Amatoxin The Toxic Substances Found in Mushrooms and Its Effects on Human Body

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Abstract: Amatoxin is a toxic substance commonly found in death cap mushrooms, and is responsible for most deaths caused by mushroom ingestion. This paper summarizes the known information of the poisoning mechanism, symptoms and treatments for the toxicity of amatoxin, and it also provides some future perspectives of the potential use of this substance. The mechanism of amatoxin poisoning is rooted in its ability to bind to the enzyme RNA polymerase II and inhibit transcription, which may result in numerous conditions ranging in severity, including single or a small range of cell apoptosis to liver necrosis. A series of symptoms usually occur after people digest mushrooms that contain the poisonous amatoxin. The time of occurrence of symptoms is also divided into three main stages: within one day, one to two days, three days or later. More detailed symptoms and reactions will be described in this article. However, each person's reaction may not be exactly the same as the symptoms mentioned in the article, because the manifestation of symptoms will be related to many factors, such as each person's physical fitness, whether they have taken the relevant drugs and so on. To detoxify and treat effectively after poisoning, scientists have discovered several different treatments. The main types are induced vomiting, gastric lavage, catharsis, enema, infusion and diuresis, and sulfhydryl antidote.

1. Introduction

In nature, mushrooms have been around for thousands of years. Some species of mushrooms provide enough proteins, carbohydrates, dietary fibers, and vitamins, but some people can also be poisoned or even killed by some other species of mushrooms.

Amatoxin is a toxic substance produced particularly by the death cap mushrooms, or Amanita phalloides, which is 2-5 inches wide and 4-6 inches tall [1]. The most common appearance of death caps is the yellow cap, white gill, and white stem. The structure of amatoxin is a cyclopeptide, which is a polymer consisting of two or more amino groups connected by peptide bonds. Therefore, it is also in a bicyclic structure. The LD50 of amatoxin is 0.4 ~ 0.8mg/kg, and its main effect is leading to liver necrosis [2]. Most fatal cases of amatoxin ingestion are accidental, as it is hard for people to distinguish the death cap mushrooms from normal mushrooms. There are multiple subtypes of amatoxin, but the most common ones are alpha and beta [3]. If you consume mushrooms containing amatoxin, the toxic peptides will enter the liver cells and severely damage the liver function, then lead to other organ failure and eventually death [4].

2. Mechanism of Amatoxin

After ingestion, amatoxins are rapidly absorbed by the organisms' bodies, and are also quickly distributed to the various organs. After amatoxin is absorbed by the body, it begins to hit its primary targets—the intestinal mucosa, the liver cells, and the proximal tubules of the kidney [5-6]. The core

of the poisoning mechanism of amatoxin is its tendency to bind and form a complex with the subunit of the DNA-dependent RNA polymerase II. It binds 1:1 with RNA polymerase II, and by forming a complex with the enzyme, which is needed during the process of transcription, or the process of transcribing DNA to RNA, it inhibits the function of the enzyme and thus the synthesis of mRNA [5]. The cells of the organism will be then unable to synthesize proteins, as the mRNA molecules play a key role in translation. The disability of the cells to produce new proteins leads to a series of toxic effects including apoptosis, tissue injuries, and liver necrosis.

Apoptosis, the programmed process of cell death designed for cells that are no longer in use, can occur in normally functioning cells with the presence of amatoxin. It is a result of the combined effect of the toxicity of amatoxin, together with the endogenous tumor necrosis factor (TNF-α) [5]. TNF-α is a cytokine that's naturally produced by macrophages and monocytes that may cause adverse effects [7]. The reduced transcription of mRNA resulted from the inhibition of RNA polymerase II can make the liver cells prone to the toxic effects of TNF-α, which eventually induces apoptosis [5].

Amatoxin poisoning is also associated with a great chance of developing complications as well as a high mortality rate. The levels of the organisms' responses after amatoxin are absorbed can vary from single-cell apoptosis to wide-range necrosis of hepatocytes or the biliary epithelium. The liver cells are hit the hardest because they are the first ones to encounter the toxin after ingestion of the Death Cap, and amatoxin causes death mainly through its ability to cause hepatic necrosis. Hepatic necrosis, or liver necrosis, is the situation in which the large number of liver cells are damaged over an indefinite period time, with the membrane of liver cells broken down and the cytoplasmic membrane ruptured, eventually leading to cytolysis and death of organelles [8]. Low levels of liver necrosis are curable, but severe ones are fatal.

3. Symptoms of Amatoxin Poisoning

The intoxication with amatoxin causes some symptoms of intoxication and discomfort, which can be divided into three stages. At each stage, there are different conditions, and patients who are poisoned have different physical feelings because of their physical conditions. Of course, the influencing factors of each patient's feeling after poisoning are not only related to their physical condition but also related to many factors, such as whether they are sent to the hospital immediately after poisoning and receive timely treatment or whether their condition deteriorates due to the delay of time. Whether they took medicine that can relieve amatoxin poisoning before entering the hospital, drugs or food that can worsen their illness, or whether they have a history of congenital diseases or genetic diseases in their families. So, in general, what is described below is what happens to most patients under normal circumstances, not just a few patients.

