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Review

Bisphosphonates: The first 40 years

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ABSTRACT

The first full publications on the biological effects of the diphosphonates, later renamed bisphosphonates, appeared in 1969, so it is timely after 40 years to review the history of their development and their impact on clinical medicine.

This special issue of BONE contains a series of review articles covering the basic science and clinical aspects of these drugs, written by some of many scientists who have participated in the advances made in this field.

The discovery and development of the bisphosphonates (BPs) as a major class of drugs for the treatment of bone diseases has been a fascinating story, and is a paradigm of a successful journey from 'bench to bedside'. Bisphosphonates are chemically stable analogues of inorganic pyrophosphate (PPi), and it was studies on the role of PPi as the body's natural 'water softener' in the control of soft tissue and skeletal mineralisation that led to the need to find inhibitors of calcification that would resist hydrolysis by alkaline phosphatase.

The observation that PPi and BPs could not only retard the growth but also the dissolution of hydroxyapatite crystals prompted studies on their ability to inhibit bone resorption. Although PPi was unable to do this, BPs turned out to be remarkably effective inhibitors of bone resorption, both in vitro and in vivo experimental systems, and eventually in humans.

As ever more potent BPs were synthesised and studied, it became apparent that physico-chemical effects were insufficient to explain their biological effects, and that cellular actions must be involved. Despite many attempts, it was not until the 1990s that their biochemical actions were elucidated.

It is now clear that bisphosphonates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of the bone-resorbing osteoclasts. Bisphosphonates are internalised by osteoclasts and interfere with specific biochemical processes. Bisphosphonates can be classified into at least two groups with different molecular modes of action. The simpler non-nitrogen containing bisphosphonates (such as etidronate and clodronate) can be metabolically incorporated into non-hydrolysable analogues of ATP, which interfere with ATP-dependent intracellular pathways. The more potent, nitrogen-containing bisphosphonates (including pamidronate, alendronate, risedronate, ibandronate and zoledronate) are not metabolised in this way but inhibit key enzymes of the mevalonate/cholesterol biosynthetic pathway. The major enzyme target for bisphosphonates is farnesyl pyrophosphate synthase (FPPS), and the crystal structure elucidated for this enzyme reveals how BPs bind to and inhibit at the active site via their critical N atoms. Inhibition of FPPS prevents the biosynthesis of isoprenoid compounds (notably farnesol and geranylgeraniol) that are required for the post-translational prenylation of small GTP-binding proteins (which are also GTPases) such as rab, rho and rac, which are essential for intracellular signalling events within osteoclasts. The accumulation of the upstream metabolite, isopentenyl pyrophosphate (IPP), as a result of inhibition of FPPS may be responsible for immunomodulatory effects on gamma delta ($\gamma\delta$) T cells, and can also lead to production of another ATP metabolite called ApppI, which has intracellular actions. Effects on other cellular targets, such as osteocytes, may also be important.

Over the years many hundreds of BPs have been made, and more than a dozen have been studied in man. As reviewed elsewhere in this issue, bisphosphonates are established as the treatments of choice for various diseases of excessive bone resorption, including Paget's disease of bone, the skeletal complications of malignancy, and osteoporosis. Several of the leading BPs have achieved 'block-buster' status with annual sales in excess of a billion dollars.

As a class, BPs share properties in common. However, as with other classes of drugs, there are obvious chemical, biochemical, and pharmacological differences among the various BPs. Each BP has a unique profile

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in terms of mineral binding and cellular effects that may help to explain potential clinical differences among the BPs.

Even though many of the well-established BPs have come or are coming to the end of their patent life, their use as cheaper generic drugs is likely to continue for many years to come. Furthermore in many areas, e.g. in cancer therapy, the way they are used is not yet optimised. New 'designer' BPs continue to be made, and there are several interesting potential applications in other areas of medicine, with unmet medical needs still to be fulfilled.

The adventure that began in Davos more than 40 years ago is not yet over.

This article is part of a Special Issue entitled Bisphosphonates.

