

Overdose of Digoxin Leading to Thrombocytopenia: Exceptional Side Effects: A Case Report

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Abstract

Case Report

Digoxin is extracted from digitalis and is commonly used in patients with atrial fibrillation and in patients with heart failure. Advanced digitalis intoxication can have a fatal outcome, particularly in patients with underlying cardiac dysfunction (1). Drug-induced thrombocytopenia (DITP), although frequent, remains exceptional in the event of overdose with digoxin. An overdose of Digoxin is usually iatrogenic and mainly leads to cardiac effects but can also cause severe thrombocytopenia. However, this latter complication related to digoxin is “exceptional”. The lifelong prognosis does not depend on a hemostasis disorder but rather on a secondary cardiac arrhythmia. We hereby report the observation of a 62-year-old patient followed for a dilated cardiomyopathy with a severe left ventricular dysfunction, and also an atrial fibrillation treated with acenocoumarol and digoxin. She has been admitted to the emergency room due to a partial loss of consciousness associated with dizziness and vomiting. Hence, we will discuss here explanatory approaches to the unresolved mechanism of this undesirable effect, scarcely described in the literature.

Keywords: Digoxin, intoxication, thrombocytopenia.

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INTRODUCTION

Drugs are important, sometimes common, culprits of blood dyscrasias, including granulocytosis, anemia, and thrombocytopenia [1]. Digoxin is a cardiac glycoside that is being used as an inotrope like to improve systolic dysfunction in patients with congestive heart failure (CHF). It may improve the quality of life in CHF patients and the recommended range for the serum digoxin concentration has been reduced over the past decade from 0.8–2.0 nanogram/mL to 0.5–0.9 nanogram/mL [2]. The toxicity of digoxin may result from overdose or from iatrogenic causes, especially if renal function is impaired. The thrombocytopenia induced by digoxin remains exceptional and very little described in the literature. Thrombocytopenia caused by drug dependent antibodies occurs suddenly, is typically severe, is often misdiagnosed and therefore commonly recurrent [3]. It is a recognized side effect of treatment with a wide range of medications. Epidemiologic studies performed in the United State and Europe suggest that about 10 persons per million are affected by drug induced immune thrombocytopenia (DITP) annually [4].

We hereby present a case which illustrates a rare adverse event related to the use of digoxin in a 62-year-old patient followed for heart failure with chronic renal failure discovered during his hospitalization.

CASE REPORT

A 62-year-old patient with the following cardiovascular risk factors: age, menopause, hypertension under treatment with losartan; also followed for dilated cardiomyopathy and atrial fibrillation under oral anticoagulant therapy and digoxin 0.25 mg / day for 19 years.

A month before her admission she developed bradycardia at 48 beats /min and digoxin was discontinued. One week later, the patient resumed her treatment on her own.

Three weeks later, she was admitted to the emergency room due to an incomplete loss of consciousness following a minimal exertion associated with an asthenia, a sweating, a tinnitus, a dyspnea on exertion, a vomiting and then an epigastralgia.

The clinical examination on admission, described out a conscious patient with a respiratory rate at 23 cycles/min, a bradycardia at 34 beats/min, an arterial pressure at 100/68 mmHg, a saturation at 98% at the ambient air, regular heart sounds and a systolic murmur at the mitral focal point without signs of heart failure.

Furthermore, the electrocardiogram (EKG) showed a regular bradycardia at 33 beats/min equivalent to a 3rd degree atrioventricular block, a wide QRS at 140ms with a left QRS axis and a digitalis cup indicating an overdose of digoxin (Figure 1.). A chest X-ray (Figure 3.) showed a cardiomegaly with a rectilinear left middle arch. Plus, the transthoracic echocardiography. (Figure 4.) showed a left ventricle dilated to 64 mm, a global hypokinesia with a left ventricular systolic function estimated at 35%, a moderate mitral leak by dilation of the annulus, some dilated right chambers, a right ventricle with a preserved systolic function, her pulmonary pressures calculated at 55mmhg and a compliant inferior vena cava not dilated.

A laboratory test has been performed and showed (see Table 1). Her platelets had dropped at $16 \times 10^3/uL$, it could be noted that that her platelet count was normal at $130 \times 10^3/uL$. However, a digoxinemia was not established out due to lack of reagent.

The patient was then admitted at the cardiology intensive care unit. Her initial treatment has

been consisted of stopping digoxin accompanied with an atropine test whose outcome was negative requiring then a temporary pacing. The patient has also received a transfusion of two red blood cells units as well as the correction of hydroelectrolytic disorders. Given the unavailability of digoxin-specific antibody fragments, we therefore opted to force a diuresis by means of a furosemide syringe pumping. Hemodialysis was not possible; urine output was maintained despite severe renal impairment.

