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Mini-Review

Bone Diseases Utilization of Bisphosphonates as Therapeutic Agents

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Abstract

The human body is composed of hard tissue (bones) and soft tissues. Bones are living growing tissues which constantly go through a cycle of renewal. When bone strength and flexibility are affected by certain conditions bone diseases could develop. They are different types of bone diseases including osteoporosis, Paget's disease, osteogenesis imperfect etc. Treatment of bone diseases may involve physical therapy, surgery, lifestyle measures and pharmacologic therapy. With pharmacologic therapy, bisphosphonates have demonstrated good efficacy and tolerability in the management of post-menopausal osteoporosis and other different skeletal disorders. In the present article, attempts will be made to present bone diseases and the types; management of the disorders including the use of bisphosphonates as the therapeutic agents of choice.

Introduction

The human body is composed of hard tissue (skeleton) and soft tissues. It contains about 206 bones. Bones are living growing tissues which constantly go through a cycle of renewal in a process called remodeling [1]. Bones (consisting of mainly collagen and calcium) provide a rigid framework (the skeleton), which

support the body and protect soft organs. Bones also provide anchorage points for striated muscles, which permit movement and posture. Health abnormalities (complications) leading to certain conditions that affect bone strength and flexibility are termed bone diseases. These conditions of bones are measured by bone mineral density (BMD) or bone mass [2].

Bone diseases can develop secondary to some autoimmune diseases such as Type I diabetes (minimal or no insulin production), systemic lupus erythematosus (SLE, widespread inflammation affecting many parts of the body), rheumatoid arthritis (RA, the body's immune system attacks the membranes around the joints and causes the cartilage to degrade), and celiac disease (the body develops an intolerance to gluten- a protein commonly found in wheat, rye, and barley) [3]. An autoimmune condition occurs when the body immune system begins to attack the body's own cells, tissue, and organs.

Bone diseases may be caused by nutrition imbalance (vitamin D and mineral(s) deficiency) aging, sex hormonal changes (estrogen or testosterone), drugs (corticosteroids, thyroid medicines, and others capable of reducing levels of sex hormones), genetic changes, and lifestyle (excessive alcohol consumption, low physical activity levels and smoking) [4].

Some of the symptoms of bone diseases may include joint pain, joint fracture, back pain, weakness low energy activities sprains infections, weight loss, fatigue, and lump (in the case of cancer tumour). It also may show no symptoms until a broken bone appears as in the case of osteoporosis (known as a "silent" disease) [5].

The diagnosis may involve (i) medical history of the patient, (ii) physical examination (checking out for weight loss, changes in muscle strength, changes in balance etc.), (iii) instrumental tests (X-ray imaging- to measure the body's bone mineral density, MRI scans- gives detailed images of bones and other tissues, including cartilage and ligaments), (iv) blood tests (in case of bone cancer), (v) biopsy (examination of small amount of bone tissue from the affected area under a microscope) [6].

Bone diseases can be classified as follows [7,8]:

1. Osteoporosis: is a progressive disease of skeletal system that results in a decrease in bone mass and mineral density. Bones namely hip, spine and distal forearm are brittle and weak and prone to easily fracturing. It is a clinically heterogeneous disease and can be iatrogenic (glucocorticoid-induced and transplant-related), physical (immobility), genetic and a result of hormone loss (postmenopausal and androgen-deprivation). An imbalance between osteoclast- mediated bone resorption (in excess) and osteoblast-mediated bone formation is the cause of osteoporosis.

2. Paget's Disease: This is a bone disorder that affects the bone remodeling (bone renewal) process. The renewal process occurs too quickly, resulting in bone deformities. In chronic condition, the process of rebuilding bones occurs at a faster rate, resulting in an unusual bone structure namely softer or larger bones and making bones prone to bending or fractures.

3. Osteomyelitis (bone infection): is an infection of the bone accompanied by inflammation of the fatty tissues within the bone (myelitis). It could be caused by bacteria or fungal infection of the bone. The disorder is rare but serious condition and can occur at any age however more common in young children.

4. Osteonecrosis (avascular necrosis or aseptic necrosis): It refers to bone tissue death as a result of disruption of blood flow to the bone. In most cases, it occurs due to trauma to the bone or in people with history of corticosteroid use, or excessive alcohol intake. The disorder commonly affects the hips, knees and shoulders.

5. Osteopenia: It is a disorder of the bone arising from mineral density decrease below a normal level but the decrease is not sufficient to cause osteoporosis. The prevalence of the disorder is higher (about 4 times) in females when compared with males.

6. Osteomalacia (bone softening): It is a health condition arising from the lack of appropriate bone hardening following its formation. In other words, it occurs due to incomplete bone mineralization leaving the collagen soft and vulnerable.

