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AUTHORS: Fatih SEZER, Sevil ÖZGER ILHAN

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***Amanita phalloides* Poisoning and Treatment Approaches**

Fatih Sezer¹, Sevil Özger İlhan¹

¹ Gazi University, Faculty of Medicine, Department of Pharmacology, Ankara, Turkey

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Abstract

It is common to pick and eat mushrooms in nature. Poisonous mushrooms are difficult to distinguish from edible ones. Consuming poisonous mushrooms can cause severe consequences, ranging from mild gastrointestinal complaints to death.

The major fatalities happen due to mushrooms containing amatoxin. Particularly, *Amanita phalloides* contains high amounts of amatoxin. The targets of toxins taken into the body are the gastrointestinal mucosa, renal tubule cells, liver. Alpha amanitin is one of the most toxic among amatoxins and inhibits RNA polymerase II. Liver cells are most affected by toxicity. Amatoxins are taken into the liver by organic anion transporting polypeptides. No symptoms are seen in the first hours of poisoning. Gastroenteritis-like symptoms are seen when toxins damage the gastrointestinal epithelium. Then liver and kidney begin to be affected. Death usually occurs due to liver failure.

Early diagnosis and treatment enhance chances for survival. There is no specific antidote for amatoxins. Absorption should be prevented with activated charcoal and gastric lavage. Adequate hydration should be ensured. The most commonly used drugs in the clinic are penicillin G, silibinin, N-acetylcysteine. In addition to this, extracorporeal methods should be applied. Approaches other than liver transplantation are supportive. The mortality rate remains over 10% in large case series.

Specific substances that would prevent the uptake of toxins into the liver or eliminate their effect have not yet been developed. Since there is no effective treatment, cultivated mushrooms should be preferred instead of wild mushrooms in nature to avoid *Amanita phalloides* poisoning.

1. Introduction and Objective

Mushrooms are common in nature. The picking and eating of wild mushrooms is common but can be deadly. There are over 5000 species of mushrooms worldwide (Gonmori & Yoshioka, 2003). About 100, from the total of 5000 mushroom species, are toxic to humans (Smith & Davis, 2016).

Mushroom poisoning is one of the important public health problems in rural areas (Eren et al., 2010). *Amanita phalloides*, a poisonous mushroom species, has high mortality rates. Early diagnosis and treatment are essential as it increases the chance of survival.

Early diagnosis is difficult due to delayed onset symptoms and misdiagnosis such as gastroenteritis. Initially, reducing the absorption of amatoxins and preventing liver uptake are crucial for treatment.

The aim of this article is to contribute to clinical practice and current treatment approaches of *Amanita phalloides*.

2. Mushroom Poisoning

Mushroom poisoning is frequently seen in emergency departments due to the organic food movement and the use of mushrooms for hallucinogenic effects (Eren et al., 2010). Recently, people think that mushrooms boost immune function and promote health so there is increasing interest in the use of mushrooms or mushroom extracts as dietary supplements (Wong & Ng, 2006). However, the picking and eating of wild mushrooms has become increasingly popular all over the world and foragers may confuse edible with toxic species (Wong & Ng, 2006).

Serious consequences, due to ingestion of mushrooms, range from simple gastrointestinal complaints to organ failure and death (Brayer & Froula, 2016; Eren et al., 2010). Most of the cases are mild and symptomatic treatment is sufficient (Schmutz, Carron, Yersin, & Trueb, 2018). Few of mushroom toxins have antidote (Hall, Spoerke, & Rumack, 1987).

In most cases, the type of mushroom is unknown (Diaz, 2018). However, the most common cause of death is due to *Amanita phalloides* which contains high amounts of amatoxin (Garcia, Costa, Carvalho, Baptista, et al., 2015; Karlson-Stiber & Persson, 2003).

The color of mushrooms is not a reliable feature to identify poisonous species as it varies depending on weather, soil conditions and age of the mushroom (Olson et al., 1982). There are no simple rules or tests to identify mushrooms quickly and accurately (Hall et al., 1987).

Most poisonings are accidental (Karlson-Stiber & Persson, 2003). The severity of poisoning is related to the amount of mushroom consumed, the age of the mushroom, the season, the region and the processes applied to the mushroom before consumption (Brayer & Froula, 2016; Lin & Wang, 2004).

Mushroom poisoning occurs in children who accidentally eat mushrooms, mushroom pickers, people who eat it to commit suicide and people who consume it for hallucinogenic effects (Brayer & Froula, 2016; Eren et al., 2010).

Poisonings are considered a forensic case under all circumstances and must be reported (Gürpınar & Aşirdizer, 2006).

