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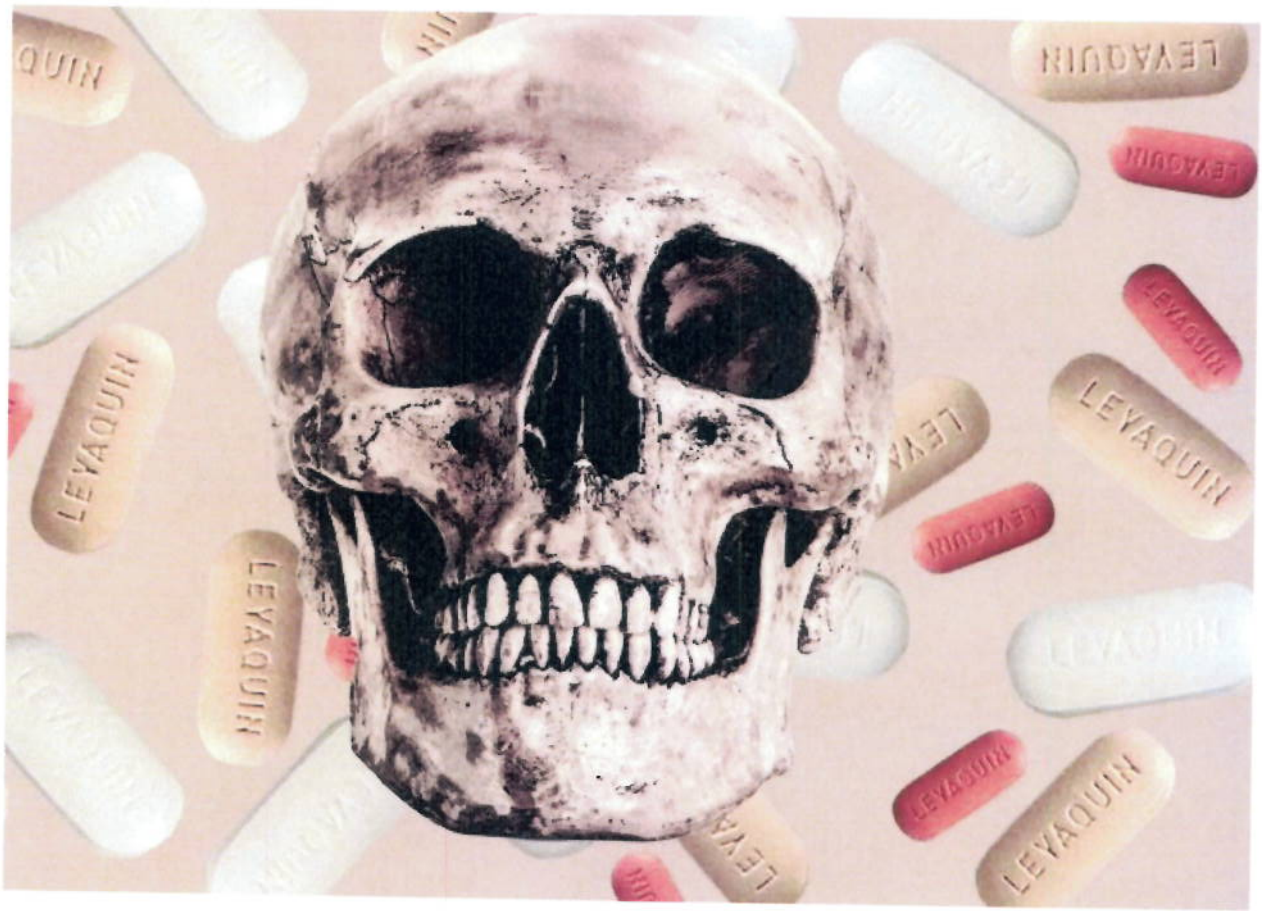
A NEW THEORY OF FLUOROQUINOLONE-ASSOCIATED DISABILITY

Impurity-Induced Lipid Peroxidation and Impaired Detoxification of Aldehydes



Graphic Excerpted from The Daily Beast

← A New Theory of Fluoroquinolone-Associated Disability: I...

