J R Coll Physicians Edinb 2009; 39:4–9

CLINICAL

Bisphosphonate prescribing in chronic kidney disease

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ABSTRACT Osteoporosis and chronic kidney disease (CKD) are both increasingly prevalent with advancing age. Bisphosphonates are licensed for use in osteoporosis, but the appropriateness and safety of this class of drug in CKD is uncertain. This study assessed the use of bisphosphonates for persons with CKD in clinical practice. The prescribing pattern of bisphosphonates in all 595 persons attending renal services in one UK hospital was analysed. The mean estimated glomerular filtration rate (eGFR) of the population was 44 + 23 ml/min/1.73m^2. Bisphosphonate treatment was prescribed for 32 patients (5%), of whom 13 had an eGFR <30 ml/min/1.73m^2 and two patients received maintenance dialysis therapy. Thirty-nine (7%) patients were prescribed corticosteroid therapy; 9/23 with an eGFR >30 ml/min/1.73m^2 were not prescribed bisphosphonate medication. Twenty-two (4%) patients had osteoporosis; 5/9 with an eGFR >30 ml/min/1.73m^2 were not prescribed bisphosphonate medication. Bisphosphonate medication was not prescribed to a proportion of persons with early CKD (stages 1–3) who could potentially benefit from such therapy; conversely such treatments were used in some patients with severe CKD (stages 4 and 5). This pattern of bisphosphonate prescribing arguably reflects the uncertainty about the efficacy and safety of such treatment for persons with CKD.

KEYWORDS Bisphosphonate, chronic kidney disease, osteoporosis, prescribing, renal bone disease

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***February 2009***

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INTRODUCTION

Bone disease is commonly associated with chronic kidney disease (CKD), and the prevalence of skeletal abnormalities in those with end-stage renal disease approaches 100%. While renal osteodystrophy is the collective term for various types of uraemia-related bone remodelling, including hyperparathyroid bone disease, adynamic bone disease and osteomalacia,[1] persons with CKD can also develop osteoporosis. This group has a higher prevalence of risk factors for osteoporosis compared with the general population, including chronic metabolic acidosis, poor nutrition, vitamin D deficiency, hyperparathyroidism, pre-menopausal oestrogen deficiency in females, chronic use of heparin in haemodialysis patients, long-term steroid prescription for some renal conditions, hypogonadism and hyperprolactinaemia.[2]

Bisphosphonates are anti-resorptive agents that are of proven benefit in the prevention and treatment of postmenopausal and corticosteroid-induced osteoporosis.[3,4] They are also used in less common conditions where there is an increased risk of low trauma fracture, such as asymptomatic primary hyperparathyroidism, post-transplant bone disease, osteogenesis imperfecta and fibrous dysplasia.[2]

The use of bisphosphonate therapy in patients with CKD who sustain a bone fracture is curtailed by two main issues, appropriateness and safety. The diagnosis of osteoporosis in persons with reduced kidney function is challenging as other forms of renal osteodystrophy will also result in fragility fractures.[5] Some of these patients will already have reduced bone turnover and, given the mechanism of action of bisphosphonates, the use of these agents may be detrimental. The safety profile of bisphosphonate drugs in CKD is uncertain. Due to early concerns about the renal accumulation of bisphosphonates in rodent models[6] and reports of acute renal failure related to the rapid intravenous infusion of certain bisphosphonates,[7–9] persons with reduced renal function were excluded from clinical trials. In addition, approximately 50% of oral bisphosphonate is renally eliminated and the pharmacokinetics in renal impairment have not been fully elucidated.[10] Current guidelines, although specific for each drug, are therefore arbitrary. Table I summarises the manufacturers' recommendations for each bisphosphonate licensed in the UK;[11] most suggest avoidance if the creatinine clearance is low.

