Four patients with Amanita Phalloides poisoning

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Abstract

Mushroom poisoning by Amanita phalloides is a rare but potentially fatal disease. The initial symptoms of nausea, vomiting, abdominal pain and diarrhea, which are typical for the intoxication, can be interpreted as a common gastro-enteritis. The intoxication can progress to acute liver and renal failure and eventually death. Recognizing the clinical syndrome is extremely important. In this case report, 4 patients with amatoxin intoxication who showed the typical clinical syndrome are described. The current therapy of amatoxin intoxication is based on small case series, and no randomised controlled trials are available. The therapy of amatoxin intoxication consists of supportive care and medical therapy with silibinin and N-acetylcysteine. Patients who develop acute liver failure should be considered for liver transplantation. (Acta gastroenterol. belg., **2014**, 77, **353-356**).

Key words : amanita phalloides, mushroom poisoning, acute liver failure.

Introduction

Poisoning with Amanita Phalloides is a rare cause of acute liver failure. Amatoxin poisoning occurs worldwide, but most published case reports are European. About 50 to 100 fatal cases of amatoxin poisoning are reported yearly in Western Europe. However, the true incidence of mushroom poisoning is not precisely known due to a high number of unreported or unrecognized cases (1,2,3). We report four concomitant cases of amatoxin intoxication, the most deadly cause of mushroom poisoning.

Case report

Four women, between 49 and 79 years old, living together in a convent, were admitted to the hospital because of nausea, vomiting and diarrhea. Symptoms started approximately ten hours after eating wild mushrooms, self-picked in the forest. Laboratory data, 24 hours after ingestion, showed normal liver enzymes in 2 patients and normal INR and bilirubin in all 4 patients. Because of suspected amatoxin intoxication, a therapy with intravenous fluid, N-acetylcysteine and silibinin was started. 36 hours after intoxication, complaints of vomiting and diarrhea improved in all 4 patients. Blood analysis however showed a dramatic increase of the liver enzymes in 3 of 4 patients, and an elevation of bilirubin and INR in all 4 patients (Fig. 1). Two patients were transferred to a transplant centre 48 hours after the mushroom poisoning because they developed stage 2 hepatic encephalopathy. With maximal supportive therapy, all patients gradually improved from day 3 and recovered without the need for liver transplantation. They were discharged from the hospital between 6 to 10 days after admission.

Discussion

Among mushroom intoxications, amatoxin intoxication accounts for 90% of all fatalities. Amatoxin poisoning is caused by mushroom species belonging to the genera Amanita, Galerina and Lepiota. Amanita phalloides, commonly known as the "death cap", causes the majority of fatal cases. The mortality of amatoxin poisoning ranges between 10 and 20% (1,2,3). In the literature, only a few case reports of intoxication of several 'family' members are found what makes this case particularly interesting (4,5,6).

Amanita phalloides contains two main groups of toxins : phallotoxins and amatoxins. The phallotoxins damage the cellular membrane of the enterocytes and are responsible for the initial gastrointestinal symptoms of nausea, vomiting and diarrhea. Phallotoxins are not absorbed from the intestine. The amatoxins are cyclopeptides, that are not destroyed by cooking or long periods of cold storage. The lethal dose is very low (0.1 mg/kg body weight), i.e. one mushroom can be lethal. The amatoxins are rapidly absorbed through the intestinal epithelium and bind weakly to serum proteins. In the liver, the amatoxins are transported in the hepatocytes where they inhibit RNA polymerase II, resulting in cellular necrosis. 60% of the absorbed amatoxins is excreted in the bile and returned to the liver via the enterohepatic circulation (2,3,7,8).

The clinical picture of amatoxin intoxication varies from mild to very serious, potentially lethal. The severity of intoxication depends on the amount of toxin ingested (8). Our patients showed the typical clinical syndrome of an amatoxin intoxication. The syndrome can be divided into three phases. The first phase, the gastrointestinal

