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Amanitine poisoning - cases, management, therapy results

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ABSTRACT

Mushroom poisoning continues to be a serious clinical problem. The most serious are intoxications with mushrooms containing cytotropic toxins with predominant injury of liver, kidneys and heart. The toxic properties of the phalloides are mainly due to α-amanitin, which is an inhibitor of RNA polymerase II. The clinical course of poisoning can be divided for 4 periods. The asymptomatic period usually lasts 6-24 hours after mushroom consumption. Then the period of the gastrointestinal disorder lasting on average 12-24 hours. The second latency period with apparent improvement of the patient's general condition lasting 12-24 hours is subjected to the stage, during which biochemical markers of hepatocyte activity appear. After a few days (usually on the 4-5th day) from poisoning, kidney function may occur (oliguria or anuria), and circulatory system disorders may also occur. Death usually occurs between 4-16 days after poisoning. The treatment of poisoning with amanita phalloides includes a number of procedures, including rapid removal of toxins, blocking the penetration of amatoxins into the hepatic cell, compensation of systemic metabolic disorders, and extracorporeal support of liver function.

KEYS WORDS:"amatoxin", "amanitin toxicity", "mushrooms poisoning"

INTRODUCTION: Amanita phalloides is the most dangerous species of poisonous mushroom in Poland. The toxic properties of the phalloides are mainly due to α-amanitin, which is an inhibitor of RNA polymerase II. One of the main medical problems in poisoning with amanita phalloides is a long asymptomatic period of about 8-24 hours from ingestion of the mushroom, with the simultaneous toxic effect of the absorbed toxin. In severe cases of α-amanitin poisoning, death occurs between 6 and 16 days after intoxication, as a result of irreversible multi-organ changes. Suspicion of mushroom poisoning is greatest in the autumn. The following review presents the case of a patient after poisoning with phalloides admitted to the Toxicology and Cardiology Department, as well as a review of information on mushroom poisoning based on the found publications.

THE PURPOSE OF THE REASERCH WORK: The purpose of the reaserch work was to describe a case of poisoning with amanita phalloides, treatment procedures and results of therapy useful in medical practice.

MATERIALS AND METHODS: The case of a patient admitted to the Toxicology and Cardiology Department of the WSS in Lublin and scientific publications in the Pubmed database were used to write the article. The base was searched on January 9 2023 using phrases: "amatoxin", "amanitin toxicity", "mushrooms poisoning". After reading the titles of the found articles, 10 articles were selected. After pre-analysis of the abstracts, 4 full-text papers were selected for the preparation of the article.

A CASE REPORT

The case of a patient admitted to the Department of Toxicology and Cardiology at the WSS in Lublin concerns poisoning with amanita phalloides. The patient ate one cap of a mushroom in the evening thinking it was a goose mushroom. The next morning, after the latency period, the patient experienced nausea, vomiting and abdominal pain, followed by diarrhea. On the second day, the presence of amanitin in the urine was determined. In physical examination, the patient was circulatory and respiratory efficient, an enlarged liver was found. In laboratory tests, high liver parameters were present (ALT 2524U/I, AST 1780 U/I, INR 1.15). The patient was treated symptomatically and with specific antidotes: Acetylcysteine and Legalon. The patient's clinical condition improved quite quickly and liver parameters systematically decreased in the following days of hospitalization. The patient refused a follow-up USG examination and was discharged home in good clinical condition.

The clinical course of poisoning can be divided for 4 periods. The asymptomatic period (latent period) usually lasts 6-24 hours after mushroom consumption. Then the period of the gastrointestinal disorder lasting on average 12-24 hours, followed by severe pain of the gastrointestinal tract, as well as the vomiting and diarrhea leading to on the water-electrolyte (hyponatremia, hypochloremia, hypokalemia) and acid-base disorders. The second latency period with apparent improvement of the patient's general condition lasting 12-24 hours is subjected to the stage, during which biochemical markers of hepatocyte activity appear. The course of the hepatic phase depends on severe poisoning. Mild poisoning causes gradual jaundice. In process poisoning, jaundice and consciousness functions may develop rapidly, to the point of coma. Usually, a bleeding diathesis is revealed with persistent bleeding from the gastrointestinal tract. After a few days (usually on the 4-5th day) from poisoning, kidney function may occur (oliguria or anuria), and circulatory system disorders may also occur. Death usually occurs between 4-16 days after poisoning.

Important aspects in their work were included by Slovak authors, whose work is based on a review of the results of treatment and diagnostics in the years 2004-2020. They report that in order to detect amanitin poisoning, they used the Quantitative determination of amanitines in blood (ATOs) and urine (ATOu) with the original ELISA kit, which were performed on the basis of mycological history and clinical symptoms of poisoning. Negative ATOu results excluded amanitin poisoning. However, studies prove the usefulness and reliability of the ATOu ELISA for the determination of amanitin levels in the urine. The severity of poisoning correlates with urinary ATO, which changes the perspective of diagnosis and treatment of amanitin poisoning. Criteria have been defined, the fulfillment of which is an indication for the determination of amanitin. These are:

- the poisoned patient reported ingestion of mushrooms belonging to the genus: Amanita, Agaricus, Russula or Macrolepiota
- the asymptomatic period from mushroom ingestion to the onset of symptoms was 4 hours or more
- the spectrum of first symptoms included profuse diarrhoea

The second important aspect raised in the this work concerns the use of antidotes. In general, administration of silibinin is preferable to administration of high-dose penicillin with or without silibinin. The results, however, prove more effective administration of both antidotes. In addition, the authors present a treatment protocol based on the acronym REELDADCOM

RE - Intensive hydration to compensate for loss of body fluids and the daily need to replenish body fluids to achieve diuresis without the use of diuretics; aimed at the treatment of dehydration, prevention and treatment of pre-renal acute renal failure - AKI; dextrose solutions to prevent hypoglycemia;

EL - Elimination of fungal residues and their spores from the intestine and amantines from their enterohepatic circulation by administering large doses of charcoal together with lactulose for a minimum period of three days;

D - Body fluid overload for urinary elimination of amanitin, supported by low molecular weight dextran 40;

AD- antidote: Crystalline potassium salt of penicillin G in doses and silibinin.

