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CASE REPORT

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Venoarterial extracorporeal membrane oxygenation in combination with Levosimendan as a bridge to recovery for a case of severe yew intoxication in a 13-year-old patient

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Key Clinical Message

In an adolescent patient with severe yew intoxication and consecutive cardiac arrest, non-responsive to conventional resuscitation necessitating extracorporeal life support, Levosimendan has been implemented in the early acute phase of hemodynamic stabilization, without obvious side effects. However, the additive value of this treatment in severe yew intoxication remains speculative.

KEYWORDS

echocardiography, ECPR, extracorporeal membrane oxygenation, Levosimendan, yew

1 | INTRODUCTION

The common yew (*Taxus baccata*) is an evergreen conifer, widely cultivated in Western Europe. The entire plant and its typical leaves are displayed in Figure 1. All parts of the plant with the exception of the red aril, are poisonous. In humans, accidental consumption is frequent in infants up to 3 years but is mostly asymptomatic due to the small amount. Ingestion in suicidal attempt is rare but has a severe prognosis as the median lethal dose in humans is about 0.6–1.3 yew leaves/kg body weight, equivalent to approximately 50–100 g of leaves in an average adult person.[1]

The plant contains Taxine A (13% of total yew alkaloids) and B toxins (30% of total). Especially the latter is responsible for cardiac toxicity by elevation of cytoplasmatic calcium in cardiac myocytes by blocking sodium and calcium channels. The effect is therefore similar to the calcium channel blocking drug verapamil.[1] A broad spectrum of cardiac arrhythmias has been described: The blockage of the sodium channels leads to widening of the QRS complex, resulting in polymorphic ventricular tachycardia and fibrillation, whereas the blockade of the calcium channels induces bradycardia and atrioventricular block. In addition to the arrhythmogenic potential, myocardial contractility is impaired. Further symptoms consist of nausea, vomiting, abdominal pain, mydriasis, polyuria, hypokalemia, and respiratory distress.

There is no common laboratory test to identify taxines in the blood. Ingestion can be detected by analyzing specific alkaloids and metabolites such as 3,5-dimethoxyphenol in the urine and blood. The time from ingesting a lethal dose to death is usually 2–5 h, the first symptoms can

Abbreviations: ARDS, acute respiratory distress syndrome; ECLS, extracorporeal life support system; eCPR, extracorporeal cardiopulmonary resuscitation; ILE, intravenous lipid emulsion; TEE, transoesophageal echocardiography; (V-A) ECMO, (venoarterial) extracorporeal membrane oxygenation.

occur after 30 min. The biologic half-life of taxine metabolites ranges between 11 and 13 h and after ingestion they may still be detectable in the blood up to 120 h following digestion. Symptomatic yew intoxication is a major challenge for attending physicians for multiple reasons. First, the treatment is entirely symptomatic since there is no specific antidote for the intoxication. One of the few suggested measures investigated further in an animal model was hypertonic sodium bicarbonate, however, without a demonstrable benefit.[2] Other suggested pharmacologic interventions for taxine removal include the use of anti-digoxin antibodies, so-called fab fragments and intravenous lipid emulsions (ILEs).[3] Nevertheless, ILE has been associated with severe side effects such as acute kidney and lung injury, venous thromboembolism, hypersensitivity, and fat overload syndrome, while the optimal dosing time and mechanism of action remains unclear.[3,4] Second, recurrent ventricular arrhythmias usually do not respond to amiodarone administration.[1,5] Third, bradycardia and hypotension might prompt the use of a temporary external or transvenous pacemaker. Eventually, with increasing doses of ingested taxines, refractory asystole often occurs with the need for an extracorporeal life support system (ECLS) as salvage intervention. After elimination of the taxines, the myocardial function usually recovers completely in patients surviving the intoxication; however, prognosis might be limited by hypoxic brain damage or complications of ECLS.[6]