7. Osteoarthritis It affects the body's joints by degrading cartilage (the tissue that covers joints surface) and has the capacity to change the shape of bones. Osteoarthritis most often affects the hands, hips, and knees.

8. Osteogenesis imperfecta (brittle bone disease): It is a disease of the osteoblast that leads to a high bone turnover rate. Bone turnover rate increase is compounded by secondary bone loss induced by immobilisation generated by lower limb fractures.

Change or mutation in the genes responsible for the production of type I collagen. (protein necessary for strong bones formation) is implicated.

9. Bone metastasis: It is the proliferation or dissemination of bone cancer cells to other parts of the body. Any of the cells in the bone can develop into cancer cells. The most common types of primary bone cancers are osteosarcoma and Ewing sarcoma and the most common site for bone metastases is the spine.

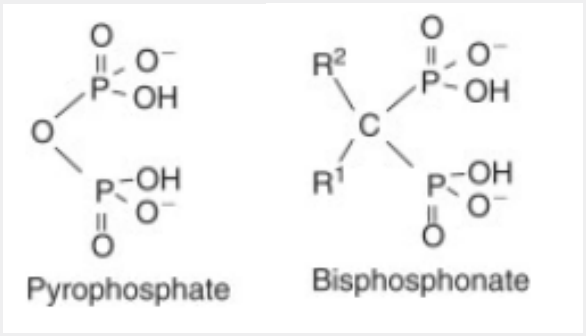
10. Rickets (childhood bone disorder): It occurs due to imperfect mineralization (a condition similar to osteomalacia) as a result of vitamin D deficiency. Deficiency of vitamin D causes inability of the body to metabolize calcium and phosphorous, which are essential for proper bone development and growth. The bones become soft and weak

All the above-named bone diseases including others not enumerated can be managed by a number of clinical procedures.

Treatment of bone diseases

The most appropriate treatment option depends on the degree of severity and type of bone disease. The purpose of treatment is to prevent or control symptoms and improve muscle strength and bone mass. Thus treatment may involve: (a) physical therapy to improve muscle strength and mobility, (b) surgery to preserve the joints or removal of bone tumor, (c) lifestyle measures-adequate calcium and vitamin D, exercise, counseling on fall prevention, avoidance of excessive use of alcohol, and smoking cessation to reduce bone loss and (d) pharmacologic therapy. Pharmacologic therapy is the mainstay of treatment of bone diseases in particular patients at high risk for fracture [9]. The therapeutic agents of choice are the bisphosphonates Bisphosphonate Therapeutic Agents:

Bisphosphonates are chemical analogues of the naturally occurring molecule (pyrophosphate) in which a carbon atom (P–C–P) is substituted for an oxygen atom (P–O–P).: The structures are



Within humans, pyrophosphates are released as a by-product of degradation of adenosine triphosphate (ATP) and many of the body's synthetic reactions, thus are readily detected in many tissues including blood and urine. Clinically, bisphosphonates are primary therapeutic agents against osteoclast-mediated bone loss namely low bone density, osteogenesis imperfecta, osteoporosis, Paget disease, bone metastatic, and hypercalcemia etc [10,11,12].

The mechanisms of action are (i) inhibition of osteoclast-mediated bone resorption by binding to hydroxyapatite crystals in bone, (ii) promotion of the apoptosis of osteoclasts actively engaged in the degradation of mineral on the bone surface., (iii) decreases mineral release and collagen or matrix breakdown in bone [13]. Each bisphosphonate has its own physicochemical and biological characteristics. The presence of a nitrogen or amino group on the structural side chains increases the bisphosphonate's antiresorptive potency (by 10 to 10,000) relative non–nitrogen-containing bisphosphonates. The skeletal retention of bisphosphonate depends on availability of hydroxyapatite binding sites and those not retained are rapidly cleared from the systemic circulation by renal excretion. The bisphosphonates are: (i) aledronate (ii) clodronate (iii) etidronate (iv) ibandronate (v) neridronate (vi) olpadronate (vii) pamidronate (viii) risedronate (ix) tiludronate (x) zoledronate (zoledronic acid). The amino bisphosphonates are ibendronate, pamindronate, risedronate, zoledronate and the rest belong to non-amino bisphosphonates class,

Bisphosphonates given orally are alendronate, ibandronate and risedronate while ibandronate, pamidronate zoledronic acid are by parenteral administration. The oral ones may be administered once weekly (alendronate and risedronate) or once monthly (ibandronate and risedronate) while the parenteral ones are given once yearly (zoledronic acid), and quarterly (ibandronate). Although all the above-named bisphosphonates are commercially available in most countries of the world for use in human bone diseases, the present study will consider some of the first line bisphosphonate therapeutic agents.

