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Prognostic Utility of Serum Potassium in Chronic Digoxin Toxicity:

A Case-Control Study

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Abstract

Objective—In contrast to patients with acute digoxin overdose, the prognostic utility of the serum potassium concentration for patients with chronic digoxin toxicity is unclear. In such patients, we aimed to evaluate the relationship between pre-treatment serum potassium and survival.

Methods—This was a case-control study at an urban Poison Control Center affiliated with a large urban medical center. We compared the serum potassium concentration between patients with chronic digoxin toxicity resulting in fatality (cases) over a 7-year period (2000–2006) versus survivors (controls) over a 1-year period (2007–2008).

Results—During the study period, there were 13 fatalities (cases) and 13 survivors (controls), of whom seven cases and five controls received appropriately dosed digoxin-specific antibody Fab fragments (Fab). There were no statistically significant differences between cases and controls with respect to serum digoxin concentration, creatinine, age, or sex. Serum potassium elevation pre-Fab was significantly associated with fatality both in mean difference ($p < 0.03$) and using a dichotomous cutoff of 5.0 mEq/L ($p < 0.001$), which performed with 92% sensitivity (95% CI 67, 99). In 86% of deaths despite appropriate Fab administration, the clinical presentation included the combination of bradycardia plus hyperkalemia.

Conclusion—In these patients with chronic digoxin toxicity, elevated serum potassium was associated with fatality. The combination of bradycardia and hyperkalemia strongly predicted fatality even in cases with appropriate Fab administration.

Introduction

According to the National Center for Health Statistics, digoxin toxicity accounted for eight cases per 100 000 US civilian population in 2004, down from 23 per 100 000 in 1991.^[1]

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Despite this downward trend, chronic toxicity in patients on maintenance digoxin is relatively common – out of 3391 patients prescribed digoxin to treat heart failure in the Digitalis Investigators Group (DIG) Trial, 12% were suspected to have digoxin toxicity over a mean duration of 37 months' follow-up.^[2] The most common presentations of reported digoxin toxicity in the National Poison Data System are unintentional or adverse reactions (62% and 33%, respectively); in contrast, acute intentional ingestions are exceedingly rare, making up only 4% of the total reporting volume.^[3] Thus, prognostic indicators for the evaluation of chronic digoxin toxicity are needed and would be more commonly applicable than indicators for acute toxicity.

In comparison to acute digoxin toxicity, chronic toxicity is more common and its treatment is more controversial.^[4] Chronic digoxin toxicity may be exacerbated by concurrent electrolyte disorders of potassium, magnesium, and calcium. With chronic digoxin use, concurrent electrolyte abnormalities may occur at a relatively high rate due to co-administration of diuretics in the majority of patients taking therapeutic digoxin.

Elevation of the serum potassium concentration after administration of cardioactive steroids (e.g. digoxin) is the result of inhibition of the sodium-potassium-ATPase pump. This results in the inhibition of potassium uptake in exchange for sodium by skeletal muscle, which represents a large anatomical potassium reservoir.^[5] Clinically, hyperkalemia is a well known predictor of fatality in acute presentations of digoxin toxicity.^[6,7] In the presence of digoxin toxicity, when potassium exceeds 5.0 mEq/L, treatment with digoxin-specific antibody Fab fragments (Fab) is indicated. If Fab is not available immediately, hyperkalemia should be treated in a standard fashion (e.g. intravenous sodium bicarbonate) with two exceptions: calcium salts and β -2 agonists should be avoided due to concerns of provoking hypocontractility and dysrhythmias,^[8] respectively.