2 | CASE SUMMARY

A 13-year-old girl with a background of anorexia nervosa (bodyweight at admission 40 kg) was admitted to an university hospital with a yew intoxication with suicidal intent. A family member found her at home somnolent with berries and leaves of yew in her vomit. Upon arrival of the paramedics, the patient had a seizure with further decrease of consciousness culminating in cardiac arrest and therefore cardiopulmonary resuscitation (CPR) was initiated. The underlying rhythm alternated between pulseless electric activity and asystole. Only intermittently, return of spontaneous circulation was achieved and the patient was eventually brought to the emergency department under ongoing CPR. On site, immediate extracorporeal life support with venoarterial extracorporeal membrane oxygenation (V-A ECMO) was initiated with a 17 French arterial cannula, distal perfusion cannula and a 23 French venous return cannula (Maquet GmBH Getinge Group, Rastatt, Germany), in femoro-femoral configuration, according to local standard protocols.

Furthermore, a parallel bundle of supportive measures to reduce toxin load and effect has been administered in the emergency department, consisting of activated charcoal, sodium bicarbonate 8.4% and 30 mg of ILE. Emergency gastroscopy was not attempted.

After a total of 110 min of chest compression, including the prehospital period, ECMO blood flow was initiated at 3.1 L/min and a cerebral computer tomography was performed, ruling out an acute intracranial lesion. Further treatment was conducted in the ICU.

Laboratory tests on admission revealed normal renal and liver function, as well as normal blood count, featuring respiratory acidosis with a minimal pH of 7.1, a $p\mathrm{CO_2}$ of 9.8 kPa and a lactate of maximal 16 mmol/L. The cardiac biomarkers were elevated in the context of resuscitation measures with a high-sensitive troponin T of maximally 687 ng/L and a creatinine kinase of 2.602 U/L.

Upon arrival in the ICU, echocardiography showed severely reduced left ventricular function with no evidence of ejection over the aortic valve; a respective video of the severely impaired left ventricle can be found in

FIGURE 1 Common yew (*Taxus baccata*) plant and typical leaves.

Video S1. The electrocardiogram on admission is displayed in Figure 2 and showed unspecific broad complex bradycardia. Therefore, inotropic support with adrenaline 0.03 µg/kg/min and milrinone 0.2 µg/kg/min was initiated to increase contractility, establish forward flow over the aortic valve, and ultimately prevent intracardial thrombus formation. Severe hypotension occurred, which was attributed to the vasodilatory effects of milrinone therapy, which then was ceased, and noradrenaline was added instead to the vasoactive therapy, up to a maximum dose of 1.6 µg/kg/min.

On Day 1 after admission, intermittent hemodynamically relevant ventricular tachycardia occurred. Video S2 shows a representative apical four-chamber view of this episode of treatment. Repeated electrical cardioversions had no effect. After the administration of amiodarone 150 mg and substitution of electrolytes, a conversion into a stable sinus rhythm was achieved.

Despite improved electric activity of the heart and extended inotropic support with adrenaline and milrinone as well as escalated noradrenaline doses, echocardiography on Day 2 still showed a severe biventricular dysfunction with a left ventricular ejection fraction of an estimated 10%, insufficient pulsatile flow, and a complete dependency on V-A ECMO. After interdisciplinary discussion with pediatric intensive care providers, Levosimendan was started at 0.05 µg/kg/min. After 24 h, summing up to a total dose of 2.9 mg, left ventricular function improved with the pulse-pressure difference averaging at 40 mmHg compared to less than 20 mmHg before Levosimendan and markedly improved contractility in the echocardiography (Videos S3 and S4). Subsequently, inotropic support and ECMO blood flow could be weaned. Figure 3 displays a timeline of events and crucial treatment steps. Our institutional standard for ECMO weaning involves targeting a minimal flow of 1.5 L/min while monitoring with echocardiography. However, considering the patient's weight and height, it was believed that aiming for lower ECMO flow would better indicate sufficient left ventricular recovery, even if the physiologic cardiac output is numerically smaller compared to that of an adult. To implement this approach, we modified our protocol and gradually reduced the ECMO flow in steps of 1 L/min until reaching 0.8 L/min. Throughout the process, echocardiography showed a return to normal biventricular contractility, and there was no need for additional vasoactive support. Blood gas analysis also revealed no increase in lactate levels. Based on these positive indicators, the patient was considered suitable for ECMO removal. The procedure was carried out smoothly on the fourth day after admission, and there was no recurrence of the need for vasoactive medication.

