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Review

Bisphosphonates: Pharmacokinetics, bioavailability, mechanisms of action, clinical applications in children, and effects on tooth development

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ABSTRACT

Bisphosphonates (BPs) avidly bind to calcium crystals and inhibit osteoclastic bone resorption, making them useful for treatment of skeletal disorders such as osteoporosis, Paget's disease, osteogenesis imperfecta and metastatic bone diseases. BPs therapeutically act by causing toxic effects on osteoclasts or interfering with specific intracellular pathways in those cells. BPs that possess nitrogen in their composition are called nitrogen-containing BPs (NBPs) and include alendronate, pamidronate, risedronate, ibandronate, and zoledronate. Simple BPs or non-NBPs do not have nitrogen in their composition, include etiodronate and clodronate, and were the first to be tested in animals and clinically used. Because BPs may be administered to pregnant women or children during deciduous and permanent teeth development, it is expected that they might disturb tooth eruption and development. A review of current literature on pharmacokinetics, bioavailability, mechanisms of action, and clinical applications of BPs in children, and their effects on tooth eruption and development is presented.

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Contents

1. Introduction

Bisphosphonates (BPs) avidly bind to calcium crystals and inhibit osteoclastic bone resorption (Fleisch, 2007), making them useful for treatment of skeletal disorders such as osteoporosis, Paget's disease, osteogenesis imperfecta (OI) and metastatic bone diseases (Baroncelli and Bertelloni, 2014; Russell, 2011; Cremers

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and Papapoulos, 2011; Fleisch, 1998; Massa et al., 2006). BPs therapeutically act by causing toxic effects on osteoclasts or interfering with specific intracellular pathways in those cells (Fleisch, 1998; van Beek et al., 1999, 2002). These chemical compounds are analogs of pyrophosphate (PPi; P—O—P) in which the geminal oxygen has been substituted by carbon, originating the P—C—P bond, which is resistant to enzymatic hydrolysis (Rodan and Fleisch, 1996). They were first studied as inhibitors of calcification that would resist to hydrolysis by alkaline phosphatase.

BPs are effective inhibitors of bone resorption depending on the dosage (Cremers and Papapoulos, 2011; Russell, 2011). These drugs have a molecule formed by one central carbon atom (C) linked to two phosphate atoms (P) plus two side chains (R1 and R2). The presence of these side chains enables the synthesis of numerous compounds with different properties. The basic P—C—P structure allows a great number of variations, either by changing the two side chains R1 and R2 on the carbon atom, or by esterifying or altering the phosphate groups (Fleisch, 1998). In general, a hydroxyl substitution at R1 enhances the affinity of BPs for calcium crystals, while the presence of a nitrogen atom in R2 enhances their potency and determines their mechanism of action (Russell, 2011). BPs that possess nitrogen in their composition are called nitrogen-containing BPs (NBPs) and include alendronate, pamidronate, risedronate, ibandronate, and zoledronate. Simple BPs or non-NBPs do not have nitrogen in their composition, include etiodronate and clodronate, and were the first to be tested in animals and clinically used. Alendronate, pamidronate and zoledronate are widely used for treatment of children with bone diseases. The molecular formulas of alendronate [alendronic acid or (4-amino-1-hydroxy-1-phosphonobutyl) phosphonic acid], pamidronate [pamidronic acid or (3-amino-1-hydroxy-1-phosphonopropyl) phosphonic acid] and zoledronate [zoledronic acid or (1-hydroxy-2-imidazol-1-yl-1-phosphonoethyl) phosphonic acid] are $C_4H_{13}NO_7P_2$, $C_3H_{11}NO_7P_2$ and $C_5H_{10}N_2O_7P_2$, respectively (http://pubchem.ncbi.nlm.nih.gov/).

Because BPs are used in many bone pathologies and may be administered to pregnant women or children during deciduous and permanent teeth development (Maasalu et al., 2003; Massa et al., 2006; McCarthy et al., 2002), it is expected that they might disturb odontogenesis and lead to defects in dental structures. Although BPs' mechanisms of action have been exhaustively studied in bone, little is known about their effects on tooth development, and just a few studies on the association between dental defects and the use of those chemical compounds are available (do Espírito Santo et al., 2010; Fuangtharnthip et al., 2000; Nelson-Filho et al., 2012; Simmelink, 1987; Wakamatsu, 1991; Weile et al., 1990, 1993; Yamada et al., 2000).

This paper presents a review of current knowledge on BPs' pharmacokinetics, bioavailability, mechanisms of action, clinical applications in children and effects on tooth development.

2. Pharmacokinetics, bioavailability and mechanisms of action

BPs can be administered either orally or intravenously. They are poorly absorbed in humans (NBPs have an absorption of about 0.7%, whereas non-NBPs have a slightly higher gastrointestinal absorption of 2–2.5%) (Baroncelli and Bertelloni, 2014; Cremers and Papapoulos, 2011). Since they exhibit a poor bioavailability via the oral route, most BPs are usually administered via intravenous route (Baroncelli and Bertelloni, 2014; Cremers and Papapoulos, 2011). They are distributed widely throughout the body – primarily in bone, but also in soft tissues such as the liver, kidney and spleen (Baroncelli and Bertelloni, 2014; Cremers and Papapoulos, 2011). BPs bind preferentially to bones with high turnover rates thus their distribution in bones is not homogeneous (Baroncelli and Bertelloni, 2014). Skeletal retention of BPs shows a very wide range (Cremers and Papapoulos, 2011). For example, in patients with osteoporosis skeletal retention of pamidronate ranged between 47% and 74% (Cremers et al., 2002), while in patients with breast cancer and bone metastases it ranged between 12 and 98% (Cremers et al., 2005). Skeletal retention of zoledronate in patients with breast cancer has been shown to range between 25% and 93% (Chen et al., 2002). If monthly administration of zoledronate 4 mg to patients with bone metastases will provide 48 mg in one year, individual patients will retain in their skeleton a BP amount ranging between 12 and 45 mg, a 3-fold difference (Cremers and Papapoulos, 2011).

The overall pharmacological effects of bisphosphonates on bone appear to depend upon two key properties: affinity for bone mineral and inhibitory effects on osteoclasts (Ebetino et al., 2011). BPs enter the extracellular space by paracellular transport and bind to free hydroxyapatite that is available on the surface of bone. Though the knowledge is still incomplete, there has been significant progress in understanding the binding properties of BPs (Cremers and Papapoulos, 2011). Studies indicate that BPs can be located in bone forming and resorbing surfaces (Masarachia et al., 1996). Different mineral affinities between BPs can influence their distribution, and lower affinity compounds have more penetrating factor to the osteocyte network (Roelofs et al., 2010). Because of the presence of hydroxyapatite also in enamel and dentin, it may be hypothesized that BPs could be incorporated in those structures, altering their mechanical properties and reducing their resistance to acids released by cariogenic bacteria.

Once adsorbed to bone mineral surfaces, BPs enter into close extracellular contact with osteoclasts, osteoblasts and osteocytes. The bone resorption process promoted by osteoclasts causes the disassociation of BPs from the bone surface followed by intracellular uptake into osteoclasts by fluid phase endocytosis (Coxon et al., 2008).

Inside osteoclasts, non-NBPs and NBPs present different mechanisms of action. The former can be incorporated into ATP in place of the β, γ pyrophosphate, producing AppCp-type (a non-hydrolysable ATP analog). This incorporation occurs due to the similarity of the non-NBPs to PPi, which leads into the accommodation in the class II of aminoacyl-tRNA ligase active site in place of PPi. This allows a back-reaction involving the condensation of a non-NBP with AMP thus resulting in the AppCp-type, which interferes with ATP-dependent intracellular pathways leading to osteoclast apoptosis (Lehenkari et al., 2002; Rogers et al., 2011). NBPs are much more potent than non-NBPs in inhibiting bone resorption. They can block the formation of intermediates along the mevalonate biosynthesis pathway that leads to synthesis of cholesterol and other sterols. Specifically, it inhibits farnesyl pyrophosphate synthase (FPPS), a key branch-point enzyme in the mevalonate pathway that generates isoprenoid lipids utilized in sterol synthesis and for the post-translational modification of small GTP-binding proteins essential for osteoclast function (Baroncelli and Bertelloni, 2014; Ebetino et al., 2011; Luckman et al., 1998). Inhibition of FPPS generates the accumulation of isopentenyl pyrophosphate (IPP), the metabolite immediately upstream of FPPS in the mevalonate pathway. This accumulation causes a transient inflammatory acute phase response soon after intravenous administration of the drug and also leads to the production of ApppI (a non-hydrolysable ATP analog), which inhibits the mitochondrial adenine nucleotide translocase (ANT) and can result in apoptosis (Mönkkönen et al., 2006). Isoprenoid lipids like farnesyl pyrophosphate (FPP) and geranylgeranyl diphosphate (GGPP), generated by the melavonate pathway, are required for post-translational modification (prenylation) of proteins. As aforementioned, prenylation of small GTP-binding proteins is essential for osteoclast

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