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Safety and Efficacy of Digoxin Therapy—Where Are We Now?

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Abstract: The aim of our study was to determine the criteria and key factors for the effectiveness of digoxin therapy. A prospective opened-type study was carried out in conditions of everyday clinical practice. The concentrations of digoxin were quantified from blood samples taken following the achievement of drug steady-state (using AxSYM microparticle enzyme immunoassay-MEIA). The risk/benefit ratio was evaluated based upon the correlation between measured blood concentrations of the drug and clinical response. Study results (100 decompensated patients) revealed that therapy indication field was correctly covered, showing a higher prevalence in elderly. On average, each examinee had 2 or 3 comorbidities. Applied daily dose of digoxin ranged from 0.053 mg to 0.25 mg. Renal function was assessed by creatinine clearance which is one of the key factors for the accomplishment of optimal digoxin serum concentrations ($p < 0.05$). Co-administration of seven drugs was complicating factor for the management of rational therapy. 76/100 patients were within referent range (0.8-2.0 ng/mL), while 13/100 were above the upper limit. Four side effects in total were recorded (nausea, vomiting, confusion), whereas in only two patients digoxin was excluded from the therapy. Digoxin confirmed the justifiability of its use in contemporary clinical practice.

Key words: Digoxin, interrupted dosage regimen, risk/benefit ratio.

1. Introduction

Digoxin is a cardiac glycoside, which increases the force of myocardial contractions and reduces conduction velocity at AV node. There are two correct indications for the use of digoxin: HF (heart failure) and AF (atrial fibrillation). Due to its narrow therapeutic index and elimination by the kidneys, elderly patients should be monitored closely when digoxin treatment initiated [1, 2].

It is well-known that digoxin is a difficult drug to administer, because of the lack of a clear relationship between the dose and desired therapeutic effect, its narrow therapeutic range and variation in the pharmacokinetic characteristics of the drug [3].

The variation in digoxin clearance creates difficulties for clinicians in choosing appropriate drug dosage. According to the recommendations, majority of patients should benefit from daily dose of 0.125 to 0.25 mg, while in some patients a dosage of 0.0625 mg or 0.375 mg per day may suffice. As a result of distinct target concentrations for HF and AF, in some guidelines it may be observed that typical dosing regimens are different as well: 0.0625-0.125 mg/day for HF and 0.125-0.25 mg/day for AF [4, 5].

It is common practice among cardiologists to prescribe daily digoxin dosage regimen and interrupted dosage regimen. A digoxin "holiday" is given where the patient is given the dose five or six days a week to minimize digoxin toxicity due to the lack of therapeutic drug monitoring. It is not clear whether this "holiday" is justified in all cases, since digoxin plasma levels might decrease to below therapeutic levels [6, 7].

Some investigators believe that the role of digoxin may need to be redefined, especially in modern age of the heart failure management [8].

Furthermore, therapeutic drug monitoring of digoxin is highly recommended for the purpose of toxicity investigation, patient compliance assessment and in cases of therapeutic failure [9].

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In the past decade, the use of digoxin in therapeutic range from 0.8 to 2 ng/ml has been challenged, especially in management of HF. It is believed, that lower therapeutic dosage range is equally effective in managing of symptoms without exposing patients to an increased risk of toxicity [10].

The aim of our study was to determine the criteria and key factors for the effectiveness of digoxin therapy.

2. Material and Methods

The prospective study was conducted at the Cardiology Clinic, Clinical Centre of University of Sarajevo, Bosnia and Herzegovina. Our study complies with Declaration of Helsinki and was approved by Institutional Review Board of Clinical Centre of University of Sarajevo. We enrolled 100 consecutive hospitalized patients at Cardiology Clinic with AF and/or HF. The inclusion criteria was clinical indication for digoxin administration NYHA class ≥ 2, in patients aged $\geq$ 18 years, both genders. Exclusion criteria were mainly related to absolute or relative contraindication to digoxin, including severe renal insufficiency (creatinine clearance (CLcr) $\leq$ 15 ml/min, hypokalaemia (< 3.5 mmol/L) or hypercalcaemia (> 2.64 mmol/L) (which is not correctable with medical treatment), pregnancy, severe dementia, unwillingness or inability to give inform consent. CLcr was calculated using Cockroft-Gault equation based on TBW (total body weight) [11].

