Slovenian Medical Journal

Ricin poisoining: Case report

Zastrupitev z ricinom: Prikaz primera

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Key words:
ricinus; ricin; poisoning; terrorism; bioterrorism

Ključne besede:
kloščevec; ricin; zastrupitev; terorizem; biološki terorizem

Received: 16. 3. 2019
Accepted: 9. 10. 2019

Abstract

In Slovenia, Ricinus (*Ricinus communis*) is best known as a decorative plant. However, in warmer climates the plant is widely distributed in nature and grows as a weed. The whole plant is poisonous since it contains a highly poisonous toxin ricin. The highest concentration of ricin is found in Ricinus seeds. Ricinus is grown commercially especially for its oil.

This report presents a case of ricin poisoning following oral ingestion of ricin seeds. The main symptoms were dizziness, headache, chest pain, choking sensation, nausea, vomiting and diarrhoea.

Ricin is a toxic protein and one of the most potent plant toxins. Its cellular mechanism is inhibition of protein synthesis. The main routes of ricin administration are oral, inhalation, transdermal and parenteral. Both lethal dose and clinical presentation are dependent on the route of administration. Treatment of ricin poisoning is supportive. The use of ricin for acts of bioterrorism is of major concern. Active and passive immunisations are being developed.

Izvleček

Kloščevec (*Ricinus communis*) v Sloveniji poznamo predvsem kot okrasno rastlino, medtem ko v toplejših delih sveta raste prosto v naravi kot plevel. Rastlina je v celoti strupena, saj vsebuje močan strup ricin, katerega največja koncentracija se nahaja v semenih. Kloščevec je gospodarsko pomemben za proizvodnjo ricinusovega olja.

Prispevek opisuje zastrupitev z zaužitjem semen kloščevca. Zastrupitev z ricinom je potekala z omotico, glavobolom, bolečino v prsnem košu, dušenjem, slabostjo, bruhanjem in odvajanjem tekočega blata.

Ricin je toksični protein in eden najmočnejših znanih rastlinskih strupov. Mehanizem njegovega delovanja je zaviranje sinteze proteinov v celici. Z ricinom se lahko zastrupimo z zaužitjem, vdihom, preko kože in z vnosom v podkožje ali v mišice. Način vnosa vpliva na smrtni odmerek in klinično sliko. Zdravljenje zastrupitve z ricinom je simptomatsko. Skrbi nas uporaba ricina v teroristične namene, predvsem v obliki aerosola. Razvija se aktivna in pasivna imunizacija.

Cite as/Citirajte kot: Razinger G, Brvar M. Ricin poisoining: case report. Zdrav Vestn. 2020;89(5–6):327–34.

DOI: https://doi.org/10.6016/ZdravVestn.2938

1 Introduction

In Slovenia, poisoning with plants accounts for approximately 3% of all poisoning cases in adults. The most common plants from which people in Slovenia suffer severe

poisoning include autumn crocus (lat. *Colchicum autumnale*), false helleborine (lat. *Veratrum album*), taxus, thorn apple (lat. *Datura stramonium*) and others. Poisoning with a poisonous plant can present a great challenge, as patients might also ingest different invasive and decorative plants. One such plant is Ricinus (lat. *Ricinus communis*), which can be found in many Slovenian gardens. Ricinus grows as weeds in tropical and subtropical areas, such as Africa, Middle East, Central America, and India (1,2,3).

In Slovenia, Ricinus is an annual plant and is planted for decorative purposes. It belongs in the euphorbiaceae family. It can grow several metres high. The high trunk is straight, with long-stalked palmate leaves in alternating green to reddish-violet colour, measuring up to 90 cm in width (Figure 1). Ricinus roots are fibred and sparsely branched out. The spiny fruit grows in clusters. Every fruit contains one seed (Figure 2). Ingested seeds have a pleasant taste, but are highly poisonous, as they contain ricin, a strong poison. The poison is extracted from the seeds if the envelope of the seed is broken, e.g. when bitten. Other parts of the plant also contain ricin, but in smaller quantities (2,4).