Noteworthy, the patient suffered from gastroparesis and paralytic ileus despite prokinetic measures. The gastrointestinal function only recovered at Day 4 and a significant

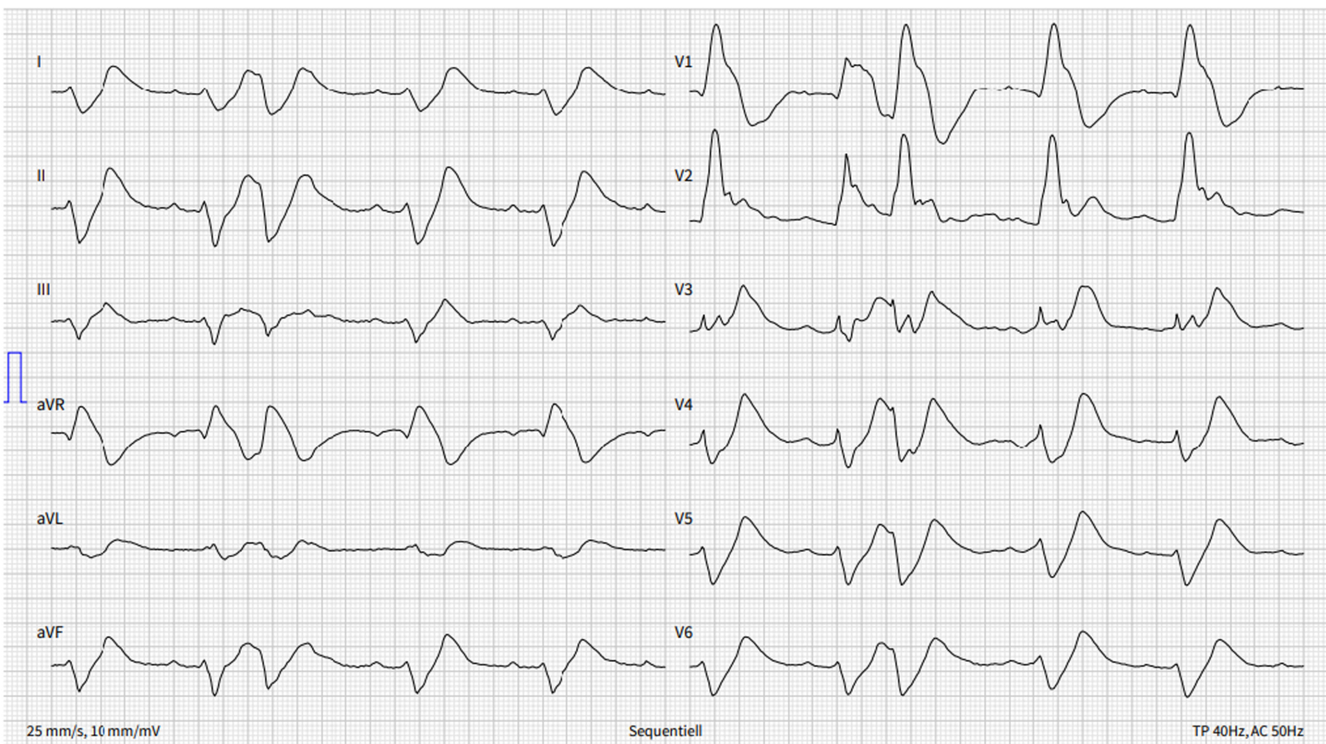

FIGURE 2 ECG at admission on intensive care (ECMO blood flow 3.5 L/min).