Mushroom toxicity can be divided into 3 groups: The time duration of symptom onset; early-onset (less than 6 hours), late-onset (between 6-24 hours), delayed-onset (over 24 hours) (Diaz, 2005). Early onset symptom cases are generally mild (Berger & Guss, 2005; Schmutz et al., 2018). Delayed onset symptom cases are usually life-threatening (Eren et al., 2010).

3. History and Epidemiology

The first recorded mushroom poisoning in history was in the 5th century BC. The Athenian poet Euripides and his family passed away after ingesting poisonous mushrooms (BVV. & LF., 1935). The first mushroom poisoning in the USA was recorded in 1871 (Abul-Haj, Ewald, & Kazyak, 1963).

Mushroom poisoning constitutes 0.4% to 0.5% of all poisonings in the USA (Beug, Shaw, & Cochran, 2006). 1.6% Of toxicity cases were recorded in Switzerland between 1995 and 2009 (Schenk-Jaeger et al., 2012). Mushroom poisoning is the most common cause of plant toxicities in Turkey (Eren et al., 2010). Mushroom poisoning accounts for 1.2% of all poisonings in Turkey (Hocaoğlu, Kalkan, & Tunçok, 2010). More than 90% of mushroom poisoning in Turkey is caused by mushroom picking (Eren et al., 2010).

According to the 2019 report of the American Association of Poison Control Center, 5.799 mushroom poisoning cases were seen in the country (Gummin et al., 2020). In Turkey, 5228 mushroom

poisoning cases were reported in 2014 (Pekşen, 2015).

Mushroom poisonings are frequently seen during spring, late summer, autumn (Schmutz et al., 2018).

4. Poisonous Mushrooms

Poisonous mushrooms are classified according to the toxins they contain and the symptoms they cause (Jo, Hossain, & Park, 2014). According to their clinical presentations, poisonous mushrooms can be divided into 8 groups as cyclopeptide, orellanin, monomethylhydrazinic, coprinoid, muscarinic, psilocybinous, ibutenic acid-musimolic, gastrointestinal irritants (Hall et al., 1987).

There are three genera within the cyclopeptide group containing amatoxin namely: *Amanita* (9 species), *Galerina* (8 species), *Lepiota* (20 species) (Diaz, 2018). Toxicity caused by the *Amanita phalloides* species is the most common cause of death (Garcia, Costa, Carvalho, Baptista, et al., 2015).

5. *Amanita phalloides* Poisoning and Toxins of *Amanita phalloides*

Due to many unreported cases, the incidence is not accurately documented (Santi et al., 2012). Toxicity due to amatoxins are responsible for 90-95% of deaths (Diaz, 2018).

Amanita phalloides smells and tastes good; It can be mistaken for edible mushrooms (Diaz, 2018). If a mature *Amanita phalloides* (20-25 grams) is eaten, a lethal amount of amatoxin is taken into the body (Wong & Ng, 2006).

Amanita phalloides is in the genus *Amanita*, family Amanitaceae, order Agaricales, class Agaricomycetes, division Basidiomycota (P. Zhang, Tang, Cai, & Xu, 2015). It is known as "death cap" (Allen, Desai, & Lisenbee, 2012). *Amanita phalloides* contains the most toxins relative to its weight in the genus *Amanita* (Karlson-Stiber & Persson, 2003).

Amanita phalloides has 3 main toxins: amatoxins, phallotoxins, virotoxins (Vetter, 1998). Amatoxins are one of the most dangerous natural toxins that cause liver failure (Letschert, Faulstich, Keller, & Keppler, 2006). Absorption of phallotoxins and virotoxins from the gastrointestinal tract in humans is very low (Karlson-Stiber & Persson, 2003). Therefore, amatoxins are responsible for mortality in mushroom poisoning (Letschert et al., 2006).

Other *Amanita* species, containing high levels of amatoxin, include: *A. phalloides*, *A. virosa*, *A. ocreata*, *A. verna* (Jo et al., 2014). Amatoxins are highest in the lamellar part of the cap of *Amanita phalloides* and lowest in the volva part (Kaya et al., 2015). The amount of toxin varies according to the type of mushroom, region, climate (Kaya et al., 2015).

Amanita phalloides contains 8 different amatoxins (α amanitin, β amanitin, γ amanitin, ϵ amanitin, amanulin, amanulic acid, amanin amide, amanin) and the most toxic one is alpha amanitin (Baumann, Münter, & Faulstich, 1993). They are resistant to heat, acids and enzymatic effects (Allen et al., 2012; Poucheret, Fons, Doré, Michelot, & Rapior, 2010). The lethal dose of alpha amanitin in adults is as low as 0.1 mg per body weight (Santi et al., 2012).

