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Extra Corporeal Life Support in Life-Threatening Digoxin Overdose: A Bridge to Antidote

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Abstract

Digoxin poisoning is a potentially life-threatening overdose that may result in refractory atrioventricular block and ventricular arrhythmias. The efficacy of digoxin-specific Fab fragments in controlling all manifestations of digoxin toxicity was consistently evidenced. However, specific Fab fragments are very expensive meanwhile digoxin poisoning is very rare. The likelihood of occurrence of a severe digoxin overdose in a setting where specific Fab fragments are not available is very high. We report a case of poisoning with 22.5 mg of digoxin in a previously healthy 50-year-old male who experienced the onset of an atrioventricular block followed by a refractory electromechanical dissociation. The installation of an arteriovenous extracorporeal support prevented further development of a multi-organ failure in this patient in refractory cardiac arrest while allowing for the supply of Fab fragments, as well as the infusion of that expensive antidote over a period of time, resulting in the optimization of the Fab fragments' binding capacity. This case report along with another one support the addition of life-threatening digoxin poisonings as a possible cause of refractory electromechanical dissociation. Digoxin-specific Fab fragments should be considered as first-line treatment. However, in case of sudden hemodynamic compromise while Fab fragments are not immediately available, arterio-veinous extracorporeal life support might be life-saving, enabling a "bridge to antidote" along with the infusion of digoxin-specific Fab fragments using the most efficient dosage regimen.

Keywords: Digoxin poisoning; Antidotes; Extracorporeal circulation; Resuscitation; Cardiac arrhythmia

Introduction

Nowadays, digitalis overdoses are rarely observed because the indications for treatment with digoxin are limited [1,2]. Overdoses may occur during chronic treatment with digoxin or acutely following a massive intake in a suicidal attempt [3,4]. Digitalis poisoning is a potentially life-threatening overdose. However, reports of large series on digoxin-specific antibodies fragments (Fab) consistently evidenced the efficacy in controlling all the manifestations of digoxin toxicity. However, the mortality rate of digoxin poisoning is about 15 percent even nowadays without digoxin-specific fragments, while the mortality rate in series treated with digoxin-specific Fab fragments is about 6% [4].

Although digoxin poisoning is very rare, the likelihood of a severe digoxin overdose occurrence in a setting where the expensive Fab fragments are not available is very high. Furthermore, the dosage regimen of Fab resulting in the best compromise between cost and efficacy is a pending question regarding both the lowest efficient dose of Fab as well as the most efficient dosage regimen [5]. We report a case of acute oral digoxin poisoning resulting in a refractory cardiac arrest. Due to the severity of the poisonings we combined immediate life-saving ECLS with the continuous infusion of Fab fragments over a 7 hour period of time. This period of time was recommended by Schaumann et al in human digoxin poisoning [6] that showed that this dosage regimen resulted in the greatest amount of Fab bound to digoxin eliminated in the urine.

Case Presentation

A 59-year-old man (100 kg), general practitioner, called for medical assistance, self-reporting the ingestion of 90 tablets of 0.25 mg digoxin (total dose: 22.5 mg). His past medical history was significant for depression and a previous suicidal attempt. The medically staffed team arrived at the patient's home four hours after ingestion. At the time of presentation, the patient was obtunded, with a Glasgow Coma Scale (GCS) estimated at 13, a heart rate at 35 b/min and a blood pressure of 98/49 mmHg. The pulse oximetry while breathing room air gave a result of 98%. Within three minutes, the heart rate decreased to 24 b/min, the GCS suddenly decreased to 3 meanwhile the O_2 saturation decreased to 80%. The patient was endotracheally intubated, he received repeated doses of atropine up to a total of 4 mg, but in spite of atropine administration his heart rate remained at 35 b/min. During the transfer to the hospital, there was a pulse less arrhythmia which resulted in two electrical shocks delivered by a semi-automatic defibrillator. The patient was admitted in intensive care unit while receiving cardiopulmonary resuscitation, 5 hours after ingestion. In the context of a severe digoxin intoxication, which is a reversible cause of cardiac arrest, we decided to continue resuscitation. However, owing to the refractoriness of cardiac arrest during 20 minutes related to refractory electromechanical dissociation in spite of resuscitation, we initiated ECLS which started 5.50 hours after ingestion. The blood pressure was not recordable till 6.5 hours after ingestion; the first measured value was 54/28 mmHg

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Table 1: Findings in two cases of acute severe digoxin treated with ECLS and equimolar dose of digoxin-specific Fab fragments.

