

Inappropriate use of digoxin in elderly patients presenting to an outpatient cardiology clinic of a tertiary hospital in Turkey

Üçüncü basamak bir hastanenin kardiyoloji polikliniğine başvuran yaşlı hastalarda yanlış digoksin kullanımı

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ABSTRACT

Objectives: We investigated the prevalence and indications of digoxin use in elderly patients presenting to a cardiology outpatient clinic of a tertiary hospital in Turkey.

Study design: On a prospective basis, the study included 800 consecutive patients aged 70 or over (mean age 77±6 years) who presented to our cardiology outpatient clinic. There were 124 patients (15.5%) receiving digoxin. All the patients underwent transthoracic echocardiography. Digoxin use was considered inappropriate if the patient had normal left ventricle systolic function or if there was no atrial fibrillation (AF).

Results: The reasons for use of long-term digoxin were persistent AF (n=55, 44.4%), heart failure (HF) (n=51, 41.1%), and paroxysmal AF (n=8, 6.5%). The exact reason could not be determined in 10 patients (8.1%). Digoxin use was based on appropriate indications in 76 patients (61.3%), whereas 48 patients (38.7%) were taking digoxin with inappropriate indications. Of 51 patients for whom HF was the only reason for digoxin therapy, diagnosis of HF was incorrect in 30 patients (24.2%). Other inappropriate indications were paroxysmal AF and undetermined indication for digoxin prescription. Concerning digoxin dose, 24 patients (19.4%) received one tablet (0.25 mg) and 30 patients (24.2%) received a half tablet (0.125 mg) on a daily basis, while 10 patients (8.1%) used six tablets per week with one day off (0.214 mg/day) and 60 patients (48.4%) took five tablets per week with two days off (0.179 mg/day). The median daily dose was 0.182 mg/day. Digoxin dose was higher than the recommended doses for elderly patients in 75.8% of the patients.

Conclusion: Our findings show that nearly 40% of elderly patients receive digoxin with inappropriate indications and 75% of these patients take digoxin at higher doses than the recommended doses for this age group.

ÖZET

Amaç: Üçüncü basamak bir hastanenin kardiyoloji polikliniğine başvuran yaşlı hastalarda digoksin kullanım sıklığı ve endikasyonları araştırıldı.

Çalışma planı: Çalışmaya, ileriye dönük bir tasarımla, kardiyoloji polikliniğine başvuran, 70 yaş ve üzerinde (ort. yaş 77±6) 800 ardışık hasta alındı. Bu hastaların 124'ü (%15.5) digoksin kullanmaktaydı. Tüm hastalara transthorasik ekokardiyografi yapıldı. Sol ventrikül sistolik fonksiyonu normal olan ya da atriyal fibrilasyonu (AF) olmayan hastalarda digoksin endikasyonunun yanlış olduğu kabul edildi.

Bulgular: Hastalara uzun dönemli digoksin verilmesinin nedenleri kalıcı AF (n=55, %44.4), kalp yetersizliği (n=51, %41.1) ve paroksizmal AF (n=8, %6.5) idi. On hastada (%8.1) ise digoksin kullanımının kesin nedeni belirlenemedi. Digoksin tedavisinin 76 hastada (%61.3) doğru endikasyonla verildiği görülürken, 48 hastada (%38.7) yanlış endikasyonla digoksin verilmişti. Digoksin tedavisi için tek nedenin kalp yetersizliği olduğu 51 hastanın 30'unda (%24.2) kalp yetersizliği tanısı yanlış tanı olarak kabul edildi. Yanlış endikasyonun diğer nedenleri paroksizmal AF ve endikasyonun belirsizliği idi. Digoksin dozları, 24 hastada (%19.4) günlük bir tablet (0.25 mgr), 30 hastada (%24.2) günlük yarım tablet (0.125 mgr), 10 hastada (%8.1) bir gün ilaçsız haftada altı tablet (0.214 mgr/gün) ve 60 hastada (%48.4) iki gün ilaçsız haftada beş tablet (0.179 mgr/gün) şeklindeydi. Ortanca digoksin dozu 0.182 mgr/gün bulunurken, hastaların %75.8'inde digoksin dozu bu yaş grubu için önerilen dozdan yüksekti.

