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

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Background

Bisphosphonates are inhibitors of bone resorption and increase bone mineral density by altering the activation and function of osteoclasts. Four oral bisphosphonates are currently licensed for treatment of osteoporosis in the UK; alendronate, disodium etidronate, ibandronic acid and risedronate. The National Institute for Clinical Excellence has reviewed three bisphosphonates (alendronate, etidronate and risedronate) and concluded by recommending their use for both primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women.

In the main, bisphosphonates are not metabolized and are excreted unchanged in urine. There are concerns about using them in chronic kidney disease (CKD) and end-stage renal disease (ESRD) because of their potential nephrotoxicity and hypocalcaemic effects and also in older people (because of their increased risk of renal failure complicating other risk factors for osteoporosis). Adynamic bone disease is also a serious concern and it is recommended that it is excluded before initiating bisphosphonates in people with CKD or on renal dialysis.

Answer

Whilst bisphosphonates are widely used and have a reasonably good safety profile, there are a number of serious side effects that require monitoring. These include:

- Upper gastrointestinal effects
- Renal toxicity
- Influenza like illness
- Osteonecrosis of the jaw

The table below includes details from the Summaries of Product Characteristics for the four bisphosphonates being considered.

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Advice on Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax)</td>
<td>Use in renal impairment: No dosage adjustment is necessary for patients with GFR(^a) greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.</td>
</tr>
<tr>
<td>Disodium etidronate (Didronel PMO)</td>
<td>Contraindicated in the treatment of patients with severe renal impairment. Due to the lack of clinical experience the treatment of patients with impaired renal function should be undertaken with due caution. The use of etidronate disodium is discouraged in patients with severely impaired kidney function. In patients with impaired renal function or a history of kidney stone formation, serum and urinary calcium should be monitored regularly.</td>
</tr>
<tr>
<td>Ibandronate (Bonviva)</td>
<td>No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal or greater than 30 mL/min. Bonviva is not recommended for patients with a creatinine clearance below 30 mL/min due to limited clinical experience.</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Renal Impairment: No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30ml/min).</td>
</tr>
</tbody>
</table>

\(^a\) GFR – Glomerular Filtration Rate
The use of bisphosphonates in people with glomerular filtration rates (GFR) above 30-35mL/min generally falls within the terms of the product license and dosage adjustment is not needed at this level.

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

The first study\(^1\) is based on an analysis of data from nine placebo controlled clinical trials of risedronate in 8996 osteoporotic women. The women were classified according to their renal function, estimated by their creatinine clearance (CrCl) calculated by the Cockcroft Gault method. Risedronate 5mg daily was shown to be safe and effective in osteoporotic women with mild (CrCl 50-80mL/min), moderate (CrCl 30-50mL/min) and severe (CrCl <30mL/min) age-related renal impairment. These women experienced no increased incidence of adverse events compared with placebo, with an average duration of exposure to risedronate of 2 years.

301 patients who took risedronate were in the “severe” renal impairment group. Whilst the range of CrCl in this group was 13.2-29.9mL/min, the median CrCl in this was 26.4mL/min and the inter-quartile range was 23.1-28.5mL/min, implying that there may have been relatively few women in the group with a CrCl at the lower end of this range.

Overall it was concluded that risedronate 5mg daily was safe and effective in the studied population, even in those with CrCl of 15-30mL/min. This study was in patients with age-related renal impairment and the authors noted the need for studies to establish the safety and efficacy of risedronate in ESRD or stage 5 CKD (CrCl <15mL/min). The authors did not find any evidence of risedronate causing greater suppression of bone turnover or impairment of mineralisation in the patients studied. However, they advise that any clinician who suspects adynamic bone disease in a patient with osteoporosis and stage 4 CKD (CrCl 15-30mL/min), should perform a bone biopsy to exclude this possibility.

The second study\(^1\) used data from 6458 subjects from the Fracture Intervention Trial. This was a placebo controlled randomized clinical trial of alendronate in post menopausal women. The renal function was estimated, using Cockcroft Gault, for these subjects allowing them to be categorized as having severely reduced renal function (CrCl <45mL/min) or moderately reduced or normal renal function (>45mL/min). There were 581 women with CrCl <45mL/min (9.9% of the sample).

Women with severely reduced renal function who took alendronate had a higher increase in hip bone mineral density (BMD) compared to those with CrCl>45mL/min but similar increases in spinal and femoral neck BMD. The risk of fractures was higher in women with CrCl<45mL/min. Alendronate reduced the risk of fracture compared to placebo regardless of renal function. There was no difference in adverse events between the two groups, (CrCl>45mL/min vs. CrCl<45mL/min), including adverse renal events.