Digoxin dosage regimens were in the form of tablets (Lanibos® tablets, Bosnalijek, Sarajevo, Bosnia and Herzegovina) [12], once a day each day of a week or with off drug period one or two days a week. The Protocol allowed an additional therapy according to contemporary guidelines for the target unchanged digoxin therapy, for the assurance that drug steady-state was reached. Compliance was assessed using interview done by the attending physician.

During regular medical visits, data of patients were collected in Case Report Forms, including demographic characteristics (weight, height, age, gender, information on allergies), clinical data (diagnosis and history of disease, comorbidities), para-clinical data (ECG and echocardiography), laboratory data (serum creatinine, urea, serum transaminases, albumin, INR, status of K, Na, Ca), treatment data (dosing regimen, time of the last dose, concomitant therapy), schedule of blood sampling, digoxin serum concentrations and adverse reactions.

Digoxin dosing regimen was unchanged for at least 3-4 weeks before admitting patients to the Cardiology ward, and thus sampling occurred while patients were hospitalized. Blood samples (three to four per a patient) were taken during one dosage interval (8, 12 hours after the last dose in drug steady-state, just before morning dose (24, 48 or 72 hours), and additional one that was sampled before dosing pause (24 hours after the last administered dose). Exact times of blood sampling were recorded.

We used Abbot AxSYM MEIA (Microparticle Enzyme Immunoassay), techniques for quantitative determination of digoxin in the laboratory of the Clinical Centre. The AxSym imprecision coefficient of variation for the assay was less than 10% and minimum detectable concentration for digoxin was $\leq$ 0.3 ng/mL [13, 14].

Statistical data analysis was carried out using Med Calc Programm for Windows, version 12.6.1.0. (MedCalc Software, Mariarke, Belium). Statistical significance was defined when calculated probability value (p) was less than 0.05.

3. Results

One hundred patients were included in this study. Based on study criteria, two patients were excluded due to toxicity. Study results revealed that therapy indication field was correctly covered, showing a higher prevalence in elderly. On average, each examinee had 2 or 3 comorbidities. Co-administration of seven drugs was complicating factor for the management of rational therapy. The characteristics of

the patients included in the study are presented in Table 1 and concomitant therapy in Table 2.

In this study, we evaluated digoxin regimen as one of several important parameters, which affect digoxin serum concentration. We identified different dosage regimens used in clinical settings. Summary of dosage regimens and digoxin concentrations are presented in Table 3.

Logistic regression was performed to assess the effect of several independent variables (creatinine clearance, urea) on the dependent variable i.e. the concentration of digoxin. The whole model (with all predictors) was statistically significant (χ^2 (3, n = 90) = 14.830, p = 0.002), indicating that model can differ subjects in whom increased digoxin would be found. Table 4 shows all independent variables.

4. Discussion

The reasons for describing digoxin therapy in our study were HF in 33 patients and AF with HF in67 patients what is accordance with recommendations [1, 2].

Table 1 Demographic patients data.

Characteristic	Number (percent)/ Mean ± Standard deviation	Range
Gender		
Male	32 (33%)	
Female	68 (67%)	
Age (years)	72.37 ± 10.6	47-94
Body weight (total) (kg)	80.82 ± 16.5	50-135
Height (cm)	168.48 ± 8.99	145-190
BMI	29.05 ± 5.07	19.5-42.2
CLcr (mL/min)*		
≥ 60, Male, n = 24 Female, n = 23	85.19 ± 24.21	60-166.2
< 60 Male, n = 10 Female, n = 43	41.87 ± 11.1	14.8-59.7
HF	33 (33%)	
Co-morbidity		
- Diabetes	38 (34.8%)	
- Hypertension	72 (66,06%)	
- COPD	29 (26.6%)	
Daily digoxin dose (mg)	0.127 ± 0.057	0.053-0.25

*calculated according to Cockroft-Gault formula which included total body weight.

Table 2 Concomitant drugs.

Drug	Percent of patients
Furosemide (with KCl)	91%
Spironolactone	56%
β-blockers	38%
Acetylsalicylic acid	44%
Calcium channel blockers	25%
Proton pumps inhibitors	48%
ACE inhibitors	20%
Vasodilators	56%
Antidiabetics (insulin and/or oral antidiabetic drugs)	34.6%
Anticoagulant drugs	64%
Statins	36%

Table 3 Relationship between trough digoxin concentration and dosage regimens in two therapeutic (0.8-2 ng/mL i 0.5-1.5 ng/mL).

