Bulletin of Faculty of Pharmacy, Cairo University (2016) xxx, xxx–xxx

Cairo University

Bulletin of Faculty of Pharmacy, Cairo University

www.elsevier.com/locate/bfopcu
www.sciencedirect.com

ORIGINAL ARTICLE

A pharmacokinetic study of digoxin holiday dosing practice in Egypt: A prospective-randomized trial

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Received 24 March 2016; revised 18 April 2016; accepted 20 April 2016

KEYWORDS

Digoxin;
Interrupted regimens;
Atrial fibrillation;
Digoxin holiday;
Quality of life

Abstract *Background:* Because of the narrow therapeutic index of digoxin, most cardiologists in Egypt give digoxin holiday for atrial fibrillation and heart failure, it is not clear if the interrupted digoxin regimens are effective since serum digoxin concentrations might fall below the therapeutic range.

Objective: To evaluate and compare the digoxin serum concentration and patient's quality of life in the continuous versus interrupted digoxin dosing regimens.

Methods: Patients were randomized to receive one of four regimens: regimen 1: 0.25 mg daily except Friday ($N = 17$); regimen 2: 0.25 mg daily except Thursday and Friday ($N = 17$); regimen 3: 0.125 mg daily ($N = 17$); and regimen 4: a tailored dose was calculated based on renal function and given daily ($N = 23$). After reaching steady state in the two holiday regimens, two plasma samples were collected (preholiday and post holiday trough concentrations); in the other two groups one trough plasma sample was collected. Quality of life questionnaire for atrial fibrillation (QLAF), was administered to all patients at baseline and then after at least one month of digoxin therapy.

Results: There was a statistically significant difference between the preholiday trough concentration and the trough steady state concentration across the four regimens ($p = 0.002$). There was no significant difference in the QLAF questionnaire domains, total scores at baseline, or after the follow up between the four regimens.

Conclusion: Once daily tablet (0.25 mg) was suitable in maintaining digoxin serum concentration in the recommended therapeutic range, fluctuation in digoxin serum concentration did not affect quality of life for atrial fibrillation patients.

1. Introduction

Digoxin is a cardiac glycoside prescribed in heart failure and certain supraventricular tachyarrhythmias. It exerts a positive inotropic, neurohormonal, and electro physiologic actions on the heart.[1] For heart failure patients, the targeted steady state

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Peer review under responsibility of Faculty of Pharmacy, Cairo University.

http://dx.doi.org/10.1016/j.bfopcu.2016.04.004

serum digoxin level is between 0.5 and 0.8 ng/ml.[2–6] Ventricular rate control in atrial fibrillation patients will usually require higher digoxin steady state serum concentrations.[1] However, serum digoxin level higher than 2 ng/ml is associated with an increased incidence of adverse drug reactions and should be avoided.[1] Because of inter and intra-patient variability, narrow therapeutic index, and risk of toxicity, digoxin doses are calculated based on patient weight, renal status, indications and drug interactions. Due to substantial overlap between therapeutic and toxic levels of digoxin, therapeutic drug monitoring is a must especially in patients with deteriorating renal function and electrolyte disturbance.[7–9] In Egypt, most cardiologists give a digoxin holiday for patients with atrial fibrillation and/or heart failure where patients skip the drug doses on Thursday and Friday or Friday only every week to avoid possible drug accumulation and toxicity. It is not clear if these interrupted digoxin regimens really offer safer alternative over the continuous dosing regimens without compromising the effectiveness and patient quality of life. It is anticipated that plasma digoxin levels may fall below the therapeutic range during the holiday which may affect patient clinical status.

To the best of our knowledge this is the first study to assess the quality of life (QoL) for atrial fibrillation patients taking different digoxin treatment regimens.

The aim of our study is to evaluate and compare the continuous versus interrupted digoxin dosing regimens by measuring digoxin trough steady state plasma concentrations, evaluating patients' quality of life using quality of life questionnaire for atrial fibrillation patients (QLAF),[10] and using specific structured questions to evaluate signs and symptoms of digoxin side effects and toxicity.

