International Journal of Infectious Diseases 78 (2019) 50–56

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

The risk of cardiac events in patients who received concomitant levofloxacin and amiodarone☆

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ARTICLE INFO

Article history:
Received 1 August 2018
Received in revised form 22 October 2018
Accepted 24 October 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Levofloxacin
Amiodarone
Cardiac risk
Cardiac death
QT interval

ABSTRACT

Objectives: Levofloxacin and amiodarone are both known to prolong the QT interval. This study was conducted to estimate the risk of cardiac events in patients receiving concomitant levofloxacin and amiodarone.

Methods: The study included patients who were admitted to a large academic community medical center from 1/2012 to 12/2015 and received both levofloxacin and amiodarone at some point during their hospitalization. Patients received concomitant or non-concomitant levofloxacin and amiodarone during hospitalization. The primary outcome was the occurrence of cardiac events during therapy. The secondary outcome was the proportion of patients with an electrocardiogram performed before and after initiation of therapy. Odds ratios for cardiac events were calculated using a multivariable logistic regression model with and without adjusting for the study variables. The concomitant group was further evaluated for predictors of the primary outcome using multivariable logistic regression.

Results: This study included 240 patients, 164 (68.3%) of whom received concomitant levofloxacin and amiodarone. Concomitant medication therapy was associated with a greater than six-fold increased risk of cardiac events after adjusting for the study variables (Odds Ratio = 6.20; 95% Confidence Interval = 1.34–28.62).

Conclusions: Patients receiving concomitant amiodarone and levofloxacin experienced a five-fold increase in cardiac events compared to patients given either medication alone.

Introduction

The prolongation of the QT interval is associated with *Torsades de Pointe* (TdP) (Nachimuthu et al., 2012). This alteration in the action potential duration of ventricular myocytes can occur spontaneously, especially in individuals with genetic predisposition (i.e., mutations in rapidly (IKr) and slowly (IKs) activating delayed rectifier potassium channels or sodium channels and may occur secondary to a variety of medications (Nachimuthu et al., 2012). The true incidence of drug-induced TdP is unknown; however, estimates range from 2% to 12% in the literature (Tisdale, 2016). Various risk factors have been identified including age, female sex, polypharmacy, and electrolyte imbalance (Nachimuthu et al., 2012; Franchi et al., 2016; Zeltser et al., 2003; Bednar et al., 2002). The use of medications that prolong the QT interval is common, with one study reporting that >50% of patients were taking a least one QT-prolonging medication upon hospital admission (Franchi et al., 2016). Further, many hospitalized patients have multiple risk factors for QT prolongation, placing them at an increased risk of cardiac events (Zeltser et al., 2003). While the American Heart Association and the American College of Cardiology Foundation have published a statement that highlights the importance of electrocardiogram (EKG) monitoring in patients at high risk for drug induced QT prolongation (Drew et al., 2010); few data are available to describe how often clinicians use this tool to identify patients at high risk of cardiac events in the setting of drug interactions.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijid.2018.10.017

Both levofloxacin and amiodarone are commonly used in clinical practice and are known to prolong the QT interval. Levofloxacin is a commonly-used second-generation fluoroquinolone antibiotic agent effective for a variety of infections. Levofloxacin blocks the rapid component (IKr) of the human Ether-à-go-go-Related Gene (hERG) encoded delayed rectifier potassium current (Owens and Nolin, 2006). IKr, also known as the hERG channel, is essential for the regulation of the outward flow of potassium ions from myocytes, which allows for ventricular repolarization. Blocking the function of IKr, therefore, results in accumulation of intracellular potassium and altered ventricular repolarization. Amiodarone is an antiarrhythmic agent commonly used in clinical practice which was approved in the United States by the FDA for treatment of life-threatening ventricular tachyarrhythmias in December 1985. Although amiodarone is known to prolong the QT interval, it is unlikely to induce TdP without additional risk factors present, a characteristic seen with many drugs that prolong the QT interval (Hohnloser et al., 1994; Vorperian et al., 1997). Like levofloxacin, amiodarone blocks the IKr, but the duration of the myocyte action potential duration is prolonged in a homogenous manner, which makes the myocardium less susceptible to re-entry (Drouin et al., 1998). Nonetheless, cases of amiodarone-associated TdP have been reported, especially when other risk factors are present (Brown et al., 1986; Atar et al., 2003; Foley et al., 2008). For example, Abo-Salem et al. reported that approximately half of antibiotic-induced QT prolongation cases reviewed were attributed to a drug interaction and are commonly amiodarone-related (Abo-Salem et al., 2014).