Contents

Introduction . . . 3
How studies on calcification mechanisms and the role of pyrophosphate led to the discovery of the bisphosphonates . . . 3
Dating the anniversary . . . 6
Bisphosphonates inhibit bone resorption in many different experimental systems, and this enabled the pharmacological development of bisphosphonates . . . 7
Special features of the pharmacology of bisphosphonates . . . 7
Defining structure activity relationships . . . 9
Understanding the mechanisms of action of bisphosphonates at a cellular level . . . 9
Understanding the mechanisms of action of bisphosphonates at a biochemical level . . . 10
Clinical applications of bisphosphonates . . . 11
Current challenges and new directions with bisphosphonates . . . 13
Reflections on the past, present and future . . . 14
References . . . 15

Introduction

All the bisphosphonates (BPs) currently in use as drugs in clinical medicine possess two P–C bonds, linked through a single carbon to give a geminal bisphosphonate with the core structure made up of P–C–P bonds. They are chemically stable analogues of pyrophosphate compounds, which are found widely in nature. The simplest of the naturally occurring pyrophosphates is inorganic pyrophosphate (PPi), and it was the discovery that this compound circulates in the body as an endogenous 'water softener' that led on to the work with bisphosphonates.

Chemically the bisphosphonates were first synthesised in the 1800s [1], but it is only in the past 40 years that they have been used to treat disorders of calcium metabolism. Even etidronate, which was the first bisphosphonate to be used in humans, was originally synthesised over 100 years ago [2].

The early uses of bisphosphonates were mainly as corrosion inhibitors, also as complexing agents in the textile, fertiliser and oil industries, as well as for many other industrial processes [3]. Their use as 'water softeners' was based on their ability to act as sequestering agents for calcium, and in particular their ability to inhibit calcium carbonate precipitation, as do polyphosphates. This has been applied in the prevention of scaling in domestic and industrial water installations.

A recent search in PubMed under the term 'bisphosphonates' revealed over 19,000 publications, and even this large list this does not cite abstracts, nor all publications and the many books and review articles available that describe the chemistry, pharmacology, and clinical applications of bisphosphonates [4–12].

The discovery of the biological effects of the BPs has its origin in studies of calcification mechanisms and the role of pyrophosphate. It is instructive to trace the steps by which this came about. This review will focus on the historical aspects, and on topics not covered elsewhere in this issue, including aspects of pharmacology, and the interrelationship between BPs and pyrophosphate metabolism, bearing in mind that disturbances in pyrophosphate metabolism have an important role in several diseases.

How studies on calcification mechanisms and the role of pyrophosphate led to the discovery of the bisphosphonates

The beginning of this story can be traced back to 1962, when Herbert Fleisch spent a postdoctoral year at the University of Rochester with Bill Neuman. W F Neuman (1919–1981)[1] headed the biochemistry section in the Department of Radiation Biology in conjunction with the U.S. Atomic Energy Commission at the university, and with his wife, Margie, had published their landmark book entitled *The Chemical Dynamics of Bone Mineral* in 1958 [13].

In those days studies of bone were dominated by the evolving understanding of the biochemistry of the constituents of bone matrix, and the physical chemistry of bone mineral, in contrast to today's emphasis on genetics and bone cell biology.

The Neuman laboratory had been established to study the effects of radioisotopes in bone in the aftermath of the use of atomic weapons in the second-world war. The prevention of skeletal uptake of hazardous bone-seeking isotopes, such as uranium, radium, and strontium, was a research priority, and the study of calcification mechanisms was part of this endeavour.

Herbert Fleisch had recently graduated in medicine from the University of Lausanne where his father was Professor of Physiology. He had plans to become an orthopaedic surgeon, but his time with the Neumans was to change that forever, much to the benefit of the field of bone research. However Herbert retained close contact and collaboration with the orthopaedic community throughout his career, and Davos was the venue for the AO training courses for many years.

The key observation made by Neuman and Fleisch was that body fluids were super-saturated with respect to calcium phosphate and that the addition of collagen could act as a nucleating agent for the deposition of hydroxyapatite crystals in vitro [14]. They reasoned that

[1] The William F. Neuman Award is still presented annually by the American Society for Bone and Mineral Research for "outstanding and major scientific research" in bone and mineral research.