Treatment with Digoxin – is it a clinical challenge? A Retrospective Analysis of Hospitalizations due to Digoxin intoxication

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Abstract

Introduction and purpose: Digoxin, a cardiac glycoside derived from Digitalis lanata, has stood as a cornerstone in the treatment of various cardiovascular disorders for centuries. This study aims to delve into the demographic aspects, clinical characteristics, and outcomes associated with Digoxin poisoning. By drawing upon a dataset involving 22 patients hospitalized for Digoxin intoxication at the Clinical Department of Toxicology and Cardiology in Lublin, Poland, spanning from April 2014 to December 2023, our investigation seeks to provide an understanding of this issue.

Brief description of the state of knowledge: Despite the efficacy of Digoxin, the potential risk of intoxication, especially in the elderly, necessitate a comprehensive examination. Age-related changes, such as declining renal function, electrolyte imbalances, comorbidities and polypharmacy affect how drugs like Digoxin work. The symptoms of Digoxin poisoning can manifest in various organ systems such as cardiovascular, gastrointestinal, nervous system, highlighting the importance of prompt recognition to seek medical attention.

Methods and results: In our study, we analyzed data from 22 patients hospitalized due to Digoxin intoxication, focusing on demographic aspects, clinical characteristics and outcomes. The cases of Digoxin poisoning were categorized according to several factors, including the quantity and nature of substances consumed, the cause of intoxication, gender, age brackets, health conditions, peak serum Digoxin levels, length and outcomes of hospitalization.

Conclusions: Our study provides insights into the characteristics and outcomes of patients hospitalized due to Digoxin intoxication. The findings underscore the association of Digoxin poisoning, and emphasize the importance of monitoring serum levels to prevent adverse outcomes. As Digoxin continues to be relevant in treating cardiovascular conditions, our study calls for careful management and monitoring.

Key words: Digoxin poisoning; Digoxin serum level; elderly patients, atrial fibrillation, congestive heart failure, chronic renal failure

1. Introduction

Digoxin, a cardiac glycoside derived from the Digitalis lanata [1], has been a foundation of the treatment of various cardiovascular disorders for centuries [2]. As one of the oldest medications still in use, it continues to play a vital role in managing conditions such as congestive heart failure, atrial fibrillation, and certain arrhythmias [3]. Despite its therapeutic benefits, the utilization of Digoxin is associated with inherent risks, particularly in vulnerable populations, notably the elderly. This demographic merits particular attention due to age-related alterations in physiology, including declining renal function, which can significantly influence the pharmacokinetics and pharmacodynamics of the drug. Furthermore, elderly individuals commonly experience electrolyte imbalances, comorbidities, and polypharmacy, further heightening the risk of adverse effects associated with Digoxin therapy. The manifestations of Digoxin toxicity encompass various organ systems. Cardiac manifestations may include bradycardia, tachycardia, arrhythmias such as atrial fibrillation or ventricular ectopic beats, and conduction abnormalities. Non-cardiac symptoms can manifest as gastrointestinal disturbances such as nausea, vomiting, abdominal pain, and diarrhea. Neurological symptoms may include dizziness, headache, confusion, visual disturbances, and even psychiatric manifestations such as delirium or depression. Moreover, electrolyte imbalances, particularly hyperkalemia, may exacerbate the toxicity and contribute to adverse outcomes. Given the complexity and variability of these presentations, prompt recognition and accurate diagnosis of Digoxin toxicity are paramount to initiate appropriate management strategies and prevent potentially life-threatening complications.

2. Methods

In our study, we collected data on 22 patients hospitalized due to Digoxin intoxication in the Clinical Department of Toxicology and Cardiology of Cardinal Stefan Wyszynski Regional Hospital in Lublin, Poland. The time interval from April 2014 to December 2023 has been included. The data comprehend 22 patients with T46.0 diagnosis (poisoning by, adverse effect of and underdosing of cardiac-stimulant glycosides and drugs of similar action). The cases of Digoxin poisoning were subdivided based on the number and type of substances ingested by patients, reason of intoxication and taking Digoxin, gender, age groups, co-morbidities, maximum serum Digoxin concentrations, duration of hospitalization and hospitalization outcomes. The results are presented below.