Sonuç: Bulgularımız, yaşlı hastaların yaklaşık %40'ının digoksini yanlış endikasyonla kullandığını ve bu hastaların %75'inde kullanılan dozun yaşlı hastalar için önerilen dozdan yüksek olduğunu göstermektedir.

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Hear failure is the only major cardiovascular syndrome expected to increase in incidence over the next years.^[1] It is the commonest hospital discharge diagnosis in patients over the age of 65 years and one of the most common causes of disability in the elderly. However, there are limited data regarding optimal drug therapy for HF in the very old and the role of digoxin in the treatment of HF remains controversial. Digoxin should not be used to treat patients with preserved left ventricular ejection fraction or if they have no atrial fibrillation. It should not be used for suppression of AF paroxysms or for acute conversion of AF to normal sinus rhythm. There are two appropriate indications for the use of digoxin (Table 1):^[1,2] (i) Heart failure with a reduced LVEF and symptoms of HF despite use of diuretics, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone receptor blockers; (ii) atrial fibrillation.

Due to its narrow therapeutic index and elimination by the kidneys, elderly patients should be monitored closely when digoxin treatment is initiated. Guidelines recommend an initial digoxin dosage of 0.125 mg daily or every other day in patients >70 years of age.^[1,2] Current evidence suggests that digoxin should be dosed to achieve a serum drug concentration of 0.5 to 1 ng/ml in HF, despite the fact that the conventional therapeutic digoxin concentration is defined as 0.8 to 2 ng/ml. However, there are no reported data on the dosing of digoxin use among Turkish patients.

Abbreviations:

AF Atrial fibrillation
 HF Heart failure
 LVEF Left ventricular ejection fraction

This study aimed to identify which patients receive digoxin treatment, and to determine the median daily doses of digoxin in these patients. For this purpose, we prospectively monitored the prescription of digoxin in a single tertiary hospital in Istanbul.

PATIENTS AND METHODS

Study design

On an observational, single-center, noncomparative basis, we enrolled 800 consecutive patients (aged 70 years or older) who presented to our outpatient cardiology clinic of Haydarpaşa Numune Education and Research Hospital from November 2009 to November 2010. All of the patients were eligible if they were ≥70 years old. The mean age of the patients was 77±6 years and 464 (58%) were females. Age, sex, weight, the presence of AF, HF or both, diagnosis, and reason for admission were recorded. The attending cardiologist recorded demographic characteristics, history of disease(s), electrocardiographic findings, and clinical signs and symptoms. A detailed account of digoxin use was derived including dose, frequency of dosage, time of the last dose, and concurrent medications. Symptoms of probable toxicity were checked by the cardiologist. The study protocol was approved by the regional ethics committee, and all participants gave written informed consent.

Examinations

Each patient underwent a thorough clinical examination, transthoracic echocardiography, evaluation

Table 1. Current recommendations for digoxin use in heart failure and atrial fibrillation^[1,2]

Recommendation class	Statement
Heart failure (HF)	
Class IIa	Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced left ventricular ejection fraction (LVEF) to decrease hospitalizations for HF (Level of evidence: B).
Atrial fibrillation	
Class I	Intravenous digoxin can be used to control heart rate in patients with AF and HF with no accessory pathway (Level of evidence: B); oral digoxin is effective in controlling resting heart rate in patients with AF and is indicated in patients with HF, low LVEF, and in those who are sedentary (Level of evidence: C).
Class IIa	Combination therapy using digoxin and a beta-blocker or nondihydropyridine calcium channel antagonist is reasonable to control heart rate at rest and during exercise (Level of evidence: B).
Class III	Digoxin should not be used as the sole agent for rate control in patients with paroxysmal AF (Level of evidence: B).

