

Editor's Note: Adverse drug reactions experienced by HMC, SCCA, or UWMC patients and reported via Patient Safety Net (PSN) are reviewed quarterly by the UW Pharmacy & Therapeutics Committee. Following the Committee's review, a literature-based companion article regarding some aspect of adverse drug reactions is published in this newsletter. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, "No drug has only one action." By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you feel is experiencing an Adverse Drug Reaction, please report it via Patient Safety Net.

ADR Focus by Elizabeth Rudy, DVM, RPh

Fluoroquinolone-Induced Tendinopathies: Rare but Debilitating ADRs

Reprinted from *Drug Therapy Topics*, Vol 30 (9), 2001 (with some recent literature added to bibliography)

The fluoroquinolone antibiotics are useful agents with a wide spectrum of activity against many gram-negative and gram-positive organisms. These drugs are generally well tolerated, producing a minimum number of side effects. For example, during clinical trials for ciprofloxacin, the drug needed to be discontinued in only 3.5% of the patients tested. Adverse reactions were considered to be drug related in 7.3% of patients treated and possibly related in 9.2% of patients. The most commonly reported adverse reactions were nausea, diarrhea, vomiting, abdominal pain/discomfort, headache, restlessness, and rash.¹

Fluoroquinolone-induced tendinopathy can be considered a rare adverse drug reaction, some authors estimate its occurrence at 15 to 20 cases per 100,000 treated patients.^{2,3} Fluoroquinolone antibiotics were initially associated with tendinopathies in 1983. From 1987 to July 1997, 201 cases of fluoroquinolone-associated tendon disorders were reported to the FDA.¹ To date, nearly 1000 cases of fluoroquinolone-attributed tendon disorders have been reported internationally to the WHO Collaborating Center for International Drug Monitoring.⁴

Fluoroquinolone-associated tendinopathies include both tendinitis and actual tendon rupture (most commonly of the Achilles tendon but other tendons may be affected).⁵ Symptoms, including rupture, usually occur within the first several weeks after treatment with the fluoroquinolone antibiotic has been started.⁶ Although, there are reports of symptoms and tendon disruptions occurring months after discontinuation of the medication.⁵ In one review of 100 reports of fluoroquinolone-associated tendinopathies, the Achilles tendon was involved in 96% of the cases. Tendinitis occurred in 69% of the cases, and tendon rupture in 31% of the cases. Average time between start of therapy and onset of symptoms was 13 days, with a range of 1 to 90 days.⁷ Other risk factors for the development of these tendinopathies include: the concurrent use of corticosteroids, end-stage renal disease, mechanical stress, and advanced age.¹ In one study, the frequency rate of tendon rupture, tenosynovitis, and tendinitis was 1/11,000 patients for ciprofloxacin, 3/11,000 patients for norfloxacin, and 11/11,000 patients for ofloxacin.⁸

The pathophysiological mechanism of fluoroquinolone-induced tendinopathy remains unclear, although it is probably multifactorial in nature. Jorgensen et al., attributed the

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The fluoroquinolone antibiotics are generally well tolerated and fluoroquinolone-induced tendinopathy is considered a rare adverse drug reaction.

Fluoroquinolone-associated tendinopathies include both tendinitis and actual tendon rupture (most commonly of the Achilles tendon).

A majority of tendon ruptures occur at a site deficient of a good blood supply, sometimes after only a single dose of a fluoroquinolone antibiotic.

At the other extreme, tendon disruptions have occurred months after discontinuation of the medication.

Other risk factors for the development of these tendinopathies include: the concurrent use of corticosteroids, end-stage renal disease, mechanical stress, and advanced age.

Even with prompt discontinuation of the fluoroquinolone and tendon rest, the mean recovery time reported for tendon rupture is three months.

histological changes seen in fluoroquinolone-damaged Achilles tendons to be due to an ischemic process.⁹ They hypothesized that tendon rupture may be due to a vascular phenomenon leading to ischemia. A majority of tendon ruptures occur at a site deficient of a good blood supply, lending plausibility to this theory.¹ Another theory proposes the possibility of a direct toxicity of the drug on the collagen fibers.³ The sudden onset of some tendinopathies, sometimes after only a single dose of a fluoroquinolone antibiotic, would support this hypothesis.³

Even with prompt diagnosis and management (discontinuation of the fluoroquinolone and tendon rest), tendinitis resolves slowly. One study reported that only 50% of patients with fluoroquinolone-associated tendinitis recovered in 1 month; another study reported that 25% of patients were symptomatic for at least 2 months.^{2,10} Harrell states that the mean recovery time reported for tendon rupture is 3 months.¹

Because fluoroquinolone antibiotics are so commonly prescribed, it is important for health care practitioners to be aware of the potential effects that they may have on tendons. Practitioner awareness of the association between fluoroquinolone therapy and tendinopathies may lead to earlier recognition of symptoms in patients and the institution of measures to minimize adverse effects. Similarly, because adverse effects may not show up until months after treatment, practitioners with knowledge of this ADR will be more likely to recognize an association between a tendinopathy and past fluoroquinolone use and report it.

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FDA's Electronic Health Initiative: Package Inserts Get a New Look

The new package insert format will be phased in gradually beginning on June 30, 2006.