3. Results

Figure 1 shows the correlation between the number of patients and the number of substances they ingested. As T46.0 diagnosis included patients who were poisoned with digoxin only, Digoxin and another single substance and Digoxin and several other substances.

Distribution of digoxin poisoning in relation to the number of substances ingested by patients
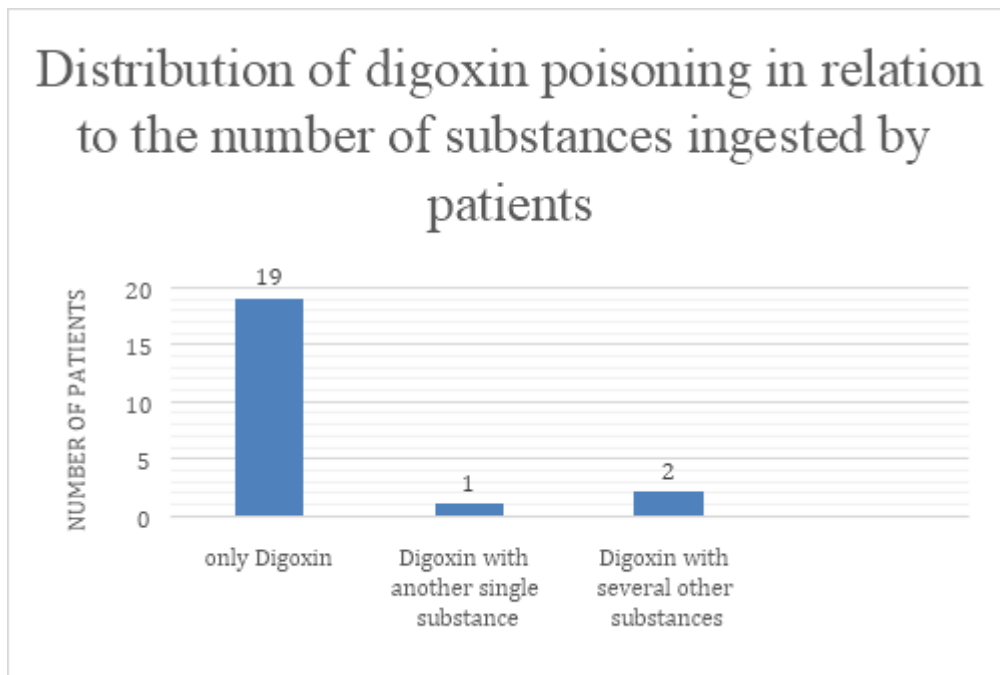
The Figure 2 shows the reason for Digoxin poisoning.

Figure 2: Digoxin poisoning - the reason
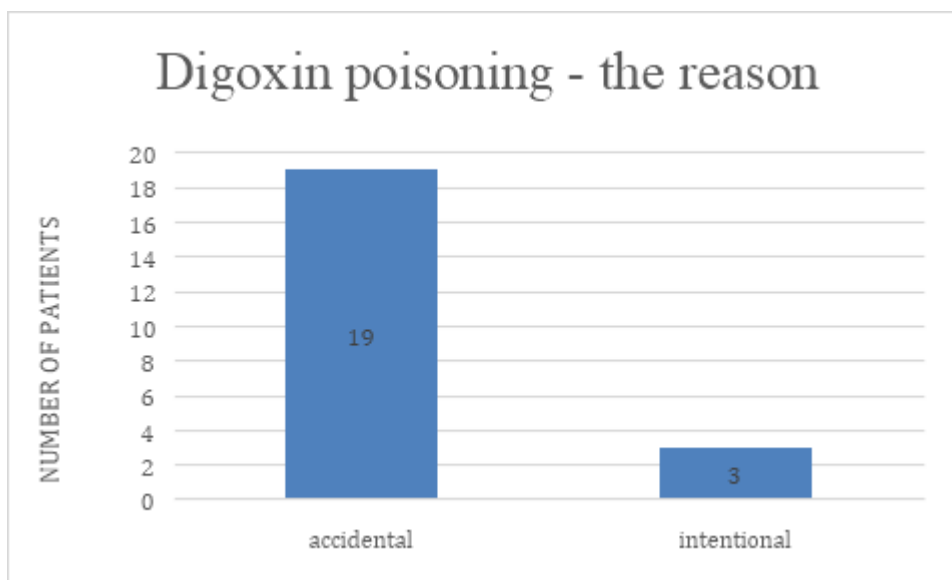
The Figure 3 shows the division by gender.

