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Weighing the Adverse Cardiac Effects of Fluoroquinolones: A Risk Perspective

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Abstract

A rare side effect of fluoroquinolone (FQ) antibiotics is QT prolongation, which may result in serious arrhythmias. Most published comparative trials describe the relative risks among the drug class but do not focus on the incidence of serious arrhythmias. It is important for the prescriber to have a sense not only of relative risk but also of incidence to balance the risks against the other attributes of the individual members of the drug class. A review of English-language literature was performed to identify trials that provide data on the relative risk and, when able to be calculated, the incidence of adverse cardiac events among the commonly used FQs. Moxifloxacin had a several-fold higher risk of cardiac arrhythmias than levofloxacin or ciprofloxacin in randomized trials. However, the actual event rate was low in 2 of 3 studies. Given inconsistencies among the studies and the relative rarity of the events, the clinician need not base the choice of drug primarily on concern for a cardiac arrhythmia except in patients at the highest risk of such an event.

Keywords

fluoroquinolones, QT interval, QT prolongation, torsades de pointes, side effects

Fluoroquinolones (FQs) have been widely employed for the treatment of bacterial infections for nearly 25 years. There are currently 6 FQ on the US market approved for systemic administration by the oral or intravenous route, namely, ciprofloxacin (intravenous, oral), ofloxacin (oral), levofloxacin (oral, intravenous), moxifloxacin (oral, intravenous), norfloxacin (oral), and gemifloxacin (oral). In addition, ofloxacin, levofloxacin, and moxifloxacin are available as topically applied drops. The drugs exhibit a broad antibacterial spectrum, good oral bioavailability, and a generally acceptable safety profile. A rare but serious concern with the use of FQs is their potential to cause prolongation of the QT interval, which may result in arrhythmias such as torsades de pointes (TdP). Indeed, sparfloxacin was withdrawn from the US market, and grepafloxacin was withdrawn worldwide because of reports of cardiac arrhythmias related to prolongation of the QT interval.[1,2]

Faced with case reports and a number of clinical trials indicating a risk of fatal arrhythmias with some of these drugs, it is challenging for the practicing clinician to weigh the relative risk for a cardiac arrhythmia against the other differences among the drugs, for example, in their antibacterial spectrum and in other side effects. An important consideration in the evaluation is the *base rate* of the adverse event, that is, the rate of events in subjects not exposed to the drug of interest or exposed only to a drug class not believed to increase the propensity to arrhythmia. If the rate is exceedingly low, even a multiple thereof may not be clinically worrisome. The purposes of this review are to assess the relative risk of the various FQs to cause prolongation of the QT interval, TdP, and cardiovascular deaths and to estimate the incidence of such events from the published literature.

The QT Interval

The QT interval is a measure of the cellular ventricular action potential generated by the passage of current through ion channels.[3] A variety of drugs, including FQs, can act on the channels to cause prolongation of this interval. One consequence can be torsades de pointes (TdP), a polymorphic ventricular tachycardia (VT) that can evolve into ventricular fibrillation and cause sudden death.[4] Although all FQs can impede this ionic current, they differ in their magnitude of effect, presumably because of structural differences among them.[5–7] Importantly, the degree to which the individual FQ agents inhibit the potassium current (I_{kr}), correlates with the risk

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of a cardiac event.[8,9] According to 1 study based on the I_{kr} inhibition, the proposed rank order of potency in QT prolongation of a number of FQs, some not on the US market, is: sparfloxacin > grepafloxacin > moxifloxacin > gatifloxacin > levofloxacin > ciprofloxacin > ofloxacin.[10]

In healthy individuals, the QT interval should be <430 milliseconds in men and <450 milliseconds in women. Generally, a QT interval greater than 450 milliseconds is considered prolonged, whereas a QTc greater than 500 milliseconds is associated with an increased risk of TdP.[11] Despite this association, the degree of lengthening of the QT interval is not precisely related to the risk of TdP.[12] Moreover, the QT interval may vary in repeated measurements within an individual with a standard deviation of 20 milliseconds.[13] Because we recognize that prolongation of the QT interval is not necessarily highly correlated with cardiac arrhythmias, we have explored not only QT prolongation but also TdP and cardiovascular deaths related to these drugs.