Although the independent frequencies of developing cardiac events with these medications are low (1% for levofloxacin and 1-to-3% for amiodarone) (Janssen Co., 2018; Wyeth Pharmaceuticals Inc., 2018); we hypothesize that the concomitant usage of levofloxacin and amiodarone may markedly increase the risk of developing pro-arrhythmic effects. Several case reports have been published describing the dangerous pro-arrhythmic characteristics associated with fluoroquinolones and amiodarone (Maxa et al., 2006; Prabhakar and Krahn, 2004; Zeineh, 2010), but no studies have assessed this risk in a real-world clinical setting. The objectives of this study were to estimate the risk of cardiac events in patients receiving levofloxacin with amiodarone, to identify predictors of cardiac events in this population, and to compare the frequency of using EKG to screen patients for QT prolongation.

Material and methods

Study design and patients

The study was performed at a 355-bed regional academic community medical center located in central New Jersey. A retrospective cohort study design was utilized to compare the composite of cardiac events between two groups: concomitant administration of levofloxacin and amiodarone versus non-concomitant administration of these medications. All patients in the study had exposure to both agents during the hospital stay, which increases the homogeneity of the patients in both groups. All patients aged $\geq$18 years admitted between January 1, 2012 and December 31, 2015 who received levofloxacin and amiodarone were eligible for inclusion. Patients on acute amiodarone therapy immediately upon admission were excluded from the study. Acute amiodarone therapy was defined as a dose of >800 mg or 900 mg administered orally or intravenously, respectively. This decision was based on the likelihood that the patient had an acute arrhythmia require a loading dose of amiodarone to control.

In order to detect a clinically relevant difference in the primary outcome, 58 patients or more were required in each group, assuming a cardiac event rate of 2% in non-concomitant users and 12% in concomitant users with 80% statistical power and a 5% significance level. The cardiac event rates of 2% versus 12% were based on previous reports of the frequency of drug induced TdP reported in the literature since.

The primary outcome was occurrence of cardiac events, defined as ventricular arrhythmia or cardiac death confirmed through medical record review. The secondary outcome was evaluation of how often clinicians monitor the EKG in the setting of QT prolonging drug interactions. There is no requirement for EKG monitoring when two QT prolonging drugs are used concomitantly at the medical center. This study assessed whether a baseline and post drug initiation EKG was present in the electronic medical record.

Data collection

Data were extracted from the hospital electronic health record and discharge database. Data extracted included length of stay, age, sex, race, body mass index (BMI), comorbidities identified using International Classification of Diseases of Ninth Revision (ICD-9) codes, procedures, admission status, discharge status, medication use, relevant laboratory values, and inpatient charges. The protocol for this study was reviewed and approved by the Institutional Review Boards of Robert Wood Johnson University Hospital Somerset and Rutgers Biomedical and Health Sciences (IRB protocol number; PRO20150001910).

Drug exposure

Concomitant usage of levofloxacin and amiodarone was determined based upon the timing of drug administration. A patient was defined as having concomitance if there was overlap in therapy. Due to the long half-life of amiodarone (~58 days), if a patient received this drug within the previous 58 days preceding levofloxacin use, it was considered concomitant usage. A review of home medications recorded in the medication reconciliation record within the medical record was also performed to screen for amiodarone use prior to admission. Patients who received levofloxacin first and received non-overlapping amiodarone at any later point during the admission would be placed in the non-concomitant group. The rationale for this decision is based on the short half-life of levofloxacin.

Study variables/identification of outcomes

Cardiac events (ventricular arrhythmias, cardiac arrest, and death) were identified using ICD-9 codes and discharge disposition records, respectively. Cardiac events were identified using the following validated ICD-9 codes ventricular arrhythmias and cardiac arrest (427.1, 427.4, 427.41, 427.42, 427.5, 427.69), and unspecified cardiac arrhythmias (427.2, 427.60, 427.8, 427.89, 427.9) (De Bruin et al., 2005). These ICD-9 codes have a positive predictive value for ventricular arrhythmias and cardiac arrest of 82%. The criteria were expanded with the addition of long QT syndrome (426.82), sudden death (798.1). Once cardiac events were identified using ICD-9 codes, a review of the electronic health record confirmed the occurrence of the event in relation to drug therapy.