Figure 3: Division of patients based on gender
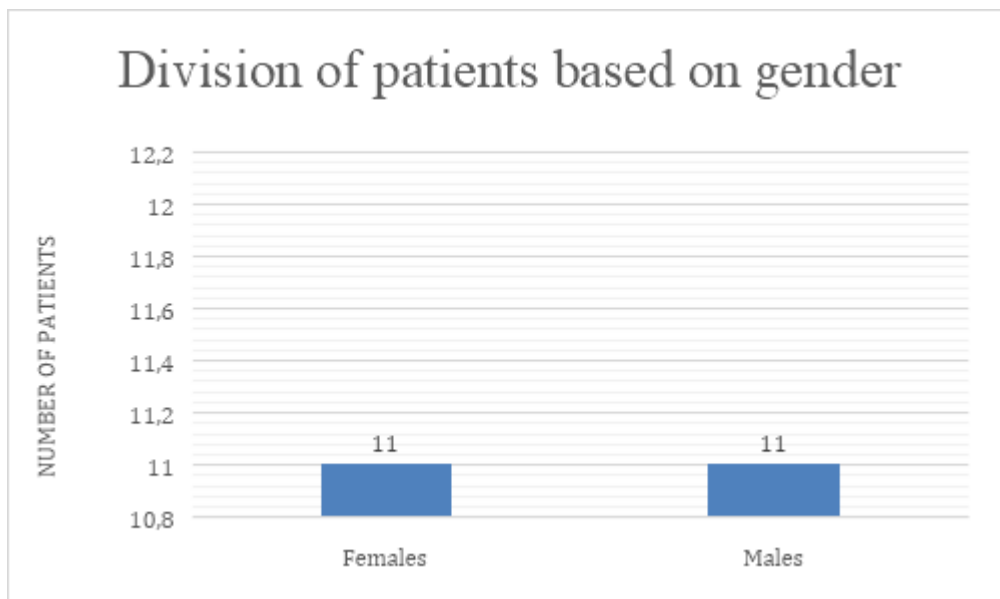
In Figure 4, patients are assigned to different age groups.

