

ALTERNATIVE VIEWPOINTS

Comparison of Clinically Significant Cardiovascular Events Between Three Fluoroquinolones

Christopher P. Bunce, M.D., John L. Lock, Pharm.D., and Ranita Kirit Patel, Pharm.D.

Key Words: Fluoroquinolones, Infectious disease, Pharmacology
(Pharmacotherapy 2010;30(10):479e–480e)

We applaud Dr. Li and his colleagues on their thorough literature review and interpretation of drug-induced QT interval prolongation in the July issue of *Pharmacotherapy*. The review article documented a large number of trials and did an excellent job of delineating the method of drug-induced QT interval prolongation and patient predisposition to cardiac abnormalities with use of specific agents. While we do not disagree with the data presented throughout the article, we would like to dispute that moxifloxacin “should be reserved for treatment in those patients who fail therapy with another fluoroquinolone.”¹

Moxifloxacin was introduced into the market during increased speculation about drugs associated with QTc interval prolongation and torsades de pointes (TdP), and therefore has more associated case reports. However, in head to head studies, the difference in clinical cardiovascular events including torsades was either minimal or insignificant when comparing the fluoroquinolones.²

A prospective, randomized, double-blind trial evaluated the cardiac rhythm safety profiles of levofloxacin and moxifloxacin.³ The ultimate contributor to cardiac events was patient risk factors and the only case of TdP was in the levofloxacin group. In an exhaustive review on the topic of fluoroquinolone safety, Owens and Ambrose found no difference in postmarketing studies and clinical trials with regard to cardiac risk associated with moxifloxacin and levofloxacin use. They concluded that moxifloxacin and levofloxacin are similar from a clinically relevant cardiac safety perspective and deemed them interchangeable in therapy.⁴

Through the above literature review, we believe

incidence of clinically significant QTc interval prolongation is similar amongst the fluoroquinolones. We believe all fluoroquinolones should be avoided or used cautiously in patients at risk for cardiac events. Furthermore, based on common resistance mechanisms, failure of one fluoroquinolone should dictate change of therapy to another drug class.

References

1. Li EC, Esterly JS, Pohl S, Scott SD, McBride BF. Drug-induced QT-Interval Prolongation: Considerations for Clinicians. *Pharmacotherapy* 2010;30(7):684–701.
2. Falgas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias Associated with Fluoroquinolone Therapy. *International Journal of Antimicrobial Agents* 2007;29:374–79.
3. Morganroth J, DiMarco JP, Anzueto A, Niederman MS, Choudhri S. A Randomized Trial Comparing the Cardiac Rhythm Safety of Moxifloxacin vs Levofloxacin in Elderly Patients Hospitalized with Community-Acquired Pneumonia. *CHEST* 2005;128:3398–406.
4. Owens RC, Ambrose PG. Antimicrobial Safety: Focus on Fluoroquinolones. *Clinical Infectious Diseases* 2005;41:S144–157.

Authors' Response

We thank Drs. Bunce, Lock, and Patel for their thoughtful commentary on our article.¹ We disagree that the level of risk should be equalized across the fluoroquinolone class. Indeed, limited clinical data are available on the arrhythmogenic risk of fluoroquinolone antibiotics and how to best interpret existing data remains unclear. In constructing our article however, we adopted a translational medicine approach similar to national treatment guidelines. In so doing, we took into consideration clinical trials, case reports, post-marketing data, as well as data from animal and cellular studies where clinical data are absent.

As an example, we set forth the convention that suppression of the delayed repolarizing potassium current, IKr, leads to QT prolongation, and if exaggerated, Torsade de Pointes, a polymorphic ventricular tachycardia. While we agree that the articles cited by Bunce, Lock, and Patel show no difference in clinical impact of fluoroquinolones,

From the Department of Infectious Disease, St. Vincent Indianapolis Hospital, Indianapolis, Indiana (Dr. Bunce) and the Department of Pharmacy, St. Vincent Indianapolis Hospital, Indianapolis, Indiana (Drs. Lock and Patel)

For questions, contact Dr. Ranita K. Patel, Pharm.D., Department of Pharmacy, St. Vincent Indianapolis Hospital, Indianapolis, Indiana 46260; e-mail: rxpatell@stvincent.org.

cellular investigations clearly show moxifloxacin to be 10 times more potent at suppressing IKr compared to either ciprofloxacin or levofloxacin.² As a result, the potential exists that cases of Torsade de Pointes may be more likely with moxifloxacin.