Regimen	<0.8	0.8-2	>2	No	<0.5	0.5-1.5	>1.5	No
0.125 mg (7/7)	2	11	0	13	0	10	3	13
0.125 mg (6/7)	3	14	1	18	0	14	4	18
0.125 mg (5/7)	2	21	2	25	0	17	8	25
0.125mg (e.o.d.)	2	12	1	15	0	11	4	15
0.25mg (7/7)	1	7	1	9	0	5	4	9
0.25mg (6/7)	1	3	2	6	0	3	3	6
0.25mg (5/7)	0	3	1	4	0	2	2	4
0.25/0.125 mg	0	5	5	10	0	1	9	10
Total	11	76	13	100	0	63	37	100
Intoxication	0	1	1	2	0	1	1	2

7/7: every day 0.25 mg or 0.125 mg; intermittent usage: 6/7: one day pause; 5/7: two days pause (Wednesday/Saturday); e.o.d.: Every other day dose of 0.125 mg; 0.25/0.125mg: one day 0.25 mg/ one day 0.125 mg.

Table 4 The predicting of influence of the several independent variables on digoxin serum concentrations.

Model	B	Standard error	Freedom degree	Significance	Quotient of probability	Interval of 95% confidence for quotient of probability	
						Lower limit	Upper limit
Creatinine clearance*	-0,030	0,01	1	0,006	0,970	0,9495	0,9914
Urea	-0,122	0,07	1	0,070	0,885	0,7748	1,0101
Constant	6,888						

*calculated according to Cockroft-Gault formula which included total body weight.

The narrow therapeutic range of digoxin means that small variations in blood concentration may easily result in toxic or sub therapeutic concentration. To maintain concentrations within the therapeutic range requires consistent bioavailability and careful management of factors that may influence bioavailability [17].

In this study, we demonstrated a variability of achieved digoxin serum concentration, in acceptable guided optimization of digoxin therapy. Six different dosing regimens were applied in this study (Table 3) and efficacy and safety of each of them were determined by monitoring of the drug levels and by clinical signs and symptoms, as well.

There are few published articles that support presence of interrupted dosing regimens in other health systems as well [6, 7, 15, 16]. From our perspective, the main reason for dosing digoxin with drug holiday is in limited availability of strengths lower than 0.25 mg, as other authors agreed as well [6, 7, 16].

We presented that, in addition to kidney function, other factors played a significant role for the serum digoxin concentration. Kidneys have the most important role in digoxin clearance [18-21]. Older patients (Table 1) were the predominant examinees in this study, and with age comes the decrease in functional capacity of renal eliminating system [22]. Renal dysfunction and/ or low lean body mass (body weight minus body fat), may be the subject of a higher risk of digoxin toxicity as decrease in CL/F is accompanied with decrease in volume of distribution of the drug (Vd). This particularly applies to older patients [23, 24]. A study by authors Cusack et al. (1978) showed that mean value of digoxin half-life was significantly prolonged in elderly patients compared to younger ones, and that total clearance was significantly reduced. These observations suggest that dosage interval should be prolonged or maintenance dose lowered [25], what is in accordance with our results. Creatinine clearance was calculated based on Cockcroft-Gault equation.

When we analysed the influence of several factors on digoxin serum concentration, we found that major importance in this had a creatinine clearance with statistical significance (p = 0.006). The reported values of urea had no statistical significance in this model. The model correctly classified 82.22% cases. (Table 4).

The analysis of digoxin serum concentrations before and after the break, we found that there were no clinically or statistically significant decrease in concentration, which is partially in line with previously published results [7]. Authors Sandray et al., in their study recorded a sub-therapeutic concentration after the break in 22.77% of patients, even when that concentration was in the therapeutic range before the break.

The most optimal time for sampling was shown to be just before the next dose, which was consistent with the results of earlier studies [7, 26]. Serum digoxin values, 8 hours after the last dose, were not reliable since we were not sure (according to, the values) that distribution phase had been terminated.

Several different reports refer to the acceptable range of digoxin. Some authors suggest range between 0.8 and 2 [3, 26], while others propose range between 0.5 and 1.5 [27, 28]. In this study, we have examined both ranges; similarly as authors Sadray et al. 2004 did [7].