Figure 4: Distribution of patients into different age groups
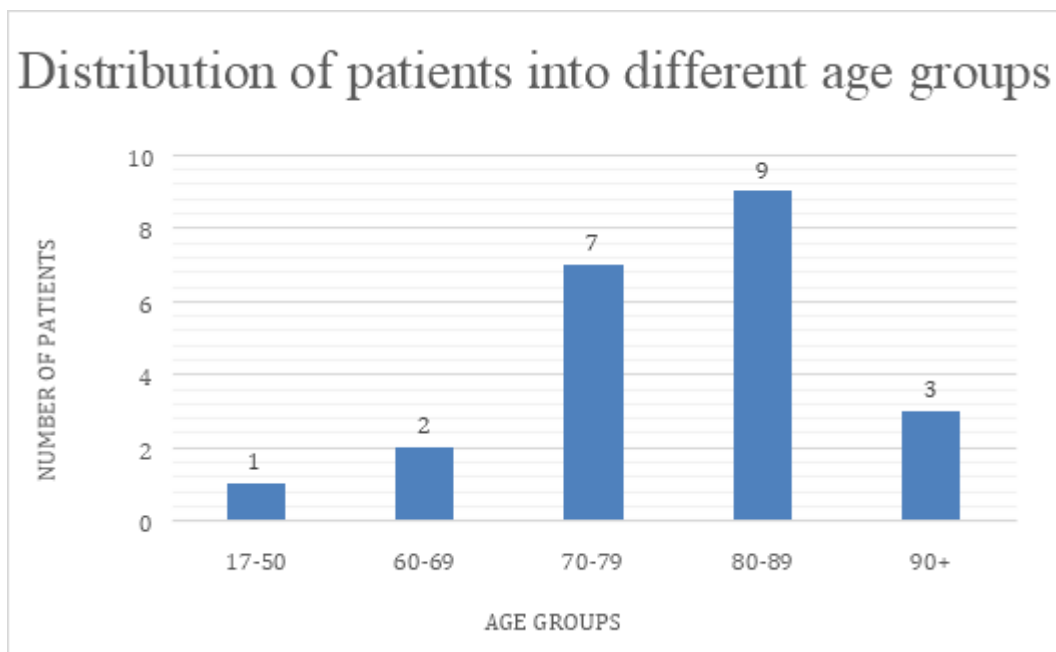
Figure 5 illustrates the duration of hospitalization.

Figure 5: Distribution of the numer of patients by the duration of hospitalization
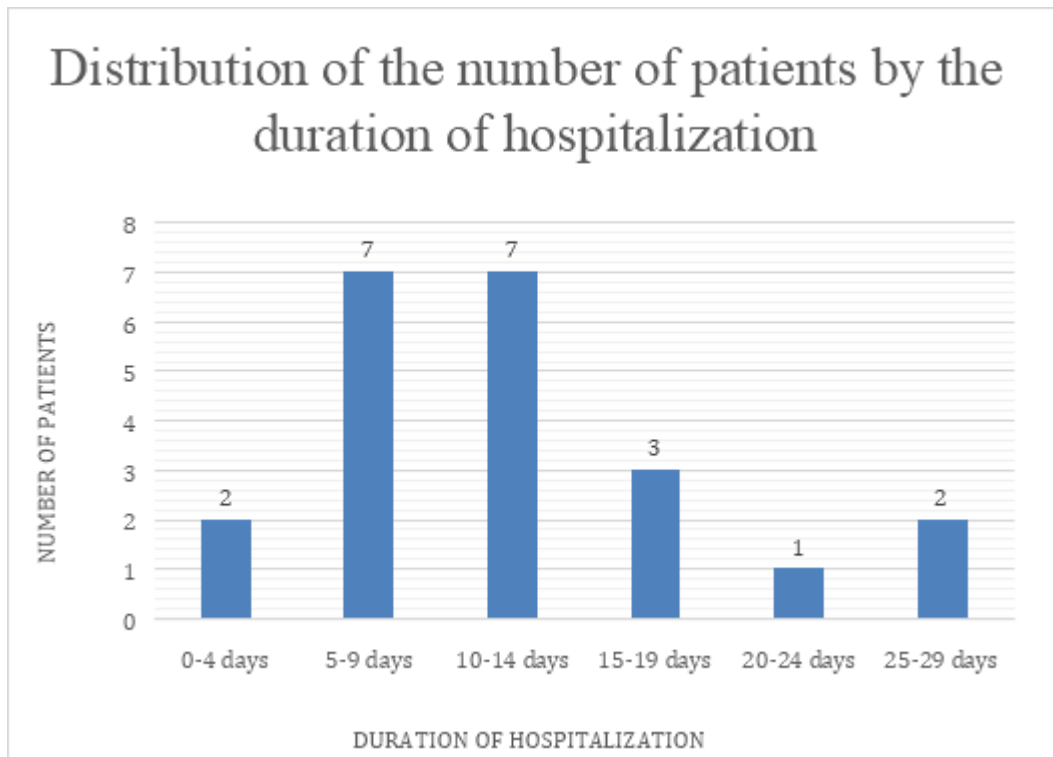
Figure 6 shows hospitalization outcomes of patients.

