

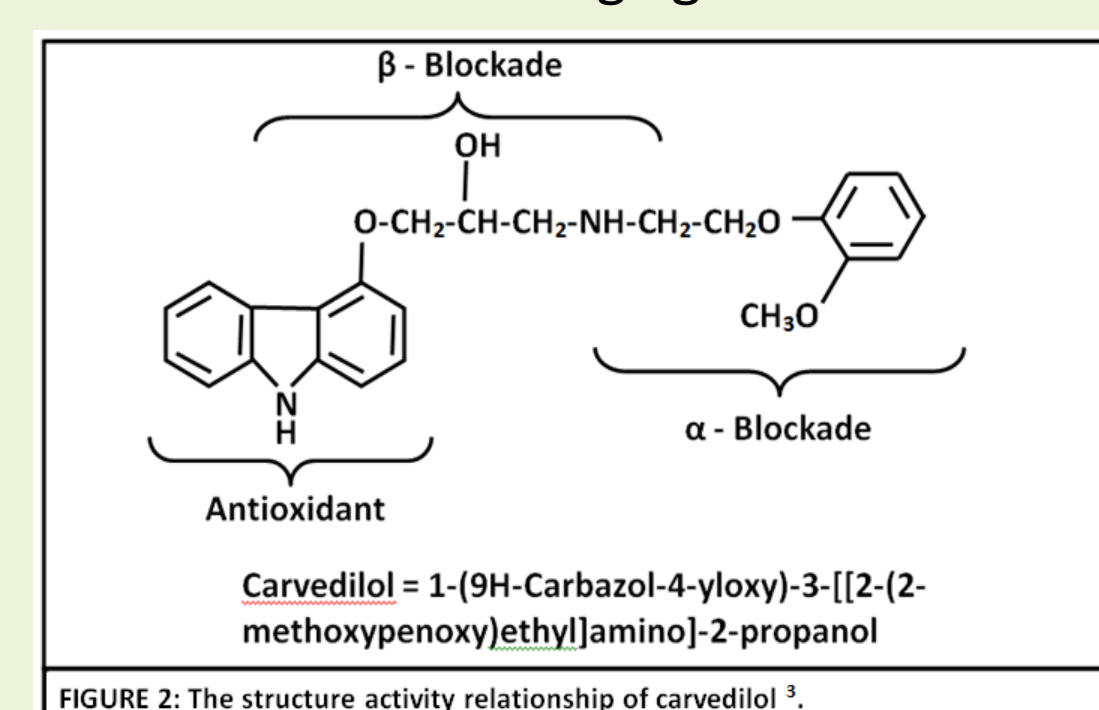
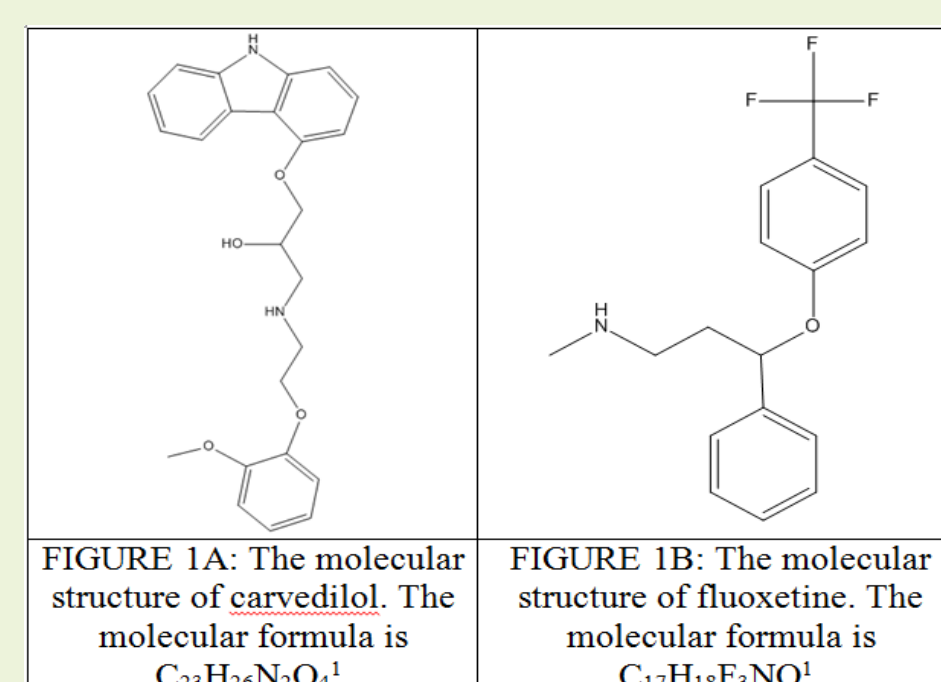
Abstract

