**Bisphosphonates – mechanisms of action**

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**SYNOPSIS**

The bisphosphonates inhibit the resorption of bone by osteoclasts and may have an effect on osteoblasts. They are structurally similar to pyrophosphate, a normal product of human metabolism. This structure gives the drugs a high affinity for bone and they probably remain in bone for many years. A high affinity for hydroxyapatite enables radiolabelled bisphosphonates to be used in bone scanning. The bisphosphonates are effective in the treatment of diseases of increased resorption.

Index words: bone metabolism, pharmacokinetics.

After the promise shown in the early clinical use of etidronate and clodronate, newer bisphosphonates were synthesised, containing a primary nitrogen atom in an alkyl chain (pamidronate, alendronate). This increased the antiresorptive potency by up to one hundred times. Later modifications of the R₂ side chain to produce compounds containing tertiary nitrogen groups, such as ibandronate and olpadronate, further increased potency. The most potent bisphosphonates to date, risedronate and zoledronate, contain a nitrogen atom within a heterocyclic ring. They are up to 10 000 times more potent than etidronate in some experimental systems. Although the structure of the R₂ side chain is the major determinant of antiresorptive potency, both phosphate groups are required for the drugs to be pharmacologically active.

**Clinical pharmacology**

Intestinal absorption is very low and variable (1–10%). It takes place by passive diffusion in the stomach and upper small intestine, and is reduced if the drug is given with calcium or iron. Bisphosphonates are therefore never given at meal times or with dairy products.
The poor and variable absorption, prolonged effects with storage in bone, together with the development of new, highly potent bisphosphonates, can explain why intermittent intravenous administration is efficacious in disorders of increased bone resorption. Although successful trials of bisphosphonates in osteoporosis have used oral formulations, a current trial is studying three-monthly intravenous injections of a potent member of this class.

Intermittent intravenous infusion is a successful and convenient means of treating hypercalcaemia of cancer, multiple myeloma, or bone metastases from solid tumours. With the ever increasing potency of bisphosphonates, single rapid intravenous injection is now being studied as an alternative to the less convenient and prolonged infusions.

**Mechanisms of action of bisphosphonates**

**Ectopic calcification**

Pyrophosphate inhibits ectopic calcification in vivo, and this was one of the earliest observed actions of bisphosphonates.\(^1\) Etidronate remains the bisphosphonate most likely to inhibit calcification when given experimentally or clinically. The concentrations of etidronate required to inhibit bone resorption are similar to those which prevent calcification. This has the disadvantage that significant undermineralisation of bone can occur if etidronate is not administered with care in limited dosage. As new bisphosphonate analogues came along, the alterations to the carbon side chains had the effect of progressively increasing their potency as inhibitors of bone resorption, so that they have essentially no effect on calcification.

**Remodelling**

When bisphosphonates are given to growing rats, remodelling at the ends of long bones is reduced and an abnormal shape results. This effect is currently used as a model to estimate the potency of new compounds.

**Resorption**

Bisphosphonates are very effective inhibitors of bone resorption in vivo and in vitro.\(^2\) They act rapidly, and the maximum effect and its duration are related to the dose. In organ cultures of bone, whatever treatment is used to enhance bone resorption can be inhibited by bisphosphonates. In many of these organ culture systems the structure-activity relationships seen among the bisphosphonates in vitro are preserved in vivo studies in the rat. When the resorption of isolated osteoclasts is studied on bone or dentine slices, this too is inhibited by bisphosphonates. The bisphosphonates appear to be taken up by osteoclasts active upon bone, and to inhibit crucial intracellular processes.

**Osteoclastic and osteoblastic activity**

Bisphosphonates may not act solely through direct actions on osteoclasts. They can inhibit the activity and proliferation of osteoblasts in vitro. Osteoblasts are important stimulators of osteoclast formation and activity, and many factors that stimulate bone resorption do so through an effect on the osteoblast. One of the possible mechanisms of bisphosphonate action is to stimulate the osteoblast to produce inhibitor(s) of osteoclast formation and therefore of bone resorption.\(^3\)
**New insights into molecular mechanisms of bisphosphonate action**

The molecular mechanisms by which these effects on osteoclasts are produced are currently being unravelled. The first pyrophosphate-like bisphosphonates (such as etidronate and clodronate) are incorporated into adenosine triphosphate (ATP), a source of energy in the cell. The resulting compounds are resistant to hydrolysis and their accumulation leads to the death of the osteoclast.

It is not known whether the nitrogen-containing bisphosphonates are also incorporated into ATP. They probably are not, since their cellular effects are produced at concentrations much lower than those of the first generation bisphosphonates. The more potent nitrogen-containing bisphosphonates have been recently shown to inhibit enzymes in the mevalonate pathway. This biosynthetic pathway is responsible for the production of cholesterol and also of isoprenoid compounds (farnesyl-diphosphate and geranylgeranyl-diphosphate) which are required for the post-translational modification (prenylation) of small GTPases. These small GTPases are signalling proteins that regulate a number of cell processes such as membrane ruffling, cytoskeletal organisation and trafficking of vesicles, which are required for osteoclast function.

**REFERENCES**


**FURTHER READING**


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**Self-test questions**

The following statements are either true or false (answers on page 139)

7. Etidronate can interfere with bone mineralisation as well as inhibit resorption.

8. The similarity of the bisphosphonate molecules means there is little variation in their potency.