# *Louis R. Cantilena, Jr.,*

# a pioneer in drug safety

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I first met Dr. Louis R. Cantilena, Jr. (AΩA, University of Kansas School of Medicine, 1984) in 1989, when I was a Navy Lieutenant and Internal Medicine resident at the (then) National Naval Medical Center Bethesda, MD. He had recently joined the Uniformed Services University of the Health Sciences (USU) after completing a PhD and MD at the University of Kansas, and an internal medicine residency and clinical pharmacology fellowship at Dartmouth.

That November, I was a resident on the cardiology ward and received an admission from the Emergency Department (ED). The patient was a healthy, 39-year-old woman who had fainted four times in the preceding day. Her most recent episode had occurred while she was driving on the Beltway, a busy highway encircling Washington, DC. Her ED evaluation had detected a solitary abnormality—a markedly prolonged QTc interval and abnormal T-wave morphology on her electrocardiogram.

Ten days before, she was prescribed terfenadine (a then-new and popular non-sedating antihistamine marketed under the brand name Seldane™) to be taken twice per day, along with cefaclor for recurrent sinusitis. On the eighth day of therapy, she stopped cefaclor and began a self-medicating course of ketoconazole, 200 mg, twice a day, for early symptoms of candidiasis (the ketoconazole had been previously prescribed for an earlier episode of antibiotic-associated candidiasis). An electrocardiogram obtained several years prior was completely normal. Counts of her remaining pills and her spouse's observations confirmed she had used her medications as directed.

When she reached the floor, I placed her on telemetry. Over the next few hours, I was called to her bedside several times for bouts of polymorphic ventricular tachycardia (also known as *Torsades de Pointes*) and recurring syncopal events.

I asked the Command Duty Officer to open the locked door to the hospital's medical library. There, I conducted a search of *Index Medicus* (a now obsolete hundred-plus volume set of medical journal citations), which contained a case report of self-inflicted overdose by a British teenager of astemazole (brand name Hismanal™), another antihistamine in common use at the time. According to the report, the drug had produced polymorphic ventricular tachycardia and QTc prolongation similar to that of my patient. I suspected my patient's use of terfenadine had something to do with her arrhythmias.

What puzzled me was that my patient had not overdosed—she was taking the recommended dosage of what was, at the time, the world's most popular new medication. I thought perhaps there was something about her, or her other medications, that caused her problem.

My department chair, Dr. Bonnie B. Potter (AΩA, Saint Louis University School of Medicine, 1974), thought the case quite interesting. She informed me that there was a new consult service at USU. The consult service was headed by Dr. Cantilena, and was available to see patients with potential adverse drug effects. I promptly submitted a request.

Dr. Cantilena immediately suspected an adverse drug interaction had occurred between terfenadine and one of my patient's other medications. As a consultant to the Food and Drug Administration (FDA), Dr. Cantilena had access to an extensive database of adverse drug reports. He was eager to discover what had caused the dangerous arrhythmias.

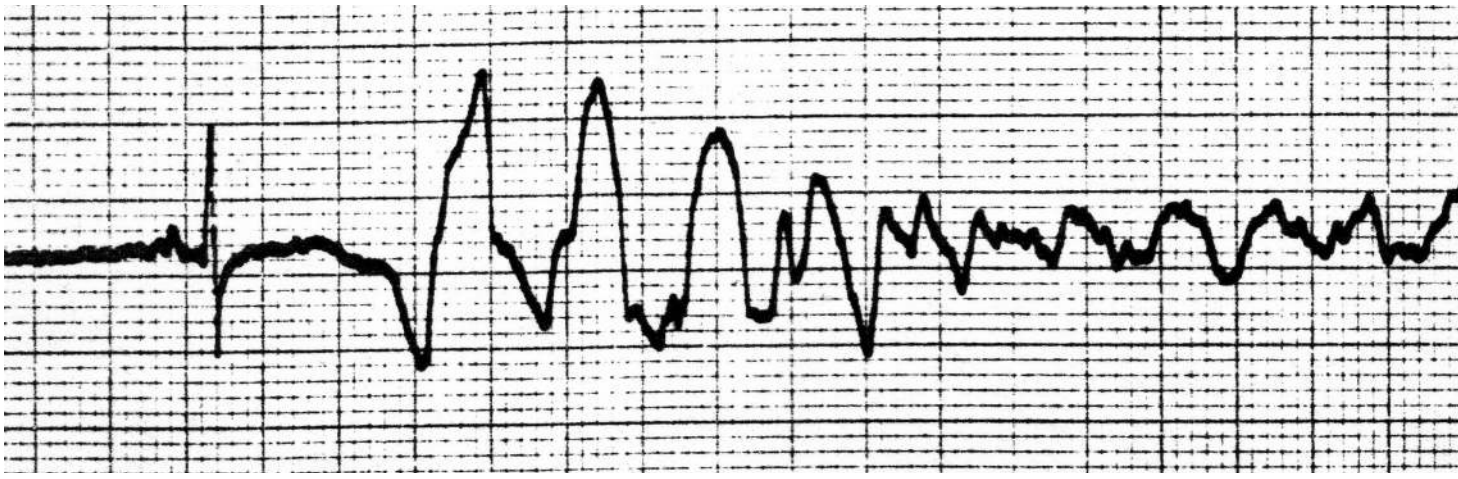
Fortunately, I had frozen several samples of the patient's plasma. Dr. Cantilena took these back to USU. He was aware of several reports in the FDA files of self-inflicted terfenadine overdose causing adverse cardiac effects and on that basis, convinced Marion Merrell Dow Pharmaceuticals Inc., the manufacturer of terfenadine, to measure the level of terfenadine and its primary metabolite, fexofenadine, in the patient's plasma. The tests revealed that my patient had a massive amount of the parent drug in her plasma and only the expected amount of the drug's metabolite.