Table 2. Baseline characteristics of the patients

	Digoxin user (n=124)			No digoxin (n=676)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			76.1±5.9			77.2±5.8	0.4
Gender							0.6
Male	60	48.4		351	51.9		
Female	64	51.6		325	48.1		
Body mass index (kg/m ²)			27.3±5.3			28.1±5.2	0.12
Smoking							
Never	85	68.6		470	69.5		0.82
Current smoker	25	20.2		136	20.1		0.95
Former smoker	14	11.3		70	10.4		0.86
Medical history							
Systemic hypertension	90	72.6		478	70.7		0.9
Diabetes mellitus	30	24.2		165	24.4		1.0
Coronary artery disease	39	31.5		234	34.6		0.002
Congestive heart failure	39	31.5		88	13.0		<0.001
Cerebrovascular event	14	11.3		65	9.6		0.5
NYHA functional capacity							
Class I	60	48.4		381	56.4		0.58
Class II	48	38.7		214	31.7		0.64
Class III	16	12.9		81	12.0		0.46
Atrial fibrillation on admission	55	44.4		156	23.1		<0.001
Medications							
Angiotensin-converting enzyme inhibitor	52	41.9		252	37.3		0.36
Angiotensin receptor blocker	20	16.1		140	20.7		0.27
Beta-blocker	44	35.5		248	36.7		0.84
Nonpotassium-sparing diuretics	12	9.7		69	10.2		0.15
Potassium-sparing diuretics	9	7.3		55	8.1		0.14
Statin	18	14.5		108	16.0		0.79
Nitrates	9	7.3		39	5.8		0.54
Warfarin	21	16.9		83	12.3		0.19
Aspirin	50	40.3		251	37.1		0.54
Calcium channel blocker	21	16.9		111	16.4		0.89
Serum creatinine (mg/dl)			1.2±1.0			1.1±0.9	0.3
Left ventricular ejection fraction (%)			51.8±12.0			57.6±9.8	<0.001

NYHA: New York Heart Association.

of functional capacity, and 12-lead electrocardiography (0.5 to 150 Hz, 25 mm/sec, 10 mm/mV). Trans-thoracic two-dimensional echocardiograms were obtained from standard parasternal and apical views in the left lateral decubitus position using available equipment (Vivid 3 pro, GE Vingmed, Milwaukee, USA). Left ventricular ejection fraction was mea-

sured with the modified Simpson's rule on two-dimensional echocardiographic tracings obtained in the apical four-chamber view according to the criteria of the American Society of Echocardiography.^[3] Valvular stenosis and regurgitation were evaluated according to the ACC/AHA (American College of Cardiology/ American Heart Association) 2006

guidelines for the management of patients with valvular heart disease.^[4]

Study criteria for appropriate digoxin use

Digoxin use was considered inappropriate if the patient had normal left ventricular systolic function (LVEF \geq 50%) or if there was no AF. Patients with documented AF and those with confirmed left ventricular systolic dysfunction by echocardiography (LVEF <50%) were classified as appropriate candidates for digoxin.

Statistical analysis

Statistical analysis was performed with the SPSS software (version 10.0). Data were presented as mean \pm standard deviation for continuous variables and as percentages for categorical variables. Continuous variables were compared using the unpaired t-test for independent samples, and qualitative variables were compared using the chi-square test. A *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients based on the presence or absence of digoxin use are presented in Table 2. At the time of admission to the outpatient cardiology clinic, 124 patients (15.5%) were receiving digoxin. The reasons for prescribing long-term digoxin therapy were persistent AF (55 patients, 44.4%), HF (51 patients, 41.1%), and paroxysmal AF (8 patients, 6.5%). The exact reason for digoxin use could not be determined in 10 patients (8.1%).

After a thorough evaluation, digoxin use was justified in 76 patients (61.3%) with appropriate indications, and 48 patients (38.7%) were concluded to receive digoxin with inappropriate indications (Fig. 1). Of 51 patients for whom HF was the only reason prompting long-term digitalis therapy, diagnosis of HF was classified as "misdiagnosis" in 30 patients (58.8% in the HF group/24.2% overall) after clinic and echocardiographic evaluation. Other inappropriate indications for digoxin use were paroxysmal AF in eight patients (6.5%), and undetermined reason of use in 10 patients (8.1%). Appropriate indications for digoxin use included AF with or without HF in 55 patients (44.4%) and symptomatic HF with sinus rhythm in 21 patients (16.9%) (Fig. 1).

