Montelukast: A CYP 2C8 Substrate

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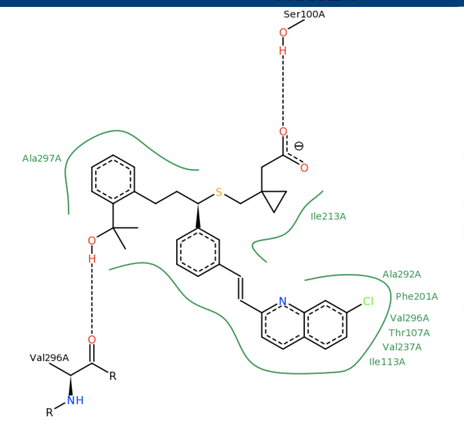
ABSTRACT

Montelukast is a leukotriene receptor antagonist that is used to treat asthma and seasonal allergies. Its main target protein is the CysLTR1 receptor in the lungs and bronchial tubes. By binding to this receptor, it blocks the action of leukotriene D4. The action of montelukast can be inhibited by binding to the enzyme CYP 2C8. Montelukast is a large anionic inhibitor that exhibits a tripartite structure and fits relatively well into the active site of the CYP 2C8 enzyme.

FIGURE 1[1]



Structure of montelukast. Black dashed lines - hydrogen bonds, salt bridges, metal interactions; green solid lines - hydrophobic interactions[1]

INTRODUCTION

- Asthma has been a concern for decades, leading medical personnel to try various methods of prevention.
- Our case begins with KT, a 54 year old woman with a history of asthma.
- Medical History:
  - Pruritis and jaundice one month after initial montelukast (Singulair®) therapy
- Current Medication List:
  - Gemfibrozil
  - Montelukast
- Drug-drug Interaction:
  - Gemfibrozil, a CYP 2C8 inhibitor, causes montelukast, a CYP 2C8 substrate, to have an increase in plasma concentration that can lead to rare cases of liver toxicity.[2]
- Mechanism of action of CYP 2C8:
  - A major enzyme that assists in the metabolism of montelukast
- Clinical importance:
  - Based on KT's reaction circumstances, it is important to recognize how montelukast can react with other medications and a patient's own metabolism.
  - Clinically, it is important to utilize a pharmacist's available resources to understand how a drug works individually and also in combination with other medications.
  - Additionally, medications should be looked at based on patient specific factors and not as a cohort.

MOLECULAR STORY

- Montelukast is a leukotriene receptor antagonist.
  - Main target protein is CysLTR1
- Montelukast is a substrate for CYP 2C8, CYP 2C9, and CYP 3A4.[3]
- In vitro, metabolism is mainly accomplished through CYP 3A4 and CYP 2C9.[3]
- However, in vivo, montelukast is extensively and primarily metabolized via CYP 2C8, accounting for about 80% of its metabolism.[4]
  - This was proven by comparing the use of a combination of the following drugs:[4]
    - Montelukast
    - CYP 3A4 inhibitor
    - CYP 2C9 inhibitor
- Using crystallized structures of CYP 2C8 and the R-enantiomer of montelukast, it was demonstrated that montelukast has a high affinity for the active site of CYP 2C8 enzyme (Figure 2).
  - Due to its large size, the active site may be able to accommodate montelukast in different binding positions, rather than only the proposed pharmacophore.[5]
- Increased binding, in addition to decreased ability to leave the liver, may cause hepatotoxicity.

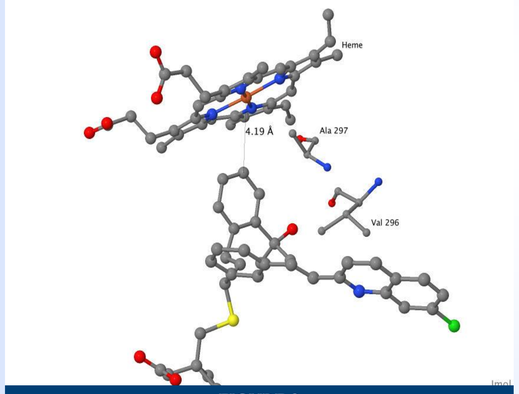


FIGURE 2

Montelukast interaction between heme prosthetic group and Val 296 of CYP 2C8

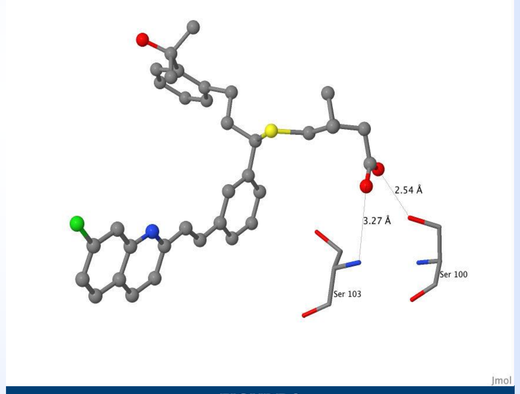


FIGURE 3

Hydrogen bonds between carboxylate moiety of montelukast and Ser 100 and Ser 103 of CYP 2C8