Chemistry and Structure of FQs

The nucleus of the FQ is a bicyclic ring. The substituent at position 5 is thought to determine both the activity against gram-positive bacteria and the potential for QT-interval prolongation.[14] Ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin all have a hydrogen atom located at position 5 of the FQ nucleus, whereas sparfloxacin has an amino and grepafloxacin has a methyl substituent at position 5. The amino and methyl substituents have been suggested to cause a greater QT prolongation than does the hydrogen ion.[15] In fact, in vitro studies show that grepafloxacin and sparfloxacin require much lower concentrations than levofloxacin and ciprofloxacin to block the HERG (now renamed *KCNH2*) channel current.[16] Despite these observations, the evidence is weak as to which structural moieties pose the greatest risk of prolongation of the QT interval.[17,18]

General Risk Factors

A number of factors can increase the risk of TdP with exposure to FQs. A retrospective review of 249 cases of TdP associated with the administration of an FQ found that 96% of patients had at least 1 predisposing factor for TdP, and 71% had at least 2 risk factors.[19] These risk factors were electrolyte abnormalities (hypokalemia, hypomagnesemia), bradycardia, cardiovascular disease, administration of another QT-interval-prolonging drug, female sex, and prolonged QT interval at baseline. Risk factors that have been observed in other studies are structural heart disease, impaired drug elimination, and congenital long QT syndrome.[20] Because many of these risk factors are common in the populations treated with FQs, it is important for clinicians to be aware of the most important ones.

Methods

A literature search was performed of the MEDLINE and Embase database from 1980 to 2014, using as keywords the drug names of FQs that are currently on the US market; combined with the words "QT interval prolongation," "ECG abnormalities," "safety," "toxicity," "adverse effect," and "adverse drug reaction."

This review examines the data regarding prolongation of the QT interval, episodes of TdP and adverse cardiac events in humans. We focused our attention on the 3 major FQs currently available in the US market, that is, ciprofloxacin, levofloxacin, and moxifloxacin, but made note of trials involving sparfloxacin, grepafloxacin, and gatifloxacin. Some authors have reported their results as QT interval, others as QTc interval (ie, corrected for heart rate). We have reported the results with the indices used by the authors.

We included randomized, controlled trials, observational studies, case-control studies, systematic reviews, and retrospective studies. We excluded case reports because they do not allow for a calculation of relative risk. We have not included reports from adverse event reporting databases such as the US Food and Drug Administration Adverse Event Reporting System because the reports are voluntary and subject to reporting bias, which makes calculation of relative risk unreliable. We included 1 report from the Taiwanese national database because its design allows for capture of adverse cardiac events without a likelihood of reporting bias.

Results

Randomized Trials in Healthy Volunteers

Five randomized trials examined the effects of FQs on the QT interval in healthy volunteers (Table 1). Four were single-dose studies; the fifth involved treatment for 7 days. There were no episodes of TdP or cardiac events or deaths in these volunteer trials.

The first study[21] assessed the effect of increasing doses of levofloxacin on the QT and QTc intervals. Compared with the 500-mg dosage, both higher dosages were associated with slight but statistically significant increases in the QTc interval (Table 1). The authors suggested that these minor QT prolongations were likely due to an increase in the heart rate rather than to prolongation of ventricular repolarization. In fact, this mechanism has been suggested for other drugs associated with QT prolongation such as amiodarone, sotalol, cisapride, and erythromycin.

