrotoxicity in rats with normal and with mildly to moderately impaired renal function. We compared rats with normal renal function (SHAM) and with impaired renal function after unilateral nephrectomy (UNX), treated either with ibandronate 1.5 mg/kg, zoledronate 1 mg/kg or placebo once (1×) or nine (9×) times. Renal function and markers of tubular toxicity were measured over a 27 week period. After last bisphosphonate treatment the rats were sacrificed and kidneys examined histologically. All bisphosphonate treated animals showed a significant tubular toxicity, which was temporary except in the ZOL-UNX-9×-group. Also the renal function was only transiently reduced except in the ZOL-UNX-9×-group. Histologically, bisphosphonate treatment led to cortical tubuloepithelial degeneration/necrosis and medullary tubuloepithelial swelling which were slightly more pronounced in ibandronate treated animals, when compared to zoledronate treated animals, especially with impaired renal function. In contrast to the previous study we found a similar nephrotoxicity of ibandronate and zoledronate in rats with normal renal function. In rats with impaired renal function the peak of toxicity had not even been fully reached until end of experiment in the zoledronate treated animals. The peak of toxicity seems to be more severe and delayed in rats with impaired renal function compared with rats with normal renal function.

1. Introduction

Bisphosphonates are potent osteoclast inhibitors used in bone diseases with an increased osteoclast activity like osteoporosis, Paget's disease or tumor induced bone disease. Bisphosphonates have been reported to have only few side effects, although in the literature there is some indication of acute renal failure and even kidney failure requiring dialysis after repeated bisphosphonate infusions [1–4]. An other adverse effect is osteonecrosis of the jaw [5,6]. The present paper focuses on renal toxicity.

After entering circulation, bisphosphonates are rapidly taken up in bone or excreted unchanged via the kidney. Bone takes up 40–60% of the dose [7–9]. The remaining 60–40% are eliminated within 24 h almost exclusively via the kidney. Bisphosphonates are not metabolized [10]. The exact route of renal elimination has still not been clearly determined. In rats during renal excretion about 0.5% of the administered drug remains in the kidney tissue with the risk of accumulation. This might be the reason for renal toxicity after repeated dosage. In rats with mild renal insufficiency the renal tissue level increases significantly after repetitive treatment

Abbreviations: 1×, group with only one injection; 9×, group with nine injections; α-GST, α-glutathione S-transferase; β-NAG, β-N-acetyl-glucosaminidase; AUC, area under the curve; BW, body weight; CREA, creatinine; GFR, glomerular filtration rate; HE, hematoxylin and eosine; IBN, ibandronate; NoOP, not operated; PBS, phosphate buffered saline; PL, placebo; SHAM, sham operated; SPF, specified pathogen free breeding; UNX, unilaterally nephrectomized; ZOL, zoledronate.

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compared to rats with normal renal function, but it is unknown whether this finding is associated with an increased renal toxicity [11].

Ibandronate and zoledronate are the most potent bisphosphonates for treatment of cancer related bone disease and tumor induced hypercalcemia. Due to an increased incidence of cancer in older people, bisphosphonate therapy is used in many cases in patients with impaired kidney function due to secondary disease (e.g. diabetes, hypertension), age related renal insufficiency or cancer induced renal disease [12,13].

Additionally, some chemotherapeutic agents (e.g. cisplatin, gemcitabine) are nephrotoxic [14]. Further drugs should therefore not deteriorate renal function. In rats with mildly impaired renal function the renal tissue level of ibandronate increases significantly after repetitive treatment in comparison to rats with normal renal function [11]. The influence of a mildly to moderately impaired renal function on the nephrotoxicity of zoledronate was not investigated so far, but zoledronate is contraindicated in severe renal insufficiency (stage IV-V, GFR < 30 ml/min). There are also no data about renal tissue concentrations of zoledronate.

To date, there are no reports about renal toxicity of ibandronate in patients, but it is assumed, that the different bisphosphonates have a different nephrotoxic potential [17–19].

To the best of our knowledge there are no clinical studies, comparing the nephrotoxic side effects of the different bisphosphonates in cancer patients. One animal experiment compared the nephrotoxic effect of zoledronate and ibandronate and demonstrated an increased incidence of renal failure and tubular damage in zoledronate treated rats [20]. But interpretation of these study results was limited because of the model of minimal nephrotoxic dosage, in that for both drugs a dosage was used which induced a minimum nephrotoxic damage after a single infusion. The dosage was 1 mg/kg BW for ibandronate and 3 mg/kg BW for zoledronate (dosage ratio 1:3, whereas in clinical use a dosage ratio of 1.5:1 is used). Moreover, the study was only performed in rats with normal renal function. Therefore, the present study investigated the nephrotoxicity of ibandronate and zoledronate in a 1.5:1 dosage ratio, as used in clinical practice, and compared the nephrotoxicity in rats with normal and first time also with mildly to moderately impaired renal function.