Given the changing demography of the general population and the greater prevalence of both osteoporosis and CKD with advancing age,[12] the appropriateness of bisphosphonate therapy for CKD patients is increasingly

TABLE 1 Summary of prescribing advice concerning renal function of the bisphosphonates currently licensed in the UK

Product	Manufacturer	Indication	Advice regarding renal impairment
Alendronate (Fosamax®)	Merck Sharp & Dohme	Osteoporosis – postmenopausal – corticosteroid – male	GFR <35 ml/min – not recommended
Disodium etidronate (Didronel PMO®)	Procter & Gamble Pharmaceuticals	Osteoporosis – postmenopausal – corticosteroid	Mild renal impairment – reduce dose Moderate or severe – avoid
Disodium pamidronate (Aredia Dry Powder®)	Novartis	Bone disease – malignancy-related – Paget's disease	CrCl <30 ml/min – avoid
Ibrandonic acid (Bondronat®) (Bonviva®)	Roche	Bone disease – malignancy-related Osteoporosis – postmenopausal	CrCl <30 ml/min – not recommended
Risedronate sodium (Actonel®)	Procter & Gamble Pharmaceuticals	Osteoporosis – postmenopausal – corticosteroid Bone disease – Paget's disease	CrCl <30 ml/min – contraindicated
Sodium clodronate (Loron®) (Bonefos®)	Roche Schering Health	Bone disease – malignancy-related	CrCl <10 ml/min – contraindicated CrCl 10–30 ml/min – reduce dose by 50%
Tiludronic acid (Skelid®)	Sanofi-Synthelabo	Bone disease – Paget's disease	CrCl <30 ml/min – contraindicated
Zoledronic acid (Aclasta®) (Zometa®)	Novartis (Aclasta®)	Bone disease – Paget's disease Osteoporosis – postmenopausal	CrCl <40 ml/min – not recommended
	Novartis (Zometa®)	Bone disease – malignancy-related	CrCl <30 ml/min – not recommended CrCl 30–60 ml/min – graded dose reduction

CrCl = creatinine clearance

relevant. We assessed the prescribing pattern of bisphosphonates in persons with an estimated glomerular fitration rate (eGFR) >30 ml/min/1.73m^2 (CKD stages 1–3) versus individuals with an eGFR <30 ml/min/1.73m^2 (CKD stages 4–5) in a population attending renal services in one UK hospital catchment area.

METHODS

Study population

The Ulster Hospital, Dundonald, Belfast, UK, is a modern, 280-bed hospital providing acute local services for a population of approximately 440,000 people. The renal unit was established in 2003 and offers all aspects of care for kidney disease, with the exception of acute transplantation facilities. All 595 patients with established chronic kidney disease that were known to the renal service on 21 September 2007 were included in this analysis. The internationally agreed classification of CKD stages 1–5 based on an estimated glomerular filtration rate (eGFR) was used to categorise renal function (Table 2). Calculation of eGFR in our region is based on the 4-variable Modification of Diet in Renal Disease[13] equation, incorporating age, gender, race and serum creatinine.

Data acquisition

All patients attending the renal unit have data prospectively recorded on an electronic database (eMed, Mediqual Health Informatics, Stevenage, UK). This includes demographic details comprising age and gender, primary renal diagnosis, other diagnoses/co-morbidities, current medications with dose and frequency of administration,

TABLE 2 Classification of chronic kidney disease and number of patients in each category

Stage	eGFR (ml/min/1.73m²)	Description Kidney function	Urinary or structural abnormalities	Patient numbers (total: 595)
1	90+	Normal	Present	36 (6%)
2	60–89	Mildly reduced	Present	67 (11%)
3	30–59	Moderately reduced	Present or absent	264 (44%)
4	15–29	Severely reduced	Present or absent	134 (23%)
5	<15	Very severe +/- dialysis-dependent	Present or absent	94 (16%)

renal function, other laboratory results and a renal timeline. There is a direct download of laboratory results from the hospital system, and clinical data are entered by medical staff. The database was complete for all demographic details, renal information and laboratory values. The other diagnoses/co-morbidities were based on patient interview and correspondence from referring physicians; additional information was specifically sought by senior clinical staff to enhance the overall utility of the database.

