Bisphosphonates in Clinical Practice.

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Bisphosphonates are analogues of pyrophosphate, where P-C-P forms the core of molecule in place of P-o-P. They suppress resorption of bone while itself getting absorbed to hydroxyapatite of bone.

Bisphosphonates are classified according to modification of side chains with differing abilities to inhibit bone resorption.

Chemical modification	Examples	Anti resorptive potency
First generation:	Etidronate	1
Short alkyl or halide side chain.	Clodronate	10
	Tiludronate	10
Second generation:	Pamidronate	100
NH ₂ - terminal group.	Alendronate	100-1000
Third generation:	Risedronate	1000-10,000
Cyclic side chain.	Ibandronate	1000-10,000
	Zoledronate	10,000

Modified from watts NB: Treatment of osteoporosis with bisphosphonates (Review) *Endo crinol metab clin North Am* 27:419-439, 1998.

Bisphosphonates are widely used for treatment of osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, prevention and treatment of metastatic cancer of bone.

Mechanism of Action.

Although mechanism of action of Bisphosphonates is not fully understood, their action and metabolic effects in the mevalonate pathway for isoprenoid lipid synthesis has been delineated.

- Bisphosphonates have strong affinity for calcium phosphate. These drugs concentrate at sites of active remodeling in acidic zone under osteoclasts. These get internalized into osteoclasts by endocytosis. Endocytosis results in accelerated apoptosis of osteoclasts and disruption of cytoskeleton. Bisphosphonates also inhibit differentiation of osteoclasts by suppressing IL-6.
- Bisphosphonates especially second and third generation ones have important metabolic effects in mevalonate pathway for isoprenoid lipid synthesis. They inhibit prenylation of certain GTP- binding proteins, the net effect results in inactivation of osteoclasts, impaired vesicle fusion and enhanced apoptosis. This may also impart anti tumor action on bony metastasis.

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Etidronate.

First generation bisphosphonate administered both intravenously and orally. Continuous therapy produces osteomalacia. It has been replaced by newer and more potent bisphosphonates.

Clodronate.

Clodronate has demonstrated efficacy in variety of diseases including Paget's disease, hypercalcemia of malignancy and osteolytic bone metastasis. Short term intravenous administration (300mg/day for 5 days) or longer course of oral clodronate (1600mg/day for 6 months) effectively reduces bone pain and improves mobility in most patients with Paget's disease(1).

Pamidronate.

It belongs to second generation bisphosphonate group. It is 10- 100 times more potent than etidronate. It is infused in a dose of 60-90 mg over 2-4 hours weekly or monthly depending upon the condition. Pamidronate has been helpful in Paget's disease, hypercalcemia of malignancy and in bony metastasis. Thrombophlebitis of injected vein, bony pains, fever and leucopenia are main adverse effects.

Alendronate.

It is an oral bisphosphonate approved by FDA for prevention and treatment of osteoporosis. Alendronate is most commonly given as once a week preparation of 70 mg for treatment of osteoporosis (2).

Adverse effects as with other oral bisphosphonates include stomach pain, esophagitis, myalgias, arthralgias and rarely osteonecrosis of jaw. Long term use can cause subtrochanteric fractures.

Risedronate.

It is a third generation oral bisphosphonate administered at a dosage of 5mg /day. Data reveals risedronate increases bone mass and reduces risk of new vertebral fractures 50% better than placebo (3, 4). Risedronate is also given 35 mg once a week or 150 mg once a month for osteoporosis. It is given for the treatment of Paget's disease (30mg/day for 2 months) and can be repeated if relapse occur after two months(5,6).

Ibandronate.

It is an amino bisphosphonate approved for prevention and treatment of post menopausal osteoporosis. It is given orally as well as intravenously. Ibandronate 150mg/ month is used for the treatment of osteoporosis (7).

Zolendronate.

Zolendronate belongs to third generation group of bisphosphonates which contain a nitrogen atom within a heterocyclic ring. It is up to 10,000 times more potent than first generation bisphosphonates (8).

Zolendronate inhibits resorption of bone. It induces apoptosis in osteoclasts. It is administered intravenously, is usually protein bound (28 -53%) and is excreted unchanged in urine (39%) and faeces (<3%) within 24 hours.

Zolendronate has proved helpful in conditions characterized by osteoclast mediated bone resorption.

- a. Hypercalcemia of malignancy.
- b. Multiple myeloma.
- c. Bone metastasis from solid tumors.
- d. Osteoporosis.
- e. Paget's disease.

Zolendronate is approved for treatment and prevention of postmenopausal osteoporosis (9). 5 mg zolendronate once a year has been shown to reduce the risk of incident vertebral fractures, hip fractures, and other major osteoporotic fractures by 68%, 40% and 20% respectively compared to placebo(9).

Dosage of zolendronate depends upon the condition for which used. For hypercalcemia of malignancy and bone metastasis 4 mg of zolendronate is infused over 15 minutes, can be repeated after 7 days and 3 to 4 weeks respectively. 5 mg of zolendronate is infused over 15 minutes in osteoporosis and Paget's disease.

Dosage of zolendronate is modified if creatinine clearance of patient is less than 60 ml/min.

Adverse effects of zolendronate.

Zolendronate can cause severe hypocalcaemia which can lead to rhythm disturbances of heart, tetany and laryngeal spasm. Adverse effects include bone pain, nausea, fever,

fatigue, anemia, vomiting, constipation, dyspnoea, diarrhea, anorexia, arthralgias, and head ache, other electrolyte abnormalities like hypophosphatemia, hypokalemia, and hypomagnesaemia.

Zoledronate has been associated with osteonecrosis of jaw (2 in 100000 patient- years) and stress fractures of lateral cortex of the femoral shaft.

Patients with preexisting cerebrovascular and cardiovascular abnormalities should be carefully monitored while receiving zoledronate (10).

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