Ricinus is also cultivated as an industrial plant. Castor oil is obtained by pressing Ricinus seeds and is highly valued and generally useful. A Ricinus seed on average contains approximately 30–50% oil. Biggest global producers of Ricinus for industrial purposes are Brazil, China and India. The latter exports more than 90% of all castor oil. Castor oil is light-yellow, viscous, and non-evaporable. It is especially valued for its high concentration of ricinoleic acid, whose characteristics make it useful in producing colours, coatings, inks and lubricants. It is also used as biofuel, when making polymer materials, soaps, waxes, brake fluids and manure. Ricinus was already used in ancient Egypt, and was even highly valued, evident from it being found in 4000-year-old sarcophagi. Even back then, its oil was used as an ointment. From ancient Egypt, the plant first spread into India, and then into China. Ancient Greeks and Romans used castor oil as a strong laxative, and this remains its main use in traditional medicine to this very day. The laxative properties of castor oil are the result of the ricinoleic acid, which is released from acylglycerols after gastric lipases affect it, activating prostaglandin receptors on smooth muscle cells, which accelerates peristalsis. Castor oil is safe for use and does not include ricin, as it is removed using physical and chemical methods during production. Besides its laxative effect, castor oil is also used for making medication and in some places also as a substance for inducing labour (1,2,3,5,16). Lately, ricin is increasingly mentioned as a possible chemical weapon for military and terrorist use.

The objective of this article is to present a case study of Ricinus plant poisoning and to explain ricin poisoning.

2 Case study

A 61-year-old retired police officer with type II diabetes chewed up and swallowed 15–20 seeds, sweet of taste, which he thought were pine nuts, at 1 PM. 7 hours after ingestion he became nauseous, and began feeling asphyxiated, along with a feeling of pressure in his chest, but this waned after he vomited. The vomit included remains of the food and was reddish in colour. After vomiting, his head began to ache, and he became dizzy. During the night, he passed liquid faeces four times. Under the left chest arch, he felt a sharp, limited pain, which was better after defecating. The next day at approximately 3 PM, 26 hours after ingesting the seeds, he called the ambulance, and was taken by ambulance to the ER at the University of Ljubljana Medical Centre. He was admitted to the department of the Centre for Clinical Toxicology and Pharmacology. He brought the seeds he ingested the day before. After the examination, the patient was oriented, afebrile, acyanotic and anic-

Figure 1: Ricinus.

teric, with a normal respiratory rate and with 96% blood oxidation, normocardic and normotensive. An examination of the head, neck, chest with lungs, stomach and limbs did not show any derogation from normal. At defecation, the faeces were brown, with no visible blood, and with a negative stool guaiac test. Laboratory results showed a glucose level of 9.3 mmol/L, leucocytes of 12.5×10^9 /L and borderline anaemia with a haemoglobin level of 139 g/L (Table 1). Gas analysis showed mild respiratory alkalosis. ECG showed a sinus rhythm. Upon admittance, we administered the patient with 50 g of activated carbon and began hydration with 0.9% NaCl 100 ml/h; when he was nauseous, he was also administered pantoprazole and thiethylperazine. Indications of poisoning tailed off the following day after the ingestion of the seeds. Control examinations, including liver and kidney function, were good. A botanical review of the remaining seeds confirmed that it was Ricinus.

3 Discussion

Ricin is a highly toxic protein (toxalbumin) and is one of the strongest known plant poisons. It represents 3–5% of the weight of a dry Ricinus seed. At room temperature, it has the form of white powder and is water-soluble. Ricin remains inactive when heating to 80°C for 10 min or to 50°C for 1 h; however, it is generally stable at temperatures below 60°C. It is also suppressed by chlorine compounds (1,6-10).