The second study[22] analyzed the effect of high doses of 3 FQs (800 mg moxifloxacin, 1000 mg levofloxacin, and 1500 mg ciprofloxacin) on the QT interval. All 3 drugs caused QT-interval prolongation compared with placebo, but the increase was greatest for moxifloxacin

Table 1. Randomized, Controlled Trials in Healthy Subjects

Study and Design	Sample Size and Type of Subjects	Treatment/Dose/ Route	QT Prolongation	TdP	Relative Risk
Noel et al[21]	47	Single dose PO	No effect on the QT interval with Levo 500 mg	0	Levo 1500 mg > 1000 mg > 500 mg for QT prolongation
Double-blind, randomized, crossover trial	Healthy volunteers	Levo 500, 1000, or 1500 mg	QT ↑ by 1.5–3.9 ms ($P \leq .05$) with Levo 1000 mg		
			QT ↑ by 6.4–7.7 ms ($P \leq .001$) with Levo 1500 mg, (24 h) compared with placebo		
Noel et al[22]	47	Single dose PO	Compared with placebo	0	Moxi > Levo > Cipro > placebo for QT prolongation
Double-blind, randomized, crossover trial	Healthy volunteers	Moxi 800 mg vs Levo 1000 mg vs Cipro 1500 mg	Moxi ↑ 16.3–17.8 ms ($P < .001$) Levo ↑ 3.5–4.9 ms ($P < .05$)		
Démolis et al[23]	18	Single dose PO	Placebo: 24 ms	0	Both Moxi dosages > placebo for QT prolongation
Randomized crossover trial	Healthy volunteers	Moxi. 400 vs 800 mg	Moxi 400 mg ↑ 33 ms Moxi 800 mg ↑ 28 ms Both significantly greater than placebo (24 ms, $P = .05$) All measured after 24 h		
Taubel[24]	32	Single-dose Moxi 400 mg PO	Compared with baseline, Fed state ↑ 11.6 ms	0	Significant increase over baseline in both fed and fasted state. No difference between white and Japanese subjects
Double-blind, randomized trial	Healthy volunteers		Fasted state ↑ 14.4 ms Both significantly greater than baseline		
Tsikouris et al[25]	13	7 days' treatment PO	Measured on day 7	0	Moxi > Levo = Cipro for QT ↑
Randomized, open-label, crossover trial	Healthy volunteers	Cipro: 500 mg twice daily. Levo: 500 mg once daily	Cipro and Levo: no change from baseline		
		Moxi: 400 mg once daily	Moxi: QTc ↑ 6 ms ($P = .022$)		

(17.8 milliseconds, $P = .001$) and was minimal for the other 2 agents.

In the third trial,[23] a single dose of 400 or 800 mg of moxifloxacin or placebo was given to 18 healthy volunteers. All treatments, including placebo, were associated with increases in the QT interval, but the effects were not dose related, and the mean resulting QT intervals were all below 400 milliseconds. There were no instances of TdP.

A fourth study[24] assessed the effect of a single dose of oral moxifloxacin 400 mg on the QTc interval in fed and fasted healthy Japanese and white patients. There was slightly greater prolongation of the QT interval in the fasting than in the fed state. No difference was found between white and Japanese subjects in the extent of QT prolongation.

The fifth trial[25] examined the effects of treatment for 7 days with ciprofloxacin, levofloxacin, and moxifloxacin in a crossover study. Neither ciprofloxacin nor levofloxacin was associated with a change in the QTc interval from baseline; however, moxifloxacin 400 mg/day was associated with a small but statistically significant increase of 6 milliseconds (Table 1). Because of the minor degree of prolongation of the QTc interval in this study, none of the drugs would be considered likely to increase the risk of TdP.

These healthy volunteer studies suggest that ciprofloxacin and levofloxacin have a minor effect on the QT interval in normal subjects, whereas moxifloxacin has a slightly greater effect. However, the trials were of short duration and involved small numbers of subjects who had no known risk factors for a cardiac arrhythmia.

