Farnesyl Pyrophosphate Synthase Bound with Alendronate

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Abstract

Alendronate is used for osteoporosis. It binds to bone and blocks osteoclasts, thus inhibiting breakdown. On a molecular level, alendronate binds to farnesyl pyrophosphate synthase (FPPS) within osteoclasts causing these cells to go through apoptosis.

Introduction

Case:
A 62 year old female was prescribed alendronate for osteoporosis. She was also receiving calcium and vitamin D supplements to promote bone health. It is crucial to space administration of alendronate and calcium two hours apart to ensure proper absorption of the medication. This is an opportunity for patient education.

Osteoporosis:

- Osteoporosis caused by the loss of organic bone matrix and decreased bone mineral density.[1]
- Bone loss is caused by excessive bone resorption—this happens when osteoclasts break down bone and release minerals causing the transfer of calcium from the bone into the blood.[1]

Alendronate:

- Member of the bisphosphonate drug class
- Models the bisphosphonate pharmacophore, but has a flexible amino group that increases specificity and potency. [2]
- Works by inhibiting osteoclasts in bone. [3]
- Farnesyl pyrophosphate synthase (FPPS) is an enzyme involved in cholesterol synthesis, which is vital to osteoclast function in bone. [4]
- Alendronate binds FPPS and inhibits the enzyme. Ultimately, osteoclasts undergo apoptosis. [5]

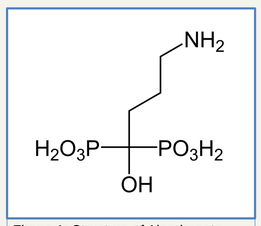

Figure 1: Structure of Alendronate. Picture adapted from: http://upload.wikimedia.org/wikipedia/commons/e/e0/Alendronate.png

Molecular Story

Alendronate Binding to Bone

- The oxygen atoms on the phosphonate groups of alendronate interact with the calcium ions in bone.[6]
- Taken up into osteoclasts via pinocytosis where it reaches its site of action.[7]

Three conformations of Farnesyl Pyrophosphate Synthase (FPPS)

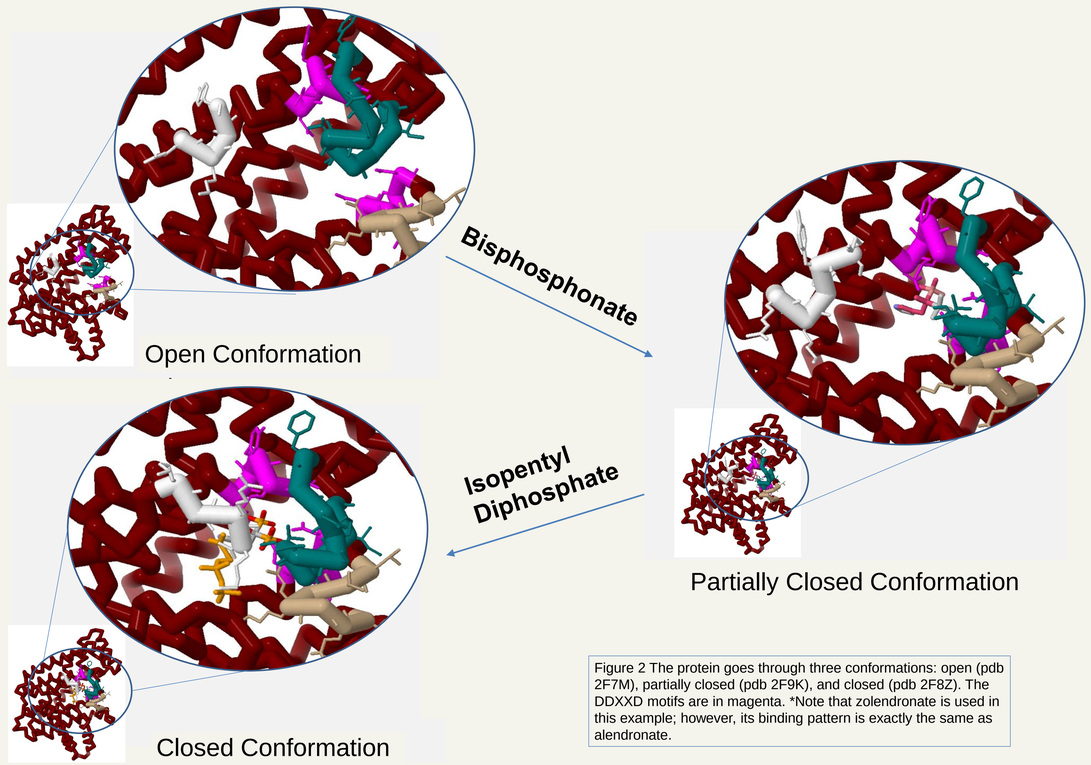

Figure 2 The protein goes through three conformations: open (pdb 2F7M), partially closed (pdb 2F9K), and closed (pdb 2F8Z). The DDXXD motifs are in magenta. *Note that zolendronate is used in this example; however, its binding pattern is exactly the same as alendronate.

- Alendronate binds the open conformation of FPPS. [8]
- Once isopentyl diphosphate binds, the protein goes into a closed conformation.[8]
- Alendronate stabilizes this conformation by interacting with the DDXXD motifs.[8]

Alendronate's Active Site

- The orientation of the R2 nitrogen binds tightly with the hydroxyl group of Thr201.[9]
- FPPS has two aspartic rich structures which helps organize the three zinc atoms within the FPPS active site to which the alendronate backbone P-C-P binds.[9]

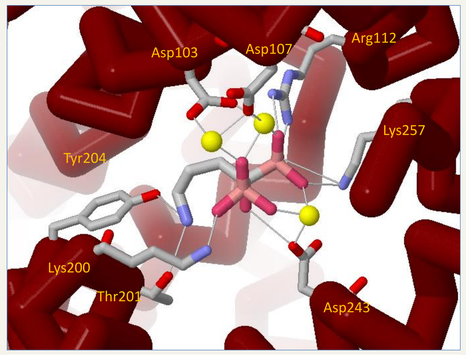

Figure 3. The binding site of FPPS with alendronate in the middle (light cpk); interacting amino acids (cpk); zinc (yellow). pdb 2F92

The Next Question

Despite the efficacy of alendronate, it is far from being the perfect drug. It has been associated with esophageal keratinocytes, leading to stomach pain, bloating, and heartburn.[10] These side effects have led to low medication adherence.

In order to increase compliance and improve efficacy, alendronate could be made into an effervescent tablet. Thus, the tablet would dissolve in water before administration. In effervescent form, there would be less contact time between bisphosphonate and the esophageal cells leading to less side effects.[11] Additionally, there may be an increase in bioavailability due to greater absorption.

A second alternative to enhance effectiveness would be to change the structure of the drug in order to increase bioavailability. Making a prodrug form of alendronate could be achieved by either adding a cyclosaligenyl or S-Acyl-2-thioethyl group to the phosphonate group. The medication could then be cleaved prior to getting to the site of action.[12] This would allow the drug to cross the GI tract more easily.

Summary

Alendronate slows osteoporosis progression by inhibiting osteoclasts from breaking down bone. Alendronate's phosphonate groups and long flexible tail interact with FPPS. For best results, patients should be on vitamin D and calcium supplementation while taking alendronate. It is the pharmacist's role to educate patients on the importance of spacing out the supplements from alendronate for better absorption of the medication.

References

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