EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Bisphosphonates – mechanisms of action

T. John Martin, Director, and Vivian Grill, Endocrinologist, St Vincent's Institute of Medical Research, Melbourne

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.

(Aust Prescr 2000;23:130–2)

Introduction

Pyrophosphate is a normal by-product of metabolism. Bisphosphonates are analogues of pyrophosphate which have potent inhibitory effects on bone resorption. They are effective drugs in bone disorders characterised by increased bone resorption, such as Paget's disease, osteoporosis, hypercalcaemia of cancer, multiple myeloma and bony metastases. The bisphosphonates adsorb very effectively to hydroxyapatite, the crystalline form of calcium and phosphate in bone. This makes them a useful component in bone scanning agents.

The pharmacological actions of all bisphosphonates are similar, but the marketing strategies of the pharmaceutical industry have directed different compounds to the treatment of particular disorders of bone resorption.

Chemistry of bisphosphonates

Pyrophosphate is produced by many anabolic processes. It is rapidly hydrolysed to its two constituent phosphate groups. If the linking oxygen atom in the pyrophosphate molecule is replaced by a carbon atom, a bisphosphonate is formed (Fig. 1). These analogues are completely resistant to hydrolysis and are chemically extremely stable. Like pyrophosphate, the bisphosphonates bind to the hydroxyapatite crystals of bone and prevent both their growth and their dissolution.

Structure-activity relationships

The biological activity of the bisphosphonates can be modified by altering the structure of the two side chains on the carbon atom. The binding to bone mineral depends upon the P–C–P structure and is enhanced by including a hydroxyl group at R_1.

The structure and three-dimensional configuration of the R_2 side chain determines the cellular effects of bisphosphonates, and their relative efficacies as inhibitors of bone resorption. Each bisphosphonate has its own profile of activity, determined by its unique side chain (Fig. 2).

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 R_2 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 R_2 side chain is the major determinant of antiresorptive potency, both phosphonate groups are required for the drugs to be pharmacologically active.

Clinical pharmacology

Bisphosphonates are characterised by poor intestinal absorption but highly selective localisation and prolonged storage in bone. Due to their stability the bisphosphonates are absorbed, stored and excreted unchanged.

Absorption

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.

Fig. 1

Chemical structure of pyrophosphate and bisphosphonates

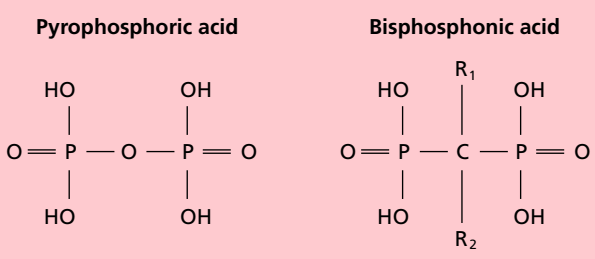
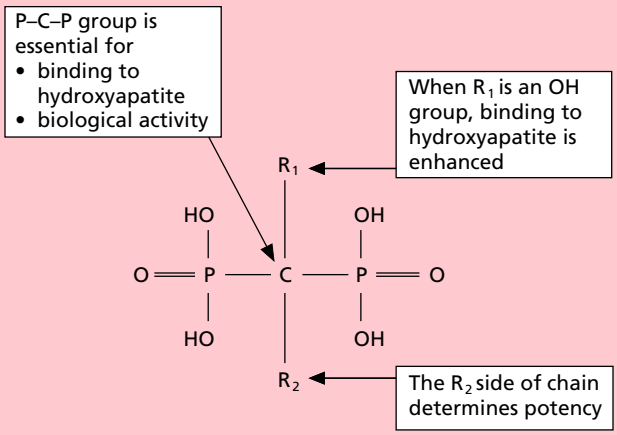


Fig. 2

Structure-activity relationships of bisphosphonates

The binding to hydroxyapatite and the biological activity of bisphosphonates depends on the P–C–P group and the structure of the R_1 and R_2 side chains. (Modified with permission from Russell et al, 1999).



Bisphosphonate	R_1 side chain	R_2 side chain
Etidronate*	OH	CH_3
Clodronate*	Cl	Cl
Pamidronate*	OH	$CH_2CH_2NH_2$
Alendronate*	OH	$(CH_2)_3NH_2$
Risedronate*	OH	CH_2–3–pyridine
Tiludronate*	H	CH_2–S–phenyl-Cl
Ibandronate*	OH	$CH_2CH_2N(CH_3)$(pentyl)
Zoledronate	OH	CH_2–imidazole
YH529	OH	CH_2–2–imidazo-pyridinyl
Incadronate (YM175)	H	N–(cyclo-heptyl)
Olpadronate	OH	$CH_2CH_2N(CH_3)_2$
Neridronate	OH	$(CH_2)_5NH_2$
EB-1053	OH	CH_2–1–pyrrolidinyl

* Indicates bisphosphonates already approved for one or more indications in one or more countries

Clearance

With 20–80% of absorbed bisphosphonate rapidly taken up by bone and the remainder rapidly excreted in the urine, the half-life of bisphosphonates in the circulation is short (0.5–2 hours). Deposition in bone takes place at sites of bone formation and resorption. This property is made use of in nuclear medicine when bisphosphonate labelled with technetium 99 is used in bone scanning.

After being taken up by bone and producing an effect, bisphosphonates are stored in bone. The half-life appears to be very long (probably up to several years) because of this skeletal storage. It is this prolonged skeletal retention that explains why single or short courses of intravenous injections can be effective for a long time in patients with diseases which have a high turnover of bone, such as Paget's disease. Bisphosphonates stored deep in bone are probably inactive, but clearly significant amounts can be released in the resorptive process.

Intravenous administration

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 *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.[4] 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.[5]

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.[6] This biosynthetic pathway is responsible for the production of cholesterol and also of isoprenoid compounds (farnesyldiphosphate and geranylgeranyldiphosphate) 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.

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FURTHER READING

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E-mail: j.martin@medicine.unimelb.edu.au

Self-test questions

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

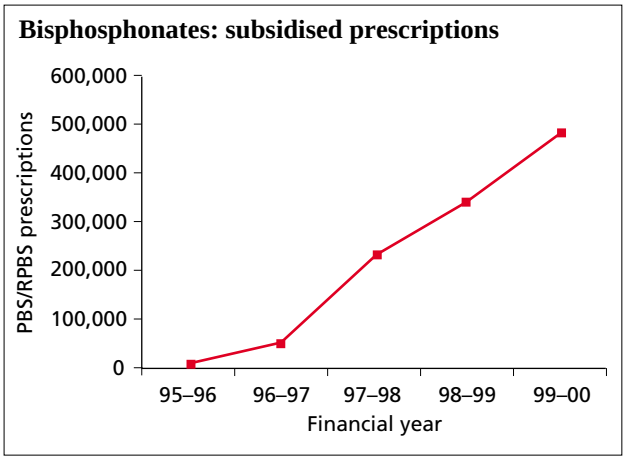
7. Etidronate can interfere with bone mineralisation as well as inhibit resorption.
8. The similarity of the bisphosphonate molecules means there is little variation in their potency.

Subsidised prescriptions for bisphosphonates

The bisphosphonates are available through the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme. Their use is increasing, with alendronate accounting for most of the prescriptions.

Bisphosphonates: subsidised prescriptions 1999–2000

Alendronate	428,912
Clodronate	5,230
Etidronate	1,932
Pamidronate	1,008
Calcium and etidronate	43,441
Tiludronate	3,022
Total	**483,545**



Data supplied by the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee