Disambiguating the bisphosphonates

The bisphosphonates comprise a class of therapeutic agents that inhibit bone resorption and are frequently used in medicine in the treatment of among others osteoporosis, skeletal metastases from solid tumours, hypercalcaemia of malignancy, multiple myeloma and Paget’s disease [1]. First synthesised in 1865 in Germany, their use had been primarily industrial as these molecules proved to be powerful inhibitors of corrosion, served as complexing agents in various industries, were added to washing powders to prevent scaling and reduced tartar formation when incorporated in toothpastes [2, 3].

The inhibitory effects of bisphosphonates on the dissolution of hydroxyapatite in vitro and bone resorption in vivo were first described by Herbert Fleisch and was quickly followed by the first clinical application of bisphosphonates in humans, when in 1969 the treatment of myositis ossificans with etidronate was described [4–6].
ambiguity

When introduced in medicine, these derivatives of endogenous pyrophosphate (Figure 1A) were erroneously dubbed 'diphosphonates', a name that would persevere in the medical literature for almost 20 years [7]. In addition, these molecules have been referred to in the English scientific literature with a variation of different names such as 'biphosphonates' and 'diphosphonates', even until the present day [8, 9].

However, these various names are not synonymous and define distinct chemical structures that are different from the actual molecules in use today. Moreover, the use of incorrect terminology has complicated the indexing of manuscripts in the US National Library of Medicine's (NLM) Medline database and researchers querying this resource should be aware of these ambiguities. Papers are catalogued in Medline using a controlled vocabulary thesaurus called Medical Subject Heading (MeSH), which consists of sets of terms naming descriptors in a hierarchical structure [10]. Updated annually, the term 'diphosphonates' was included in 1977 when it superseded the previous descriptor 'phosphonic acids' and the term 'diphosphonates' was included in 1977 when it superseded the previous descriptor 'phosphonic acids' and continues to be the preferred indexing term by the NLM even today, although the word 'biphosphonates' became a proper MeSH term in 1989 [11].

nomenclature

According to the published recommendations of the 'Commission on Nomenclature of Organic Chemistry' of the International Union of Pure and Applied Chemistry (IUPAC), the numerical prefix 'di-' is used to indicate that a chain of two identical substituents is linked to a parent group (Figure 1B) [12]. In contrast, the term 'bis-' refers to a total of two identical substituents separately bound to a parent compound (Figure 1C) [13]. The prefix 'bi-' on the other hand is used in assemblies of organic ring compounds denoting that two identical cyclic hydrocarbon systems are joined (Figure 1D). Finally, the term 'dis-' is not used in the recommended nomenclature guidelines and is most likely a contraction of 'di-' and 'bis-'.

A last point of confusion regarding the naming of bisphosphonates is the notion of geminal and vicinal functional groups. Geminal is derived from the Latin word 'gemini'—meaning twins—and refers to two functional groups that are attached to the same atom. In contrast, non-geminal structures are called vicinal (from the Latin word 'vicinus' meaning neighbour) if the two functional groups are bonded to two adjacent carbon atoms [14]. In the literature, the P–C–P structure is often quoted to be characteristic for the bisphosphonates. As follows from the previous definitions, however, this structure only defines the geminal bisphosphonates and non-geminal bisphosphonates have been described that effectively inhibit calcification in vitro and in vivo, as well as bone resorption [15].

conclusion

Over the years, the use of various different names for the geminal bisphosphonates has resulted in surprisingly little confusion in the medical literature and it appears likely that these terms will continue to be used interchangeably for many years to come. Nonetheless, an effort should be made by the scientific community and publishers to use the correct nomenclature as proposed by the IUPAC.

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disclosures

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references


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