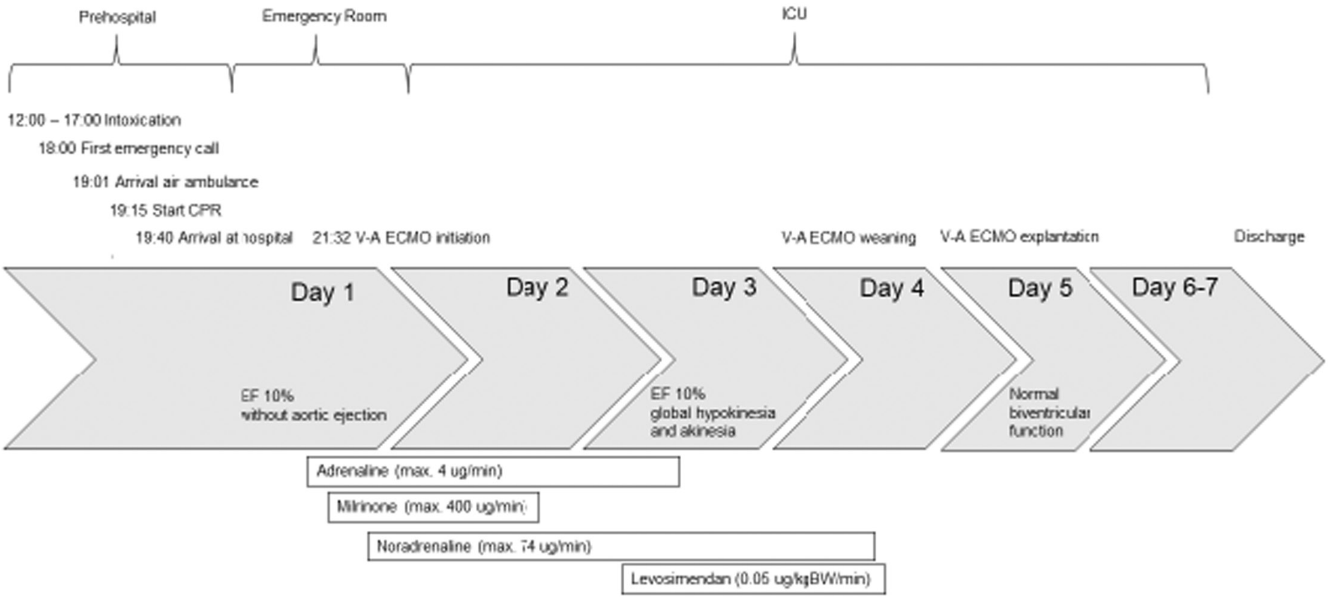

FIGURE 3 Timeline of events.

number of leaves and berries of yew could still be found in the stool. Further course of treatment was complicated by an inspiratory stridor after extubation on Day 5 after admission which was interpreted as an overhang of sedation and treated with a flumazenil infusion for 22.5 h in combination with NIV therapy and subsequently resolved after 24 h.

At Day 6, the patient was referred to the local University Children's Hospital for further treatment after full neurologic recovery. She was then referred to a psychiatric hospital 6 days later.

3 | DISCUSSION

We report the case of a 13-year-old patient who required prolonged CPR after intoxication with yew and subsequently received extracorporeal cardiopulmonary resuscitation (eCPR) and a total of 63 h of V-A ECMO support, along with extensive inotropic medication including Levosimendan administration. She was finally discharged from the ICU without major neurologic residual damage.