A post hoc analysis of cardiac death was performed to evaluate the difference in this outcome between groups. All cardiac death and its attribution to drug therapy was determined based upon independent patient chart review performed by two physicians. All discordant attributions were adjudicated by a third member of the study team. “Before” and “after” periods for EKG readings were also based upon the timing of initiation of levofloxacin and amiodarone. “Before” was the timeframe in which the first medication was

started but the second was not initiated yet. “After” was any point after the second medication was given.

The presence of drugs with the potential to prolong QT and/or to cause TdP were considered as potential confounders. Drugs with known risk included azithromycin, chlorpromazine, cilostazol, ciprofloxacin, citalopram, donepezil, erythromycin, escitalopram, fluconazole, haloperidol, ondansetron, propofol, and sotalol. Drugs with possible risk included aripiprazole, dexmedetomidine, famotidine, olanzapine, promethazine, risperidone, tacrolimus, tolterodine, and venlafaxine. Drugs with conditional risk included amantadine, diphenhydramine, fluoxetine, furosemide, galantamine, hydrochlorothiazide, hydroxychloroquine, indapamide, loperamide, metoclopramide, metronidazole, pantoprazole, paroxetine, quetiapine, ranolazine, sertraline, and torsemide (Yap and Camm, 2003; Heise et al., 2018). All of the aforementioned drugs are known to prolong the QT interval. The terms “known”, “possible”, or “conditional” risk refer to the risk of QT prolongation.

Statistical analysis

Categorical data were analyzed using chi-square or Fisher’s exact tests and continuous data were analyzed with the Student’s t-test between patients who were receiving concomitant administration of levofloxacin and amiodarone (concomitant levofloxacin) versus patients who were receiving non-concomitant administration of these medications (non-concomitant levofloxacin). The Charlson Comorbidity Index was calculated using ICD-9 codes as a proxy for patients’ comorbid disease burden (Charlson et al., 1987). In addition, medication use during hospital stay and the presence of drugs with the potential for QT prolongation and/or Torsades de Pointes were compared between these two groups using the chi-square or Fisher’s exact tests, as appropriate. Clinical outcomes that were compared between the two groups during the hospital stay included cardiac events, drug related deaths, and increased QT interval from baseline.

The risk of cardiac events for patients receiving concomitant levofloxacin was calculated using logistic regression with and without adjusting for study variables including age, sex, Charlson comorbidity index, body mass index, and the presence of drugs with known potential to prolong QT and/or cause TdP. Confounders included variables that were established in the literature as clinically meaningful or those with a p-value of <0.1. Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 240 patients were prescribed levofloxacin and amiodarone, 164 of whom received concomitant levofloxacin and 76 of whom received non-concomitant levofloxacin. Females accounted for 50.8%, with a mean age of 79.5 years. The groups were well-matched with the exception of hypothyroidism, where patients in the concomitant group had a greater prevalence compared to the non-concomitant group (35.4% versus 17.1%; p = 0.004). Length of hospital stay was similar in both groups (10 ± 9.0 days versus 10 ± 8.6 days; p = 0.076). No other baseline characteristics were found to be significantly different between the two study groups (Table 1).

Medications with the potential to influence outcomes are shown in Table 2. Angiotensin converting enzyme inhibitors were prescribed in 17.9% of the population, 10% had angiotensin receptor blockers, 56.3% were on loop diuretics, 7.1% were on potassium-sparing diuretics, and 2.9% were on thiazide diuretics. 45.4% of patients received medications with known risk, 25.8% received medications with possible risk, and 53.3% received medications with conditional risk. Distributions of QT-altering concomitant medication therapies between groups were not significantly

Table 1
Patient demographic and clinical characteristics.