Management of chronic digoxin toxicity includes definitive antidotal therapy with Fab.^[9] The indications for administration of Fab generally include the presence of any of the following in patients with suspected chronic toxicity: ECG evidence of severe toxicity, inability to tolerate symptoms of toxicity, or inability to renally clear digoxin. There is no specific serum digoxin concentration that mandates antidotal therapy in the absence of symptoms. Unfortunately, there is evidence of widespread practice variation with regard to the threshold for administering Fab in patients with suspected chronic toxicity,^[10] despite results from two open-label multicenter trials that demonstrated excellent efficacy and low risk with Fab administration.^[4,11]

The prognostic utility of the serum potassium concentration for patients with chronic digoxin toxicity is unclear. In acute toxicity, there is evidence of a worse prognosis based on a serum potassium concentration >5.0 mmol/L.^[6-7] However, the relationship between serum potassium and prognosis in chronic toxicity is less well studied. To address this gap in the literature, we aimed to evaluate the relationship between pre-treatment serum potassium and survival. We hypothesized that hypokalemia would exacerbate chronic digoxin toxicity due to theoretical synergistic predisposition to dysrhythmia, and would thus be associated with fatality.

Methods

Study Design and Setting

This was a case-control study that took place at a large urban medical center consisting of a public hospital and a tertiary-care hospital (each with approximately 50 000 annual emergency department visits and 24 hour/day board-certified emergency physician coverage) affiliated with an urban regional Poison Control Center (PCC) [approximately 70 000 annual referrals]. Cases were identified retrospectively and controls were enrolled prospectively. The study protocol was approved by the Institutional Review Board (IRB) for all participating institutions.

Study Patients

To identify fatalities due to chronic digoxin toxicity for inclusion as cases, we screened fatal PCC referrals with digoxin toxicity over a 7-year period (2000–2006). Exclusion criteria were the following: acute exposure (see definition below); no serum digoxin concentration (SDC) obtained (or available); alternative diagnosis; and subjects with incomplete survival data (i.e. data regarding in-hospital fatality). Death reports or cause of death data from the Office of the Chief Medical Examiner were also reviewed if available.

Consecutive patients presenting to the study hospitals with suspected digoxin toxicity were eligible to be control subjects. Controls were prospectively enrolled until a 1: 1 ratio of cases/controls was obtained, which occurred over a period of approximately 12 months (1 April 2007–25 March 2008). Controls all received bedside consultation with the medical toxicology service and had digoxin toxicity (definition below) as assessed by the consulting medical toxicologist. Exclusion criteria were exactly the same as those for cases listed (see above) with the additional exclusion of in-hospital fatality (one subject); thus, all controls survived to hospital discharge. Fatalities excluded as controls were not included as cases.

Definitions

Acute exposures were an exclusion criterion and were defined as a one-time overdose (i.e. more than therapeutic dosage) of digoxin tablets within 24 hours prior to presentation. Digoxin toxicity for both cases and controls was defined as the combination of both of the following criteria: (a) elevated SDC (i.e. non-zero); and (b) consistent clinical symptoms and/or abnormal ECG findings (as per the consulting medical toxicologist). The reasoning for using non-zero SDC values as a necessary criterion to define digoxin toxicity was two-fold: (a) to confirm exposure; and (b) to avoid setting an arbitrary numerical threshold for toxicity, since it is well established that clinical toxicity from chronic digoxin exposures does not correlate with SDC values. Hyperkalemia was defined as serum potassium ≥ 5.0 mmol/L in a non-hemolyzed sample. Cardiac rhythms were defined as documented in the medical record or printed on the ECG interpretation and were not interpreted independently by study investigators. Fab administration was defined as appropriate for antidotal therapy according to the following equation:

$$(\text{SDC in ng/mL}) \times (\text{weight in kg}) \div (100) = \text{number of vials (rounded up to the nearest integer)}$$

Failure to provide at least this number of vials of antidote was defined as insufficient dosing in accordance with standard guidelines.^[12]

Measurements

Electronic and paper medical records were provided for all cases and controls with IRB approval. Standardized data collection was performed by a single blinded abstractor and data were stored in a de-identified electronic database. Sources of data included hospital medical records (primary source), PCC electronic records, death reports or cause of death data from the Office of the Chief Medical Examiner (when available), and any additional paper notes (e.g. toxicology consultation service note). Using a standardized data collection instrument the following information was collected from records available: demographics (age and sex); history of exposure (acute versus chronic as defined above, and intent or lack thereof); laboratory data from the initial presentation to the emergency department (SDC, creatinine, troponin I, and serum potassium concentration), cardiovascular co-morbidities (hypertension, congestive heart failure, and coronary artery disease), cardiac rate and rhythm (as documented in the medical record); and adverse in-hospital events (ventricular tachycardia/fibrillation, and mortality) were recorded. The following laboratory values were considered to be not clinically useful and were thus not used for the analysis or interpretation of data: (a) hemolyzed serum samples (due to falsely elevated potassium concentrations); (b) SDC drawn less than 6 hours after patients received their last dose of digoxin (due to pre-steady-state SDC); (c) subsequent SDC and post-treatment laboratory values, even if changed or abnormal.

