

INTOXICATION BY DIGITALIS PURPUREA IN SUICIDAL INTENTION – A CASE REPORT

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Summary

We report a case of a 27 year old female with a known progressive major depression, who ingested an unknown amount of leaves of *Digitalis purpurea* (Figure 1) for attempted suicide. The patient developed nausea, emesis and a reduction of color vision. Furthermore, the ECG showed atrioventricular block II° (Wenckebach, Mobitz) with the necessity of pacemaker implantation.

The therapeutic range of digitalis compounds are narrowed by the toxic side effects due to interindividual variability of the pharmacologic impact and may be accompanied by potentially life-threatening outcomes. The intoxication by *Digitalis purpurea* is a potentially life-threatening serious adverse event and requires an ICU monitoring. The diagnosis of intoxication by digitalis derivatives is a demanding issue due to the various and often unspecific clinical symptoms and ECG manifestations. The underlying diseases, however, may lead to comparable symptoms and ECG manifestations without the possibility of prompt distinction. Due to the different composition of glycosides, their different half-time values and different cross-reactivity features to common assays, the clinical course, the extent of the severity of symptoms and long-term ECG monitoring represent the adequate method of surveillance and treatment control.

Case report

A 27 year old female ingested an unknown amount of leaves of the common foxglove plant (*Digitalis purpurea*) in the garden of her parents. The patient was suffering from a known major depression with a marked progression within the last six months. The patient felt the desire for quietness regardless of the potentially lethal outcome of an intake of digitalis purpurea. After 4-6 hours, the parents found their daughter vomiting and called the ambulance. There was a known family history of depressive diseases (grandmother, aunt and cousin), other relevant diseases were not known.

The woman was transferred to the emergency room. The patient now reported nausea and a marked reduction of color vision. The physical examination revealed a normal status. The blood pressure was 145/65 mmHg, the ECG showed a sinus rhythm (40-60/min) with an atrioventricular block II° (Wenckebach and Mobitz). Furthermore, the ECG showed marked concave ST-segment depression in the leads II, III, aVF, V4-6 (Figure 2). The rel. QT-Interval was 110%. Blood samples showed a marked elevated level of digitoxin (112 nmol/l, therapeutic range: 10-35 nmol/l), a low level of digoxin (0.6 nmol/l, therapeutic range: 1.0-2.5 nmol/l), a leukocytosis (12280/μl) and a normal potassium value (4.45 mmol/l). The patient was transferred to the intensive care station (ICU). Due to recurrent bradycardia (30/min), a temporary pacemaker was implanted via the right internal jugular vein. Activated carbon and colestyramin were administered per os. After three days, the ECG showed a sinus rhythm (60/min) and an atrioventricular block I° (PQ-interval 220 ms) and a recurrent atrioventricular block II° (Wenckebach, Mobitz). Later on, the temporarily implanted pacemaker was removed. The digitoxin level abated within four days to a therapeutic value (23 nmol/l) and the initially reported color vision symptoms diminished after three days. The patient was transferred to the intermediate care station (IMC) for further monitoring. Even eleven days after the intoxication and seven days after the assessment of a subtherapeutic digitoxin blood level (Figure 3), the holter monitoring revealed a sinus rhythm and an intermittent

atrioventricular block II° (type 1). Later on, the patient was transferred to the psychiatric ward.

Discussion

Digitalis compounds historically played a major role in the therapy of congestive heart failure. William Withering already described the effect of the leaves of the common foxglove plant (*Digitalis purpurea*) in 1785⁽¹⁾. The composition and amount of glycoside underlies interindividual variability between all sorts of foxglove plant compounds (e.g. *Digitalis purpurea* and *Digitalis lanata*). *Digitalis purpurea* leaves contain secondary glycosides such as digitoxin, gitoxin and gitaloxin. These secondary glycosides are produced by the enzymatic conversion of the primary glycosides of *purpurea* glycoside A, *purpurea* glycoside B, and glucogitaloxin⁽²⁾. Using a high-performance liquid chromatography (HPLC), the amounts of digitoxin, gitoxin, and gitaloxin were estimated to be 22.6, 14.0, and 54.7 µg per 100 mg of dry leaf powder⁽³⁾. The cardiac glycoside digoxin became one of the most commonly prescribed digitalis derivatives for treatment of congestive heart failure⁽⁴⁻⁶⁾. The positive inotropic effects of digitalis compounds result from increase of intracellular Ca^{2+} by specific inhibition of the intrinsic Na^+K^+ -ATPase resulting in a shift upward and left of the Frank-Sterling curve^(4, 7). Today, digitalis derivatives like digoxin and digitoxin are used for their ability to slow conduction through the atrioventricular node in the context of atrial fibrillation or flutter⁽⁸⁾. Furthermore, recent findings suggested the regulation of several important cellular processes. As a consequence, glycoside-based anticancer drugs were investigated in recent studies⁽⁹⁾. Digitoxin is completely absorbed (bioavailability 95-97%) and largely excreted in the bile. It passes a gastrointestinal circulation by means of an extensive recycling of the compound. Furthermore, digitoxin is protein-bound, metabolized and excreted in the urine as metabolites, resulting in a long half-time of five to seven days irrespective of renal function⁽¹⁰⁾.

