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Zoledronic acid: Heterocyclic Nitrogen Containing Bisphosphonate

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Abstract

Zoledronic acid is an imidazole compound. Its other name is Zoledronate and trade name is reclast, zometa. It is a nitrogenous bisphosphonate having chemical composition $C_5H_{10}N_2O_7P_2$. It is third generation bisphosphonate drug share common phosphorus-carbon-phosphorus “backbone”. Zoledronic acid lowers high blood calcium levels by reducing the amount of calcium released from bones into blood. It works by slowing the breakdown of bones by cancer to prevent bone fractures. Zoledronic acid is used to treat osteoporosis (loss of bone density) and hypercalcemia, a condition resulting in high blood calcium levels due to cancer and delay bone complications resulting from multiple myeloma and bone metastases. Zoledronic acid is given by injection into a vein. It is used in the treatment of Paget’s disease and Duchene Muscular Dystrophy (DMD).

Keywords: Zoledronic acid, bisphosphonate, imidazole compound, Paget’s disease and Duchene Muscular Dystrophy (DMD).

Introduction

Zoledronic acid belongs to a class of drugs known as bisphosphonates. Bisphosphonates are the pioneer and gold standard drugs for osteoporosis treatment. The development of bisphosphonates started decade ago. There are four bisphosphonates in the osteoporosis market, alendronate, risedronate, ibandronate and

zoledronate. Zoledronic acid is a medication that treats Paget’s disease, osteoporosis, DMD. It works by slowing calcium loss from bones. Calcium is a mineral that keeps bones healthy. It lowers high blood calcium levels by reducing the amount of calcium released from bones. It works by slowing the breakdown of bones by cancer to prevent bone fractures. Its generic name is Zoledronic acid. Its brand name is aclasta, reclast,

zometa. Its chemical formula is $C_5H_{10}N_2O_7P_2$. Its molar mass is $272.090\text{g}\cdot\text{mol}^{-1}$. As a nitrogenous bisphosphonate, it is a potent inhibitor of bone resorption, allowing the bone forming cells time to rebuild normal bone and allowing bone remodeling. It was patented in 1986 and approved for medical use in 2001. It is on the World Health Organizations List of Essential Medicines.

Zoledronic acid prevents problems with the bones such as breaks in the bones (fractures) in myeloma and cancers that have spread to the bone (advanced cancers). It lowers the chance of breast cancer coming back after surgery in certain situations. It prevents bone loss for people having aromatase inhibitors. It lowers high levels of calcium in the blood (hypercalcaemia), which can happen in secondary bone cancer. Zoledronic acid (Zometa) is not cancer chemotherapy, and it will not slow or stop the spread of cancer. However, it can be used to treat bone disease in patients who have cancer. Zoledronic acid is in a class of medications called bisphosphonates. For bone cancer and multiple myeloma, zoledronic acid is usually given every 3 to 4 weeks. This treatment will continue until body responds to the medicine. For osteoporosis, this medicine is usually given once a year and will continue until your body responds. Zoledronic acid is a third-generation amino bisphosphonate and is currently used in adult patients for different bone diseases. Zoledronic acid is known to form stable chelates with many metals and envisaged as a possible carrier moiety to develop metal- based radio pharmaceuticals with great potential applications in the nuclear medicine. This drug is a valid option in patients with metastasis of prostatic or breast cancer and in patients with Paget disease or osteoporosis [1–4].

Zoledronic acid was used in a paediatric population in a randomized and controlled analysis, in which Barros et al. [5] compared the uses of zoledronic acid and pamidronate in 23 children affected by osteogenesis imperfecta. Results suggested that zoledronic acid is safe and effective in improving clinical and densitometric characteristics, similar to pamidronate.

At present, bisphosphonates are widely used in the treatment of cancer [6, 7], and zoledronic acid, a third-generation bisphosphonate, is commonly prescribed. Studies of zoledronic acid have mainly focused on the prevention and treatment of bone metastasis, pain control, and delaying the onset of skeletal complications [8]

