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Journal of Clinical Epidemiology 56 (2003) 646–650

Journal of Clinical Epidemiology

Digoxin therapy and the risk of primary cardiac arrest in patients with congestive heart failure
Effect of mild–moderate renal impairment

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Abstract

Background and Objective: The cardiac safety of digoxin therapy for congestive heart failure (CHF) is a source of concern, especially among those with renal impairment.

Methods: Using a case–control design, we examined the risk of primary cardiac arrest (PCA) associated with digoxin therapy within three levels of renal function.

Results: After adjustment for other clinical characteristics, digoxin therapy for CHF was not associated with an increased risk of PCA [odds ratio (OR) = 0.97, 95% confidence interval (CI) 0.59–1.62] among patients with normal renal function (serum creatinine ⩽1.1 mg/dL). In contrast, digoxin therapy was associated with a modest increase in risk (OR = 1.58, CI 0.89–2.80) among patients with mild renal impairment (serum creatinine = 1.2–1.4 mg/dL); and a twofold increase in risk (OR = 2.39, CI 1.37–4.18) among patients with moderate renal impairment (serum creatinine = 1.5–3.5 mg/dL).

Conclusions: These findings suggest that the risks of digoxin may offset the benefits among patients with moderately impaired renal function, but not among patients with normal renal function.

Keywords: Heart arrest; Digoxin; Kidney; Heart failure

1. Introduction

Although treatment with digoxin has been a cornerstone of drug therapy for congestive heart failure (CHF) for more than a half century, questions remain about its efficacy and cardiac safety [1–3]. In the Digitalis Investigation Group (DIG) trial, a large clinical trial designed to determine the effects of digoxin therapy for CHF on mortality and morbidity, treatment with digoxin was not associated with a reduction in overall mortality, in part, because of an increased risk of death due to cardiac causes other than heart failure, including mortality from cardiac arrest [4]. In contrast, digoxin therapy was associated with a reduction in hospitalization for CHF.

Because digoxin therapy alters cardiac conduction, it may potentially cause life-threatening arrhythmias [5]. Digoxin is excreted primarily by the kidney. Consequently, the clearance of digoxin is reduced in the presence of renal impairment [6]. Indeed, digoxin toxicity, including the occurrence of cardiac dysrhythmias, has been reported among patients with renal insufficiency [7,8]. For this reason, current clinical recommendations are to reduce the dose of digoxin in patients with mild-moderate impairment of renal function.

Prior studies in patients with CHF have not focussed on the cardiac safety of digoxin therapy as it relates to out-of-hospital primary cardiac arrest (PCA). Additionally, it is

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0895-4356/03/$ – see front matter
doi: 10.1016/S0895-4356(03)00075-1

unknown whether the cardiac safety of digoxin therapy differs among CHF patients with normal and mild–moderate impairment of renal function. To address these questions, we examined whether digoxin therapy for CHF was associated with an increased risk of out-of-hospital PCA in patients with normal and mild–moderate impairment of renal function, after taking into account other clinical characteristics.

2. Methods

2.1. Study setting and design

The data used in this analysis is part of a larger population-based case–control study that examined potential clinical and medication determinants of PCA among patients who received their health care at a staff-model Health Maintenance Organization (HMO) with an enrollment of over 350,000 people, 80% of whom live within a single county. The study was approved the investigators' institutional review committee.

2.2. Study subjects

Cases were all HMO enrollees who experienced an incident PCA during a 15-year period (January 1, 1980 to December 31, 1994) and had had a prior physician diagnosis of CHF based upon medical record review. PCA was defined as the occurrence of a sudden pulseless condition without a known noncardiac cause [9,10]. Cases were initially identified from either emergency medical service incident reports or the HMO's death records. All cases were confirmed by a review of the ambulatory care medical record to ensure that the PCA event was due to heart disease. As part of the case definition, we excluded those who had had prior life-threatening noncardiac conditions, including end-stage kidney disease, end-stage liver disease, metastatic cancer, brain tumor, or respiratory failure. We also excluded potential cases who (1) were <18 or >79 years old, or (2) had been enrolled in the HMO for <1 year or had less than visits for ambulatory care prior to their index date. For this analysis, we also excluded cases who had not filled a prescription for digoxin or nitroglycerin, pharmacologic markers of prior clinically diagnosed heart disease, at an HMO pharmacy during the year prior to their index date. The date of the PCA was the case patient's index date.