We came to believe that ketoconazole had blocked metabolism of terfenadine in her liver allowing the parent drug to rise to the point that it caused the toxic cardiac effects. Other scientists would go on to characterize the specific basis of this toxicity—blockade of cardiocyte potassium channels—leading to its arrythmogenic effects.[1]

Forty-eight hours after admission, my patient felt well and her electrocardiogram returned to normal. A multi-day intensive cardiovascular workup revealed no abnormal findings.

The encounter with Dr. Cantilena produced a discovery that influenced the fate of a multinational corporation, potentially saved thousands of lives, provided a new area of research interest for dozens of scientists, and forever changed fundamental concepts of drug development, safety, licensure, and regulation.

First synthesized 10 years prior to commercial release, terfendine had a structure similar to other drugs such as



Sample EKG of patient experiencing bouts of polymorphic ventricular tachycardia (also known as *Torsades de Pointes*) and recurring syncopal events.

haloperidol and some selective serotonin re-uptake inhibitors. Successive chemical substitutions eliminated its centrally-mediated side effects. Furthermore, neither terfenadine nor its metabolites easily penetrated the blood-brain barrier. This explained its lack of sedating effects. Terfenadine was a prodrug, almost completely and immediately metabolized in the liver to its active metabolite, fexofenadine, which produced the desired effects.

Example of FDA Black Box Warning.

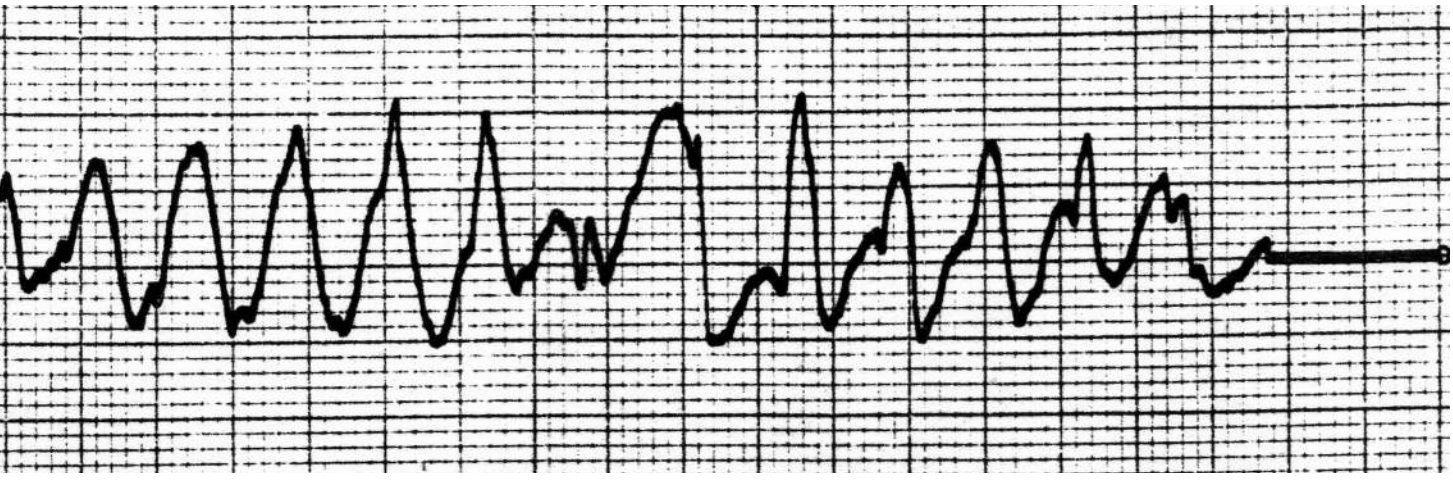
From the late 1980s to the 1990s, terfenadine was one of the world's most prescribed drugs. At the time I admitted my patient, it was used by more than 200 million people. When released for sale in 1985, it was heralded as a breakthrough for allergic rhinitis, because patients could relieve their itchy noses and sneezing without becoming sleepy. There had been no documented serious adverse effects at standard dosage, and no significant drug interactions. Potential approval for over-the-counter sale was under consideration. Marion Merrell Dow earned $500 million from Seldane in 1991, and over-the-counter sales were projected to triple that annual income.

