Bisphosphonates are widely prescribed to treat Paget’s disease of the bone and to prevent and treat osteoporosis. Soon after the release of alendronate, esophagitis and esophageal strictures were encountered, resulting in labeling changes. Subsequent endoscopic studies in normal subjects showed that alendronate also caused gastric erosions and ulcers. Although the clinical significance of these is still uncertain, the anatomic distribution of both the gastric ulcers and esophageal damage is consistent with a topical irritant effect. Recent data also suggest a synergistic ulcerogenic potential of concurrent alendronate and NSAID use. A 70-mg once-weekly dosage form of alendronate has recently been approved and clinical experience with its gastrointestinal tolerability is ongoing. Risedronate, a third-generation bisphosphonate, appears to have less ulcerogenic potential than alendronate, and esophageal stricture has not been reported. Experience with the bisphosphonates provide a paradigm for the critical role of endoscopists in evaluating the gastrointestinal profile of new drugs. As bisphosphonates are more widely prescribed and more types of bisphosphonates are developed, the role of the gastroenterologist is likely to assume even more importance.

KEY WORDS: bisphosphonates; risedronate; alendronate; tolerability; endoscopy.

The bisphosphonates comprise a class of drugs that has been developed over the past 20 years, primarily as antiresorptive agents capable of treating diseases related to bone remodeling. Chemically, the bisphosphonates are analogs of pyrophosphates and show differing antiresorptive potencies in in vitro studies that vary over several orders of magnitude, depending on the nature of the alkyl substituents R1 and R2 (Figure 1) (1). The bisphosphonate class continues to expand, with newer variants such as ibandronate and zoledronate in active clinical trials (2).

The differences in chemical structure are reflected not only in differing antiresorptive potencies but also in the nature and extent of side effects, with the gastrointestinal tract as the principal locus of safety concern (3). The present review focuses on the question of gastrointestinal tolerability of the bisphosphonates.

GASTROINTESTINAL TOLERABILITIES OF COMMON BISPHOSPHONATES IN CLINICAL PRACTICE

The bisphosphonates discussed here fall into two main groups: those containing a nitrogen atom as part of their R2 substituent and those that do not. In attempts to assess the overall issue of gastrointestinal safety, investigators have supplemented data from...
clinical trials with comparative studies using animal model systems, work that is incorporated here. In addition, because the bisphosphonates are often prescribed to patients who also use nonsteroidal antiinflammatory drugs (NSAIDs) with the well-known potential for gastrointestinal toxicity, particular reference is made to studies that have examined the potential for a synergistic action between NSAIDs and bisphosphonates in causing gastrointestinal irritation.

**Non-Nitrogen-Containing Bisphosphonates**

This group comprises the first generation of bisphosphonates, the least potent on a molar basis in preventing bone resorption (1).

**Clodronate.** Clodronate is a chlorine-containing bisphosphonate used to treat several bone-associated conditions related to malignancy. Clinical trials have shown the effectiveness of oral clodronate at doses ranging from 800 to 1600 mg/day to treat hypercalcemia and reduce fracture risk in patients with osteolysis induced by breast cancer and myeloma (4–7). A recent interim analysis also provided support for the ability of clodronate to reduce vertebral fracture risk in patients with osteoporosis (8). Upper gastrointestinal side effects in clodronate studies were not different from placebo, even when patients took the medication in the middle of the night; diarrhea was slightly more common in patients taking clodronate, an effect also observed in earlier work (9). Although there has not been a formal subsequent examination of the upper gastrointestinal tolerability of clodronate, there is no evidence that the postmarketing experience differs from the reports of the clinical trials.

**Etidronate.** Etidronate is a first-generation bisphosphonate, one of the least potent on a molar basis in preventing bone resorption (1). It was the first to be assessed extensively as a treatment for osteoporosis, but trial data determined that the high concentrations required for effective antiresorptive activity also interfered with mineralization, leading to induction of osteomalacia and spontaneous fractures (10). These concerns were obviated by a cyclical dosing regimen that still proved effective in reducing bone resorption (11). In a seven-year trial of patients with established postmenopausal osteoporosis, cyclical etidronate, given at 400 mg/day for 14 consecutive days in each three-month period, significantly reduced the vertebral fracture rate but only in patients at highest risk of fracture (12). Because of this limitation, the Food and Drug Administration (FDA) withheld labeling of etidronate for treatment of osteoporosis, but it has been so labeled in Canada and Europe (13). Currently, etidronate is approved by the FDA for the treatment of symptomatic Paget’s disease and heterotopic ossification following hip replacement surgery or spinal cord injury. However, etidronate has proved less effective than later-generation bisphosphonates in treating conditions such as Paget’s disease or osteoporosis (14–16).

In terms of its gastrointestinal safety profile, etidronate has been described as remarkably well tolerated, to the degree that it is often used “off-label” for patients who cannot tolerate other oral bisphosphonates (3). In the seven-year osteoporosis trial (12) (see above), treatment with etidronate did not cause any increase in the incidence of gastrointestinal events as compared with control. Moreover, an extended postmarketing survey in the United Kingdom involving general practitioner reports of almost 8000 patients confirmed this conclusion, and the concomitant use of NSAIDs, aspirin, or corticosteroids with cyclical etidronate did not appear to increase the incidence of upper gastrointestinal events (17).

**Nitrogen-Containing Bisphosphonates**

Pamidronate and alendronate are second-generation bisphosphonates with $R^2$ substituents that end in amino groups; the only difference between them is an additional methyl group in the alkyl side chain of alendronate (see Figure 1). Risedronate is a third-generation bisphosphonate with a nitrogen atom that forms part of a pyridine ring.