2. Methods

96 female Wistar rats (HsdHan:Wist) from a specified pathogen free breeding (SPF) (Harlan GmbH, Roßdorf, Germany), aged 8 weeks and weighing 210 ± 10 g at arrival, were randomly assigned to thirteen groups of eight or four animals, respectively. The rats were assigned to three treatment groups (ibandronate (IBN), zoledronate (ZOL) and sodium chloride 0.9% (placebo, PL)). Each treatment group was then subdivided into one group with a single injection (1×) and one group with nine repeated injections (9×). Finally every subgroup was additionally divided into sham operated rats (SHAM) with normal renal function and unilaterally nephrectomized rats (UNX) with impaired renal function. In the placebo treated rats a non-operated group (NoOP) was carried along as a baseline for comparison of possible effects related to the experimental procedures. Fig. 1 gives an overview over all groups and time points of measurements.

The rats were group-housed (4 animals/cage) in macrolon cages (1800 cm^2) on soft bedding (Lignocel 3/4 S, Ssniff Spezialdiäten GmbH, Soest, Germany) provided with nesting material. The had ad libitum access to water and pelletized standard rodent diet; 19% protein, 3.3% fat, 4.9% fiber, energy 12.8 MJ/kg, (Ssniff Spezialdiäten GmbH, Soest, Germany).

After an adaptation period of two weeks animals underwent unilateral nephrectomy (UNX) or sham surgery (SHAM) as described in a recent publication [11]. From the age of 16 weeks the 9×-groups received a total of nine injections of ibandronate 1.5 mg/kg BW, zoledronate 1 mg/kg BW or sodium chloride 0.9% 1 ml, not BW adapted (placebo), at a dosing interval of 3 weeks. All injections were administered into the tail vein over a time period of maximum 30 s. The 1×-groups received only one injection of ibandronate, zoledronate or placebo at the age of 38 weeks. All animals were sacrificed, perfused and necropsied 3 days after the last injection.

The dosage was calculated on the base of the previously published paper from Pfister et al., who demonstrated a minimal nephrotoxic dosage of zoledronate with 1(-3) mg/kg BW [20]. The ibandronate dosage was adjusted in a 1:1.5 ratio (zoledronate/ibandronate), as used in clinical practice.

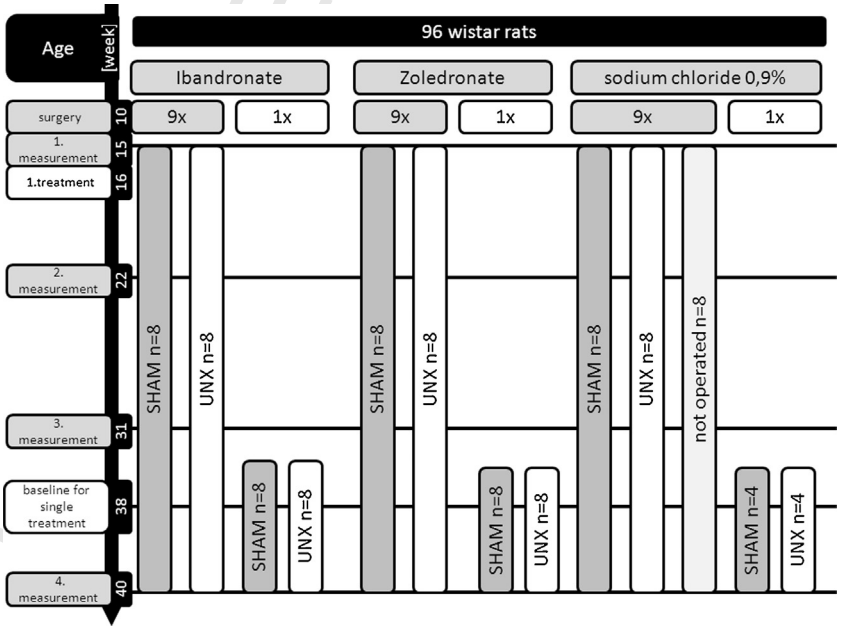

Fig. 1. Overview of treatment groups and animal numbers per group and time points of measurement of creatinine clearance, α-GST and β-NAG at weeks 15, 22, 31 and 40.

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