Those patients prescribed a bisphosphonate were identified by searching for both the generic and proprietary names of all agents in the current *British National Formulary*. A similar search was performed for corticosteroid therapy.

A diagnosis of osteoporosis or osteoporotic fracture was sought using all relevant codes in the secondary diagnoses section for each patient. The codes comprised osteoporosis, osteoporosis due to corticosteroids, senile osteoporosis, osteoporotic kyphosis, osteoporosis with pathological fracture of thoracic vertebrae, osteoporosis with pathological fracture of lumbar vertebrae, collapse of thoracic vertebrae due to osteoporosis, collapse of lumbar vertebrae due to osteoporosis and osteoporosis not otherwise specified.

Statistical analysis

Descriptive analysis of the demographics and clinical variables are reported as mean with standard deviation (SD) or median values with interquartile range (IQR) as appropriate to their distribution. The Mann-Whitney U test was used for comparative purposes in non-parametric analysis.

Values of $p<0.05$ were considered statistically significant. SPSS for Windows® (SPSS® Inc., Chicago, IL, USA) version 15.0 was employed for analyses.

RESULTS

Demographics

There were 595 patients with CKD known to the renal unit and included in the analysis. There were 328 (55%) men, and the median age was 70 (IQR 57–77) years (Table 3).

Chronic kidney disease

Of all the patients, 87 were on maintenance dialysis therapy, 84 were on haemodialysis therapy and three were on peritoneal dialysis. Seven patients were transplant recipients, and the mean eGFR in this group was 54 ml/min/1.73m². Table 2 details the number of patients in each CKD category. Almost half of the patients (44%) had stage 3 CKD, and 39% had severe or very severe renal impairment (stages 4 and 5). The mean eGFR, excluding those on dialysis, was 44 + 23 ml/min/1.73m².

Bisphosphonate therapy

A total of 32 patients were prescribed bisphosphonate therapy. There were 12 (38%) men, and the median age was 73 (IQR 65–80) years.

Agent and dose

Fifteen patients were prescribed 35 mg of risedronate sodium weekly. Alendronic acid was documented for 13 patients, all of whom were taking 70 mg weekly. Of the other four patients, three were taking ibandronic acid (each 34.5 mg weekly) and one patient was prescribed sodium clodronate at a dose of 7,280 mg per week (1,040 mg daily).

Indication

There was concurrent use of corticosteroid therapy in 19 patients (59%), three of whom had documented osteoporosis. Of the other patients, a further seven also had osteoporosis. Thus a bisphosphonate was prescribed for reasons other than the prevention of steroid-induced bone disease or treatment for osteoporosis in 6/32 patients (19%). One of these patients had myeloma-associated hypercalcaemia and one had previously sustained a fracture of the neck of femur. There was no available information on the reason for bisphosphonate prescription in the other cases.

Renal function

Thirteen (41%) of those prescribed a bisphosphonate had an eGFR less than 30 ml/min/1.73m², and two (6%) were receiving maintenance dialysis therapy. The mean age of this cohort was 78 (IQR 73–85) years; five were receiving corticosteroid therapy, and six had osteoporosis.

Corticosteroid therapy

Thirty-nine (7%) patients were prescribed corticosteroid therapy; 23 (59%) had CKD stages 1–3 and 16 (41%) had stages 4 and 5, including six patients on dialysis therapy (Table 3). Nine of the 23 patients with an eGFR over 30 ml/min/1.73m² were not prescribed bisphosphonate medication.

