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Original Research Article

Effect of digoxin on corrected QT interval in geriatric inpatients: a prospective observational study

Roberto Lozano[1]*, Carina Bona[2]

[1]Department of Pharmacy, University Clinical Hospital "Lozano Blesa", Zaragoza, Spain
[2]Unit for the Rational Use of Medicines, Aragon Health Service, Zaragoza, Spain

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***Correspondence:**
Dr. Roberto Lozano,
Email: jrlozanoo@gmail.com

ABSTRACT

Background: QT interval prolongation is a recognized surrogate marker for torsades de pointes risk. Digoxin, a cardiac glycoside used for atrial fibrillation and heart failure, is not typically associated with torsades but may shorten QTc, particularly in toxicity. Whether therapeutic digoxin shortens QTc in elderly inpatients remains unclear. Objective was to evaluate the effect of digoxin on QTc interval in geriatric inpatients at therapeutic plasma concentrations.
Methods: We performed a prospective observational study over six months (November 2012-February 2013) in 201 geriatric inpatients. QT intervals were measured ≥15 days after digoxin initiation and corrected using Bazett's (QTcB) and Fridericia's (QTcF) formulas. Patients on amiodarone, donepezil, salbutamol, or venlafaxine were excluded. Covariates included demographics, comorbidities (hypertension, heart failure, diabetes, renal disease, atrial fibrillation/flutter, COPD), and clinical presentation. High QTc was defined as >460 ms in women and >450 ms in men.
Results: Twenty-three patients received digoxin (mean dose 151±88 µg/day; mean plasma level 1.2±0.4 ng/ml) and 152 served as controls. Digoxin patients had lower QTcB (427.7±33.5 ms versus 447.1±56.2 ms; p=0.1166) and QTcF (408.4±36.1 ms versus 423.2±48.5 ms; p=0.1642). High QTc prevalence was lower in the digoxin group for QTcB (13.0% versus 28.9%, p=0.082) and QTcF (8.7% versus 23.0%, p=0.162), though differences were not statistically significant. Baseline characteristics were otherwise similar between groups.
Conclusions: In elderly inpatients, digoxin therapy was associated with a non-significant trend toward QTc shortening and lower prevalence of high QTc. These findings do not support initiating digoxin solely to reduce QTc but suggest a potential ancillary benefit in patients already indicated for the drug. Larger studies at higher therapeutic plasma levels are warranted.

Keywords: Digoxin, Heart failure, QT interval

INTRODUCTION

The QT interval on the surface electrocardiogram (ECG) represents the total duration of ventricular depolarization and repolarization. Prolongation of the corrected QT interval (QTc) is an established surrogate marker for the risk of torsades de pointes (TdP), a polymorphic ventricular tachycardia that can degenerate into ventricular fibrillation and cause sudden cardiac death.[1] Numerous medications across therapeutic classes can prolong QTc, including antiarrhythmics, psychotropics, and antimicrobials.[2,3] Because TdP is rare, QTc prolongation is widely used as a safety endpoint in both clinical practice and drug development.[4]

Digoxin is a cardiac glycoside that has been in use for over a century, primarily for rate control in atrial fibrillation and for symptomatic improvement in heart failure with reduced ejection fraction. Its pharmacological effects result from inhibition of the sodium-potassium ATPase

pump, leading to increased intracellular calcium and enhanced myocardial contractility. However, digoxin also exerts vagotonic effects on the atrioventricular node, reducing conduction and heart rate. Despite its known proarrhythmic potential- particularly for atrial and ventricular ectopy- digoxin is rarely implicated in TdP. On the contrary, QTc shortening is considered a characteristic ECG finding in digoxin toxicity.[5,6]

Evidence on whether therapeutic digoxin shortens QTc is conflicting. Some observational studies and small clinical trials have reported modest QTc reductions, whereas others have found no significant effect.[7] Most prior research has not specifically addressed elderly populations, who may be more susceptible to both QTc changes and digoxin toxicity due to altered pharmacokinetics, polypharmacy, and comorbidities.[8]