Control patients were a stratified random sample of HMO enrollees who had had a prior physician diagnosis of CHF based upon a medical record review. The strata used for sampling control patients included age (in decades), gender, and calendar year. Control patients were assigned an index date randomly chosen from the distribution of index dates among the case patients. We excluded potential control patients who (1) were <18 or >79 years old, or (2) had been enrolled in the HMO for <1 year or had less than visits for ambulatory care prior to their index date. We also excluded potential controls who had not filled a prescription for digoxin or nitroglycerin at an HMO pharmacy during the year prior to their index date.

We also excluded case and control patients who had had a serum creatinine level >3.5 mg/dL prior to their index date, because we sought to focus on the potential effect of mild–moderate impairment of renal function on the risk associated with digoxin therapy. Of the 978 CHF patients who (1) received care at the HMO, (2) were identified as cases of PCA during the study period or sampled as potential controls, and (3) met the inclusion criteria for this analysis, 935 (95.6%) had complete information on clinical characteristics (described below). Because of the population-based case–control design and the relatively low prevalence of CHF in the HMO population, we used commonly used drugs (treatment with digoxin or nitroglycerin during the year prior to the index date) as markers to conduct a preliminary screen of automated pharmacy records for evidence of prior heart disease for both cases and controls as noted above. As expected, among patients with prior heart disease, CHF was associated with an increased risk of PCA. For these reasons, there are more case patients ($n = 573$) than control patients ($n = 362$) in this analysis.

2.3. Assessment of exposures

The HMO's computerized pharmacy database was used to assess treatment with digoxin and other medications. The pharmacy database includes all prescriptions filled for enrollees since 1976. Previous surveys suggested that 98% of all prescriptions for enrollees were filled at pharmacies included in the database. Each pharmacy record includes a patient identifier, the drug type and dose, the date, the quantity dispensed, and dosing instructions. From this information, we estimated whether a patient had received enough digoxin (sufficient numbers of pills) to have been treated with a specific dose on the index date.

The ambulatory medical record of the HMO was used to obtain information on renal function and other clinical characteristics. The record includes not only notes from the ambulatory-care visits, but also results of laboratory and diagnostic tests, discharge summaries of hospitalizations, consultant reports, responses to annual HMO health questionnaires, and updated problem lists. Renal function was determined by using the most recent serum creatinine measurement recorded prior to the index date. At steady state, the serum creatinine is inversely proportional to the glomerular filtration rate, an index of overall renal function [11]. Creatinine measurements were recorded for 98% of patients, with similar proportions of cases (2%) and controls (3%) missing data. Creatinine was measured within 1 year in 77% and within 2 years in 89% of patients. Cases had a shorter interval between creatinine measurement and the index date (median = 110 days for cases and 189 days for controls, $P = .001$).

Other clinical characteristics determined through the review of the ambulatory care medical records included:

age, sex, weight, physician-diagnosed hypertension, diabetes mellitus, angina pectoris (stable and unstable), myocardial infarction, stroke, peripheral vascular disease, atrial or ventricular arrhythmia, congenital or valvular heart disease, coronary revascularization (coronary artery bypass surgery and graft and percutaneous transluminal angioplasty), chronic obstructive pulmonary disease, smoking status, heavy alcohol consumption, and serum potassium. Atrial tachyarrhythmia was defined as atrial fibrillation, paroxysmal atrial tachycardia, or paroxysmal supraventricular tachycardia. The severity of CHF was graded on a 1 to 3 scale, with 1 corresponding to symptoms only with exertion, 2 corresponding to symptoms with activities of daily living, and 3 corresponding to symptoms at rest. The computerized pharmacy database was used to assess treatment on the index date with antiarrhythmic therapy, antihypertensive therapy (beta-adrenergic blocking agents, calcium channel blocking agents, thiazide diuretics, angiotensin-converting enzyme inhibitors), and other medications, such as nitroglycerin and loop diuretics.

