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Suicidal digoxin intoxication in 61 year old patient

Erwin Ciechański[1], Krystian Ciechański[2], Michał Tchórz[3]

[1] Department of Cardiology, Regional Specialist Hospital in Lublin
[2] Student's Research Group at the Department of Toxicology, Medical University of Lublin
[3]Department of Toxicology, Medical University of Lublin

Abstract: Digoxin is one of the oldest drugs used in cardiology. It belongs to subgroup of cardiac glycosides. Currently, due to limited indications for use, cases of poisoning with this group of drugs are becoming less common. Ease of poisoning results from the low therapeutic index and symptoms of intoxication may include many different systems. The most serious symptoms of overdose are cardiac arrhythmias. We present a case of a patient with suicide poisoning due to ingestion of 30 tablets of 0.1mg digoxin.

Key words: digoxin intoxication, suicide, toxicology

Introduction

Digoxin is a drug belonging to the subgroup of cardiac glycosides obtained from Digitalis Purpurea species which are commonly named foxglove glycosides. Historically, it has been used in the treatment of oedemas [1]. However, it is currently used as an inotropic agent to improve systolic dysfunction in patients with congestive heart failure and to control ventricular rhythm frequency in patients with supraventricular tachyarrhythmia with accelerated ventricular function. Digoxin is well tolerated and inexpensive. That is why it is often used in groups of patients with these diseases. Digoxin is typically used at dose of 0.125- 0.25 mg daily (mg/day), with a dose reduction of 0.0625-0.125 mg daily (mg/day) in elderly, low body weight or among patients with renal disfunction. The therapeutic index of the drug is 0.6- 1.2 nanograms per milliliter (ng/ml) [2]. Digoxin is well absorbed from the gastrointestinal tract (about 75% of the dose) and weakly binded by plasma proteins (20-

30%). The onset of action occurs after approximately 3 hours, while peak activity about 5 hours after oral dosis [2].

The basic mechanism of action, similarly to catecholamines, is the increase the amount of calcium ions available in the cell during its contraction phase. Instead of catecholamines amines, which act through β-adrenergic receptors, digitalis glycosides causes increasing of calcium by blocking sodium-potassium pump located in the cell membrane of cardiomyocytes. This leads to an increase in sodium concentration, which leads to a block of Ca2+ release to extracellular fluid in the mechanism of sodium to calcium ion exchange and increases the release of Ca2+ from cell stores [3]. Intracellular calcium level increases. It contribute to increase the strength of myocardial contraction (positive inotropic effect). Digoxin also increases the excitability of the heart muscle (positive bathmotropic effect). This effect is due to the shifts caused by ionic digoxin (changes in potassium ion concentration gradient on both sides of the cell membrane). With the ability to increase cardiac contractility, the drug is used in advanced heart failure (II-NYHA class IV). Therefore, this drug increases cardiac output and helps to relieve the symptoms of heart failure.

It reduces heart rate and slows down conduction in the atrioventricular node (negative chrono- and dromotropic effects). This is done by releasing conduction in the atrioventricular node, by direct action on the node cells and by stimulation of the parasympathetic system and inhibition of the sympathetic system. The slowdown in sinus rhythm is due to the activation of the parasympathetic system. This is used to treat some supraventricular arrhythmias, especially chronic atrial flutter and fibrillation.

Digoxin also has less effect on the central nervous system, alpha-adrenergic receptors and reduces renin secretion [4].

With the emergence of newer drugs, such as beta-blockers, angiotensin-converting enzyme inhibitors and aldosterone receptor blockers, the indications for digoxin have been limited to:

1. Heart failure with an impaired ejection fraction (LVEF ≤40%) with fibrillation or atrial flutter with rapid ventricular action and instability hemodynamic (as an alternative to amiodarone,
2. Heart failure with an impaired ejection fraction (LVEF ≤40%) with fibrillation or atrial flutter with rapid ventricular action without hemodynamic instability, but with intolerance of β-blockers, contraindications to their use or together with β-blocker if this does not provide adequate frequency control chambers in monotherapy;
3. as an alternative to ivabradine in patients with preserved sinus rhythm, LVEF ≤45% and persistent symptoms of NYHA II-IV heart failure, despite the use of β-blocker, angiotensin-converting enzyme inhibitor and aldosterone antagonist in optimal doses.

Contraindications for digoxin include: severe ventricular arrhythmias, preexcitation syndromes, hypercalcemia, hypokalemia, hypertrophic cardiomyopathy with outflow narrowing, multifocal atrial tachycardia, amyloid heart disease or significant conduction disturbances that may exacerbate the drug, such as bradycardia, sinus node syndrome, atrioventricular blocks II and III degree [5]. On Digoxin sensitivity may also affect hypomagnesemia [6].

