TREATMENT OF AMANITA PHALLOIDES INTOXICATION: A REPORT OF 3 CASES AND A REVIEW OF THE LITERATURE

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INTRODUCTION

The mortality associated with the ingestion of mushrooms of the amanita phalloides group has been reported to be approximately 30 % (1), and 95 % of all fatal cases of mushroom poisoning are from this cause (2). Amanita mushroom poisoning is not uncommon in Turkey. Last year in Adana an epidemic of mushroom poisoning caused the deaths of over 20 individuals and cases of poisoning are not uncommon in Istanbul during the late summer and early autumn.

In this paper we report three cases of amanita mushroom ingestion and their management and discuss briefly the pathogenesis and treatment.

Key Words: Amanita palloides, Benzylpenicillin,Haemodialysis, Intoxication.

CASE REPORTS

Case report 1. A six year old 16 kg male child (HB) picked some mushrooms from the grass near to his house and ate an unknown number which had been fried for him by his father for his lunch. At midnight, 11 hours following ingestion of the mushrooms he began to suffer from violent nausea and vomiting. This prompted a visit to a local hospital where he was immediately treated with induced emesis and lavage containing charcoal slurry. He was rehydrated with intravenous fluid therapy and his vomiting and diarrhoea improved, but his mental state slowly deteriorated and at four o'clock the following afternoon he was transferred to Marmara University Hospital.

On arrival at the hospital the child was acutely ill. He was drowsy but responded to verbal commands and was able to answer simple questions. He was mildly hypotensive with a blood pressure of 85/65 mm Hg and a pulse rate of 120 beats/minute. Electrocardiography revealed a sinus tachycardia. His respiration rate was 16 per minute and his temperature 37° C. He was not clinically icteric. Examination of the cardiovascular system and pulmonary systems was unremarkable, and examination of the central nervous system revealed no motor or sensory abnormalities.

Examination of the abdomen revealed generalised abdominal tenderness, an enlarged liver palpable five cm below the costal margin, and no evidence of splenomegaly.

Examination of the patient's urine revealed urine of specific gravity 1.015 containing glucose (+++) and bilirubin (+). No protein was detected and examination of the urinary sediment was unremarkable. Haematological and biochemical parameters measured on admission were as follows: Hb 12.6 g/dl, Hct 38%, white cell count 10.4 x 10^9/litre, BUN 23 mg/dl, glucose 100 mg/dl, SGOT 22 IU/L, SGPT 31 IU/L, prothrombin time 19 seconds, PTT 28 seconds.

Therapy consisted of administration of 0.9 % saline solution and 10 % dextrose solution intravenously, high dose IV benzylpenicillin (1 million IU/kg/day given 4 hourly), lactulose (40 ml 8 hourly), neomycin (250 mg 8 hourly), IV prednisolone (2 mg 6 hourly), and haemodialysis.

Haemodialysis was commenced within four hours of admission to our hospital. Venous access was acheived using a double lumen femoral vein catheter. The patient was dialysed for a period of 12 hours in the first session and for 10 hours in each of the 3 succeeding 24 hour periods.

During the second dialysis the patient developed

mild upper GI bleeding which did not require transfusion and was commenced on IV ranitidine (3 mg/kg/day given as a continuous infusion). Prednisolone therapy was discontinued. Bleeding did not reccur. Eighteen hours following admission to our hospital liver function tests revealed an SGOT of 3850 IU/L, SGPT 5450 IU/L, PT 17 seconds and PTT 29 seconds. At this point he had marked abdominal distension and the liver was palpable six cm below the costal margin.

On the second day following admission the patient passed Ascaria in one of his bowel movements but therapy was not commenced at this point. Over the course of his treatment the patient's condition gradually improved and 10 days following admission the patient's abdominal signs had disappeared and his liver function tests returned to normal. He was discharged on a dose of Mebandazole for his ascariasis.

Case report 2. KB, the four year old, 14 kg brother of HB ate mushrooms at the same time and developed vomiting and diarrhoea 12 hours following ingestion. Undigested mushroom caps were visible in his vomitus. He too was admitted to a local hospital and treated with induced emesis, charcoal slurry lavage and intravenous fluid replacement therapy prior to admission to our hospital at the same time as his brother.

