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Inappropriate use of digoxin in patients presenting with digoxin toxicity

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Abstract

Background Digoxin remains widely used today despite its narrow therapeutic index and toxicity. The objective of this study was to investigate the percentage of inappropriate use of digoxin and long-term outcomes of elderly patients hospitalized for digoxin toxicity. **Methods** The study included 99 consecutive patients hospitalized for digoxin toxicity. The other study criteria for the inappropriate use of digoxin was regarded if participants having depressed left ventricular systolic function (ejection fraction < 45%) who were not on optimal medical therapy including beta-blocker and angiotensin-converting-enzyme inhibitor therapy or if participants having permanent AF who were not on optimal beta-blocker therapy. **Results** Appropriate digoxin usage was confirmed in 33 of patients in spite of its narrow therapeutic index. A total of 16 of 99 patients died, with a mean follow-up time of 22.1 ± 10.3 months. **Conclusions** Contrary to popular belief, the rate of inappropriate digoxin usage remains high. On account of its narrow therapeutic index and toxicity, digoxin should be used more carefully according to the current evidence and guidelines.

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Keywords: Digoxin; Ejection fraction; Indications; Toxicity

1 Introduction

Digoxin remains widely used today despite its narrow therapeutic index and toxicity. According to the current guidelines, digoxin is recommended in patients with an ejection fraction (EF) ≤ 45% and persisting symptoms [New York Heart Association (NYHA) class II–IV] despite treatment with a beta-blocker, an angiotensin-converting-enzyme (ACE) inhibitor.[1] Digoxin is indicated in patients with permanent atrial fibrillation (AF), heart failure and left ventricular dysfunction, and inactive patients.[2] The objective of this study was to investigate the percentage of inappropriate use of digoxin and long-term outcomes of elderly patients hospitalized for digoxin toxicity.

2 Methods

2.1 Study design

The study included 99 consecutive patients hospitalized for digoxin toxicity from 1 January to 1 December, 2012 at the Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Hospital. A digital 12-lead standard electrocardiogram (ECG) was obtained immediately after admission. Demographic and clinical data including age, sex, blood pressure, diabetes mellitus, hyperlipidemia, hypertension, NYHA class, laboratory data, digoxin plasma concentration, and medication use were assessed at baseline. Left ventricular ejection fraction was evaluated by transthoracic echocardiography immediately after admission. Informed consent was obtained from each patient involved in this study. The study was approved by the Institutional Ethics Committee. Clinical follow-up was performed by telephone interviews with the patient and/or relatives and by review of hospital medical records.

2.2 Study criteria for inappropriate use of digoxin and toxicity

The study criteria for the inappropriate use of digoxin was permitted whether participants had transient AF, or they had preserved left ventricular (LV) systolic function (EF > 45%). Also, the inappropriate use of digoxin was permitted whether participants with depressed systolic LV who are not on optimal medical therapy (beta-blocker and ACE inhibi-

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tor), or participants with permanent AF who are not on optimal beta-blocker therapy. A normal digoxin level was not considered as an excluding criteria for toxicity due to the fact that the normal plasma concentration cannot exclude the toxicity.[3] Clinical diagnoses, such as loss of appetite, nausea, vomiting, diarrhea, headaches, visual disturbance, confusion, fatigue and ECG finding was used for exclusion.

2.3 Statistical analysis

All statistical analyses were carried out using SPSS, version 21.0 (SPSS for Mac; SPSS Inc., Chicago, Illinois, USA) and a P value less than 0.05 was considered statistically significant. Categorical variables are expressed as n (%) and continuous variables are expressed as mean ± SD. Continuous variables were checked for the normal distribution assumption using the Kolmogorov–Smirnov statistics. Differences between patients and control participants were evaluated using the two-sample t-test and the Mann–Whitney U-test as appropriate. Categorical variables were tested using Pearson's X^2 test and Fisher's exact test.

3 Results

The study included 99 consecutive patients hospitalized for digoxin toxicity. Their baseline demographic and clinical data are presented in Table 1. The mean age of the patients was 78.8 ± 9.7 years old and seventy-five patients (76%) were female. A total of 91 of 99 patients had permanent AF and left ventricular systolic dysfunction was seen in 44 (44%) of patients. A total of 91 (91%) of 99 patients had gastrointestinal complaints, such as loss of appetite, nausea, vomiting, and diarrhea. Appropriate digoxin usage was confirmed in 33 (33%) of patients in spite of its narrow therapeutic index.

