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NEWSLETTER

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AUCKLAND Bonedensity
Managing Bone Health

Side effects of bisphosphonates

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Bisphosphonates (BPs), given orally or intravenously, are widely used in the management of osteoporosis. Although generally well-tolerated, some side effects can occur when using these agents. Considering these adverse effects is important for patients deliberating over whether to take treatment to reduce fracture risk. The more important and/or publicized adverse effects are discussed below:

1. **Dyspepsia with oral bisphosphonates:**
   This is a relatively common side effect (approximately 20% of treated individuals) but can be minimised by proper education (swallow the tablets with a large glass of water, and do not lie down for at least two hours afterwards). Taking oral BPs fasting is important for adequate absorption. In those with established oesophageal disease it may be best to opt for intravenous therapy. Proton pump inhibitors may reduce the risk of dyspepsia in those with reflux.

2. **Acute constitutional symptoms ('acute phase reaction') following intravenous bisphosphonate:**
   This occurs in about 30% of individuals with their first infusion, and comprises an illness with variable combinations of pyrexia, myalgia, arthralgia, headache and flu-like symptoms lasting about 1-3 days, usually responding to simple analgesics. The incidence falls to 1-3% with successive infusions. The problem occurs more frequently in younger patients, non-Japanese Asians, and those on NSAID treatment, and may be less frequent in patients previously treated with oral BPs. Similar symptoms with first use of oral BPs are very rare.

3. **Renal impairment with intravenous BPs:**
   IV BPs are not recommended for individuals with advanced renal impairment, where severe worsening of renal function can occur. Renal function should thus be checked prior to use of IV BPs. A reduction in dose and/or slower delivery in a generous volume of IV fluid is recommended if the eGFR is 35-45 ml/min, and intravenous BPs should not be used if the eGFR is < 35 ml/min. In formal trials, there was no evidence of sustained long term renal dysfunction in those treated with bisphosphonates.

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4. **Hypocalcaemia:**
   This has very occasionally been seen following IV BP administration, in the context of very low vitamin D levels. A vitamin D supplement (100,000 IU as a stat dose) prior to IV administration may reduce this risk, especially in those at risk of D-deficiency (sunlight-deprived elderly).

5. **Atypical fractures:**
   These can occur as rare events, mainly in the upper femur, particularly in patients on oral bisphosphonates, usually when the medication has been taken over prolonged periods of time (median time to onset 7y). The problem appears to be caused by inhibition of bone formation so that repair of microfractures is impaired, eventually leading to complete fracture. It is seen with oral BPs, possibly more frequently with alendronate than risedronate, where there is constant loading of BP onto bone surfaces, whereas this side effect is extremely rare with intermittent IV administration using zoledronate. Studies suggest there may be a fracture rate of 5-10/10,000 treated patients during long-term therapy, with relative risk increased with longer duration of therapy, leading to the recommendation to consider a "medication holiday" of several years in those who need long term oral therapy.

6. **Osteonecrosis of the jaw (ONJ):**
   The side effect is defined as exposure of bone in the alveolar-dental ridge without healing by 6-8 weeks. It is seen mainly in cancer patients receiving high-dose IV BPs (usually in monthly infusions given to patients with multiple myeloma or other cancers). The risk of ONJ in such patients is about 4% in a series from the Mayo Clinic. The risk in those treated with oral BPs for osteoporosis is very low and less severe than seen in the cancer patients (1 per 50,000 individuals in a German registry exposed to oral BPs). It usually follows potential bone-exposing procedures such as tooth extraction or implants. Risks increase with poor dental hygiene and deeper initial bone lesions. The risk of ONJ in patients with osteoporosis treated with a BP is so low that, for the vast majority of patients, there is no need to adjust therapy, even if dental procedures are being planned.

7. **Orbital inflammation:**
   Iritis, episcleritis and/or conjunctivitis are rare side effects of IV bisphosphonate (about 6/1000 patients), requiring ophthalmology review and, usually, topical steroid treatment. They probably constitute part of the acute phase response discussed above, and are therefore predominantly a 'first dose' effect.

8. **Others:**
   Previously, increased rates of atrial fibrillation and upper GI tract cancers have been associated with use of BPs but these associations have not been replicated in subsequent studies.