



Interaction of fluoroquinolones with collagen

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Abstract

The results of this study have shown that the primary side effects of fluoroquinolone usage, those being tendinopathy, tendon rupture, and ligament/cartilage damage, can be traced to type I collagen, which makes up a great portion of protein within the human body. While other side effects may be linked to drugs which are externally consumed, type I collagen is compound bound to the human body, and thus, proves to be a significant hurdle in the path of mitigating the health risks rightfully associated with the consumption of fluoroquinolones.

Keywords: fluoroquinolones, collagen, helix, α chain, tendon, metal ions, chelation, hydroxylation, synthesis, cross-linking, tendinopathy, tendon rupture, ligament, cartilage

Introduction

Yash Raj Mehta, a student of A level from DPS International, Saket, New Delhi, has been an activist in My Right to Breathe and anti-pollution activities. In class 6th, he went to Gazipur landfill himself to make a project and has been vocal about anti-smog, garbage disposal, and its threats to our lives. He has participated in many protests at a very young age, and feel a sense of responsibility towards our society and country by proposing doable solutions through his write ups and talks in school. A chemical engineer aspirant and blue coat scholar badge holder, Yash Raj, loves nature and marine world. He strongly believes that we all are deeply connected and taking care of our natural resources is our collective responsibility. This study was done under the supervision of Dr. Imran Khan.

Fluoroquinolones: The fluoroquinolones are a family of broad spectrum, systemic antibacterial agents that have been used widely as therapy of respiratory and urinary tract infections. Fluoroquinolones are active against a wide range of aerobic gram-positive and gram-negative organisms.

The issue: Fluoroquinolones notoriously cause multiple side effects, including but not limited to:

- Pain in your joints or swelling in your shoulder, arms or legs
- Abdominal or back pain
- Weakness in your body, or unusual sensations (such as persistent pins and needles, tingling, numbness or burning), especially in your legs or arms
- Severe tiredness, depressed mood, anxiety or problems with your memory or severe sleeping
- Changes in your vision, taste, smell or hearing.
- Tendon pain or swelling, often beginning in the ankle or calf

Identifying the specific compounds and reactions behind each side effect is quintessential when providing dosages or prescriptions to patients, and also paves the way for new drugs to be created within this compound family which

would either not cause side effects or have a much more minimized effect. The following example showcases one such compound that results in a negative reaction, its related equations, and the connected side effects.

Compound: Collagen

Collagen is the main structural protein in the extracellular matrix of a body's various connective tissues. As the main component of connective tissue, it is the most abundant protein in mammals. 25% to 35% of a mammalian body's protein content is collagen.

Collagen is the main structural protein in the extracellular matrix of a body's various connective tissues. It is found in tendons, skin, artery walls, cornea, the endomysium surrounding muscle fibers, fibrocartilage, and the organic part of bones and teeth.

Fluoroquinolones in particular react negatively with Type I collagen, the most common type of collagen in the body. It is commonly found in tendons, ligaments, skin, cornea, cartilage, bone, and other connective tissues. Type I collagen is a major structural component, providing tensile strength and structural integrity to these tissues.

Molecular structure

Type I collagen is a triple helix made up of two $\alpha 1(I)$ chains and one $\alpha 2(I)$ chain. The primary structure is composed of repeating Gly-X-Y sequences, where X and Y are frequently proline and hydroxyproline, respectively.

Each α chain in type I collagen has approximately 1050 amino acids, and each α chain has a weight of around 95 kDa.

A simplified representation of a segment of the collagen triple helix (without specifying the exact sequence) could be: (Gly-Pro-Hyp) n

Here:

- Gly is glycine
- Pro is proline
- Hyp is hydroxyproline
- nnn represents the number of repeating units in the collagen molecule

