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Letters to the Editor

New drugs for osteoporosis

Editor, – I read 'New drugs for osteoporosis' by Peter Ebeling with interest (Aust Prescr 2011;34:176-81). I must compliment him on a lucid, comprehensive and informative article about a very common disease. The comparative table about the new drugs gives almost all the information at a glance. I understand that these drugs are to be given when usual treatment is ineffective. However, I have a few questions to ask the author:

1. Which is the drug of first choice amongst the new drugs, especially in refractory cases?
2. In some countries or ethnicities menopause starts early. Does the line of management change?
3. For therapeutic menopause, which invariably is earlier than usual, what should be the management since oestrogen is missing and replacement therapy is contraindicated?

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Peter Ebeling, author of the article, comments:

I would like to thank Professor Yadav for her thoughtful questions. In response, I would say that in Australia three of the four osteoporosis medications mentioned in my article are first-line treatments for osteoporosis – zoledronic acid, denosumab and strontium ranelate. They are all used as alternative options to the other first-line treatments – oral bisphosphonates or raloxifene. However in patients with severe osteoporosis, teriparatide is used when fractures occur after 12 months of therapy with other medications or when intolerance to these medications occurs.

In answer to question 1, if fractures have occurred on oral bisphosphonates it could be because the medications have been taken incorrectly or they are ineffective in patients with severe osteoporosis. If compliance or correct dosing is thought to be the main issue, parenteral therapy with either zoledronic acid or denosumab would be best. However, if the treatment was truly ineffective, teriparatide would be a better option for patients with severe osteoporosis.

In answer to question 2 about early menopause, most specialists would reserve treatment with these drugs until later in life when the absolute fracture risk is higher (calculated using the FRAX or Garvan Institute tools). However if the absolute fracture risk was already high, all would be options for treatment with the exception of teriparatide.

With therapeutic menopause (question 3), it would depend on whether the absolute fracture risk was elevated. Oral or intravenous bisphosphonates, denosumab or strontium ranelate could all potentially be used to prevent bone loss in these younger postmenopausal women.

Dental notes: Bisphosphonates and osteonecrosis of the jaw

Editor, – As a clinician I was concerned to read the dental note by Michael McCullough (Aust Prescr 2011;34:181), in which the incidence of osteonecrosis of the jaw in bisphosphonate users was quoted as being 1/500 to 1/1500. The reference quoted is a retrospective survey of 13 946 individuals. It is worth noting that other studies, in some cases with much larger sample sizes, have concluded that the incidence is rather lower. One review estimated the risk with oral bisphosphonates for osteoporosis to be between 1/10 000 and less than 1/100 000 patient-treatment years.[1] Another study of medical claims from 714 217 individuals concluded that intravenous, but not oral, bisphosphonates seem to be strongly associated with adverse outcomes in the jaws.[2] This conclusion was reiterated by Canadian guidelines.[3] It also appears that the risk of osteonecrosis of the jaw is substantially higher in patients being treated for cancer than it is in patients with senile osteoporosis.

My concern is that patients may be discouraged from using bisphosphonates because of concerns about osteonecrosis of the jaw. I understand that clinical experience with a patient suffering from this condition is likely to have a powerful effect on a practitioner, but we should aim to help our patients make quality decisions based on objective assessments of the risks and benefits.

Let us use the example of a 70-year-old woman who is estimated to have a 5% risk of sustaining a fractured neck of femur over five years, using a tool such as FRAX or the Garvan calculator. If we assume a 20% death rate in the 12 months following

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such a fracture, then the absolute risk of death is 1%. Intravenous zoledronate has been shown to reduce the incidence of hip fracture by 41%. Treating the patient would reduce the five-year hip fracture risk to 2.95%, in turn reducing the risk of death to 0.59%. This absolute reduction of the risk of hip fracture of 2.05% equates to a number needed to treat of 49 to prevent a hip fracture, or 243 to prevent a premature death subsequent to a hip fracture. This compares very favourably with the potential harms of bisphosphonate use, even assuming the higher rates quoted by Dr McCullough.

It is entirely appropriate to use bisphosphonates carefully, preferably having estimated absolute fracture risk, and to take steps to optimise oral health before starting treatment.

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Michael McCullough, author of the dental note, comments:

Dr Vanlint raises some very interesting points regarding the risk of bone fracture and osteonecrosis of the jaw. We agree that the careful use of bisphosphonates after clinical assessment and estimation of fracture risk is entirely appropriate and can have significant benefits for patients.

