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Bisphosphonates in the Treatment of Osteoporosis

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Bisphosphonates are compounds derived from pyrophosphate, a byproduct of cellular cleavage of adenosine triphosphate (ATP), and are resistant to alkaline phosphatase by virtue of replacement of oxygen by carbon. The high affinity of the P–C–P structure for hydroxyapatite accounts for deposition in bone. Modification of the two side chains of carbon alters the potency of the drugs. Of those that have either completed or are undergoing clinical trials, the order of increasing potency for inhibition of bone resorption is etidronate, clodronate, tiludronate, pamidronate, alendronate, residronate and ibandronate (potency range: 1 to 10,000). Less than 5% of bisphosphonates are absorbed and the half life is a few hours. The drugs must be given on an empty stomach because food and beverages interfere with gastrointestinal absorption. Of the absorbed fraction, as much as 60% is taken up by the skeleton and the remainder is excreted unchanged in the urine. Etidronate, tiludronate, residronate, and alendronate are given orally, clodronate intravenously, and pamidronate and ibandronate by either route. At lower concentrations, bisphosphonates inhibit osteoclatic bone resorption, whereas at higher concentrations they may inhibit mineralization and cause osteomalacia. Inhibition of mineralization diminishes with increasing potency. In postmenopausal women, etidronate and alendronate for 3 yr were shown to inhibit bone resorption, increase bone mineral density (BMD) of the lumbar spine and hip, and prevent fractures without producing osteomalacia. Bone formation also is reduced as a consequence of diminished bone resorption but reduction is less than the reduction of bone resorption. In higher doses bisphosphonates may cause upper gastrointestinal disturbances but in recommended doses they generally are well tolerated and have an excellent safety profile.

Key Words: Bisphosphonates; bone resorption; osteoclasts; osteoporosis.

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Introduction

The development of bisphosphonates for clinical purposes began with the discovery that inorganic pyrophosphate is present in blood and urine and inhibits precipitation of calcium and phosphate *(1)*. Derivatives of pyrophosphate had been widely used for industrial purposes because of their property of inhibiting precipitation of calcium carbonate. Their principal use was as antiscaling additives in washing powders, water, and oil brines to prevent deposition of calcium carbonate scale *(2)*.

It was then found that pyrophosphate binds strongly to calcium phosphate, prevents both the formation and dissolution of calcium phosphate crystals, and inhibits calcification in vitro. Furthermore, ectopic calcification was prevented by parenteral administration, but not oral administration of pyrophosphate *(2)*.

Pyrophosphate itself was found to have two clinical uses: for bone scintigraphy when attached to ^{99m}Tc and as a main antitartar agent in toothpaste *(2)*. This restricted application led to a search for analogs with similar biologic activity that would not undergo hydrolysis by phosphatases *(2)*.

Chemistry

Pyrophosphate has as its core the structure P–O–P, and bisphosphonates have as their core P–C–P with substitution of the connecting oxygen by a carbon atom *(1–4)*. The P–C–P structure is essential for biologic activity and potency can be altered by changing the two lateral chains of the carbon atom or by esterification of the phosphate groups (Table 1) *(2–4)*. The structures of pyrophosphate and of geminal bisphosphonate are shown in Fig. 1, and the drugs that have been developed and their chemical structure and companies are listed in Table 2 *(2–4)*.

Mechanism of Action

Bisphosphonates block bone resorption by inhibiting osteoclastic function and by altering the morphology of osteoclasts both in vivo and in vitro. Bisphosphonates inhibit osteoclast resorption when added to osteoclasts that have been exposed to bone *(2)*. The activity persists even if the bones are treated with bisphosphonates before addition of osteoclasts. These findings indicate that osteoclasts are inhibited when they come into contact with bisphosphonate-

Table 1
Relative Potency of Bisphosphonates for Inhibiting Bone Resorption

Drug	Relative potency
Etidronate	1
Clodronate	10
Tiludronate	10
Pamidronate	100
Neridronate	100
Alendronate	100 – < 1000
Climadronate	100 – < 1000
EB-1053	100 – < 1000
Olpadronate	100 – < 1000
Ibandronate	1000 – < 10,000
Risedronate	1000 – < 10,000
YH 529	>10,000
Zoledronate	>10,000

containing bone. When given in small amounts, bisphosphonates are deposited preferentially beneath osteoclasts so that the concentration at that site can become very high. This may explain why a single administration of a bisphosphonate can have a prolonged effect in animals and humans *(2)*. Bisphosphonates can reduce production of lactic acid, lysosomal enzyme activity, production of reactive oxygen species, membrane permeability, proton adenosine triphosphatase (ATPase) of the ruffled border, and synthesis of prostaglandins. Bisphosphonates are effective when exposed to osteoblasts *(2)*. It was found that this effect is mediated by osteoblasts and that secretion of osteoclast-stimulating products by osteoblasts is inhibited *(2,5)*.