Heart failure causes the muscle in the heart wall to slowly weaken and enlarge over time, preventing the heart from pumping enough blood¹. Carvedilol is one of three beta blockers that are currently approved by the FDA for the indication of heart failure. Due to its structure, carvedilol has several important pharmacodynamic effects for the management of heart failure. However, these benefits may be outweighed by risk if a patient is also taking a strong inhibitor of CYP2D6, such as fluoxetine.

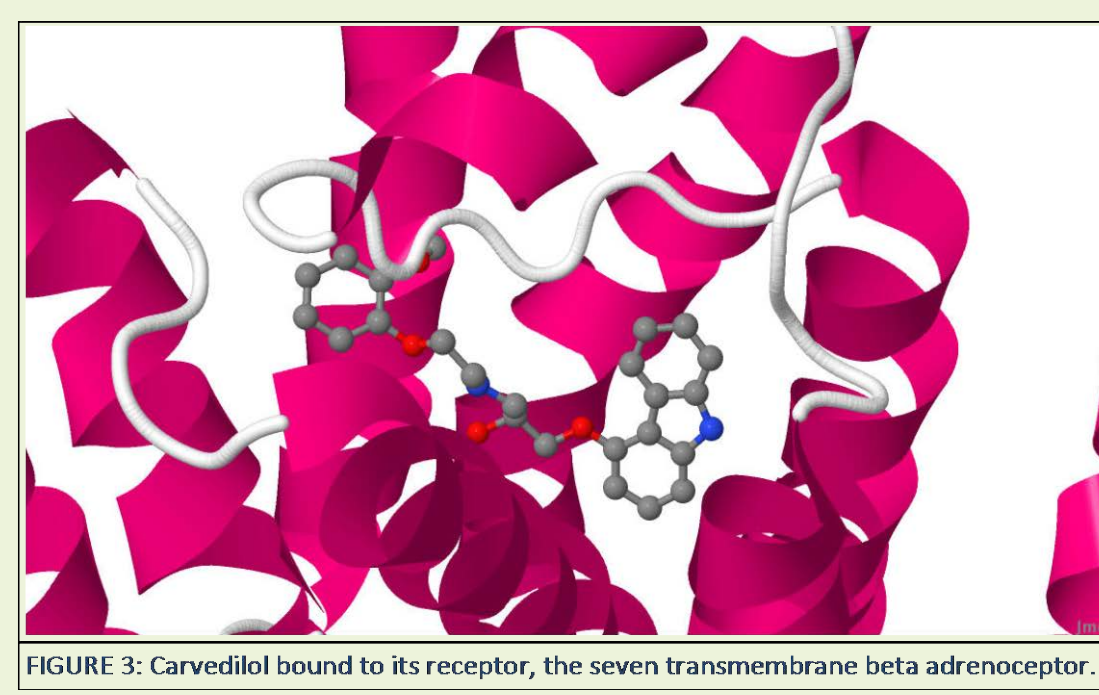
Introduction

A patient was admitted to the hospital for shaking, fever, and a heart arrhythmia. Her past medical history was significant for dementia with depressed mood, hypertension, and congestive heart failure. The patient was on many medications, including carvedilol, and had recently started taking fluoxetine. The pharmacist reviewing the profile noted a potential interaction between fluoxetine and carvedilol. Carvedilol, as shown in Figure 1A, is a non-selective beta-blocker which is metabolized by CYP2D6. Fluoxetine, as shown in Figure 1B, is a strong inhibitor of CYP2D6. Concomitant use of these two medications can increase the concentration of carvedilol in the blood, resulting in increased effects^{2, 5}.

Carvedilol has multiple mechanisms of action that make it a beneficial medication in the treatment of heart failure due to its structure (shown in Figure 2). The beta-blockade moiety binds to the beta-adrenoreceptor, a seven-transmembrane-helix receptor³. This relationship is shown in Figure 3. The alpha-blockade moiety of carvedilol allows it to bind to the alpha-adrenoreceptor. These two binding moieties of carvedilol's structure cause it to be a non-selective beta-blocking agent.