Ricin is a glycoprotein, consisting of chains A and B, which are interconnected with a disulphide bond. The chain A is an enzymatically active chain, while chain B serves to insert ricin into the cell, as it contains binding locations for galactose remains, present in glycolipids and glycoproteins on the surface of a cellular membrane. Ricin enters a cell through endocytosis. A few ricin molecules are disintegrated in lysosomes, a few of them leave the cell through exocytosis, and a few

Figure 2: Ricinus seeds.

travel through retrograde transfer into the Golgi apparatus, and from there onto the endoplasmic reticulum. Here, chains A and B diverge. Chain A enters the cytosol through translocation, where it removes the adenine residue over a major subunit 28S of the ribosome. This blocks binding elongation factors, which stops protein synthesis. Ricin can also directly harm cellular membranes, crash the electrolytic balance, trigger apotheosis, and cause the release of inflamed mediators (6,7,8).

Ricin poisoning can also occur by ingesting, breathing in, through the skin, and by inserting into subcutaneous tissue or muscles (Table 2). The method of exposure also affects the lethal dose of ricin. It is known that the lethal dose of ingested ricin is significantly higher than with inhalation or parenteral exposure. With mice, LD_{50} was at 20 mg/kg for ricin ingestion, 24 μg/kg for administration into subcutaneous tissue, and only 3–5 μg/kg for inhalation. After inhaling ricin, animals died within 60 hours, while after ingestion it took 100 hours (1).

The most frequent method of ricin poisoning is ingestion of Ricinus plant seeds. The clinical image of poisoning depends on the characteristics of the seeds, which can differ by geographic area where the plant is growing, the time of harvesting, the hydration of the seeds, their size, number and concentration of individual isoforms of ricin in the seeds. Unripe seeds are much more toxic than ripe ones. It is also important whether the person only swallows the seeds, or also bites down on them, as in the former case, the symptoms often fail to manifest. The reason for this is most likely in ricin's high molecular mass, and therefore poor ricin absorption in the intestines. When ingesting Ricinus seeds, the symptoms of poisoning manifest within 12 hours, and are atypical, which can present issues with diagnosis, if there is no history on the ingestion of seeds. Patients who ingest seeds generally suffer from symptoms in their digestive tract, such as pain, nausea, vomiting, pain in the stomach and diarrhoea, which was also the case with our patient. Ricin poisoning can also lead to a development of melaena, haematemesis and haematuria. Accompany-

Table 1: Laboratory values at admittance.

Examination	Value	Unit	Orientation ref. values
S-Glucose	**H** 9.3	mmol/L	3.6–6.1
S-Urine	6.5	mmol/L	2.8–7.5
S-Potassium	4.3	mmol/L	3.8–5.5
S-Sodium	140	mmol/L	135–145
S-Creatinine	85	µmol/L	44–97
oGF (MDRD)/1,73 m^2	79	mL/min	
S- Bilirubin cel.	15	µmol/L	up to 17
S- Bilirubin dir.	**H** 5	µmol/L	up to 5
S-A. Phosphatase	0.92	µkat/L	up to 2.15
S-AST	0.23	µkat/L	up to 0.58
S-ALT	0.34	µkat/L	up to 0.74
S-gamma-GT	0.35	µkat/L	up to 0.92
S-alpha-Amylase	1.37	µkat/L	up to 1.67
S-Lipasys	0.73	µkat/L	up to 1.00
S-CK	1.6	µkat/L	up to 2.85
S-LDH	2.49	µkat/L	up to 4,13
S-CRP	below 5	mg/L	0–5.0
Hemogram			
K-Lkci	**H** 12.5	10^9/L	4.0–10.0
K-Erci	5.1	10^12/L	4.5–6.3
K-Hb	**L** 139	g/L	140–180
K-Ht	0.412	1	0.40–0.54
MCV	**L** 80.7	fl	81.0–94.0
MCH	27.3	pg	26.0–32.0
MCHC	332	g/L	310–350
RDW	13.4	%	11.5–14.5
K-Thrombocytes	207	10^9/L	140–340
MPV	8.7	fl	7.8–11.0
P-PČ	0.94	1	0.7–1.0
INR	1.04		

ing signs can be tachycardia, tachypnoea, sweating and peripheral cyanosis. Patients may also suffer from hallucinations and spasms. Pathophysiologically, it may also lead to the necrosis of the intestinal epithelium and bleeding, as well as the necrosis of liver, spleen and kidneys. This is followed by the onset of dehydration, a break in the electrolyte balance, and can lead to kidney and/or liver failure, which can then lead to multiorgan failures. The results of laboratory blood and urine tests are uncharacteristic and include elevated liver enzymes, creatine kinase, lactate dehydrogenase and bilirubin, we can detect leucocytosis, metabolic acidosis, hypoglycaemia or hyperglycaemia and proteinuria. Different types of changes in the ECG are also possible (1,6-9,15).

