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Selected Topics: Toxicology

THE EFFECTS OF INTRAVENOUS CALCIUM IN PATIENTS WITH DIGOXIN TOXICITY

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□ **Abstract—Background: Digoxin is an inhibitor of the sodium-potassium ATPase. In overdose, hyperkalemia is common. Although hyperkalemia is often treated with intravenous calcium, it is traditionally contraindicated in digoxin toxicity. Objectives: To analyze records from patients treated with intravenous calcium while digoxin-toxic. Methods: We reviewed the charts of all adult patients diagnosed with digoxin toxicity in a large teaching hospital over 17.5 years. The main outcome measures were frequency of life-threatening dysrhythmia within 1 h of calcium administration, and mortality rate in patients who did vs. patients who did not receive intravenous calcium. We use multivariate logistic regression to ensure that no relationship was overlooked due to negative confounders (controlling for age, creatinine, systolic blood pressure, peak serum potassium, time of development of digoxin toxicity, and digoxin concentration). Results: We identified 161 patients diagnosed with digoxin toxicity, and were able to retrieve 159 records. Of these, 23 patients received calcium. No life-threatening dysrhythmias occurred within 1 h of calcium administration. Mortality was similar among those who did not receive calcium (27/136, 20%) compared to those who did (5/23, 22%). In the multivariate analysis, calcium was non-significantly associated with decreased odds of death (odds ratio 0.76; 95% confidence interval [CI] 0.24–2.5). Each 1 mEq/L rise in serum potassium concentration was associated with an increased mortality odds ratio of 1.5 (95% CI 1.0–2.3). Conclusion: Among digoxin-intoxicated humans, intravenous calcium does not seem to cause malignant dysrhythmias or increase mortality. We found no support for the historical belief that calcium administration is contraindicated in digoxin-toxic patients.** © 2011 Elsevier Inc.

□ **Keywords—digoxin; digoxin toxicity; hyperkalemia; calcium**

INTRODUCTION

Digoxin is a cardiac glycoside that is commonly prescribed to patients with congestive heart failure, especially those with co-existing atrial fibrillation. Digoxin, like other cardiac glycosides, inhibits the sodium-potassium ATPase pump, thereby increasing the intracellular sodium concentration (1–5). The increased intracellular sodium inhibits sodium-dependent calcium transport out of the cytoplasm, resulting in increased intracellular calcium, and thus increased inotropy. In overdose, digoxin's inhibition of the sodium-potassium ATPase frequently results in hyperkalemia (3,6).

In experimental models, calcium potentiates the positive inotropic effects of cardiac glycosides (7). However, in animal models, calcium was found to increase digoxin toxicity (8–12). This effect was found to be dose-dependent and related to the rate of infusion, but only at unrealistically high calcium concentrations (10,12). The "stone heart" theory views calcium as the

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precipitant of an irreversible non-contractile state, due to failure of diastolic relaxation resulting from calcium binding to troponin-C (5). In addition to the "stone heart" theory, another concern stems from delayed after-depolarizations resulting in ventricular dysrhythmias, as a result of calcium excess. Despite the questionable applicability of these animal models, intravenous calcium traditionally has been contraindicated in digoxin toxicity (3).

Due to obvious ethical concerns, the administration of calcium to digoxin-toxic patients cannot be performed in a randomized trial. Furthermore, a prospective collection of data would be difficult, due to the relative rarity at which calcium is given to digoxin-toxic patients. Therefore, we conducted a medical record review in a large teaching hospital to find instances of intravenous calcium administration to digoxin-intoxicated patients. If either the "stone heart" theory or the delayed after-depolarization theories are correct, the incidence of malignant dysrhythmias and mortality should be higher in such patients than in digoxin-intoxicated patients not given calcium. We sought to test this hypothesis.

MATERIALS AND METHODS

This study was conducted at a 745-bed university-affiliated, tertiary care medical center in Boston, Massachusetts. We reviewed medical records of all adult patients (age $\geq$ 18 years) who had been diagnosed with digoxin toxicity from January 1, 1989 through May 31, 2005. If a person had multiple hospital admissions for digoxin toxicity during the study period, only the first hospitalization was included in the analysis.