Findings/Authors	Behringer et al (9)	Present case
Sex	Male	Male
Age (years)	79	59
Supposed ingested dose of digoxin (mg)	11	22
Delay in presentation	4 h 11	4 h
Delay ingestion –collapse	4 h 42	4 h 03
Initial rhythm	Electromechanical dissociation	Electromechanical dissociation
Serum potassium (mmol/l)	6.3	5.8
Duration of No-Flow (min)	0	0
Time from ingestion to ECLS	5h17	5h50
Time from ingestion to Fab	5h40	15h
Delay in return of spontaneous circulation	6h07	22 h
Duration of ECLS	9h30	120 h
Outcome	Died from sepsis on day 12	Discharge alive. No sequelae at 78th day post ingestion

using an arterial catheter. The blood flow provided by ECLS was 5.3 l/min. Norepinephrine was infused following a dosage of 6.5 mg/h and dobutamine with a dosage of 10 µg/kg/min. The mean blood pressure rose up to 61 mmHg while there was a flat non-pulsatile blood pressure recording. Arterial blood gases measured on a blood specimen collected 1.20 h after the start of ECLS showed a pH of 7.21, a PaCO2 of 41 mmHg, and a PO_2 of 213 mmHg (FiO_2 both with the mechanical ventilator and ECLS was 100%). Blood bicarbonate concentration was 15.6 mmol/l and blood lactate concentration was 5.1 mmol/l, the blood potassium level measured on admission was 5.8 mmol/l and the level of serum creatinine was 140 µmol/l. The plasma digoxin concentration on ICU admission -5 hours after ingestion- was 30.2 µg/l (toxicity threshold > 2 ng/ml). Fab was infused 15 hours after ingestion, corresponding to 9 hours after ECLS initiation. The plasma digoxin concentration just before Fab infusion was 22 µg/l. An equimolar dose of Fab was administered with a half dose infused over 1 hour and the remaining half over 6 hours. The electrical activity assessed by continuous recording showed a heart rate after initiation of ECLS and just before Fab administration ranging from 83 to 190 b/min. However, there was no hemodynamic efficiency as evidenced by a flat blood pressure without any detectable systolic and diastolic pressure suggesting a long-lasting episode of electromechanical dissociation.

In contrast, simultaneously with the completion of Fab administration, the heart rate dropped suddenly from 150 to 65 b/min meanwhile there was a return of spontaneous circulation 7 hours after injection. The return of spontaneous circulation was evidenced by the on-off occurrence of a systolic blood pressure of 113 mmHg with a diastolic blood pressure of 74 mmHg meanwhile the patient received dobutamine at 12 µg/kg/min and 4.5 mg/h of norepinephrine. The withdrawal of catecholamines was effective at day 4. ECLS was removed at day 5 and mechanical ventilation at day 8 post-ingestion.

The echocardiography 5 days after removal of ECLS showed a complete recovery of the systolic and diastolic left ventricular functions. The patient could leave the intensive care unit at day 13 post-ingestion with a Cerebral Performance Categories score of 1. The follow-up of the patient showed no sequelae or complaint whatsoever at day 78 post-ingestion. The patient gave his written informed consent for publication of his case.