Laboratory parameters of the study population are presented in Table 2. The mean digoxin plasma concentration of the patients was 3.34 ± 1.23 ng/mL. Digoxin plasma concentration was 3.61 ± 1.27 ng/mL in patients taking 0.25 mg daily. On the other hand, digoxin plasma concentration was 2.93 ± 1.06 ng/mL in patients taking 0.125 mg daily. The correlation between the digoxin plasma concentration and the dose of digoxin was found to be r = 0.26 (P = 0.01). Besides, the correlation between the digoxin plasma concentration and the creatinine level was found to be r = 0.29 (P = 0.01). However, there was no correlation between the digoxin plasma concentration and age (r = 0.01, P = 0.95).

In-hospital and long-term adverse cardiac events are presented in Table 3. A total of 16 (16%) of 99 patients died, with a mean follow-up time of 22.1 ± 10.3 months.

Table 1. Baseline characteristics of study population

Characteristics	Study group (n = 99)
Age, yrs	78.8 ± 9.7
Female gender	75 (76%)
AF	91 (91%)
Hypertension	86 (87%)
Diabetes	18 (18%)
Hyperlipidemia	16 (16%)
Coronary artery disease	43 (43%)
LV sistolic dysfunction	44 (44%)
Chronic renal failure	30 (30%)
Admission complaints	
Gastrointestinal complaints	91 (92%)
Syncope/Presyncope	5 (5%)
Palpitation	1 (1%)
Visual disturbance	2 (2%)
Previous medications	
Acetylsalicylic acid	68 (68%)
Warfarin	31 (31%)
Beta blockers	57 (58%)
Calcium channel blockers	35 (35%)
ACE-I	47 (47%)
ARB	8 (8%)
Potassium-sparing diuretics	24 (24%)
Loop diuretics	23 (23%)
Statins	19 (19%)
NYHA class 1	14 (14%)
NYHA class 2	21 (21%)
NYHA class 3	8 (8%)
NYHA class 4	1 (1%)
Previous digoxin dosage	
0.25 mg/d	61 (61%)
0.125 mg/d	38 (38%)
Indications for digoxin treatment	
LV systolic dysfunction with AF	33 (33%)
LV systolic dysfunctionwithout AF	8 (8%)
AF without LV systolic dysfunction	58 (58%)
Appropriate digoxin usage	33 (33%)
Inappropriate digoxin usage	66 (66%)
LV ejection fraction (%)	48.7 ± 12.4

Parametric variables are reported in mean ± SD or n (%). ACE-I: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB; angiotensin receptor blocker; LV: left ventricular; NYHA: New York Heart Association.

Five patients represented in-hospital mortality, who had documented ventricular tachycardia/ventricular fibrillation.

Table 2. Laboratory parameters of the study population.

Characteristics	Study group, *n* = 99
BUN, mg/dL	37.3 ± 23.7
Creatine, mg/dL	1.43 ± 0.73
AST, U/L	24 (10)
ALT, U/L	16 (8)
Na, mmol/L	137 ± 5.8
K, mmol/L	5.1 ± 4.1
Mg, mg/dL	2.2 ± 0.9
Ca, mg/dL	8.8 ± 1.9
TSH, μIU/mL	1.5 (1.4)
Digoxin, ng/mL	3.34 ± 1.23

Parametric variables are reported in mean ± SD or median (interquartile range). AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Ca: calcium; K: potassium; Mg: magnesium; Na: sodium; TSH: thyroid stimulating hormone.

Table 3. In-hospital and long-term adverse cardiac events.

Cardiac events	Study population (*n* = 99)
In-hospital mortality	5 (5%)
Long-term mortality	11 (11%)
Total mortality	16 (16%)
Temporary pacemaker implantation	11 (11%)
Permanent pacemaker implantation	8 (8%)
Cardiopulmonary arrest	6 (6%)

Data are presented as n (%).

During the follow-up, 11 patients died, six of whom had been hospitalized for acute ischemic stroke. In the remaining five patients, sudden cardiac death occurred. As shown in Table 3, eleven of patients required temporary pacing, and eight patients required permanent pacing.

