Robert Wood Johnson University Hospital Somerset | RWJBarnabas HEALTH

Increased cardiac risk with concomitant levofloxacin (LVQ) and amiodarone (AMIO) therapy

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Background & Significance

- 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.
- Concomitant levofloxacin and amiodarone are often flagged as a major interaction in many drug information databases; however, many clinicians choose to proceed with therapy.[3,4]
- Case reports have been published describing the pro-arrhythmic potential due to the drug combination but no studies have been completed on in a real-world, clinical setting. [5,6]

Objective

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

Methods

- Cohort study of all patients that were given levofloxacin and amiodarone when admitted to RWJS from January 1st, 2012 to August 31st, 2015.
- Inclusion: Patients ≥18 years of age; only patients with available electrocardiograms before and after treatment
- Exclusion: Acute amiodarone therapy defined as >800 mg orally or 900 mg intravenously immediately upon admission.
- **Figure 1** outlines the patient selection process.
- Patients were stratified into two groups: concomitant usage of levofloxacin plus amiodarone and non-concomitant usage of levofloxacin or amiodarone.

Methods

- 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 considered concomitant usage. All other patients that did not meet the overlap criteria were considered as having received non-concomitant therapy.
- Groups were further balanced using a 2:1 propensity score matching algorithm based on age, gender, race, and Charlson comorbidity index.
- Primary outcome: Occurrence of cardiac events (ventricular arrhythmia and cardiac arrest) identified using validated ICD-9 codes and verified through patient chart review. [7]
- Secondary outcome: change in adjusted QT interval (QTc) from baseline to post-treatment.

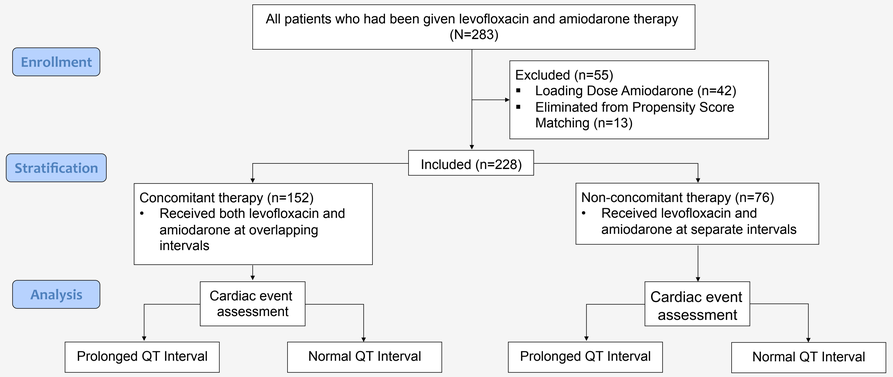

Figure 1: Schematic of patient selection. Note: Baseline period for the QTc change comparison was defined as the interval between when the first medication was started but not the second. Post-treatment period was defined as the length of time after the second medication was started.

Results

Table 1: Comparison of patient characteristics

	Concomitant (n=152)	Non-concomitant (n=76)
Mean age ± SD	79.7 ± (9.7)	79.3 ± (10.2)
Female (N,%)	76 (50.0)	40 (52.6)
Race (N,%) Caucasian Other	 127 (83.6) 25 (16.4)	 62 (81.6) 14 (18.4)
Comorbidity Index ± SD	4.55 ± (2.82)	4.34 ± (2.63)

Table 2: Summary of patient outcomes

	Concomitant (n=152)	Non-concomitant (n=76)	OR (95% CI)	P-value
Cardiac events*	15.1%	2.6%	6.6 (1.74 – 42.3)	0.004
All cause mortality	9.9%	9.2%	1.07 (0.42 – 2.74)	0.885
Mean change in QTc interval (msec)	30.54	(-) 0.50		<0.0001

- A total of 228 patients were included in the analysis
- Demographics between groups were well matched (**Table 1**)
- Patients who received concomitant therapy were 6.6 times more likely to experience a cardiac event versus non-concomitant therapy (**Table 2**)
- Mean change from baseline in QTc interval of 30.54 milliseconds (ms) for the concomitant group and -0.50 ms for the non-concomitant group.
- Mean difference in QTc between the two groups was 31.03 milliseconds (p<0.0001; 95% CI, 18.28 ms, 43.79 ms).
- Upon further patient chart review of the 25 total deaths, 7 were determined to be cardiac related deaths and 3 of which were possibly related to target drugs. All 3 patients were classified as having concomitant therapy

Discussion

- Patients given concomitant amiodarone and levofloxacin had a statistically increased QTc intervals.
- Patients on combination amiodarone and levofloxacin therapy had a higher rate of cardiac events.
- There was no increase in overall mortality.
- Cardiac related death was deemed to be possibly drug related in 3 cases, all of which were in the concomitant therapy group
- Caution in using this combination is warranted.
- Further study to evaluate other contributing cofactors is needed since the risk of QTc prolongation is multifactorial.[3]

Limitations

- As with any database study, there is a potential for misclassification bias; however, chart review was performed to minimize this risk.
- Sample size was limited and capture of confounding variables was not complete at the time of preliminary analysis.

Conclusions

- A statistically significant increase in cardiac events and QTc interval prolongation was found in patients given concomitant LVQ and AMIO versus levofloxacin alone.

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Disclosure
All affiliations and persons represented on this presentation have no conflicts of interests or financial interest.