

# Original article

## Clinical features, laboratory findings and imaging appearances of venous diethylene glycol poisoning in patients with liver disease

LUO Ming-yue, LIN Bing-liang and GAO Zhi-liang

**Keywords:** liver disease; vena; diethylene glycol; poisoning

**Background** There was a hospital outbreak of venous diethylene glycol poisoning in Guangzhou, China. It is the only massive episode of venous diethylene glycol poisoning in history. Here we report its clinical features, laboratory findings, and imaging appearances.

**Methods** The clinical features of 15 venous diethylene glycol poisoning patients with liver disease were analyzed and summarized. Their laboratory findings and imaging appearances were comparatively analyzed before and after poisoning.

**Results** All poisoned patients presented with oliguric acute renal failure with anuria after a mean of 6 days. Carbon dioxide combination power of 13 patients dropped after a mean of 9 days with valley value on the 10th day, when metabolic acidosis developed. Gastroenteric symptoms or aggravation of gastroenteric symptoms were displayed in 11 patients after a mean of 9 days. Neurological system impairment was observed in 10 patients after a mean of 14 days. Seven patients had low fever after a mean of 6 days. Causes of death of 14 patients included multiple organ dysfunction syndrome, severe lung infection and massive haemorrhage of digestive tract. Blood creatinine and urea nitrogen were abnormal after a mean of 5 days with peak value on the 11th and 14th days, respectively. Serum calcium had no obvious change, and phosphorus was distinctively increased. Liver functions did not change significantly. Poisoned patients had higher white blood cell counts, but lower red blood cell counts and hemoglobin value. Of the 7 patients who exhibited mild, moderate or severe patchy consolidation shadowing in the lung, 2 manifested mild or severe gaseous distention and dilation of gastroenteric tract.

**Conclusions** Main features of venous diethylene glycol poisoning in patients with liver disease include oliguric acute renal failure, metabolic acidosis, gastroenteric symptoms or aggravation of gastroenteric symptoms, neurological system impairment and low fever, with a mortality rate of 93.33% in poisoned patients. There is also higher white blood cell counts and anemia, patchy consolidation shadowing in the lung, gaseous distention and dilation of gastroenteric tract, which occurs later than mild patchy consolidation shadowing and earlier than moderate patchy consolidation shadowing in the lung.

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Diethylene glycol (DEG) is a highly toxic organic solvent used mainly for industrial purpose. Experimental studies in animals indicated that DEG induces kidney toxicity with acute renal failure, but the mechanism of toxicity is unknown.<sup>1-5</sup> Up until now, there were 9 reported cases of oral or topical administration of DEG poisoning, mostly involving children with concurrent mild disease.<sup>6-13</sup> Between 19 April and 1 May 2006, venous DEG poisoning occurred in 15 patients with liver disease in the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. This was the only massive episode of DEG poisoning with venous administration in history. We report its clinical features, laboratory findings, and imaging appearances.

### METHODS

#### Patients

Sixty-four patients with liver disease were treated with armillarisin-A injection, which was produced by the Second Qiqihar Pharmaceutical Co. Ltd. (China), in the third Affiliated Hospital of Sun Yat-sen University, Guangzhou,

China, between 19 April and 1 May 2006. Of the 64 patients, there were 49 men and 15 women. Twenty-one patients had chronic active hepatitis, 16 had liver cirrhosis resulted from hepatitis B virus, 14 had severe hepatitis, 6 had primary hepatocellular carcinomas, 2 had biliary cirrhosis, 2 underwent orthotopic liver transplantation, 1 had cholangiocarcinoma, 1 had liver impairment caused by malignant lymphoma, and 1 had hepatocellular degeneration. Their ages ranged from 5 to 75 years with a mean of 49 years.

#### Diagnosis criterion for DEG poisoning

According to literature and consensus of experts,

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Department of Radiology, the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510655, China (Luo MY)

Department of Infectious Disease, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510630, China (Lin BL and Gao ZL)

Correspondence to: Dr. LUO Ming-yue, Department of Radiology, the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510655, China (Tel: 8620-38254100. Fax: 8620-38254159. Email: myluo720@163.com)

diagnosis criterion established by the Health Bureau of Guangdong Province for DEG poisoning is definite administration history of DEG, developing acute renal impairment or renal failure characterized by severe oliguria or anuria within 2 weeks of the last administration, and elimination of other causes of acute renal impairment or failure.