2. Materials and methods

2.1. Patients

Patients with atrial fibrillation (AF) with or without congestive heart failure (CHF) taking digoxin tablets were enrolled from the Egyptian National Heart Institute (NHI) outpatient's clinics, in the period between October 2012 and October 2014. Patients were excluded if they were below 18 or above 70 year old, taking the following drugs concurrently: amiodarone, verapamil, quinidine and propafenone,[6,11–13] diagnosed with thyroid disorders (hyperthyroidism and hypothyroidism), with creatinine clearance less than 10 ml/min, or pregnant. All patients were on interrupted digoxin regimens before the study.

The study protocol was approved by the Faculty of Pharmacy, Cairo University Ethics Committee. Written informed consent was obtained from all patients. Clinical trials.gov identifier (NCT02489786).

2.2. Study design

This was a prospective randomized parallel study. Randomization was done by assigning a number for each subject and using a table of random digits. Patients received one of four regimens; either regimen 1: one tablet (0.25 mg) daily except Friday, regimen 2: one tablet (0.25 mg) daily except Thursday and Friday, regimen 3: half tablet (0.125 mg) daily), or regimen 4: a tailored daily dose was calculated according to the patient's renal function and ejection fraction.

In addition, the following data were collected for each patient: demographics, chief complaint, past medical history, medication history, family history, social history, the previous digoxin dosage regimen, echocardiography, electrocardiogram, serum creatinine, potassium (K^+), calcium (Ca^{++}), and magnesium (Mg^{++}) and physical examination at the study baseline. A specific questionnaire to assess signs and symptoms of digoxin toxicity as nausea, vomiting, diarrhea, loss of appetite, fatigue, uneven heart beats (slow, fast), blurred vision, seeing yellow or green halos around lights or objects, skin rash, bloody black tarry stool was administered at baseline and at least after one month of digoxin therapy. A quality of life questionnaire (QLAF) with domains that assessed the common symptoms and interventions of atrial fibrillation as palpitation, breathlessness, chest pain and dizziness, drugs, direct current cardio version and ablation[10] was administered as well. All patients received the same brand of digoxin tablet (0.25 mg) for at least one month to ensure that the steady state was reached. Monitoring of trough concentrations (immediately before the next dose) was used for therapeutic digoxin monitoring.[14] In the two groups of digoxin holiday, two plasma samples were collected, for regimens 1 and 2 the preholiday trough samples were collected predosing on Thursday and Wednesday respectively while the post holiday trough samples were withdrawn on Saturday for both regimens. In the other two groups, one trough plasma sample was collected at any day of the week. Samples were frozen at −20°C[15] and assayed with Enzyme Linked Fluorescent Assay VIDAS® DIGOXIN, BIOMEREUX SA, France with measurement range 0.2–5 ng/ml. The tailored dose that was calculated and given daily was calculated using JUSKO–KOUP method for digoxin dosing.[16,17] Creatinine clearance in ml/min was estimated from the patient's serum creatinine using Cockcroft and Gault equation.[18] The target steady state (C_{SS}) used in calculating the digoxin dose was 0.9 ng/ml. Digoxin compliance was assessed by phone calling the patients twice weekly.

There is a direct relation between creatinine clearance and digoxin clearance.

$$\mathrm{Cl} = 1.303(\mathrm{CrCl}) + \mathrm{ClNR} \quad (1)$$

where Cl is digoxin clearance in ml/min. CrCl is creatinine clearance in ml/min and Cl_{NR} is the digoxin clearance by non-renal routes which equals 40 ml/min in patients with no or mild heart failure (NHYA CHF class I or II) or left ventricular ejection fraction (LVEF) >45%, and 20 ml/min in patients with moderate or severe heart failure (NYHA CHF class III or IV) or (LVEF) ⩽45%.[16,19,20]

Maintenance dose was calculated using this formula:

$$D/\tau = (C_{SS} * \mathrm{Cl})/F \quad (2)$$

where D is the digoxin dose in μg, τ is the dosage interval in days, C_{SS} is the desired steady state (C_{SS} = 0.9 μg/l) and Cl is digoxin clearance in L/d, F is the bioavailability constant (F = 0.7 for the tablet).[16,17]

2.3. Statistical analysis

Statistical analysis was performed using SPSS software package version 20. Categorical variables were reported as