

Bisphosphonates: Calcium Antiresorptive Agents

Jack DeRuiter and Randall Clark

I. Introduction and Overview

Bisphosphonates, synthetic bone-seeking compounds, are used in the management of patients with various disorders affecting the skeleton, including osteoporosis, metastatic bone disease, and Paget's disease of bone. Their specific pharmacological properties include selective uptake at active bone sites, suppression of osteoblast and osteoclast-mediated bone resorption, reduction in the number of osteoclasts and long skeletal retention. These properties in turn depend on the structure of the bisphosphonate molecule, shown in general form in Figure 1 below. The “bis” prefix is a term indicating two groups - phosphonates groups, in this case - attached to a common carbon atom. The bioactive moiety comprising the R_2 chain of the molecule is considered primarily responsible for their effect on resorption and small changes in this part of the structure of can result in large differences in their anti-resorptive potencies. The uptake and binding to bone mineral is determined by the bi- or tridentate ligand (hydroxybisphosphonate) of the molecule, which is also thought to be responsible for the physicochemical effects, the most important being the inhibition of growth of calcium crystals. The most effective structures for binding to bone mineral consist of the two phosphonate groups attached to a central carbon and substitution at R_1 with a hydroxyl or amino group that provides tridentate binding.

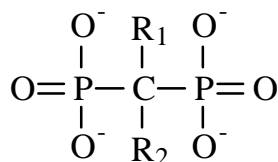


Figure 1: General Bisphosphonate Structure

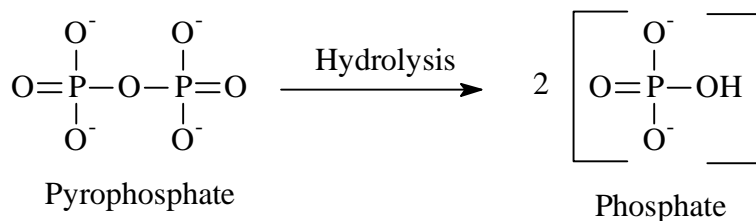
Both phosphonates groups are required for maximal bone affinity and may be related to the ability to simultaneously bind/chelate with more than one calcium site per molecule. Bone affinity and antiresorptive abilities appear to be two separate properties of the bisphosphonates, the bone binding properties of these compounds may simply serve to localize these drugs at the site of osteoblast and osteoclast activity.

Binding to bone is a requirement for antiresorptive activity, however two compounds with similar bone binding affinity can show vastly different antiresorptive properties. Alendronate is 200 to 1000 times more active in inhibiting bone resorption than etidronate and appears to increase bone mass density by 4 to 7%. Pamidronate is about 10 times less potent than alendronate.

II. Bisphosphonate Development and Chemistry

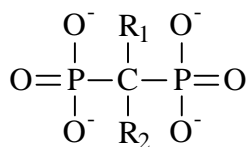
- Pyrophosphates and polyphosphates:

1. Have been used for decades as anti-scaling agents, additives to washing powders, active ingredient in anti-tartar toothpastes and additives to water to prevent calcium carbonate deposits.
2. Pyrophosphate and alkaline phosphatase are present in plasma, urine, teeth and bone: Possible role as physiologic regulator of bone calcification (formation) and/or decalcification (destruction).
3. In vitro studies show that pyrophosphate and polyphosphates bind to calcium phosphate (hydroxyapatite) of bone and inhibits the formation and dissolution of bone calcium phosphate crystals.
4. Pyrophosphate and polyphosphates are rapidly hydrolyzed. Thus these compounds are ineffective in modifying bone when administered orally. Even when administered by injection, activity is limited by rapid hydrolysis.



- Bisphosphonate Development:

1. Analogs of pyrophosphate in which the linking oxygen is replaced with a carbon atom resulting in:
 - Resistance to hydrolysis: Chemically stable P-C-P bond
 - Ability to vary structure and activity by varying R₁ and R₂ groups



Bisphosphonate Drugs: General Structure

2. Physical-Chemical Properties of bisphosphonates: Effects on calcium phosphate and multiple independent factors involved in activity:

- High affinity for calcium phosphate: Imparts bone specificity and low systemic toxicity

- Ability to alter function of cells involved in bone remodeling
 - Inhibit crystal formation
 - Inhibit crystal aggregation
 - Inhibit crystal dissolution