Variables	Non-concomitant use (n = 76)	Concomitant use (n = 164)	All (n = 240)	P-value
Age				
(Mean ± SD)	(79.0 ± 10.1)	(79.8 ± 9.6)	(79.5 ± 9.7)	0.599
38–64	6 (7.9)	12 (7.3)	18 (7.5)	0.885
65–74	12 (15.8)	32 (19.5)	44 (18.3)	
75–84	31 (40.8)	68 (41.5)	99 (41.3)	
85+	27 (35.5)	52 (31.7)	79 (32.9)	
Gender				
Male	33 (43.4)	85 (51.8)	118 (49.2)	0.226
Female	43 (56.6)	79 (48.2)	122 (50.8)	
Race				
Non-white	15 (19.7)	25 (15.2)	40 (16.7)	0.385
White	61 (80.3)	139 (84.8)	200 (83.3)	
Body mass index				
(mean ± SD)	(28.0 ± 9.3)	(26.9 ± 7.0)	(27.3 ± 7.8)	0.388
<18.5	3 (3.9)	8 (4.9)	11 (4.6)	0.368
18.5–24.9	33 (43.4)	67 (40.9)	100 (41.7)	
25.0–29.9	15 (19.7)	48 (29.3)	63 (26.3)	
≥30	25 (32.9)	41 (25.0)	66 (27.5)	
Laboratory data (mean ± SD)				
Potassium	4.16 ± 0.54	4.21 ± 0.82	4.19 ± 0.74	0.624
Calcium	8.59 ± 0.65	8.58 ± 0.69	8.59 ± 0.68	0.994
Creatinine clearance	49.7 ± 46.5	42.1 ± 22.9	44.5 ± 32.4	0.180
Charlson comorbidity index				
0–4	42 (55.3)	80 (48.8)	122 (50.8)	0.350
5+	34 (44.7)	84 (51.2)	118 (49.2)	
Comorbidity				
Atrial fibrillation	59 (77.6)	128 (78.0)	187 (77.9)	0.942
Atrial flutter	3 (3.9)	15 (9.1)	18 (7.5)	0.155
Hypothyroidism	13 (17.1)	58 (35.4)	71 (29.6)	0.004
Myocardial infarction	10 (13.2)	19 (11.6)	29 (12.1)	0.728
Congestive heart failure	52 (68.4)	109 (66.5)	161 (67.1)	0.764
Ischemic heart disease	48 (63.2)	108 (65.9)	156 (65.0)	0.684

Table 2
Medication use during hospital stay and presence of drugs that can prolong the QT interval or cause Torsades de Pointes.

Variables	Non-concomitant use (n = 76) n (%)	Concomitant use (n = 164) n (%)	All (n = 240) n (%)	P-value
Medication use				
Levofloxacin				
Dose: (mean ± SD: mg)	(638.2 ± 160.2)	(468.0 ± 201.9)	(521.9 ± 205.3)	<0.001
250 mg	6 (7.9)	65 (39.6)	71 (29.6)	<0.001
500 mg	22 (29.0)	55 (33.5)	77 (32.1)	
750 mg	48 (63.2)	44 (26.8)	92 (38.3)	
ACE inhibitors	15 (19.7)	28 (17.1)	43 (17.9)	0.617
Angiotensin receptor blockers	7 (9.2)	17 (10.4)	24 (10.0)	0.781
Loop diuretic	44 (57.9)	91 (55.5)	135 (56.3)	0.727
K-sparing diuretic	7 (9.2)	10 (6.1)	17 (7.1)	0.382
Thiazide diuretic	3 (3.9)	4 (2.4)	7 (2.9)	0.518
Drug at risk of prolonging QT or causing TdP				
Known risk	37 (48.7)	72 (43.9)	109 (45.4)	0.489
Possible risk	22 (28.9)	40 (24.4)	62 (25.8)	0.453
Conditional risk	38 (50.0)	90 (54.9)	128 (53.3)	0.481

ACE inhibitors; Angiotensin converting enzyme inhibitors, TdP; Torsades de Pointes.

different (Table 2). Patients who received concomitant levofloxacin were prescribed lower doses of levofloxacin compared to those that received non-concomitant levofloxacin (levofloxacin 750 mg: 26.8% versus 63.2%; levofloxacin 500 mg: 33.5% versus 29.0%; levofloxacin 250 mg: 39.6% versus 7.9% respectively; $p < 0.05$ for all comparisons).

Patients who received concomitant levofloxacin were 6.2 times more likely to experience a cardiac event compared to patients who received non-concomitant levofloxacin (95% confidence interval (95% CI), 1.34–28.62), after adjusting for the study variables (Table 3). The occurrence of cardiac deaths was significantly greater in the concomitant group compared to the non-concomitant group (13.4% versus 2.6%; P = 0.001) (Table 4). A baseline and post-therapy initiation EKG was available for 50% of patients (48.1%, concomitant levofloxacin versus 53.8%, non-concomitant levofloxacin; p = 0.20). The change in EKG from baseline was significantly greater in patients who received concomitant levofloxacin versus non-concomitant levofloxacin (32.4 ± 30.6 ms versus −2.2 ± 28.0 ms; $p < 0.001$).

