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Renal Safety of Intravenous Ibandronic Acid in Breast Cancer Patients with Metastatic Bone Disease

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Abstract

Introduction: Renal adverse events are a troublesome complication of bisphosphonate therapy. This study investigated the effect of intravenous ibandronic acid (ibandronate) treatment on renal function in breast cancer patients with metastatic bone disease.

Methods: 74 patients were randomised to double-blind (but not dose-blind) treatment with bolus injections of ibandronic acid 2mg (n = 23), 1-hour infusions of ibandronic acid 6mg (n = 28), or placebo injections or infusions (n = 23). According to randomisation, patients received either three injections or three infusions over the 3-month period, one at the start and two subsequent doses at 4-weekly intervals. Measurements of urinary excretion of total protein, albumin, α_1-microglobulin, *N*-acetyl-β-D-glucosaminidase, haematuria and serum creatinine were performed before, during and after treatment.

Results: Treatment with ibandronic acid was not associated with impairment of renal function; the renal safety profiles of ibandronic acid 2 and 6mg were similar to that of placebo. Assessments of proteinuria, haematuria, enzymuria and serum creatinine indicated that there were no statistically significant changes between pre- and post-treatment levels in patients receiving ibandronic acid 2 or 6mg or between patients receiving ibandronic acid or placebo. Urine parameters varied during treatment in the same range with approximately similar frequency in the ibandronic acid and placebo groups.

Conclusions: Short-term administration of intravenous ibandronic acid did not impair renal function in breast cancer patients with metastatic bone disease. Because tolerability profiles vary between bisphosphonates, the lack of renal toxicity with ibandronic acid makes the drug an attractive treatment option for metastatic bone disease.

Bisphosphonates are a class of antiresorptive drugs used in the management of hypercalcaemia of malignancy and other diseases affecting the skeleton. The increasingly important role of these agents in the treatment and prevention of metastatic bone disease has recently been emphasised.[1-3] The investigation of not only antiresorptive effects but also adverse events is very important for the clinical use of bisphosphonates. Very few adverse effects from treatment with clodronic acid and other bisphosphonates have been reported.[1] The most frequently observed adverse effect for oral alendronic acid, pamidronic acid and clodronic acid is gastrointestinal disturbance.[4,5] Following administration of intravenous bisphosphonates such as pamidronic acid, the main adverse effects are injection site reactions and 'flu-like syndrome.[6]

Renal adverse events are a troublesome complication of bisphosphonate therapy. Renal toxicity normally manifests as deterioration of renal function, which may progress to renal failure. Risk factors for this deterioration include elevated baseline serum creatinine, multiple cycles of treatment with the bisphosphonate, and time on study. Clodronic acid, pamidronic acid and zoledronic acid are associated with similar nephrotoxic potentials. Transient mild proteinuria has been reported in 20% of patients treated with clodronic acid.[7] Furthermore, rapid bolus injection of clodronic acid has been reported to lead to renal failure, probably because of the formation of a solid drug phase in the blood, which is then retained in the kidney.[8] However, this type of nephrotoxicity can be avoided by use of a slow intravenous infusion.[9,10] Pamidronic acid has also been associated with nephrotoxicity at high doses,[11] although renal damage is rarely seen when pamidronic acid is administered via 2-hour intravenous infusion at the commonly used dose of 60–90mg.[12] In a comparative phase III trial of zoledronic acid and pamidronic acid in patients with bone metastases from breast cancer, the study protocol was amended to increase the 5-min infusion time for zoledronic acid 4mg to 15 min because of concerns over renal safety.[12] Before the amendment, 13% of patients experienced renal impairment, whereas 9% of patients still experienced deterioration of renal function when the infusion time was increased.