Randomized Trials in Patients

Three randomized trials in patients (Table 2) examined effects on the QT interval, episodes of TdP, and "cardiac events" in recipients of FQs.

A randomized, double-blind study by Morgenroth et al conducted at 47 hospitals in the United States compared the effects of moxifloxacin with those of levofloxacin on cardiac rhythm in 387 patients with community-acquired pneumonia (Table 2). Each drug was given first by the intravenous route and then by the oral route. Seventy-two hours of digital continuous 12-lead Holter monitoring,

Table 2. Randomized Trials in Patients

Study and Design	Sample Size and Type of Subjects	Treatment/Dose/Route	QT Prolongation	TdP	Relative Risk
Morganroth et al[26]	387 (192 given Moxi, and 195 given Levo)	Moxi 400 mg IV or PO vs Levo 500 mg IV or PO for 7–14 days	Sixteen moxifloxacin-treated patients (8.3%) and 10 levofloxacin-treated patients (5.1%) had a primary composite cardiac event ($P = .29$)	Moxi: 0	Moxi ≈Levo
Randomized, controlled trial	Patients >65 years old with community-acquired pneumonia and cardiac risk factors. Those with known QT prolongation or receiving class IA or III antiarrhythmics excluded		Moxi: $+6.4 \pm 23.2$ (SD) ms ($P = .04$) Levo: -2.5 ± 22.9 ms ($P = .04$)	Levo: 1	
Makaryus et al[27]	38 (27 patients given Levo, 11 given Cipro)	Cipro 250 mg PO twice daily vs Levo 500 mg PO once daily 2 days (48 h)	The average changes in the longest QT interval were 0.01 and -0.02 for Levo ($P = .04$) and 0.01 and -0.02 for Cipro ($P = .09$)	0	Slight increase in QTc over baseline for Levo; no change for Cipro
Randomized, controlled trial	Patients >65 years old with community-acquired pneumonia or urinary tract infection without cardiac risk factors				
Lipsky et al[28]	603 Patients	Sparflox: 400-mg loading dose followed by 200 mg once daily for 10 days PO	Mean change in QTc from baseline to the maximum on-treatment value greater with Sparflox (9 ms) than with Cipro (3 ms); $P = .005$	Sparflox: 0	Sparflox > Cipro for QT prolongation
Double-blind, randomized, multicenter trial	Community-acquired, complicated skin and skin-structure infections	Cipro: 750 mg twice daily for 10 days PO		Cipro: 0	

and 12-lead ECGs at baseline and at maximum serum concentration on day 3 were performed; adverse events were recorded. Most patients were elderly, and three-quarters had a history of heart disease; however, patients with known QTc prolongation or receiving class IA or III antiarrhythmics were excluded. A primary cardiac event occurred in 8.3% of patients treated with moxifloxacin compared with 5.1% in the levofloxacin group; the difference was not statistically significant ($P = .29$). The most common arrhythmia was nonsustained ventricular tachycardia. Interestingly, there was no relationship between the occurrence of cardiac events and prolongation of the QTc interval duration. One patient treated with moxifloxacin had a sustained monomorphic ventricular tachycardia (>30 seconds), and 1 patient treated with levofloxacin had TdP. Although the FQs could have contributed to the arrhythmia in these 2 patients, the authors considered the evidence insufficient to prove causation.[26]

The second randomized trial[27] involved a single dose of levofloxacin or 2 doses of ciprofloxacin given to 38 elderly patients hospitalized with either pneumonia or urinary tract infection; the patients had no known cardiac risk factors. Twelve-lead electrocardiograms were obtained at baseline and at least 48 hours after the first dose of the antibiotic was administered. Both the longest QT interval and the mean QT interval were evaluated. The average change in the longest QT interval measured was ± 0.01 millisecons, a negligible change. There were no episodes of TdP, "cardiac events," or deaths from cardiovascular disease. The small number of patients and doses limits the utility of this trial.

