Pharmacological Reports 70 (2018) 184–189

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original article

Therapeutic drug monitoring of digoxin–20 years of experience

Grzegorz Grześk, Wioleta Stolarek*, Michał Kasprzak, Marek Krzyżanowski, Katarzyna Szadujkis-Szadurska, Michał Wiciński, Elżbieta Grześk

Department of Pharmacology and Therapeutics, Faculty of Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

ARTICLE INFO

Article history:
Received 21 October 2016
Received in revised form 21 August 2017
Accepted 25 August 2017
Available online 30 August 2017

Keywords:
Digoxin
Digitalis glycosides
Serum digoxin concentration
Heart failure
Atrial fibrillation

ABSTRACT

Background: Digoxin is the oldest drug used in the pharmacotherapy of heart failure (HF). However, digoxin remains an important therapeutic option for patients with persistent symptoms of HF occurring despite the implementation of standard pharmacotherapy. Digoxin concentration serum (SCD) should equal 1–2 ng/ml. The aim of our study was to measure of SCD among the hospitalized patients as well as to determine the selected factors influencing the concentration of the digoxin in the blood.
Methods: The presented research was based on a retrospective analysis including 2149 patients treated with digoxin and hospitalized between 1980 and 2000. Was used for the determination of SCD automatic analyzer TDX ABBOTT GmbH – fluorescence polarization immunoassay (FPIA), with therapeutic range for digoxin of 0.8–2.0 ng/ml.
Results: Average SCD result in the study population was located within the therapeutic range and amounted 1.06 ng/ml (55.7% of patients). Statistically significant differences in digoxin level were observed depending on the way of medicine administration ($p = 0.000001$) and the daily amount ($p = 0.001$). Moreover, statistically significant differences in digoxin level were observed depending on sex ($p = 0.00002$).
Conclusions: An elevated level of digoxin was observed in the case of patients who received the medication both orally and intravenously, together with an increase in the daily amount of digoxin doses. It was confirmed that an elevated digoxin level occurs in the course of treatment in the case of women.

Introduction

Properties of digoxin were discovered by an English doctor William Withering. He showed that extracts from foxglove plant leaves support the treatment of edema caused by blood circulation failure. His findings were published in 1785 [1,2]. Digoxin has positive inotropic and batmotropic effect on heart muscle and negative chronotropic and dromotropic effect. The use of digoxin in heart failure (HF) improves heart functions, reduces peripheral resistance, causes venous vasodilation and decreases central venous pressure thus increasing cardiac output [3].

Cardiac glicosides are characterized by a narrow therapeutic range, which makes blood plasma concentration assay a reliable method for checking dosage. Monitoring concentration levels is useful mainly because of small differences occurring between a therapeutic and a toxic dose, as well as because of the possibility of accumulation. In patients taking the medication, therapeutic concentration should be 1–2 ng/ml. Toxic symptoms occur in the case of concentration levels >2.8 ng/ml. The risk of undesirable effects exists even if the full effectiveness level has not yet been reached, particularly in the case of older patients [4]. Toxic symptoms mainly take the form of heart arrhythmias and conduction disturbances (e.g. sinus bradycardia, supraventricular and atrial tachycardia, 1st, 2nd and 3rd degree atrioventricular blocks, ventricular extrasystoles, as well as ventricular tachycardia and ventricular fibrillation) especially with a co-existent hypokalemia. Visual disturbance such as inappropriate perception of colors (yellow as a predominant color) is characteristic for poisoning with the medication [5–7].

The aim of our study was to measure of SCD among the hospitalized patients due to HF, tachycardia and a suspicion of poisoning with digoxin, as well as to determine the selected factors influencing the concentration of the digoxin in the blood.

Materials and methods

Patients

The trial was designed as a retrospective analysis and included 2149 patients treated with digoxin and hospitalized between 1980

* Corresponding author.
E-mail address: wioletaplazuk@o2.pl (W. Stolarek).

http://dx.doi.org/10.1016/j.pharep.2017.08.014
1734-1140/

and 2000 in Kujawy and Pomorze voivodeship. Since 2001, hospital wards stopped the routine monitoring of serum digoxin. Since then determination of the concentration was performed mainly for the purpose of court- medical related poisoning (erroneously or suicide). Therefore, these results were not included in the analysis.

Procedures

All patients underwent determination of the concentration of digoxin in the blood serum (without anticoagulant) taken during hospitalization. Was used for the determination of serum digoxin concentration (SCD) automatic analyzer TDX ABBOTT GmbH – fluorescence polarization immunoassay (FPIA). The therapeutic range for digoxin was established at 0.8–2.0 ng/ml, according to manufacturer's requirements. 2149 cases were analyzed, including 1074 men and 1049 women (Table 1).