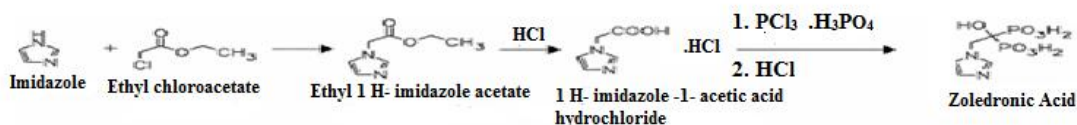
It has been demonstrated that zoledronic acid affects both osteoclast inhibition and myeloma cell apoptosis. It inhibits osteoclast recruitment and maturation, prevents the development of monocytes into osteoclasts, induces osteoclast apoptosis, and interrupts osteoclasts' attachment to bone [10]. Researchers have reported that zoledronic acid can be given safely over several minutes and produce similar antiresorptive effects, as assessed by bone resorption markers [11–13]. Recent studies have also shown that zoledronic acid is effective in the treatment of multiple myeloma and some solid tumors, such as lung cancer, breast cancer, and prostate cancer, having the potential for an antitumor effect [9, 14–16]. Zoledronate used to treat bone disease such as osteoporosis and Paget's disease. **Osteoporosis** is a condition that causes bones to be thinner and weaker than normal. This means that they can break (fracture) easily, such as after a small bump or fall. In osteoporosis zoledronate prevent bone loss, increase bone thickness and lower your risk of spine and hip fractures. For the treatment of osteoporosis, zoledronate injection is used if the tablet forms of bisphosphonates are unsuitable for you. In **Paget's disease** the abnormal bone growth causes deformity and pain. Zoledronate can help with this. Zoledronate may also be used to reduce the high levels of calcium in the blood (called hypercalcaemia) which can happen with some cancers. Zoledronate is given by injection, as a drip into the vein. It belongs to a group of medicines called **bisphosphonates**. Zoledronic acid attenuates accumulation of DNA damage in mesenchymal stem cells and protects their function. A case of a paediatric patient affected by mandibular fibrous dysplasia (FD) with severe and chronic pain who was successfully treated with zoledronic acid.

Fibrous dysplasia (FD) is a benign fibrous bone disease characterized by the replacement of bone with cellular fibrous tissue [17]. It is a genetic condition caused by a postzygotic, activating mutation of GNAS (on chromosome 20), a gene encoding the α -subunit of the stimulatory G-protein; in mutated cells, this alteration results in a constitutive activation of adenylate cyclase and in a high production of cAMP affecting the proliferation and differentiation of preosteoblasts which leads to overproduction of fibrotic bone matrix [18]

Treatment [19] of MCF-7 cells with a range of zoledronic acid concentrations had little effect on apoptosis at 0.1 and 1.0 μM , however, an increase in the proportion of apoptotic cells was observed with 10 μM and 100 μM zoledronic acid compared with control (28.7% and 70.7% vs 22.57%, respectively). Treatment of MDA-MB-

231 cells with 0.1–1 μM zoledronic acid did not cause an increase in apoptosis, but treatment with the 10 and 100 μM zoledronic acid resulted in a significant increase in the proportions of apoptotic cells (126.6% and 126.6% of control). A significant time-dependent increase in MCF7 cell apoptosis was confirmed when cells were incubated with 100 μM zoledronic acid for 24–96 hours. Treatment [20] of mice bearing 5T2MM cells with zoledronic acid clearly prevented the development of osteolytic bone disease, decreased tumor burden in bone, and increased survival in a model of established myeloma.

Preparation of Zoledronic acid: In a mixture of 20 ml of propylene carbonate and 15 ml of PEG 600 was dissolved 7.44 g of phosphorous acid at 40°C. 2-(1H-imidazol-1-yl) acetic acid (3.0 g) was added while stirring and the reaction mixture was heated to 40°C.



Structure: Zoledronic acid is an imidazole compound having a 2, 2-bis(phosphono)-2-hydroxyethane-1-yl substituent at the 1-position.

It is a bisphosphonate drug share a common phosphorus-carbon-phosphorus “backbone”.

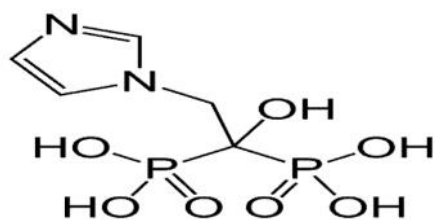


Fig. Zoledronic Acid

Affect of zoledronic acid on immune system: It weakens the immune system. It affects anti-cancer immunity. In addition to its effects on bone cells, it has profound effects on the immune system, including a plethora of immune cell subsets expressing the mevalonate pathway enzymes, leading to a general increase in anti-tumor immunity.

