Ciprofloxacin: An Antibiotic Interaction with a Topoisomerase Complex

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Abstract

Fluoroquinolones (FQ) are ideal antibiotics: they have high oral bioavailability, broad spectrums that cover Gram-positive, Gram-negative, and atypical microorganisms, and a lower incidence rate of side effects. Typically, this class of antibiotics is used to treat common infections such as lower respiratory tract infections.

While side effects are less common, they still occur. In this case-based patient study, we explore the interaction between ciprofloxacin, prescribed for a lower respiratory tract infection (LRTI), and tizanidine, after a patient developed symptoms of drowsiness, fatigue, and low blood pressure. To do this, we utilized the Jmol imaging software to demonstrate the binding of ciprofloxacin to its topoisomerase target and discuss the interactions that are integral interrupting the replication of the bacterial DNA and thereby eradicating the infection.

Introduction

A 68 year-old male presented to the urgent care unit with symptoms of shortness of breath, wheezing, cough, discolored sputum, and a fever. After microbiologic tests were performed to determine the pathogen as *Streptococcus pneumoniae*, the physician wrote a prescription for oral ciprofloxacin, 500mg, every 12 hours for 14 days. One week later the patient returned to the urgent care unit with symptoms of severe drowsiness, fatigue, and low blood pressure. During a profile review, the pharmacist noted the concomitant use of tizanidine, as needed for muscle spasms.

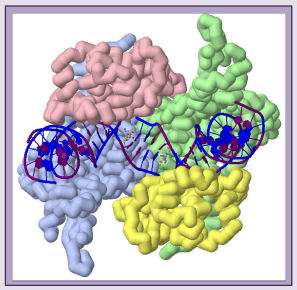

Fig. 1 Interaction between topoisomerase (four polypeptide chains), DNA & ciprofloxacin

Pharmacologically, ciprofloxacin binds to topoisomerase II, inhibiting DNA replication and promoting double-stranded DNA breaks.[1] The interaction between ciprofloxacin, a topoisomerase inhibitor, and tizanidine, an alpha-2 adrenergic agonist, may result in increased tizanidine levels. This occurs due to a CYP1A2 interaction.

CYP1A2
- Binding site requires two carbonyl groups and a nitrogen group
- Inhibition leads to increased serum levels of tizanidine

Topoisomerase Enzyme
- Essential for DNA replication; regulates double helix uncoiling
- Numerous classes I-IV; DNA manipulation variability

Ciprofloxacin
- A second generation FQ; inhibits both topoisomerase II and IV, depending on concentration
- Potent inhibitor of CYP1A2
- Treatment option for: *Haemophilus, Pseudomonas, Enterobacteriaceae, Staphylococci, and Streptococci* species

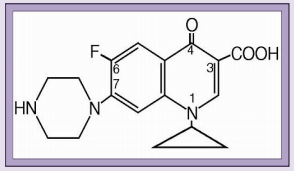

Fig. 2 Ciprofloxacin Structure[2]

Molecular Story

Magnesium (Mg^{2+}) ions
- With topoisomerase, Mg^{2+} ions promote enzyme-substrate interactions
  - Enzyme-mediated DNA cleavage reactions
  - Participate in ATPase reactions[3]
    - Facilitate interaction between the antibiotic and topoisomerase
- Demonstrates the importance of keto-acid group in the structure
- Forms octahedral coordination sphere with:
  - Two oxygen atoms from the quinolone[4]
  - Four water molecules[4]

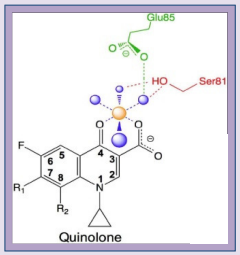

Fig. 3 Interaction between a quinolone & magnesium; Mg^{2+} in yellow[5]

Carbon Positions
- C4 and C3 (acid) are crucial participants in the binding mechanism
- N1 and C7 possess large, bulky substituent groups
  - Act as a "wedge" to disfigure DNA
  - Inhibit topoisomerase binding

Interactions with Host Cell and Enzyme
- Two water molecules form hydrogen bonds with Ser84 and Glu88 residues on topoisomerase, binding the antibiotic, and allowing disruption of the enzyme's normal mechanism of action
- With drug bound to topoisomerase, it is able to interact with the DNA of the replicating cell
- To achieve contact with DNA, the antibiotic forms a ParC55 closed homodimer with ParE30 (TOPRIM, metal-binding domain) monomers on each side[1]
- The α1 helix forms a long chain-like segment that holds the ParE domain close to the external side of the ParC55 domain[1]