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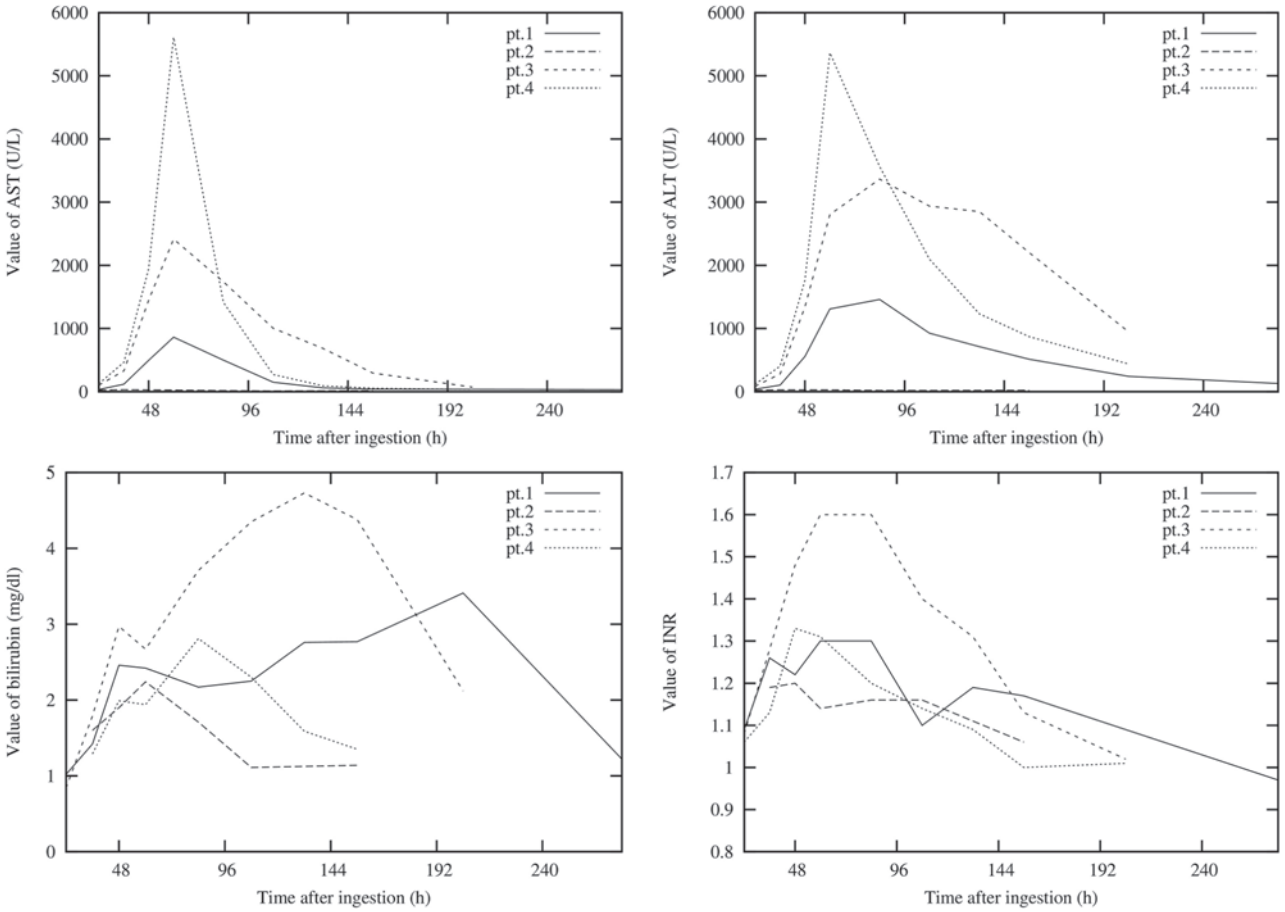

Fig. 1. — Evolution of the liver enzymes, bilirubin and INR in the 4 patients

phase (6-40 hours after consumption), is characterized by vomiting, crampy abdominal pain and diarrhea and lasts 12-24 hours. In amatoxin intoxication, symptoms develop typically more than 6 hours after ingestion, while other toxic mushrooms cause symptoms earlier, after 0.5-3 hours (8). Blood analysis at this initial stage can show acid-base disturbances and electrolyte abnormalities, but shows normal liver and kidney function. The second phase is characterised by an apparent recovery 36-48 hours after ingestion, while biochemistry shows a progressive increase of transaminases and lactic dehydrogenase. In the third phase (2-6 days after ingestion), patients can develop acute liver failure (ALF) with severe coagulopathy, often complicated by renal failure. This can evolve in multi-organ failure and death within 1-3 weeks after ingestion (8,9).

Establishing the diagnosis of a mushroom intoxication is difficult. A careful history is very important, to avoid the risk that patients are discharged too early with a false diagnosis of a common gastroenteritis (8). The diagnosis of mushroom intoxication is based on 3 cornerstones : the clinical picture, the description of the ingested mushroom and if possible an analysis of the mushroom (3,10). The description of the ingested mushroom by the patient is not very reliable because the appearance of amanita phalloides changes during its growth. A mycological analysis of the mushroom is rarely possible (< 5%) (2). In this case however, a similar mushroom, found at the harvest place by the patients' general practitioner, was analysed by a mycologist and confirmed to be an Amanita phalloides. The diagnosis can be confirmed by the determination of alpha amanitin in urine, but this test isn't performed in Belgium. There are different methods of analysis. These techniques are very sensitive if performed in the first 48 h after ingestion (3,9).

The management of amatoxin poisoning includes preliminary medical care, supportive measures, specific treatment and liver transplantation if necessary. The efficacy of treatments for amatoxin intoxication is based on case reports and small series. There are no well-designed randomized controlled trials available. An analysis of the world experience in treatment of amatoxin poisoning was published by Enjalbert *et al*. in 2002. If an amatoxin intoxication is suspected, treatment should be initiated as soon as possible, even in asymptomatic patients (2,3).