In cell culture, bisphosphonates inhibit formation of pits by isolated osteoclasts. In organ culture, they inhibit resorption by embryonic long bones and cultured calvaria. Inhibition occurs in the presence or absence of stimulation of bone resorption produced by parathyroid hormone, 1,25-dihydroxy vitamin D, prostaglandins, and products of tumor cells *(2)*. Inhibition of bone resorption by bisphosphonates correlates both in vivo and in vitro by cultured mouse calvariae *(2,6)*. In studies with clodronate, pamidronate, alendronate, and ibandronate, potency in the rat correlates with potency in humans *(7)*. Thus, the rat can be used to assay new bisphosphonates since the response in rats will predict the response in humans.

No well-defined structure–function relationship has been found. However, length of the aliphatic carbon chain is important for activity. The effect on bone resorption increases and then decreases with chain length *(2)*. Addition of a hydroxyl group at carbon 1 increases potency and addition of a nitrogen atom in the side chain markedly increases potency *(2)*. The length of the side chains of nitrogen-containing side chains is important with four carbons being the most active, as found with alendronate. A primary amine is not required for biologic activity since

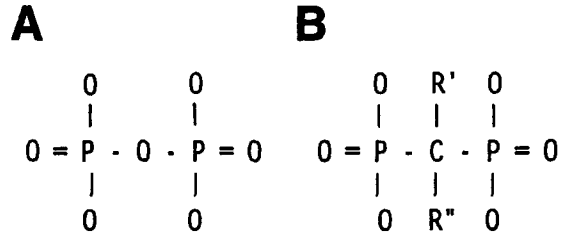

Fig. 1. Chemical structure of pyrophosphate **(A)** and geminal bisphosphonate **(B)**.

dimethylation of the aminonitrogen of pamidronate—as found with olpadronate increases potency. Activity is further enhanced by addition of other groups to the nitrogen atom—as found with ibandronate *(2)*.

Cyclic geminal bisphosphonates are also very potent, particularly those with a nitrogen atom on the ring as found with risedronate *(2)*. Compounds with the highest activity, YH 529 and zoledronate, contain an imidazol ring with a nitrogen atom *(2)*.

The P–C–P structure is required for activity and potency is dependent on the side chain. There is evidence that a three-dimensional structure is required and activity of stereoisomers show as much as a 10-fold difference in activity. This could mean that the action of bisphosphonates is mediated by a yet to be identified receptor *(2)*.

Pharmacokinetics

Bisphosphonates are given orally and systemically by iv injection *(2–4)*. Less than 5% of the drugs are absorbed and absorption is diminished by food, orange juice, coffee, milk, iron supplements, calcium, and dairy products *(3,4)*. Thus, bisphosphonates must be administered in the morning on an empty stomach with a glass of water and patients should remain in the upright position. The more potent bisphosphonates, particular those containing nitrogen, are even more poorly absorbed. Some absorption occurs in the stomach, more occurs in the small intestine, and absorption declines with age *(2)*.

In blood, two-thirds or more of etidronate and clodronate, half of pamidronate, and much less of other drugs—such as alendronate—are ultrafilterable. The remainder is bound to proteins, mostly albumin, or is present in small aggregates *(2)*. About 20% of clodronate, 50% of etidronate, and more of alendronate and pamidronate are taken up by bone. Some bisphosphonates, especially pamidronate, are deposited in other organs, particularly liver and spleen, and deposition is dose-dependent. This is attributed to formation of complexes with metals or to formation of aggregates caused by too rapid iv administration. The complexes undergo phagocytosis by macrophages of the reticuloendothelial system *(2)*. Too rapid administration can result in renal failure, an event attributed to formation of aggregates.

Bisphosphonates are rapidly taken up by bone, and findings indicate that blood is cleared in the first passage.

Table 2
Bisphosphonates, Chemical Structure, and Companies that Manufacture Them

Drug	Chemical structure	Company or companies
Alendronate	(4-amino-1-hydroxybutylidene)-bisphosphonate	Gentili; Merck
Cimadronate	[(cycloheptylamino)-methylene]-bisphosphonate	Yamanouchi
Clodronate	(dichloromethylele)-bisphosphonate	Astra; Boehringer Mannheim; Gentili; Leiras; Rhône-Poulenc Rorer
EB-1053	[1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bisphosphonate	Leo
Etidronate	(1-hydroxyethylidene)-bisphosphonate	Gentili; Procter & Gamble
Ibandronate	[1-hydroxy-3-(methylpentylamino)propylidene]-bisphosphonate	Boehringer Mannheim
Neridronate	(6-amino-1-hydroxyhexylidene)-bisphosphonate	Gentili
Olpadronate	[3-(dimethylamino-1-hydroxypropylidene]-bisphosphonate	Gador
Pamidronate	(3-amino-1-hydroxypropylidene)-bisphosphonate	Ciba-Geigy; Gador
Risedronate	[1-hydroxy-2-(3-pyridinyl-ethylidene)-bisphosphonate	Procter & Gamble
Tiludronate	[[(4-chlorophenyl)thio]-methylene]-bisphosphonate	Sanofi
YH 529	[1-hydroxy-2-imidazo-(1,2-a)pyridin-3-ylethylidene]-bisphosphonate	Yamanouchi
Zoledronate	[1-hydroxy-2-(1H-imidazol-1-yl) ethylidene]-bisphonate	Ciba-Geigy