2.4. Statistical analysis

We used conditional logistic regression to compute the odds ratios of PCA, an estimate of the relative risk, associated with digoxin therapy at varying levels of renal function. First, we categorized patients into six groups based on digoxin therapy (yes/no) and three levels of renal function (serum creatinine ⩽1.1 mg/dL representing normal renal function, 1.2–1.4 mg/dL representing mild renal impairment, and 1.5–3.5 mg/dL representing moderate renal impairment). After adjusting for other clinical covariates, we estimated the odds ratio of PCA associated with digoxin therapy and the three levels of renal function, compared to the category of "no digoxin therapy, serum creatinine ⩽1.1 mg/d–" (the reference group). We then estimated the odds ratio of PCA associated with digoxin therapy *within* each stratum of renal function after adjusting for other clinical covariates. In the logistic regression models, we examined digoxin therapy as a dichotomous exposure (yes/no) after confirming that the relationships (presented in Tables 2 and 3) were similar for the principal doses of digoxin, 0.125, 0.25, and 0.375 mg/day. To minimize confounding, clinical and demographic characteristics that may affect the serum creatinine, digoxin use, or the risk of PCA were included as covariates in the logistic models [12,13].

3. Results

As expected, case patients were more likely to have a physician diagnosis of diabetes, prior myocardial infarction, unstable angina, peripheral vascular disease, and were more likely to have symptoms related to CHF and smoke than control patients (Table 1). The mean serum creatinine was greater among case than control patients (1.43 ± 0.49 vs. 1.30 ± 0.41 mg/dL, $P = .001$). Because of the stratified random sampling of control patients, the proportions who were male and the mean age were similar among the cases and controls. Impairment of renal function, as reflected by measured serum creatinine levels, was associated with treatment with lower doses of digoxin on the index date [for digoxin dose of 0.0625 mg, mean creatinine = 1.93 mg/dL; for digoxin dose of 0.125 mg, mean creatinine = 1.46 mg/dL; for digoxin dose of 0.25 mg, mean creatinine = 1.31 mg/dL; and for digoxin dose ⩾0.375 mg, mean creatinine = 1.19 ($P = 0.01$ for trend)].

Table 1
Risk factors for primary cardiac arrest according to case–control status among patients with CHF

Risk factor	Case patients ($n = 573$)	Control patients ($n = 362$)
Age ± SD, years	69.4 ± 8.0	70.6 ± 7.4
Men, %	71.1	70.8
Degree of CHF, %		
1	79.8	92.2
2	13.5	7.2
3	6.7	0.6
Diabetes, %	26.0	17.7
Hypertension, %	50.8	51.4
Smoker, %	22.2	16.6
Atrial Tachyarrythmia, %	34.8	41.2
History of myocardial infarction, %	55.0	38.9
Unstable angina, %	8.1	2.3
History of cardiac revascularization procedure, %	13.4	14.6
Stroke, %	11.6	8.7
Peripheral vascular disease, %	31.6	21.7
Antiarrhythmic therapy, %	11.0	12.3

