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Yew poisoning– pathophysiology, clinical picture, management and perspective of fat emulsion utilization

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Abstract

The article presents pathophysiology, clinical picture and management of yew poisoning. Authors present also their own experiences with treating yew poisoning with fat emulsion.

Plants of the yew genus, of which in Europe predominates *Taxus baccata*, are well known for their toxic properties. Particularly high concentrations of poisonous alkaloids are present in the needles of this evergreen and highly popular decorative plant. The danger associated with accidental or intentional ingestion of yew is primarily related to the cardiotoxic effects of the alkaloids (taxine A and B). Taxine B shows a much stronger toxic effect on the heart than taxine A. It affects atrio-ventricular conduction, what may result in a widening of the QRS complexes, atrio-ventricular blocks (A-V) of II/III degree and even in asystole.

Yew poisoning is relative rare and evidence-based treatment guidelines on management of such poisoning is hard to prepare. The first-line treatement should base on suportive therapy. In some cases extracorporeal life support therapies such veno-arterial ECMO should be consider. There are also premise based on case reports and mechanism of action that the use of fat emulsion may be effective rescue treatment.

Key words: yew, poisoning, lipid emulsions, heart arrhythmias.

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Plants of the *Taxus* genus, including common yew (*T. baccata*) that predominates in Europe, have been known for ages for their toxic properties. Particularly high concentrations of toxic pseudoalkaloids are present in the needles of this evergreen and highly popular decorative plant. Toxic substances are also found in the other plant parts, except for an aril, and their ingestion may be life-threatening.

The literature published in the last decade includes many case reports describing yew poisoning. The statistical data indicate that most cases are incidental and mainly regard children attracted by red arils. According to the data provided by one of the Czech centres of toxicology and covering the years 2005–2014, children < 3 years of age constitute 45% to 75% of all patients consulted due to yew poisoning [1]. The most severe cases are suicidal attempts associated with the ingestion of high amounts of yew needles; they often concern young individuals and can be lethal in some cases. The information on various methods of committing suicide are easily available on the Internet. There are numerous portals and fora for suicides and one of the methods described there is the ingestion of yew needles.

Yew poisonings are statistically rare (in the centre mentioned above, they constituted 0.55–1.25% of all consultations) yet highly challenging for toxicology and intensive care centres due to severe arrythmias they induce, which may be refractory to standard management.

In the present paper, the pathomechanism and clinical picture of yew poisoning were described. Based on literature analysis, the options of treatment were also discussed. Moreover, the authors presented their experience regarding the effective use of fat emulsions in cases of yew-induced arrythmias refractory to electrotherapy.

PATHOPHYSIOLOGY AND CLINICAL PICTURE

Case report

In the morning hours, a 17-year-old female patient was admitted to the Emergency Department (ED) with the diagnosis: "a condition after sudden cardiac arrest – poisoning suspected". According

to the patient's father who called an ambulance, she woke up at night, went to the toilet and had diarrhoea. He heard her collapsing and found her unresponsive in the corridor. She defecated again. A team of paramedics was deployed to the incident site. According to the history taken from the patient's father, she had depression. Moreover, he suspected drug poisoning. The patient was immediately transported to the ED. During transportation, the paramedics diagnosed sudden cardiac arrest (SCA) resulting from ventricular fibrillation. Cardiopulmonary resuscitation was initiated. It is likely, however, that the patient did not develop SCA and that the paramedics observed polymorphic tachyarrhythmia with a high pulse deficit.