Figure 6: Hospitalization outcomes
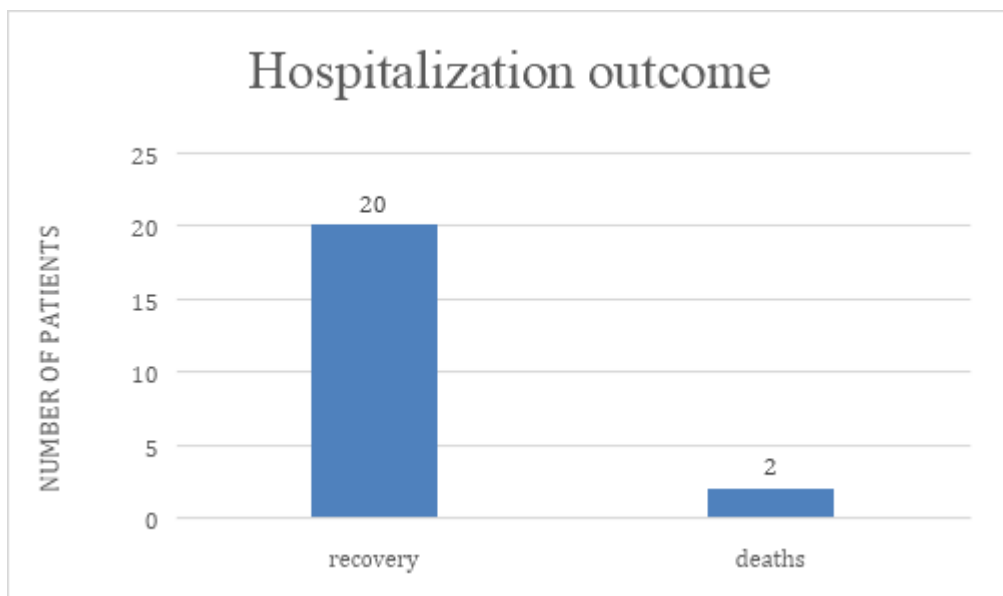
Out of the total 22 cases reported, 19 of them concerned exclusively digoxin intoxication. A single case of digoxin poisoning with the single substance carvedilol and two cases of mixed poisoning (Theophylline with Zolpidem and Theophylline with Carvedilol) have been documented. Accidental poisoning was reported in 19 cases, 3 persons took the drugs for suicidal purposes. Among cases of intentional drug poisoning, blood alcohol concentration was not detectable. Women and men constituted an equal number of poisoning cases, but all 3 cases of intentional poisoning occurred in men. Among all cases, 19 patients were older than 70 years old. The average duration of hospitalization was around 11,5 days, with a median of 10 days (excluding two deaths). Of the 22 cases, two resulted in fatalities. The immediate cause of death in these patients was implications of heart failure. In the discussion, we included data on the maximum serum Digoxin concentration, the reason for taking this drug and comorbidities in our patients.

4. Discussion

Digoxin is commonly used in the treatment of heart disease, including CHF (Congestive Heart Failure), AF (Atrial Fibrillation) or flutter and certain arrhythmias [3]. Currently its primary application lies in managing AF with rapid ventricular response [4]. The mechanism of action of digoxin is based on its binding to cardiac Na+/ K+-ATPase in the cell membrane [5]. It acts directly on cardiac muscle and vascular smooth muscle and indirectly has a positive inotropic effect, a negative chronotropic and antiarrhythmic effect by reducing AV node conduction [6]. Bioavailability of digoxin after oral administration varies between 50% and 90%, a half-life is 1.5-2 days and may be prolonged in patients with renal dysfunction [7]. In healthy people, 50-70% of an intravenously administered dose of digoxin is excreted unchanged in the urine, and removal by dialysis, exchange transfusion or during extracorporeal circulation is ineffective because the majority of the drug is binding to extravascular tissues [8]. Out of the 22 cases reported, only one person had an intravenous administration of digoxin.