Affect of zoledronic acid on liver: Hepatotoxicity due to zoledronic acid therapy is a rare, but possible adverse effect which may be relieved after subsequent infusions. Attention is given to patients with concomitant liver or systemic diseases and monitor the liver biochemical indicators after treatment.

The cardiovascular side effects of zoledronic acid: Atrial fibrillation (AF), bradycardia and hypertension or hypotension. In HORIZON-PFT study, which is performed included 3900 patients, it was demonstrated that the risk of AF has increased twofold in patients treated with zoledronic acid in comparison to the normal population (21).

How is zoledronate given?

Zoledronate is given by intravenous infusion or 'drip', so medication is injected into the vein in the arm and drips in slowly over 15 to 30 minutes.

The number of doses will be given will depend upon why it has been prescribed for. Many people need only a single dose. Extra doses may be needed for people with osteoporosis and in some cancers. Zoledronic acid is given once a year as an intravenous (iv) infusion to treat osteoporosis. It is also given every two years as an infusion to prevent osteoporosis. Zoledronic acid increases bone density and reduces the spine and non-spine fractures, including hip fractures.

Special instructions

Blood tests: Before having zoledronate infusion, it will need blood tests to check the calcium levels in blood and how well kidneys are working.

Avoid dehydration: It is important that do not become dehydrated during treatment with zoledronate. Doctor will advise how much water needs to drink – this is usually one or two large glassfuls before and after treatment.

Calcium and vitamin D: For zoledronate to work, it may need to take vitamin D (also called cholecalciferol) supplements and ensure that have enough calcium in diet.

Possible side effects of zoledronate

Like all medicines zoledronate can cause side effects, although not everyone gets them.

Problems with jaw: Zoledronate can cause osteonecrosis of the jaw, which is a problem with the jaw that can be caused by delayed healing in the mouth after some dental procedures. This is quite rare. To reduce the risk of this problem, it is best to take good care of teeth and mouth (such as brushing teeth twice a day and regular flossing between teeth). Have regular dental check-ups. If need any dental treatment, it is best that have this done before start treatment with zoledronate. Let dentist know that patient are having zoledronate treatment. Talk to doctor or dentist if having any loose teeth, tooth pain, or swelling or numbness in your jaw.

Other side effects: Flu-like symptoms such as muscle and joint pains, fever, headache. These symptoms are quite common with zoledronate injection. They tend to go away after a few days.

Irritation or burning at the site of the injection: Doctor can recommend a mild pain reliever such as paracetamol to reduce these side effects. Tell doctor if troublesome.

Eye pain, Red eye, Changes in your vision Sensitive to light, Floating spots in vision: These symptoms are related to inflammation in the eye. This is quite rare. Contact doctor immediately if experience these symptoms.

Conclusion

Zoledronic acid has been found to have a direct antitumor effect and to synergistically augment the effects of other antitumor agents in osteosarcoma cells [22]. Zoledronic acid has shown significant benefits versus placebo over three years, with a reduced number of vertebral fractures and improved markers of bone density [23-24]. An annual dose of zoledronic acid may also prevent recurring fractures in patients with a previous hip fracture [25]. Zoledronic acid administration can effectively increase lumbar bone density and reduces the risk of vertebral fracture in patients with osteoporosis [26].

