Clinical Use of Bisphosphonates for Postmenopausal Osteoporosis

Osteoporosis becomes a critical health threat for aging postmenopausal women by predisposing them to a higher risk of fracture. In 1991, it was estimated that 75 million women worldwide have the disease of which 1/3 of those aged between 60-70 years and 2/3 of those over 80 years were diagnosed of osteoporosis. Accordingly, a survey in a northern province of Thailand revealed that the incidence of hip fracture rapidly increased after the age of 65.1

The sequelae of osteoporosis are tremendous in term of morbidity and mortality. It worsens the quality of life in those surviving from a fracture episode. Those having vertebral fractures may suffer from kyphosis, chronic back pain, limitation of back movement, reduced thoracic volume, poor lung ventilation and as a consequence be prone to lung infection. Patients may suffer from neck pain and muscle fatigue due to marked thoracic kyphosis that requires the patient to hyperextend the neck. The reduced abdominal volume causes the abdominal contents to protrude, and characteristically, gives rise to creases on the abdominal wall and hiatus hernia. Psychologically, patients may be distressed because of the cosmetic effect on body shape, become isolated and prone to depression. With hip fractures, the consequences are often severe and devastating. Reports showed that 20% of patients die within one year of their fracture, 30% have permanent disability, 40% are unable to walk independently, and 60% cannot carry out at least one activity of daily living.2

The universal recommendation for the management of osteoporosis and fracture includes maximizing peak bone mass during the period of young adulthood, slowing bone loss after midlife and minimizing risk and severity of fall in the elderly. General advice for encouragement of healthy lifestyle and avoidance of health risk behaviors is advocated as a standard measure to reduce osteoporosis-related morbidity and mortality. Nevertheless, treatment of osteoporosis using a pharmacological modality has become one of the most advanced domains in science that seems to play a pivotal role in those having osteoporosis or being at a high risk of fracture.

With recent advances in bone biology, scientists have better insight into the regulation of bone cell differentiation and function. It has been discovered that bone remodeling is dependent on the delicate interaction among osteoblastic (bone forming cell) and osteoclastic (bone resorbing cell) lineages. This latest discovery has lead to an innovative pharmaceutical development towards efficient and safe medication for fracture risk reduction. Among the available pharmacological agents, bisphosphonates are considered to be the first line drug for the treatment of osteoporosis and fracture risk reduction.

Bisphosphonates are small molecules with a P-C-P structure that is similar to the P-O-P structure of pyrophosphate. It can be divided into two classes according to their modes of action i.e., the non-amino (non-nitrogen containing) bisphosphonates and the amino (nitrogen containing) bisphosphonates. The non-amino bisphosphonates including etidronate, clodronate, and tiludronate can be transformed into an analog of ATP in the cell resulting in potential cytotoxic metabolites. An accumulation of this analog of ATP in the cell cytoplasm probably results in inhibition of numerous enzymes, and as a consequence, increases the rate of osteoclast apoptosis. The amino bisphosphonates including ibandronate, alendronate, zoledronate and risendronate are not metabolized by osteoclasts. The amino bisphosphonates inhibit the mevalonate pathway by inhibiting farnesylpyrophosphate synthase leading to a decrease of the formation of isoprenoid lipids such as geranylgeranylpyrophosphate that are essential for osteoclastic functions. Disruption of its activity will induce cell death by apoptosis.3,4

In clinical practice, bisphosphonates can be divided according to the route of administration. Oral intake includes alendronate 10 mg daily or 70 mg once weekly, risedronate 5 mg daily or 35 mg once weekly and ibandronate 150 mg once monthly. The intravenous infusion regimen that has recently been published in its phase III trial (the Horizon trial) is zoledronate 5 mg once yearly. The rationale of the long-interval dose-frequency regimen is to enhance drug adherence that was found to be less than 50% after the first year of use in the daily doses.

The bioavailability of an oral dose of amino bisphosphonates that is widely used in clinical practice, is approximately 1%. Absorption is substantially diminished when the drug is given with meals, milk, dairy products or fruit juice. It is strongly recommended to take the drug with an empty stomach, probably one hour before breakfast and with a big glass of plain water (180-240 ml). The patient should also be in the upright position for at least half an hour to avoid any side effects relating to reflux such as esophagitis that may lead to a serious consequence of esophageal stricture. After administration, between 20% and 80% of the absorbed bisphosphonate is taken up very rapidly by the bone, the remainder being rapidly excreted in the urine.3,4

The key to success in the use of bisphosphonates
is dependent upon the proper use of the drug with appropriate indications and considering its safety precautions. Cost-benefit deliberation should be applied on an individual basis. Current indications for drug use includes: those with a history of fragility fracture or low impact fracture such as falling from a standing height, those who are diagnosed of osteoporosis (bone mineral density, BMD $\pm 2.5$ standard deviation below the young adult mean using the same ethnic group reference database of BMD), those who have a significant risk for osteoporosis and fracture, for instance, prolonged use of a glucocorticoid for over three months ($\geqslant 7.5$ mg of Prednisolone daily over three months).