- Montelukast has a tripartite structure that fits into the three branches of the binding site cavity.
  - The shortest branch interacts with the side chain of serine-100 and amide hydrogen of serine-103 donates hydrogen bonds to the carboxylate moiety (Figure 3).[5]
  - The longest and most sterically demanding branch with the terminal cholorquinoline ring of montelukast sits in the distal hydrophobic pocket (Figure 4).[5]
  - The last branch with a terminal tertiary alcohol group is closest to the heme iron where the reactive iron-oxo intermediate is generated during catalysis (Figure 2).[1]
    - Close contacts <4Å allows for interactions between side chains[4]
- Many interactions are hydrophobic in nature.[1]

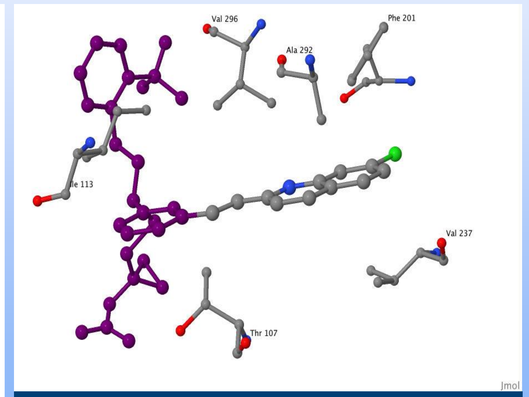


FIGURE 4

Chloroquinoline ring of montelukast within hydrophobic binding pocket of CYP 2C8. Portions of montelukast shown in purple represents other branches not within the hydrophobic pocket. Carbon (gray), chlorine (green), nitrogen (blue), oxygen (red), and sulfur (yellow).

THE NEXT QUESTION

- Future Research
  - Leukotriene receptor testing in patients for better efficacy and improved therapy
  - Structure and ligand based approaches can be utilized to identify new compounds that have higher affinity for the CysLTR1 receptor.
  - Determine the metabolism of montelukast by CYP 2C8 and CYP 3A4 to minimize liver toxicity.
    - Rearrange montelukast structure to avoid this drug-drug interaction issue.
    - Change the structure of montelukast to make it mainly metabolized by CYP 3A4 instead of CYP 2C8 to avoid drug-drug interaction.
    - Add chlorobenzene at the end of the structure to inhibit hydroxylation via CYP 2C8 enzyme (Figure 5).

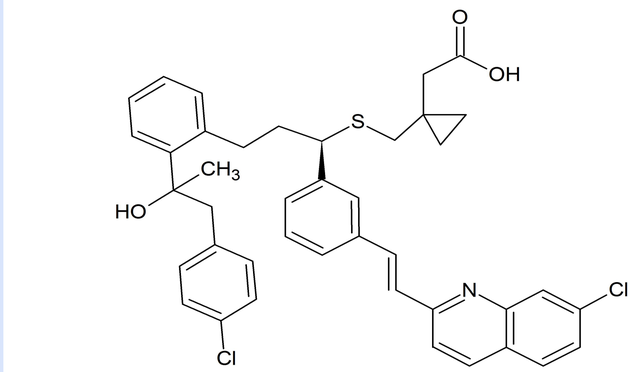


FIGURE 5

Addition of chlorobenzene to limit hydroxylation via CYP 2C8. Thus, preventing interactions with gemfibrozil

SUMMARY

The CYP 2C8 enzyme is partially involved in the metabolism of a number of drugs. Inhibitors of CYP 2C8 will have the greatest effect on drugs in which CYP 2C8 is the primary metabolic pathway. An inhibitor or inducer of CYP 2C8 can result in adverse drug reactions, and a drug therapy change should be made. Due to gemfibrozil's inhibition of CYP 2C8, it caused a significant rise in montelukast's serum concentration. Therefore, montelukast should be discontinued to prevent liver toxicity.

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