Cardiac risk of concomitant levofloxacin with amiodarone

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Background

- Levofloxacin, a commonly used fluoroquinolone antibiotic, is generally well tolerated among patients, however, its interaction with the human Ether-à-go-go-Related Gene (hERG) can lead to a prolonged QT interval and prime conditions for provoking lethal arrhythmias. [1,2]
- Amiodarone, a class III antiarrhythmic, is well known to interfere with various ion channels and prolong the action potential and repolarization of myocytes.
- Levofloxacin and amiodarone is specifically flagged with a risk rating of X suggesting avoidance of the combination and is generally recognized as being contraindicated. [3,4]
- The dangers of this combination manifests with torsade de pointes (TdP), which is a potentially fatal heart rhythm. [2]
- Independent frequencies for TdP is low (<1% for levofloxacin and 1-3% for amiodarone), the concomitant usage of levoflaxacin and amiodarone may have a marked increase in risk of developing pro-arrhythmic effects. [2]
- Several case reports have been published describing the reality of the dangerous pro-arrhythmic characteristics due to the drug combination but no studies have been completed on the risk rates in a real-world, clinical setting. [5,6]

Objective

- To investigate the impact of the concomitant usage of levofloxacin and amiodarone on QT interval prolongation and the occurrence rate of cardiac events.

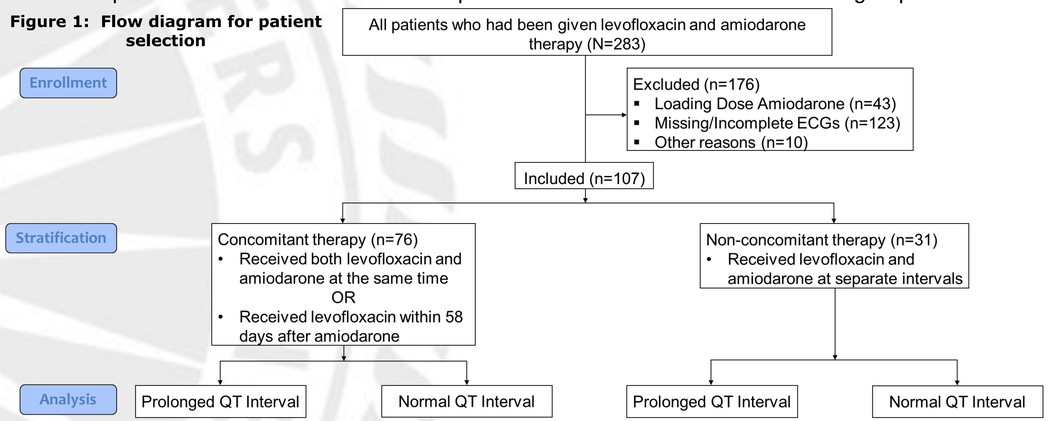
Study Design

- Conducted a retrospective cohort study of all patients that were given levofloxacin and amiodarone when admitted to RWJS from January 1st, 2012 to August 31st, 2015.
- Only adult patients (≥18 years of age) were included. Only patients with available electrocardiograms before and after treatment were eligible for inclusion.
- Patients on acute amiodarone therapy immediately upon admission were excluded from the study. Acute amiodarone therapy was identified by a dose and route of >800 mg orally or 900 mg intravenously.
- Patients were stratified into two groups: concomitant usage of levofloxacin plus amiodarone and non-concomitant usage of levofloxacin or amiodarone.
- A patient was defined as having concomitance if there was overlap in therapy. Patients that received amiodarone within 58 days prior to receiving levofloxacin were also concomitant usage due to the extensive half-life of amiodarone. All other patients that did not meet the overlap criteria were considered as having received non-concomitant therapy.
- QTc intervals were manually extracted from patient records and assessed for changes from baseline.

