Amlodipine: The Delicate Balance between Drug Design and Desired Effect

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Abstract

Hypertension affects 1 in 3 Americans. It can be treated in a variety of ways but most often, drug interventions are needed. Amlodipine, a calcium channel antagonist; commonly used for hypertension, is a CYP450 inhibitor. When using multiple CYP450 inhibitors concurrently drug interactions need to be monitored closely.

Introduction

A patient taking amlodipine for hypertension has recently been prescribed itraconazole for a fungal infection. After taking the first dose of itraconazole the patient became dizzy and lost consciousness. At the ER the patient was diagnosed with a hypotensive episode caused by a major interaction between itraconazole and amlodipine.

This project explored the pharmacokinetic action/process that was the basis behind this pharmacodynamic event.

Amlodipine is an L-type calcium channel antagonist (CCA). CCAs bind calcium channels located on cardiac and smooth muscle, preventing the influx of calcium into the cell[1], inhibiting calcium-dependent muscle contraction; resulting in muscular relaxation. This vasodilation results in a reduction in peripheral vascular resistance causing a decrease in blood pressure[2]. Amlodipine was created to improve cardioselectivity. CCAs are primarily metabolized into inactive metabolites through the hepatic CYP450 isoenzyme[2]; CCAs are also an inhibitor of the enzyme.

Itraconazole is a triazole antifungal agent with broad spectrum activity via inhibition of the CYP450 dependent synthesis of ergosterol. Ergosterol is found in fungal cell membranes. The itraconazole alters the function[3] of the membrane by preventing erogestrol production.

The concurrent use of multiple CYP450 inhibitors will alter the concentration of free drug in the serum. Since itraconazole and amlodipine are both CYP450 inhibitors, the free serum concentration of both will increase, leading to adverse effects[3]. In clinical trials, the concurrent use of amlodipine and itraconazole resulted in approximately a six time increase in total drug exposure and an eight time increase in maximum serum drug concentration[3].

Molecular Story

Amlodipine (fig 1a) is a CCA recently found to be metabolized by CYP450 2B6[4]. Itraconazole is a member of a class of compounds called imidazoles.

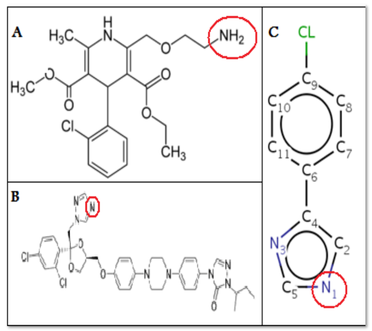

Figure 1. Nitrogens responsible for binding Heme. (A) Amlodipine[3] (B) Itraconazole[4] (C) 4-CPI[6]

To date, itraconazole has not been cocrystalized with CYP450 2B6; therefore we explored the interaction with 4-CPI. 4-CPI (fig 1c) inhibits CYP450 2B6 and also belongs to the imidazoles class of which Itraconazole (fig 1b) is a member[5]. Both Imidazoles and CCAs inhibit CYP450. Taking these medications together can increase the chances of adverse drug reactions. Analyzing their molecular interactions with CYP450 2B6 helps to explain how these potential drug reactions occur.

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Amlodipine and 4-CPI both have covalent reactions with the heme molecule found within CYP450 2B6 , which helps orient the drug in the active site[7, 6].

- The 2-aminomethoxymethyl of amlodipine forms a covalent bond with the heme iron (fig 2)[7]
- The nitrogen on the imidazole ring of 4-CPI is covalently bound to the heme iron (fig 3)[6]

Amlodipine and 4-CPI both interact with Thr302 in CYP450 2B6

- The ethoxy oxygen of amlodipine forms a hydrogen bond with the hydroxyl oxygen of Thr302 (fig 2)
- The second nitrogen within the imidazole ring of 4-CPI forms a hydrogen bond with the hydroxyl oxygen of Thr302 (fig 3)

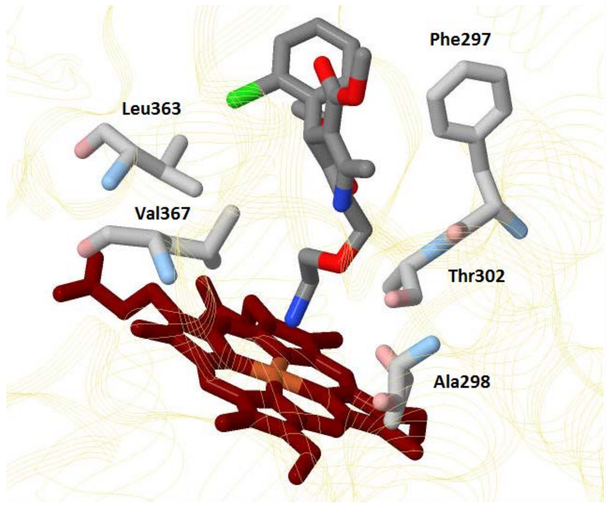

Figure 2. Wireframe model of amlodipine (darker shades) interacting with the heme of P450 2B6 (dark red); amino acids within 4 Å of the compound are also shown (lighter shades)[7]