In California, 84 patients who ingested Ricinus were treated between 2001 and 2011. In half of the cases, the poisoning was intentional. Slightly less than a half of the patients ingested intact seeds, while just over a half chewed or crushed the seeds. The latter had more symptoms and were more frequently hospitalised. Two thirds of patients had symptoms in the digestive tract, and no other signs of poisoning (15).

Inhaling ricin in aerosol form is the most dangerous type of ricin poisoning; however, no such case has ever been described. In animal testing, it has been shown that when inhaling ricin, the size of aerosol particles is important, as smaller parts can penetrate deeper into the lungs. Particles above 10 micrometres cannot reach the alveolus and therefore only cause a mild clinical image of poisoning. In test animals, signs of poisoning after inhaling ricin occurred 4-8 hours after exposure, and included coughing, shortness of breath, nausea, sweating, fever and pain in joints. 36–72 hours after inhaling ricin, the animals developed a pulmonary oedema and necrosis, leading to respiratory failure and death within a few days (1,6,8,9,11).

In animal tests various types of Ricinus

were used with different proportions of ricin isoforms, and ricin aerosols were made to discover that the lethal dose depends on the ricin isoform. Animal testing has also shown that most of ricin collects in the lungs, and some also in the heart, kidneys, and lymph tissue. No ricin was detected in blood and the digestive tract, even though other studies have shown that ricin can also enter into the blood through the lungs and from there into other organs (1).

Parenteral ricin administration, e.g. into a muscle, subcutaneous tissue, or a vein, is the least likely cause of poisoning. The characteristics of parenteral ricin administration into the blood is a fast distribution of the toxin through the body into most organs. The only known case of such ricin administration in a human is an assassination of the Bulgarian journalist Georgy Markov in 1978 in London. He was shot with an air rifle, masked as an umbrella, which shot a ricin-soaked projectile into Markov's leg. The description of his case served as a foundation for studying such administration. A few hours later, systemic inflammation occurred, first manifested as influenza, with nausea, vomiting, tiredness, and fever. This was followed by bleeding in the digestive tract, hypovolemic shock, and kidney failure. Markov died 3 days later. The autopsy found necrosis of lymph nodes and liver, inflammation of the spleen and kidneys, haemorrhagic necrosis of the small intestine, pancreas, and testicles. Studies on rats have shown that with administration in a muscle, the characteristic location of the inflammation is the small intestine. With animals, there was also local necrosis of the muscles, areal lymphadenopathy and internal organ damage present. When intravenous administration of radioactively marked ricin was studied, it was established that half of ricin was stored in the liver, a good 10% in the spleen, and the rest in other organs (1,8,9).

When skin and mucosa come into contact with ricin and other content of Ricinus seeds, which also include glycoproteins, susceptible people can develop allergy reactions, which are manifested clinically as dermatitis, conjunctivitis and asthma (3,9).

Ricin poisoning is, regardless of the route of administration, difficult to establish, as the clinical image is uncharacteristic and the differential diagnosis of similar clinical conditions is very broad. When establishing Ricinus poisoning, the most helpful is a good history with the description of the circumstances and a botanical analysis of the remaining seeds, if the patient brought them into the hospital, as was the case in our case.

Through a toxicology analysis at the Institute of Forensic Medicine of the Faculty of Medicine in Ljubljana, we can prove ricin or its indirect marker ricinine, which is located alongside ricin in Ricinus solutions. Ricinine can be detected in the urine of poisoned patients up to 48 hours after exposure. A fast immunochemical test for ricin does not exist in clinical use, however there are numerous studies for finding ricin in biological samples and food, e.g.