One week later, the evolution was marked by clinical and biological improvement with an absence of recurrence of lipothymia, a disappearance of signs of digoxin overdose such as a 3rd degree atrioventricular, a digitalis cup, an atrial fibrillation at 60 beats/minute on the EkG.

(Figure 2.) and hemoglobin at 9.8 g/dl. It has been also noted an improvement related to the platelet count that increased to 88,000/uL, the serum calcium to 69 mg/L, and the serum potassium to 3.6 mmol/L as well as the phosphoremia at 55 U/L. The temporary pacing, for its part, was removed after one week and the patient discharged after two weeks of hospitalization with the indication of an arteriovenous fistula.

One month after discharging, the EKG control still found an atrial fibrillation at 60 beats/min, a hemoglobin at 13g/dL and the platelets at 83,000/ul. Eventually, the digoxin was permanently stopped for this patient and marked in her follow-up diary.

Table-1: Result of laboratory test

Com lete blood count		Biochemistry	
Hemoglobin	7.4 g/dL	Na	129mmol/L
Hematocrit	24 %	K	6 mmol/L
Leucocyte count	$5.88 \times 10^3/uL$	Cl	88 mmol/L
Platelet count	$16 \times 10^3/uL$	Creatinine	73.6 mg/L
Reticulocyte	11730 /uL	Urea	1,99 g/L
Neutrophils	$4.38 \times 10U/L$	ALT	16 U/L
Lymphocytes	$0.52 \times 10U/L$	AST	26 U/L
Monocytes	$0.78 \times 10U/L$	Ca ²⁺	58 mg/L
Eosinophils	$0.15 \times 10U/L$	Phosphor	75 U/L
		Vitamin D	3.08 ng/L
Inflammatoy markers		HbA1C	60 %
ESR	Mm	Albumin	38 g/L
CRP	30 mg/L	TSH	1.34 mUI/L
		Parathormone	45 pg/mL
Serology		Troponin US	113 pg/mL
HIV antibody	Negative	LDH	632 UI/L
Hepatic serology	Negative	Bicarbonates	13 mmol/L
syphilitic serology	Negative	serum Ferritin	286 ng/mL

CRP: C reactive Protein; ESR: Erythrocyte Sedimentation Rate; HIV Human Immunodeficiency Virus; WBC: White Blood Cell.

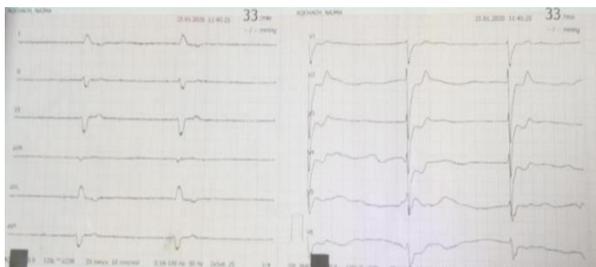


Fig-1: EKG on admission showed a regular bradycardia at 33 beats / min equivalent to a 3rd degree atrioventricular block, a wide QRS at 140ms with a left QRS axis and a digitalis cup indicating an overdose of digoxin

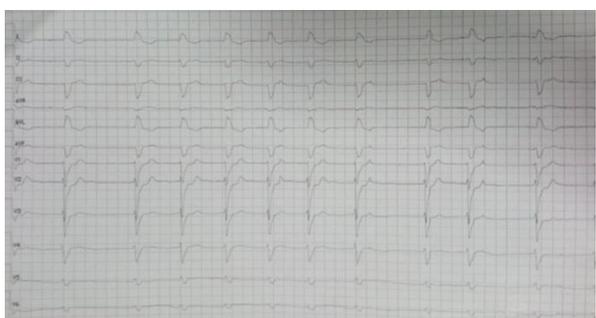


Fig-2: EKG one week later disappearance of signs of digoxin overdose such as a 3rd degree atrioventricular, digitalis cup and atrial fibrillation at 60 beats / minute



Fig-3: Chest x-ray found cardiomegaly with a rectilinear left middle arch



Fig-4: Transthoracic echocardiography in parasternal section long axis

DISCUSSION

Digitalis toxicity is infrequent but serious drug intoxication. The incidence of digoxin toxicity increases with age, largely because the two most common conditions that benefit from use of digoxin, congestive heart failure and atrial fibrillation, are markedly more prevalent in old age. The elderly are more sensitive to the effects of digoxin because of age; these include a decline in renal function, an increase in the number of comorbid conditions. There are also interactive medications among elderly persons who receive most of the prescriptions than any other population [5, 6].