TABLE 3 Demographics of patients with chronic kidney disease

		N	Gender (N, %)		Age yr (median, IQR)	CKD stage	
			Male	Female		1–3	4+5
Total population		595	328 (55%)	267 (45%)	70 (57–77)	367 (62%)	228 (38%)
Corticosteroid therapy	All	39	20 (51%)	19 (49%)	72 (63–76)	23 (59%)	16 (41%)
	On BP	19	9 (47%)	10 (53%)	72 (63–76)	14 (74%)	5 (26%)
Patients with documented osteoporosis	All	22	6 (27%)	16 (73%)	77 (70–82)	9 (41%)	13 (59%)
	On BP	10	2 (20%)	8 (80%)	75 (66–83)	4 (40%)	6 (60%)

BP = prescribed a bisphosphonate.

Of the 19 who were receiving bisphosphonate therapy, five had an eGFR below 30 ml/min/1.73m^2, one patient was receiving regular haemodialysis therapy and in the others the eGFR ranged from 21–29 ml/min/1.73m^2. The mean eGFR of all 19 prescribed bisphosphonate treatment was 38 ml/min/1.73m^2. This was not significantly different from the 20 patients who were receiving corticosteroid therapy but without bisphosphonate treatment (U=142, p=0.18).

Osteoporosis

Osteoporosis was noted in 22 patients, of whom three had documented vertebral collapse. Nine (41%) had CKD stages 1–3 and 13 (59%) had stages 4+5, with two on maintenance dialysis therapy (Table 3).

Five of the nine patients with an eGFR over 30 ml/min/1.73m^2 were not prescribed bisphosphonate medication.

Of the ten who were receiving bisphosphonate therapy six had an eGFR below 30 ml/min/1.73m^2 of whom two received regular dialysis treatment. The mean eGFR of all ten in this group was 28 ml/min/1.73m^2. This was not significantly different from the 12 patients with documented osteoporosis who were not receiving bisphosphonate treatment (U=55, p=0.77).

DISCUSSION

The appropriate use and safety of bisphosphonate therapy in persons with chronic kidney disease is relevant given the prevalence of both osteoporosis and CKD in the ageing population.[12] Currently the majority of bisphosphonate manufacturers recommend that these agents should not be prescribed in persons with a creatinine clearance less than 30 ml/min.[4,11] However, this population is at higher risk of low bone mineral density than a comparable age and sex matched cohort. This study assessed the prescribing patterns of bisphosphonate therapy across a spectrum of CKD, where 7% of patients were taking corticosteroid therapy and 4% had documented osteoporosis. Overall, 5% of patients were prescribed a bisphosphonate, almost half of whom had an eGFR below 30 ml/min/1.73m^2.

Our data suggest that bisphosphonate therapy may be withheld from persons with early stages of CKD who could potentially benefit from such treatment; this may reflect uncertainty over the safety of such agents when there is reduced renal function. In patients on corticosteroid therapy and with an eGFR exceeding 30 ml/min/1.73m^2, more than a third of individuals (39%) were not prescribed a bisphosphonate. In patients with documented osteoporosis, more than half of those with an eGFR greater than 30 ml/min/1.73m^2 were not receiving a bisphosphonate.

Since patients with CKD are at higher risk of bone disease, independent of the prescription of corticosteroid therapy, prophylactic therapy with bisphosphonates may be of particular benefit to this group. Skeletal abnormalities, including adynamic bone disease and mixed renal osteodystrophy, probably begin by stage 3 of CKD.[14] However, pooled analysis of risedronate therapy does suggest a benefit in fracture reduction in patients with low bone mineral density and mild or moderate CKD.[15]

Half of all patients in our study who were on bisphosphonate therapy had an eGFR below 30 ml/min/1.73m^2. The prescribing recommendations for the four drugs used in this cohort are avoidance if the creatinine clearance is less than 35 ml/min (alendronic acid) or 30 ml/min (ibandronic acid, and risedronate sodium), or a reduction in dose by 50% if the creatinine clearance is in the 10–30 ml/min range (sodium clodronate).

