Allopurinol Interaction with 6-Mercaptopurine: A Patient Case Related to Medicinal Chemistry and Drug Design

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Abstract

Gout is a medical condition in which levels of uric acid build up in the blood causing deposits to form in the joints, tendons and tissues. Uric acid is the product of oxidation of purines by xanthine oxidase. Allopurinol is a common medication used to treat gout, and it functions as a xanthine oxidase inhibitor to reduce the production of uric acid in the body. Allopurinol gets converted to oxipurinol in the body, which is an active metabolite of the drug that also binds to xanthine oxidase.

Xanthine oxidase, which is located in the synovial joints, is a major target of a systemic inflammatory disorder known as rheumatoid arthritis. Azathioprine is a medication used to suppress the body's immune response from damaging the joints, and it is a prodrug which undergoes conversion to 6-mercatopurine. Like allopurinol, azathioprine also binds to xanthine oxidase.

Concomitant administration of allopurinol with azathioprine is problematic because azathioprine is broken down in the body via the same xanthine oxidase enzyme that allopurinol inhibits, which creates higher concentrations of azathioprine in the body, thereby increasing its effective concentration in the body and leading to toxic levels.

Introduction

A 57 year old male patient was prescribed both allopurinol for gout and azathioprine for rheumatoid arthritis. Due to a known drug interaction between the two, in which allopurinol increases the levels and thus the potential toxicity of azathioprine, the dose of azathioprine was empirically lowered. The patient was monitored for signs and symptoms of azathioprine toxicity.

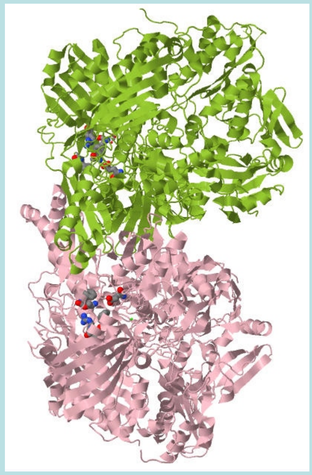

Figure 1: Xanthine oxidase labeled as two dimers (green and pink). Amino acids for both binding sites are highlighted. (PDB file: 3NS1)

Xanthine oxidase is an enzyme found in high concentrations in synovial fluid of the joints. Its normal function is to convert hypoxanthine and xanthine to uric acid while simultaneously reducing NAD+ to NADH. In gout patients, a buildup of uric acid in the joints leads to pain and inflammation. Allopurinol inhibits xanthine oxidase and thus reduces the amount of uric acid produced in the joints, leading to fewer overall gout flare-ups.

One important drug interaction of allopurinol is its reaction with azathioprine. Azathioprine is metabolized by the enzyme xanthine oxidase (Figure 1), which allopurinol inhibits. The inhibition of xanthine oxidase by allopurinol leads to reduced metabolism of azathioprine.

Molecular Story

Allopurinol and azathioprine are structurally very similar and affect each other's interactions in the body. Concomitant administration of allopurinol with azathioprine is problematic because azathioprine is broken down in the body via the same xanthine oxidase enzyme that allopurinol inhibits. Both drugs bind to various amino acids on xanthine oxidase (Figures 2 and 3). The two drugs use some of the same amino acids when binding to the enzyme, while other amino acids are unique to each drug (Figures 4 and 5). The table below summarizes the interactions the two drugs have with xanthine oxidase.

Relevant Amino Acids On Xanthine Oxidase	Amino Acid Used With Both Drugs?	Oxipurinol Bond Type	6-Mercaptopurine Bond Type
Arg880	Yes	Hydrogen Bond	Hydrogen Bond
Thr1010	Yes	Hydrogen Bond	Hydrogen Bond
Glu802	Yes	Hydrogen Bond	Hydrogen Bond
Ala1079	No	Hydrogen Bond	N/A
Phe1009	No	N/A	Pi-Pi Interaction
Phe914	No	N/A	Pi-Cation and Hydrophobic Interaction

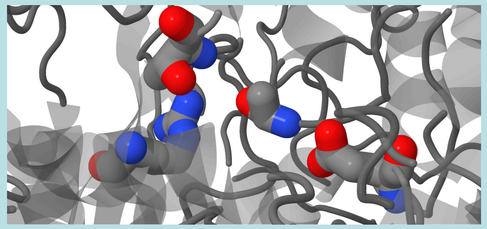

Figure 2: Amino acids on xanthine oxidase involved in the binding oxipurinol. (PDB file: 3BDJ)

