Use of bisphosphonates in renal impairment

By Matthew Fanning

Learning objectives

After reading this article you should be able to:
- Discuss the pathophysiology of renal osteodystrophy
- Describe the major risks of bisphosphonate use in renal impairment and dialysis
- Make recommendations for the management of osteoporosis in patients with renal impairment including those undergoing dialysis.

Competencies addressed:
3.1.1, 3.1.2, 3.1.3, 3.1.4

Case background

Mr MD is an 82-year-old nursing home resident. His past medical history includes:
- right cerebral ischaemic stroke (2001)
- bilateral carotid stenosis
- chronic renal failure (haemodialysis Monday, Wednesday and Friday)
- osteoporosis (history of fragility fractures)
- gastro-oesophageal reflux disease
- ischaemic heart disease
- hypertension
- dyslipidaemia
- gout.

He is currently taking the following medications:
- Alendronate 70 mg tabs – 1 tablet once weekly
- Allopurinol 100 mg tabs – 1 tablet every 2nd day
- Aspirin 100 mg tabs – 1 tablet daily
- Atorvastatin 40 mg tabs – 1 tablet daily
- Calcitriol 0.25 mcg caps – 1 capsule after haemodialysis three times weekly
- Fentanyl 25 mcg/hr patch – 1 patch every 72 hours
- Metoprolol 50 mg tabs – 1 tablet twice daily
- Omeprazole 20 mg tabs – 1 tablet daily
- Ramipril 2.5mg tabs – 1 tablet each morning
- Temazepam 10 mg tabs – 1 tablet at night.

He has recently been admitted to the aged care facility and the GP has requested a RMMR as part of his comprehensive medical assessment.

Introduction

Renal osteodystrophy encompasses a spectrum of metabolic bone disorders that are common in people with severe renal impairment. It is caused by a derangement of normal bone metabolism arising from reduced circulating active metabolites of vitamin D. This leads to decreased intestinal absorption of calcium, increased serum phosphate and secondary hyperparathyroidism. (Figure 1)

Most patients with renal osteodystrophy present with osteitis fibrosa alone or with osteomalacia. Osteitis fibrosa is a condition characterised by abnormally high bone turnover resulting in bone pain and pathological fractures, and usually responds well to treatment with calcitriol. Some of these patients may progress to tertiary hyperparathyroidism where parathyroid hormone (PTH) is elevated despite restoration of serum calcium.
Bisphosphonate use in CKD

Bisphosphonates form the mainstay of treatment of post-menopausal osteoporosis. However, there is very little evidence for their use in osteoporosis in those with CKD. There is general agreement that the proven benefits are likely to translate to people with CKD. However, current recommendations limit their use in patients with advanced renal impairment because of safety concerns. There are two broad areas of concern about the safety of bisphosphonates in CKD.

i. Direct nephrotoxicity: This appears to be of main concern in the oncological setting where high doses of bisphosphonates are used. While there is no strong evidence to support their safety, expert opinion generally agrees the risks are small when used in appropriate doses and according to guidelines for osteoporosis.

ii. Effects on the skeleton itself: Since bisphosphonates potently inhibit bone resorption, there is a risk that this may worsen bone quality in a population that has a very low bone turnover rate. However, subgroup analyses have failed to prove this as clinically significant except in adynamic bone disease.

Due to the above concerns, patients with elevated serum creatinine were excluded from the large clinical trials with alendronate and risedronate. However, a recent analysis of the clinical trials identified a subgroup of patients receiving risedronate 5 mg daily who had an overestimated glomerular filtration rate (GFR) despite having an actual CrCl <30 mL/min (n=301). The analysis showed no significant difference in efficacy (in terms of fracture risk reduction) or adverse effects (including renal adverse drug reactions (ADRs)) between the cohort with CrCl <30 mL/min and the cohort with CrCl >30 mL/min. The study authors concluded that risedronate may be used in those with CrCl <30 mL/min but possibly at reduced dose, the safety and efficacy of alendronate in this cohort of patients.

Additional management issues of renal osteodystrophy in CKD

Calcitriol, calcium supplementation (if necessary, guided by serum calcium) and phosphate restriction form the mainstay of treatment of renal osteodystrophy. For treatment of hypocalcaemia in patients undergoing haemodialysis, calcitriol should be dosed three times a week after each treatment.

Case discussion

Mr MD is at an increased risk of fracture due to chronic renal failure and subsequent osteodystrophy. Furthermore, use of fentanyl, temazepam and anti-hypertensives increases his risk of falling. As all forms of osteodystrophy are associated with a reduced bone mineral density, diagnosis of osteoporosis should only be made after excluding other related disorders of deranged bone metabolism (e.g. ostestis fibrosa, osteomalacia). The safety and efficacy of alendronate has not been well established in renal impairment. However, small studies and expert opinion suggests that they are well tolerated and confer an increased bone mineral density in all stages of renal impairment and during haemodialysis. While there is some consensus that bisphosphonates may be used in those with a CrCl of 20–30 mL/min at a reduced dose, the use of alendronate is discouraged in by haemodialysis in a similar manner to that in individuals with normal renal function. The kinetics of other bisphosphonates are less well understood, but should be similar to that of clodronate. However, the authors cautioned against using repeated doses of bisphosphonates because of a lack of safety data.

