Can oral bisphosphonates be given to people with renal impairment to treat osteoporosis?

Prepared by UK Medicines Information (UKMi) pharmacists (or other as appropriate) for NHS healthcare professionals

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Background

The prevalence of osteoporosis and chronic kidney disease (CKD) increases with age and with the deterioration of kidney function there is an increase in the incidence of renal bone disease [1]. Bisphosphonates inhibit bone resorption and increase bone mineral density by altering activation and function of osteoclasts [2]. There are three oral bisphosphonates used for the primary and secondary prevention of osteoporotic fragility fractures in the UK: alendronic acid, ibandronic acid and risedronate sodium. They are recommended first line where the 10-year probability of fragility fracture is above the treatment threshold [3].

Bisphosphonates are not metabolised or taken up by other organs, and the residual drug that is not absorbed by osteoclasts is excreted by the kidney [2,4]. There has been concern over excessive accumulation of bisphosphonates in the skeleton, resulting in over suppression of bone remodelling, when they are used in patients with renal impairment [4]. Bisphosphonates can be associated with nephrotoxicity, which complicates their use further in patients with impaired renal function [2].

Answer

All bisphosphonates are associated with several rare but significant side-effects, which should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card scheme. These include:

- Atypical femoral fractures [5]
- Osteonecrosis of the jaw [6]
- Osteonecrosis of the external auditory canal [7]

Other adverse effects of bisphosphonates include gastrointestinal side-effects, influenza-like illness and renal impairment [8].

Advice regarding the dosing of bisphosphonates in renal impairment is conflicting. Dosing advice for the bisphosphonates suggested by the Summaries of Product Characteristics (SPCs) is summarized in table 1. Table 2 summarises the dosing advice provided by the Renal Drug Database [9].

Table 1: Manufacturers' dosing advice for bisphosphonates in renal impairment

Bisphosphonate	Dosing advice in renal impairment
Alendronic acid (Fosamax)	No dosage adjustment is necessary for patients with creatinine clearance (CrCl) >35mL/min. Alendronic acid is not recommended for patients with renal impairment (CrCl <35mL/min), due to lack of experience [10].
Ibandronic acid (Bonviva)	No dosage adjustment is necessary for patients with mild or moderate renal impairment (CrCl ≥30mL/min). Ibandronic acid is not recommended for patients with a CrCl <30mL/min due to limited clinical experience [11].
Risedronate (Actonel)	No dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30mL/min). The use of risedronate sodium is contraindicated in patients with severe renal impairment (CrCl <30mL/min) [12].

Table 2: Specialist dosing information taken from the Renal Drug Database [9].

Bisphosphonate	Dosing advice in renal impairment
Alendronic acid	• GFR*: 35-50mL/min – Dose as in normal renal function • GFR: <35mL/min – Avoid Anecdotally, several renal units have successfully used either 70mg weekly or standard doses of all preparations in patients with CKD 3, 4 and 5. If using in patients with end stage renal disease (ESRD), ensure the patient has an adequate parathyroid hormone (PTH) level, at least 3 times the upper limit of normal.
Ibandronic acid	• GFR: 30-50mL/min – 50mg every 48 hours • GFR: 10-30mL/min – 50mg weekly • GFR: <10mL/min – 50mg weekly
Risedronate sodium	• GFR: 30-50mL/min – Dose as in normal renal function • GFR: 10-30mL/min – No definitive dose recommendation given • GFR: <10mL/min – No definitive dose recommendation given Renal clearance is decreased by 70% in patients with CrCl<30 mL/min. If using in patients with ESRD, ensure the patient has an adequate parathyroid hormone (PTH) level, at least 3 times the upper limit of normal.

* GFR – Glomerular Filtration Rate

The use of bisphosphonates in people with CrCl above 30-35mL/min (refer to individual SPC for specific CrCl value) falls within the terms of the product license and therefore dosage adjustment is not required at this level.

Published literature

Data about the long-term use of oral bisphosphonates in people with renal impairment come from the following main studies.