On admission, the patient was unconscious (GCS 4/15); endotracheal intubation was performed. Cardiac monitoring displayed polymorphic arrhythmia tending towards tachycardia with wide QRS complexes accompanied by a significant peripheral pulse deficit (irregular pulse within the range of 35 min^{-1}); SaO_2 was 96% while the arterial pressure 90/45 mm Hg. A cardiologist consulting the patient suggested possible digoxin intoxication. He advised against the use of antiarrhythmic drugs, which could enhance the pathology. Due to tachycardia, one electrical cardioversion was attempted, which failed. The Centre for Acute Poisonings was consulted by phone and the blood was sampled for drug poisoning testing. The consultation, however, provided no significant suggestions regarding the causes of disease. During the ER stay, the patient gradually regained consciousness; the cough reflex was restored, and she started to reach for the endotracheal tube. She was sedated with continuous infusion of propofol and transferred to the Intensive Care Unit (ICU).

On admission to the ICU, sedation and mechanical ventilation were continued. Owing to hypotension, the cardiovascular system was supported with an infusion of adrenaline and noradrenaline. Polymorphic arrhythmias, periodically with bradycardia, intermingled with episodes of tachycardia were still present (Figure 1). During one of them, another unsuccessful electrical cardioversion was performed. Since the observed rhythm was accompanied by significant cardiac failure, stimulation with an endocavitary electrode was attempted, which failed. Haemodynamic monitoring using transpulmonary thermodilution ($PiCCO_2$) was initiated. Substantial pulse deficits were observed. A cardiologist was asked for assistance; he performed echocardiography confirming the correct placement of the endocavitary electrode. Despite the defibrillator replacement, the regular heart rhythm was not restored; therefore, the external electrodes were applied. Although the skeletal muscle contractions were found to be consistent with the stimulation rhythm, the heart rhythm was still not captured. In the meantime, the Centre for Acute Poisonings informed us by phone that testing of the material sent did not reveal any drugs, including digoxin, betablockers, theophylline, neuroleptics and tricyclic antidepressants. The blood contained only benzodiazepine in non-toxic concentration (the patient received diazepam in the ambulance). As for the congenital heart defects considered, the paediatric anaesthesiology and intensive care department was consulted by phone – digoxin toxicity was re-suggested, yet this possibility had already been excluded.

Despite the negative results of toxicology, the entire clinical picture and history were suggestive of poisoning. Intensive fluid therapy was administered, diuresis was forced with mannitol and an infusion of furosemide. The pharmacological treatment did not result in the desired effects. Since the patient's condition deteriorated, shock deepened and the picture was totally insensitive to heart electrostimulation with persistent rhythm abnormalities, rescue administration of 20% Intralipid® (Fraseni Kabi AB, Upsalla, Sweden) was decided. The protocol for acute poisoning with local anaesthetics (LAs) was followed. Moreover, hemodiafiltration was started. About five minutes after the initiation of fat emulsion infusion, a haemodynamically efficient regular sinus rhythm was restored. Shortly after, the dose of pressor amines was reduced yet sedation was maintained. During the third day of hospitalisation, the patient was extubated. No further cardiac arrhythmias were observed; likewise, no neurological deficits were found.

Initially, the patient clearly avoided any conversations with the staff and negated attempted suicide and deliberate drug poisoning. During her talk with a psychiatrist, she finally admitted to ingesting a handful of hashed yew needles, mixed with cheese to improve the taste. Her words were confirmed by nurses who observed atypical hay-resem-

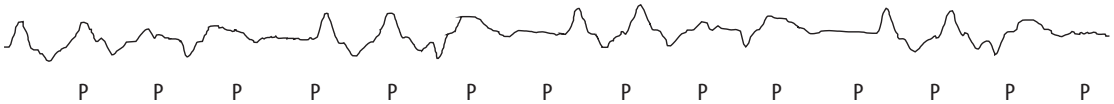

FIGURE 1. Polymorphic arrhythmias recorded by a cardiac monitor in Intensive Care Unit

bling faeces. After six days in the ICU, the patient was transferred to the department of psychiatry.