Cardiac failure caused by taxines is known to be resistant to catecholamine treatment and causing chaotic arrhythmias that are exceptionally hard to treat with conventional shock management.[5] Furthermore, despite the desirable effect of increased contractility, inotropic medication increases cardiac oxygen consumption, adrenergic stimulation, and wall tension while being pro-arrhythmic. Thus, inotropic support itself might counteract the underlying goal of shock therapy apart from ensuring systemic perfusion, namely cardioprotection and metabolic rest to promote cardiac recovery, which is precisely the starting point for implementation of mechanical devices in shock therapy.[7] In this case, ECLS proved to be largely effective in restoring cerebral and systemic perfusion. One of the most feared side effects and risks in peripheral V-A ECMO, namely formation of intracardiac thrombi, can only be prevented by aggressive anticoagulation and maintaining pulsatile flow through the heart as well as output through the aortic valve.[8] Due to the downsides of inotropes, we aimed to minimize adrenergic medication but as this turned out to be not sustainable and not effective in creating a satisfying pulsatile flow through the heart, we introduced Levosimendan as an additional agent. Levosimendan is considered a superior inotrope by some authors in the situation of shock,[7] however based on limited data and especially without any data available for yew intoxication. With the pressing issue of avoiding intracardiac thrombus formation at all costs, Levosimendan was thought to be the last resort to improve pulsatility and therefore contribute to safe operation of the ECMO circuit. To our knowledge, this is the first implementation of a calcium sensitizer in the acute therapy of yew intoxication in combination with ECLS in an adolescent patient; however, any additional value of Levosimendan is purely speculative. Hermes-Laufer et al. report the use of Levosimendan to support ECLS weaning after yew intoxication, administered when left ventricular function had already recovered to a mild impairment and right ventricular function was back to normal.[6] In contrast, our rationale was the support of native cardiac output as other pharmacologic interventions had failed to restore contractility, while still depending on V-A ECMO. Hereby, it is purely speculative if the mode of action of Levosimendan as a calcium sensitizer is especially suitable as a treatment in the context of sodium and calcium channel blockage by taxines and if the absence of increased oxygen consumption has a positive influence on resolving shock.

Furthermore, it is impossible to distinguish the proportion of influence on improved cardiac function from toxin clearance and altered inotropic therapy. Thus, our report of implementation of Levosimendan in the acute phase of yew intoxication is limited to safe use without any related complications or further deterioration, without drawing a deduction on its impact on the clinical course of the patient.

V-A ECMO has been used successfully as a bridge to recovery before in the treatment of yew intoxication, as a distinctive feature of cardiac failure caused by taxines is the potential for complete recovery after metabolization of toxins.[6] A recent review of the literature sums up 11 cases of ECLS in yew intoxication, reporting a mean support time of 70 h, in the range of 24–120 h, in patients of a mean age of 28 years (range 19–46 years).[6] The duration of support in our case was within described time limits; at the same time, gastroparesis and paralytic ileus might have delayed full taxine clearance. Given the prolonged period of conventional CPR and ECLS implementation of a total of almost 2 h, not including the unknown downtime at home, the benefit of gastroscopy with attempted clearance of leaves containing taxines might have been limited as uptake of lethal dose typically occurs within 2–5 h after ingestion.[6] Thus, the treating team prioritized further hemodynamic stabilization and transfer to the ICU. However, endoscopy more than 2 h after yew ingestion has been described as well as early charcoal administration.[6]

Successful prolonged mechanical CPR in the context of yew poisoning has been described in minors, but not the use of V-A ECMO.[5] Thus, this case represents a novelty in this regard; however, intake of other cardiotoxic drugs in suicidal attempt in minors has been treated in a comparable manner. Ferry et al. report the case of a 14-year-old girl, weighing 68 kg, requiring eCPR for chloroquine intoxication.[9] The exact specifications of the circuit are not described; however, the maximum flow is cited at $2\,L/min/m^2$ which resembles flows in the presented case. Our patient was connected to a standard adult circuit, primed with balanced electrolyte solution as per adult protocol. Current Extracorporeal Life Support Organization guidelines are in line with our approach and only recommend smaller tubing and priming with red blood cells for patients under 10–15 kg and opt for femoral cannulation above 30 kg bodyweight.[10] Also, our weaning procedure represents a somewhat hybrid approach between adult weaning protocols that might call for higher minimal flows and pediatric approaches implementing retrograde perfusion.[10]