Table 1 summarises the heart disease in our patients taking digoxin, excluding 1 young man without chronic disease, who took the drug for suicidal purposes.

Table 1: Heart disease in our patients taking digoxin

	Heart Diseases		
	AF + CHF	AF	CHF
Number of patients	12	3	6

AF- Atrial Fibrillation, CHF – Congestive Heart Failure

The main co-morbidities that could affect the outcome of digoxin poisoning in our patients were CAD (Coronary Artery Disease), AH (Arterial Hypertension), DM2 (Diabetes Mellitus type 2) and CRF (Chronic Renal Failure). In their cohort study investigating populations with advanced CRF, Lii-Jia Yang et al. explored the impact of digoxin usage on

mortality, cardiovascular events, and renal outcomes within the Taiwanese demographic. The study compared outcomes between individuals receiving digoxin and those not receiving it. Results indicated no significant variance in the risk of acute coronary syndrome, ischemic stroke, or rapid eGFR decline between the two cohorts. However, the investigation revealed a notable association between digoxin use and heightened mortality rates, while no significant correlation was observed regarding cardiovascular events or deterioration of renal function among patients with advanced CRF [9]. In the analysis which utilized administrative health care data from ICES in Ontario, Canada, the authors focused on adults aged 66 or older with an eGFR < 60 mL/min/1.73 m², newly prescribed oral digoxin between 2008 and 2019. Among the 25,698 older adults initiating digoxin during the study period, 11,755 (46%) had an eGFR below 60 mL/min/1.73 m². Of this subset, 1,671 individuals (14%) were prescribed doses exceeding 0.125 mg/day, while 10,084 (86%) adhered to or were prescribed doses equal to or below 0.125 mg/day. The median dosage observed in each group was 0.25 mg/day (interquartile range [IQR], 0.15-0.25) and 0.125 mg/day (IQR, 0.06-0.125), respectively. Those receiving higher doses had a nearly sixfold higher 90-day risk of toxicity. These findings highlight the need for adherence to dosing guidelines and careful monitoring in older adults initiating digoxin therapy [10].

Table 2 compares the combinations of multimorbidities with the number of patients suffering from them.

Table 2: Coexisting Diseases in our patients

Coexisting Diseases	Number of patients
CAD + CRF + AH + DM2	2
CAD + CRF + DM2	1
CAD + AH + DM2	2
CAD + DM2	1
CRF + AH + DM2	2
CRF + AH	2
CRF	2
AH+ DM2	2
AH	4
DM2	2

CAD-Coronary Artery Disease; CRF-Chronic Renal Failure;, AH-Arterial Hypertension;
DM2-Diabetes Mellitus type 2

From the data we collected, it clearly appears that Digoxin poisoning typically occurs in the elderly patients. Excluding one case of intentional poisoning in young man, the average age of our patients was 80,8 years. This aligns with a retrospective cohort study by Ferrando et al. which reported a mean age of 85.2 years for Digoxin poisoning [11]. Hospitalization data from the Monash Toxicology Unit in Australia revealed mean ages of 80.2 years (Digoxin-Fab administered) and 79.2 years (Digoxin-Fab not administered) [12].

Manifestations of Digoxin poisoning can be cardiac and non-cardiac symptoms. Common cardiac complications include bradycardia, compensation disorders, 1st degree AV block, frequent extrasystoles, bigeminy, supraventricular tachycardia with block and other arrhythmias [3]. During digoxin treatment, a characteristic cup-shaped ST-segment depression may occur [13]. Severe conditions may lead to AV block III° and sinus block III° and even fibrillation [14]. Gastrointestinal symptoms include nausea, vomiting, abdominal pain, and diarrhea [15]. Central nervous system effects include dizziness, headache, confusion [15] and even visual disturbances such as colored floaters [16]. Major electrolyte disturbance is hyperkalemia, correlating with the risk of death in acute poisoning. Toxic symptoms may occur after a dose of 2 mg, severe intoxication after 5 mg; the lethal dose is 10 mg,with increased toxicity in people with renal failure, especially in chronic intoxication [14]. Due to the non-specific symptoms, the possibility of Digoxin poisoning is crucial in elderly patients being treated with Digoxin, particularly in those with multimorbidity and taking various types of medication [15].