In a short term trial, 31 healthy haemodialysis patients were treated with low dose alendronate (40 mg/week) for six weeks. This appeared to be well tolerated and was associated with a small increase in vertebral bone mineral density. However, further trials with longer durations are necessary to establish the safety and efficacy of alendronate in this cohort of patients.

Figure 1. Pathogenesis of renal secondary hyperparathyroidism.

- Decreased formation of 1,25(OH)2D
- Reduced suppression of PTH by 1,25(OH)2D
- Decreased intestinal calcium absorption
- Increased serum phosphate
- Increased PTH secretion
- Secondary hyperparathyroidism

patients undergoing dialysis due to a lack of quality safety data.

**Actions and recommendations**

The following recommendations were carried out after discussion with Mr MD, his GP and nursing staff:

1. Alendronate is predominately renally cleared and is contraindicated by the manufacturer in patients with a creatinine clearance less than 35 mL/min. Although there is limited data suggesting it may be well tolerated in patients undergoing haemodialysis, its use is discouraged due to the lack of safety data. Studies have shown a persistence of benefit of alendronate in non-renally impaired patients for a significant time after cessation, most likely due to its long half-life within bone. This is likely to apply to those with CKD also, although there is no direct evidence to support this. Consider ceasing alendronate. Calcitriol should be continued for management of hypocalcaemia.

2. There is significant evidence for atorvastatin for the reduction of cardiovascular risk in people with normal renal function. However, there is doubt as to whether statins improve outcomes in patients undergoing haemodialysis. A recent study of atorvastatin used in diabetic patients undergoing haemodialysis showed no improvement in mortality in the treatment group. The authors concluded that due to the very high short term cardiovascular risk and all cause mortality in this group, statin therapy may not have sufficient time to improve outcomes consistently. Furthermore, there is a significant risk of myopathy in renally impaired individuals. While Mr MD does not have diabetes, his short term cardiovascular risk due to his renal failure and past medical history is also very high. Since the benefits of atorvastatin are most likely to be gained over a long period of time, it may no longer be beneficial and may pose a significant risk of harm. Consider ceasing atorvastatin.

3. While temazepam is hepatically cleared, CNS effects may be more pronounced with people with renal impairment and may contribute to cognitive impairment, ataxia and falls. Furthermore, long term use may result in tolerance and dependence. Consider gradually reducing the dose of temazepam with the view of eventual cessation or PRN use.

**Outcomes**

Mr MD's doctor elected to cease alendronate due to the discussed safety concerns. Atorvastatin was continued with close monitoring of clinical signs of myopathy and serum creatine kinase. Mr MD was resistant to ceasing temazepam but agreed to review this with his doctor periodically.

**Summary**

Renal osteodystrophy encompasses a spectrum of metabolic bone disorders which can be difficult to distinguish using standard diagnostic techniques. Osteoporosis is common in patients with CKD but there is little evidence for the safety and efficacy of bisphosphonates in this cohort. The manufacturer of alendronate contraindicates its use in individuals with a CrCl <35 mL/min, however evidence suggests that it may be well tolerated in individuals with a CrCl >20 mL/min. While there is weak evidence to suggest bisphosphonates may be well tolerated in patients undergoing haemodialysis, use of these agents is discouraged due to lack of safety data.

**References**


**Questions**

1. Renal osteodystrophy is a result of:
   a) Secondary hyperthyroidism.
   b) Primary hyperparathyroidism.
   c) Secondary hyperparathyroidism.
   d) Insufficient cutaneous synthesis of vitamin D.

2. Theoretical safety concerns of bisphosphonates in CKD do not include:
   a) Inhibition of bone resorption, resulting in a worsening of bone quality.
   b) Direct nephrotoxic effects.
   c) Hypocalcaemia.
   d) Hypercalcaemia.

3. Which statement is false?
   a) Approved product information contraindicates the use of bisphosphonates in individuals with CrCl <35 mL/min.
   b) Reanalysis of risedronate trial data showed no significant differences in efficacy or ADRs in a cohort of patients with CrCl 20–30 mL/min.
   c) Bone mineral density is useful for defining the type of metabolic bone disease in patients with CKD.
   d) There is insufficient safety data to support using bisphosphonates in dialysis.

4. Which of the following is unlikely to increase a patient's risk of falling?
   a) Fetanyl.
   b) Omeprazole.
   c) Temazepam.
   d) Ramipril.