Study Subjects

Patients were initially identified via a computerized search of discharge diagnoses for "poisoning by cardiac glycoside." When searching for a discharge diagnosis, however, the database identified only patients with a primary or secondary diagnosis of cardiac glycoside toxicity. Therefore, we subsequently reviewed the medical record of every patient who had a serum digoxin concentration $>$ 2.0 ng/dL while admitted to the hospital. These values were identified via an electronic database of laboratory results. If the treating clinicians had clearly documented digoxin toxicity as one of the problems during the admission, then these patients were also included in the analysis. Thus, all patients in the study had "digoxin toxicity" documented as one of their diagnoses.

Data Collection

Data abstracted from the medical records included age, gender, initial vital signs, electrocardiogram interpretations, and laboratory values (initial blood urea nitrogen and creatinine, as well as the initial and peak serum potassium and digoxin concentrations). In addition, the treatment rendered and the presence of any potentially fatal dysrhythmias were recorded. If any potentially fatal dysrhythmias were recorded, the temporal relationship to the administration of intravenous calcium salts was also recorded.

The data were collected on a pre-designed data abstraction form and then were entered into a standard spreadsheet (Excel 2000, version 9.0.2720; Microsoft Corporation, Redmond, WA).

Data Analysis

We compared categorical variables using the chi-squared test and Fisher's exact test (as appropriate). We compared continuous variables using Student's *t*-test. We used multivariate logistic regression to analyze the association between calcium administration and death while controlling for the following covariates: age, blood urea nitrogen, creatinine, peak digoxin concentration, and peak potassium concentration. All *p*-values are two-tailed. The statistical tests were performed using SAS, version 9.12 (SAS Institute Inc., Cary, NC). Our institutional review board approved this study.

Study Definitions

For purposes of this study, we defined potentially fatal dysrhythmias as ventricular fibrillation, sustained ventricular tachycardia, Mobitz II second-degree heart block, complete heart block, or asystole. If a potentially fatal dysrhythmia occurred within 1 h of the administration of calcium salts, we designated it as temporally related to the administration of calcium. However, we also recorded potentially fatal dysrhythmias that occurred within 4 h of intravenous calcium administration. For patients who received digoxin immune fragments (Digibind or DigiFab), the peak digoxin concentration was defined as the highest concentration before the administration of the antidote.

RESULTS

During the study period of January 1, 1989 through May 31, 2005, we identified 2220 unique patient encounters

Table 1. Characteristics of Digoxin-Intoxicated Patients, by Intravenous Calcium

Characteristics	Mean (Standard Deviation)		
	Calcium n = 23	No Calcium n = 136	All Patients n = 159
Age	73.7 (17.5)	70.0 (13.3)	70.5 (14.0)
Blood urea nitrogen (mg/dL)	72.2 (51.2)	51.8 (31.6)	54.7 (35.6)
Creatinine (mg/dL)	3.34 (2.39)	2.62 (3.23)	2.72 (3.13)
Initial digoxin (ng/mL)	3.14 (0.71)	3.37 (1.37)	3.33 (1.30)
Peak digoxin (ng/mL)	3.22 (0.69)	3.49 (1.36)	3.45 (1.29)
Initial potassium (mEq/L)	5.75 (1.07)	4.94 (0.939)	5.06 (0.999)
Peak potassium (mEq/L)	5.99 (0.988)	5.30 (0.959)	5.40 (0.991)

with elevated digoxin levels. Of these patients, 161 were documented as having digoxin toxicity. The complete records were available for all but 2 patients (159/161; 98.8%), comprising the final study population. Characteristics of the study population are presented in Table 1. Among the 159 patients, 133 had a primary admission diagnosis of digoxin toxicity. The remaining 26 patients developed digoxin toxicity after admission, primarily as a result of developing renal failure or multi-system organ failure as a complication of their underlying disease process (data not shown).

Of the 159 patients, 32 died, for an overall fatality rate of 20% (95% confidence interval [CI] 14–27%). All of the patients in the study population were on digoxin; there were no cases of digitoxin, oubain, or any other cardiac glycoside. Only one case represented a single, acute ingestion in a suicide attempt; all of the other cases were either chronic or sub-acute ingestions. Mortality is summarized in Table 2.