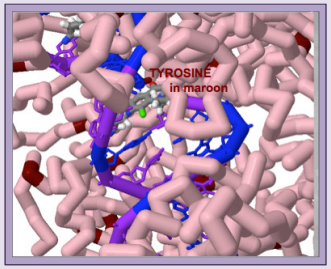

Fig. 4 Ciprofloxacin active site

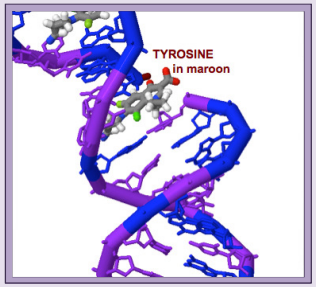

Fig. 5 Ciprofloxacin-induced DNA break

- Linkage likely responsible for subsequent interactions; after nicking the DNA, two ciprofloxacin molecules intercalate between nucleotides on either side of a 4bp "sticky end" at positions -1 and +1 on the DNA
- The cyclopropane ring is close to ParC residues on Ser79 and Asp83
  - Resistance occurs with mutation of either residue
- FQ resistance may be related to the octahedral coordination sphere
  - The most common mutations involve S79F and S79Y

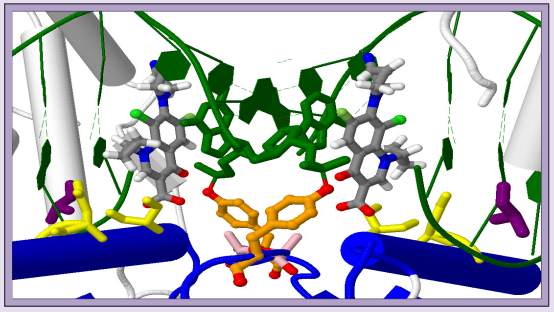

Fig. 6 Helix-turn-helix structure; Contains Arg117 and Tyr118 within its binding site, where the antibiotic ligand is able to bind and intercalate between base pairs.[1,4]

Further Drug Development

Ciprofloxacin is small enough to fit in the active site of CYP1A2 and possesses the correct molecular structure to bind. The core nitrogen in position 1, the carboxylate group, and the keto group are likely the most important.[6]

When comparing ciprofloxacin to other FQs, such as levofloxacin, that have been proven to have a significantly less CYP1A2 interaction,[7] it is evident that adding steric bulk to the core nitrogen hinders the drug from binding.

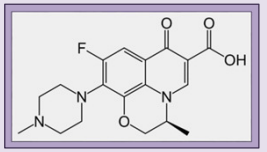

Fig. 7 Levofloxacin

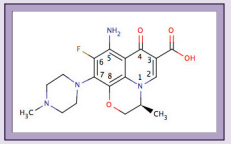

Fig. 8 Antofloxacin

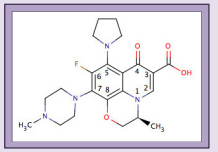

Fig. 9 Antofloxacin with steric bulk; pyrrolidine group at C5

Antofloxacin, a new FQ being researched,[8] has a unique nitrogen group at position 5. This resulted in significant CYP1A2 interactions, leading one to believe antofloxacin was able to bind with the similar components at a different angle.[8] A prodrug could be formed by changing the C5 amine substituent into a pyrrolidine group, theoretically deeming the CYP1A2 interaction insignificant.

Summary

Ciprofloxacin is a FQ antibiotic used to treat LRTIs, which works by inhibiting DNA replication via topoisomerase II and IV, ultimately leading to apoptosis of the replicating cell. The presence of a magnesium ion is believed to facilitate the overall mechanism. The antibiotic binds to Ser84 and Glu88 residues on topoisomerase, allowing for subsequent interactions and intercalation between base pairs. However, the use of this antibiotic may cause unintentional drug-drug interactions (DDIs) when used in combination with other medications due to its metabolism by CYP1A2. The transformation of a nitrogen group into a prodrug should lessen this interaction.

Patients taking ciprofloxacin should refrain from concomitant use of drugs associated with CYP450 enzymes. In our case, the patient was advised to refrain from using tizanidine until completion of the ciprofloxacin course to prevent further side effects.

References

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