The intoxication by digitalis derivatives is a potentially life-threatening disease and difficult to diagnose because of the various and often unspecific clinical symptoms and ECG manifestations. The underlying diseases, however, may lead to comparable symptoms and ECG manifestations without the possibility of prompt distinction. During an open-label multicenter clinical trial of Fab treatment for life-threatening digitalis intoxication, 50% of the intoxications resulted from a long-term administration of digitalis derivatives, 10% from an unintentionally acute overdosing and 40% from an ingestion in suicidal intention⁽¹¹⁾. Intoxication by digitalis derivatives increases cardiac automaticity - particularly in the Purkinje fibers - and evokes any kind of cardiac arrhythmias like uni- or multifocal ventricular extrasystoles (VES), atrioventricular block I°-III°, paroxysmal atrial tachycardia with consecutive atrioventricular block, right or left bundle branch block or fascicular block. Furthermore, even junctional atrioventricular node tachycardia and ventricular tachycardia has been described⁽¹²⁻¹⁴⁾. The intoxication by digitalis leads to an atrioventricular block II° in about 11-16%^(8, 15).

Clinical symptoms vary: 98% exhibited extreme fatigue or a serious visual disturbance. Other typical symptoms included weakness, nausea, dizziness, headache, anorexia, abdominal pain, diarrhea, vomiting, and abnormal dreams⁽¹⁶⁾. Moreover, the clinical symptoms depend on the type of intoxication: acute intoxication often leads to nausea, vomiting, and cardiotoxic effects (cardiac arrhythmias), whereas chronic intoxication leads to symptoms like weakness, color vision alteration or inappetence⁽¹³⁾. The further treatment of digitalis intoxication depends on the clinical and electrocardiographic manifestation. The common manifestations like ectopic beats, first-degree atrioventricular block or atrial fibrillation with a slow ventricular response requires ECG monitoring and pausing of the drug. Sinus bradycardia, sinoatrial arrest and second- or third-degree atrioventricular block may be treated with

atropine or (as in this case report) by implantation of a temporary pacemaker. Because of its large volume of distribution, a hemodialysis is ineffective in the treatment of digitalis toxicity⁽⁴⁾. After application of atropine or implantation of a pacemaker, a gastrolavage and the application of cholestyramin or derivate is useful for treatment of an acute intoxication. The potassium level should be elevated to a high-normal value. Furthermore, in the context of a marked intoxication (atrioventricular block III°, hemodynamic instability, long-lasting elevation of the digitoxin or digoxin level), the administration of Fab fragments is useful: Fab fragments bind digoxin and digitoxin due to their higher affinity to the glycosides than the cardiac glycoside receptors themselves and result in a renal elimination.

In this case report, the patient presented typical clinical symptoms (nausea, vomiting, color vision disturbance) and ECG signs (atrioventricular block II°) consistent with the admitted ingestion of *Digitalis purpurea*. The initial decrease of the digitoxin level showed a half-time of 2-3 days. Since the glycoside and aglycone composition of *Digitalis purpurea* possess different cross reactivity regarding the assay used at that time (Figure 4), the pharmacodynamically effective amount of glycosides was presumably underestimated. This may explain the fact that despite of the normalization of the digitoxin levels to subtherapeutic values, the cardiac effects of the intoxication persisted for a considerable time. Regarding the intoxication with non-therapeutic compounds of digitalis, the diagnostic and therapeutic measures have to be determined by the severity of the symptoms. Due to the fact that the patient presented with a stable hemodynamic status, normal potassium level and marked decrease of the digitoxin level in the course of time, the administration of digitoxin Fab fragments was not indicated. Due to the different composition of glycosides, their different half-time values and cross-reactivities to common assays, the clinical course, the extent of the severity of symptoms and long-term ECG monitoring represent the adequate method of surveillance and treatment control.