Statistical Analysis

Descriptive statistics included percentages, ranges, means $\pm$ standard error, as well as medians with interquartile range for potassium analysis. Categorical and continuous variables were assessed using the chi-squared (χ^2) test (or Fisher exact test when appropriate) and t-test, respectively, with two-tailed alpha equal to 5%. Odds ratios with 95% confidence intervals (CIs) were calculated to evaluate clinical associations with fatality. Receiver operating characteristic (ROC) statistics were created to evaluate the performance of serum potassium concentration as a predictor of fatality per the diagnostic test characteristics. Computer analysis was performed using SPSS version 17 software (SPSS, Inc., Chicago, IL, USA).

Results

Enrollment

Out of 418 fatal human PCC referrals during the study period, there were 15 referrals with digoxin toxicity, of which two were excluded (two acute ingestions; none lacked SDC, or had an alternative diagnosis, or incomplete survival data) leaving 13 cases for analysis. Out of 14 prospective control subjects with suspected digoxin toxicity during the study period, one was excluded (one death; none were acute ingestions, lacked SDC, or had an alternative diagnosis, or incomplete survival data), leaving 13 controls for analysis. Thus, after application of inclusion and exclusion criteria, we analyzed 26 patients with chronic digoxin toxicity with 13 fatalities (cases) and 13 survivors (controls).

Baseline Characteristics

Overall, patients were 73% female with a mean $\pm$ SE age of 73 ± 4 years, SDC 3.4 ± 0.4 ng/mL (4.2 ± 0.5 nmol/L), and creatinine 2.3 ± 0.3 mmol/L. Significant cardiovascular co-morbidities included hypertension (84%), congestive heart failure (80%), and coronary artery disease (48%). There were no statistically significant differences between cases and controls with respect to age, sex, SDC, creatinine, or cardiovascular co-morbidities. Baseline characteristics of subjects are summarized in table I.

Overall there was adequate documentation of presenting ventricular rate in 21 patients (11 cases and 10 controls) and cardiac rhythms in 20 patients (10 cases and 10 controls). Of these, the most common presenting cardiac rhythms included sinus (35%), atrial fibrillation (30%), and junctional rhythm (25%). Mean $\pm$ SE ventricular response rate was 59 ± 5 , 52% had bradycardia, and 10% had tachycardia. No patients exhibited sinus tachycardia.

Serum Potassium

Overall, the initial serum potassium concentration was 5.4 ± 0.3 mmol/L, ranging between 3.3 and 7.8 mmol/L. One subject (case) had hemolyzed serum and was thus excluded from potassium analysis. Cross-tabulation of serum potassium with cases versus controls is demonstrated in table II. Cases had significantly higher mean potassium (t-test $p < 0.03$) and were significantly more likely to present with hyperkalemia ($\chi^2 p < 0.001$). Using a serum potassium cutoff of 5.0 mEq/L yielded 92% sensitivity (95% CI 60, 99) and was associated with over 36-fold increased odds of fatality (odds ratio [OR] 36.7; 95% CI 3.2, 412). The ROC area under the curve was 0.76 (95% CI 0.55, 0.98). The relationship between serum potassium concentration and fatality is illustrated in figure 1.

Hospital Course

All 26 analyzed subjects initially presented to the emergency department, of whom there were 23 medical admissions (11 [85%] controls and 12 [92%] cases), two transfers for psychiatric evaluation following medical clearance (two controls), and one patient who died in the emergency department. In control subjects there were two troponin elevations with unclear relationship to digoxin toxicity. Prior to cardiac arrest in cases, there were five recognized troponin elevations and two episodes of ventricular tachycardia/fibrillation. Deaths for cases occurred on average after a mean of 5 ± 2.3 hospital days. Medical examiner results were available for two cases of which neither led to any alternative diagnosis per WHO International Classification of Diseases (ICD)-10 coding.