The mechanism of toxic action of taxines

The toxicity of yew is caused by its pseudoalkaloids, mainly taxine A and taxine B. They have cardiotoxic effects; taxine B has significantly stronger effects on the myocardium than taxine A. An estimated lethal dose of taxines is 3–6.5 mg kg^{-1}. Such an amount is contained in 50–100 mg of needles [1–3].

By acting on the stimulus-conduction system, taxine B impairs atrioventricular and intraventricular conduction, which may result in widened QRS complexes, tachyarrhythmias, second- and third-degree atrioventricular (A–V) block or even asystole. The most recent analyses demonstrate that the mechanism of toxic action of taxine B is associated with its calcium channel antagonism. Moreover, it inhibits the early sodium current [1, 2, 4]. The studies carried out since the first half of the 20th century have demonstrated that hypotension observed in yew poisoning is not related to the activation of the vegetative nervous system (administration of atropine and vagotomy did not result in the desired therapeutic effects) [1, 4]. Beside direct effects on the myocardium, a more likely mechanism is a reduction in vessel wall tone associated with the inhibition of calcium influx to the myocytes [4].

The symptoms usually develop over 1-3 days after the ingestion of yew. The initial stage of poisoning is characterised by gastro-intestinal complaints, including nausea, vomiting, abdominal pain and diarrhoea [4]. Subsequently, severe, life-threatening and often refractory arrhythmias start to predominate. The following abnormalities have been described – second- and third-degree atypical A–V blocks, bradycardia, asystole, ventricular fibrillation and ventricular tachycardia, alternating tachyarrhythmia and bradycardia, "electrical storm", and cardiogenic shock [1, 4–8]. The physicians from Wels (Austria), who treated a 20-year-old patient, described her electrocardiogram using a suggestive term of "a dying heart" [5]. The cardiovascular symptoms may be accompanied by severe disorders of consciousness and paralysis of the respiratory centre [1, 4, 5, 8]. In some cases, metabolic acidosis is observed as well [1, 7–9].

Noteworthy, the mechanism and course of poisoning with arrhythmias are likely to recall digitalis glycoside poisonings [1]. Interestingly, in some patients, toxicology demonstrated the presence of digoxin in blood although the respective history was negative [4].

TREATMENT

In most cases analysed, the management was started with symptomatic treatment, support of respiratory failure (endotracheal intubation, mechanical ventilation), infusion of pressor amines and fluid resuscitation. In some patients, the treatment described above was found to be sufficient [5]. Moreover, at an early stage gastric lavage was attempted [1]. In cases of bradyarrhythmia, transdermal electrical stimulation of the heart or electrical stimulation using an endocavitary electrode was applied [1, 4, 5]. In some cases, electrotherapy was completely ineffective. In some other cases, its initial effectiveness was increasingly weak due to developing myocardial non-excitability [1, 4, 7].

In some centres, mechanical support of the heart was decided. In Bergamo (Italy), a 44-year-old man in cardiogenic shock was subjected to intra-aortic counterpulsation with good results; subsequently, venoarterial ECMO was provided (femoral-femoral access) [7]. The ECMO method was also used in a man poisoned with yew and treated in the hospital in Poitiers (France). Although the procedure was started during cardiopulmonary resuscitation already lasting 90 minutes, the patient was discharged from the ICU without neurological deficits [6]. In 2014, Czech researchers described a case of an otherwise healthy man, in whom initial bradycardia quickly progressed to ventricular fibrillation. During resuscitation, an automated chest compression device was used and then the patient was connected to the ECMO system. Knowing the cause of poisoning, a rescue antidote used in digoxin poisonings was administered (Fab fragments of digoxin-binding antibodies – DigiFab®). Although the circulatory system was stabilised, the patient developed complications in the form of severe hypoxic brain injury. The authors were not able to determine whether circulatory stabilisation was related to DigiFab® administration or rather resulted from supportive treatment [9]. This was not the first case in which Fab fragments of anti-digoxin antibodies were applied in yew poisonings. It is still unclear whether they were responsible for improved clinical conditions of patients. It should be emphasised, however, that false positive results observed in patients poisoned with yew may evidence cross-reactions between taxine and digitalis alkaloids [4].