The first stage symptoms usually occur when amatoxin is digested, and the body begins to feel the presence of the toxin, usually within 6-24 hours [9]. That is, one day after eating amatoxin, some obvious symptoms and changes will occur. Usually, most people will react with a severe feeling of vomiting, noticeable abdominal cramps, more serious diarrhea with water, and even fecal matter that may have a large amount of blood visible in it [10]. Symptoms during this period are concentrated in the gastrointestinal tract. Severe gastrointestinal disorders may result in electrolyte abnormalities, hypoglycemia, dehydration, and hypotension as the patient has a large amount of excretion with water [11]. In the first 24 hours, massive fluid loss can lead to death. Therefore, during these hours, the worst outcome is that most of the patient's body fluids are lost, and if the patient's resistance and health are not very good, the patient may die from eating mushrooms containing amatoxin.

The second stage of poisoning mainly occurs 18 to 36 hours after eating food containing amatoxin, that is, the next day after eating [9]. If the patient manages to endure the symptoms of the first day because they are strong and healthy, the patient will have a very different and incredible experience on the second day. Patients with a specified period usually have a short period of improvement. We say that his symptoms of poisoning during this period time will be significantly improved and relieved. For example, he does not have severe abdominal pain and has frequent bouts of diarrhea [12]. Nevertheless, while the patient's symptoms appeared to be alleviating, his liver enzyme levels

continued to rise without her knowing it. At the same time, some patients may be rushed to the hospital with liver or kidney failure due to their reasons or the high toxin content in mushrooms [11]. Suppose the patient has exceptionally severe liver or biological failure, but the patient's family's financial situation is not ideal enough to afford the organ transplant, or there is no suitable liver for the patient [13]. In that case, some patients will give up treatment.

The third stage is about three to four days after the patient ingested the poisonous mushrooms [14]. At this stage, the main features of the patient are some coagulation disorders, hypoglycemia, brain disorders due to liver dysfunction, multiple organ failure, coagulation problems, and even fainting in severe cases [14]. These symptoms are gradually becoming more and more serious, and it is more and more difficult for doctors to cure them. After coming to the hospital at this stage, saving their lives is even the most essential thing for some patients. However, even if they survive, the brain, liver, and other organs are severely affected or even deteriorated. Although the death time of most poisoned patients is 6-16 days after ingesting amatoxin, the symptoms, poisoning, infection, and coagulation disorder are all predicted symptoms before death.

In conclusion, the symptoms of mushrooms with amatoxin usually vary from person to person. Because the severity of the poisoning is different at each stage, the patient's pain also depends on the length of time the poisoning lasts. So, in the best case, people should be taken to the hospital if they experience a little discomfort or a very unusual sensation after eating this particular mushroom. Otherwise, the patient's condition will get worse and worse, and even die. In this case, giving patients correct treatments is the most vital thing to do.

4. Treatments of Amatoxin Poisoning

There are many kinds of wild mushrooms and toxins, and many of the exact toxins that cause disease have not been identified, so the treatment for most wild mushroom poisoning is not specific, but mostly supportive treatment and symptom-specific treatment. The principles of treatment are to immediately stop the absorption of toxins, carry out emergency resuscitation and symptomatic treatment, expel the unabsorbed toxins from the body, and prevent complications. Due to the difficulty of conducting controlled studies and the poor knowledge of the pharmacodynamics of amine toxins in human poisoning, there is still considerable controversy regarding appropriate treatment, especially in terms of detoxification [15]. There are different ways to classify the types of mushroom poisoning, basically they can be divided into six types. 1. gastrointestinal type (incubation period of 10 minutes to 6 hours, the phenomenon of acute gastroenteritis) 2. neuropsychiatric (incubation period of 10 minutes to 4 hours, parasympathetic excitement symptoms) 3. hemolytic (incubation period of 6 to 12 hours, triggering the phenomenon of hemolysis) 4. liver and kidney damage type (incubation period of 5 to 24 hours, mostly 12 (incubation period of 5-24 hours, mostly 12 hours, with a maximum lethality of about 60%-80%) 5. respiratory and circulatory failure 6. photoallergic dermatitis, etc. The highest percentage of amanita verna poisoning is the liver and kidney damage type. Toxins are mainly amatoxin and phalloidin. Amatoxins contain six toxins: alpha-amanitin, beta-amanitin, gamma-amanitin, epsilon-amanitin, amanin, amanullin. And phallotoxins also contain 5 types of toxins: three phallisin with 1-3 hydroxyl groups, phallicidin, phallinB. Detoxification in the early stages of poisoning is necessary and effective for all types of poisoning. Detoxification involves two different approaches, which are reducing absorption and enhancing excretion [16].