In demonstration of their point, Bunce, Lock, and Patel cite a randomized controlled trial of 394 elderly patients (mean age 77.8 years) with community-acquired pneumonia that evaluated the cardiac safety of levofloxacin and moxifloxacin.³ In this study patients received IV/oral moxifloxacin 400 mg daily or IV/oral levofloxacin 500 mg daily. Patients were monitored by continuous ECG for the first 72 hours of therapy and mean QTc changes were $+6.5 \pm 23.2$ ms and -2.5 ± 22.9 ms for moxifloxacin and levofloxacin respectively. Although there was no significant differences in primary composite cardiac events and no patients experienced death related to a study drug during the study period, the study was not powered to detect the incidence of Torsade de Pointes as an individual primary endpoint. Further, there was more nonsustained ventricular tachycardia in the moxifloxacin group, and the QTc on moxifloxacin was higher, even though the most optimal QT correction formula (Framingham) was not used.

In support of our recommendation, we also point to the following data. Demolis et al found that single oral doses of moxifloxacin 400 mg (FDA recommended dose) and 800 mg increased the QT interval by $4.0 \pm 5.1\%$ and $4.5 \pm 3.8\%$ respectively in healthy volunteers.⁴ Tsikouris et al compared 7 days of oral therapy with moxifloxacin 400 mg once daily, ciprofloxacin 500 mg twice daily, and levofloxacin 500 mg once daily in healthy volunteers.⁵ While study subjects taking ciprofloxacin and levofloxacin experienced no observed increase in QT interval after 7 days, subjects taking moxifloxacin experienced a mean increase in QT interval of 6 milliseconds (ms) from baseline ($p=0.022$). It should be noted however, that patients frequently take higher doses of ciprofloxacin and levofloxacin in clinical practice than those studied. To that end, another randomized controlled trial conducted by Noel et al looked at high doses of moxifloxacin (800 mg), ciprofloxacin (1500 mg) and levofloxacin (1000 mg) once daily in a cross-over study of healthy volunteers.⁶ Moxifloxacin increased QTc by a mean of 16.3–17.8 ms ($p<0.001$), ciprofloxacin increased QTc by a mean of 2.3–4.9 ms ($p<0.05$), and levofloxacin increased QTc by a mean of 3.5–4.9 ms ($p<0.05$) all of which were significant when compared to placebo.

Bunce, Lock, and Patel refer to well-done reviews of clinical trials and post-marketing studies that suggest there are no clinically significant differences

in cardiac risk amongst fluoroquinolones. In point of fact, for events that are rare, prospective studies struggle to bear out differences between treatments in a manner that may be interpreted as significant. For example, an event that would be expected occur at a difference of 1% between two treatments would require a sample size of nearly 40,000 patients per group to reach statistical significance based on gold standard statistical methodologies used in clinical trials. While post-marketing studies do provide valuable data, they can be fraught with incomplete or confounding information and events are frequently underreported. Thus, in patients at risk for an uncommon event that could result in death, clinicians must often rely on surrogate markers instead of clinical endpoints to guide them in stratifying the potential risk between two treatments.

We do agree with Bunce, Lock, and Patel that fluoroquinolones should be avoided or used cautiously in patients at risk for cardiac events. Unfortunately factors such as drug allergies, limited antimicrobial susceptibilities, and the potential toxicities of other therapeutic options dictate that clinicians must frequently use risk/benefit assessment in choosing therapy for their patients. We stand behind our recommendation that patients indicated to receive antimicrobial therapy with a fluorquinolone be offered such therapy except in cases where arrhythmia control *de novo* is tenuous.

To best minimize risk when fluoroquinolone therapy is necessary for such patients, moxifloxacin should be selected when other fluoroquinolone options do not exist.

References

1. Li EC, Esterly JS, Pohl S, Scott SD, McBride BF. Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy* 2010;30:684–701.
2. Kang J, Wang L, Chen XL, Triggler DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K⁺ channel HERG. *Mol Pharmacol* 2001;59:122–6.
3. Morganroth J, Dimarco JP, Anzueto A, Niederman MS, Choudhri S. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. *Chest* 2005;128:3398–406.
4. Demolis JL, Kubitzka D, Tenneze L, Funck-Brentano C. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther* 2000;68:658–66.
5. Tsikouris JP, Peeters MJ, Cox CD, Meyerrose GE, Seifert CF. Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol* 2006;11:52–6.
6. Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003;73:292–303.

John S. Esterly, Pharm.D., BCPS
Brian F. McBride, Pharm.D.