The discussion regarding the incidence of bisphosphonate-associated osteonecrosis of the jaw continues and it was once thought to be low and of an order of 1/10 000 to 1/100 000. More recent studies show the risk to be more likely around 1/1000 (95% confidence interval 1/500 to 1/1500).[1] This was previously quoted in an information pamphlet produced for Australian doctors and dentists by both Osteoporosis Australia and the Australian Dental Association. Interestingly, some specialist single centre studies show the risk following dental extraction to be of the order of 1/300.[2] Other ongoing studies will shed more light on the true incidence and risk factors for delayed dental healing and its association with bisphosphonate use.

Irrespective of the exact incidence of this adverse event, Dr Vanlint is entirely correct in stating that optimising oral health before bisphosphonate treatment is ideal, and will diminish the likelihood of osteonecrosis of the jaw occurring.

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Medicinal mishap: Dabigatran – a new safe drug to replace an old poison?

Editor, – Boehringer Ingelheim suggests an alternative title for the feature about dabigatran (Aust Prescr 2012;35:64-5) – Medicinal mishap: Always read the product information before prescribing.

Given the case history of the elderly woman with nephropathy (creatinine clearance (CrCl) 29 mL/min), she should clearly not have been prescribed dabigatran. This serves to reinforce the need for appropriate patient selection consistent with the approved product information which includes the contraindication 'severe renal impairment (CrCl <30 mL/min)'.

Prescribers should always read the product information before prescribing, regardless of whether a drug is new or old. As the sponsor for dabigatran, we are concerned the authors of this article did not include the dabigatran product information as a reference. The product information provides information pertinent to many of the issues raised in this case history.

On presentation to hospital, the patient was reported as having an INR of 2.5. As the authors mention later in the article, interpretation of an INR 2–3 weeks after starting dabigatran is meaningless. This information is provided in the product information. Further, and very importantly, when switching from warfarin to dabigatran, prescribers should only commence dabigatran once the INR is under 2. It is not clear whether this was confirmed in this clinical scenario.

The authors quote the Queensland Health guidelines for managing patients on dabigatran who present to hospital.[1] These recommendations appear broadly consistent with the product information for dabigatran. Interventions recommended for the reversal of moderate-to-severe or life-threatening bleeding by the Queensland Health document

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and the product information include platelets, oral charcoal, recombinant factor VIIa, activated prothrombin complex concentrates (for example, factor eight inhibitor bypassing activity FEIBA), haemodialysis and charcoal haemofiltration. These were not used in this case.

Lastly, the authors incorrectly assert 'Currently, no assay of dabigatran's effect on coagulation is available'. A direct thrombin inhibitor assay (Hemoclot) is commercially available in Australia for assessing the anticoagulant activity of dabigatran.[2]

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Joel Iedema, one of the authors of the medicinal mishap, comments:

We thank Boehringer Ingelheim for highlighting the importance of patient selection. This principle underlies safe and effective prescribing of all medicines, but is particularly critical for medicines such as anticoagulants. This patient was not a suitable candidate for dabigatran and we reinforce the need to read the product information and other independent literature for unfamiliar medicines before prescribing.

In response to the letter, the Australian product information states that the INR is 'too insensitive' to be used for therapeutic monitoring. A problem with inconsistent INR results related to certain assays was described post-marketing.[1] While a dabigatran assay is now available, it is provided by select pathology providers and evidence-based guidelines for rational use are lacking.

Evidence for dabigatran reversal is very limited. Inactivated prothrombin complex has no effect in dabigatran reversal[2] and no human data are available for other treatments.[3] Many of these treatments carry significant risks of their own and the costs are considerable. Anticoagulant reversal is critical to the management of bleeding and the current lack of specific reversal should be included in harm-benefit discussions with patients.[4]

These issues further reinforce the key message of our article that the real-world risk of any medicine is often not fully appreciated until considerable post-marketing experience has been gained. Regrettably, real-world risk does include inappropriately prescribed medication. Postmarketing surveillance may identify other patient groups at increased risk of adverse events, which would only reinforce the need for careful patient selection.[5]

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Editorial note:

The Editorial Executive Committee believes that the approved product information is an important document for all drugs and should be consulted before prescribing. It is therefore unnecessary to cite it as a reference for every drug mentioned in *Australian Prescriber*. Our editorial practice is therefore to not reference the product information at the end of every article. The authors of the Medicinal mishap included the product information for dabigatran in their original draft, but it was deleted in accordance with our usual practice.