References

1. A. Giusti and G. Bianchi. Treatment of primary osteoporosis in men. *Journal of Clinical Interventions in Aging*. 10: 105–115, 2015.
2. B. Ferraz-de-Souza and P. H. S. Correa. Diagnosis and treatment of Paget's disease of bone: a mini-review. *Arquivos Brasileiros de Endocrinologia & Metabologia*. 57(8):577–582, 2013.
3. P. Taxel, P. Choksi, and C. Van Poznak. The management of osteoporosis in breast cancer survivors. *Maturitas*. 73(4): 275–279, 2012.
4. J. N. Graff and T. M. Beer. Reducing skeletal-related events in metastatic castration-resistant prostate cancer. *Oncology*. 29(6): 416–423, 2015.
5. E. R. Barros, G. L. Saraiva, T. P. de Oliveira, and M. Lazaretti-Castro. Safety and efficacy of a 1-year treatment with zoledronic acid compared with pamidronate in children with osteogenesis imperfecta. *Journal of Pediatric Endocrinology and Metabolism*. 25(5-6):485–491, 2012.
6. G. J. Morgan, J. A. Child, W. M. Gregory et al. Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. *The Lancet Oncology*. 12(8):743–752, 2011.
7. L. Lacerna and J. Hohneker. Zoledronic acid for the treatment of bone metastases in patients with breast cancer and other solid tumors. *Seminars in Oncology*. 30(5): supplement 16, 150–160, 2003.
8. S. Dhillon and K. A. Lyseng-Williamson. Zoledronic acid: a review of its use in the management of bone metastases of malignancy. *Drugs*. 68 (4): 507–534, 2008.
9. L. Costa and P. P. Major. Effect of bisphosphonates on pain and quality of life in patients with bone metastases. *Nature Clinical Practice Oncology*. 6(3):163–174, 2009.
10. F. C. Tamburrelli, L. Proietti, L. Scaramuzzo, V. de Stefano, and C. A. Logroscino. Bisphosphonate therapy in multiple myeloma in preventing vertebral collapses: preliminary report. *European Spine Journal*. (21):1, S141–S145, 2012.
11. J. R. Berenson, B. E. Hillner, R. A. Kyle et al. American society of clinical oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *Journal of Clinical Oncology*. 20(17): 3719–3736, 2002.
12. L. S. Rosen, D. Gordon, M. Kaminski et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer Journal* 7. (5): 377–387, 2001.
13. J. R. Berenson, L. S. Rosen, A. Howell et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer*. 91(7):1191– 1200, 2001.
14. R. Mahtani, R. Khan, and M. Jahanzeb. The potential application of zoledronic acid as anticancer therapy in patients with non-small-cell lung cancer. *Clinical Lung Cancer*. 12 (1): 26–32, 2011.
15. K. Zarogoulidis, E. Boutsikou, P. Zarogoulidis et al. The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis. *International Journal of Cancer*. 125(7): 1705– 1709, 2009.
16. B. Ory, M.-F. Heymann, A. Kamijo, F. Gouin, D. Heymann, and F. Redini. Zoledronic acid suppresses lung metastases and prolongs overall survival of osteosarcoma-bearing mice. *Cancer*. 104(11): 2522–2529, 2005.

17. C.D. Pede, S. Congedi, S. Rossin et al. Case Report Use of Zoledronic Acid in Paediatric Craniofacial Fibrous Dysplasia. *Hindawi Publishing Corporation Case Reports in Pediatrics*. 2016, Article ID 2329483, 6 pages
<http://dx.doi.org/10.1155/2016/2329483>.
18. G. Jundt. Pathologic-anatomic characteristics of benign bone tumors. *Der Orthopade*. 24(1): 2-14, 1995.
19. S.P. Jagdev, R.E. Coleman, C.M. Shipman, et al. The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: evidence for synergy with paclitaxel. *Br J Cancer*. 84(8): 1126-34, 2001.
20. P.I. Croucher, R. De. Hendrik, M.J. Perry et al. Zoledronic Acid Treatment of 5T2MM-Bearing Mice Inhibits the Development of Myeloma Bone Disease: Evidence for Decreased Osteolysis, Tumor Burden and Angiogenesis, and Increased Survival. *J Bone Miner Res*. 18(3): 482-9, 2003.
21. S. Mittal, C. Movsowitz, J.S. Steinberg. Ambulatory external electrocardiographic monitoring: Focus on atrial fibrillation. *Journal American College of Cardiology*. 2011 Oct 18; 58(17): 1741-1749, 2011.
22. K. Koto, H. Murata et al. Zoledronic acid inhibits proliferation of human fibrosarcoma cells with induction of apoptosis, and shows combined effects with other anticancer agents. *Oncology Reports*. 24 (1): 233-239, 2010.
23. I.R. Reid, J.P. Brown et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *The New England Journal of Medicine*. 346 (9): 653-661, 2002.
24. K.W. Lyles, C.S. Colón-Emeric, J.S. Magaziner, J.D. Adachi, C.F. Pieper, C. Mautalen, et al. "Zoledronic acid and clinical fractures and mortality after hip fracture". *The New England Journal of Medicine*. 357 (18): 1799-1809, 2007.
25. D.M. Black, P.D. Delmas, R. Eastell, I.R. Reid, S. Boonen, J.A. Cauley, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *The New England Journal of Medicine*. 356 (18): 1809-1822, 2007.
26. S.L. Han, S.L. Wan, Q.T. Le et al. Is vertebroplasty a risk factor for subsequent vertebral fracture, meta-analysis of published evidence? *Osteoporosis International*. 26(1), 113-122, 2015.

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