4.1 Treatments by Induced Vomiting

You can use physical or medication to induce vomiting, such as giving the patient a large amount of warm saline, either 200-300 ml of 4% warm saline or 200 ml of 1% magnesium sulfate, 5-10 ml at a time and then stimulating the pharynx with a safe object such as a chopstick or fingertip (preferably wrapped in non-woven gauze) to induce vomiting. Or under the guidance of medical staff, use copper sulfate, vomiting syrup, injection of apomorphine hydrochloride and other drugs to induce vomiting, but be especially careful that pregnant women should use vomiting with caution.

4.2 Treatments by Gastric Lavage

Patients with severe vomiting do not need gastric lavage, and should not give up gastric lavage if vomiting is not frequent. The earlier the gastric lavage, the better. Generally, the effect of gastric lavage is best within 4-6 hours of ingestion of the poison, but even if it exceeds 6 hours or even 12-18 hours, gastric lavage can still be performed according to the absorption of the poison. Stomach lavage generally uses lukewarm boiled water and physiological saline. Potassium permanganate solution (1:2000-5000) can also be used. After gastric lavage, activated carbon can be poured as an adsorbent. The usage is to take 30-50g into 500ml warm water and mix it into a suspension. Egg whites can also absorb poisons.

4.3 Figures and Tables Treatments by Catharsis

To remove the poison that stays in the intestines, 10% magnesium sulfate can be taken orally for catharsis, but magnesium sulfate should not be used for patients with central nervous system, respiratory and cardiac depression, or those with poor renal function. The use of magnesium sulfate can cause hypermagnesemia and cause magnesium poisoning. It is usually better to catharsis with sodium sulfate. You can also use mannitol or sorbitol as a cathartic agent, especially after infusion of activated carbon can increase the excretion effect of unabsorbed poisons. It is also suggested to take 30～60ml castor oil orally as a catharsis agent.

4.4 Treatments by Enema

Saline or soapy water high enema can be used for patients who do not have diarrhea. 200-300ml each time, 2-3 times in a row.

4.5 Treatments by Infusion and Diuresis

Toxicokinetic reports of human mushroom poisoning have shown that diuresis substantially enhances the amatoxin elimination rate. Large amounts of amatoxins （60-80% ） are filtered through the glomeruli [17]. A large amount of infusion can be used in the early stage to excrete a large number of toxins from the urine. 10% glucose, physiological saline, etc. can be used for infusion, and intravenous diuretics are used at the same time. Generally, furosemide 20-40mg or 20% mannitol 250ml is used for intravenous injection, and repeated injections can be repeated if necessary. However, attention should be paid to fluid balance, water and electrolyte balance, and potassium chloride supplementation for patients with hypokalemia.

4.6 Treatments by Sulfhydryl Antidote

Toadstool poisoning such as poisonous agaric and white poisonous agaric is often ineffective in the treatment of atropine. Using antidote containing sulfhydryl groups to treat such poisonous weeds has a certain effect. The mechanism of action may be that such drugs combine with certain toxins such as parabens to block the sulfo bonds in the molecules, weaken their virulence, and protect the activity of sulfhydryl enzymes in the body. It even restores the vitality of some enzymes that have been combined with toxins. Commonly used ones are:

1) *Disodium dimercaptosuccinate (Na-DMS) 0.5～1g diluted intravenously, once every 6 hours, the first dose is doubled after the symptoms are relieved, the injection is changed to 2 times a day, 5-7 days as a course of treatment.*
2) *Intramuscular injection of 5ml of sodium dimercaptopropane 5% solution, once every 6 hours, after the symptoms are relieved, the injection is changed to 2 times a day, 5-7 days as a course of treatment.*

In conclusion, in the poisoning of amatoxin, we recommend measures to avoid further absorption of toxins, such as gastric lavage and duodenal drainage, in combination with the use of charcoal [18]. Methods such as vomiting, gastric lavage, catharsis, and an enema should be used in time to quickly eliminate unabsorbed poisons. Especially for those who accidentally eat toadstools such as toadstools and white toadstools, they have eaten mushrooms for more than 6 hours at the time of the onset.

However, treatments such as gastric lavage and catharsis should still be given. After gastric lavage and enema, the introduction of tannic acid and activated carbon can reduce the absorption of toxins. Patients with wild mushroom poisoning seek medical attention and diagnosis as early as possible after the onset of symptoms, and most can recover after active and effective treatment, but because the wild mushrooms and toxins that can cause wild mushroom poisoning are very complex, there are no targeted antidotes or specific treatments for most toxins, and some patients are unable to seek medical attention and receive treatment as soon as possible. The disease still has a much higher mortality rate than other poison categories.

5. Conclusion

Amatoxin, though toxic most of the time, can potentially be used for many purposes including defense, protection and therapy in the future. As a defense mechanism, mushroom toxins can warn animals to stay away and protect poisonous mushrooms from mass consumption, while these toxins can also be used in humans as a natural biochemical weapon, and maybe developed as organic coatings to protect important resources in the wild. The natural extracts also indicate that they do not pollute nature too much. Toxins that affect the nervous system are also thought by scientists to be used to treat neurological diseases such as Alzheimer's disease and psychosis. What's more, the present invention relates to oncology therapy, and in one aspect, the present invention relates to target binding molecules and binders of toxins that are useful in the treatment of cancer [19].

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