Alendronate is preferentially deposited beneath osteoclasts, and this also is true, but to a lesser extent for etidronate when given in comparable doses. The effects of the bisphosphonates occur very rapidly and the time required for maximal effect and duration of effect is dose-dependent *(2)*.

Bisphosphonates are not metabolized because the carbon atom is resistant to hydrolysis by alkaline phosphatase *(2–4)*. However, some metabolism may occur in the side chains. Most of the drug is bound to bone, 20–50% depending on the drug, and the remainder is excreted unchanged in urine. The half-life in serum is short, a few hours or less, whereas the half-life in bone may be several years *(2–4)*. Bisphosphonates are deposited in bone and released during resorption and uptake is dose-dependent. The rate of removal is dependent on the rate of skeletal remodeling *(2)*. Renal clearance is higher than glomerular filtration. This indicates that there may be one or more mechanisms for renal tubular transport *(2)*.

Side Effects and Toxicity

Studies in experimental animals indicate little in the way of toxicity. Investigations of teratogenicity, mitogenicity, and carcinogenicity have been negative *(2)*. Care must be taken when administering bisphosphonates intravenously. If given too rapidly, hypocalcemia may result as a consequence of formation of aggregates with calcium so that the rate of infusion in humans must be carefully regulated *(2)*. Toxicity varies widely from one drug to another, and there is no way to predict the effects of an individual drug. Bisphosphonates may produce upper gastrointestinal irritation and bleeding when given in toxic or near toxic doses, and the effect is dose-related *(2,4)*. Etidronate increases serum phosphorus by inhibiting tubular transport *(4)*. Some drugs such as etidronate and pamidronate cross the placenta and, therefore, could affect the fetus *(2)*. Several bisphosphonates including clodronate, etidronate, and pamidronate may alter renal function when given in toxic doses *(2)*. Etidronate in large doses inhibits mineralization and produces osteomalacia, but this does not occur with the cyclic regimen recommended for treatment of osteoporosis *(2,4)*. Etidronate and clodronate can cause fractures, possibly by decreasing skeletal remodeling and increasing bone mass and bone fragility as occurs in congenital osteopetrosis and, in the case of etidronate, by producing osteomalacia as well *(2)*.

Clinical Uses

Bisphosphonates are effectively utilized for treatment of Paget's disease, hypercalcemia of malignancy, and osteoporosis *(2,4)*. The drugs also are used as derivatives of ^{99m}Tc for bone scans to identify fractures, metastases, and other skeletal lesions, for inhibition of calcification in patients with ectopic calcification and ossification, and as antitartar agents in toothpastes *(2)*.

Osteoporosis

Under normal circumstances, bone undergoes continual remodeling. Osteoclasts are activated and resorb a small segment of bone, called a resorption pit or Howslips lacunae. Osteoblasts are then recruited and repair the site, but repair is never complete. Remodeling with incomplete repair causes age-related bone loss and the higher the rate of remodeling, the higher the rate of bone loss. The rate of skeletal remodeling and bone loss are accelerated in postmenopausal women as a consequence of loss of ovarian function and diminished production of estrogen. The primary effect of estrogen on bone is to inhibit osteoclastic bone resorption *(2)*.

Bisphosphonates are very effective for the treatment of postmenopausal osteoporosis, and do so by markedly inhibiting bone resorption and skeletal remodeling. For

example, alendronate was shown to reduce urinary *N*-telopeptide of type I collagen, a highly specific marker of bone resorption, by more than 50% and when given for 3 yr, to increase bone mineral density (BMD) of the lumbar spine by 8%, femoral neck by 5%, trochanter by almost 8%, and total body by 1.5% *(8,9)*. In addition to alendronate *(8,9)*, clodronate *(10)*, etidronate *(11)*, pamidronate *(12,13)*, and tiludronate *(14,15)* have each been shown to be effective in increasing bone mass, and bone density remained unchanged for 2 yr after treatment with pamidronate was discontinued *(14)*. Alendronate *(9)* and etidronate *(11)* were shown to reduce the incidence of fractures of the spine and other sites. More recently, alendronate was shown to reduce the incidence of hip fractures by 50%.

Bisphosphonates probably reduce the incidence of fractures by increasing bone mass and the mechanical properties of bone. For example, alendronate was shown to increase bone mass and the mechanical properties of bone of baboons *(16)* and rats *(17)*.

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