Twenty-three patients received intravenous calcium salts during treatment for digoxin toxicity and hyperkalemia. There was no association between calcium administration and death in the study population. Among those patients who received calcium, 5/23 (22%) died at some point during their hospitalization, compared with 27/136 (20%) deaths in patients who did not receive calcium ($p = 0.78$ by Fisher's exact test, odds ratio for death 1.1, 95% CI 0.38–3.3). In the group who did receive calcium, only 3/5 (60%) of the deaths were felt to be due to digoxin toxicity. No patient who received calcium had a fatal or potentially fatal dysrhythmia within 1 h of calcium administration. In fact, the first dysrhythmia that occurred in the study sample was more than 4 h after calcium administration. In the no-calcium group, only 15/27 (56%) deaths were attributed to digoxin toxicity, as the remainder of the deaths occurred after the patient was no longer felt to be digoxin toxic. In a subgroup analysis of those who were admitted with digoxin toxicity vs. those who developed digoxin toxicity while in the hospital, the administration of calcium was also not associated with death (data not shown). Only 2 patients received both calcium and digoxin immune fragments. Neither of these patients died. Table 3 provides characteristics of those patients who received intravenous calcium salts.

Table 3. Characteristics of Calcium Administration

	Mean Peak Digoxin Concentration (IQR)	Mean Peak Potassium Concentration (IQR)
Calcium gluconate	3.18 (2.9–3.2)	5.87 (5.3–6.5)
Calcium chloride	2.7 (2.3–3.3)	6.03 (5.7–6.2)

IQR = interquartile range.

To control for the possibility that we missed an association between calcium and death due to negative confounders, we conducted a multivariate controlled analysis. We used a logistic regression model to predict death according to calcium administration vs. none, while controlling for age, creatinine, systolic blood pressure, peak serum potassium concentration, digoxin concentration, and time of development of digoxin toxicity (admitted with digoxin toxicity vs. developed digoxin toxicity while in the hospital). The model did not reveal any association between calcium administration and death, but rather revealed a non-significant trend toward decreased mortality in patients who received calcium (odds ratio 0.76; 95% CI 0.24–2.5).

In this multivariate analysis, only peak potassium concentration was associated with increased odds of

Table 2. Mortality of Digoxin-Intoxicated Patients, by Intravenous Calcium

	Calcium	No Calcium	All Patients
Mortality	5 (22%)*	27 (20%)*	32 (20%)
Calcium as predictor of mortality	Odds ratio	95% Confidence interval	
Univariate analysis	1.1	0.38–3.3	
Controlled analysis	0.76	0.24–2.5	
Potassium as predictor of mortality			
Increased odds for each 1 mEq/L	1.5	1.0–2.3	

* p-Value for difference in proportions 0.78.

death. With each increase of 1 mEq/L of serum potassium, the odds of death increased by 1.5 (95% CI 1.0–2.3).

We used a cutoff peak serum potassium ≥ 5.5 mEq/L to define a "marked hyperkalemia" group. There were 67 patients with marked hyperkalemia. Among them, the mean peak potassium concentration was 6.3 (± 0.68) mEq/L. In this group, there were 18 deaths, for a fatality rate of 27% (95% CI 17–39%). Among the 92 patients without marked hyperkalemia, the fatality rate was 15% (95% CI 9–24%). Among those with marked hyperkalemia vs. those without, the odds ratio for death was 2.0 ($p = 0.07$, 95% CI 0.93–4.5).

DISCUSSION

Our study found no increased risk of death after calcium administration to digoxin-toxic patients. Among 23 patients who received intravenous calcium while digoxin toxic, there was not a single case of a potentially life-threatening dysrhythmia within 4 h after calcium administration. Only serum potassium concentration was associated with an increased risk of death.

We set 1 h as the time span during which we would expect to see a life-threatening dysrhythmia after calcium administration. We chose 1 h based on earlier work that demonstrated the additive or synergistic relationship between intravenous calcium and cardiac glycoside administration (8,10,11). Excess intracellular calcium induces delays in the after-depolarization during the fourth phase of an action potential (5). This effect, if it is to be observed, should occur relatively soon after the intravenous administration of calcium. Not only did we not see any significant dysrhythmias at 1 h, we did not see any within 4 h of calcium administration.