The study population was divided into two groups: group 1 (n = 33) prescribed digoxin therapy with appropriate indication, and group 2 (n = 66) prescribed digoxin therapy with inappropriate indication, as shown in Table 4. In-hospital mortality in groups 1 and 2 was 6% (n = 2) and 5% (n = 3), respectively (P = 0.75). All-cause mortality at long-term follow-up in groups 1 and 2 was 6% (n = 2) and 14% (n = 9), respectively (P = 0.26). There was no significant difference between the two groups with regard to the need for temporary pacing (P = 0.82), and the need for permanent pacing (P = 0.61).

4 Discussion

The objective of this study was to investigate the percentage of appropriate use of digoxin and long-term outcomes of elderly patients hospitalized for digoxin toxicity. Despite the recommended dosage of digoxin is 0.125 mg daily, especially in the elderly, and patients with impaired renal function;[4] the number of patients taking 0.125 mg daily was only 38, (Table 1). Serum digoxin level is also useful to allow adjustment of dosage.[5,6] Lindenfeld, *et al.*[5] determined decreased mortality in men as long as the digoxin plasma concentration was maintained between 0.5 ng/mL and 1.0 ng/mL. They also showed higher risk (23%) of death among women. There is also evidence that digoxin may be harmful in women. In our study, the mean digoxin plasma concentration of the patients was 3.34 ± 1.23 ng/mL, where seventy-five patients (76%) were female.

Table 4. In-hospital and long-term adverse cardiac events in appropriate and inappropriate digoxin usage.

Cardiac event	Group 1 (n = 33)	Group 2 (n = 66)	*P* value
In-hospital mortality	2 (6%)	3 (5%)	0.75
Long-term mortality	2 (6%)	9(14%)	0.26
Total mortality	4(12%)	12(18%)	0.57
Temporary pacemaker implantation	4(12%)	7(11%)	0.82
Permanent pacemaker implantation	2 (6%)	6 (9%)	0.61
Cardiopulmonary arrest	2 (6%)	4 (6%)	0.99

Data are presented as *n* (%).

Digoxin is still widely used despite its limited indication. In light of the current evidence and guidelines, digoxin has not been recommended as first line therapy for patients with systolic heart failure (HF), or permanent AF.[1,2] Digoxin can be used for patients with an EF ≤ 45% and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, an ACE inhibitor.[1] Withdrawal studies[7] and prospective studies, such as the Digoxin Investigator Group (DIG) trial, showed that digoxin reduced hospitalizations.[8] However, they found that digoxin did not affect mortality. Despite this recent evidence, digoxin is still used in patients with systolic HF who are not on optimal medical therapy (beta-blocker and ACE inhibitor). In this study, eight of 99 patients with systolic HF were not on beta-blocker therapy. Moreover, digoxin can be used for patients with permanent AF for control of heart rate at rest, but not during exercise.[2] Digoxin can be combined with a beta-blocker which may be effective either with or without HF, especially with inactive patients. However, digoxin should be used carefully in patients without HF. Nonetheless, a total of 58 of 99 patients without systolic HF were not on optimal beta-blocker therapy. Our study also shows that old habits die hard.

Multiple studies have already reported inappropriate digoxin use in patients with systolic HF. For instance, Aro-

now studied 500 consecutive patients admitted to a nursing home.[9] A total of 96 of 500 patients were receiving digoxin and inappropriate digoxin usage was confirmed in 47%. Ahmed, *et al.*[10] studied 603 older patients hospitalized for HF in whom inappropriate digoxin usage was confirmed in 37% of patients. Biteker, *et al.*[11] investigated inappropriate digoxin usage in elderly patients presenting to an outpatient cardiology clinic and found that forty-eight of the 124 patients receiving digoxin had an inappropriate indication for digoxin use. See, *et al.*[12] showed that an estimated 5156 emergency departmentvisits for digoxin toxicity occurred annually in the United States.

The study was carried out in a tertiary referral hospital in Istanbul and the study population was aged 67–92 years. Therefore, the results should not be generalized to all patients receiving digoxin.

In conclusion, contrary to popular belief, the rate of inappropriate digoxin usage remains high. Due to its narrow therapeutic index and toxicity, digoxin should be used more carefully according to the current evidence and guidelines.

The authors declare that there is no conflict of interest

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