Digoxin-Specific Fab Fragment Administration

Out of 26 patients analyzed, 12 received sufficient antidote dosing, two received insufficient dosing (one case and one control), and 12 received no Fab. Of those who received the appropriate dose of Fab, there were seven cases and five controls. In six of seven (86%) deaths despite appropriate Fab dosing, the initial presentation included the combination of both bradycardia (range 22–53 ventricular beats/min) and hyperkalemia (potassium range 3.3–7.6 mmol/L). Bradycardic ventricular response was significantly associated with death despite appropriate Fab dosing in both mean ventricular response (t-test $p < 0.05$) and using a dichotomous cutpoint of <60 ventricular beats/min ($\chi^2 p < 0.05$). The latter was associated

with 7-fold increased odds of death despite appropriate Fab dosing (OR 7.0; 95% CI 1.1, 42.9). Finally, in six of seven (86%) deaths with appropriate Fab dosing, the clinical presentation included the combination of bradycardia plus hyperkalemia ($p < 0.05$).

Discussion

The predominant finding of this study is that in chronic digoxin toxicity, elevated serum potassium correlates with both (a) fatality and (b) death despite appropriate Fab dosing. Previously, the prognostic utility of serum potassium concentration for patients with chronic digoxin toxicity was unclear. Some authors argued that hypokalemia was the major electrolyte abnormality associated with cardiotoxicity in the setting of chronic digoxin toxicity due to the theoretical risk for dysrhythmias.^[13] To treat chronic toxicity, potassium administration has been recommended as the treatment of choice (over Fab) even when the serum potassium is in the normal range.^[14] In this study, hyperkalemia was not associated with the pre-study hypothesized cardioprotective effect toward dysrhythmia; on the contrary, hyperkalemia was associated with an 86% rate of death despite appropriate Fab dosing. This is the first report to our knowledge correlating hyperkalemia with fatality in presentations of chronic digoxin toxicity.

This study builds upon previous reports evaluating prognostic factors for the development of digoxin toxicity. Renal insufficiency is the most common predisposition to the development of toxicity in digitalized patients due to decreased clearance of digoxin. Hypomagnesemia due to enhanced urinary magnesium clearance from diuretic coadministration^[15] has been correlated with cardiotoxicity.^[16] Clinically, neurological manifestations have been correlated with early detection of digoxin toxicity.^[17] Two large inpatient cohorts have identified a correlation between elevated serum digoxin concentration and both cardiotoxicity^[18] and mortality.^[19] Mahdyoon and colleagues^[18] reviewed charts of 241 inpatients with a discharge diagnosis of digitalis poisoning and found that laboratory correlates of definite cardiotoxicity (i.e. dysrhythmia that resolved after discontinuation of digoxin) included elevated serum potassium, creatinine, and blood urea nitrogen. Our data add to the above prognostic literature by identifying hyperkalemia and bradycardia as correlates of mortality and death despite appropriate Fab dosing in chronic digoxin toxicity.

In the previous literature, the definition of Fab ‘failure’ has been inconsistent. In the initial multicenter clinical trial of 150 patients given Fab by Antman and colleagues,^[11] treatment failure was defined as “failure of any signs of toxicity to improve”. However, according to this classification, 32 patients who actually were categorized as ‘complete resolution’ or ‘incomplete responders’ actually died in the hospital despite the fact that all were thought to have required inpatient admission due to a primary diagnosis of digoxin toxicity. In a subsequent study of 717 adults receiving Fab, investigators asked the treating clinicians to record adverse clinical outcomes “irrespective of attribution”,^[4] which severely limited interpretation of true antidote failures. In contrast, in the present study we do not use ‘failure’ terminology but rather describe death despite appropriate Fab dosing in order to avoid subjectivity in our data analysis and thus improve the validity of our results.