Package inserts are compilations of information, approved by FDA, based on the agency's review of the new drug application (NDA) or biologics license application (BLA). This information is considered necessary for safe and effective drug use. It is written for the health care practitioner because prescription drugs require "professional supervision of a practitioner licensed by law to administer such drug."

The newly designed package insert will contain up-to-date information in an easy-to-read format designed to draw attention to the most important information to consider before prescribing a drug.

The new format is designed to be better understood, more readily accessible, and more memorable for physicians.

It is hoped that the introduction of the new labeling will lead to a sea change in how physicians assess medication risks and that this in turn will reduce medical errors.

Introduction: FDA has revised its rules for the content and format of prescribing information for prescription drug and biological products that are regulated as drugs. The new look is expected to make prescribing information easier to read and help healthcare professionals find information more easily and quickly. Simultaneously, FDA's electronic health initiative also will make the updated prescribing information available via the Internet, creating a more efficient way for health professionals to obtain information critical to safe drug prescribing.

Products Affected: The new prescribing information requirements apply to newly approved prescription drugs, drugs that were approved within the last 5 years, and older drugs when there is a major change in the prescribing information (e.g., approval of a new use).

Benefits: The changes to drug prescribing information are intended to improve patient safety by making it easier for healthcare professionals to access, read, and use prescribing information, thereby increasing the extent to which healthcare professionals will rely on it. FDA made these changes to the rules for package inserts in an effort to standardize the increasingly complex nature of prescribing information and to make it easier for health care practitioners to quickly discern the most critical information. The revised format is hoped to enhance the safe and effective use of prescription drug products and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information. Under the new format, some critical prescribing information will be located in newly created sections of the labeling while other information will be moved or combined to allow for a more balanced risk assessment between products. In addition, some new information (e.g., a drug's approval date) that was not mandatory under the old requirements is now required.

The New Look: Under the new rules, introductory *Highlights*, will be added to the beginning of the prescribing information. *Highlights* will provide a concise summary of information most important to prescribers and will refer them to the appropriate section(s) in the Full Prescribing Information (FPI) for more detailed information. *Highlights* will include:

- **Recent Major Changes:** A list of all substantive changes made within the last year to the following FPI sections: *Boxed Warning, Indication and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions*. The corresponding new or revised text in the FPI will be identified by a vertical line in the left margin. This visual clue will help healthcare professionals quickly identify important new information that has been added to the prescribing information.
- **Drug Approval Date:** The date of FDA approval of the original drug to make it easier to determine how long a product has been on the market.
- **Adverse Event Reporting:** A toll-free number and Internet site to report suspected adverse reaction.
- **Table of Contents:** A list of all the sections and subsections in the FPI.

Additionally, much of the information contained in the FPI will be reorganized and reordered. Frequently used sections, such as the *Indications and Usage*, and *Dosage and Administration* sections, have been moved to the front of the prescribing information. By creating a *Patient Counseling* section, information that healthcare professionals can use when counseling patients has been made more prominent. If the drug also has an FDA-approved patient information sheet, it will be printed immediately after the *Patient Counseling* section. Importantly, sections containing risk information are now all located together. For example, risk information that had been listed separately in either the *Warnings* or *Precautions* sections is combined into a new *Warnings and Precautions* section. In addition, new sections have been created that address specific safety issues (e.g.,

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“Providing healthcare professionals and patients with clear and concise information about prescriptions will help ensure safe and optimal use of drugs, which translates into better health outcomes for patients and more efficient delivery of healthcare.” —HHS Secretary Mike Leavitt

“By improving the package insert to make it more useful for healthcare providers in their day-to-day clinical practice, we are making it easier for them to explain the benefits and risks of medications for their patients.” —HHS Secretary Mike Leavitt

Drug Interactions, Precautions for Use in Specific Populations). Certain graphical features including minimum type size and bolding also are standardized for the new format.

The FDA Change Process: Before publishing the final rule in the January 24, 2006 issue of the Federal Register (21 CFR Parts 201, 314, and 601 “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices”), the FDA evaluated the usefulness of prescription drug labeling to determine whether, and how, its content and format could be improved for its principal audience. The agency used focus groups, two national physician surveys, public meetings, and written comments to develop prototypes and to ascertain how prescription drug labeling is used by health care practitioners, what labeling information practitioners consider most important, and how practitioners believed labeling could be improved. See <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of how the new inserts will look or for further information.

DailyMed and facts@fda: The new package insert format is timed to accompany the recently launched DailyMed website (<http://dailymed.nlm.nih.gov>), a health information clearinghouse created by FDA and the National Library of Medicine. This complimentary FDA initiative is another step toward improving access to drug safety and effectiveness information so that prescribers can more easily get up-to-date information at the point of care. Free of charge, the DailyMed site will make current information about FDA-regulated products readily available to physicians, other healthcare professionals, and patients. In the future, this new information will also be provided through a website called *facts@fda*, a comprehensive Internet resource designed to give one-stop access for information about all FDA-regulated products.

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Update: Fluoroquinolone-Induced Tendinopathies: Rare but Debilitating ADRs, 21-22

FDA's Electronic Health Initiative: Package Inserts Get a New Look, 23-24

P&T Committee Actions: No meeting last month.



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drug therapy topics