In this context, we conducted a prospective observational study to quantify the effect of digoxin on QTc in geriatric inpatients, carefully excluding patients on other QT-prolonging drugs. We also examined whether digoxin use was associated with a lower prevalence of high QTc, defined using sex-specific thresholds, and evaluated baseline differences between digoxin-treated and untreated patients.[9,10]

METHODS

Study design and population

We performed a six-month prospective observational study between November 2012 and February 2013 in a geriatric inpatient population at a tertiary care center. Eligible patients were aged ≥65 years, admitted for any medical condition, and had a QT interval measurement obtained at least 15 days after initiating digoxin therapy, ensuring steady-state drug levels.

Inclusion and exclusion criteria

We included all consecutive patients meeting the above criteria. Patients were excluded if they were receiving medications known to significantly prolong QTc, specifically amiodarone, donepezil, salbutamol, or venlafaxine, as per the Woosley, QT-prolonging drug list.[5] Additional exclusions were applied to those with incomplete ECG or clinical data.

Data collection

Data were extracted from electronic medical records, including demographics, clinical presentation, comorbidities, laboratory results, medication use, and ECG measurements. Covariates of interest were: hypertension, heart failure, urgent admission, diabetes mellitus, chronic kidney disease, atrial fibrillation, atrial flutter, and chronic obstructive pulmonary disease (COPD). For atrial flutter and COPD, we derived binary variables from admission diagnosis text using keyword searches.

ECG analysis

Standard 12-lead ECGs were recorded at admission. QT intervals were measured manually and corrected for heart rate using Bazett's formula (QTcB) and Fridericia's formula (QTcF). High QTc was defined as >460 ms for women and >450 ms for men.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and compared using Student's t-test for independent samples. Categorical variables are presented as percentages and compared using Fisher's exact test or chi-square test as appropriate. A p value <0.05 was considered statistically significant. Statistical analyses were conducted using standard software.

Ethics statement

According to national regulations and institutional policies, observational studies based on routinely collected, anonymized clinical data that do not involve any intervention or modification of patient management are exempt from formal ethics committee review. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision, Fortaleza, Brazil). All patient information was handled in a strictly confidential manner, and data were anonymized prior to analysis to ensure privacy.

RESULTS

Study population

A total of 201 patients met initial screening criteria. After exclusions, 175 patients remained for analysis: 23 in the digoxin group and 152 in the no-digoxin group. The mean digoxin dose was 151±88 mcg/day, with a mean plasma concentration of 1.2±0.4 ng/ml.

Baseline characteristics

Table 1 summarizes baseline demographics, comorbidities, and QTc measures by treatment group. There were no statistically significant differences in age, sex distribution, or most comorbidities between groups. The prevalence of high QTc was lower in the digoxin group for both QTcB and QTcF, although these differences did not reach statistical significance.

QTc analysis

Patients receiving digoxin had mean QTcB values 19.4 ms shorter and QTcF values 14.8 ms shorter than controls. While these differences were not statistically significant, effect sizes were moderate (Cohen's d=0.56 for QTcB;

0.45 for QTcF). The prevalence of high QTcB and QTcF was numerically lower in the digoxin group, corresponding to odds ratios of 0.37 (95% CI: 0.11-1.15; p=0.0819) for QTcB and 0.34 (95% CI: 0.08-1.54; p=0.1622) for QTcF.

Table 1: Baseline characteristics and QTc by group (digoxin versus no digoxin).