6. Toxicokinetics of Amatoxins

After ingestion, Organic Anion Transporter Polypeptides (OATP), found in the gastrointestinal epithelium, provide rapid absorption of toxins (Smith & Davis, 2016). Later, amatoxins are transported to the liver by OATPs and begin to inhibit RNA polymerase II (Letschert et al., 2006; Wong & Ng, 2006). Transport occurs via OATP1B1, OATP1B3 (mostly) and OATP2B1 located on the liver cell surface (Letschert et al., 2006).

Amatoxins do not bind to plasma proteins (Faulstich, Talas, & Wellhöner, 1985). Most of the alpha amanitin is excreted in the urine and a small part in the bile (Faulstich et al., 1985). Sixty percent of the alpha amanitin excreted into the enterohepatic circulation (Smith & Davis, 2016). Therefore, toxins remain in the body for a long time (Faulstich et al., 1985).

Amatoxins are detectable in plasma, urine, gastrointestinal tract and feces (Brayer & Froula, 2016). Amatoxins can be detected up to 104 hours in gastroduodenal aspiration (Piqueras, 1989). They are present in plasma for up to 36 hours and in urine for up to 4 days (Jaeger, Jehl, Flesch, Sauder, & Kopferschmitt, 1993). The level of amatoxin detected in biological samples is not related to the severity of poisoning (Allen et al., 2012).

7. Mechanism of Toxicity

Various toxicity mechanisms have been attributed to amatoxins (Garcia, Costa, Carvalho, Baptista, et al., 2015).

The main accepted mechanism is that amatoxins bind to eukaryotic RNA Polymerase II and inhibit transcription and protein synthesis (Poucheret et al., 2010). Alpha amanitin irreversibly inhibits RNA polymerase II in vivo and in vitro (Nguyen et al., 1996).

Amatoxins are toxic to all eukaryotic cells; however, cells with high protein synthesis activity, such as liver cells, are most affected (Faulstich, 1979). Amatoxin mostly targets the gastrointestinal mucosa, hepatocytes and cells of the proximal tubule in the kidney (Karlson-Stiber & Persson, 2003).

Depletion of mRNAs causes a decrease in protein synthesis resulting in cellular necrosis and apoptosis (Wong & Ng, 2006). Mushrooms containing amatoxin are responsible for delayed-onset hepatocellular necrosis (Diaz, 2018). Amatoxins cause hyperinsulinemia and hypoglycemia by affecting pancreatic beta cells (Poucheret et al., 2010).

8. Clinical Stages

8.1. First (Lag) Stage

The first stage is usually asymptomatic, its about 10 hours and may last up to 40 hours (Santi et al., 2012).

8.2. Second (Gastrointestinal) Stage

This stage may last up to 2 days and include: Watery diarrhea, abdominal pain, vomiting (Karlson-Stiber & Persson, 2003).

If the diagnosis of mushroom induced toxicity is missed, the patient may be misdiagnosed with gastroenteritis and discharged (Berger & Guss, 2005).

Hypoglycemia, dehydration, hypokalemia, oliguria, metabolic acidosis are often observed (Karlson-Stiber & Persson, 2003). Liver enzymes and coagulation parameters remain within normal limits (Piqueras, 1989).

8.3. Third (Apparent Convalescence)

This stage lasts 12-24 hours (Berger & Guss, 2005). Gastrointestinal complaints disappear (Santi et al., 2012). Therefore, patients can be discharged early (Allen et al., 2012). Toxins begin to damage the liver and kidneys resulting in raised serum transaminases and lactate dehydrogenase levels (Santi et al., 2012).

8.4. Forth (Multiorgan Failure) Stage

Liver transaminases, LDH and bilirubin levels rise; coagulation disorders, bleeding, hypoglycemia, metabolic acidosis, encephalopathy, hepatorenal syndrome occur (Karlson-Stiber & Persson, 2003). Death usually occurs between 6-16 days after poisonous mushroom ingestion (Karlson-Stiber & Persson, 2003). Death might occur early due to hypoglycemia (Brayer & Froula, 2016). The rapid fall of liver enzymes indicates a decrease in liver mass and extensive hepatocellular damage (Piqueras, 1989).

Chronic active hepatitis with elevated liver transaminases may develop in those who survive (Brayer & Froula, 2016). Abnormal transaminases may remain abnormal for several weeks after symptoms cease (Piqueras, 1989).