The evaluation of renal function is usually based on the determination of serum creatinine, but this test is neither sensitive nor specific enough to detect nephropathy at an early stage. Recently, urinary proteins and enzymes have been proposed as sensitive indicators for the diagnosis of toxic effects of drugs on the kidney.[13-16] Albuminuria has been defined as an early marker of glomerular lesions.[14,17] The determination of α_1-microglobulin (MG) and *N*-acetyl-β-D-glucosaminidase (NAG) has been proposed for the evaluation of tubular nephrotoxicity.[16,18,19] Quantitative measurement of urinary proteins and enzymes thus gives additional information about the degree of tubular and glomerular dysfunction, in addition to the standard urinalysis including haematuria and leucocyturia.

Ibandronic acid (ibandronate), one of the most potent bisphosphonates, has demonstrated efficacy in hypercalcaemia of malignancy.[20-22] A recent multicentre phase III trial has shown that ibandronic acid can also significantly reduce the occurrence of skeletal complications, minimise bone pain, and improve quality of life in metastatic bone disease caused by breast cancer.[23,24] Because of interest in the renal toxicity of bisphosphonates, we report here a subset analysis of the data from those patients recruited by the Russian study centre to investigate the effect of intravenous ibandronic acid treatment on renal function.

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Materials and Methods

Study Design

This was a double-blind (not dose-blind), placebo-controlled, randomised trial that formed part of a larger phase III multicentre efficacy study carried out between 1994 and 1997 at centres in Europe, Kuwait, Russia, South Africa and the US. The patients described in this study were all recruited at the Russian centre.

Patients and Sample Collection

Admission Criteria

Breast cancer patients were included if they had bone metastases confirmed by x-ray. In total, 74 female patients with histologically confirmed breast cancer were enrolled in the subtrial (International Classification of Diseases [ICD] Code 174.9). All had adequate performance status (WHO grade 0–2), serum calcium in the normal range (2.0–2.7 mmol/L, albumin corrected) and serum creatinine <265 μmol/L prior to entry into the study. Patients had experienced one or two relapses, and had a life expectancy >60 weeks. Patients were excluded if they had liver or brain metastases, or had received high-dose chemotherapy. During the study patients received endocrine therapy and/or an anthracycline-containing regimen. Some of the patients had additional local radiotherapy in the event of clinical symptoms (e.g. bone pain, instability).

All patients gave informed, written consent in accordance with the Ethics Committee of the Russian Cancer Research Centre.

Treatment Regimen

Patients were treated with ibandronic acid or placebo administered at 4-weekly intervals over 3 months, in addition to antineoplastic therapy. Patients were randomised into three groups in a doubleblind manner. Group 1 received a single bolus injection of ibandronic acid 2mg, group 2 received a 1-hour infusion of ibandronic acid 6mg in saline, and group 3 received placebo either by bolus injection or by 1-hour infusion. Patients and investigators were blinded to placebo or ibandronic acid, but the dose administered was open label. According to randomisation, patients received either three injections or three infusions over the 3-month period, one at the start and two subsequent doses at 4-weekly intervals.

Sample Collection

Urine samples were collected prior to the administration of each of the three successive doses of ibandronic acid or placebo and at 1, 2, 5 and 10 days after each dose. Second morning spot urine was collected within 60–120 min of discarding the first morning urine. Venous blood samples were taken before ibandronic acid or placebo administration each month and at the end of the study. Urine and blood serum samples were analysed within 1 day of collection.

Methods

Test-strip assay including blood, leucocytes and total protein was performed by Combur-10 Test®[1] (Roche, Mannheim, Germany). For quantitative protein and enzyme analysis on automated system Hitachi 911, urine was centrifuged for 10 min at 1200*g*. Total protein was determined by the turbidimetric method with benzethonium chloride (Urinary/CSF Protein, Roche, Mannheim, Germany). Albumin and MG were measured by immunoturbidimetry (Tina-quant® Albumin and Tina-quant® α_1-Microglobulin, Roche, Mannheim, Germany). NAG was determined by colorimetric assay (*N*-acetyl-β-D-glucosaminidase/NAG, Roche, Mannheim, Germany), and serum and urine creatinine by the kinetic Jaffe method. All urinary para-