Discussion

In this cohort of acutely ill hospitalized patients, the concomitant levofloxacin was associated with a significant increase in the risk of cardiac events. These results provide evidence that the concomitant use of levofloxacin and amiodarone should be avoided when possible.

Data describing the arrhythmic potential and cardiac risks of levofloxacin have been previously cited; however, much of the data are from small case reports and observational studies (Paltoo et al., 2001; Patel et al., 2010; Gandhi et al., 2003; Nykamp et al., 2005). While there is currently a lack of sufficient data which describe the additive effects of concomitant levofloxacin, a common theme in the majority of levofloxacin reports suggests that risk factors are often present. In one analysis, over 70% of patients who experienced an antibiotic-related cardiac rhythm event had two or more risk factors present (Abo-Salem et al., 2014). Approximately 20% had an electrolyte imbalance (i.e., potassium). Fifty percent of QT prolongation cases were related to a drug interaction,

Table 3
Risk of cardiac events in concomitant use of levofloxacin with amiodarone.

Variables	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Levofloxacin with amiodarone		
Non-concomitant use	1	1
Concomitant use	5.73 (1.31–25.04)	6.20 (1.34–28.62)
Levofloxacin dose		
250 mg	1	1
500 mg	1.21 (0.43–3.44)	1.44 (0.48–4.32)
750 mg	0.87 (0.30–2.53)	1.38 (0.44–4.35)
Gender		
Male	1	1
Female	0.71 (0.30–1.68)	0.92 (0.34–2.45)
Age (years)		
<75	1	1
≥75	0.44 (0.19–1.06)	0.54 (0.21–1.40)
Charlson's comorbidity index		
0–4	1	1
5+	1.83 (0.77–4.36)	1.65 (0.65–4.15)
Body Mass Index		
<25	1	1
≥25	1.82 (0.75–4.44)	1.68 (0.64–4.40)
Drug at known risk of prolonging QT or causing TdP		
No	1	1
Yes	1.48 (0.63–3.45)	1.67 (0.69–4.08)

95% CI: 95% confidence interval, TdP; Torsades de Pointes.

Table 4
Clinical outcomes occurring during hospital stay.

Outcomes	Non-concomitant use (n = 76)		Concomitant use (n = 164)		All (n = 240)		P-value
	N	(%)	N	(%)	N	(%)	
Cardiac events[a]							
Yes	2	(2.6)	22	(13.4)	24	(10.0)	0.001
No	74	(97.4)	142	(86.6)	216	(90.0)	
Changes in QTc from baseline (msec)							
Number of patients	41	(53.9)	79	(48.1)	120	(50.0)	
(Mean ± SD)	(−2.2 ± 28.0)		(32.4 ± 30.6)		(20.6 ± 30.9)		<0.001
≤0	20	(26.3)	9	(5.5)	29	(12.1)	<0.001
0.1–9.9	9	(11.8)	9	(5.5)	18	(7.5)	
10.0–19.9	4	(5.3)	10	(6.1)	14	(5.8)	
≥20.0	8	(10.5)	51	(31.1)	59	(24.6)	
Missing	35	(46.1)	85	(51.8)	120	(50.0)	

QTc: corrected QT interval.
[a] Cardiac events included drug-related death (i.e., 3 cases in the concomitant use group).

with the majority being secondary to concomitant amiodarone use. Amiodarone is considered a first line drug for the treatment of atrial and ventricular arrhythmias it has a pro-arrhythmic potential. Although amiodarone may increase the QTc interval, a small case series failed to find a correlation between QTc prolongation and TdP (Román et al., 2012). In general, cardiac adverse effects including bradycardia have been reported in 5% of patients. TdP is less common and has been reported in 1-to-2% of patients (Merino and Isla, 2011). These data underscore the importance of evaluating all patient risk factors in order to adjust for confounders. Access to electronic health record data facilitates inclusion of risk factors and addresses some of these concerns.