9. Diagnosis

Early diagnosis is vital but can be challenging as cases are often misdiagnoses as gastroenteritis due to atypical symptoms initially (Ye & Liu, 2018). Meixner colorimetric tests can be used to detect the presence of amatoxin (Brayer & Froula, 2016). This test is sensitive but not specific (Brayer & Froula, 2016).

Urine sample can also be used for analysis and early diagnosis. Detection of alpha amanitin levels, more than 5 ng/ml within the first 36 hours, is highly sensitive and specific for the diagnosis of amatoxin poisoning (Butera, Locatelli, Coccini, & Manzo, 2004).

10. Treatment

There is no specific antidote for alpha amanitin toxicity (Diaz, 2018; Santi et al., 2012). Except for liver transplantation, all treatments are supportive (Diaz, 2018). Many recommendations are controversial for amatoxin poisoning (Ward, Kapadia, Brush, & Salhanick, 2013). This is one of the most important difficulties for treatment (Ye & Liu, 2018).

Many substances used in treatment inhibit hepatic uptake of toxins (Letschert et al., 2006). There are no controlled clinical studies in amatoxin poisoning due to ethical and practical reasons (Mengs, Pohl, & Mitchell, 2012). Admission to the intensive care unit and close monitoring are required (Smith & Davis, 2016).

10.1. Inhibition of Absorption

If the patient is admitted within 6 hours, gastric lavage should be performed (Karlson-Stiber & Persson, 2003). Due to the asymptomatic initial stage, patients often arrive at hospitals late which reduce the effectiveness of gastric lavage (Ye & Liu, 2018).

If the toxin is in the gastrointestinal tract, frequent administration of activated charcoal inhibits enterohepatic circulation (Enjalbert et al., 2002). Multi-dose active charcoal should be administrated. The recommended dose of activated charcoal is 50 grams in adults and 25 grams in children (Karlson-Stiber & Persson, 2003).

10.2. Supportive Therapies

The patient should be stabilized and intravenous fluid support should be provided (Ward et al., 2013). It is important to maintain urine output (Enjalbert et al., 2002). Forced diuresis is not recommended (Ye & Liu, 2018). Electrolyte abnormalities, metabolic acidosis, hypoglycemia, and coagulation factor deficiencies should be corrected (Enjalbert et al., 2002). Fresh frozen plasma should be given if there is active bleeding or hemodynamic instability (Smith & Davis, 2016).

10.3. Pharmacologic Approaches

Many substances such as penicillin G, silibinin, N-acetylcysteine, ceftazidime, cimetidine, thioctic acid, steroid, vitamin C, vitamin E, insulin, glucagon, human growth hormone have been used alone or combined (Enjalbert et al., 2002).

In multidimensional multivariate analyzes, survival was shown to be high in those using silibinin, N-acetylcysteine, and high-dose ceftazidime (Poucheret et al., 2010). Penicillin and silibinin are the most commonly used in combined therapy (Enjalbert et al., 2002).

Penicillin G: The most commonly used monotherapy is high-dose penicillin G (benzylpenicillin) (Enjalbert et al., 2002). Penicillin G act via several different mechanisms (Smith & Davis, 2016). The most important of these mechanisms is the inhibition of OATP1B3-mediated transport of amanitin to the liver (Letschert et al., 2006). However, penicillin G alone has low efficacy (Enjalbert et al., 2002).

Penicillin G is recommended to be given 1.000.000 U/kg/day on the first day and 500.000 U/kg/day IV for the next 2 days (Allen et al., 2012). Its use in *Amanita phalloides* poisoning has not been approved by the FDA (Enjalbert et al., 2002). It is not recommended in some countries due to its low efficacy and possible allergic reactions (Ye & Liu, 2018).

Silibinin: Silymarin is extracted from the seed of the plant *Silybum marianum* (Saller, Meier, & Brignoli, 2001). Silibinin is produced from silymarin (Saller et al., 2001). Silibinin inhibits the intestinal absorption of amatoxins via OATPs and their uptake into the liver (Letschert et al., 2006). Silibinin also reduces free oxygen radicals and lipid peroxidation (Saller et al., 2001).

In observational studies and case reports intravenous silibinin administration during early stages has been shown to be a successful treatment (Mengs et al., 2012). Silibinin should be given intravenously within

the first 48 hours and its dose is 20-50 mg/kg/day (Santi et al., 2012). The treatment is applied for 4-5 days (Saller et al., 2001). In some countries, there is no IV preparation of silibinin and its oral bioavailability is low (Magdalan et al., 2010). It has been claimed that mortality decreased more than 50% after silibinin was available (Mengs et al., 2012).