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

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Table I. Excretion of urine proteins (mg/g creatinine) and enzymes (IU/g creatinine) in breast cancer patients with bone metastases receiving (a) ibandronic acid 2mg, (b) ibandronic acid 6mg, or (c) placebo. Values shown are means (SD)[a]

Parameters	Pretreatment level	Post-treatment level			
		day 1	day 2	day 5	day 10
a) Ibandronic acid 2mg					
First course					
Total protein	87.2 (5.2)	83.2 (7.7)	78.4 (4.7)	90.1 (7.8)	101.2 (16.4)
Albumin	10.2 (2.2)	8.2 (3.1)	10.6 (2.1)	13.5 (3.6)	20.1 (3.0)
α_1-Microglobulin	10.9 (2.4)	6.2 (1.0)	7.9 (1.5)	9.1 (1.2)	6.6 (1.1)
NAG	4.6 (0.5)	5.2 (0.5)	5.8 (0.4)	5.0 (0.3)	5.2 (0.6)
Second course					
Total protein	87.4 (8.8)	77.7 (6.9)	81.0 (7.9)	97.9 (13.0)	91.7 (9.4)
Albumin	10.9 (2.4)	10.1 (2.6)	11.2 (3.4)	15.3 (4.4)	14.7 (4.1)
α_1-Microglobulin	8.6 (2.6)	9.1 (2.6)	10.2 (3.4)	8.8 (2.6)	7.1 (1.1)
NAG	5.3 (0.7)	5.1 (0.7)	5.1 (0.6)	5.7 (0.9)	5.6 (0.9)
Third course					
Total protein	88.4 (9.8)	92.1 (8.3)	72.7 (8.2)	76.5 (11.8)	95.3 (10.2)
Albumin	9.3 (4.4)	7.0 (2.4)	8.9 (2.0)	11.9 (1.5)	17.8 (4.1)
α_1-Microglobulin	11.0 (7.4)	4.2 (1.1)	5.2 (2.4)	9.6 (1.4)	6.7 (1.3)
NAG	4.5 (0.3)	5.3 (0.4)	6.4 (0.8)	4.6 (0.4)	5.1 (0.9)
b) Ibandronic acid 6mg					
First course					
Total protein	81.4 (11.3)	104.3 (17.5)	81.2 (10.8)	98.4 (14.1)	82.3 (10.2)
Albumin	14.4 (4.4)	14.4 (5.7)	14.0 (5.2)	19.6 (6.4)	11.8 (5.6)
α_1-Microglobulin	7.2 (1.8)	9.9 (3.2)	10.5 (4.1)	11.2 (2.4)	7.7 (1.6)
NAG	5.1 (0.4)	5.3 (0.7)	5.3 (0.7)	5.8 (0.8)	4.9 (0.5)
Second course					
Total protein	82.6 (11.9)	76.5 (11.3)	93.5 (13.2)	86.9 (15.9)	99.1 (14.5)
Albumin	10.4 (3.3)	10.1 (3.6)	15.7 (4.1)	14.6 (4.0)	18.8 (6.6)
α_1-Microglobulin	9.3 (4.5)	8.3 (2.5)	7.8 (2.4)	10.7 (3.3)	11.4 (3.6)
NAG	4.5 (0.5)	5.1 (0.5)	4.7 (0.5)	5.1 (0.5)	4.6 (0.7)
Third course					
Total protein	108.7 (9.8)	77.6 (8.8)	67.0 (6.6)	72.3 (12.8)	77.6 (13.5)
Albumin	16.7 (3.8)	11.0 (1.9)	14.7 (4.6)	11.9 (2.1)	11.3 (2.3)
α_1-Microglobulin	9.9 (3.7)	12.1 (2.1)	8.0 (2.0)	8.3 (2.1)	9.3 (2.5)
NAG	4.9 (0.6)	4.7 (0.6)	3.9 (0.4)	4.6 (0.5)	4.8 (0.7)
c) Placebo					
First course					
Total protein	75.3 (9.3)	70.9 (8.5)	81.9 (10.4)	73.1 (8.9)	95.1 (19.4)
Albumin	8.2 (2.3)	7.5 (2.7)	4.2 (2.0)	7.8 (3.5)	9.2 (4.6)
α_1-Microglobulin	5.2 (1.4)	12.0 (8.1)	8.7 (1.9)	6.6 (1.9)	4.8 (1.9)
NAG	5.0 (0.3)	5.6 (0.7)	5.7 (0.6)	4.6 (0.5)	6.2 (0.7)
Second course					
Total protein	83.6 (13.1)	82.1 (12.4)	84.2 (13.6)	91.9 (12.5)	90.3 (18.1)
Albumin	8.4 (1.9)	7.4 (1.8)	6.6 (1.4)	10.2 (2.2)	10.2 (1.7)