### Laboratory investigation

Concentration of DEG in armillarisin-A injection was tested with spectrophotometry. Renal and hepatic functions, blood cell counts, and biochemical examinations were performed with an automatic analyzer. For each poisoned patient, the last data before poisoning and the peak data after poisoning were comparatively analysed.

### Imaging evaluation

Imaging examination included posteroanterior and lateral chest radiographs, bedside chest radiographs, and plain CT scanning of the chest. Chest radiographs were performed with a DR Revolution XQ/I X-ray machine (GE Medical Systems, Milwaukee, Wis, USA), and bedside chest radiographs were done with a 12 A bedside chest radiograph machine (Toshiba Co, Tokyo, Japan). CT examination was performed with a LightSpeed QX/i MDCT scanner (GE Medical Systems) using the following parameters: section thickness, 5.0 mm; pitch, 6.0; voltage, 120 kV; electric current 200 mA; matrix, 512×512; field of view, 3500–4000 mm. When necessary, contrast enhancement CT scanning of the chest was performed at 35 seconds after injection of contrast media (Iopamiro 300, Bracco S.P.A., Milano, Italy). The dosage of contrast medium was 2 ml/kg, and was administered with a power injector at a rate of 3.0 ml/s through a catheter placed in the peripheral vein of the antecubital fossa.

Imaging appearances before and after poisoning were analyzed by comparison. According to its extent in both left and right lung fields, lung lesions were classified as mild (extent≤1/3 lung field), moderate (1/3 lung field<extent≤2/3 lung field), and severe (2/3 lung field<extent). Gastroenteric gaseous distention and dilation was classified as mild (extent≤1/3 gastroenteric tract), moderate (1/3 gastroenteric tract<extent≤2/3 gastroenteric tract), and severe (2/3 gastroenteric tract<extent) based on its extent.

### Statistical analysis

Data are reported as mean±standard deviation (SD) unless otherwise specified. Data before and after poisoning were tested using Student's *t* test. Statistical analysis was performed with SPSS version 13.0 for Windows. A *P* value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### Clinical features

Of the 64 patients with liver disease treated with

armillarisin-A injection, their cumulative dosage of DEG was 2.4–114 ml, 15 patients were poisoned with DEG and 49 were not, so the poisoning rate was 23.44%. The 15 poisoned patients aged from 33 to 76 years with a mean of 50 years, including 14 men and 1 woman. Oliguric acute renal failure was developed after a mean of 5 days (range from 2 days to 12 days), and anuria was presented after a mean of 6 days (range from 3 days to 13 days). Abnormal serum creatinine and blood urea nitrogen were noted after a mean of 5 days (range from 2 days to 12 days) with peak value on the 11th and 14th days, respectively. Carbon dioxide combination power of 13 patients dropped after a mean of 9 days with valley value on the 10th day, and metabolic acidosis developed. Presentation or aggravation of gastroenteric symptoms, such as nausea, vomiting, abdominal bloating and pain were exhibited in 11 patients after a mean of 9 days (range from 3 days to 19 days). Appearance of nervous system impairment of 10 patients occurred after a mean of 14 days (range from 7 days to 24 days) involved cranial nerves, including optic, oculomotor, facial, and glossopharyngeal nerves. In addition, of the 10 patients, 5 had impairment of peripheral nerves and 6 had impairment of central nerves. They developed optic neuritis, slowness in light reacting of pupil, different size of two pupils, impediment to movement of eyeball, incomplete closing of the eyelid, slanting of corner of the mouth, unilateral facial paralysis, tinnitus aurium, impediment to swallowing, limb tremor and paralysis, dizziness, blurred eyesight, agitation and coma. Respiratory muscle paralysis was present in severe cases. Seven patients had low fever after a mean of 6 days (range from 1 day to 13 days).

Fourteen patients died, so the mortality of poisoned patients was 93.33%. Of the 14 died patients, 8 died of multiple organ dysfunction syndrome, 4 died of severe lung infection, and 1 died of massive haemorrhage of the digestive tract, with a mean of 12.5 days from administration of armillarisin-A injection to death (range from 8 days to 65 days) for these 13 patients. Another 1 patient was treated with haemodialysis on the 2nd day after acute renal failure and had urine on the 6th day, received combined kidney-liver transplantation on the 16th day and had normal urine volume at the 23rd day; however, he had lung fungus and bacterial infection and septicaemia on the 32nd day after transplantation, and died of severe lung infection and shock and multiple organ dysfunction syndrome on the 607th day after transplantation.