N-acetylcysteine(NAC): N-acetylcysteine is a glutathione precursor an antioxidant, and a free radical scavenger (Diaz, 2018). It is recommended to be used in amatoxin poisoning, but its effectiveness is limited (Santi et al., 2012).

In a retrospective study, it was shown that mortality was lower in the group given additional NAC compared to the group given activated carbon, penicillin, and supportive treatments (Akın, Keşkek, Kılıç, Aliustaoğlu, & Keşkek, 2013). As a result of the evaluation of many clinical studies, it was thought to be useful and safe to use with other treatments (Liu et al., 2020).

Ceftazidime: It has been reported that survival is high in amatoxin poisonings given ceftazidime (Poucheret et al., 2010). But the number of cases is limited (Daoudal et al., 1989).

Polymyxin B: Polymyxin B was found effective in mice studies. It has been shown that polymyxin inhibits the effect of the toxin by binding to the region where alpha amanitin binds to RNA Polymerez II and prevents the toxicity of alpha amanitin in mice (Garcia, Costa, Carvalho, Silvestre, et al., 2015). Clinical studies are required.

Rifampicin: Rifampicin is an OATP1B3 inhibitor and may be useful for the treatment of amatoxin poisoning (Letschert et al., 2006). It is easily accessible in emergency departments. However, further clinical studies are needed to establish the efficacy of rifampicin in amatoxin related mushroom poisoning (Zuker-Herman, Tong, & Wong, 2021).

Cimetidine: High dose administration of intravenous cimetidine has been shown to reduce liver damage in animals poisoned with amatoxin (Ward et al., 2013). Few cases have been recorded (Enjalbert et al., 2002).

Extracorporeal Methods: Hemodialysis and plasmapheresis can excrete very small amounts of amatoxin due to the very low plasma concentrations (Grabhorn et al., 2013).

The benefit of dialysis is yet to be proven in cases of amatoxin poisoning (Ward et al., 2013). Therefore, dialysis should be considered in renal failure (Horowitz & Moss, 2020).

Plasmapheresis is superior to hemodialysis (Jander, Bischoff, & Woodcock, 2000). It is beneficial if used in the early stages of poisoning (Faulstich et al., 1985). It is recommended to be applied within the first 36 hours (Jander et al., 2000).

The use of Therapeutic Plasma Exchange (TPE) and Molecular Adsorbent Recirculating System (MARS) has been shown to improve biochemical parameters (J. Zhang et al., 2014).

It has been shown that when Fractionated Plasma Separation Adsorption (FPSA) is used in combination with activated charcoal, silibinin, NAC

treatment, the total amount of alpha amanitin in the urine is reduced (Bergis et al., 2012).

10.4. Liver Transplantation

Current treatment approaches other than liver transplantation are supportive and there are no controlled clinical studies (13). In Europe, 1, 3, 5, 10-year survival rates in liver transplantation are 74%, 70%, 68%, 64% respectively (Germani et al., 2012).

11. Prognosis

The severity of poisoning depends on the amount of toxin ingested and the time lapse before initiation of treatment (Santi et al., 2012). The earlier the treatment is started, the better the prognosis (Smith & Davis, 2016).

The mortality rates, due to *Amanita phalloides* poisoning, is over 40% when supportive treatment is given versus over 10% with combined treatments and intensive care management (Enjalbert et al., 2002). The prognosis is worse in children, as children are more susceptible to electrolyte imbalances and the ratio of mushrooms consumed to body weight is higher (Jander et al., 2000).

12. Conclusion And Recommendations

Mushroom poisoning is an important health problem worldwide, especially in rural areas and countries where mushroom picking is common. *Amanita phalloides* is life-threatening as it contains amatoxin, and there is no specific antidote. Early diagnosis and effective treatment cannot be provided in many cases because the first symptoms are late.

Close monitoring and intensive care are important. Early diagnosis and combined treatments improve survival. The lack of standard treatment guidelines remains a challenge. It is essential to reduce the absorption of amatoxins, increase excretion, prevent liver uptake and use advanced extracorporeal methods.

Many cases cannot be treated with conservative methods and progress to liver failure. Despite all treatment options, mortality rates remain over 10% in researched large case series. Antidotes of toxins and effective substances that prevent their absorption into the liver have not been developed yet. For these reasons, cultivated mushrooms should be preferred instead of consuming wild mushrooms to avoid *Amanita phalloides* poisoning. Selective and potent OATP1B3 inhibitors may play a key role in effective treatment in the future.

Conflicts of interest

The authors declare that there is no conflict of interest.

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