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FAST FACTS AND CONCEPTS #113

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Background

Bisphosphonates are used for the treatment or prophylaxis of cancer-related bone complications, including pain. The mechanism of action is thought to be related to inhibition of bone resorption. All bisphosphonates inhibit osteoclast activity and some also inhibit the maturation of mononuclear precursors into active osteoclasts. In the United States, two preparations are used: zoledronic acid and pamidronate.

Analgesic Therapy

Breast cancer and multiple myeloma have been found to be the most responsive tumors to bisphosphonates. Pain relief has been shown to a lesser degree in lung, GI and prostate carcinomas. Standard starting doses include: zoledronic acid 4 mg IV over 15 minutes and pamidronate 90mg IV administered over 2 hours. 50-70% of patients achieve a 30% reduction in pain within a week. The average duration of pain relief is 12 weeks after a single 90 mg infusion of pamidronate. If analgesia is not achieved within a week, the patient can be retreated. Analgesic effect is related both to the dose per week and the total dose per infusion for pamidronate. Typically patients are treated every 3-4 weeks to achieve maximal effect. If the pain is well controlled the dosing interval can be extended to a longer period without change in effect.

Prophylaxis

In patients with breast cancer or multiple myeloma, and asymptomatic bone metastases, monthly bisphosphonates decrease skeletal-related events (SRE) (pathologic fractures, spinal cord compression, surgery to bone, or radiation therapy to bone) by 30%. The dosages of pamidronate and zoledronic acid are the same as used in analgesic therapy. There is no evidence that these medications prevent SRE in patients without known bone involvement.

Toxicity

Pamidronate and zoledronic acid have the same safety profiles. Both cause an injection site reaction and a flu-like syndrome that responds well to acetaminophen. Less common side effects include hypocalcemia and scleritis. Renal dysfunction is a side effect of long-term, high dose or short interval/frequency use of bisphosphonates; this is typically reversible with discontinuation of the drug. Bisphosphonates are contraindicated in renal failure and with patients who experience an increase in creatinine (>0.5 mg/dl over baseline or >1.0 in patients with pre-existing renal insufficiency). In moderate renal dysfunction ($Cr > 3.0$ mg/dl) the dose of both agents should either be reduced and/or the infusion time increased. Fast Fact #196 discusses bisphosphonate induced osteonecrosis of the jaw.

Cost

The average wholesale price for zoledronic acid 4mg is \$856; the AWP of pamidronate 90 mg is \$88. In considering the cost difference between these two drugs it is important to acknowledge the added costs to patients, physicians and medical facilities for the infusion time of pamidronate (average appointment time 2h 52 min vs. 1h 6min for zoledronic acid).

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