The side effects of digoxin usually appear in the upper range of therapeutic index of the drug in blood (>1.0-1.2 ng/ml). A small therapeutic index of digoxin is a great difficulty in its safe use and is the cause of the most frequent accidental poisoning. The drug has a low therapeutic index and that is why it can contribute to intoxication. In the case of poisoning, early symptoms may reveal as gastrointestinal disorders such as reduced appetite, nausea and vomiting and abdominal pain. They are often accompanied by neurological symptoms such as headaches, dizziness, fatigue and sleepiness. A less common symptom is a colour perception disorder - the presence of yellow or green borders when looking at a light source.

The most dangerous complications of poisoning are cardiac conduction disorders and heart rhythm disturbances. High concentrations of digoxin intensify the chronic, dromo- and bathmotropic effects. It typically occurs as sinus bradycardia or, rarer in case of flickering or fluttering atria, a slowdown in the ventricular action below 60/min is observed. Intoxication of digoxin can also be presented as atrioventricular block, from stage I to total block, as well as in various stages of sinus block. Symptoms of cardiac conduction disorders are more severe with coexisting hyperkalaemia. Such situation may appear during renal failure occurred by digoxin therapy [7].

Case report

A 61-year-old patient was referred from a regional hospital to the Toxicology Department because of digitalis glycosides poisoning. Patient admitted to swallowing 30 tablets of digoxin, 0.1 mg each. Patient had also pathological obesity, history of heart failure, heart rhythm disorders, insulin-dependent diabetes mellitus, Leriche syndrome complicated by lower limb paralysis. In history he had pulmonary embolism, NSTEMI myocardial infarction and anterior wall infarction. At the time of admission the patient was in a very severe condition, conscious in difficult contact, with cyanosis, circulatory insufficient, with massive swelling and hydrocephalus. In ECG examination atrial flutter with atrioventricular block III degree with ventricular action 45/min was observed. Due to the observed bradycardia, an endocavitary electrode was inserted and an effective stimulation was obtained. In toxicological tests he had, digoxin level of 8.8 ng/ml. Laboratory tests showed respiratory acidosis, third degree of chronic kidney disease and slight hyperkalaemia. Detailed examinations: morphology, hepatic, renal, electrolyte level, arterial blood gasometry are presented in Table 1.

RBC (4,00-5,20 M / L)	5.4	eGFR (ml / min / 1.73m3)	38.4
HGB (12,0-16,0 g / dl)	12.8	Urea (15-46 mg / dl)	82.41
WBC (4,3-10,0 K / uL)	10.4	Saturation (95-98%)	81.5
PLT (130-400 K / l)	217	(ALT 5-41 U / L)	90
INR	2.9	(AST 1-32 U / L)	27
pH (7.35-7.45)	7,295	Na + (132-145 mmol / l)	135
pCO2 (mmHg 38.9-48.9)	68.1	K + (3,7-5,1 mmol / l)	5.5
pO2 (75-100 mmHg)	51.6	Cl- (95-107 mmol / l)	92
BE (-3: 3 mmol / l)	3.6	Total calcium (2,12-2,62 mmol / l)	2.07
HCO3- (21-24 mmol / l)	32.4	Creatinine (0.6-1.1 mg / dl)	1.81

Table 1. Results of tests on the day of patient admission to Toxicology Department

Due to the severe condition of the patient, intensive pharmacological treatment was started and a central injection with an infusion of catecholamines was performed. On the second day of hospitalization, the patient still presented abnormal consciousness. Furthermore, he removed the central puncture and the endocavitary electrode. During the treatment, psychological and psychiatric consultations were ordered. The patient denied suicidal thoughts and tendencies, but reported a reduced mood, lasting for several days. No indications for psychiatric hospitalization were found.
Proper therapy consisted of monitoring heart rate and multiple diagnostic tests of laboratory parameters (electrolytes, acid-base balance, drug level, renal function exponents). After pharmacological treatment, the patient's general condition was initially improved, heart rate and blood pressure were normal. Control concentrations of digoxin on consecutive days of hospitalization were respectively: 9.5 ng/ml, 4.29 ng/ml, 3.22 ng/ml, 3.07 ng/ml, 2.41 ng/ml, 2.52 ng/ml and 2.49 ng/ml. On the fifth day of hospitalization a high level of inflammatory markers was observed: CRP- 100.84 mg/l (standard 0-5 mg/l)- use of amoxicillin antibiotic was recommended. In the next days we observed deterioration of renal function (creatinine - 3.31 mg/dl, urea - 158 mg/dl), oliguria. Due to the above symptoms, the patient was consulted nephrologically, without any qualification for dialysotherapy. On the 8th day of hospitalization due to severe patient condition, cyanosis, periodically decreased saturation to 54%, hypotension 80/50 mmHg, patient had anaesthesiological consultation. After it he was transferred to the Intensive Care Unit (ICU). In ICU the patient was intubated, connected to a respirator, circulatory system was supported by infusion of catecholamines, antibiotic therapy was continued. In addition, nutritional treatment has been included. The diuresis was stimulated by furosemide infusion and intermittent dialysis. The patient was surgically consulted, the right pleural cavity lumbar puncture was performed. Despite intensive treatment, the patient remained in a general state of severe respiratory failure. On the second day of hospitalization in ICU, sudden cardiac arrest (SCA) occurred - effective resuscitation. About 30 minutes later, another SCA appeared. Despite immediate resuscitation, the patient died.