Table 2: Expected symptoms and signs for individual paths of ricin administration.

Method of ricin administration	Oral	Inhalation	Parenteral
Expected symptoms and signs of poisoning	Nausea, vomiting, diarrhoea, stomach pain, hematemesis, haematochezia, melaena, tachycardia, tachypnoea, peripheral cyanosis.	Coughing, dyspnoea, nausea, pain in joints, sweating, fever, pulmonary oedema.	Nausea, vomiting, tiredness, fever, hematemesis, haematochezia, melaena, signs of shock.

by detecting specific antibodies and ribonucleic acids, mass spectroscopy and measuring ricin activities. The most promising methods for ascertaining the presence of ricin are the enzyme-linked immunosorbent assay (ELISA), electrochemiluminescence, immunochromatographic methods, PCR and mass spectrometry.

Because of the possibility of using ricin for terrorist and military purposes, a fast and reliable method with a high enough level of sensitivity and specificity will have to be developed (1,6,7).

The treatment of ricin poisoning is symptomatic, namely performs a supportive role, as there is no antidote for ricin. Dialysis is not effective because of ricin's high molecular mass.

When ingesting whole seeds, no special therapy is needed. When ingesting chewed-up seeds, the patient is given activated carbon; with digestive symptoms, we ensure patient hydration and nausea treatment. With symptomatic patients, we monitor their laboratory results, and focus especially on the electrolytic balance and kidney operation. Patients who are without signs of poisoning after ingesting the seeds, and for whom we do not know whether they had chewed the seeds, are kept under observation for 12 hours after ingestion. When there is skin contact with ricin, we wash the skin properly; hospitalisation is not needed, except if skin is exceptionally damaged and there is a high probability for system absorption of ricin.

Active immunisation, i.e. vaccine, is in development, which would be suitable for protection from ricin exposure and used for military purposes. The effectiveness of ricin vaccines has already been confirmed with animal models. Passive immunisation with antibodies or antidotes is also in development, and could be used prophylactically and administered also to civilian population in the event of a terrorist attack with ricin. Antibodies neutralise ricin by binding to the chain A or B or both. It is not yet clear whether the neutralising antibodies will also be effective after the time frame required for recognising ricin poisoning (4,6-8). The development of ricin antidotes is becoming increasingly topical because of the potential use of ricin in terrorist attacks, which is also evident from publications in the public media. Towards the end of 2018, there were two major cases where in Germany, police discovered during a raid of a suspected terrorist's home 1000 seeds of Ricinus and an electric coffee grinder, along with a case of a letter containing white powder that turned out to be ricin, addressed to a specific person at the US Pentagon (12,13,14).

Ricin is suitable for terrorist attacks because Ricinus is a common plant and it would be fairly simple to produce the poison in large quantities. Recipes and procedures for producing highly toxic ricin solutions are easily available on the internet, as well as on the black market; fortunately, because these result in low concentrations of ricin in the final product, they do not pose a major danger to being used as a terrorist weapon of major proportions. From the perspective of military use and terrorism, the most significant path of administration is in aerosol form, with also the option of administering it into the muscle, subcutaneous tissue or a vein. Ricin could be administered into the muscles of a large number of people with explosive devices that contain sharp elements, soaked in ricin. Such a path of administration would most likely include all paths. In the USA, ricin was classified as a category B biological terrorist asset, which means that it is fairly easy to disperse among a large group of people, it causes significant health impact, yet has a low mortality rate. Natural toxins, such as ricin, are not contagious, compared to living organisms, so medical personnel do not require special protective equipment or measures (1,9,11).

4 Conclusion

With patients who suffer from digestive issues after eating seeds, we should consider Ricinus poisoning. Ricin poisoning

can be confirmed with a biological and/or toxicological analysis of the remains of the plant and the patient's biological samples. Therapy is mainly symptomatic. With a terrorist attack that utilizes a powder or an aerosol, we must also consider the potential of ricin poisoning.

The patient agrees with the publication of the article.

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