Carbon (gray), nitrogen (blue/light blue), oxygen (red/pink), chloride (green)

Amlodipine and 4-CPI share other interactions with CYP450 2B6[7, 6]

- Amlodipine has Van der Waals interactions with Phe297, Ala298, Leu363 and Val 367 of CYP450 2B6 (fig 2)[7]
- A pi-pi bond is formed between Phe297 of CYP450 2B6 and the 4-chlorophenyl ring of 4-CPI. Van der Waals interactions are also found between amino acids Ala298, Leu363 and Val367 of CYP450 2B6and 4-CPI (fig 3)[6]

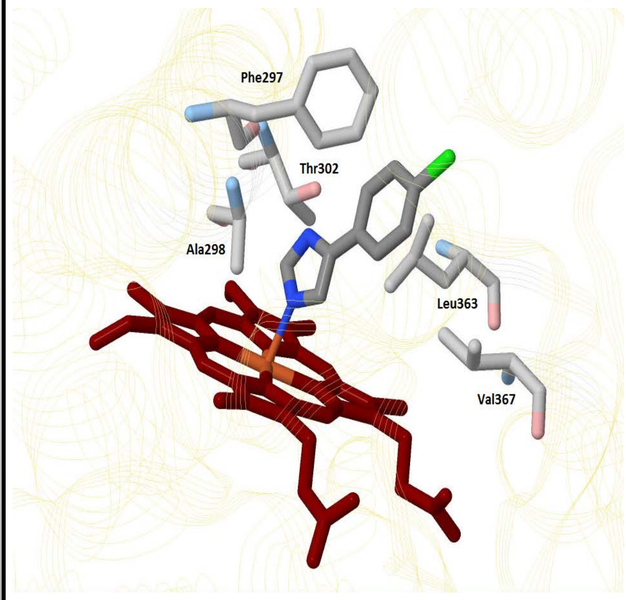

Figure 3. Wireframe model of 4-CPI (darker shades) covalently bound to heme P450 2B6 (dark red); amino acids within 4 Å of the compound are also shown (lighter shades)[6]

Carbon (gray), nitrogen (blue/light blue), oxygen (red/pink), chloride (green)

Itraconazole and amlodipine both act on CYP450 2B6 and bind in a very similar fashion (fig 4a and 4b)[7, 6]. When both drugs are present, serum concentrations of each drug increase, potentially resulting in adverse effects of the drugs[3].

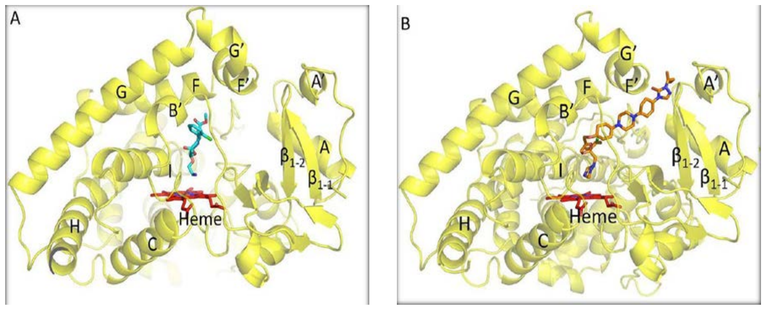

Figure 4. CYP450 2B6 with bound A)amlodipine and B) itraconazole [7]

Future Work

Creating a new form of amlodipine, which would not to bind in CYP450 2B6, would effectively stop this interaction from happening. Since both of the major interactions between amlodipine and CYP450 2B6 (terminal nitrogen and ethoxy oxygen of amlodipine) result from the 2-aminoethoxymethyl arm of amlodipine[3], removing this area of the molecule would likely cause it to avoid binding to CYP450 2B6. If possible, this molecule would need to be tested to ensure maintained efficacy and therapeutic effect, without decreased safety. If successful, this new formulation could be a possible resolution to the interaction between itraconazole and amlodipine.

Summary

Amlodipine is a calcium channel blocker effective in controlling hypertension[8]. Itraconazole is a triazole antifungal agent with broad spectrum capabilities[9]. Both are very effective drugs for their indications. In order to be used together, we would have to formulate a new amlodipine that could reduce the interaction between amlodipine and itraconazole. Until then, an alternate broad spectrum antifungal should be considered to protect the patient from any possible interaction.

References

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