The Austrian authors reported a case of an underage man poisoned with yew who developed shock and metabolic acidosis. Therapeutic hypothermia was used for neuroprotection and haemodialysis was started. Toxicological testing of blood and urine enabled to determine the concentration of taxine B before, during and after haemodialysis. Although the course of poisoning was satisfactory (the patient survived), haemodialysis was found to be inefficient for the elimination of taxines due to their high volume of distribution, relatively low

hydrophilicity and high molecular weight [8]. Nonetheless, its use is well-founded to correct acid-base imbalances.

Fat emulsions in treatment of acute poisonings

The Toxicology Data Network (TOXNET) suggests the use of fat emulsions in the treatment of yew poisonings [10]. This kind of management has not been included in official guidelines and has not been substantiated by more comprehensive studies. Moreover, the number of case reports confirming the efficiency of fat emulsions in severe yew poisoning is scarce. Nevertheless, a certain justification for their use is the fact the taxines are lipophilic compounds.

Fat emulsions were initially introduced as an element of parenteral feeding. Shortly, their potential efficiency in the treatment of severe LA poisonings was realised. The most likely mechanism of their action was the "lipid sink" phenomenon [12]. At present, in cases of sudden cardiac arrest or circulatory insufficiency in the course of LA poisonings, the Guidelines of the European Council of Resuscitation recommend fat emulsions as the drugs supplementing standard resuscitation management. The protocol of management in such cases involves a 1.5 mL kg^{-1} body weight 20% fat emulsion bolus followed by an infusion of 15 mL kg^{-1} h^{-1} [13].

Moreover, the number of cases of effective administration of fat emulsions in poisonings caused by other lipophilic xenobiotics is increasing high [12–15].

In 2016, the international evidence-based guidelines were formulated regarding the use of fat emulsions in the treatment of acute poisonings. The level D recommendations included in them (strong recommendation, very low quality of evidence) are limited only to SCA in bupivacaine poisonings. In poisonings caused by other LAs, the recommendations are neutral in nature (the use of drugs is neither recommended nor rejected by the majority of experts). The neutral recommendations also regard poisonings with LAs, including bupivacaine, without SCA. Similar recommendations (neutral) concern the use of fat emulsions in the treatment of SCA caused by amitriptyline, baclofen, beta-adrenalin receptor blockers calcium channel blockers, cocaine, lamotrigine, neuroleptics, and others. In poisonings with the above drugs, which are not accompanied by SCA, experts do not recommend fat emulsions as the first-line treatment (level 2D). [15]. As far as yew poisonings are concerned, no recommendations have been formulated. It is worth noting, however, that in the comprehensive paper presenting the above recommendations, a case of yew poisoning with arrhythmias, hypotension and coma reported by Ovakim *et al*. was referred to [11]. Unfortunately, the authors did not provide any information about the kind, concentration and dose of the fat emulsion used [15].

CONCLUSIONS

Cardiotoxic effects of taxine B are essential in yew poisonings, with arrhythmias being of prime importance. Differential diagnosis of causes of poisonings should consider antiarrhythmics, mainly digoxin. The promptest evacuation of the yew parts swallowed, including gastric lavage, seems justifiable. In yew poisoning patients with circulatory insufficiency, symptomatic treatment and support of failing organs is pivotal. In slow and/or haemodynamically inefficient heart rhythms, electrotherapy may be effective. In electrotherapy-refractory cases and progressive shock, extracorporeal circulation seems to be well-founded. Moreover, there is some evidence to believe that fat emulsions are likely to be effective in severe yew poisonings. Unfortunately, yew poisonings are rare; therefore, it is difficult to design clinical studies regarding the above-mentioned methods of treatment. New case reports and animal studies may be of key importance.

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