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Table I. Contd

Parameters	Pretreatment level	Post-treatment level			
		day 1	day 2	day 5	day 10
α_1-Microglobulin	7.8 (2.9)	7.6 (2.4)	12.1 (3.1)	14.8 (3.2)	9.4 (3.4)
NAG	6.3 (0.9)	6.0 (0.9)	7.3 (1.4)	7.5 (1.5)	7.6 (2.0)
Third course					
Total protein	104.6 (13.6)	82.6 (14.0)	84.0 (18.8)	83.5 (16.1)	81.9 (18.3)
Albumin	9.0 (3.1)	14.3 (3.4)	12.1 (2.8)	15.7 (4.2)	19.3 (5.3)
α_1-Microglobulin	7.7 (2.4)	12.0 (4.0)	8.5 (2.9)	6.3 (2.7)	8.8 (3.7)
NAG	6.5 (1.4)	7.0 (1.5)	7.2 (1.4)	7.1 (1.4)	7.1 (1.1)

a $p > 0.05$ ibandronic acid vs placebo.

NAG = *N*-acetyl-β-D-glucosaminidase.

meters were corrected to urinary creatinine. The upper limit of the reference intervals was 100 mg/g creatinine for total protein, 20 mg/g creatinine for albumin, 14 mg/g creatinine for MG, and 5 IU/g creatinine for NAG. The upper normal limit for serum creatinine was 115 μmol/L.

Statistical Evaluation

Statistical analyses were carried out using Friedman's ANOVA. The placebo bolus and placebo infusion groups were pooled for analysis.

Results

Proteinuria and enzymuria were compared in three groups of patients. In the first group, 23 patients received ibandronic acid 2mg (mean age 52 years, range 36–70 years). The second group of 28 patients received ibandronic acid 6mg (mean age 54 years, range 34–70 years) and, in the third group, 23 patients received placebo (mean age 52 years, range 34–67 years). The single injection/infusion of ibandronic acid or placebo was followed by a 4-week observation period, during which renal function parameters in patients' serum and urine were investigated.

Table I shows the mean urinary protein (total protein, albumin, MG) and enzyme (NAG) excretion during the 3-month study phase. No significant differences were observed in proteinuria or enzymuria levels between patients receiving ibandronic acid or placebo. Mean pre- and post-treatment levels of urinary parameters were in the normal range, with the exception of NAG, which was excreted at higher levels, on average, than the normal limit (5 IU/g creatinine) at various timepoints in all three treatment groups. This elevation of enzymuria was not statistically significant.

The frequency of pathological proteinuria, enzymuria and haematuria in patients before (day 0) and after (days 1–10) administration of ibandronic acid or placebo within three courses of treatment is shown in table II. Protein and enzyme levels varied in the same range with similar frequency between the three treatment groups.

Test-strip-positive haematuria was also detected before drug administration and during the follow-up period. Pretreatment haematuria was found in 9% of patients receiving ibandronic acid 2mg, 7% of patients receiving ibandronic acid 6mg, and 5% of patients receiving placebo. Patient monitoring during the 3-month treatment period on days 1–10 after administration of ibandronic acid 2 and 6mg revealed haematuria in 0–15% and 0–14%, respectively, and in 0–15% of patients in the placebo group.