Ray and colleagues performed a cohort study evaluating the risk of cardiovascular death with azithromycin using the Tennessee Medicaid database (Ray, 2014; Ray et al., 2012). While the focus of their study was azithromycin, the authors also included a levofloxacin-treated group (number of prescriptions, n = 193,906) for comparison and found that compared to amoxicillin, levofloxacin use was associated with a 50% increase in cardiovascular death (hazard ratio, HR = 1.50; 95% CI = 0.82–2.72; p = 0.18, trend towards significance). When comparing levofloxacin to azithromycin, the difference in cardiovascular mortality was non-significant (HR = 1.27; 95% CI = 0.66–2.47; p = 0.48). Similarly, we did not find a significant increase in drug-related deaths, which is strengthened by our ability to use electronic health record data to confirm clinical endpoints, capture a more robust assessment of potential confounders, and confirm actual administration of medications.

Rao and colleagues performed a cohort study using claims data from a population of US Veterans receiving levofloxacin as outpatients (Rao et al., 2014). Unlike the aforementioned study, they found that patients receiving levofloxacin had a significant increase in the risk of death for days 1 to 5 (HR = 2.49; 95% CI = 1.7–3.64) and serious cardiac arrhythmia (HR = 2.43; 95% CI = 1.56–3.79) compared to amoxicillin. The increase remained significant for days 6 to 10. Similarly, a large study (n = 360,088 treatment episodes) using claims data from the Swedish National Prescribed Drug Register found that fluoroquinolones (~78% of subjects were on ciprofloxacin) were associated with an increased risk of aortic aneurysm or dissection (HR = 1.66; 95% CI = 1.12–2.46) compared to amoxicillin (Pasternak et al., 2018). One could argue that using amoxicillin as the comparison group could have introduced bias, as levofloxacin may be used in a sicker cohort and amoxicillin is not typically an alternative to levofloxacin.

Levofloxacin is used frequently for community acquired pneumonia, the alternative option in hospitalized patients is a beta-lactam plus azithromycin based on clinical practice guidelines (Mandell et al., 2007). Using the later treatment regimen as a control group introduces another drug that may cause an increase in cardiac events (azithromycin). Alternatively, using a broader spectrum antibiotic such as piperacillin/tazobactam or a carbapenem would suggest healthcare associated pneumonia and be associated with greater morbidity (Kalil et al., 2016). Community acquired pneumonia is associated with an increased risk of cardiac events; therefore, using antibiotic comparators that are not used for pneumonia may confound the results (Griffin et al., 2013). We acknowledge that no perfect control group exists, but in the current study design using two groups that required levofloxacin at some point during hospitalization suggests similar patient characteristics.

Contrary to the findings of Rao and Ray, another large cohort study derived from a population of Danish and Swedish adults did not find an increase in cardiac events with the use of oral fluoroquinolones (Inghammar et al., 2016). An important limitation of this study is that 82.6% of the population received ciprofloxacin, the fluoroquinolone with the lowest risk of cardiac effects. Less than 1% of the study population received levofloxacin, limiting the generalizability of the findings.

To summarize, while there are large cohort studies using claims data to identify the risk of cardiac events with levofloxacin therapy, these studies are challenged by their inability to confirm the accuracy of claims data using electronic health record data. Another difficulty when using claims or electronic health record data in evaluating cardiac events is the difficulty in identification of TdP and availability of an EKG around the time of the cardiac event. While we confirmed events through review of the electronic medical record, there is a possibility that some events may not have been captured because of lack of information. Performance of a prospective study could be designed to capture these data but would not be ethical since we would knowingly place patients at risk for cardiac events. EKG data at the time of event would provide a mechanism related to increased cardiac events, but ultimately the actual cardiac outcome is of most clinical interest. In addition, previous studies were not focused on the additive risk of cardiac events when using levofloxacin and amiodarone concomitantly, but rather on whether levofloxacin confers an increased cardiac risk. Our study provides data suggesting that concomitant use of levofloxacin with amiodarone confers a significant risk of cardiac events, even after adjusting for various patient factors.

As with any observational study, confounding and misclassification bias are important considerations when interpreting results. In order to minimize the effects of confounders on the results of the analysis, we compared baseline characteristics such as age, sex, race, body mass index, Charlson comorbidity index, comorbidities,

electrolytes, and concomitant medications between groups. Additionally, these covariates were considered in the multivariable regression analysis. The identification of cardiac events using ICD-9 codes may result in misclassification bias; however, the positive predictive value of ICD-9 codes for the identification of ventricular arrhythmias and cardiac arrest was 82% (95% CI, 72–92%) in a previous study (De Bruin et al., 2005). Once identified using ICD-9 codes, the causality of cardiac events was further assessed through review of the electronic health record. In comparison to using solely ICD-9 codes for identification of cardiac events, incorporating review of the electronic health record increases confidence in our findings. Additionally, electronic health records were reviewed to exclude those who were admitted to the hospital with a cardiac event prior to receiving either medication, as this event could not be attributed to the medication combination but is not identifiable when solely relying on ICD-9 diagnosis codes. Finally, two independent physicians adjudicated deaths and determined whether the deaths were drug related based on chart review. We considered recording time to event but determined that the value was inherently biased. Documentation inaccuracies in documentation of exact drug administration and event times would make this value inaccurate. The availability of these data would be of interest to clinicians in understanding the time course of risk.