However, the evidence of harm from bisphosphonate treatment in advanced CKD is not robust. A literature review suggests that the initial concern regarding deterioration in renal function associated with bisphosphonate therapy is unsubstantiated, particularly with oral administration. A pooled analysis of nine randomised placebo-controlled phase III trials involving risedronate concluded that this medication was safe even in severe CKD.[15] A total of 301 patients with stages 4 or 5 of CKD who received bisphosphonate therapy were considered, and the incidence of adverse events, both renal and non-renal related, was comparable between the placebo and treatment groups.

Additionally, this analysis supported the hypothesis that risedronate therapy was not only safe but also effective in this group. There was a significant reduction in vertebral fracture rate in all strata of CKD. This finding is of particular importance given the potential constellation of bony pathology in any individual with impaired renal function. It is improbable that there is isolated low bone mineral density in these persons but rather a mix of hyperparathyroidism, low bone mineral density, vitamin D deficiency or adynamic bone disease. Thus the report that irrespective of the underlying skeletal abnormality there was an improvement in a clinically relevant endpoint with bisphosphonate therapy in this cohort is of interest.

A reduction in the dose of bisphosphonate prescribed in patients with CKD may be intuitive, based on the assumption that there will be greater bone retention of these agents in the presence of reduced renal excretion. However, the limited data available suggest that dose reduction is not justified, at least when the creatinine clearance is 20 ml/min or more.[16]

We acknowledge the limitations of our study design. It captures cross-sectional data at a single point of time; longitudinal data, which is of greater utility, is best provided by prospective collection. Additionally, the actual number of patients with severe CKD prescribed bisphosphonate therapy was small, and any specific contraindications or intolerance of bisphosphonates were unknown as these data were not extractable from the dataset.

The robustness of the diagnosis of osteoporosis is equivocal. National guidelines suggest that persons in high-risk groups for osteoporosis should have bone densitometry testing, but no data that evaluate compliance with this directive in patients with CKD are available. The number of patients in this study whose diagnosis was based on imaging was unknown, and the relationship between low bone mineral density and fractures in persons with impaired renal function is not established as robustly as in the general population. A clinical diagnosis, if based on the occurrence of a low fragility fracture, is also potentially misleading given that other forms of renal osteodystrophy will also result in this clinical outcome. Rather than invalidating the analysis, however, we feel that the challenges in diagnosis demonstrated in this study are reflective of common clinical practice in the UK.

Consistent with UK guidelines, the majority of stage 3 CKD in our region is managed by primary care clinicians: 264 patients is 0.06% of the 440,000 catchment population, with the expected percentage in adults of 4.7%,[17] and a substantial proportion of those with stage 4 CKD were also unknown to the renal team. It would be of interest to determine the prevalence of bisphosphonate prescribing in this CKD population managed solely in general practice, and also in an age- and gender-comparable group with normal renal function. It may be that prescribing is not any more restricted in this cohort than the general population but that there is global underutilisation of these agents in persons with osteoporosis or at risk of glucocorticoid-mediated bone thinning.

CONCLUSION

Assessing the utility of bisphosphonate therapy in patients with CKD is relevant given the prevalence of risk factors for osteoporosis in this population. In this analysis there is evidence that a proportion of CKD patients with an eGFR greater than 30 ml/min/1.73m^2, who could potentially benefit from bisphosphonate therapy, are not prescribed this medication. Conversely, more than half of all bisphosphonates were prescribed to patients with an eGFR less than 30 ml/min/1.73m^2. This arguably reflects concern regarding the safety and utility of this class of drug in persons with reduced renal function.

Despite the complexity of skeletal abnormalities associated with reduced renal function and the practical difficulties in the precise diagnosis of the bone architecture in clinical practice, there is evidence to suggest that bisphosphonate treatment reduces fracture risk without an increase in adverse events in patients with CKD. While a dose reduction in such patients may be advocated based on pharmacokinetic studies, the literature to support this is limited. Appropriate prospective trial data with bone histomorphometry and clinically important endpoints in the CKD population are awaited to guide therapy.

Acknowledgements AE Courtney is funded by the Northern Ireland Kidney Research Fund.

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