3. Ionization of the Bisphosphonates: Note the pKas and physiologic species.

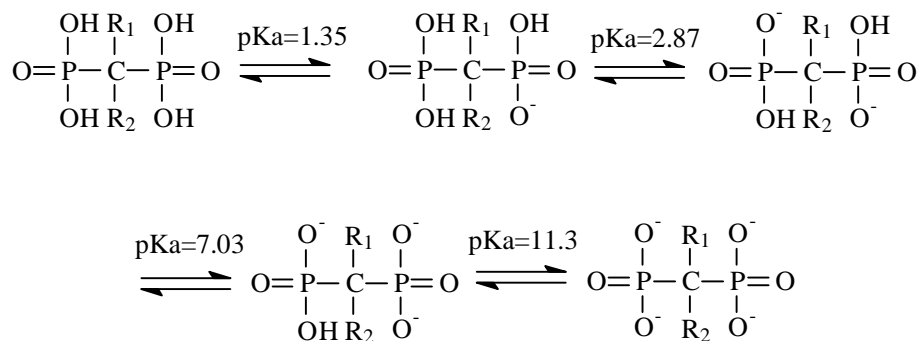
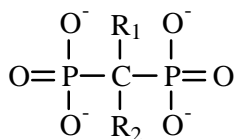
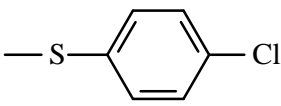
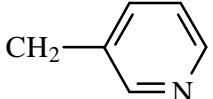


Figure 2. Bisphosphonate Ionization

III. Bisphosphonate Structures and General Structure-Activity Relationships

1. Bisphosphonate Products:



	Bisphosphonate	R ₁	R ₂
First Generation	Etidronate:	OH	CH ₃
	Clodronate:	Cl	Cl
Second Generation	Pamidronate:	OH	CH ₂ CH ₂ NH ₂
	Alendronate:	OH	CH ₂ CH ₂ CH ₂ NH ₂
	Tiludronate:	H	
Third Generation	Risedronate:	OH	

2. Structure-Activity Relationships (SAR): See mechanism of action section to interpret SAR
 - Bisphosphonate moiety is essential for hydroxyapatite affinity. The monophosphonates are not active!
 - Side chain (R₁ and R₂ groups): responsible for inhibition of resorption. A single carbon atom between phosphate residues required
 - Dichloro (clodronate) and hydroxy-alkyl (etidronate) derivatives (first generation agents): Inhibit bone mineralization (at higher doses) and resorption (see mechanism below)
 - Incorporation of an OH at C1 optimizes affinity for for hydroxyapatite and increases anti-resorptive activity (increases both components of activity)
 - Incorporation of a 4-chlorothiophenyl substituent at C1 (tiludronate): 10X more active than etidronate
 - Incorporation of an aminoalkyl side chain at C1 increases anti-resorptive potency 10-fold, allows for separation between antiresorptive and bone mineralization effects (see mechanism below).
 - Length of carbon chain important: 2-5 is tolerated and 3 Cs is optimal as in alendronate. Alendronate is about 1000X more potent than etidronate and pamidronate is 100X more active than etidronate.
 - Incorporation of a nitrogen heterocycle (pyridine) at C1 further enhances anti-resorptive potency (Third generation agents: Risedronate): Risedronate is as much as 5000X more potent than etidronate

IV. Mechanism of Action

- Mechanism of action not clearly elucidated at this point:
 - Inhibition of bone resorption and mineralization: Action dependent of BP drug structure and concentration (dose).
 - Etidronate actions: Inhibition of bone resorption=inhibition of mineralization
 - Other bisphosphonates: Inhibition of bone resorption>inhibition of mineralization
- Relative anti-resorptive activities: Risedronate>Alendronate>Pamidronate>Clodronate> etidronate)

- Anti-resorptive activity (animal models):

First generation agents: 0.1-10mg P/kg s.c.

Second generation agents: 0.01-1 mg P/kg s.c.

Third generation: as low as 0.001-1 mg P/kg s.c.

- Reduce bone turnover accompanied by a small increase in bone balance: Utility in osteoporosis
- Continuous administration of BPs does **not** result in a continuous, progressive increase in bone anti-resorptive activity. Bone resorption reaches a plateau, the height of which is dependent on dose: remains constant and does not increase. Daily administration for short periods of time during a 90 day cycle. For example, dosed 1Xdaily for 3 weeks during a 90 day cycle.
- Effective in preventing bone loss associated with osteoporosis and experimental osteoporosis associated with sciatic nerve section, orchidectomy, ovariectomy, paraplegia, hypokinesia, heparin, corticosteroids and thyroid hormone.
- BPs have a positive effect on mechanical characteristics of bone: increase bone mineral density(BMD) and mechanical strength.
- Mechanisms by which BPs decrease bone turnover and increase BMD:
 - Decrease in bone resorption is followed by a coupled, induced decrease in bone formation, producing a temporary gain in calcium balance
 - Lowered bone turnover lengthens the time span until bone is again destroyed, permitting more complete mineralization.
 - Bone is turned over continuously as "packets" referred to as basic multicellular units (BMUs). In osteoporosis the amount of bone formed in BMUs is less than the amount resorbed (net bone loss). BPs decrease bone turnover resulting in a decrease in bone loss in the BMU.
- Direct (osteoclast) and/or indirect (osteoblast) actions: Not clearly elucidated
 - Osteoclasts: Catalyze bone resorption: BPs bind to hydroxyapatite (under the osteoclasts) resulting in decreased cell activity (alter enzyme activity, morphological changes) and decreased numbers of cells (lower recruitment or induction of apoptosis)
 - Osteoclasts: Catalyze bone formation: BPs induce osteoblasts to produce a substance that decreases osteoclasts recruitment