One patient survived, accounting for 6.67% of poisoned patients. He was treated with haemodialysis on the 1st day after renal failure, had urine on the 7th day and normal urine volume on the 9th day. His renal function had returned to normal and hepatic function clearly improved. His nervous system impairment began to take a turn for the better 1 month after the renal failure, and improved remarkably 4 months later, with only limb

numbness at present.

### Administration concentration and dosage of DEG

Concentration of DEG contained in 10 ml armillarisin-A injection was 30.00%, tested by the Center for Drug Inspection of Guangdong Province. The practical concentration of DEG in 10 ml armillarisin-A injection was 2.73%, 1.15% after being diluted with 100 ml, 250 ml glucose respectively. The practical concentration of DEG in 20 ml armillarisin-A injection was 5.00%, 2.22% after being diluted with 100 ml, 250 ml glucose respectively. The accumulative dosage of DEG was 9.0–72.0 ml for poisoned patients.

### Laboratory findings

Renal functions, hepatic functions and blood cell counts of DEG poisoned patients before and after poisoning are listed in Table 1, Table 2 and Table 3, respectively.

**Table 1.** Renal functions of DEG poisoned patients before and after poisoning

Item	Case	LD	PD	P values
Blood urea nitrogen (mmol/L)	15	7.40±3.90	31.20±9.68	0.000
Serum creatinine (μmol/L)	15	94.20±24.10	691.60±197.80	0.000
Carbon dioxide combination power (mmol/L)	13	24.40±3.90	13.10±2.60	0.000
Calcium (mmol/L)	14	2.38±0.18	2.41±0.22	0.474
Phosphorus (mmol/L)	14	0.73±0.45	1.31±0.50	0.001

LD: last data before poisoning. PD: peak data after poisoning.

**Table 2.** Hepatic functions of DEG poisoned patients before and after poisoning

Item	Case	LD	PD	P values
Total bilirubin (μmol/L)	15	376.70±244.60	354.70±257.10	0.362
Prothrombin time (s)	15	24.40±13.10	22.40±8.80	0.210
Alanine aminotransferase (U/L)	14	163.20±225.50	109.40±115.80	0.170
Alkaline phosphatase (U/L)	14	217.00±265.40	146.70±148.80	0.082

**Table 3.** Blood cell counts of DEG poisoned patients before and after poisoning

Item	Case	LD	PD	P values
White blood cells ( $10^9/L$ )	15	6.59±2.33	9.78±3.75	0.008
Red blood cells ( $10^{12}/L$ )	15	2.99±0.94	2.32±0.76	0.014
Platelet ( $10^9/L$ )	15	119.60±50.10	94.60±72.60	0.211
Hemoglobin (g/L)	15	99.60±25.10	79.50±23.60	0.018

### Imaging appearances

Of the 14 patients who died, 2 had developed mild patchy consolidation shadowing in the lung on the 1st and 3rd day, respectively, after administration of armillarisin-A injection. Their shadowing was ill-defined with nonhomogeneous density, and one of them had severe gastroenteric gaseous distention and dilation on the 7th day (Figure 1). One patient displayed mild gastroenteric gaseous distention and dilation on the 6th day after administration of armillarisin-A injection, and had moderate patchy consolidation shadowing on the 13th day, progressing to severe patchy consolidation shadowing on the 23th day, ultimately dying from it (Figure 2). Three patients exhibited mild patchy consolidation shadowing in the lung at a mean of 21 days (range from 6 days to 24 days) after administration of armillarisin-A injection, progressing to severe patchy consolidation shadowing at

a mean of 33 days (range from 8 days to 42 days) and dying from it (Figure 3). One patient was treated with haemodialysis on the 2nd day after acute renal failure, received combined kidney-liver transplantation on the 16th day, had lung fungus and bacterial infection with irregular cavity in right upper lung on the 32nd day after transplantation, and died of severe lung infection and shock and multiple organ dysfunction syndrome on the 607th day after transplantation (Figure 4). Multiple pulmonary metastatic tumors progressed for one patient with hepatocellular carcinoma and orthotopic liver transplantation. Another patient with hepatocellular carcinoma had an excision. Old pulmonary tuberculosis of 1 patient had no change. No pulmonary abnormality was seen for 4 patients.