The first-study is based on the *post hoc* analysis of nine randomised, double-blinded, placebo-controlled trials investigating the effect of oral risedronate 5mg daily on postmenopausal women. The studied population consisted of 8996 women, with a mean age of 75 years. The women were identified as having kidney impairment on the basis of their CrCl, calculated by the Cockcroft Gault method. Of the patients studied, 48% were classified as having mild renal impairment (CrCl 50-80mL/min), 45% were in the moderate renal impairment group (CrCl 30-50mL/min) and 7% in the severe group (CrCl <30mL/min). The median CrCl in the 'severe renal impairment' group was 26.4mL/min and the interquartile range was 23.1-28.5mL/min (lowest value 13.2mL/min), implying that there may have been relatively few women in the group with a CrCl at the lower end of this range. The women in the treatment arm experienced no increased incidence of adverse events compared to placebo, with an average duration of exposure to risedronate of 2 years. There were no statistically or clinically significant differences in the incidence of overall, urinary- and renal function– related, adverse events between treatment groups in the subgroups of patients with severe, moderate, or mild renal impairment. Evaluation of changes from baseline in serum creatinine over 24 months of treatment period revealed no difference in renal function between the placebo and risedronate groups in any of the renal impairment subgroups. Risedronate treatment resulted in significant increase in bone mineral density (BMD) and reduction in vertebral fractures compared to women treated with placebo. Mean percent changes (SD) from baseline to endpoint in lumbar spine BMD were -1.37% (1.72%) in the placebo group versus +4.23% (1.82%) in the risedronate group in patients with severe renal impairment; -0.47% (0.50%) in the placebo group versus +4.33% (0.51%) in the risedronate group in patients with moderate renal impairment; and -0.14% (0.19%) in the placebo group versus +3.96% (0.18%) in the risedronate group in patients with mild renal impairment. The *p* value for all comparisons was <0.001 [13].

Limitations of this study include the study design, the differences between studies in the methods used for fracture assessment and the lack of women with severely impaired renal function. The authors state that their results may not apply to patients who have renal failure known to be related to a systemic or renal-specific intrinsic cause, patients with ESRD, patients on dialysis, or patients pre- and post-renal transplantation They conclude that additional studies are needed to establish the safety and efficacy of risedronate treatment in patients with ESRD or stage 5 CKD (GFR<15 mL/min) [13].

The second study is a secondary *post hoc* data analysis of a randomised, placebo-controlled clinical trial in 6458 postmenopausal women which investigated the effects of oral alendronate over 3-4 years [14]. The dose of alendronate was 5mg per day for the first 2 years, increased to 10mg daily for the remainder of the trial [15]. The renal function was estimated using the Cockcroft Gault method and was categorised into normal (CrCl ≥60mL/min), moderately reduced (CrCl 45-59mL/min) or severely reduced renal function (CrCl<45mL/min). The subgroup of postmenopausal women that were identified as having severely reduced renal function consisted of 581 women, with a mean age of 75 years. Throughout the study period the subjects experienced no significantly increased incidence of adverse events compared to people with a normal CrCl ($p = 0.189$), including adverse renal events ($p = 0.68$). There was a small, statistically significant increase in serum creatinine observed from baseline to the 3-year follow-up (mean at baseline: 1.05 ± 0.16 versus mean at follow-up: 1.06 ± 0.16;

p < 0.00001). This effect was the same in those with and without reduced renal function, and in the groups treated with placebo and alendronate. Women with severely reduced renal function who took alendronate had a 5.6% (95% CI: 4.8-6.5) increase in total hip BMD compared with 4.8% (95% CI: 4.6-5.0) among women with normal to moderate renal dysfunction (*p*=0.04). Alendronate treatment, compared with placebo, resulted in a reduced risk of clinical fractures across all renal impairment subgroups (OR = 0.8; 95% CI: 0.70-0.9) [14].

It is important to note that the group of women with severely reduced renal function in this analysis was predominantly comprised of individuals with CrCl above 30mL/min. These findings therefore cannot be directly extended to people with ESRD. Additionally, the study was a secondary post hoc data analysis, and therefore had limited power to assess interactions between renal function, alendronate therapy, and fracture outcomes [14].

The third study is a randomised, placebo-controlled pilot trial investigating the effect of oral alendronate 70mg weekly, or placebo, on vascular calcification in patients with CKD stages 3 and 4. The study was run for 18 months and comprised of 50 subjects, 70.8% male, with a median age of 64.5 years. The study assessed a secondary endpoint of renal function after 18 months of treatment. The renal function of participants was determined by their glomerular filtration rate, estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. The mean estimated GFR value was 35.1mL/min/1.73m^2 and no patients with a CrCl below 25mL/min were enrolled in this study. Adverse effects were similar in both groups. Kidney function deteriorated at 18 months in those treated with alendronate when compared to the placebo group, characterised by a decrease in eGFR of -1.2mL/min/1.73m^2.(95% CI:-4.0-1.7; *p* = 0.3). However, this decrease was neither statistically nor clinically significant. It is important to interpret these results with caution due to small study size and the baseline differences between the groups at study start [16].