Causality in the present study remains difficult to interpret regarding both hyperkalemia and fatality. For instance, while digoxin-mediated blockade of the sodium-potassium-ATPase pump can cause hyperkalemia, so can end-organ damage such as acute renal failure. (It should be noted that serum creatinine was not associated with fatality in the present study, but this is just one example.) Similarly, it is not clear whether patients in the present study died as a result of digoxin toxicity or another underlying disease process that existed concomitantly in the initial presentation. Suggestion of the latter may include data on hospital day of death (average >5 days), and interpretation is further hampered by lack of medical examiner interpretation in the majority of subjects (only 2 of 13 available). Furthermore, interpretation of death despite appropriate Fab dosing provokes similar uncertainty vis-à-vis interpretation of causality; Fab may not fail to work so much as patients fail to survive the underlying disease process. However, the association of hyperkalemia with fatality remains important for clinicians to recognize, regardless of causality, to allow overall risk stratification of the patient's presentation.

Based on these data, we feel it is appropriate to make clinical recommendations for patients with chronic digoxin toxicity. Firstly, Fab antidotal therapy for patients with chronic digoxin toxicity should be mandated in patients with hyperkalemia. Secondly, utility of screening potassium should not be limited to acute presentations. Recommendations regarding higher or maximum empiric dosing of Fab cannot be made based on these data, but may be considered by clinicians evaluating chronic digoxin toxicity with hyperkalemia and/or bradycardia; the presence of both signs elicited a very poor prognosis in this study.

Limitations

Our data has several limitations including those common to all case-control studies, namely the inability to calculate incidence or prevalence of digoxin toxicity or fatality. The study was performed in an urban tertiary referral center, and results might not be applicable to all centers; however, our population demographics were similar to previous reports in terms of age and co-morbid disease and there was no difference in baseline characteristics between cases and controls.^[4,11] The presence of a bedside medical toxicology consultation may have improved outcomes for controls as opposed to cases; however, this would have been biased towards the null as control subjects with high potassium would presumably have better prognoses than similar cases. Co-medication with diuretics may have influenced the potassium levels and biased the results, and small sample size precluded additional regression analysis to attempt to exclude this as a potential cause of confounding. Additional limitations of this study include lack of baseline potassium values, small number of cases, and theoretical possibility of misclassification of chronic (versus acute) toxicity by history.

Conclusion

In these patients with chronic digoxin toxicity, elevated initial serum potassium was associated with fatality. In addition, bradycardia was associated with death even in cases with appropriate Fab dosing. The combination of hyperkalemia and bradycardia was correlated with very poor prognoses in these patients. Prospective studies are warranted to confirm these findings.

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Fig. 1.

Comparison of serum potassium for cases vs controls. This figure demonstrates a box-plot (left side for each) and scatterplot (right side for each) of serum potassium concentration in cases (fatalities) and controls (survivors). The box-plot represents the median, 25th and 75th quartiles, and outliers by a line, a box, and open circles (o), respectively.

Table IBaseline clinical characteristics^a

Characteristic	Overall (n = 26)	Case (n = 13)	Control (n = 13)
Mean age (y)	73 ± 3.6	70.6 ± 5.4	76.2 ± 5.1
Women	73	85	64
Past medical history			
hypertension	84	92	77
coronary artery disease	48	33	62
congestive heart failure	80	67	92
Laboratory			
SDC (ng/mL)	3.4 ± 0.4	3.3 ± 0.7	3.4 ± 0.5
creatinine (mmol/L)	2.3 ± 0.3	2.5 ± 0.3	2.2 ± 0.5

^aData are given as percent or mean ± SE.

SDC = serum digoxin concentration; SE = standard error.

Table II

Cross-tabulation of serum potassium with cases vs controls

Serum potassium concentration	Controls (n = 13)	Cases (n = 12) ^a	Total (n = 25)
Hyperkalemia (K ≥ 5.0 mEq/L)	3	11	14
Normal or hypokalemia (K < 5.0 mEq/L)	10	1	11

^aOne subject (case) had hemolyzed serum and was thus excluded from potassium analysis.**K** = serum potassium concentration.