Comparison of the two patient groups with or without digoxin use showed similar characteristics with respect to demographic parameters (age, gender), concurrent medications, smoking, functional capacity, body mass index, blood pressure, serum creatinine levels, history of cerebrovascular disease, diabetes, and hypertension (Table 2). However, congestive HF and AF were more frequent, and LVEF and prevalence of coronary artery disease were significantly lower in patients on digoxin therapy. Nonischemic dilated cardiomyopathy was more frequent in patients receiving digoxin (69.4% vs. 30.6%, *p*=0.02), whereas ischemic cardiomyopathy was less common (28% vs. 72%, *p*<0.001).

Concerning digoxin dose, 24 patients (19.4%) received one tablet (0.25 mg/day), 30 patients (24.2%) received a half tablet (0.125 mg/day), 10 patients (8.1%) used six tablets per week with one day off (0.214

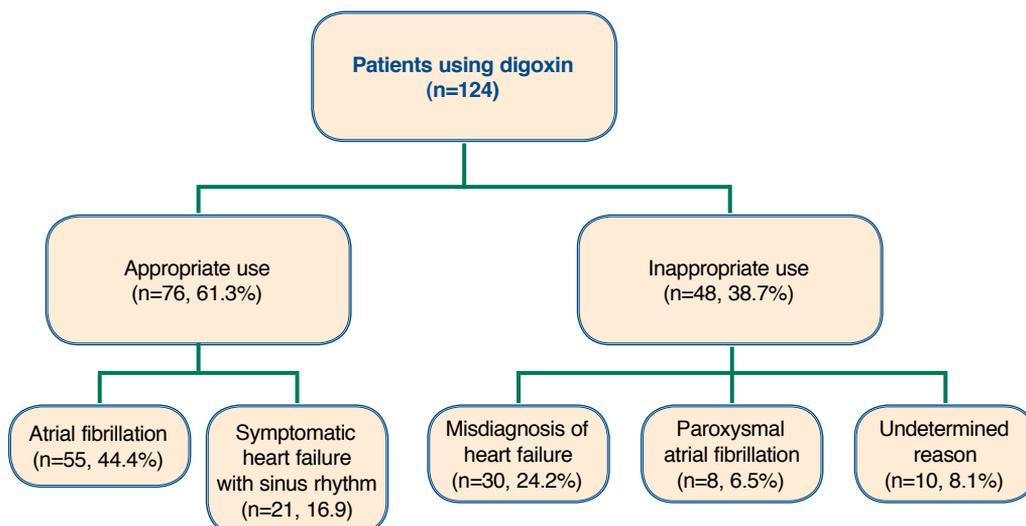


Figure 1. Indications for digoxin use.

mg/day), and 60 patients (48.4%) took five tablets per week with two days off (0.179 mg/day). The median daily dose of digoxin was 0.182 mg.

DISCUSSION

The reasons for prescribing long-term digitalis therapy in our study were HF in 51 patients, AF with or without HF in 63 patients, and undetermined in 10 patients. In as much as 38.7% of the patients receiving digoxin, however, we concluded that the indications for long-term digoxin therapy were wrong, either because the signs of HF, judged by clinic and echocardiographic evaluation, were overestimated or AF occurred only temporarily and did not persist. Furthermore, the median daily digoxin dosage was significantly higher than the recommended doses in the literature in 75.8% of the patients.

Digoxin has been used to treat HF patients for more than 200 years. However, the Digitalis Investigation Group trial cast significant doubt on its prestige in 1997.^[5] This study showed that digoxin did not reduce overall mortality, but did reduce the rate of hospitalization both overall and for worsening HF.

In the light of the current guidelines, digoxin should be used for slowing of a rapid ventricular rate in patients with supraventricular tachyarrhythmias and/or to treat patients with systolic HF and persistent symptoms despite optimal use of diuretics, angiotensin-converting enzyme inhibitors, aldosterone receptor antagonists and beta-blockers to reduce hospitalization for HF (Table 1).^[1,2] Digoxin should not be used to treat patients with HF in sinus rhythm and diastolic HF and should not be used to treat patients with paroxysmal AF.