To our knowledge, there have been only five case reports of patients who have sustained fatal dysrhythmias after receiving calcium while being on a cardiac glycoside. The circumstances were too confounded for any inference of causality. In the original paper by Bower and Mengle, 2 patients were presented (8). The first case occurred in 1933, and involved a 55-year-old man with bilateral femur fractures who was felt to have either multiple myeloma or hyperparathyroidism. He underwent a right-sided thyroidectomy and "possible" parathyroidectomy. This patient had received 8.5 cc of Digalen (a purified digitalis preparation available from 1904–1964) over 20 h. On the second post-operative day, he was noted to have a fine tremor in both hands, which was felt to possibly be "beginning tetany." The patient was given 10 cc of 10% calcium chloride intravenously, and shortly thereafter died. The second case occurred in 1935, and involved a previously healthy 32-year-old woman who presented with nausea, vomiting, and abdominal pain. She underwent a cholecystectomy, during which a single gallstone and hemorrhagic bile were found. On post-operative day 2, she received several doses of Digalen for a heart rate of 100 beats/min and a blood pressure of 90/50 mm Hg. By the sixth post-operative day, she had received approximately 15 cc of Digalen, and the heart rate was 120 beats/min. More than 24 h after the last dose of Digalen, she received 10 cc of 10% calcium gluconate through a peripheral intravenous line for rate control. Approximately 2 min later, the pupils were dilated, and "she had a generalized convulsion with only slight muscular fibrillations." She was pronounced dead shortly thereafter. Neither of these patients had any documentation of the type of dysrhythmia, and there was no mention of any cardiac-glycoside toxic symptoms (i.e., nausea, vomiting, anorexia, fatigue, visual disturbances, etc.) before the administration of calcium gluconate. Serum levels of Digalen were not available.

Two additional cases were reported by Shrager in 1957, in which 2 patients each received 10 cc of 10% calcium gluconate to treat hypocalcemia (13). Both patients were "fully digitalized." We interpret the term "fully digitalized" to imply adequate rate control, but this is just speculation on our part. The first patient died approximately 10 min after the calcium was administered, and the second patient developed bigeminy and died 3 days after the first administration of calcium. The fifth case involved an 88-year-old woman who presented complaining of weakness for 3 days (14). She had renal insufficiency, a serum potassium concentration of 6.4 mEq/L, and a digoxin level of 6.2 ng/mL. Five hours after arrival she received 30 g kayexalate per rectum, 10 units intravenous insulin, ½ amp of intravenous 50% dextrose, and 1 amp of calcium chloride. She was found asystolic 15 min later. Although three of these five case reports indicate a temporal association between the administration of calcium and death, none provides good evidence for a cause-and-effect relationship.

There have previously been other case reports of patients receiving intravenous calcium for unrecognized digoxin toxicity without any adverse effects (15,16). In addition, animal studies mimicking acute digoxin toxicity have failed to demonstrate any adverse outcomes (4). The previous animal studies that indicated increased toxicity are not generalizable to clinical practice. In the study by Gold and Edwards, as well as the study by Nola and colleagues, the animals were made hypercalcemic before the administration of any cardiac glycoside (9,12). In the study by Nola, a synergistic effect between calcium and digoxin was observed only once serum calcium levels were > 15 mEq/L (20 mg/dL). No increased toxic effect was observed with lower serum calcium levels.

Lown and colleagues reviewed the relationship between calcium and digoxin and found no relationship (17). They report that digitalis toxic dysrhythmias were only precipitated by calcium in the setting of severe hypercalcemia (up to 23 mEq/L), once digoxin was infused at up to 95% of the "toxic dose." Although they did not define "toxic dose," we presume it meant the LD_{50}.