The third trial[28] was a double-blind multicenter study involving 603 patients with community-acquired skin and skin-structure infections. There is no mention of excluding patients with cardiac risk factors. The patients received sparfloxacin or ciprofloxacin for 10 days. Twelve-lead electrocardiograms were obtained at baseline and at the end of the treatment course. The maximum change in QTc interval from baseline was significantly greater in the patients receiving sparfloxacin than in those receiving ciprofloxacin (9 vs 3 milliseconds, $P = .005$), but the extent of prolongation was slight for each drug and the average maximum QTc intervals were well below 450 milliseconds. There were no reported clinical cardiac events.

Retrospective Studies

Retrospective studies allow for risk estimates in large populations. This leads to a greater number of events but

raises issues of underreporting and failure to adjust for differences in host factors that may predispose to adverse events. Several of the studies reported their results with more than 1 analytical method, such as shorter or longer durations of observation after initiation of the drug, use of alternative controls, and different adjustments for host factors. We have picked the formats that seem most pertinent for the practitioner (Table 3).

Frothingham undertook a retrospective analysis of episodes of TdP among a large number of recipients of prescriptions for gatifloxacin, levofloxacin, ciprofloxacin, ofloxacin, and moxifloxacin. Gatifloxacin had by far the highest rate of episodes of TdP per 10 million prescriptions (27), followed by levofloxacin (5.4). Ciprofloxacin and ofloxacin each had a low rate (0.3), and there were no reported episodes with moxifloxacin. The author did not report on the potential role of other risk factors.[29]

In a large, retrospective study of a cohort of Tennessee Medicaid patients, Ray et al[30] calculated the risk of death related to short-term cardiac events in patients treated with azithromycin, levofloxacin, or ciprofloxacin, compared with those in patients receiving amoxicillin, considered free of cardiac effects. Relative to amoxicillin, azithromycin was associated with an increased risk of cardiovascular death (hazard ratio, 2.49). There was a nonsignificant trend toward an increased risk of cardiovascular death with levofloxacin but not with ciprofloxacin.

A third study, by Lapi and colleagues,[31] reviewed episodes of TdP and cardiac events among patients treated for respiratory conditions with gatifloxacin, moxifloxacin, ciprofloxacin, or levofloxacin. Current use, recent use, past use, and no use of FQs were compared between cases and their matched controls. The relative risk for a cardiac event for current users compared with controls was 7.38 for gatifloxacin, 3.3 for moxifloxacin, and 2.15 for ciprofloxacin. The lowest rate ratio (1.29) was observed for levofloxacin, which was not significantly different from controls.

A fourth study, by Zambon et al,[32] provides data for the FQs as a class. This population-based study examined the risk of ventricular arrhythmia and cardiac arrest in association with FQs or macrolides compared with matched controls in a province of Italy from 1998 to 2003. The data were analyzed using three different methods: case-control, case-crossover, and case-time-control designs. Depending on the method, the adjusted