In our patients, the initial symptoms of intoxication were weakness, nausea, vomiting and abdominal pain, which occurred especially in patients who had recently started taking digoxin at the recommended doses (2-3 weeks before). Cardiac manifestations included bradycardia, chest pain, palpitations and exacerbation of heart failure in the form of peripheral edema, dyspnoea, decreased exercise tolerance and pulmonary oedema. The ECG changes observed in our patients were AF, downward and cup-shaped ST-segment reductions, AV block I°, AV block I° with AV block II° (Weckenbach's periodization) and AV block III°.
We noted one case of myocardial infarction due to digoxin poisoning, this patient had a digoxin serum level of 4.79 ng/ml and troponin increased from 223,7 ng/l to 835 ng/l on the second measurement (0-14 ng/ml norm); ECG changes was highly dynamic, the main abnormality was downward ST-segment ,depression in leads I, II, aVF and V2-V6. There were no significant abnormalities in potassium metabolism in our 22 patients.

Digoxin has a narrow therapeutic window, with serum levels recommended to be below 1.2 ng/ml according to ESC 2021 guidelines for heart failure treatment [17]. The risk of death in patients with AF taking this drug was independently associated with serum levels and was highest in patients with serum levels ≥1.2 ng/ml [18]. The risk of Digoxin toxicity increases with serum concentrations above >2.0 ng/ml, and a value higher than 3.0 ng/ml is almost certain [19].

Figure 6: Maximum Serum Digoxin Concentrations in our Patients
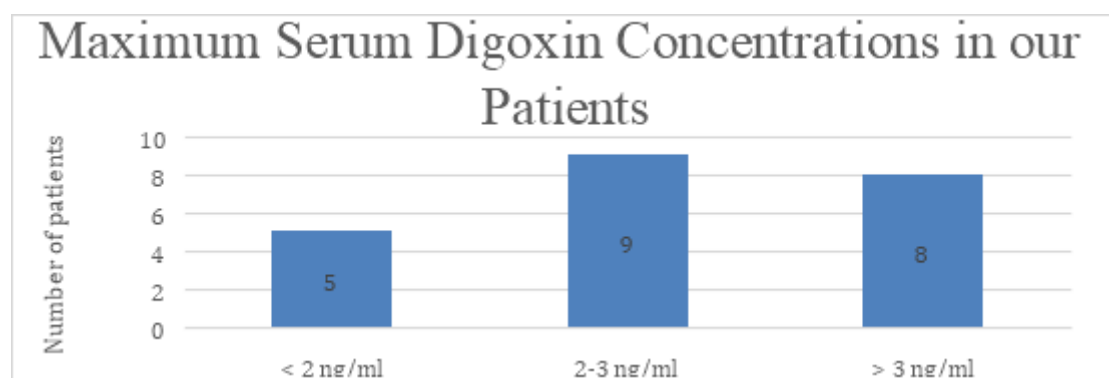
Analysing the collected hospitalization data, we wondered whether there was a possible correlation between digoxin levels and the occurrence of specific ECG changes. The ECGs of 3 patients with levels >6 ng/ml showed varying degrees AV blocks, but periodically a grade III AV block also occurred in a patient with a level of 4.46 ng/ml. In three patients with the lowest recorded digoxin concentrations, ranging from 0.9 to 1.32, no additional changes were detected in the ECG except for the persistent AF, which these patients suffered from. However, it is essential to acknowledge the limitations of our study due to the small sample size. A more comprehensive retrospective analysis involving a larger cohort of patients poisoned by digoxin is needed. Find the relationship between digoxin concentration and ECG changes and typical symptoms, and also to assess co-existing diseases.

