Do gastric adverse events influence the choice of bisphosphonate for the treatment of osteoporosis?

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Background

The bisphosphonates are a group of drugs used to reduce bone turnover in conditions including osteoporosis, Paget's disease, and bone malignancies. (1) The therapeutic effect is achieved by inhibiting bone resorption.

As a group the bisphosphonates are generally well tolerated, but have a well documented adverse effect (AE) profile, and gastrointestinal effects are a known issue. (2, 3) Strict administration requirements have been introduced to reduce the risk of oesophageal AEs, and inability to meet these requirements is considered a contraindication to treatment. There have been reports of pain, nausea, vomiting and gastric ulcers associated with bisphosphonate use. (3)

Answer

Four oral bisphosphonates are licensed for the treatment of osteoporosis in the UK; alendronic acid, disodium etidronate, risedronate sodium, and ibandronic acid. (1)

The National Institute for Health and Clinical Excellence (NICE) published multiple technology appraisals in 2008 for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. (4, 5) In each case the recommended first line option for women who require treatment for osteoporosis is alendronate, and the guidance states that the cheapest available form should be used. Risedronate and etidronate are considered as alternatives to alendronate only if:

♦ The patient is unable to comply with the special instructions for the administration of alendronate, has a contraindication to its use (abnormalities of the oesophagus, factors that delay oesophageal emptying, hypersensitivity, hypocalcaemia), or is intolerant of therapy and
♦ The patient has a combination of T-score, age and independent clinical risk factors that indicate further treatment is appropriate.

For the purposes of the guidance intolerance to alendronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and which occurs even though the instructions for administration have been followed correctly. Gastric adverse events may therefore indirectly affect prescribing of bisphosphonates.

In choosing an alternative to alendronate, the effectiveness, tolerability and adverse effects (AEs) of available preparations in individual patients should be taken into consideration. In 2006 NICE commissioned a systematic review of AEs associated with bisphosphonates, including evidence on gastrointestinal AEs. (6) Findings included:

♦ Prescription-event monitoring studies in the UK found that dyspepsia is less common after one month of treatment with risedronate than with alendronate, with 26.9 events per 1000 patient-months compared to 32.3 events. The background rate of dyspepsia in women over 60 is 6 events per 1000 patient-months. However, this result may be biased by greater awareness of the necessity for adherence to the administration requirements at the time when risedronate was marketed.
♦ A retrospective cohort study reported that patients treated with alendronate have a 42% higher risk of experiencing any GI event than risedronate users (p=0.016)
♦ In a second retrospective study of 150 women given risedronate and followed up for approximately one year, only 3% reported any GI symptoms.
♦ A further retrospective cohort study reported that there was no statistically significant difference in the incidence of all upper GI events between patients taking cyclical etidronate.
and osteoporotic controls (relative rate 0.92, 95% confidence interval 0.78 to 1.09). After adjustment for risk factors the same was true when compared to non-osteoporotic controls for all upper GI events and for individual AEs including peptic ulcer and gastritis. There was no evidence GI events were more common during the 14 days of active etidronate treatment than in the remainder of the 90-day treatment cycle.

The study reporting low rates of gastric AEs associated with etidronate is corroborated by reports from clinical specialists and patient experts which state that etidronate may be associated with fewer upper GI AEs than other bisphosphonates. (4, 5) The non-nitrogenous bisphosphonates, including etidronate, have previously been reported to be associated with fewer upper GI AEs. (7) It should be noted that all of the studies mentioned above are retrospective and that no prospective trials examining the gastric safety of the bisphosphonates were found. There is also a larger body of randomised controlled trial (RCT) evidence for the efficacy of risedronate than for etidronate. (4, 5)

Several other trials were located in addition to the systematic review. A short, prospective RCT comparing daily alendronate 10mg and risedronate 5mg in postmenopausal women with no endoscopic abnormalities at baseline found that gastric ulcer was significantly more common with alendronate after 14 days treatment (13.2% vs. 4.1%, p<0.001). (8)

In contrast, some studies have found no difference in the incidence of gastric AEs between alendronate and risedronate. The one-year Fosamax Actonel Comparison Trial (FACT) and its 12 month extension compared the efficacy and safety of alendronate 70mg once weekly with risedronate 35mg once weekly. Both the one-year and two-year results found no difference in the rate of upper GI AEs, discontinuation due to upper GI AEs or serious upper GI AEs. (9, 10) A large observational cohort study enrolled over 10,000 patients in order to examine the rate of upper GI bleeding in patients using oral alendronate and risedronate. (11) No difference in any upper GI outcome was detected, including hospitalisation for bleeding, upper GI disease, and upper GI symptom.

The bulk of evidence therefore indicates that risedronate and etidronate are associated with fewer gastric AEs than alendronate, and may both represent suitable alternatives in patients who are unable to tolerate alendronate. There is more available RCT evidence for the efficacy of risedronate than for etidronate, and risedronate is considered a drug of choice for the treatment of osteoporosis by the BNF. (1) No comparative data were located for ibandronate.

**Summary**

Alendronate should be the first choice of bisphosphonate for the treatment of osteoporosis in postmenopausal women, and the cheapest suitable preparation should be chosen. If severe adverse events (including gastric effects) occur and persist despite proper administration, and the patient has a combination of T-score, age and independent clinical risk factors that indicate further treatment is appropriate, risedronate and etidronate may be considered. If alendronate is not tolerated the choice of bisphosphonate is a clinical decision based on the individual requirements of the patient. Data suggest that risedronate is may be associated with fewer upper GI AEs than alendronate, although some studies found no difference between the two. Etidronate, a non-nitrogenous bisphosphonate, may be associated with fewer gastric AEs than either alendronate or risedronate. Risedronate is a preferred option for the treatment of osteoporosis in the BNF, and its efficacy is supported by a greater body of RCT evidence than etidronate. Prospective, head-to-head trials (adequately powered to detect differences in gastric AEs) are required to definitively establish relative efficacy and safety. No evidence could be located on the comparative gastric tolerability of ibandronate.

**Limitations**

This document considers gastric adverse effects only, and not other adverse effects. The majority of the available data relate to postmenopausal women with osteoporosis, and may not be applicable to other patient groups. The available data are largely restricted to retrospective and observational studies. Zoledronic acid is not licensed for oral administration and is not covered in this document.
Quality Assurance

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**Search strategy**
Embase: bisphosphonic acid derivative/ AND adverse drug reaction/
Medline: diphosphonates/ AND Drug-Related Side Effects and Adverse Reactions/

**NICE guidance**
Summaries of product characteristics

**References**
6. The University of Sheffield School of Health and Related Research. Adverse effects and persistence with therapy in patients taking oral alendronate, etidronate or risedronate: systematic reviews. 2006.