They include:

(a) Alendronate: chemically defined as 4-Amino-1-hydroxy-1-phosphonobutyl-hydroxyphosphinate. Clinically, it is effective in the prevention and treatment of postmenopausal osteoporosis, Paget disease, malignant hypercalcemia, metastatic bone diseases and hyperparathyroidism. The recommended dosage for the treatment of osteoporosis in men and women is 70 mg tablet once weekly or 10 mg tablet once daily. Treatment and prevention of osteoporosis in postmenopausal women may require dosage regimen of 5 mg tablet once a day or 35 mg tablet once weekly.

In the case of Paget disease the recommended dosage regimen is 40 mg tablet once a day for 6 months.

(b) ibandronate: chemically defined as 3-(N-methyl-N-pentyl) amino-1-hydroxypropane-1,1diphosphonic acid, monosodium salt. It is used in the prevention and treatment of osteoporosis.

Recommended dosage is 150mg film-coated tablet once-monthly by oral administration and as a 3mg/3ml prefilled syringe for IV bolus administration over 15 to 30 seconds once every 3 months.

(c) risedronate: is chemically designated as sodium; hydroxy-(1-hydroxy-1-phosphono-2-pyridin-3-ylethyl) phosphinate. Risedronate is therapeutically used for the treatment of osteoporosis, heterotopic ossification, Paget's disease, and cancer-induced bone loss

(d) zoledronic acid (zoledronate): chemically defined as 1-Hydroxy-(1H-imidazol-1-yl)-phosphonoethyl. It has the most pharmacological activity amongst the bisphosphonates and belongs to the third generation. It is used to prevent skeletal fractures in patients with cancers such as multiple myeloma and prostate cancer, as well as for treating osteoporosis. The recommended dose for the treatment of postmenopausal osteoporosis and treatment to increase bone mineral density in men with osteoporosis is a once yearly single intravenous infusion of 5 mg zoledronic acid.

(e) Pamidronate: is chemically defined as 3-amino-1-hydroxypropylidene-1,1- bisphosphonate. The first nitrogen-containing bisphosphonate investigated in clinical studies. The drug is used to treat malignant hypercalcemia, Paget's disease, osteolytic bone metastases of breast cancer, and osteolytic lesions of multiple myeloma.

Discussion

Bones provide a rigid framework which support the body and protect soft organ such as the skull shielding the brain. They also produce blood cells (bone marrow), provide storage for minerals (calcium, phosphorus), release hormone that helps control blood sugar levels. With all these ways bones contribute to good health, their importance in maintaining healthy states cannot be over-emphasized. However, disruption of bone healthy states leads to disease conditions which will invariably require treatment. Such treatments may be physical therapy, surgery, lifestyle measures and pharmacologic therapy. Pharmacologic therapy with bisphoshonates is the gold standard for the management of bone diseases [14].

Clinically, bisphosphonates are the most widely prescribed and used medications for the treatment of osteoporosis, owing in large part their good tolerability and the ability to dose them infrequently (from once weekly to once yearly, depending on the drug).

Bisphosphonates are poorly absorbed (when taken by mouth) thus making transport across lipophilic cell membranes difficult [15]. The ability to bind to bone mineral is a very vital pharmacological feature of bisphosphonates. Their binding to bone mineral can be through the two phosphonates (bidentate binding), a typical example is clodronate, or through a third moiety, namely hydroxyl or a nitrogen attached to the carbon atom (tridentate binding). Most of the bisphosphonates currently in clinical use, employ tridentate binding.

Their therapeutic effectiveness and mechanisms of action differ based on their pharmacological classes. The efficacy of the bisphosphonates increased from first generation (etidronate and clodronate), over second generation (pamidronate, alendronate), to third generation (risedronate) [16]. Etiodronate the least potent of bisphosphonates is currently rarely prescribed. The most common side effect of bisphosphonates is precipitation or aggravation of gastroesophageal reflux, although most patients tolerate the drugs without difficulty.

Conclusion

Attempts to improve bone mass and structure (for example in osteogenesis imperfecta) with calcitonin, cortisone, growth hormone, parathyroid hormone, thyroxin, vitamins A, C, and D, and minerals (aluminium, calcium, fluoride, magnesium phosphate, and strontium) have not been encouraging.

The arrival of bisphosphonates, a class of pharmacologically active chemical compounds that inhibit osteoclast action and the resorption of bone has provided effective and efficient therapy for bone diseases. Finally, bisphosphonates efficacy are in large part due to their good tolerability and the ability to dose them infrequently.

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