The physician should carefully assess any possible adverse effects that may be aggravated by the use of bisphosphonates. These include patients with pre-existing gastrointestinal (GI) irritation. Association of GI side effects with oral administration of bisphosphonates in dose and dose-frequency dependent manners has been reported. The use of a long-interval dose-frequency regimen has been shown to reduce the incidence of GI irritation. Bisphosphonates can impair calcium homeostasis due to its antiresorptive activity. Some suggest a test for serum calcium prior to drug initiation. Precaution should be exercised in those with renal compromise due to reports of renal failure induced by a high bolus dose of intravenous bisphosphonate. In addition, most of the bisphosphate trials have been conducted in patients with a creatinine clearance of 30 ml/min or over. Bisphosphonates should probably be avoided in those who are using aminoglycoside. Events of severe hypocalcemia with the co-medication have been reported. It is suggested to avoid bisphosphonates in those who have a history of aspirin sensitive asthma.1,3,4

Possible disadvantages of daily dose bisphosphonates are poor drug adherence and a significant incidence of GI irritation. Hence, the long-interval dose-frequency has been introduced to maximize drug adherence and minimize GI side effects. In contrast, long-interval dose-frequent bisphosphonates may induce some undesirable effects for example, the acute-phase reaction. Patients who are first exposed to a high dose bisphosphonate may experience symptoms such as fever, headache, muscle pain or flu-like symptoms. This reaction seems to be related to a systemic cytokine flare probably due to the activation of gamma, delta-T-cells via a mevalonate pathway specific mechanism though the etiology of this reaction is not well understood. The reaction mostly occurs within a few days and can usually be managed with simple analgesia (paracetamol).1,3,4

There are also other concerns for long-term user of bisphosphonates which include the occurrence of osteonecrosis of the jaw (ONJ), the possibility of frozen bone and its effects on bone healing after fracture. In most of the cases, ONJ has been reported in cancer patients who received chemotherapy, high dose intravenous bisphosphonate and underwent dental surgery e.g., tooth extraction or dental implantation. The incidence of ONJ in millions of patients using the standard dose of bisphosphonates for osteoporosis has been extremely rare. However, some recommend to have a dental check up and to undergo any dental surgery prior to the initiation of bisphosphonates. Patients are suggested to avoid unnecessary dental surgery during drug continuation. Special precaution is needed if dental surgery is indicated during drug use such as antibiotic prophylaxis, minimal trauma and suture socket.3

The issue on frozen bone has been a grave concern among physicians due to previous animal experiments using a much higher dose of bisphosphonates. Those studies revealed increases in microcracks that probably worsen bone strength. There is a report of severe suppression of bone turnover in nine patients using bisphosphonates for 3-8 years. Nonetheless, when you consider the reported nine cases out of millions of bisphosphate users, it is less convincing to relate the occurrence of frozen bone directly and solely to the use of bisphosphonates for osteoporosis purpose.

Effects of bisphosphonates on bone healing after fracture is another questionable issue that causes reluctance among orthopedic surgeons. Evidence in animal experiments reveal that bisphosphonates can delay callus formation in the healing phase post-fracture though there is no effect on bone strength. In human studies, bisphosphonates may theoretically exert its antiresorptive effects during the remodeling phase of the fracture healing that normally proceeds stepwise with the hema toma phase, soft callus formation, hard callus formation and the remodeling phase. However, there is no research evidence at the moment to support the notion that bisphosphonates delay or compromise bone healing.

More questions regarding the use of bisphosphonates include: how long should a bisphosphonate be continued? Are there any advantages for combination therapy with other antiresorptives or bone formative agents? Is there any age limitation in the use of bisphosphonates? Concerning the first issue, while Herbert Fleisch, the father of bisphosphonates voices no reason to discontinue the drug, others suggest to use a bisphosphonate for five years according to the available randomized controlled trials. Some suggest to use the drug for five years then reduce its dose-frequency. By the same token, there is neither any well-accepted guideline to use bisphosphonates as a combined therapy with other bone medication nor the issue of specific age range that will benefit most from bisphosphonates. These are still arbitrary and dependent on expert opinion at the moment.

REFERENCES


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