However, a high prevalence of inappropriate digoxin use has been reported in outpatients.^[6-8] Carlson et al.^[6] examined the reasons for long-term digitalis therapy in 150 outpatients (mean age 68 years) by medical-record review and concluded that 42% of the patients were on long-term digitalis therapy for a questionable reason. Inappropriate use of digoxin was also reported in 47% of elderly patients at the time of admission to a nursing home,^[8] in 43% of older patients in an academic hospital-based geriatrics practice,^[9] and in 59% of older hospitalized HF patients.^[10] Ahmed et al.^[10] studied older hospitalized HF patients with documented left ventricular function and electrocardiography. In this study, 62% of the patients (mean age 79±7 years) were discharged on digoxin, and 37%

had no indication for its use. Half of the patients without an indication for digoxin received the drug. Moreover, digoxin was initiated in 29% of patients who already had no indication.

Digoxin has a narrow therapeutic index and is eliminated by the kidneys. The physiology of normal aging and pharmacokinetic and pharmacodynamic changes explain a portion of the adverse drug reactions observed in the elderly.^[11] Elderly patients are also more likely to be prescribed medications that interact with digoxin. Therefore, the therapeutic window may be much narrower in this population and adverse events are more likely.

On the other hand, the safety and effectiveness of digoxin in elderly HF patients have been documented in a post-hoc analysis of the Digitalis Investigation Group trial.^[12] This study showed that the use of digoxin at low doses (≤ 0.125 mg/day) was a strong predictor of low serum concentrations, which was significantly associated with reduced mortality and hospitalization in the elderly patients. The latest ACC/AHA treatment guidelines for HF recommend an initial dosage of 0.125 mg daily or every other day in patients >70 years of age.^[1] However, there have been no published data regarding the indications for prescribing digoxin and its daily dosage in elderly Turkish patients. Our study showed that 75.8% of elderly patients who were on digoxin therapy were taking digoxin higher than the recommended doses. The median daily digoxin dose was 0.182 mg/day in our study population. The results of our study show that digoxin is frequently used with wrong indications and usually in wrong doses in geriatric population in Turkey. Because physical examination per se is inadequate to assess reduced systolic function, assessment of left ventricular function with echocardiography should be undertaken in elderly patients diagnosed with HF, especially if there is no AF. An educational program to reduce inappropriate and wrong use of digoxin in elderly patients should also be addressed.

A recent study by Lleva et al.^[13] showed that an educational program designed and implemented to reduce inappropriate use of digoxin was very effective. Among 136 patients, (5%) the prevalence of inappropriate digoxin use was 5% (n=7) and the only inappropriate indication was paroxysmal AF.

This study has some limitations. First, the participants were aged 70 years or over, so the results cannot be generalized to other groups. Second, since it was carried out in a single tertiary referral hospital in

İstanbul, which is the most populous city in Turkey, there may be limitations in generalizing the results beyond similar populations. Third, serum digoxin concentrations were not routinely evaluated because of technical difficulties. Finally, LVEF was not measured with any other technique other than transthoracic echocardiography and was not prospectively evaluated.

In summary, inappropriate prescription of digoxin is a common and serious global healthcare problem in older people, leading to increased risk for adverse outcomes. In this study, we showed that nearly 40% of patients aged 70 years or above, presenting to the outpatient cardiology clinic in a tertiary hospital in Turkey were receiving digoxin with inappropriate indications and 75% of these patients were taking digoxin at higher doses than the recommended doses for this age group. An educational program to reduce inappropriate use of digoxin in elderly patients is urgently needed.

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Key words: Atrial fibrillation/drug therapy; digoxin/therapeutic use; drug utilization; heart failure/drug therapy.

Anahtar sözcükler: Atrial fibrilasyon/ilâç tedavisi; digoksin/terapötik kullanım; ilâç kullanımı; kalp yetersizliği/ilâç tedavisi.