Table 3. Retrospective Studies

Study and Design	Sample Size and Type of Subjects	Treatment	QT Prolongation	TdP p Million Prescriptions	Relative Risk
Frothingham[29] Database analysis; comparison of incidence of TdP	10 Million prescriptions Mixed subjects	Gati, Levo, Cipro, Oflox, Moxi	Not assessed (N/A)	Gati: 27 Levo: 5.4 Cipro: 0.3 Oflo: 0.3 Moxi: 0	Gati > Levo > Cipro = Oflox > Moxi for TdP episodes
Ray et al[30] Database analysis; incidence of cardiovascular deaths Case-control study; risk of cardiac event	Azithromycin (347 795 prescriptions) Cipro, Levo vs amoxicillin or no antibiotics Mixed subjects Mixed subjects	Azithromycin Amoxicillin Cipro Levo No antibiotics	N/A	N/A	Azithromycin similar to Levo = penicillin > Cipro > no antibiotic use for risk of death from cardiac cause
Lapi et al[31]	605 127 Patients treated for respiratory conditions	Gati	N/A	N/A	Gati > Moxi > Cipro > Levo for risk of cardiac event
Zambon et al[32] Case-control study; risk of cardiac event	1275 Cases, 9189 controls	N/A Moxi Levo Cipro	N/A	N/A	FQs > macrolides for risk of cardiac event
Chou et al[33] National database; risk of ventricular arrhythmia or cardiovascular death	Approximately 10 million prescriptions, in outpatient settings	PO Azithromycin Clarithromycin Moxifloxacin Levofloxacin Ciprofloxacin Amoxicillin-clavulanate	N/A	N/A	Moxi > Levo > Cipro for risk of ventricular arrhythmias and cardiovascular deaths

odds ratios associated with recent exposure to FQs were 3.58, 1.98, and 1.59, respectively, whereas the corresponding estimates for macrolides were 2.13, 1.70, and 1.62. The authors concluded that recent use of macrolides and FQs may be associated with increased risk of ventricular arrhythmias and cardiac arrest. They did not distinguish among the specific agents within the drug classes.

A fifth study, by Chou et al,[33] derived from the Taiwan national health insurance database, examined the risks of severe cardiac arrhythmias and cardiovascular death associated with the administration of ciprofloxacin, levofloxacin, and moxifloxacin as well as with azithromycin and clarithromycin, each compared with amoxicillin-clavulanate. The adjusted odds ratio of the risk of ventricular arrhythmia was significantly greater with moxifloxacin (3.3) than with amoxicillin-clavulanate. For levofloxacin, the risk was elevated (1.4) but not statistically significantly so, and for ciprofloxacin, the ratio was close to 1.0. When drugs within the FQ class were compared, both moxifloxacin and levofloxacin significantly increased the risk of cardiovascular death compared with ciprofloxacin. The authors raised the possibility that their population might differ from a white population in susceptibility to arrhythmias with FQs.

Not shown in Table 3 because it does not allow for evaluation of the effect of the FQs per se is a study by Zeuli and coauthors.[34] They examined the potential interaction between azole antifungal drugs (fluconazole, voriconazole) and FQs (ciprofloxacin or levofloxacin) in prolonging the QT interval. The majority of patients received the combination of levofloxacin and voriconazole. The mean overall QTc change from baseline was 6.1 milliseconds (95%CI, 0.2–11.9 milliseconds). Twenty-one patients (22.3%) had clinically significant increases in the QTc while receiving combination therapy. However, the 95% confidence intervals were wide and showed considerable overlap among the combinations, making it difficult to identify a "worst" combination or to compare the 2 FQs.

The relative ranking of the FQs for risk in 4 retrospective studies is shown in Table 4. The differing designs, outcome measures, populations studied, host factors, and other issues inherent in retrospective studies probably explain the differing rank order from study to study. Thus, ciprofloxacin ranked lowest in risk in 3 studies,[29,30,33] but in the middle in 1.[31] Levofloxacin varied from highest risk[29] to lowest risk.[31] Moxifloxacin was highest in 2 studies[31,33]; it was associated with no adverse events in a third study, but there were far fewer prescriptions than for the other two drugs.[29]

Incidence Rates of Adverse Cardiac Events

To put the risk of an adverse cardiac event into practical context for the prescriber, it is useful to estimate the incidence of such events. There were too few events in the randomized, controlled trials (RCTs) to allow for a meaningful calculation. Therefore, we turned to the much larger retrospective studies, from which we could estimate incidence rates, as summarized in Table 5.

The 4 studies used different end points, as shown in Table 5. For the trial by Lapi et al,[31] in which the incidence was calculated per 10 000 person-years, the authors used a 2-week exposure window for their principal analysis so that 1 person-year would be equivalent to about 26 prescriptions. We selected "new current users" as the population of interest in that study.