Based on our results lower digoxin levels (0.5-1.2 ng/mL) are achieved in patients with HF than HF + AF indications what is an accordance with recommendations [29]. The safety and effectiveness of digoxin in elderly HF patients have been documented in a post-hoc analysis of the Digitalis Investigation Group trial [30]. Results of post hoc DIG trial determined that drug concentrations above 1.2 ng/mL in HF patients, increase mortality rate and hospitalizations [30-32]. This study showed that the use of digoxin at low doses was strong predictor of low serum concentrations, which was associated with reduced mortality and hospitalization in elderly patients.

Respectably high proportion of patients (n = 13), belonged to a group in which digoxin serum concentration was above 2.0, while digoxin serum concentration below 0.5 was not recorded even in a one single case. At concentrations above 2, there was a case in which the most common side effects were nausea, vomiting and bradycardia, indicating intoxication. In other patients, concentrations above 2 ng/ml showed a good tolerability i.e. a positive benefit risk ratio. From our experience, it can be concluded that the increase in digoxin concentration above 2 is also acceptable, similarly to results in previously published studies [33, 34]. For better judgment, additional studies with a greater number of respondents are required. The reasons why 13 examinees were in the group of patients having digoxin serum concentration above 2 ng/ml were AF with HF without associated conduction pathways. Results of DIG and other controlled studies aimed to determine the optimal drug concentration for an appropriate response [31, 32], left opened the upper limit for the AF indication. It is allowed to use a dose that will be well tolerated. For this reason, it was recorded a large number of examinees with a concentration of 1.5-2 ng/ml i.e. greater than 1.0 ng/m, which corresponds to portion of the primary indication.

It is certain that concomitant medications have a significant role in digoxin serum levels (Table 2). As a high number of co-administered drugs (about 7 drugs) were present in the study, it was difficult to distinguish the predominant role of co-therapy. The following drugs were applied in high percentage: furosemide, spironolactone, inhibitors of calcium annals, drugs that increase the concentration of digoxin in serum, as well as vasodilators and other drugs that lower drug concentration [18, 35].

In this study, we confirmed that in patients with serum creatinine within the reference range, creatinine clearance was lower than 60 ml/min, similar to the previous studies [36]. By this result, we confirmed the

importance of creatinine clearance calculating in routine practice. During the course of research, side effects were reported in four patients. All of them had normal electrolyte status, while results of thyroid tests and other conditions showing digoxin serum levels were far above the upper limit, but by carefully reviewing dose therapy was continued. In one patient, concentration of 2.6 ng/ml was observed and even after dose adjustment side effects persisted. Digoxin is excluded from therapy, as well as one patient who had signs of intolerance at digoxin concentration of 1.5 ng/ml. In these patients, there was no correlation between signs and symptoms of digoxin toxicity and serum digoxin concentration.

5. Conclusion

Digoxin confirmed the justifiability of its use in contemporary clinical practice. Interrupting regimen is acceptable for daily practice with carefully guided individualization of dosages based on creatinine clearance, comorbid diseases and concomitant therapy. The challenges of the managing/monitoring of digoxin therapy suggest that understanding of the response will rise by combining of pharmacokinetic modelling with clinical pharmacology, resulting in pharmacokinetic-pharmacodynamic models.

Population pharmacokinetic analysis has to be designed by a proper decision about the dosage adjustment in patients participating study.

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Dr. Malone has warned of this risk for several months. What are we to do? Malone says that instead of relying on the flawed vaccines, Doctors should use drugs for treating Covid that have proved effective, such as Ivermectin (more about that following the video), is neutralizing Covid: What should scare the hell out of you is the extraordinary efforts being taken to silence and discredit Dr. Malone. I encourage you to read Michael Haynes piece from July 5, which details Maloneâ€™s Kafkaesque ordeal. Here are some relevant paragraphs from his article Digoxin intoxication occurs frequently and may require treatment with digoxin-specific Fab therapy. Little is known, however, regarding the biological fate.Â Digoxin immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. J Am Coll Cardiol 1991; 17: 590â€“8. PubMed Article CAS Google Scholar. Download Citation | On Mar 1, 2016, Azra BajraktareviÄ‡ published Safety and Efficacy of Digoxin Therapyâ€”Where Are We Now? | Find, read and cite all the research you need on ResearchGate.Â Taking the cardiovascular drug digoxin as an example, we collected the records of 513 patients who received the pertinent therapy during hospitalization at a tertiary medical center in Taiwan. Considering serum digoxin concentration (SDC) is the primary indicator for assessing the risk of digoxin therapy, patients with SDC being controlled at the recommended range before their discharge were defined as a low-risk population; otherwise, patients were defined as the high-risk population.