Carvedilol has nonselective beta-adrenoreceptor and alpha-adrenergic blocking activity due to the racemic mixture of its S(-) and R(+) enantiomers. The structure of carvedilol allows it to have several pharmacodynamic effects important in the management of heart failure. These effects include vasodilation, decreased systemic vascular resistance, reduced plasma renin activity, and decreased heart rate⁴.



Molecular Story

Carvedilol (Coreg) is a mixed α/β -adrenergic antagonist. It is an antihypertensive agent with α_1 , β_1 , and β_2 blocking activity. Carvedilol is administered as a racemic mixture where the S(-) enantiomer is both an α - and nonselective β -blocker, whereas the R(+) enantiomer is an α_1 -blocker⁵. Figures 4A and 4B show carvedilol binding in the beta-adrenergic receptor.

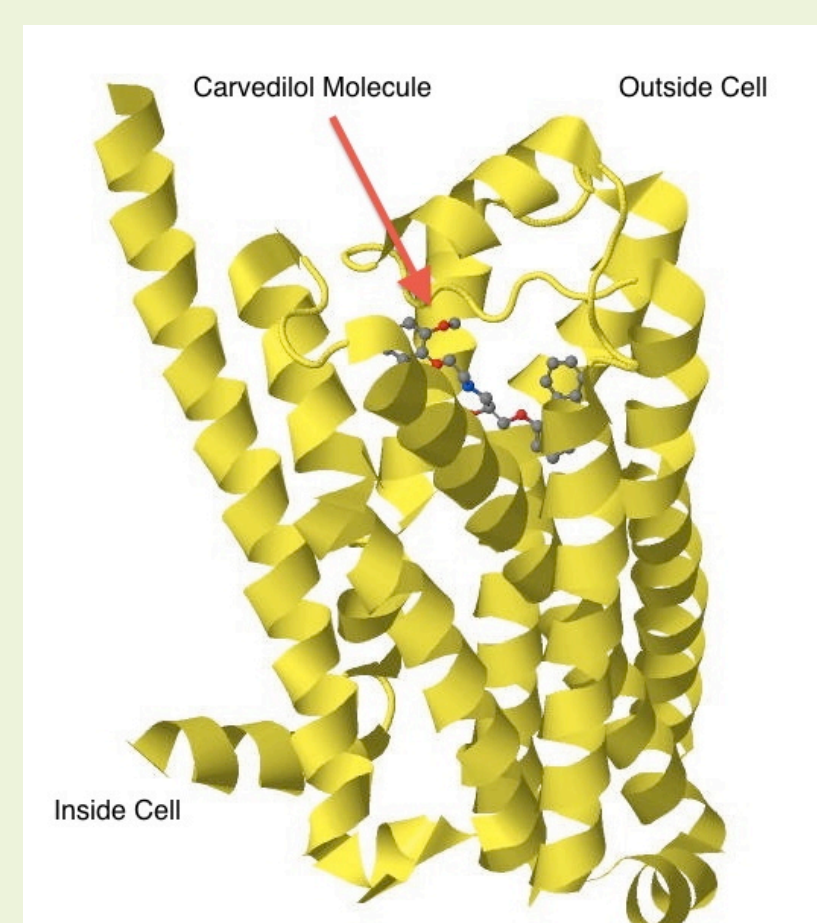


FIGURE 4A: Side view of carvedilol binding to the β -receptor.