Table III shows the mean serum creatinine values before, during and at the end of all three courses of treatment. Pretreatment serum creatinine exceeded the upper normal limit (115 μmol/L) in only one

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Table II. Percentage of patients with pathological proteinuria, enzymuria and haematuria in breast cancer patients with bone metastases receiving (a) ibandronic acid 2mg, (b) ibandronic acid 6mg, or (c) placebo

Parameters	Pretreatment frequency (mean)	Post-treatment frequency (mean)			
		day 1	day 2	day 5	day 10
a) Ibandronic acid 2mg					
First course					
Total protein	30.4	27.3	19.0	26.1	33.3
Albumin	26.1	13.6	9.5	8.7	14.3
α_1-Microglobulin	25.0	0[a]	11.1	33.3	0[a]
NAG	39.1	45.5	33.3	34.8	33.3
Blood	8.7	9.1	0	13.0	0
Second course					
Total protein	35.0	27.8	26.3	35.0	38.9
Albumin	5.0	5.6	10.5	20.0	22.2
α_1-Microglobulin	17.6	20.0	38.5	15.4	7.1
NAG	35.0	33.3	31.6	36.8	44.4
Blood	5.0	11.1	15.4	10.0	5.5
Third course					
Total protein	41.1	37.5	18.8	25.0	20.0
Albumin	17.6	25.0	12.5	6.3	20.0
α_1-Microglobulin	29.4	25.0	12.5	18.8	13.3
NAG	35.3	43.7	50.0	31.3	40.0
Blood	0	12.5	12.5	6.3	13.3
b) Ibandronic acid 6mg					
First course					
Total protein	25.0	40.7	25.0	39.3	18.5
Albumin	17.9	18.5	17.9	21.4	7.4
α_1-Microglobulin	15.8	27.8	15.8	30.8	11.1
NAG	35.7	35.7	32.1	32.1	29.6
Blood	7.1	11.1	14.3	3.6	3.7
Second course					
Total protein	13.0	22.7	36.4[a]	27.3	31.8
Albumin	17.4	13.6	31.8	31.8	22.7
α_1-Microglobulin	22.7	19.0	26.7	20.0	36.4
NAG	21.7	31.8	27.3	40.9	22.7
Blood	0	9.1	4.5	13.6[a]	13.6[a]
Third course					
Total protein	30.4	21.7	14.3	8.7	8.7
Albumin	30.4	17.4	19.0	8.7	17.4
α_1-Microglobulin	34.8	39.1	23.8	17.4	13.0
NAG	34.8	30.4	23.8	21.7	30.4
Blood	8.7	4.3	9.5	4.3	0
c) Placebo					
First course					
Total protein	36.4	13.0	21.7	9.1[a]	21.7

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Table II. Contd

Parameters	Pretreatment frequency (mean)	Post-treatment frequency (mean)			
		day 1	day 2	day 5	day 10
Albumin	18.2	17.4	8.7	9.1	13.0
α_1-Microglobulin	14.3	14.3	21.4	0	12.5
NAG	54.5	43.5	39.1	31.8	47.8
Blood	4.5	0	0	4.5	0
Second course					
Total protein	30.0	20.0	28.6	23.8	15.8
Albumin	15.0	10.0	4.8	14.3	15.8
α_1-Microglobulin	11.8	20.0	25.0	42.9[a]	16.7
NAG	50.0	55.0	47.6	42.9	38.9
Blood	5.0	10.0	0	4.8	10.5
Third course					
Total protein	40.0	25.0	20.0	10.0[a]	20.0
Albumin	30.0	25.0	10.0	20.0	30.0
α_1-Microglobulin	20.0	26.3	20.0	10.0	15.0
NAG	45.0	60.0	55.0	60.0	60.0
Blood	5.0	10.0	5.0	5.0	15.0

a $p < 0.05$ post-treatment frequency vs pretreatment frequency.