The FDA recently defined Fluoroquinolone- Associated Disability ("FQAD") as a formal review identification for a constellation of symptoms that have been identified in the FDA's Adverse Event Reporting System (FAERS) in review of data in the fluoroquinolone safety reports. Adverse Reactions and events associated with FQAD that have been reported and documented are: tendonitis and tendon rupture, central nervous system effects, peripheral neuropathy, myasthenia gravis exacerbation, QT prolongation, Torsades de Pointes (TdP), phototoxicity, hypersensitivity, arthritis, brain fog and anxiety. [1]

Recent experiments have illustrated that fluoroquinolones can illicit a lipid peroxidation chain reaction within 15 minutes of administration in mice. The resultant overload of aldehyde acids can be causally linked to many of the symptoms experienced by victims of fluoroquinolone toxicity, including extracellular matrix and collagen damage, cardiovascular damage, pain,

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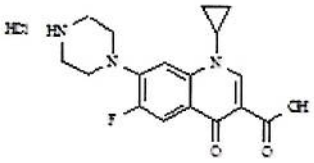
Fluoroquinolone Impurities and Lipid Peroxidation

Ciprofloxacin HCl
CAS No. 93107-08-5
C17H18FN3O3.HCl M.W. 331.35 36.46
C-081



Federal guidelines allow for a percentage of impurities in manufactured drugs, and recent research indicates those present in commercial fluoroquinolone medications may trigger lipid peroxidation[2] chain reactions within 15 minutes of administration of the drug in mice. In theory, a single molecule of the impurity could start a lipid peroxidation chain reaction. This chain reaction can continue until the body's antioxidant system stops the process. This may potentially explain the drop in glutathione and SOD that was found in another study.[3] The end products of lipid peroxidation can be mutagenic and carcinogenic[4], and may damage the liver and CYP27a1 gene. At certain levels, they act to inhibit the genes that produce the enzymes that detoxify aldehydes[5], so with enough exposure clearance pathways can be impaired, leaving the patient more sensitive to future exposure.

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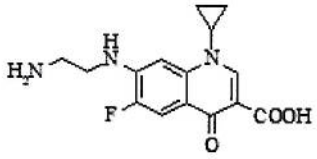
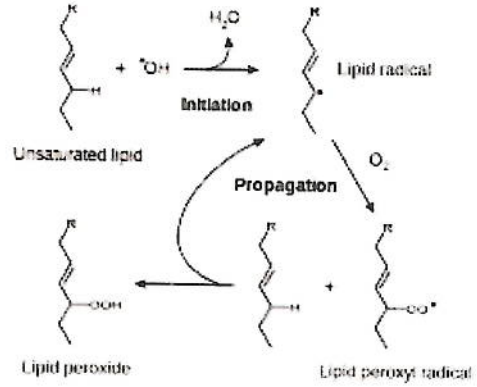
CAS No. 528851-31-2
C15H16FN3O3. HCl M.W. 305.31 36.46
C-087



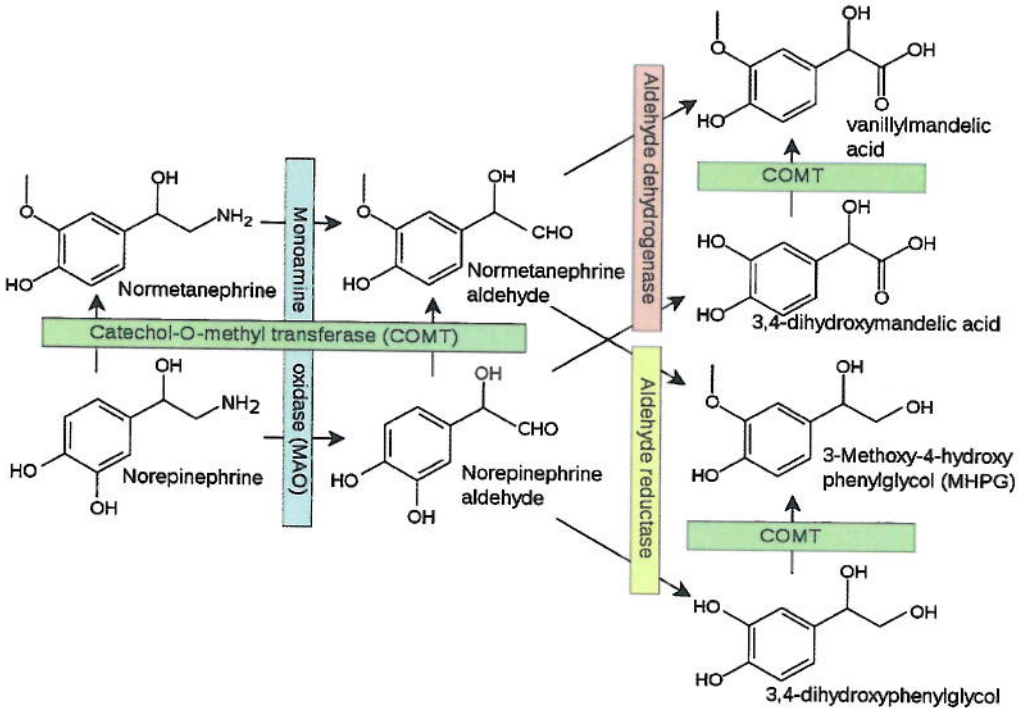


Victims experiencing fluoroquinolone toxicity may have received larger doses of impurities in

chain-breaking antioxidant which is recycled by glutathione and vitamin C. Vitamin E is considered extremely hydrophobic, and as a result it is expelled when a cell is oxidized and is unavailable for use to stop lipid peroxidation chain reactions.