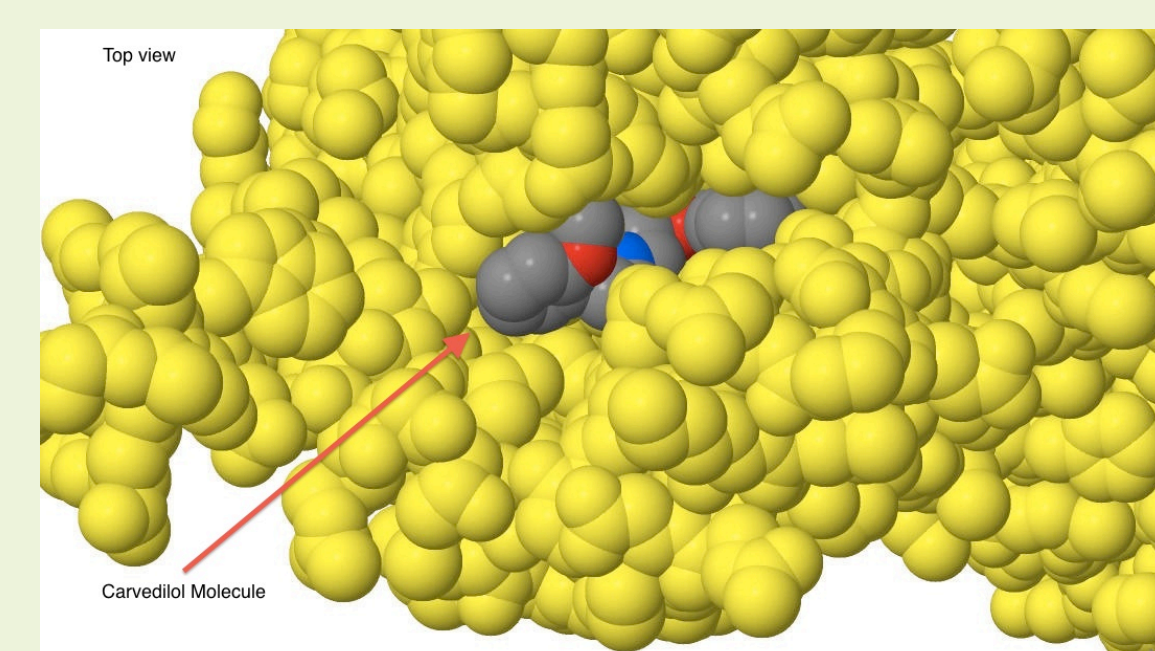


FIGURE 4B: This is a spacefill model of a carvedilol molecule in the binding pocket of the G-coupled protein β -receptor.

Carvedilol binds to three important amino acids in the G-coupled protein β_1 -receptor:

- **Serine 211 (SER211):**
 - The oxygen atom of serine hydrogen bonds to the nitrogen atom in the tricyclic domain of the carvedilol molecule⁶
- **Asparagine 329 (ASN 329)**
 - The oxygen atom of asparagine hydrogen bonds to the nitrogen atom in the middle of the carvedilol molecule⁶
- **Aspartate 121 (ASP 121)**
 - The oxygen atom of aspartate hydrogen bonds to the oxygen atom in the middle of the carvedilol molecule⁶

Since the carvedilol molecule binds to the β -receptor in this way, it blocks the binding of the natural ligand norepinephrine. These interactions are shown in Figure 5.