NAG = *N*-acetyl-β-D-glucosaminidase.

patient in the placebo group (157 μmol/L). During and after treatment, serum creatinine levels remained within the normal range in all patients who received ibandronic acid 2 or 6mg or placebo. A significant increase between the creatinine levels measured during the 3-month treatment period and post-treatment was observed in the placebo group only.

Discussion

This study shows that treatment with intravenous ibandronic acid does not impair renal function. In our study, test-strip analysis before and after ibandronic acid administration revealed that 26 (35%) of the tested urine specimens contained leucocytes. Most of these samples (21/26) showed no pathological proteinuria or enzymuria and, according to the clinical signs, could be interpreted as lower urinary tract infection.

Test-strip-positive haematuria was transient and, because of the presence of leucocyturia, was mostly attributed to post-renal causes. During treatment, hypertension, pyelonephritis and other urinary tract infections were recorded for more than 50% of our patients. The incidence of pyelonephritis and urinary tract infections was the same in the three treatment groups. A combination of haematuria and abnormal proteinuria was observed in only one patient before and after treatment with ibandronic acid 2mg. In total, haematuria and protein concentrations outside the normal range were detected in five of 28 patients treated with ibandronic acid 6mg. Similarly, simultaneous haematuria and abnormal proteinuria was seen in five of the 23 patients in the placebo group. Haematuria coupled with pathological albuminuria was detected in four patients from the placebo group and in three receiving ibandronic acid 6mg, and indicated glomerulopathy. Haematuria in combination with the excretion of MG outside the normal range was detected in five patients after treatment with ibandronic acid 6mg and in two patients in the placebo group, indicating tubulointestinal involvement. Taken together, these results indicate that the frequency of simultaneous haema-

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Table III. Serum creatinine concentration in breast cancer patients with bone metastases who received ibandronic acid 2 or 6mg or placebo

Treatment regimen	Pretreatment creatinine (μmol/L)		Creatinine during treatment (μmol/L)		Post-treatment creatinine (μmol/L)	
	mean (SD)	range	mean (SD)	range	mean (SD)	range
Ibandronic acid 2mg (n = 23)	84.8 (2.0)	68.0–105.0	86.9 (2.6)	62.0–110.0	89.4 (2.5)[a]	72.0–107.0
Ibandronic acid 6mg (n = 28)	80.9 (2.0)	58.0–102.0	84.7 (2.9)	59.0–114.0	84.8 (2.2)[a]	63.0–107.0
Placebo (n = 23)	83.4 (3.9)	66.0–157.0	80.0 (2.6)	51.0–112.0	89.1 (3.0)[b]	62.0–112.0

a Nonsignificant difference between post-treatment level and level during treatment ($p > 0.05$).

b Significant difference between post-treatment level and level during treatment ($p < 0.05$).

turia and proteinuria in the patients receiving ibandronic acid was similar to the placebo group.

Our results of quantitative protein measurements show that increased total protein excretion was closely paralleled by an increase of albuminuria in eight of the 23 patients (34.8%) receiving ibandronic acid 2mg and in 13 of the 28 patients (46.4%) receiving ibandronic acid 6mg, as well as in ten (43.5%) placebo-treated patients. MG was elevated together with total protein at approximately the same rate: 34.8% in the ibandronic acid 2mg group, 35.7% in the ibandronic acid 6mg group, and 43.5% in the placebo group. NAG and total protein were outside the normal range in 52%, 39% and 48% of patients receiving ibandronic acid 2mg, ibandronic acid 6mg or placebo, respectively. The frequency of pathological proteinuria and enzymuria in patients receiving ibandronic acid was similar to those receiving placebo. Elevations of urinary parameters were transient, and levels of NAG and proteins did not show any significant increase after ibandronic acid treatment.