Convinced our observation was important, Dr. Cantilena and I wrote a brief case report.[2] We hypothesized that ketoconazole had inhibited the P-450 metabolic pathway in the liver, and had inhibited metabolism of terfenadine causing the parent drug to accumulate in the plasma to a dangerous degree. In view of the widespread use of the drug, Dr. Cantilena had the foresight to caution that other drugs, in addition to ketoconazole, could block metabolism of terfenadine. These included Tagamet™, then the world's most popular stomach acid suppression drug, and erythromycin, a commonly prescribed antibiotic.

The first journal we sent the manuscript to rejected it as a "specialty-limited narrow interest observation." Fortunately, *JAMA* published it in December 1990. The paper prompted a torrent of subsequent investigations, and publications. The manufacturer was required to send all physicians an "Important Drug Warning Letter" disclosing the serious adverse events and patient deaths.[3] In 1992, the FDA issued a Black Box Warning with respect to potentially fatal adverse cardiac effects, and sent FDA "Dear Prescriber" letters alerting prescribers to the hazard.[4]

As later chronicled in the *New York Times Magazine*, and other newspapers, our case report caused considerable distress for Marion Merrell Dow.[5] Initially, it attempted to attribute our observations to a self-inflicted drug overdose. Dr. Cantilena had the wisdom to be personally present at the corporation's presentation to the FDA's adverse event monitoring committee; and swiftly rebutted the assertion. Following the FDA actions, the corporate stock dropped 18 percent in one day, and the company's over-the-counter status application was "re-evaluated."[6]

In subsequent years, other scientists at USU and



Georgetown University would conduct novel investigations of terfenadine. Their work led to the discovery of additional drug interactions that can produce serious adverse effects. The FDA dramatically revised its pre-approval drug safety and interaction testing requirements for all new drugs. Doctors would need to consider the combined effects of the medical therapies they prescribed, in addition to drugs prescribed by other providers.[7]

The potential economic value of a drug's metabolites inspired the creation of "patent-estates" surrounding new molecules that would anticipate further use of a parent drug and its metabolites for additional clinical indications, marketing, and profit.

A few years later, terfenadine went off-patent and was picked up by other manufacturers seeking to market it throughout the world. But in 1997, the FDA reversed its prior approval of a generic version of terfenadine. Given its potential for severe adverse drug interactions, the FDA saw no purpose in allowing its sale.

This story, now 28 years old, has three epilogues: 1) terfenadine's metabolite, fexofenadine, was later approved for sale as Allegra.™ It proved to be so safe that it is now sold without a prescription; 2) Tragically, Louis Cantilena died in 2017 in a plane crash that also claimed the life of his medical student daughter, Amy, and a colleague, Paul Schuda. Although we mourn their deaths, we celebrate the vast impact Cantilena had on drug safety; 3) In an era of internet searches, big data, and massive multicenter trials, the lowly case report may have lost its luster. But, as this story shows, sometimes an eager resident, a gifted young attending, and a case report can change the practice of medicine.

**Note:** The views and opinions represented here reflect the author's personal opinion and do not reflect the views, policies or positions of any branch or department of the United States Government.

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