The base rates for the 3 studies in which we could estimate it differed. In the study by Ray et al,[30] using amoxicillin recipients as the reference, it was 50 deaths per million treated. In the study by Lapi et al,[31] in which 95% of subjects were controls, we used the "overall" rate of severe ventricular arrhythmias in the study population. This was 4.7 events per 10 000 patient-years, or 18 events per million treated. Of note, in the study by Chou et al,[33] in which amoxicillin-clavulanate served as the reference, the base rate was 120 severe ventricular arrhythmias per million treated, a much higher rate than in the other 2 studies.

Given the differences in end points, populations, and design, as well as issues of underreporting, it is difficult to compare the studies directly. Rather, we offer the data to provide the reader with a "sense" of the magnitude of the problem. Based on the studies by Ray et al[30] and Lapi[31] (Table 5), we conclude that, at least for ciprofloxacin, levofloxacin, and moxifloxacin, the excess of adverse cardiac events over the base rate may be in the range of 20–40 cases per million courses of drug. This represents roughly a doubling of the base rate in those same studies (Table 5). At these rates, the number of prescriptions

Table 4. Relative Ranking of Fluoroquinolones for Adverse Cardiac Effects

	Study End Point	Cipro	Levo	Moxi
Frothingham	Episodes of TdP	Low (0.3)	Highest (5.4)	0
Ray[29]	Excess cardiovascular deaths	Lower (no increased risk vs amoxicillin)	Higher than amoxicillin (but not statistically significant)	
Lapi[31]	Additional serious arrhythmias	Middle (2.15)	Lowest (1.29)	Highest (3.3)
Chou[33]	Additional severe ventricular arrhythmias	Lowest (1.0)	Middle 1.4 (NS)	Highest (3.3)

Table 5. Incidence Rates of Adverse Cardiac Events in Retrospective Studies

	Episodes				
Reference	Ciprofloxacin	Levofloxacin	Moxifloxacin	Other	Comment
Frothingham[29]	0.3 TdP per 10 million prescriptions	5.4 TdP per 10 million prescriptions	0 TdP per 10 million prescriptions (but only 1.4 million prescriptions)	Gatifloxacin 27 TdP per 10 million prescriptions	Based on voluntary reporting; somewhat higher rates if confined to first 16 months after FDA approval of drug
Ray[30]	No "excess cardiovascular deaths" per million treated	40 "Excess cardiovascular deaths" per million treated		Azithromycin 47 "excess cardiovascular deaths" per million treated	Tennessee Medicaid cohort "excess cardiovascular deaths" based on comparison with amoxicillin, which had ≈50 deaths per million treated (similar to no antibiotic). About 75% were "sudden cardiac deaths"
Lapi[31]	20 Additional serious arrhythmias per million courses	No excess cases; similar to control	42 Additional serious arrhythmias per million courses	Gatifloxacin 116 additional serious arrhythmias per million courses	Incidence calculated from authors' data for excess cases per 10 000 patient years. Assuming a 2-week exposure period (per authors), 1 person-year = 26 treatment courses; 10 000 person-years = 260 000 treatment courses. Data adjusted to 1 million courses. Base rate estimated from "overall" rate, as 18 cases per million treated
Chou[33]	30 Additional severe ventricular arrhythmias per million treated	140 Severe ventricular arrhythmias per million treated	225–450 Additional severe ventricular arrhythmias per million treated (significantly greater than for amoxicillin-clavulanate)		Amoxicillin-clavulanate (reference) = 120 severe ventricular arrhythmias per million courses. Data for FQs are events in excess of those for amoxicillin-clavulanate. The rate of "cardiac deaths" was similar to that for ventricular arrhythmias for each drug

needed to cause 1 additional serious cardiac event would be 25 000–50 000. However, in the study by Chou and others,[33] both the base rates and the excess rates for levofloxacin and moxifloxacin were much higher than in the other 2 studies. The excess rate for moxifloxacin was 225–450 severe ventricular arrhythmias per million treated which corresponds to 1 event per 2222–4444 prescriptions (Table 5).