One survival patient revealed mild patchy consolidation shadowing in left lower lung at the 5th day after administration of armillarisin-A injection, which was improved at the 7th day and absorbed at the 14th day with anti-infective treatment.

## DISCUSSION

Armillarisin-A can regulate and promote immune function, enhance phagocytosis, and improve protein metabolism.<sup>14</sup> It is widely used in clinical therapy, mostly as auxiliary drug for liver disease. Adverse effect rate of armillarisin-A is very low in normal condition, with only case reports of a few mild irritative symptoms of blood vessel and rare mild allergic reactions.

Between 19 April and 1 May 2006, of the 64 patients with liver disease in the third Affiliated Hospital of Sun Yat-sen University treated with armillarisin-A injection by venous route administration, 15 were poisoned, with a poisoning rate of 23.44%. Of the 15 poisoned patients, 14 died, with poisoning death rate of 93.33%. It is now confirmed that the armillarisin-A injection was produced by the Second Qiqihar Pharmaceutical Co. Ltd., and the Second Qiqihar Pharmaceutical Co. Ltd. had substituted of DEG for the more expensive propylene glycol and added it into armillarisin-A injection as subsidiary material, which caused the DEG poisoning episode.

Differing from the 9 previously reported cases of oral or topical administration of DEG poisoning episode, which mostly involved children with concurrent mild disease,<sup>6-13</sup> this hospital outbreak of DEG massive poisoning was administrated by venous route, and had not only definite concentration and dosage of DEG given to patients with liver disease, but also comprehensive and detailed record of the clinical course with diagnosis and treatment through time.

DEG is highly toxic to human beings, but its mechanism of toxicity is unknown. Experimental studies on animals demonstrated that DEG poisoning is closely related to the activity of alcohol dehydrogenase and acetaldehyde



**Figure 1. A:** Mild patchy ill-defined consolidation shadowing with nonhomogeneous density in the lung on the 3rd day after administration of armillarisin-A injection. **B:** Severe gastroenteric gaseous distention and dilation on the 7th day.  
**Figure 2. A:** Mild gastroenteric gaseous distention and dilation on the 6th day after administration of armillarisin-A injection. **B:** Moderate patchy consolidation shadowing on the 13th day. **C:** Progressed to severe patchy consolidation shadowing on the 23rd day.  
**Figure 3. A:** Mild patchy consolidation shadowing in the lung on the 24th day after administration of armillarisin-A injection. **B:** Progressed to severe patchy consolidation shadowing on the 42nd day.  
**Figure 4. A:** Lung fungous and bacterial infection with irregular cavity in right supper lung on the 32nd day after combined kidney-liver transplantation. **B:** Severe lung infection on the 607th day after transplantation, and died the same day.

dehydrogenase, which are mainly distributed in liver.<sup>15</sup> Retrospective chart review of our study group demonstrated that there was no statistical difference in DEG concentration and dosage between the poisoned and non-poisoned patients, and that poisoning relates to the degree of liver disease and activity of alcohol dehydrogenase and acetaldehyde dehydrogenase.<sup>16,17</sup> Activity of alcohol dehydrogenase and acetaldehyde dehydrogenase is lowered for patients with liver disease, and affects DEG metabolism and leads to poisoning.<sup>1,2,18</sup> Of the 15 poisoned patients, 12 had terminal liver disease in our study.

All poisoned patients developed oliguric acute renal failure with a mean incubation period of 5 days and a mean time of 1 day from oliguria to anuria. Poisoned patients died in a mean of 7.5 days after acute renal failure. The mortality of poisoned patients was 93.33%. Gastroenteric symptoms or aggravated gastroenteric symptoms were disclosed after 3 days to 19 days for 73.33% of poisoned patients. Nervous system impairment manifested after 7 days to 24 days for 66.67% poisoned patients. Poisoned patients had increased serum creatinine and blood urea nitrogen, decreased carbon dioxide combination power, but peak value time of serum creatinine was 3 days earlier than that of blood urea nitrogen, 1 day later than valley value time of carbon dioxide combination power. Generally, metabolic acidosis showed at the 9th day after administration of armillarisin-A injection, which was 4 days later than that of renal impairment, and the most serious time was the