Treatment of Digoxin poisoning is mainly symptomatic, with gastric lavage and activated charcoal considered if less than one hour has passed since ingestion of the toxic dose [14]. All of our 22 hospitalized patients were treated symptomatically, one 61-year-old man required endocavitary electrode stimulation. This patient had the highest serum digoxin concentrations (9,5 ng/ml) of all hospitalized patients and exacerbation of heart failure was presented, with symptoms including peripheral oedemas, ascites and cyanosis. ECG changes in this patient showed atrial flutter with 3rd degree AV block with a ventricular response of 45/min.

Digoxin has a specific antidote - the Digoxin-Fab and its efficacy in acute poisoning was described in 1976 [20], but our patients did not receive this antidote, due to its unavailability in Poland and the necessity of importing it. Arbabian et al. reported that Digoxin-Fab could have a slight benefit in increasing heart rate in cases of heart rate below 51/min, especially in patients also taking other chronotropic-negative drugs; however, it should be considered as an adjunct to other interventions for the treatment of bradycardia, low blood pressure, or hyperkalemia [12]. A physiologically based pharmacokinetic (PBPK) model of Digoxin poisoning created by Bracken et. al compared to conventional two-compartment modeling is better in generating realistic simulations of acute digoxin toxicity and response to Digoxin-Fab treatment, and the capacity of this simulation provides realistic data that can validate the use of alternative, cost-effective and safer Digoxin-Fab dosing strategies in acute poisoning [21]. Chan et. all. in their study suggest that in chronic digoxin poisoning, routine administration of Digoxin-Fab does not appear to reduce mortality, duration of hospitalization, change in potassium concentration or heart rate over time [22].

Considering the key problems in elderly patients, such as multimorbidity and multidrug use, the management of Digoxin is a clinical challenge and is associated with a risk of intoxication, especially in patients with chronic renal failure. In the elderly, progressive cognitive impairment, loss of memory, depressive disorders and physical processes due to ageing should also be considered, so if possible patients should not take digoxin independently. If patients taking digoxin experience nonspecific digestive system symptoms such as nausea, vomiting, and abdominal pain, it is advisable to determine the concentration of this drug, as these symptoms could potentially indicate the onset of poisoning.Various factors should be considered in the choice of treatment for Digoxin poisoning: the potential benefit to the patient and the optimization between the cost of potential using Digoxin-Fab and the duration of hospitalization.

5. Conclusions

In conclusion, our study provides insights into the characteristics and outcomes of patients hospitalized due to Digoxin intoxication at the Clinical Department of Toxicology and Cardiology in Lublin, Poland, over the period from April 2014 to December 2023. Digoxin, as one of the oldest drugs acting on the cardiovascular system, continues to be relevant in treating various heart conditions. Our data analysis emphasizes its association with poisoning. Clinical manifestations varied widely, emphasizing the need for prompt recognition and tailored management. While serum Digoxin levels showed potential correlations with specific ECG changes, further research with larger cohorts is warranted to validate these findings. Treatment remains primarily symptomatic, with challenges such as the unavailability of Digoxin-Fab prompting the exploration of alternative strategies. Future research should focus on elucidating the relationship between Digoxin levels, clinical outcomes, and treatment efficacy, while clinicians should adopt a personalized approach to management, considering individual patient characteristics and potential treatment benefits. Further research and awareness efforts are warranted to enhance the safety of Digoxin use in clinical practice.

Supplementary Materials:

- Figure 1: Distribution of digoxin poisoning in relation to the number of substances ingested by patients
- Figure 2: Division of patients based on gender
- Figure 3: Distribution of patients into different age groups
- Figure 4: Distribution of the numer of patients by the duration of hospitalization
- Figure 5: Hospitalization outcomes
- Figure 6: Maximum Serum Digoxin Concentrations in our Patients
- Table 1: Heart disease in our patients taking digoxin
- Table 2: Coexisting Diseases in our patients

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