Statistics

Statistic software Statistica 10.0 in Polish version (StatSoft, Tulsa, USA) was used to calculate statistical parameters. Shapiro-Wilk test assay revealed that distribution of random variables did not comprise criteria of normal distribution. According to that quantitative variables were shown as medians and quartile ranges. To compare between medians of independent variables Mann-Whitney test, Kruskal-Wallis test and multiple comparison test were performed. Qualitative variables were presented as number of patients with particular feature and as a percent of analyzed group. Comparison between qualitative variables was performed using $\chi 2$. Values $p < 0.05$ were treated as statistically significant. Values $p \geq 0.05$ and <0.10 were treated as a trend towards statistical significance. Values $p \geq 0.10$ as not significant were replaced with shortcut ns (not significant).

Results

2149 cases were analyzed, including 1074 men and 1049 women. Clinical, demographic and anthropometric profile and pharmacotherapy with digoxin of the study population is presented in Table 1. Average age of the study people was 68, average height −165 cm, weight −70 kg. The most common reason for hospitalization was heart failure −34.5%, followed by tachyarrhythmia −4.9% and a suspicion of poisoning with digoxin, including bradyarrhythmia −2.3%. In 58.3% of cases, the reasons for hospitalization were not indicated. The average daily digoxin intake among the examined patients was 0.25 mg. In 57.8% cases it was a single dose, 10.4% took two daily doses, and 1.9% − at least three doses per day. During the hospitalization period 7.2% of the examined patients required additional intravenous digoxin administration. Table 2 presents data concerning digoxin concentration in blood serum assay performed in the case of the study patients. The average SCD result was 1.06 ng/ml and remained within the therapeutic range. Therapeutic range was marked in 55.7% of cases. In 72.8% of cases, a single blood test was carried out to mark digoxin concentration in blood serum. Average time from the beginning of treatment with medication to SCD in blood serum was 12 days, while the average time from the last administration of digoxin to SCD was 16 h.

No statistically significant differences were shown between the marked digoxin level in blood serum and the main cause for hospitalization (Table 3, Fig. 1). Statistically significant differences in digoxin level depending on the way of medicine application were shown ($p = 0.000001$); on average the level of digoxin in the case of intravenous and oral medication application was 1.3 ng/ml (Table 4, Fig. 2). In the case of oral application only, the median was 1.05 ng/ml. Statistically significant differences depending on the number of daily doses were shown, occurring between one dose and at least three doses of digoxin per day ($p = 0.0008$), as well as between two and at least three doses of the medicine per day ($p = 0.002$) (Fig. 3). Higher level of digoxin concentration was observed when the number of doses applied per day was raised ($p = 0.001$) (Table 4). Within the tested population no statisticaly significant differences depending on the number of blood samplings were shown (Table 4). Both in the case of one blood test and in the case of multiple testing SCD median was 1.1 ng/ml. Statistically significant differences depending on the sex of the

Table 1
Clinical, demographic and anthropometric characteristics and pharmacotherapy with digoxin in study population (median (lower quartile-upper quartile) or number (percent)).

Study feature (n = 2149)	Property value
Age (years)	68 (60–77)
Height (cm)	165 (160–170)
Body mass (kg)	70 (60–80)
Sex	
Men	1074 (50.0%)
Women	1049 (48.8%)
unknown	26 (1.2%)
The main reason for hospitalization	
Heart failure	741 (34.5%)
Tachyarrhythmia	105 (4.9%)
Suspicion of digoxin toxicity (including bradyarrhythmia)	50 (2.3%)
Not specified main reason hospitalization	1253 (58.3%)
The daily dose of digoxin (mg)	0.25 (0.25)
The number of doses per day	
1	1242 (57.8%)
2	223 (10.4%)
≥3	41 (1.9%)
No data	643 (29.9%)
Intravenous administration of digoxin	154 (7.2%)

Table 2
Digoxin concentration marking in blood serum in study population (median (lower quartile-upper quartile) or number (percent)).

Study feature	Value
SCD (ng/ml) taking into account multiple measurement (n = 3037)	1.06 (0.72–1.57)
Time period from the last application of digoxin dose to SCD (h) (n = 2149)	16 (6.0–23.0)
Samplings number used for SCD marking (n = 2149)	
1	1563 (72.8%)
2	411 (19.1%)
3	104 (4.9%)
≥4	71 (3.3%)
Time period from the beginning of treatment with digoxin till SCD (days)	12 (6.0–127)
Number of samplings in the given SCD range taking into consideration multiple samplings (n = 3037)	
SCD below therapeutic level (<0.8 ng/ml)	934 (30.7%)
therapeutic level of SDC (0.8–2.0 ng/ml)	1691 (55.7%)
SCD above therapeutic level (2.0 ng/ml)	412 (13.6%)

SDC, serum digoxin concentration.