Ibandronic acid treatment with 2mg injections and 6mg infusions does not demonstrate any evidence for the development of altered renal function, even in patients with initially high values of urinary proteins. By urinalysis, there were no cases of sustained renal dysfunction attributable to ibandronic acid. Assessment of renal function by serum creatinine measurement indicated no changes between pre- and post-treatment levels in any of the patients, including those who had received ibandronic acid 6mg. No significant changes in the urine and blood serum parameters were noted in the ibandronic acid groups compared with placebo-treated patients.

Our results compare favourably with data reported by Pecherstorfer et al., who investigated the effects of ibandronic acid 3mg, injected over 60–120 seconds, in 15 breast cancer patients with bone metastases.[25] When tested by the dipstick method, proteinuria was detected in five patients (33%) before treatment with ibandronic acid. Following drug administration, seven patients (47%) experienced slight transient proteinuria. Of these patients, six also presented with leucocyturia and three with microhaematuria. Serum creatinine levels and estimates of creatinine clearance were not affected by therapy.

Possible limitations of our study are the small patient population, and the short study period. Nevertheless, the lack of renal deterioration with ibandronic acid in our cancer patients is a clinically meaningful result. The majority of these patients were at risk of renal events because of prolonged use of chemotherapy and/or hormonal therapy. Importantly, most patients only experienced slight or moderate elevations of renal function parameters with ibandronic acid. That there were no cases of pronounced renal disturbances during treatment with ibandronic acid suggests the lack of nephrotoxicity with this agent. Methods used in our 3-month study for the evaluation of kidney function were sensitive and specific to detect earlier phases of nephrotoxic injury, negating the need for such invasive techniques as renal biopsies. Multiple measurements were also made, and the extent and the frequency of

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pathological proteinuria, enzymuria and haematuria after ibandronic acid administration did not differ from those pretreatment or from those in the placebo group. According to recent diagnostic strategies in nephrotoxic injury, combining the test-strip procedure for blood and leucocytes with turbidimetry to measure urine enzymes and proteins can detect tubulointerstitial nephropathies or microalbuminuria in earlier phases of renal complications.[13-19] Moreover, during the main efficacy trial, no significant differences in serum creatinine levels were observed between ibandronic acid and placebo groups during the 96-week study phase.[23]

The variation in proteinuria and enzymuria in the current study could be ascribed to previously existing renal dysfunction or the nephrotoxic effect of antitumour therapy. Systemic therapy of breast cancer and metastatic bone disease included hormonal treatment, chemotherapy and radiotherapy. Observations from different studies indicate that long-term systemic therapy is often associated with impairment of renal function caused by various antitumour agents as well as to synergistic effects of chemotherapy and radiation.[26,27] The observed variability of our results may have another cause. Hofmann and Guder[13] and Viberti et al.[28] have noted the biological variation of urinary analytes. The reported individual variability for urinary NAG and proteins ranges between 13% and 33% on average. Moreover, during treatment, cases of arterial hypertension, pyelonephritis and/or other urinary tract infections were recorded for more than 50% of studied patients.

These findings suggest that transient increases in the proteins and NAG excretion, such as those seen in this study, do not represent structural damage of nephrons caused by ibandronic acid treatment.

Conclusion

There was no evidence for the development of altered renal function in breast cancer patients with metastatic bone disease treated with three doses of intravenous ibandronic acid. Assessments of renal function by proteinuria, enzymuria, haematuria and serum creatinine measurements indicated no statistically significant changes in pre- and post-treatment levels between patients receiving 2mg injections and 6mg infusions of ibandronic acid or between patients receiving ibandronic acid and placebo. The lack of renal toxicity with ibandronic acid suggests that, unlike with other bisphosphonates, routine monitoring of renal functioning is not required during short-term therapy. Therefore ibandronic acid can be administered short term to breast cancer patients with metastatic bone disease without risk of renal toxicity.