Prior studies demonstrate that mortality among digoxin-intoxicated patients ranges from 6.2% to 41% (18–20). As in our study, previous investigators found that many of the deaths were not the result of digoxin toxicity. For example, Antman et al. described 43 deaths, yet 32 of these patients had either complete or partial improvement in the toxicity at the time of death; the majority of the deaths were "ascribed to underlying heart disease still present after resolution of the digitalis toxicity or to other medical illness" (18).

In previous studies, hyperkalemia was associated with increased mortality among digoxin-intoxicated patients. Bismuth and colleagues examined 115 patients with acute digoxin intoxication; in their study, no patient who had a serum potassium above 5.5 mEq/L survived, whereas no patient in whom the initial serum potassium was $<$ 5.0 mEq/L died (21). In our study, we found a significant relationship between peak serum potassium concentration and death, with an increased odds of death of 1.5 for each mEq/L. However, when we arbitrarily dichotomized these data into "markedly high" vs. "not markedly high," using a cutoff of 5.5, the statistical significance was obscured. It should be noted that Bismuth's study involved acute digoxin toxicity, whereas our study primarily involved chronic digoxin toxicity.

Limitations

In our study, only one of the cases represented a single, acute ingestion. All cases of toxicity in our study were from digoxin. There were no identified cases of any other medications (i.e., oubain or digitoxin), or from any plant ingestions (i.e., foxglove, lily of the valley, oleander, or red squill). In addition, no cases resulted from a topical application of *Bufo* toad secretions, which can also cause digoxin-like toxicity (22,23). Lastly, no cases involved children. Although these factors might limit the generalizability of the study, we believe that our patient population is representative of most adult patient populations, and plant or animal exposures would account for very few, if any, cases of cardiac glycoside intoxication in most centers.

The risk of ventricular dysrhythmias may be greater in the acute digoxin-toxic patient than in the chronic digoxin-toxic patient. Thus, the administration of calcium to treat hyperkalemia in the chronic digoxin-toxic patient may be less dangerous than if it is used in the acute digoxin-toxic patient. However, there are no data supporting this hypothesis. Thus, although we demonstrated safety with the administration of calcium to the chronic digoxin-toxic patient, the results may not be able to be extrapolated to the patient with acute digoxin toxicity.

Our study identified patients via a search of discharge diagnoses and a search of a laboratory database for all digoxin levels above 2.0 ng/mL. Patients can be digoxin toxic and have serum levels in the therapeutic range, but most patients with digoxin toxicity have a mean serum concentration above 2.0 ng/mL when measured 6 h post-ingestion (3). It is possible that we missed some patients who had recognized digoxin toxicity as a diagnosis other than a primary or secondary diagnosis, and had a peak digoxin level $<$ 2 ng/mL. We feel this scenario is rare, and is unlikely to have significantly affected our conclusions. The obvious question in a retrospective study is: how can one differentiate digoxin toxicity simply from an elevated digoxin level? In our study, the diagnosis of digoxin toxicity was made by either a board-certified emergency physician or a board-certified cardiologist. The fact that 2220 charts were reviewed and only 161 patients were felt to be digoxin toxic implies that the treating clinicians were able to differentiate digoxin toxicity from simply an elevated digoxin level. No patient was included simply based on a level; all patients were felt by the treating clinician to have signs or symptoms consistent with digoxin toxicity. Thus, the diagnosis of digoxin toxicity was made in the 161 patients included in our study. The other 2059 patients who were not included in the study were felt to have an elevated digoxin level without evidence of toxicity. Although it is theoretically possible that a few patients who were included in the study merely had elevated digoxin levels without a clinical diagnosis of digoxin toxicity, we feel this is relatively rare given the clinical diagnosis documented in the medical record.

Our study was limited by its retrospective design. However, most of the data we abstracted were simple and objective (e.g., calcium or no calcium, lived or died, serum potassium or digoxin concentration).

CONCLUSION

In this retrospective study of all patients admitted to a single institution with a diagnosis of digoxin toxicity, we identified no patient who developed a potentially fatal dysrhythmia within 4 h of intravenous calcium administration. Mortality among the 23 patients who received calcium during a period of digoxin-associated hyperkalemia did not differ from mortality among the 136 who did not receive calcium. We question the "stone heart"

theory, and suggest that intravenous calcium may not be harmful in digoxin-intoxicated patients.

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