The studies discussed above provide some limited reassurance that the safety and effectiveness of bisphosphonates is not affected in people with moderately reduced CrCl however much more research is needed to determine the safety of treatment across the spectrum of renal impairment, particularly in patients with CKD stages 4 and 5.

The inhibition of osteoclastic activity induced by bisphosphonates has raised concerns about adynamic bone disease due to excessive suppression of bone remodelling. The evidence behind this remains inconclusive and more theoretical rather than based on good quality evidence. Cases of adynamic bone disease have been previously reported in an observational study involving 13 subjects with CKD on bisphosphonate therapy [17]. Increasing age, diabetes, malnutrition, calcium overload, inflammation and hypoparathyroidism are all risk factors for adynamic bone disease and these should be taken into account prior to initiating bisphosphonates in patients with CKD [1]. It is important to recognise that a recent systematic review highlighted that the evidence of the effectiveness of bisphosphonates on BMD among patients with CKD who had not received a transplant remains conflicting and insufficient. Additionally, the evidence on fracture risk reduction and the safety profile of bisphosphonates among patients with CKD was limited. The published evidence available to date may have limited applicability to the general population of patients with CKD. Diabetes, for example, is an important risk factor for fractures, and is prevalent among patients with CKD. Because of the lack of reporting in the studies, it is unclear whether diabetes status could have influenced the outcomes. More research is needed to determine the best options for patients across the spectrum of CKD to improve BMD and prevent fractures with minimal risk for adverse outcomes. In particular, we need more data among patients with stage 3 to 5 CKD. Studies should be adequately powered to show a reduction in the risk for fractures and should have sufficient follow-up (≥3 years) [18].

Guidance from expert bodies

Kidney disease – improving global outcomes (KDIGO 2017) clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) provides the following advice to managing osteoporosis in patients with chronic kidney disease [19]:

- Patients with CKD stages 1-2 with osteoporosis or high risk of fracture should be managed similarly to the general population.
- Patients with CKD stages 3a-3b with normal levels of PTH and osteoporosis and/or high risk of fracture should be managed similarly to the general population.
- For patients with CKD stages 3a-5D, with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, treatment choices should take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD. Bone biopsy may be performed to help guide therapeutic decisions. Additionally, treatment specific side effects must also be considered e.g. bisphosphonates will exacerbate low bone turnover.

Neither the National Osteoporosis Guideline Group (NOGG 2017 clinical guideline), nor the NICE technology appraisal (bisphosphonates for osteoporosis) contain any specific advice for managing osteoporosis in patients with impaired renal function [20,21].

Summary

- In the main, bisphosphonates are not metabolised and are excreted unchanged in urine.
- Oral bisphosphonates are licensed for the primary and secondary prevention of osteoporotic fractures in patients with CrCl as low as 30-35mL/min (see individual SPCs for specific information).
- Whilst there are data confirming safety and efficacy in patients with impaired renal function, scarce data exists to support the use of bisphosphonates in patients with CKD stages 4 and 5, thus more studies are needed.
- Nephrotoxicity is a potential adverse effect of bisphosphonates; however previous studies of patients with CKD have not shown greater deterioration in kidney function in patients using bisphosphonates compared with control groups.
- Cases of adynamic bone disease associated with bisphosphonate use have been reported in people with CKD. Patients should be carefully assessed, taking into account any risk factors for adynamic bone disease, prior to initiating bisphosphonate therapy.

Limitations

- This summary covers the use of oral bisphosphonates that are licensed in the UK for osteoporosis.
- This Q&A does not cover the use of bisphosphonates for vascular calcification.
- This summary does not include therapeutic management of osteoporosis in patients with renal transplant.

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Search strategy
1. Embase (exp "BISPHOSPHONIC ACID DERIVATIVE"/ AND exp "KIDNEY FAILURE"/) AND OSTEOPOROSIS/) [DT 2016-2020] [Humans])
2. Medline (exp DIPHOSPHONATES/ AND exp "RENAL INSUFFICIENCY"/) AND OSTEOPOROSIS/) [DT 2016-2020] [Humans])
3. Micromedex (alendronate sodium, risedronate sodium, ibandronate sodium)
4. In-house renal databases/ resources
5. Internet Search (NICE, Google, Clinical Key)
6. Cochrane Library (bisphosphonate and chronic kidney disease, bisphosphonate and renal)