The multivariable-adjusted odds ratios of PCA according to digoxin therapy (yes/no) and the three categories of serum creatinine considered simulataneously is shown in Table 2. As the level of serum creatinine increased, the risk of PCA increased among patients with CHF treated with digoxin therapy; but there was little evidence of an increase in risk of PCA in relation to serum creatinine among patients with CHF who were not treated with digoxin. The risk of PCA associated with digoxin therapy within each of the three levels of renal function is shown in Table 3. There was little evidence of an increased risk of PCA associated with digoxin therapy among patients with CHF and normal renal function (among those with a creatinine ⩽1.1 mg/dL, OR = 0.97, 95% CI, 0.59 to 1.62). In contrast, treatment with digoxin was associated with a modest increase in the risk of PCA in the setting of mild renal impairment (among those with a serum creatinine 1.2 to 1.4, OR = 1.58, 95% CI, 0.89 to 2.80) and more than a twofold increase in risk in the setting of moderate renal impairment (among those with a serum creatinine 1.5–3.5, OR = 2.39, 95% CI 1.37 to 4.18). The estimates of risk associated with digoxin therapy were similar when the cut points (upper limits) of the categories of serum creatinine were increased or decreased by 0.1 mg/dL.

Table 2
The odds ratio of PCA according to renal function and digoxin therapy status among patients with CHF

Serum creatinine (mg/dL)	Digoxin therapy							
	No				Yes			
	Cases (*n*)	Controls (*n*)	Odds ratio[a]	95% CI	Cases (*n*)	Controls (*n*)	Odds ratio[a]	95% CI
⩽1.1	66	58	1.0	—	111	95	0.98	0.59, 1.64
1.2–1.4	54	41	1.02	0.55, 1.87	120	71	1.60	0.94, 2.74
1.5–3.5	61	44	1.12	0.61, 2.08	161	53	2.70	1.52, 4.82

[a] After adjustment for age, weight, gender, hypertension, active smoking, atrial tachyarrhythmia, diabetes, unstable angina, myocardial infarction, stroke, peripheral vascular disease, coronary revascularization, and interval between creatinine measurement and index date.

We assessed whether the findings represented a nonspecific effect associated with the use of medication among patients with mild to moderate renal impairment. We evaluated the risk of PCA associated with treatment with nitroglycerin and loop diuretics stratified by renal function, and found no evidence of an increased risk of PCA associated with these treatments in the setting of mild–moderate renal impairment. We also assessed whether concurrent therapies or other factors that may affect the toxicity of digoxin might account for the observed effect of renal impairment on the risk associated with digoxin therapy. The results were altered only slightly by adjustment for serum potassium level, CHF severity, number of physician visits in the year prior to the index date, chronic obstructive pulmonary disease, alcohol use, or treatment with antiarrhythmic agents (quinidine, procainamide, flecainide, or ecainide), beta-adrenergic blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, or diuretics. Similarly, the inclusion of other medication-renal function interactions in the model altered the estimates associated with digoxin only minimally.

Restriction of the investigation to subjects with CHF severity of grade 1 or 2, a creatinine ⩽2 mg/dL, a creatinine measurement within 2 years of the index date, or inclusion of case subjects ascertained initially by emergency medical service incident reports or the HMO's death records provided similar results. Likewise, exclusion of those patients recently started on digoxin (3 and 6 months prior to index date) in whom the indication for digoxin treatment may have been recent clinical deterioration did not change the study findings.

Table 3
The odds ratio of PCA according to digoxin therapy status stratified by renal function among patients with CHF[a]

Serum creatinine (mg/dL)	Digoxin therapy		
	No	Yes	
	Odds ratio	Odds ratio	95% CI
⩽1.1	1.0	0.98	0.59, 1.64
1.2–1.4	1.0	1.58	0.89, 2.80
1.5–3.5	1.0	2.40	1.37, 4.22

[a] The reference group for each renal function strata (odds ratio = 1) are those not receiving digoxin therapy. After adjustment for age, weight, gender, hypertension, active smoking, atrial tachyarrhythmia, diabetes, unstable angina, myocardial infarction, stroke, peripheral vascular disease, coronary revascularization, and interval between creatinine measurement and index date.