10th day. Serum calcium of poisoned patients had no obvious change, but phosphorus increased remarkably. In our study, 73.33% poisoned patients had gastroenteric symptoms or aggravated gastroenteric symptoms, 46.67% poisoned patients simultaneously had low fever and organ function impairment developed slower. All these were different from that in literature and may have a bearing on the activity change of alcohol dehydrogenase and acetaldehyde dehydrogenase in patients with liver disease, but their mechanism need to be studied further.

The present DEG poisoning episode occurred in patients with liver disease, but hepatic functions of poisoned patients had no obvious change before and after poisoning, and had no biochemical change in drug hepatic impairment. This suggests that DEG has no impairment on the hepatobiliary system and administration of DEG by venous route may not be metabolized in the liver, but this mechanism needs to be studied further.<sup>19</sup>

Poisoned patients had anaemia with decreased red blood cell counts and hemoglobin value. Platelet counts had no remarkable change. Increased white blood cell counts with obvious increase of neutrophilic leukocyte and no remarkable change of eosinophilic leukocyte implied that DEG poisoning aggravates infection or draws forth new infection for patients with liver disease.<sup>16,17</sup> The development of patchy consolidation shadowing in the lung for 7 patients (46.67%) may have something to do with simultaneous low fever when renal failure for

46.67% patients, and it needs to be studied and verified further.

There is no special detoxification for DEG toxicosis. Management of patients with DEG poisoning relies on early diagnosis with symptomatic and supportive care for electrolyte disorder, metabolic acidosis and multiple organ dysfunction syndrome, and performing haemodialysis as soon as possible.<sup>20</sup> In our study, only one poisoned patient survived. He commenced to have urine on the 6th day and had normal urine volume on the 9th day after renal failure. His renal functions had returned to normal, and hepatic functions clearly improved. Nervous system impairment began to ameliorate after 1 month and improved remarkably 5 months after renal failure, with only limb numbness at present. His improvement was faster than that reported in the literature,<sup>21-24</sup> but now the challenge is to evaluate the rehabilitation course for poisoned patient who survived.

It is not easy for DEG to store up with a 3.4 hour half-life.<sup>25</sup> It was reported that there were patchy haemorrhage and edema in the lung. Of the 14 died patients, 2 revealed mild patchy consolidation shadowing in the lung on the 1st and 3rd days, respectively, after administration of armillarisin-A injection; the shadowing is pulmonary haemorrhage and edema. One patient had moderate patchy consolidation shadowing on the 13th day after administration of armillarisin-A injection and progressed to severe patchy consolidation shadowing on the 23th day; the shadowing is pulmonary infection. Three patients exhibited mild patchy consolidation shadowing in the lung at a mean of 21 days after administration of armillarisin-A injection and progressed to severe patchy consolidation shadowing at a mean of 33 days; the shadowing is pulmonary infection too. One patient received combined kidney-liver transplantation on the 16th day after acute renal failure, but had lung fungus and bacterial infection on the 32nd day after transplantation, and died of severe lung infection and shock and multiple organ dysfunction syndrome on the 607th day after transplantation. One survival patient had mild patchy consolidation shadowing on the 5th day, which improved on the 7th day and absorbed on the 14th day with anti-infective treatment; the shadowing is pulmonary infection. Pulmonary imaging appearances of poisoned patients and their dynamic changes need to be studied and verified further.

Of the seven patients who had patchy consolidation shadowing in the lung, one manifested mild gastroenteric gaseous distention and dilation on the 6th day and moderate patchy consolidation shadowing on the 13th day. Another had mild patchy consolidation shadowing in the lung on the 3rd day and severe gastroenteric gaseous distention and dilation on the 7th day. That is to say, two patients developed mild or severe gastroenteric gaseous distention and dilation about 1 week after administration of armillarisin-A injection, accounting for 18.18% of 11

patients with gastroenteric symptoms or aggravated gastroenteric symptoms; appearance of gastroenteric gaseous distention and dilation was later than that of mild patchy consolidation shadowing, but earlier than that of moderate patchy consolidation shadowing in the lung.

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