Impaired Detoxification of Aldehydes

There are 19 known genes that are associated with the detoxification of aldehydes from the body. Those with a large number of mutations in these genes may be more susceptible to the buildup of aldehyde acids which occur as a result of lipid peroxidation. [6]



Rang & Dale's Pharmacology; 2007; Edinburgh: Churchill Livingstone. ISBN 0-443-06911-5.

Extracellular Matrix and Collagen Damage

It has been demonstrated that the collagen damage often observed in fluoroquinolone toxicity is an effect of excess malondialdehyde (MDA), which is a byproduct of the lipid peroxidation caused by fluoroquinolones.[7] Recent research also indicates that excess malondialdehyde can dramatically alter the function of fibroblasts, negatively impacting the synthesis of the extracellular matrix and collagen. [8]

Cardiovascular Damage

It has also been demonstrated that the cardiovascular damage sometimes observed in

cell structure, making the membrane covering the red blood cell becomes stiffer. Yet in order to travel through the capillaries, which are the smallest blood vessels and which feed the trillions of individual cells, the red blood cell must be able to fold or deform. The average red blood cell diameter is 7 microns; yet a typical capillary is only 2 microns in diameter. Red blood cells stiffened through chronic AH exposure will have difficulty deforming sufficiently to pass through capillaries, reducing the ability of red blood cells to accept, hold, and transport oxygen through the bloodstream, which can cause weakening of tendons and neuropathic symptoms. [9] Recent research indicates there is a link between malondialdehyde and acetaldehyde adducts and abdominal aortic aneurysms (AAA), which are sometimes observed in fluoroquinolone toxicity. [10]

Pain and Neurogenic Inflammation

4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. Victims of fluoroquinolone toxicity may not be able to this chemical from our bodies and thus floxies are being subjected to a chronic exposure to this substance.[11]

Histamine Intolerance

Many victims of fluoroquinolone toxicity experience histamine intolerance. Both the methylation pathway and oxidation pathway for histamine require aldehyde dehydrogenase to oxidize an acetaldehyde intermediary metabolite, but this enzyme is suspected to be eliminated following fluoroquinolone toxicity. [12]

Approaches to Empirical Treatment

Recent research indicates that administering vitamin E and C prior to fluoroquinolone use inhibits cytotoxic effects. [13] Other research indicates that use of carnosine can protect neurons from the cytotoxic effects of malondialdehyde. [14] These findings indicate that water-soluble vitamin E, R-Alpha Lipoic Acid, Pantethine, Vitamin C (Buffered), Selenium, and Carnosine may help reverse the toxicity caused by fluoroquinolones. A newly-developed drug which can activate ALDH enzymes and has been shown to metabolize some or all of the toxic aldehydes associated with fluoroquinolone toxicity is also promising.

However, several popular treatments for fluoroquinolone toxicity may worsen the syndrome. As Vitamin B6 is a form of aldehyde, it may contribute to the toxic systemic levels. Fish oil can deplete vitamin E, which may be critically important to recovery. Acetaminophen depletes glutathione, which recycles vitamin E, so it can also be detrimental. Finally, iron can promote lipid peroxidation.

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[1] https://en.wikipedia.org/wiki/Fluoroquinolone-associated_disability
[2] Oxford Society of Toxicology; "Molecular Mechanisms of Acrolein Toxicity: Relevance to Human Disease"; Moghe, Ghare, Lamoreau, Mohammad, Barve, McClain, Joshi-Barve.

[7] Diabetologia (2000) 43; "The importance of lipid-derived malondialdehyde in diabetes mellitus"; Slatter, Bolton, Bailey.
[8] http://www.ncbi.nlm.nih.gov/pubmed/12064466
[9] http://intelegen.com/nutrients/prevent_the_damaging_effects_of_.htm
[10] http://www.ncbi.nlm.nih.gov/pubmed/25724613
[11] http://www.pnas.org/content/104/33/13519.full.pdf
[12]http://www.sigmaaldrich.com/technical-documents/articles/biology/rbi-handbook/non-peptide-receptors-synthesis-and-metabolism/histamine-synthesis-and-metabolism.html
[13] "Antagonism of vitamin C and vitamin E on action of quinolones"; Surjawidjaja; Department of Microbiology, Faculty of Medicine, Trisakti University.
[14] "Neuropharmacology and Analgesia The cytotoxic mechanism of malondialdehyde and protective effect of carnosine via protein cross-linking/mitochondrial dysfunction/reactive oxygen species/MAPK pathway in neurons"; European Journal of Pharmacology 650 (2011) 184–194; Cheng, Wang, Yu, Wu, Chen.