Preliminary medical care consists of gastrointestinal decontamination procedures. The efficacy of these treatments depends on an early execution after the intoxication. Because of the long asymptomatic period in amatoxin poisoning (> 6 hours), the clinical use of these measures is limited. Data to support the use of ipecac syrup to induce emesis or whole bowel irrigation are

Table 1. — **Criteria for urgent liver transplantation in patients with acute liver failure caused by Amanita phalloides poisoning (12,13,14)**

King's college criteria for nonparacetamol induced ALF	1) PT > 100 sec (INR > 6.5) *or* 2) Any three of the following criteria: a) PT > 50 sec (INR > 3.5) b) Serum bilirubin > 300 μmol/L (± 17.5 mg/dl) c) Age below 10 years or over 40 years d) Interval between jaundice and encephalopathy over 7 days e) non-A, non-B hepatitis or drug-induced
Ganzert's criteria	1) Prothrombin index ≤ 25% of normal at any time between day 3 and day 10 after ingestion *and* 2) Serum creatinine ≥ 106 μmol/L (± 1,2 mg/dl) within the same time period
Escudie's criteria	Prothrombin index < 10% of normal (INR > 6) ≥ 4 days after ingestion

insufficient. Gastric lavage should only be considered when it can be performed within 60 minutes after ingestion (2,8).

Supportive measures are directed to treat dehydration, electrolyte abnormalities, metabolic acidosis which are frequently seen in the gastro-intestinal phase (2,8).

Specific treatment consists of detoxification procedures and chemotherapies. The aim of detoxification is to reduce the absorption and enhance the excretion of amatoxins. Oral detoxification by repeated administration of activated charcoal could reduce amatoxin reabsorption in the enterohepatic circulation (20-40 g every 3-4 hours). Gastroduodenal aspiration through a nasogastric tube has been recommended to remove bile fluids and interrupt enterohepatic circulation. However, the actual benefit of these procedures is not known (2,8). In this case, the patients were not treated with activated charcoal because of vomiting and presentation of the patients 24 hours after ingestion. Because of the renal elimination of amatoxins, a diuresis of 100-200 ml/h is recommended. However, urinary detoxification by forced diuresis does not increase amatoxin elimination and is no longer recommended (2). Several extracorporeal methods for toxin removal (hemodialysis, hemoperfusion, plasma exchange, MARS) have been used. There are no convincing data supporting their efficacy (2,9,10).

There is no specific amatoxin antidote available. However, different chemotherapies have been used in the treatment of amatoxin poisoning. Silibinin and N-acetylcysteine (NAC) have a positive effect on survival of patients with Amanita Phalloides poisoning (2,11). Silibinin, a water soluble silymarin derivative, may reduce amatoxin uptake by hepatocytes. Administration of silibinin is recommended if the patient is seen within 48 hours of ingestion. The recommended dose is empirical (5 mg/kg IV over 1 hour followed by a continuous infusion of 20 mg/kg/24h). Treatment is continued during 3-4 days (3). NAC is used for ALF induced by paracetamol and in many centers for ALF not induced by paracetamol. It has also been proposed in cases of amatoxin poisoning. A retrospective multivariate analysis of 2110 patients by Poucheret in 2010 showed a positive effect on survival. The suggested dosage is 150 mg/kg in 250 ml glucose 5% over 30 min intravenously, followed by 150 mg/kg in 250 ml glucose 5% over 24 hours. It should be continued until a positive biochemical effect is seen and for maximum 5 days (2,11). Penicillin G was frequently used in the past, but a recent analysis showed no clear survival benefit for patients treated with this drug (11). Ceftazidim had a positive effect on survival in this analysis, but concerned only 12 patients and was always associated with silibinin (2,11).

When amatoxin poisoning progresses into ALF, prompt transfer to a transplant centre for emergency liver transplantation is indicated. The most widely used criteria for urgent LT in ALF are the King's College Hospital criteria (12). However, some of these criteria cannot easily be used in patients with amatoxin poisoning because some patients never develop encephalopathy. Ganzert *et al*. and Escudié *et al*. described criteria for urgent LT in patients with amanita phalloides poisoning (Table 1). However, these criteria should be larger validated. Therefore, the use of the 'King's College' criteria for nonparacetamol liver failure is advised in ALF due to amatoxin poisoning (10,13,14).

Conclusion

Intoxication by amanita phalloides is a rare cause of acute liver failure, but recognizing the clinical syndrome can save lives. In this case report, we describe 4 patients with the typical clinical syndrome of amanita phalloides poisoning and we review the literature. The therapy of amatoxin intoxication consists of supportive care and medical therapy with silibinin and N-acetylcysteine. Therapy with activated charcoal can be beneficial, if started early after the intoxication. Patients who develop liver failure should be transferred to a transplant centre for urgent liver transplantation.

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