The clinical manifestations of digitalis intoxication are nonspecific and can be conveniently divided into cardiac and non-cardiac effects. It manifests itself most often by gastrointestinal symptoms (nausea, vomiting), ocular symptoms. The cardiac manifestations of toxicity caused by digoxin are characterized by abnormal rhythms and alterations in conduction, but there is no consensus on the relative frequencies of these arrhythmias [7]. As for biological manifestations, renal failure is often found and hyperkalemia is a constant sign of serious intoxication. It is closely linked to the prognosis and it is believed to closely reflect the level of inhibition of the pump membrane Na K-ATPase, cell potassium depletion and therefore digitalis impregnation level [8, 9].

Digitalis intoxication manifests itself in priority as cardiac effects, but an overdose of digoxin can also lead to severe thrombocytopenia [10]. Among the cardiac glycosides, digitoxin has been most incriminated in some cases as the cause of an immune-thrombocytopenia [11, 12]. These cases are mainly reported for female patients of old age. Compared to digoxin which has a shorter half-life than digitoxin, thrombocytopenia induced by digoxin is poorly known; a case of severe thrombocytopenia induced after intravenous administration of digoxin in an 87-year-old woman was described [10].

Based on data found in the literature, the thrombocytopenia induced by digitalis is preferentially described in middle-aged or elderly women, like our case. Thrombocytopenia induced by the toxicity of cardiac glycosides is related to an allergic reaction [13], another patient developed digoxin-induced vasculitis which was associated with positive skin test [14]. This complication of digoxin is, according to Vidal®, "exceptional outside of an overdose". It recently became known that cardiac glycosides modulate the production of various proinflammatory cytokines [15]. The mechanism of occurrence of drug-induced thrombocytopenia has been previously evaluated, implying an inhibition of bone marrow production, platelet consumption or microangiopathy and immunological hyper destruction [16, 17]. In the case of digoxin, thrombocytopenia may be secondary to peripheral destruction, the pathophysiology of which

remains complex and under discussion, in particular due to the fact that in order to create thrombocytopenia, a long-term setting and a therapeutic overdose [18], are necessary, similar to our case. These effects may be particularly relevant in patients with atrial fibrillation for whom digoxin use could exacerbate platelet activation, which is associated with an increased cardiovascular disease incidence [19].

The diagnosis of digitalis overdose is not normally difficult when definite clinical signs are present. In our case the diagnosis was confirmed by extracardiac symptoms (anorexia, nausea, diarrhea and visual disturbances), arrhythmias and toxic blood levels of glycoside. The intoxication had come about through the patient's failure to adhere to his prescribed digoxin dosage. In addition, the patient had severe thrombocytopenia, which is known to occur as a rare complication of digoxin poisoning, even when the glycoside has previously been well tolerated for many years [2]. According to a study published in 2018, in the Journal of American Heart Association, serum digoxin is associated with increased urinary excretion of thromboxane B2 in patients with atrial fibrillation, and in vitro experiments have shown that digoxin increases platelet function in pre-stimulated platelets [19]. There are no evidence-based guidelines for the management of mild to moderate toxicity so there is a wide variation in treatment. The initial step is to assess the severity of the problems and the reason for the development of toxicity should always be thoroughly sought. Severe toxicity (the presence of major dysrhythmias) is clearly potentially life-threatening and carries a high mortality [20]. In these circumstances, a rapid and more aggressive management stratagem must therefore be followed which requires hospital admission and consideration of the need for digoxin-specific antibody fragments. Although digoxin-specific antibody fragments are safe and effective, randomized trials have not been performed. The antibody fragments form complexes with the digoxin molecules. These complexes are then excreted in the urine [2]. Atropine or temporary pacing often used in heart block; phenytoin, beta-blockers and lignocaine are used in malignant ventricular dysrhythmias [20]. In our case, atropine failed to accelerate the heart rate and we do not have an antidote, the management was therefore monitoring, a temporary pacing and correction of hydroelectric disorders.

A decision on whether to discontinue medication in a patient with possible DITP must be based on clinical considerations, as testing for drug dependent antibody requires time and is not widely available. When necessary, pharmacologically equivalent drugs with a different chemical structure can usually be substituted safely for medications essential to a patient's medical care. It is reasonable to give platelet transfusions to severely thrombocytopenic patients who

have 'wet purpura, because of their increased risk of intracranial hemorrhage [21].

CONCLUSION

Thrombocytopenia due to an overdose of digoxin is an exceptional complication. The vital prognosis does not depend on the hemostasis disorder but rather on secondary cardiac arrhythmia. Patients on digoxin should be kept within the therapeutic range of digoxin to avoid not only proarrhythmic side effects but also thrombocytopenia. Practitioners should be able to recognize the clinical manifestations of this clinical presentation, differentiate it from other causes, and manage it appropriately.

Conflict of Interests

There are no conflicts of interests for the development of this publication.

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