On admission he was well orientated, normotensive with a blood pressure of 100/60 mm Hg and a pulse of 120 beats / min sinus rhythm. Examination of the respiratory and cardiovascular systems was unremarkable. Abdominal examination revealed a liver palpable two cm below the costal margin with no evidence of splenomegaly or ascites.

Haematological parameters were within normal limits. Biochemical investigations revealed a bilirubin of 0.8 mg/dl, SGOT of 64 IU/L, and SGPT 56 IU/L. Treatment with intravenous fluids, benzylpenicillin, and prednisolone was instigated as described above. Eighteen hours following admission his liver enzyme levels had increased to 250 IU/L (SGOT) and 3400 IU/L (SGPT). Haemodialysis was commenced via the femoral route and given for 2 ten hour periods over the 2 succeeding days. Ten days following admission the patient's liver function was normal and he was fit for discharge from hospital.

Case report 3. BY, a four year old girl and neighbour of the previous patients, ingested one mushroom. She too, developed symptoms of nausea and vomiting 11 hours later and was taken to the same local hospital where an identical treatment was given. It was reported that the degree of abdominal disturbance was not very severe.

She too was transferred to our facility. On admission she was well with no abnormal physical or biochemical signs. She was treated with intravenous benzylpenicillin and prednisolone as described above. This treatment was continued for three days and when no signs of hepatic dysfunction were noted, was discontinued. The patient was discharged on the 7th day following admission.

DISCUSSION

The Amanita family of muhsrooms contribute significantly to fatal poisoning in man. The species is widely distributed occuring in Australia, Japan, The Phillipines, Africa, India, South and North America, and in Europe (3). Poisoning normally occurs following the ingestion of wild mushrooms which have been mistakenly considered to be edible.

Amanita phalloides contains two groups of toxins, only one of which is clinically significant in man. The phallotoxins are toxic only on parenteral administration and are also found in nonpoisonous species of amanita (4). The amatoxins are a group of cyclic octapeptides. They are extremely toxic, the lethal dose in man has been estimated to be below 0.1 mg/kg and a lethal amount of toxin may be contained within one mushroom weighing 20 gm (5). The amount of toxin contained in any mushroom is highly variable however, and depends upon a number of factors including site, season etc. The toxin is not destroyed by cooking or by drying.

Symptoms of poisoning normally occur between 6 and 12 hours after ingestion and include severe watery diarrhoea, nausea, vomiting, and abdominal pain. These signs frequently subside within a few hours and the patient may enter a symptom free period which lasts from 12 to 24 hours. If the diagnosis of mushroom poisoning is not suspected then during this period the patient may be diagnosed as having suffered from an episode of acute gastroenteritis from which he has recovered. Within 24 hours rapidly increasing jaundice and renal shutdown may occur with associated elevation of liver enzymes, creatinine and BUN. Where there has been severe poisoning or inadequate treatment coma may intervene and death from hepatic failure normally follows on the fourth to seventh day.

The amatoxins exert their effect by inhibiting RNA polymerase II and interfere with transcription (6). This results in cellular necrosis and prevents the reproduction of cells. This effect is most pronounced in those cells which have most contact with the poison and where the rate of cell turnover is high. Thus the gastrointestinal mucosal cells, hepatocytes, and cells lining the renal tubules are most affected by exposure to amatoxins.

Toxins which are taken up by the liver are excreted into the bile (1, 7), reabsorbed from the bowel and returned to the circulation from where they can reexert their toxic effects on the liver. This enterohepatic circulation prolongs the presence of amatoxins in the serum and thus increases the exposure of the

hepatocytes. Toxin has been detected in the sera as long as 48 hours after ingestion of mushrooms (7). Amatoxin is excreted well in the urine and sampling of urine for amatoxin levels is of diagnostic significance in poisoned persons (1).

Highly sensitive methods of detection of amatoxins have now been developed and include High Performance Liquid Chromatography (HPLC), High Performance Thin Layer Chromatography (HPTLC), and Radioimmunoassay (8). Quantitation of amatoxin by these techniques remains a specialised task outside the scope of hospital laboratories in this country, but fortunately measurement of amatoxin is not necessary to make a diagnosis of amanita phalloides intoxication.