Methods

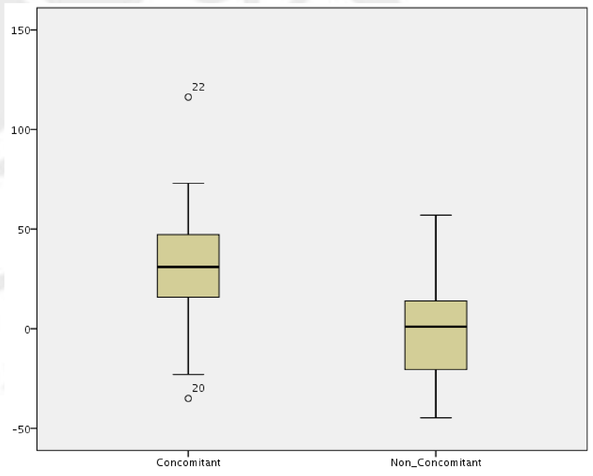
- The primary outcome was change in QTc interval from baseline to post-treatment.
- Baseline period was defined as the interval between when the first medication was started but not the second. Post-treatment period was defined as the length of time after the second medication was started regardless of the duration of overlap from the first medication.
- Results are reported as means or frequencies where appropriate. An independent samples t-test was used for parametric continuous data to compare concomitant and non-concomitant groups.

Figure 1: Flow diagram for patient selection



Results

Figure 2: Box and whisker plot of ECG changes from baseline



	Concomitant (n=76)	Non-concomitant (n=31)
Mean age ± SD	79.7 ± (10.4)	77.3 ± (11.2)
Female (N,%)	38 (50.0)	12 (38.7)
Race (N,%)		
Caucasian	66 (86.8)	24 (77.4)
African	4 (5.3)	2 (6.5)
Asian	0 (0.0)	2 (6.5)
Multiracial	3 (3.9)	2 (6.5)
Other	3 (3.9)	1 (3.2)

- A total of 107 patients were included in the analysis, 76 of which received concomitant levofloxacin and amiodarone.
- Demographics between groups were well matched. The mean age was 78.99 years and the 46.73% of patients included were women.
- There was a mean change from baseline in QTc interval of 30.60 milliseconds (ms) for the concomitant group and -0.50 ms for the non-concomitant group.
- Mean difference between the two groups was 31.10 milliseconds (p<0.001; 95% confidence interval, 18.52 ms, 43.69 ms).

Discussion

- The results from this interim analysis indicate that there is a statistically significant increase in QTc interval in patients given concomitant amiodarone and levofloxacin in comparison to patients given either medication alone.
- However, QTc prolongation alone is not definitively causative for developing TdP although it is a well-established risk factor. The current accepted methodology for assessing TdP risk involves a multi-factorial approach which carefully considers contributors such as congestive heart failure, hypokalemia, hypomagnesemia, age, gender, and also the use of drugs that delay repolarization. [3]
- Therefore, concomitant levofloxacin and amiodarone therapy can be predicted to significantly increase one of several risk factors for developing TdP and should be met with cautionary discretion in the clinical setting.
- Further analyses of cardiac outcomes have been performed and remains to be included in future reports.

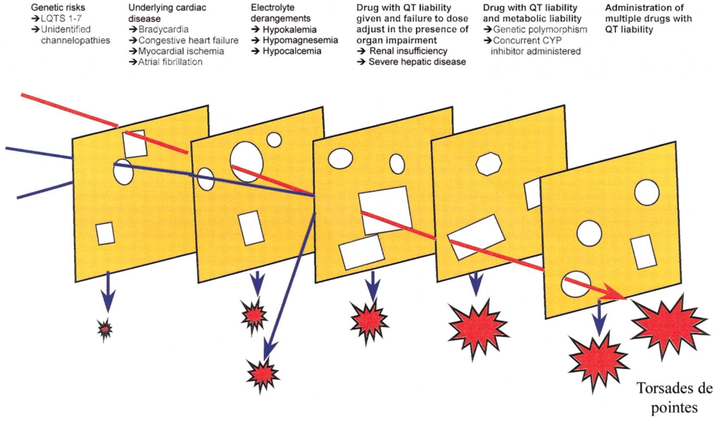


Figure 3: Multiple risk factors that increase the probability of TdP [3]

References

1. Stahlmann R, Lode H. Fluoroquinolones in the Elderly. Drugs Aging 2003; 20: 289-302.
2. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy. 2001;21:1468-1472.
3. Goldstein, E. J. C., R. C. Owens, and T. D. Nolin. "Antimicrobial-Associated QT Interval Prolongation: Pointes of Interest." Clinical Infectious Diseases 43.12 (2006): 1603-611. Web.
4. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2015; July 9, 2015
5. Prabhakar M, Krahn AD. Ciprofloxacin-induced acquired long QT syndrome. Heart Rhythm 2004;1:624-626.
6. Zeineh NS. A Toxic Combination. Am J Med 2010; 123:707-708.

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Disclosure

Nothing to disclose