Discussion

Deaths resulting from digoxin poisoning are reported to mainly result from high grade of atrioventricular block and ventricular fibrillation [7]. The present case reports the onset of a long-lasting period of electromechanical dissociation. However, electromechanical dissociation is rarely reported during the course of digoxin poisoning. Indeed, in a series of 717 adult patients poisoned by digitalis, the authors did not mention any electromechanical dissociation [8]. We found only one case of life-threatening acute digoxin poisoning resulting in electromechanical dissociation, which was initially treated with ECLS, which resulted in changing heart rhythm from electromechanical dissociation to ventricular fibrillation, yet refractory to repeated attempts of cardioversion [9]. The table 1 compares the findings in the two cases. In both cases pulse less electromechanical dissociation resumed only under ECLS and after the completion of an equimolar neutralization using Fab fragments. Several extrinsic factors may contribute to the onset of electromechanical dissociation during digoxin poisoning, including long-lasting cardiac resuscitation using a mechanical device, repeated external electric shocks, and the administration of large doses of epinephrine. Our case and the previous one suggest that ECLS in digoxin poisoning resulting in a pulse less condition with organized electrical activity may unveil a cardiac rhythm rarely reported in non-fatal poisoning. These data suggest that when Fab fragments are not available, aggressive resuscitative measures including arterio-veinous ECLS should be considered for digoxin poisoning when patients are not responding to any conventional treatment. It is noteworthy that the two patients having benefited from ECLS met prognostic factors of poor outcome in digitalis poisoning [10,11], including male gender, age older than 55, onset of atrioventricular block, and hyperkalemia greater than 5.5mmol/l. Unfortunately, the arterial-venous ECLS has been extremely rarely reported. Indeed, in an extensive review about the use of different modes of ECMO, even the case presently referred to was missed, while digitalis was not cited in the list of toxicants

treated with ECLS [12]. Actually, even in the ELSO report which is the annual report of the registry built by the extracorporeal life support organization, digoxin overdose is not listed as an indication for ECLS [13]. However, the ELSO registry is including patients benefiting of ECLS while being admitted in a center belonging to the ELSO database which merely includes departments of cardiovascular surgery. With the development of ECLS in Medical intensive care unit, a large number of ECLS performed in these departments cannot be included in the ELSO registry. As a matter of fact, in spite of our requirement to ELSO, none of the 111 acute poisonings we reported were registered in the ELSO database [14]. Noteworthy, in spite our experience in the field of ECLS in acute poisoning, the present case of digoxin poisoning is the first having benefited of ECLS. We cannot exclude that, throughout the world, ECLS may have been performed in digoxin poisoning meanwhile the cases having not been reported in the available medical literature.

Fab fragments are consistently reported as a safe and efficient treatment for dealing with digoxin poisonings [3,8,15,16]. Fab fragments are a highly specific treatment that rapidly reverses digitalis cardiotoxicity. However, Fab fragments are a highly expensive antidote with limited shelf life while digoxin overdose is a rare poisoning. Therefore, its availability might be frequently limited. In the present case, the shortage of Fab supply resulted in a delayed treatment meanwhile our intensive care unit had facilities for providing ECLS [17,18] as well as we have a large experience of arterio-veinous ECLS in poisonings [14]. Furthermore, the most efficient dosage regimen of this costly treatment still remains a matter of debate. Rapid infusion is advised when facing life-threatening arrhythmias [8]. However, the pharmacokinetics of Fab fragments in humans showed a rapid elimination that may result in the rapid elimination of Fab fragments unbound to digoxin. To address this major concern, Schaumann et al looked for the dosage regimen resulting in the greatest amount of Fab eliminated in the urine as digoxin-Fab complexes. This issue was solved using an equimolar dose of Fab, administered as follows: half the dose infused intravenously over 1 hour and the remaining half infused over 6 hours [6]. Interestingly, the present case showed a temporary relationship between the completion of Fab infusion on the one hand and the sudden return of a spontaneous efficient hemodynamic condition on the second hand. However, the present case use of that dosage regimen was closely dependent on the hemodynamic support efficiently provided by ECLS.

Conclusion

Life-threatening digoxin poisonings may result in a sudden onset of refractory electromechanical dissociation, a rhythm disturbance that ought to be included in the list of digoxin overdose-induced dysrhythmias. The analysis of prognostic factors at the time of presentation may help to focus on severe poisonings. When faced with a life-threatening digoxin overdose, the attending physician should consider the availability of not only Fab, but also arterio-veinous ECLS. Fab fragments are the first-line treatment. However, in case of sudden hemodynamic compromise, including pulse less electromechanical dissociation, when Fab fragments are not immediately available, ECLS might be life-saving enabling a "bridge to specific treatment" allowing the infusion of Fab fragments using the most efficient dosage regimen.

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