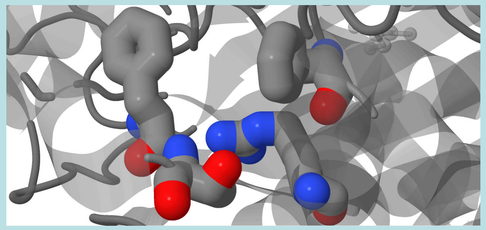

Figure 3: Amino acids on xanthine oxidase involved in the binding of 6-mercaptopurine. (PDB file: 3NS1)

Since allopurinol inhibits the enzyme by preferentially blocking the active site of xanthine oxidase, the enzyme can't interact and inactivate azathioprine. This will cause a build-up of azathioprine in the body causing toxic effects: as an antimetabolite of nucleic acid bases, it interferes with DNA replication by inserting itself into the purine positions of DNA.

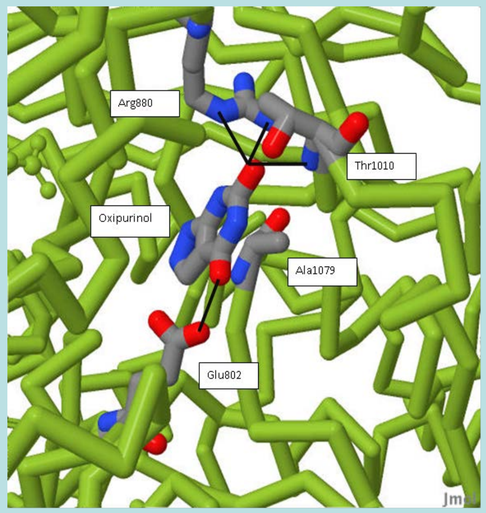

Figure 4: Oxipurinol bound to xanthine oxidase. Black lines indicate hydrogen bonding. Note the hydrogen bonding to alanine is blocked. (PDB file: 3DBJ)

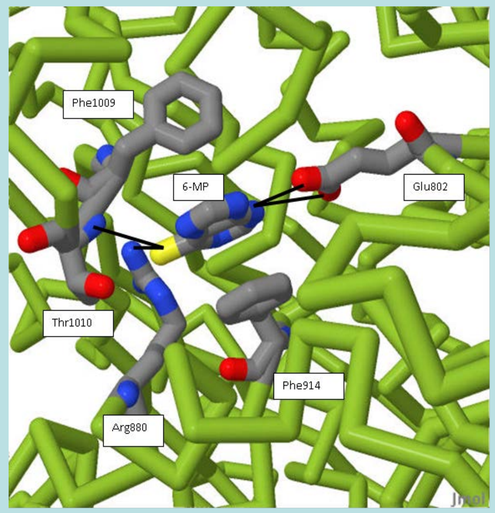

Figure 5: 6-Mercaptopurine bound to xanthine oxidase. Black lines indicate hydrogen bonding. Phe914 interacting through pi-pi interaction. Phe1009 interacting through hydrophobic and pi-cation interaction. (PDB file: 3NS1)

Future Work

Although allopurinol has great efficacy in the treatment of gout, adverse effects are sometimes experienced. The most troubling of these adverse effects are nephrotoxicity, hypersensitivity reactions, Stevens-Johnson syndrome and toxic epidermal necrosis. These side effects are due to the buildup of allopurinol in the body as a result of the high doses necessary for efficacy. Febuxostat (Figure 6) was created to combat these side effects. Although differing greatly from allopurinol, it nevertheless binds tightly to xanthine oxidase with two hydrogen bonds between the carboxylate, Arg880, and Thr1010 and an additional hydrogen bond between the nitrogen of the thiazole and Glu802. The key difference in binding between allopurinol and febuxostat is while allopurinol binds to the molybdopterin cofactor (in reduced form only), febuxostat relies only on physically blocking the channel to the active site and as such is able to inhibit the enzyme regardless of the redox status.

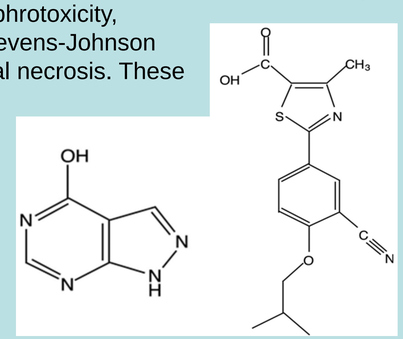

Figure 6: Structure of allopurinol (left) versus febuxostat (right)

Summary

Xanthine oxidase is a key enzyme implicated in gout. Allopurinol functions to inhibit xanthine oxidase, thus reducing the amount of uric acid produced. Concomitant administration of allopurinol with azathioprine is a significant drug-drug interaction that leads to higher concentrations of azathioprine, thereby increasing its toxicity.

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