Variables	Digoxin	No digoxin	Total	P value
Age (years), mean (SD)	82.7 (6.4)	83.8 (6.9)	83.7 (6.8)	0.4790
Female, %	52.2	55.9	55.4	0.8220
QTcB (ms), mean (SD)	427.7 (33.5)	447.1 (56.2)	444.4 (54.3)	0.1166
QTcF (ms), mean (SD)	408.4 (36.1)	423.2 (48.5)	421.0 (47.1)	0.1642
High QTcB (sex-adjusted),%	13.0	28.9	26.9	0.0820
High QTcF (sex-adjusted), %	8.7	23.0	21.1	0.1620
Hypertension, %	69.6	74.3	73.7	0.7990
Heart failure, %	17.4	25.7	24.6	0.4560
Diabetes, %	21.7	28.3	27.4	0.6190
Chronic kidney disease, %	21.7	18.4	18.9	0.7570
Atrial fibrillation, %	65.2	68.4	68.0	0.8090
Atrial flutter, %	4.3	2.0	2.3	0.4560
COPD, %	13.0	11.8	12.0	0.8790

Values are expressed as mean ± SD for continuous variables and % for categorical variables. High QTc defined as >460 ms in women and >450 ms in men. COPD = chronic obstructive pulmonary disease. High QTcB/QTcF defined as >460 ms in women and >450 ms in men. QTcB calculated using Bazett's formula; QTcF calculated using Fridericia's formula.

Table 2: Baseline characteristics and QTc by group (digoxin versus no digoxin).

Variable, Mean±SD or %	Digoxin group (n=23)	No digoxin group (n=152)	Total (n=175)	P value
QTcB (ms)	427.7±33.5	447.1±56.2	444.4±54.3	0.1166
QTcF (ms)	408.4±36.1	423.2±48.5	421.0±47.1	0.1642
High QTcB (%)	13.0	28.9	26.9	0.0820
High QTcF (%)	8.7	23.0	21.1	0.1620

Baseline characteristics and QTc intervals are presented as mean±standard deviation. High QTcB and QTcF indicate the percentage of patients exceeding standard clinical thresholds (450 ms in men and 470 ms in women for QTcB; 440 ms in men and 460 ms in women for QTcF). Statistical comparisons between digoxin and non-digoxin groups were conducted using appropriate tests, with p values <0.05 considered significant.

DISCUSSION

In this prospective observational study of geriatric inpatients, we found that digoxin therapy at therapeutic plasma concentrations was associated with a non-significant trend toward QTc shortening. Compared with controls, the digoxin group exhibited mean reductions of approximately 14-20 ms in QTcF and QTcB, respectively. While these differences did not meet conventional thresholds for statistical significance, the magnitude of change and moderate effect sizes suggest that the observed effect may be clinically relevant, particularly in selected patient subgroups.[11]

Comparison with previous literature

Our findings are consistent with earlier reports that described QTc shortening in the context of digoxin administration.[12] Cheng identified QT shortening as a hallmark ECG finding in cardiac glycoside toxicity, although the magnitude of change was generally more pronounced than observed in our cohort.[3] Saner et al and Duraković et al investigated the relationship between serum digoxin concentration and ECG parameters, reporting variable results- some showing a clear correlation, others finding minimal changes at therapeutic levels.[4,7] The present study differs in that it specifically excluded patients on QT-prolonging medications, thereby isolating the potential contribution of digoxin to QTc modification.[13] Importantly, prior studies have often included heterogeneous populations with varying baseline arrhythmic risks and comorbidity profiles. By focusing on elderly inpatients, our cohort reflects a high-risk group in whom both prolonged and shortened QT intervals may carry clinical consequences. This setting is also clinically relevant, as geriatric patients often receive multiple medications that may interact pharmacodynamically or pharmacokinetically with digoxin.[14]

Possible mechanisms of QTc shortening

The physiological basis for digoxin's effect on QTc is likely multifactorial. Digoxin inhibits the Na^+/K^+-ATPase pump, increasing intracellular sodium and indirectly

increasing intracellular calcium via the Na^+/Ca^{2+} exchanger. This action shortens phase 2 of the ventricular action potential, which could manifest as a shorter QT interval on the ECG. In addition, the drug's vagomimetic effects may alter autonomic tone in a manner that modulates ventricular repolarization.[15]

QT shortening in digoxin toxicity is well-established; however, whether therapeutic concentrations exert the same directional effect is less certain. In our study, plasma concentrations were relatively low (mean 1.2 ng/ml), potentially attenuating any effect. It is plausible that higher concentrations within the upper therapeutic range (1.5-2.5 ng/ml for atrial fibrillation) could produce more pronounced QTc changes.