V. Pharmacokinetics

- Poor (<1% to 10%) and variable intestinal absorption (**Polarity!**)
 - Inverse correlation between pharmacologic activity and oral bioavail.
 - Absorption by passive diffusion from gut
 - Milk and other dairy products, orange juice, coffee and calcium and iron products reduce absorption (**Form insoluble complexes!**)
 - Poor absorption and local actions related to GI toxicity.
- Bound to plasma proteins: Minimal impact on distribute/half-life
- 20-80% of the absorbed dose is rapidly taken up by bone: 20% clod, 50% etidronate, >50% alendronate and others)
- Remainder is rapidly excreted in urine: Short apparent half-life
- Low distribution: rapid bone uptake, polarity and rapid excretion
- Not metabolized (distribution and P-C-P bond)
- Long skeletal retention: Years
- Low penetration into many other cells: minimal metabolism, minimum toxicity

Bisphosphonate Pharmacokinetic Summary:

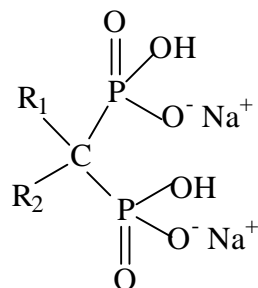
Bisphosphonate	Oral Bioav.	Food Effect	Metab	Vd	PPB	Urine	Plasma Clr	Terminal T _{1/2}
Alendr	0.7%	Decr	None	28L	78%	50%		10 years
Etidron	1-6%	Decr	None	1.4L/kg		30-50%	6 hrs	>90days
Pamidr	NA?	NA	None			51%		>300 days
Risedr	0.7%	Decr	None	6.3L/kg	24%	50%		
Tiludr	6%	Decr	Very Little					

Notes: Divalent ions interfere with absorp., Unabsorbed drug excreted in feces, All about 60% distributed to bone.

VI. Adverse Reactions

- Local/GI syndrome: Poor absorption and local, irritant actions in gut
- Systemic toxicity relatively low: Low systemic exposure (polarity!)
- Long term effects on bone structure and function????

VII. Dosage Form



Disodium salt dosage form

VIII. Therapeutic Uses:

A. Products:

- Alendronate (Fosamax[®])
- Risedronate (Actonel[®])
- Pamidronate (Aredia[®])
- Etidronate (Didronel[®] and Didronel IV[®])
- Tiludronate (Skelid[®])

B. Indications:

1. Osteoporosis: For the treatment and prevention of osteoporosis in postmenopausal women. Postmenopausal women (alendronate)
2. Paget's disease of bone: For treatment of patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic or at risk for future complications from their disease (alendronate, risedronate, tiludronate); treatment of symptomatic Paget's disease (oral etidronate); treatment of moderate-to-severe Paget's disease (pamidronate).
3. Heterotopic ossification (oral etidronate): Prevention and treatment of heterotopic ossification following total hip replacement or caused by spinal injury.
4. Hypercalcemia of malignancy: In conjunction with adequate hydration for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases (pamidronate); when inadequately managed by dietary modification or oral hydration, concurrent therapy is recommended as soon as there is a restoration of urine output (parenteral etidronate); for hypercalcemia of malignancy which persists after adequate hydration has been restored (parenteral etidronate).
5. Breast cancer/Multiple myeloma (pamidronate): In conjunction with standard antineoplastic therapy for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma.

C. Unlabeled Uses:

1. Etidronate: For the treatment of postmenopausal osteoporosis and prevention of bone loss in early postmenopausal women (intermittent cyclical therapy of 400 mg/day for 14 days followed by 76 days of elemental calcium, 500 mg/day); glucocorticoid-induced bone loss in postmenopausal women (400 mg/day \times 1 month, then 400 mg/day for 2 weeks every third month plus calcium and ergocalciferol).
2. Pamidronate: May be useful in treating the following conditions: Postmenopausal osteoporosis; hyperparathyroidism; to prevent glucocorticoid-induced osteoporosis; to reduce bone pain in patients with prostatic carcinoma; immobilization-related hypercalcemia.
3. Risedronate: Prevention of bone loss in postmenopausal women (5 mg/day cyclically for 2 years on then 1 year off therapy).