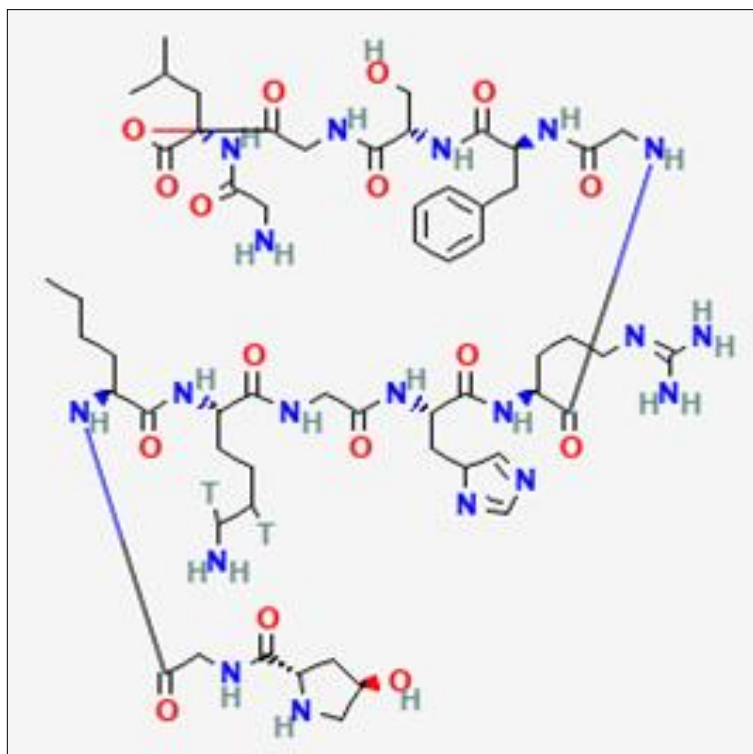


Fig 1: Image of type I collagen alpha chain

Why a reaction occurs

Fluoroquinolones can disrupt the normal function and integrity of type I collagen, potentially leading to tendinopathy and tendon rupture. The interaction can involve the chelation of essential metal ions like magnesium, which are critical for collagen stability and enzymatic processes involved in collagen synthesis and repair.

What is chelation: The formation or presence of bonds (or other attractive interactions) between two or more separate binding sites within the same ligand and a single central atom. A molecular entity in which there is chelation (and the corresponding chemical species) is called a 'chelate'. The

terms bidentate (or didentate), tridentate, tetradentate, ... multidentate are used to indicate the number of potential binding sites of the ligand, at least two of which must be used by the ligand in forming a 'chelate'. For example, the bidentate ethylenediamine forms a chelate with CuI in which both nitrogen atoms of ethylenediamine are bonded to copper. (The use of the term is often restricted to metallic central atoms.) The phrase 'separate binding sites' is intended to exclude cases such as $[\text{PtCl}_3(\text{CH}_2=\text{CH}_2)]^-$, ferrocene and (benzene)tricarbonylchromium in which ethene, the cyclopentadienyl group and benzene, respectively, are considered to present single binding sites to the respective metal atom, and which are not normally thought of as chelates.

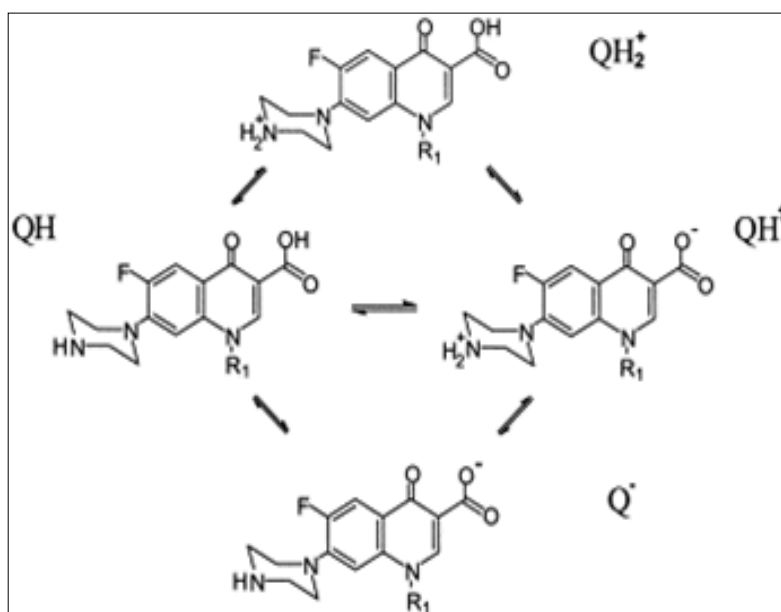


Fig 2: Chelation modes of fluoroquinolone drugs towards metal ions

Mechanism of chelation

1. Chelation Process

Fluoroquinolones contain functional groups, such as carboxyl and keto groups, that can form complexes with divalent and trivalent metal ions. This chelation is particularly strong with magnesium ions (Mg^{2+}). The fluoroquinolone molecule can bind to these metal ions, effectively sequestering them and reducing their availability for biological processes.

2. Impact on Collagen

There is initially an effect on collagen synthesis. Magnesium ions are essential cofactors for many enzymes involved in collagen synthesis and stabilization. For example, prolyl hydroxylase, an enzyme critical for the hydroxylation of proline residues in collagen, requires Mg^{2+} for its activity. Hydroxylation is crucial for the stability and proper folding of the collagen triple helix.

The collagen's cross-linking is also affected, as Magnesium also plays a role in the cross-linking of collagen fibers, which contributes to the tensile strength and integrity of connective tissues.

Connected side effects

Tendon pathology

The chelation of magnesium by fluoroquinolones disrupts the normal enzymatic activity required for collagen synthesis and repair, leading to weakened collagen fibers. This can result in tendinopathy, a disorder of the tendons that causes pain, swelling, and impaired function. Moreover, in severe cases, the structural weakening of collagen can lead to tendon rupture, particularly in weight-bearing tendons such as the Achilles tendon.

Ligament and cartilage damage

Similar to tendons, other collagen-rich tissues such as ligaments and cartilage can also be adversely affected, potentially leading to joint instability and other connective tissue disorders.

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