

The Caveats of Paget's Bisphosphonate Prescribing

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FORT LAUDERDALE, FLA. — Bisphosphonate therapy has dramatically improved the lives of patients with Paget's disease, but it's important to keep in mind the caveats when prescribing them, Dr. Kenneth W. Lyles said at a meeting sponsored by the Paget Foundation for Paget's Disease of Bone and Related Disorders.

Clinical trials have demonstrated that all bisphosphonates are capable of improving bone remodeling and reducing pain. Efficacy at normalizing serum alkaline phosphatase levels varies from 15% with etidronate to 53% with pamidronate to 73% with risedronate to 89% with zoledronic acid.

"We are developing drugs that really help control this disease and improve pain. . . . They're very good drugs, but they come with a set of considerations," said Dr. Lyles, professor of medicine at Duke University, Durham, N.C.

Potential adverse events are uncommon but have been reported with one or more of the various bisphosphonates:

► **Osteomalacia.** There have been some recent reports of patients developing osteomalacia after receiving etidronate at doses of 5 mg/kg for longer than 6 months, which exceeds the label recommendations.

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is necessary, patients can be switched to a nonaminobisphosphonate such as etidronate or tiludronate.

► **Acute phase response.** This transient flu-like syndrome consisting of fever, myalgia, and leukopenia has been reported 24-96 hours after first treatment with a bisphosphonate in 5%-40% of patients. It is seen more often with the intravenously agents than the oral ones. Its mechanism isn't completely understood, although it appears to be associated with an excessive release of tumor necrosis factor and interleukin-6 in treatment-naive patients. Patients should be warned of the possibility, and treated with aspirin, ibuprofen, or acetaminophen if it occurs, he advised.

► **Osteonecrosis of the jaw.** A series of papers since 2003 have reported this complication with alendronate, pamidronate, and zoledronate therapy. Most cases have occurred in patients who undergo tooth extraction or other dental procedures while on bisphosphonates, although malignancy and renal impairment have also been identified as risk factors. In patients who must undergo dental procedures, it may be best to give higher doses of bisphosphonate and shorten the course.

► **Hypocalcemia.** Because aminobispho-

sphonates rapidly block bone resorption, they can lead to hypocalcemia followed by a secondary hyperparathyroid response to restore normocalcemia. Although hypocalcemia has been reported in less than 1% overall among treated patients, severe cases have occurred in patients with malignancy, hypoparathyroidism, and unrecognized vitamin D deficiency. Patients should always be screened for vitamin D and parathyroid hormone prior to initiation of bisphosphonate therapy, and

should be on calcium supplementation afterward. "If you miss this, you can have substantial problems," Dr. Lyles noted.

► **Vitamin D deficiency.** Vitamin D insufficiency and frank deficiency are being observed increasingly among the elderly in general, and among patients with Paget's disease in particular. Indeed, one study of 104 subjects over age 98 years revealed that 95% had undetectable levels of serum 25-hydroxyvitamin D, and that 38 of them had sustained a total of 55 fractures (J.

Clin. Endocrinol. Metab. 2003;88:5109-15). Vitamin D supplementation is advised for patients with Paget's disease of bone before, during, and after bisphosphonate treatment, he advised.

Dr. Lyles has financial ties to Procter & Gamble, Aventis, Amgen, Roche/Glaxo-SmithKline, Merck & Co., and Novartis Pharmaceuticals.

He holds a patent for the use of zoledronate in patients who have sustained hip fractures. ■

ARTHROTEC is contraindicated in women who are pregnant or who may become pregnant. ARTHROTEC can cause miscarriage, often associated with bleeding, which may result in other serious complications.

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or its risk factors may be at greater risk.

ARTHROTEC is contraindicated for treatment of peri-operative pain in coronary artery bypass graft surgery.

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

ARTHROTEC is contraindicated in patients with hypersensitivity to diclofenac or to misoprostol or other prostaglandins and in patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac sodium have been reported.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation. Elevations in ALT and/or AST, and rare cases of severe hepatic reactions have also been reported. Transaminases should be monitored within 4-8 weeks after initiating treatment with diclofenac and should be measured periodically in patients receiving long-term therapy.

NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis which can be fatal.

The most common adverse events in ARTHROTEC-treated patients are abdominal pain (21%), diarrhea (19%), dyspepsia (14%), nausea (11%), and flatulence (9%), which can occur more frequently than with diclofenac alone.

Reference: 1. IMS Health Incorporated (September 2003).

Please see prescribing information on next page.

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