It is important to note that the group of women with “severely reduced renal function” in this analysis predominantly comprised individuals with CrCl above 30mL/min. These findings therefore cannot be directly extended to people with ESRD or on dialysis. The authors note the concern about using bisphosphonates in ESRD, as anti-resorptive agents may promote the development of adynamic bone disease. They also state that, whilst alendronate was not associated with an increased fracture risk in this study, clinically relevant trials are required to determine the degree of risk in people with severe CKD and end-stage renal failure.

This study was commented upon by Ott et al\(^1\) who added further caution to the extrapolation of these data to people with CKD stages 4 and 5 (i.e. CrCl <30mL/min and <15 mL/min respectively). The risk of low turnover bone disease is highlighted (i.e., adynamic bone disease) by the authors who cite cases subsequently reported by Amerling et al\(^\text{10}\). This is a series of thirteen cases of adynamic bone disease presenting in people with CKD stages 2-4 that were all prescribed oral bisphosphonates (alendronate or risedronate) for between 4 months and 5 years. All had been fracture free but with low BMD consistent with osteoporosis or osteopenia. Bone biopsies were indicative of adynamic...
bone disease. Whilst acknowledging the limitations of data derived from an uncontrolled observational study, Amerling et al discourage the use of bisphosphonates in CKD.

The different methods used to estimate GFR are compared in a retrospective review of patients in an osteoporosis clinic. 106 patients were included in the main analysis; the Modification of Diet in Renal Disease (MDRD) method had been used to estimate GFR prior to initiating bisphosphonates. In 10 patients (9.4%) contraindication to bisphosphonate (i.e. GFR <30mL/min) use differed depending on the method used to estimate GFR. In 9 of these patients, the MDRD method estimated the GFR to be above 30mL/min/1.73m² whereas the Cockcroft and Gault (CG) formula estimated it to be less than 30mL/min. The authors conclude that prescribers should use both estimates of GFR before prescribing bisphosphonates to older adults with renal insufficiency.

Two large studies discussed above provide some reassurance that the safety and effectiveness of bisphosphonates is not affected in people with reduced CrCl. Better data from longer and larger studies are however required to fully understand their use in people with ESRD or on dialysis. In the absence of definitive data, reducing the oral bisphosphonate dose by half has been suggested in people with stage 5 CKD who are fracturing because of osteoporosis or who are taking chronic corticosteroids. The fact that bisphosphonates are used in practice in the UK is acknowledged and empirical dosing information is available for some bisphosphonates.

A recent US study used national data sets from 2005-8 to estimate the prevalence of renal impairment in women with osteoporosis. The study concluded that nearly a quarter of postmenopausal women with osteoporosis have moderate renal impairment (GFR 30-59mL/min) and that about 3% would be ineligible for bisphosphonate use (GFR<35mL/min). These proportions would be higher in older age groups. The authors note the need for better alternatives to bisphosphonates in women with osteoporosis and severe renal impairment.

Summary

Oral bisphosphonates are licensed for use in people with creatinine clearance (CrCl) as low as 30-35mL/min. There are data confirming that the effectiveness and safety of bisphosphonates, in women with osteoporosis, are not affected by impaired renal function (CKD 1-3); but this finding has not been confirmed in people with CKD and stages 4 and 5 including those with ESRD or on dialysis. Cases of adynamic bone disease associated with bisphosphonate use have been reported in people with CKD stages 2-4. Until there are better data in these groups, oral bisphosphonates should be used with care to treat osteoporosis in people with CKD. A renal specialist should be consulted about using these agents in people with CKD stages 4 and 5 and, if used, their use should be reviewed if renal function deteriorates. Care is also needed in estimating GFR, by cross-checking MDRD estimates with the Cockcroft and Gault formula; particularly in people with CKD stage 3-5, so that renal function is not-overestimated. It is also important to recognise that people with CKD may also have elements of renal bone disease which will complicate management.

Limitations
This summary covers the use of oral bisphosphonates that are licensed in the UK for osteoporosis.

References

10. Summary of Product Characteristics - Didronel PMO. Procter & Gamble Pharmaceuticals UK Limited accessed via http://emc.medicines.org.uk/. 20/7/14 (Date of revision of Text 8/6/12)
11. Summary of Product Characteristics - Bonviva. Roche Products Limited accessed via http://emc.medicines.org.uk/. 20/7/14 (Date of revision of Text 30/12/13)
12. Summary of Product Characteristics - Actonel 30mg Warner Chilcott UK accessed via http://emc.medicines.org.uk/. 20/7/14 (Date of revision of Text 19/6/13)
Date of check
1 August 2014

Search strategy
Medline exp Diphosphonates and exp Renal Insufficiency and Osteoporosis (limited 2012-2014 and Human)
Embase exp Bisphosphonic Acid Derivative and exp Kidney Failure and Osteoporosis (limited 2012-2014 and Human)
In-house data bases and resources
Micromedex
Clinical experts – specialist renal pharmacists: North Bristol NHS Trust