4. Discussion

Our findings suggest that in the setting of normal renal function, digoxin therapy in patients with CHF was not associated with an increased risk of PCA (OR~1), after adjustment for clinical covariates. In contrast, in the setting of moderate renal impairment (creatinine = 1.5 to 3.5 mg/dL), digoxin therapy was associated with a twofold increase in the risk of PCA. The observation that moderate renal impairment modified the effect of digoxin as it relates to PCA is both a clinically and biologically plausible drug–morbidity interaction. This result has significant clinical implications given that approximately 25% of control patients with CHF had creatinine levels ⩾1.5 mg/dL, a proportion similar to other clinical reports [14,15]; and that an estimated one-third of patients with CHF in the United States are treated with digoxin [1].

We explored possible mechanisms to explain the increased risk of PCA among those receiving digoxin therapy with moderate impairment of renal function. Although hypokalemia has been associated with digoxin-induced arrhythmia [16], adjustment for serum potassium did not alter the findings of our analysis. Indeed, in our study population, potassium tended to increase as renal function declined. We were unable to detect a dose–response relationship between the dose of digoxin and the risk of PCA, possibly because patients with worsening renal insufficiency were more likely to receive a lower dose of digoxin or have higher potassium levels. Finally, the association may be explained in part if worsening renal function were simply a marker for more advanced heart failure and those with advanced disease were more predisposed to the arrhythmic effects of digoxin. The DIG trial, however, found that the overall mortality effects of digoxin therapy in patients with CHF and normal sinus rhythm did not differ significantly by the

degree of systolic dysfunction (ejection fraction ≤45% compared to >45%) [4]. Additionally, adjustment for severity of heart failure symptoms altered the findings in this report only slightly.

Several limitations of our study need to be considered. Our study assessed whether renal impairment modified the association of digoxin therapy and PCA in persons with physician-diagnosed CHF. Given the design of the study, we were not able to assess the overall association between digoxin and PCA. However, as our findings indicate, the overall risk of PCA associated with digoxin will likely underestimate the risk in some patients and overestimate the risk in others. This analysis was restricted to those patients with CHF who had filled a prescription for digoxin or nitroglycerin during the year prior to their index date, because these two drugs were common markers of prevalent clinically diagnosed heart disease during the study period. In a preliminary study, we demonstrated that 80% of HMO patients with a clinical diagnosis of heart disease were treated with these drugs. Additionally, during the study period, approximately 90% of patients with CHF enrolled in the HMO had received a prescription for digoxin or nitroglycerin in the year prior to the index date. Despite efforts to minimize confounding both in the design and analysis of the study data, we cannot exclude the possibility of uncontrolled confounding. Given the time frame of the study, few patients with CHF included in this analysis received angiotensin-converting enzyme inhibitors or beta-adrenergic blockers, treatments known to lower mortality. Whether these treatments would modify the relationships seen in this study is unknown, although angiotensin-converting enzyme inhibitors reduce glomerular perfusion pressure and thus may preserve renal function [17]. On the other hand, treatment with lower doses of digoxin, as recommended clinically, was common in the setting of mild–moderate renal impairment at the HMO. Nevertheless, digoxin therapy was associated with an increased risk of PCA in the setting of mild–moderate renal impairment.

We found that digoxin therapy for CHF was not associated with an increased risk of PCA in the setting of normal renal function. In contrast, in the setting of moderate renal impairment, digoxin therapy was associated with more than a twofold increase in the risk of PCA; suggesting that the cardiac safety of digoxin therapy as it relates to PCA depends on renal function. Consequently, clinicians need to reconsider the importance of moderate renal impairment as a potential contraindication to digoxin therapy. Clinicians should optimize alternative medical therapies such as angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, angiotensin receptor blockers, and spironolactone for patients with renal insufficiency and CHF. Although these results need to be confirmed, the findings suggest that a specific patient characteristic, the serum creatinine, can help minimize the risks and maximize the benefits of digoxin therapy in patients with CHF.

Acknowledgments

This work was supported by the Seattle Medic One Foundation and a grant from the NHLBI 5 RO1 HL 42456.

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