Discussion

Digoxin poisoning is relatively rare. About 1% of patients treated with digitalis glycosides develop symptoms of poisoning. The frequency of poisoning increases with age and occurs in about 3% of patients over 85 years of age [8]. This group of patients most often has numerous somatic diseases, which additionally intensify the toxicity of digoxin (renal failure, electrolyte disorders, hypothyroidism, lung diseases). The high toxicity of the drug results from a small difference between the therapeutic and toxic doses, while overdose symptoms in older people are observed already at therapeutic doses [9]. The most common symptoms of poisoning are gastrointestinal disorders (nausea, vomiting, anorexia, flatulence and diarrhoea). Often neurological disorders such as sensory, orientation, sleep and vision disorders occur. The pathognomonic symptom of vision disorders is yellow-green vision [9]. The cardiotoxic effects of digitalis glycosides are considered the most dangerous symptom of poisoning. Various arrhythmias and conduction disturbances may occur: A-V blocks I^{o}, II^{o} and III^{o}, extrasystole ventricular tachycardia, tachycardia and supraventricular extrasystole, including rare ventricular tachycardia and ventricular fibrillation [10].
There are no clearly defined guidelines for the treatment of digoxin poisoning [11]. In patients with acute poisoning, decontamination with activated carbon may be attempted within 2 hours of digoxin ingestion [12]. During the treatment it is important to detect and compensate electrolyte disturbances and to continuously evaluate the electrical function of the heart. Atropine is used in concomitant conduction disturbances, while in ventricular tachycardia lidocaine is used. Moreover, severe poisoning is an indication for the

administration of digoxin-specific antibody fragmentation antibodies - DSFab [13]. DSFab is indicated for life-threatening toxicity including:

- Ventricular arrhythmias
- High-grade heart blocks
- Hypotension
- Symptomatic bradycardia
- Potassium greater than five meq/L in acute overdose
- Acute ingestions greater than 10 mg in an adult or greater than 4 mg in a child
- Digoxin Concentration greater than 15 ng/mL measured at any time
- Digoxin Concentration greater than 10 ng/mL measured 6 hours post ingestion.

Suicidal digoxin poisonings are considered to be rare. From the moment of admission, severe cardiac arrhythmias were observed in the patient - AV block III^{o}. In addition, the patient reported a colour vision disorder typical of digoxin intoxication. High level of digoxin (8.8 ng/ml) marked in serum and life-threatening cardiac arrhythmias requiring the insertion of an endocavitary electrode are the reasons for the severe course of the poisoning. Despite the indications for DSFab application, no such treatment was applied due to the lack of availability of the product. Numerous somatic diseases (insulin-dependent diabetes mellitus, Leriche's syndrome, condition after two heart attacks and pulmonary embolism) and the current severe state of health undoubtedly contributed to the development of a dangerous, fatal poisoning. Initially, a decrease in digoxin levels was observed during the therapy. Unfortunately, there was a gradual deterioration of kidney function and heart function in the next days of hospitalization. In the absence of documented effectiveness in the treatment of digoxin poisoning with plasmapheresis and hemodialysis, the extracorporeal elimination of the drug was not performed. Increasing cardiopulmonary insufficiency was the cause of the patient's transfer to the ICU, where despite the therapy patient died.

In conclusion, poisoning symptoms of digoxin may occur at the therapeutic level of the drug and may pose a threat to the patient's life. Early recognition of the risk and modification of the therapy is very important. In cases of acute poisoning, it is necessary to perform proper symptomatic management and close monitoring of the patient in the hospital.

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