Clinical implications

From a practical standpoint, our results do not support prescribing digoxin with the primary aim of reducing QTc or preventing torsades de pointes. The drug's narrow therapeutic index, complex pharmacokinetics, and well-known proarrhythmic risks in other contexts preclude such a strategy. Nonetheless, for patients already indicated for digoxin- such as those with rate-controlled atrial fibrillation or symptomatic heart failure- QTc shortening might be viewed as a potential ancillary benefit, particularly in individuals with borderline QTc prolongation due to other medications or underlying conditions.

The prevalence of high QTc (>460 ms in women, >450 ms in men) was lower in the digoxin group for both QTcB and QTcF. Although these differences did not achieve statistical significance, the directionality aligns with the hypothesis that digoxin may shift the QTc distribution toward lower values. Given that high QTc is an established risk marker for TdP, even modest reductions could theoretically lower arrhythmic risk in certain populations.[1,2]

Several features strengthen our findings. First, the prospective observational design allowed for predefined inclusion and exclusion criteria, minimizing selection bias. Second, we excluded patients on well-known QT-prolonging drugs, reducing pharmacological confounding. Third, our statistical analysis adjusted for sex-specific QTc thresholds, an important consideration given known differences in ventricular repolarization between men and women. Finally, the use of both Bazett's and Fridericia's corrections provides robustness, as Bazett's formula may overestimate QTc at higher heart rates, while Fridericia's is less heart rate-dependent.

Several limitations should be acknowledged. The sample size, particularly for the digoxin group (n=23), limited statistical power, and moderate effect sizes suggest that the study may have been underpowered to detect differences of clinical relevance. The population was confined to geriatric inpatients, which may limit generalizability to younger or ambulatory populations. Plasma digoxin levels were relatively low, potentially underestimating the QTc-shortening effect at higher therapeutic concentrations. Although major QT-prolonging drugs were excluded, residual confounding from unmeasured variables remains possible. Some comorbidity data- specifically atrial flutter and COPD- were extracted from diagnostic text fields, introducing a risk of misclassification bias. Lastly, as an observational study, causality cannot be established.

Implications for future research

Future investigations should explore digoxin's QTc effects in larger, more diverse cohorts, including patients with higher therapeutic plasma concentrations and those at elevated arrhythmic risk due to concomitant medications or structural heart disease. Randomized controlled trials would be ideal to establish causality, although such studies may be logistically challenging. Incorporating continuous ECG monitoring could provide more granular data on QT dynamics and arrhythmic events.

CONCLUSION

In this prospective observational study of geriatric inpatients, digoxin therapy at therapeutic plasma concentrations was associated with a moderate, though statistically non-significant, reduction in QTcB and QTcF intervals compared with controls. The observed mean decreases of approximately 14-20 ms, coupled with a lower prevalence of high QTc values, suggest a potential beneficial effect on ventricular repolarization in this population.

While our findings align with prior reports of QT shortening in digoxin exposure, the modest magnitude and lack of statistical significance underscore the need for caution in interpretation. Digoxin should not be initiated solely to reduce QTc or mitigate torsades de pointes risk, given its narrow therapeutic index and potential for other arrhythmogenic effects. However, for patients with established indications for digoxin- particularly those with borderline QT prolongation- this QT-shortening effect may represent an ancillary advantage.

Future research in larger, more heterogeneous cohorts, particularly at higher therapeutic digoxin concentrations, is warranted to clarify the reproducibility and clinical relevance of these findings.

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