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References

1. Fleish H. Bisphosphonates in bone disease: from the laboratory to the patient. New York: The Parthenon Publishing Group Ltd, 1995: 176
2. Kanis JA, O'Rourke N, McCloskey EV. Consequences of neoplasia induced bone resorption and the use of clodronate. Int J Oncol 1994; 5: 713-31
3. Scharla SH, Minne HW, Sattar P, et al. Therapie der Tumorhypercalciämie mit Clodronat: Einfluss auf Parathormon und Calcitriol. Dtsch Med Wochenschr 1987; 112: 1121-5
4. De Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996; 335: 1016-21
5. Lufkin EG, Argueta R, Whitaker MD, et al. Pamidronate: an unrecognized problem in gastrointestinal tolerability. Osteoporos Int 1994; 4: 320-2
6. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. Drug Saf 1999; 21: 389-406
7. Yates AJ, Percival CJ, Gray RE, et al. Intravenous clodronate in the treatment and retreatment of Paget's disease of bone. Lancet 1985; I: 1474-7

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8. Bounameaux HM, Schifferli J, Montani JP, et al. Renal failure associated with intravenous diphosphonates [letter]. Lancet 1983; I: 471
9. Francis MD, Slough CL. Acute intravenous infusion of disodium dihydrogen (I-hydroxyethylidene) diphosphonate: mechanism of toxicity. J Pharm Sci 1984; 73: 1097-100
10. Kanis JA, Preston CJ, Yates AJ, et al. Effects of intravenous diphosphonates on renal function [letter]. Lancet 1983; I: 1328
11. Markowitz GS, Appel GB, Fine PL. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol 2001; 12: 1164-72
12. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001; 7: 377-87
13. Hofmann W, Guder WG. A diagnostic programme for quantitative analysis of proteinuria. J Clin Chem Clin Biochem 1989; 27: 589-600
14. Hofmann W, Regenbogen C, Edel H, et al. Diagnostic strategies in urinalysis. Kidney Int Suppl 1994; 46: S111-114
15. Scherberich JE. Urinary proteins of tubular origin: basic immunochemical and clinical aspects. Am J Nephrol 1990; 10: 43-51
16. Price RG. Urinary enzymes, nephrotoxicity and renal disease. Toxicology 1982; 23: 99-134
17. Recio E, Villamil E, Recio C, et al. Utility of filtration markers to monitor the quality of glomerular function. Clin Nephrol 1992; 38: S8-13
18. Guder WG, Hofmann W. Markers for the diagnosis and monitoring of renal tubular lesions. Clin Nephrol 1992; 38: S3-7
19. Vanderlinde RL. Urinary enzyme measurements in the diagnosis of renal disorders. Ann Clin Lab Sci 1981; 11: 189-201
20. Mühlbauer RC, Bauss F, Schenk R, et al. Ibandronate, a potent new bisphosphonate to inhibit bone resorption. J Bone Miner Res 1991; 9: 1003-11
21. Pecherstorfer M, Herrmann Z, Body JJ, et al. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. J Clin Oncol 1996; 14: 268-76
22. Ralston SH, Thiébaud D, Herrmann Z, et al. Dose-response study of ibandronate in the treatment of cancer-associated hypercalcemia. Br J Cancer 1997; 75: 295-300
23. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003 Sep; 14: 1399-405
24. Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer. In press
25. Pecherstorfer M, Ludwig H, Schlosser K, et al. Administration of the bisphosphonate ibandronate (BM 21.0955) by intravenous bolus injection. J Bone Miner Res 1996; 11: 587-93
26. Rossi RM, Kist C, Wurster U, et al. Estimation of ifosfamide/cisplatinum-induced renal toxicity by urinary protein analysis. Pediatr Nephrol 1994; 8: 151-6
27. Verplanke AJ, Herber RF, de Wit R, et al. Comparison of renal function parameters in the assessment of cis-platin induced nephrotoxicity. Nephron 1994; 66: 267-72
28. Viberti GC, Mogensen CE, Keen H, et al. Urinary excretion of albumin in normal man: the effect of water loading. Scand J Clin Lab Invest 1982; 42: 147-57

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