Simultaneous use of ILE and ECMO might represent one of the most controversial points of the management, as reports of fat emulsion agglutination, clot formation, and oxygenator failure exist. One of the most frequent circuit problems was reported to be cracking of stopcocks, the valve which restricts flow in the V-A ECMO tubing, which we did not use in our setup.[11] Attending physicians were within a highly volatile and dynamic situation and opted for ECLS while being aware of the possible interferences. With hindsight, we regard the successful eCPR with transition to medium-term ECLS and restoration of cardiac contractility as key elements of our treatment.

4 | CONCLUSION

V-A ECMO and eCRP represent valuable treatment options for cardiac arrest in the context of severe yew intoxication. We successfully implemented this strategy in a 13-year-old patient and report the first implementation of Levosimendan in the acute phase of intoxication without further deterioration. The additional value of Levosimendan remains speculative.

AUTHOR CONTRIBUTIONS

Eva Maria Peer: Conceptualization; data curation; formal analysis; project administration; writing – original draft. **Jonas Quitt:** Writing – review and editing. **Stephan Marsch:** Conceptualization; funding acquisition; writing – review and editing. **Gregor Loosen:** Conceptualization; data curation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

No data was recorded and processed. Further image material is not shared openly with regards to patient privacy.

ETHICS STATEMENT

Not applicable.

CONSENT FOR PUBLICATION

Written consent for publication was collected from the patient's legal guardian.

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REFERENCES

1. Wilson CR, Sauer J, Hooser SB. Taxines: a review of the mechanism and toxicity of yew (*Taxus* spp.) alkaloids. *Toxicon*. 2001;39(2–3):175-185.
2. Ruha AM, Tanen DA, Graeme KA, et al. Hypertonic sodium bicarbonate for Taxus media-induced cardiac toxicity in swine. *Acad Emerg Med*. 2002;9(3):179-185.
3. Cave G, Harvey MG. Should we consider the infusion of lipid emulsion in the resuscitation of poisoned patients? *Crit Care*. 2014;18(5):457.
4. Hayes BD, Gosselin S, Calello DP, et al. Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration. *Clin Toxicol (Phila)*. 2016;54(5):365-404.
5. Zutter A, Hauri K, Evers KS, et al. "Chaotic arrhythmia" during successful resuscitation after ingestion of yew (*Taxus baccata*) needles. *Pediatr Emerg Care*. 2019;35(12):e223-e225.
6. Hermes-Laufer J, Meyer M, Rudiger A, et al. Extracorporeal life support as bridge to recovery in yew poisoning: case reports and literature review. *ESC Heart Fail*. 2021;8(1):705-709.
7. Schibilsky D, Delmas C, Bonello L, Hunziker P. Cardioprotective shock management: monitoring and supportive therapies. *Eur Heart J Suppl*. 2021;23(Suppl A):A3-A9.
8. Williams B, Bernstein W. Review of venoarterial extracorporeal membrane oxygenation and development of intracardiac thrombosis in adult cardiothoracic patients. *J Extra Corpor Technol*. 2016;48(4):162-167.
9. Ferry T, Amiet V, Natterer J, et al. Extracorporeal cardiopulmonary resuscitation for severe chloroquine intoxication in a child – a case report. *Scand J Trauma Resusc Emerg Med*. 2021;29(1):48.
10. Gajkowski EF, Herrera G, Hatton L, Velia Antonini M, Vercaemst L, Cooley E. ELSO guidelines for adult and pediatric extracorporeal membrane oxygenation circuits. *ASAIO J*. 2022;68(2):133-152.
11. Lee HM, Archer JR, Dargan PI, Wood DM. What are the adverse effects associated with the combined use of intravenous lipid emulsion and extracorporeal membrane oxygenation in the poisoned patient? *Clin Toxicol (Phila)*. 2015;53(3):145-150.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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