CO - Coagulation. Administration of frozen plasma to compensate for blood coagulation in the phase of liver damage, to achieve at least 40% of normal prothrombin time values, as a prophylaxis of fatal CNS bleeding;

M – Monitoring - 2x a day - monitoring of blood glucose parameters, liver and kidney function and coagulation.

The authors Horowotz and Moss devote a lot to amanitine. Amanitin toxin is heat stable and remains toxic whether eaten raw or cooked. The mechanism of action is the inhibition of RNA polymerase, resulting in the interruption of mRNA transcription. As a result, hepatocytes cannot synthesize key protein-coding genes, leading to nucleolar lysis and pathological central lobular necrosis of the liver. This leads to the insidious onset of liver failure within 48 hours. The late onset (more than six hours after ingestion) of vomiting and watery diarrhea occurs due to the second component of some of these mushrooms, which is phallotoxin. The prognosis depends on the type of mushrooms ingested and the time to get help. Death is rare if treatment is started

immediately, although deaths continue to be reported. Children tend to absorb higher doses of the toxin compared to adults and therefore have a much higher morbidity and mortality rate. Therefore, children absolutely should not be given them.

Interesting cases of poisoning and breastfeeding are presented in the Drugs and Lactation Database article. In the example of a 20-year-old German breastfeeding mother who ate a meal consisting only of mushrooms identified in the report as green tuberous mushroom (Amanita phalloides), it can be concluded that the toxin does not pass into breast milk. About 11.5 hours after ingesting the mushroom, the woman was breastfeeding her 10-week-old baby who weighed 5 kg. The meal consisted of 80 to 100 ml of breast milk and the same amount of ready-made infant formula. At that time, the mother already had symptoms of intoxication (vomiting and diarrhoea). Due to her deteriorating condition, she could no longer breastfeed the baby, so the baby was given only formula milk afterwards. After her mother was admitted to the hospital for Amanita phalloides poisoning, she had ASAT and ALAT values of 10,000 and 40,000, respectively (normal values around 500-550). The infant was placed for observation at a children's hospital. The infant's relatives did not notice anything unusual about the infant and a clinical preliminary examination showed no apparent signs of liver, brain, or hematology disease. Six days after the mother ingested the mushrooms, the infant's laboratory values (electrolytes, serum electrophoresis, bilirubin, gamma-GT, alkaline phosphatase, creatinine, blood sugar, urine status, PTT and PT) were normal except for ASAT and ALAT, which were about twice the normal value. These values slowly declined and returned to normal around day 40 after ingestion. Just like the 33-year-old woman who picked around 200 mushrooms in a forest in France. She cooked and ate some of it and 11 hours after eating it, she developed nausea, vomiting and diarrhea. She was admitted to the hospital for treatment and had elevated liver enzymes. She breastfed her 5-month-old daughter 3 times a day for 36 hours after consuming mushrooms. Her daughter was hospitalized but showed no symptoms or biological abnormalities.

In a recent article, the issue of liver transplantation as the last resort in amanitin poisoning was discussed. A case of marriage poisoning was described. In both cases, liver transplantation was considered due to increasing liver parameters. Fortunately, in the case of the man, liver function began to stabilize 8 hours after the start of therapy with a maximum serum ALT level of 3856 IU/L and an INR of 3.5. He then recovered gradually and was discharged 10 days after admission. Unfortunately, in the case of a woman, the results were less optimistic-liver necrosis. Her INR increased further to 7.2 and a liver transplant was indicated and transplantation work began. Fortunately, an ABO compatible deceased donor liver transplant was available. Liver transplantation was performed 36 hours after admission (approximately 5 days after ingestion). The operation lasted 7 hours and the patient lost 3 liters of blood. Histopathological examination of the explant showed massive necrosis. The woman was discharged on the 30th postoperative day, requiring lifelong immunosuppression.

Management of amatoxin poisoning can be classified as supportive with specific treatments. The chance of survival is 70% to 100% with early diagnosis and intensive care. Conventional therapies fail 10% to 20% of the time. Death resulting from fulminant liver failure is inevitable if a liver transplant is not performed in time. As to when a liver transplant is needed, different sets of parameters are used, but none have gained widespread acceptance in the context of amatoxin-associated liver failure.

CONCLUSIONS

An important factor determining the success of the treatment of amanitine poisoning is its prompt implementation (at the latest within 36 hours of mushroom consumption) and careful monitoring of biochemical parameters, enabling a sufficiently quick qualification for liver transplantation. Clinicians should pay attention to thorough history taking and start treatment early. Pharmacological agents, extracorporeal methods of poison elimination and liver transplantation are used in the treatment of poisoning with amanita phalloides. Despite the progress in the treatment of acute liver failure due to poisoning with amanita phalloides, the mortality rate in this group of patients is still high and amounts to 20–30% in adults and over 50% in children. Educating the public about the dangers associated with the consumption of forest mushrooms is essential in order to reduce the number of poisonings.

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