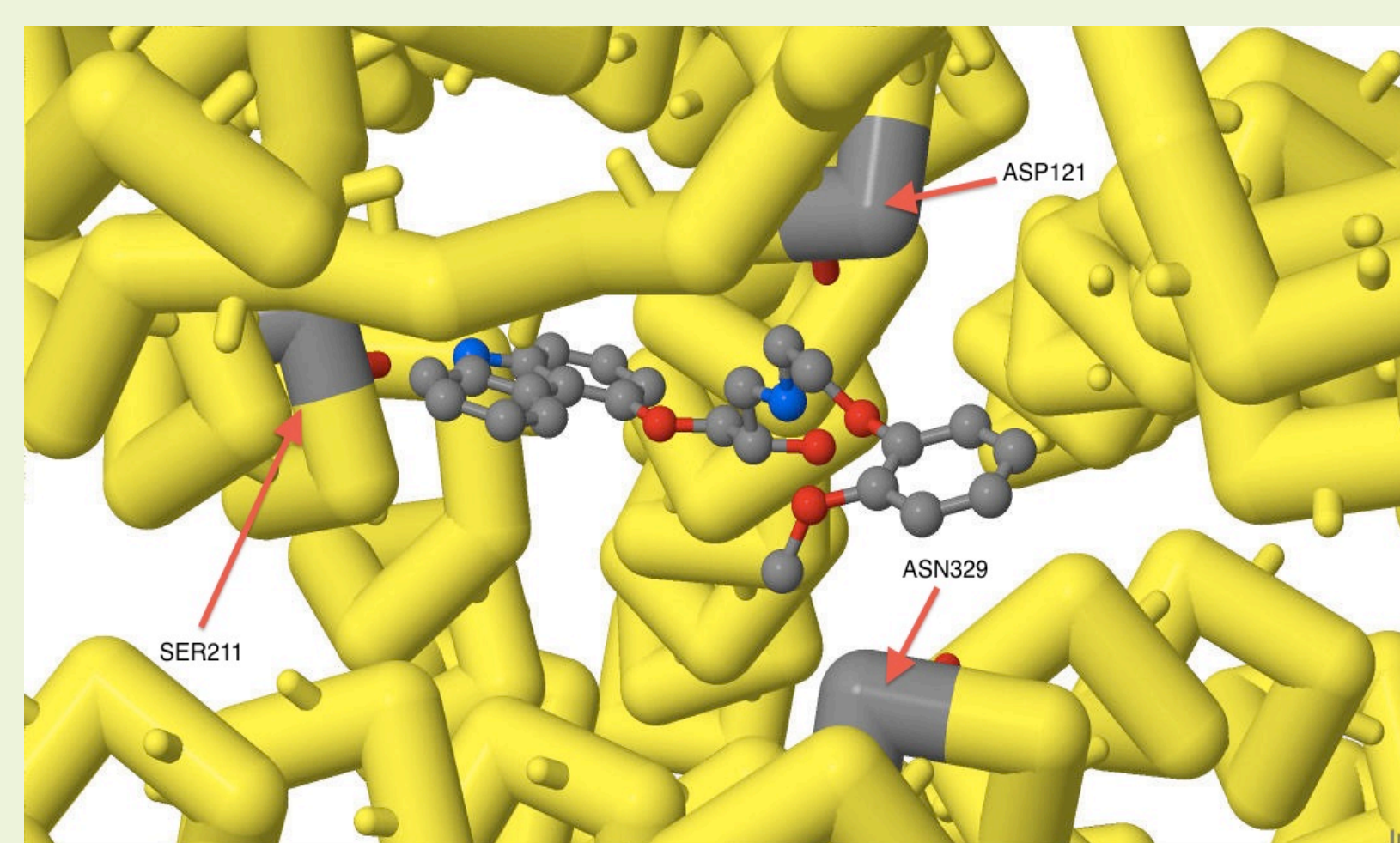


FIGURE 5: This figure shows the binding between three different amino acids and the carvedilol molecule. The orange amino acid is SER211, the green amino acid is ASP121, and the purple amino acid is ASN329.

Carvedilol and fluoxetine are both metabolized by cytochrome P450 2D6. CYP2D6 usually binds drugs that have an unprotonated amine at biological pH. As seen in Figures 1A and 1B, an amine is found in the central region of both carvedilol and fluoxetine. If fluoxetine is administered along with carvedilol, fluoxetine will bind to CYP2D6, preventing carvedilol from binding and being metabolized. This will result in an increase in the serum carvedilol concentration which will increase the amount available to bind to α_1 , β_1 , and β_2 receptors, leading to further decrease in blood pressure and heart rate^{4, 5}.

Further Studies

One major issue with carvedilol is that its amine is unprotonated at biological pH (see Figure 1A), which causes it to be metabolized by cytochrome P450 2D6. This results in many clinically relevant interactions with other drugs metabolized by CYP2D6, including fluoxetine (see Figure 2A).

In order to prevent binding of carvedilol to CYP2D6, its amine group would have to be altered or substituted. However, the amine is necessary for binding to the aspartate 121 (ASP121) amino acid on the beta-adrenergic receptor (see Figure 5). Without this binding interaction, carvedilol will be less effective at blocking the binding of the natural ligand, norepinephrine, thus resulting in significantly reduced clinical efficacy. These factors must be considered when attempting to improve the molecular structure of carvedilol.

Summary

Carvedilol, like most drugs, has the potential to cause drug-drug interactions. Both carvedilol and fluoxetine, two medications that the patient was on, contain an unprotonated amine. This allows CYP2D6 to bind to the drugs. If CYP2D6 is bound to fluoxetine, it is not available to bind and metabolize carvedilol. This would lead to an increased serum concentration of carvedilol, causing adverse effects. Altering the molecular structure of carvedilol to avoid this interaction would be ideal. However, this would decrease the effects on the beta-adrenergic receptor. This patient's healthcare provider should consider switching from carvedilol to a non-selective beta blocker that does not have this interaction (e.g. labetalol). Alternatively, carvedilol therapy could be continued if the patient's fluoxetine was changed to an SSRI that does not have this interaction (e.g. citalopram).

References

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