Reference

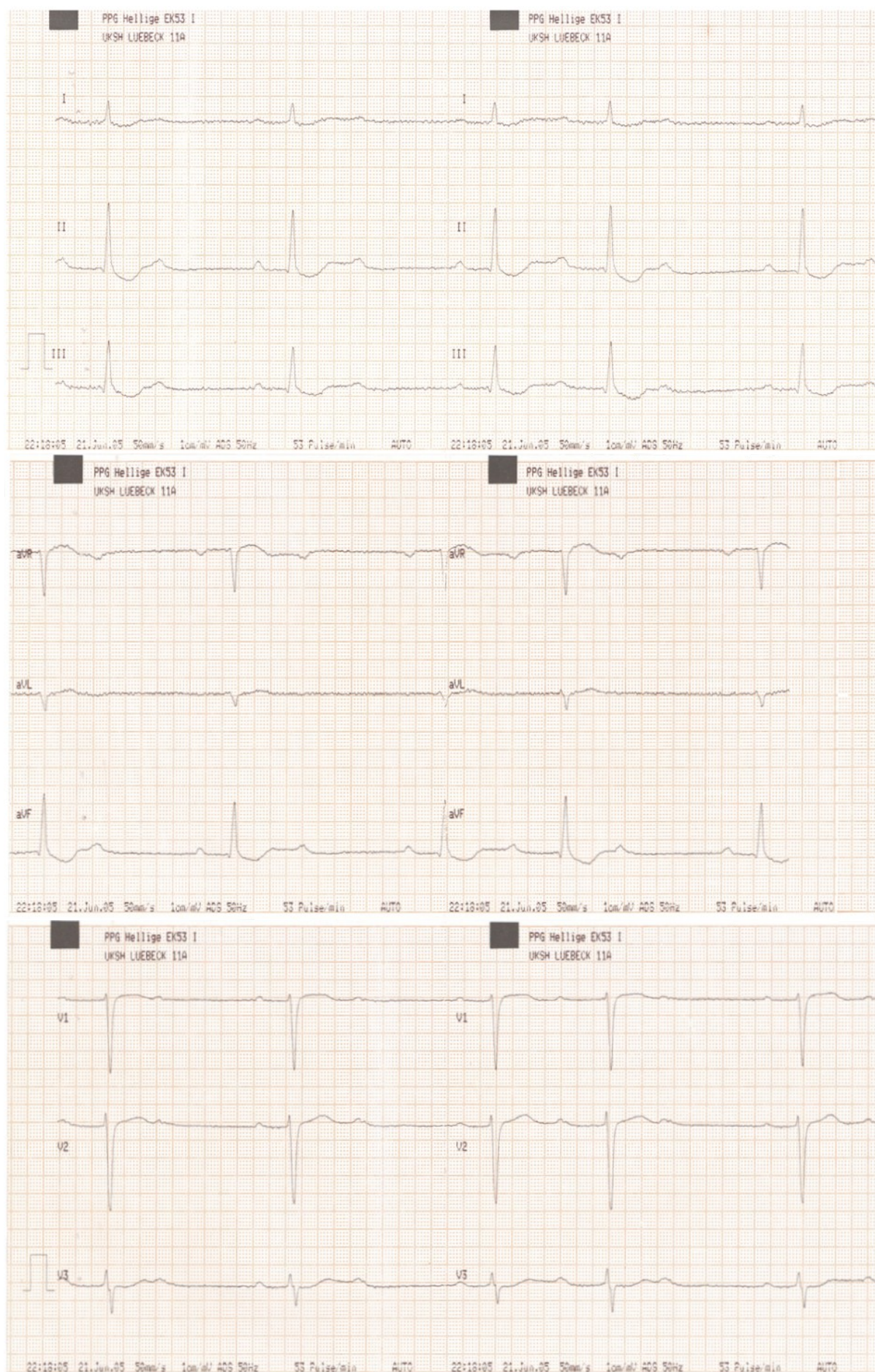
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Figure 1. Common foxglove plant (*Digitalis purpurea*)



Figure 2. Atrioventricular block II° (Mobitz)