Discussion

That FQs can cause QT prolongation, TdP, and cardiac arrhythmias is supported by in vitro studies and studies in healthy and sick humans. The evidence for a clinically significant predisposition to cardiac arrhythmias has been especially strong for sparfloxacin and grepafloxacin. Studies of sparfloxacin[35–37] have shown a significant dose-related increase in QT interval and risk of TdP; the drug was withdrawn from the US market in 2001 for several reasons. Grepafloxacin was withdrawn from the world market in 1999 on account of concerns about adverse cardiac events.[38] Gatifloxacin, which was found in retrospective studies to have a higher incidence of TdP and of cardiac events than other drugs of the class, was withdrawn from the US market in 2006, although primarily because of hypoglycemia[39]. Other FQs, namely, ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin[40] bear product warnings regarding the risk of cardiac arrhythmias.

The trials in healthy subjects suggest that moxifloxacin but not ciprofloxacin or levofloxacin, can slightly prolong the QT interval. However, the trials were small. Four of the 5 trials involved only 1 or 2 doses of the drug, and the subjects lacked other risk factors for arrhythmias. Therefore, the results have limited applicability to typical populations of patients.

The RCTs in sick patients suggest that ciprofloxacin and levofloxacin have little or no propensity for QT prolongation, whereas there was a slight prolongation with moxifloxacin in 1 trial.[26] Notably, among the 1000 patients in these trials, there was only 1 instance of TdP (levofloxacin) and 1 of sustained VT (moxifloxacin), too small an event rate to draw meaningful conclusions. Two of the 3 trials involved only 1 or 2 doses of drug.

For studies of larger populations with a sufficient number of events to determine relative risks, we turned to

the retrospective trials. From these studies, the rank order of propensity to cause cardiac arrhythmias appears to be moxifloxacin > levofloxacin > ciprofloxacin. However, there are some inconsistencies in the results of the various studies, as shown in Table 4. The inconsistencies could relate to differences in study populations, study design, end points, or other factors.

From the point of view of the practicing prescriber, faced with a choice among FQs that differ in antibacterial spectrum and side effects apart from cardiac arrhythmias, it is important to consider the actual incidence of these cardiac events (Table 5). The studies suggest that the base rates of serious arrhythmias or sudden cardiovascular deaths in the control populations (ie, those not taking a FQ) range widely, from 18 to 120 per million individuals[30,31] over the periods of interest; those periods were all 2 weeks or less after initiation of the drug. In 2 trials involving FQs, the rates of *excess* adverse events were in the range of 20–40 per million treated, which are less than a doubling of the base rate and are equivalent to 1 event per 25 000–50 000 prescriptions. However, in a third study, a much higher rate of 225–450 cases per million treated with moxifloxacin was reported. This is about 3-fold the base rate (amoxicillin-clavulanate) and corresponds to 1 excess case per 2222–4444 prescriptions. The reasons for the higher rates among both cases and controls in the third study are not clear but could possibly relate to a difference between white and Asian subjects in their susceptibility to ventricular arrhythmias.

Despite the product warnings, the FQs are widely used in clinical practice, including in hospitalized patients, many of whom are likely to have risk factors for a cardiac arrhythmia. To what extent should the choice of drug by the practicing prescriber be influenced by these cardiac risks? In view of the relative rarity of serious adverse cardiac events and the inconsistencies among the studies in the risk estimates, we suggest that the choice of an FQ should not be made primarily on the basis of concern for adverse cardiac events except in patients at the highest risk for such an event.

Declaration of Conflicting Interests

All authors declare that there are no financial, organizational, or other conflicts of interest.

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