Any individual who develops symptoms of nausea, vomiting, watery diarrhoea, and abdominal pain from 6 to 12 hours after ingesting suspicious mushrooms must be assumed to have been poisoned by amanita toxin and appropriate therapy instigated (1, 8). No other poisonous mushroom causes these symptoms with this time course. There is absolutely no doubt that all three children presented here had eaten amanita phalloides type mushrooms. The therapy started soon after their admission to our hospital was based on this diagnosis.

HB (case 1) was severely ill on admission with an enlarged liver and evidence of hepatic pre-coma. Despite normal levels of SGOT and SGPT at the time of admission we had no hesitation in initiating aggressive dialysis therapy. Dialysis was continued daily as described until there was significant improvement in both his clinical state and the liver enzyme levels (24 hours following the last dialysis SGOT was 140 IU/L, SGPT 960 IU/L).

KB (case 2) was not critically ill on admission and in view of his unremarkable abdominal examination and normal liver enzyme titres only conservative therapy was commenced. Eighteen hours following admission and 40 hours following ingestion of the mushrooms the SGOT was 250 IU/L and the SGPT 3400 IU/L. Since toxin is still present in the blood stream at this time after ingestion, we haemodialysed the patient for two 10 hour periods. At the end of this period the SGOT was 50 IU/L and the SGPT 660 IU/L.

BY (case 3) was the least ill of the group and showed only mild elevation of her liver enzyme levels. At no stage during her dmission period did her clinical condition or biochemical data give any cause for concern, and only conservative therapy was given.

Because of the difficulties involved in organising controlled trials of treatment in amanita phalloides poisoning much of the treatment recommended is based on anecdotal evidence, or upon evidence from animal studies which may not be relevant to man. A large number of treatment protocols have been used. Toxin may be removed by peritoneal dialysis (5), forced diuresis (1, 5, 9), haemodialysis (10), haemofiltration (1), haemoperfusion (1, 11), or plasmapheresis (1, 5, 12), and it is recommended that one of these techniques should be used to remove toxin from the blood of patients presenting within 48 hours of ingesting these mushrooms (1).

Despite the good results obtained with the treatments given, our treatment is open to criticism. The decision to dialyse HB was correct and in our opinion lifesaving. The decision not to actively remove toxin from KB and BY was probably incorrect since there was no doubt that these children had been exposed to amatoxin within 48 hours of presentation to our facility. In the case of KB we later initiated treatment whilst BY had fortunately not been severely poisoned and recovered with conservative therapy. It should be noted that in hospitals where dialysis is not available forced diuresis is now considered to be an excellent alternative. Intravenous fluid should be administered with low dose frusemide to obtain a urine flow of 300 ml/hour and treatment continued for 48 to 72 hours (5).

The chemotherapy we administered to our patients is only one combination amongst many others that have been used. High dose IV penicillin has been frequently recommended because it has been established that high doses of this antibiotic inhibit the uptake of amatoxin into perfused rats liver (1), and this particular drug is probably the most important of those presently available. (13).

Prednisolone has been noted to have a similiar effect to penicillin (1). Neomycin and lactulose were given to HB as part of a liver failure regime but Bastien has suggested this agent as a treatment in combination with nitrofuroxazide and high dose vitamin C (9). This combination has also been used in combination with Soludactone (1). Silymarine, a mixture of biologically active flavones found in milk thistle has also been recommended for amatoxin therapy by Vogel on the basis of animal experiments (14). Much interest has been generated by the drug thioctic acid and mortality statistics appear to provide evidence of a good therapeutic action on the part of this drug (1). It was first used by Kubicka in 1959 and has been used extensively in Eastern Europe, Italy and the United States. Unfortunately it was not available for use with our patients.

The demonstration that amatoxin undergoes an enterohepatic circulation has prompted Busi et al to suggest that a duodenal tube be placed for the removal of bile (7). Vesconi et al have used this tube to administer activated charcoal to bind toxin in the bile (5).

In conclusion amanita phalloides poisoning is not rare in Turkey and physicians should be prepared to

first recognize and diagnose and then treat this intoxication. The high mortality rate associated with untreated cases may be reduced by prompt introduction of therapy.

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