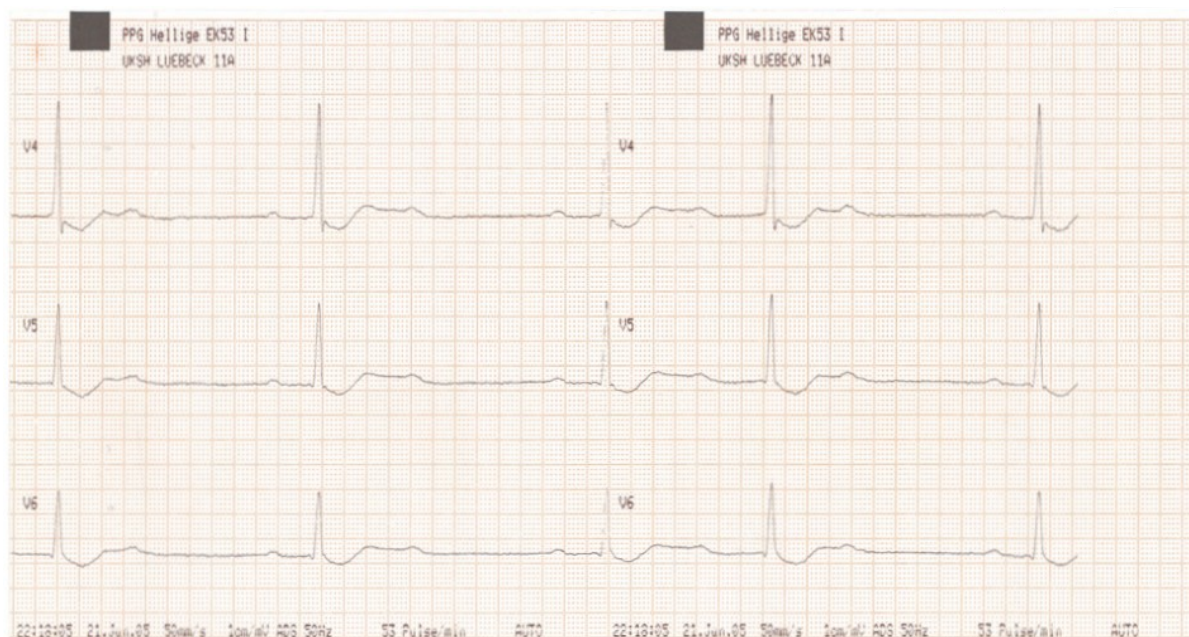


Figure 3. Plasma digitoxin level and clinical symptoms after intoxication by Digitalis purpurea

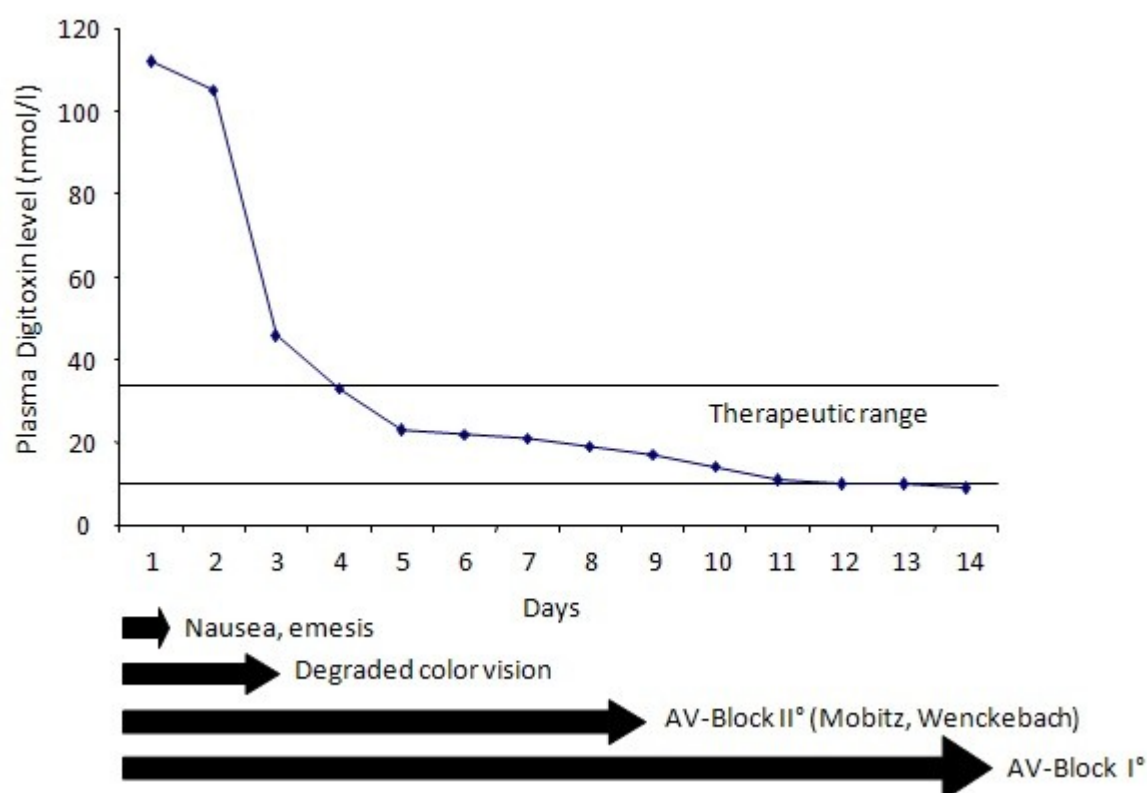


Figure 4. Results of cross-reactivity studies of the utilized digitoxin assay⁽¹⁷⁾

Tested Compound	Average % Cross-reactivity
Digitoxin	100
Digoxin	16
Digitoxigenin	169
Digitoxigenin-mono-digitoxosid	151,4

Digitoxigenin-bis-digitoxosid	132,5
Dihydrodigoxin	0
Dihydrodigitoxigenin	11
Dihydrodigoxigenin	0
Digoxigenin-mono-digitoxosid	0