Another important consideration is the degree of drug exposure (dose and cumulative dose). In general, a lower dosage of levofloxacin was prescribed to patients who received concomitant levofloxacin and amiodarone. Whether this finding is the result of clinicians considering the potential for adverse drug reaction is unknown, but despite the lower levofloxacin dosage cardiac events were significantly greater in this group. While we adjusted our primary outcome for levofloxacin dosage, a larger sample is necessary to provide enough data to infer a dose–response relationship. Further, based on the available date we cannot determine whether there is a cumulative dose effect.

Only 50% of patients with concomitant levofloxacin and amiodarone had QT measurements before and after concomitant amiodarone and levofloxacin prescription. This finding is not unexpected, as a recent study reported that only 60% of patients prescribed azithromycin (another antibiotic implicated in cardiovascular death) in the inpatient setting had a baseline EKG (Lee et al., 2016). There was no statistically significant difference in the proportion of patients who were monitored between groups. For patients who had an EKG available before and after treatment administration, there was a significant increase in QTc from baseline in patients who received concomitant levofloxacin compared to those who received non-concomitant levofloxacin.

Results produced by this retrospective analysis show that despite contraindications listed in drug information compendia and warnings issued by the FDA, levofloxacin and amiodarone are co-prescribed in the inpatient setting. While this study was not designed to detect whether concomitant therapy was warranted, there are often alternatives to fluoroquinolones when treating infections. The concomitant usage of levofloxacin and amiodarone was associated with a significant increase in cardiac events compared to the non-overlapping usage of both medications in this cohort. There are significant morbidities associated with cardiac events and the additional cost of care in patients experiencing these events is significant. While the sample evaluated in this study was small, to our knowledge this is the largest attempt to quantify the risk potential of combining amiodarone and levofloxacin therapy.

Our findings are consistent with those of other studies and a large systematic review which suggests that there is strong evidence that levofloxacin prolongs QTc interval (Vandael et al., 2017). Despite the limitations described above, this study supports major drug compendia that suggest avoiding the combination of levofloxacin and amiodarone when other treatment options are available.

Conclusions

Concomitant use of levofloxacin and amiodarone is associated with a greater than 6-fold increase in cardiac events. The greatest predictor of cardiac events with levofloxacin was concomitant amiodarone. Clinicians should consider therapy modification whenever possible and if the combination must be prescribed, careful attention must be placed to manage modifiable risk factors to reduce the risk of cardiac events.

Author contributions

L Brunetti and SM Lee contributed equally to the study design, data collection, statistical analysis, and manuscript development with guidance from DC Suh.

R. Nahass, D Suh, and B Miao participated in developing a data collection form, collecting data, analyzing data, interpreting results, and writing the manuscript. J. Bucek, DW Kim, and OK Kim participated in collecting data, writing draft the manuscript, revising the manuscript. DC Suh supervised the entirety of the project from designing the study; collecting and analyzing data; editing the manuscript; and to submitting the manuscript. All the authors read and approved the final version of the manuscript.

Funding sources

This research was supported by the Chung-Ang University Research Grants in 2017.

Conflict of interest

The authors have no conflicts of interest to disclose.

Ethical approval

The protocol for this study was reviewed and approved by the Institutional Review Boards of Robert Wood Johnson University Hospital Somerset and Rutgers Biomedical and Health Sciences (IRB protocol number; PRO20150001910).

Brief summary

The concomitant use of levofloxacin and amiodarone is associated with a 6.2 times increased risk of cardiac events compared to amiodarone alone in hospitalized patients.

Acknowledgement

This study was jointly conducted by the Institute for Medical and Pharmaceutical Economics and Policy at Chung-Ang University, Seoul, Korea and Rutgers University School of Pharmacy, New Jersey, USA under the memorandum of understanding signed on January 1, 2014.

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