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# Tetramine poisoning

## 「毒鼠強」中毒個案

We report on two patients who presented with status epilepticus due to ingestion of rat poison containing tetramine. Both had eaten the same meal, subsequently presumed to be the source of the poison. Physical examination and investigation were unremarkable and diagnosis was based on patient history. Seizures were ultimately controlled with ketamine, after unsuccessful attempt of benzodiazepine and sodium thiopentone. One week after poisoning, both patients underwent one session of high-volume haemofiltration followed by charcoal haemoperfusion to eliminate the toxin from the body. Plasma tetramine levels then decreased from 0.95 µg/mL to 0.35 µg/mL and from 0.53 µg/mL to 0.40 µg/mL, respectively.

本文報告兩名患者因攝入含「毒鼠強」的毒鼠藥出現連續癲癇。由於兩人曾一起進餐，因此懷疑飯菜內含有毒鼠藥。身體檢查和調查結果並不明顯，要根據患者病史才能作出診斷。患者曾以苯二氮草類藥物及硫噴妥鈉治療但不成功，最後施以氯胺酮穩定兩人的癲癇發作情況。中毒一星期後，兩人接受一次高量血液過濾，再接受活性碳血液灌注以清除體內毒素。血漿中毒鼠強濃度分別從 0.95 µg/mL 及 0.53 µg/mL，下降至 0.35 µg/mL 及 0.40 µg/mL。

### Case reports

#### Case 1

A 38-year-old construction worker was admitted with status epilepticus in January 2003. He had a history of epilepsy but had defaulted from follow-up and taken no anticonvulsant drugs for 3 months. While in the Accident and Emergency Department, he had a generalised tonic-clonic convulsion that lasted 30 minutes. His temperature was 37°C and Glasgow Coma Scale (GCS) score was 3/15. There was no neck rigidity and both pupils were dilated and reactive. There were no localising signs and no external evidence of head injury. Cardiovascular examination was unremarkable: pulse, 110 beats per minute regular; blood pressure, 180/100 mm Hg; electrocardiogram (ECG), normal. His chest was clear to auscultation and pulse oximeter read 95% on room air. The seizure remained uncontrolled following administration of lorazepam 8 mg, diazepam 10 mg, and phenytoin 750 mg. He was intubated and plain computed tomography of the brain revealed mild cerebral oedema. Results of laboratory investigations were shown in the Table. Osmolar gap, calcium, glucose, ammonia, and liver function tests were normal.

A further seizure occurred despite rapid escalation of anticonvulsant therapy (midazolam 14 mg immediately followed by 10 mg/h, phenytoin 2 g, thiopentone 2 g loading followed by 375 mg/h). A ketamine infusion at a dose of 120 mg/h eventually brought the seizure under control. Sodium thiopentone, midazolam, and ketamine infusion were gradually stopped after 16 hours of seizure-free activity on electroencephalography (EEG).

#### Key words:

Hemofiltration;  
Hemoperfusion;  
Ketamine;  
Status epilepticus;  
Tetramethylenedisulfotetramine

#### 關鍵詞：

血液過濾；  
血液灌注；  
氯胺酮；  
連續癲癇；  
四亞甲基二硫四胺

*Hong Kong Med J* 2005;11:511-4

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**Table. Laboratory findings**

Finding	Measured value	Reference range
Haemoglobin (g/L)	153	125-175
White cell count ( $\times 10^9$ /L)	21.1	3.8-10.0
Platelet count ( $\times 10^9$ /L)	302	150-400
Sodium (mmol/L)	140	135-146
Potassium (mmol/L)	4.0	3.5-5.0
Urea (mmol/L)	7.6	2.5-6.5
Creatinine (mmol/L)	186	62-115
Creatine kinase (IU/L)	277	24-180
Mixed metabolic and respiratory acidosis		
pH	6.7	7.35-7.45
Paco <sub>2</sub> (kPa) [mm Hg]	10.4 (78.2)	4.7-6.0 (35-45)
Paco <sub>2</sub> (kPa) [mm Hg]	15.8 (118.8)	10.7-13.3 (80-100)
Base excess (mmol/L)	-31	-3 to +3
Bicarbonate (mmol/L)	9.4	20-26

Questioning of the patient's wife revealed that her husband's colleague (patient in case 2), who shared the same meal, had also had a convulsion. A dog that ate the remains of the meal had convulsions and was found dead the following day. Probable food or drug poisoning was suspected. Activated charcoal 50 g every 6 hours was commenced on admission and continued for 2 days. Plasma cholinesterase level was 6606 IU/L. Methaemoglobin level was 0.3%. Serum lead was normal (0.3  $\mu$ mol/L) and the arsenate level was negative. Blood and urine were negative for salicylate, paracetamol, and cannabinoids.

The patient was extubated on day 7. He remained confused and exhibited frequent facial twitching. Tetramine, the active component of a rat poison 'dushuqiang', was identified in vomitus 1 week after admission. Intravenous pyridoxine 50 mg daily was prescribed for 5 days from day 7 onward. One session of high-volume haemofiltration (HVHF) followed by a session of charcoal haemoperfusion (HP) were performed this time.

Zero-balanced HVHF was performed with an on-line haemofiltration system and a high-flux polysulphone diafilter (APS900, Asahi dialyzer, Japan; 1.8 m<sup>2</sup>, removes molecules of up to 66 000 dalton). Blood flow was set at 200 mL/min and ultrafiltration flow at 200 mL/min. Predilution replacement fluid was given at 200 mL/min for 10 hours. Tinzaparin was used as anticoagulant. The plasma tetramine level decreased by 63% from 0.95  $\mu$ g/mL to 0.35  $\mu$ g/mL. The following day the tetramine level increased to 0.53  $\mu$ g/mL: a 6-hour HP was performed with a cartridge containing 300 g of activated charcoal (Adsorba 300C; Gambro Lundia AB, Sweden) coated with cellulose and at a

prescribed blood flow rate of 200 mL/min. Tinzaparin was again used as anticoagulant. This time, plasma tetramine level decreased from 0.53  $\mu$ g/mL to 0.40  $\mu$ g/mL, a reduction of 25%. Blood was taken 5 minutes after cessation of blood flow during both HVHF and HP.

The patient remained in the intensive care unit (ICU) for 16 days and was then discharged. He had normal mental function at 1-month follow-up.

### Case 2

A 33-year-old woman, who shared the same meal with the patient in case 1, presented with vomiting that was successfully controlled with prochlorperazine. She refused admission but presented again the following day with confusion and a generalised tonic-clonic convulsion. Examination revealed a GCS score of 15/15 but no focal signs. She was afebrile and cardiovascular and laboratory examinations were unremarkable: blood pressure, 117/75 mm Hg; pulse, 85 beats per minute; pulse oximeter 95% on room air; and ECG normal. Her GCS score decreased to 9/15 after a further seizure and she was intubated and given midazolam and phenytoin.

She was extubated 5 hours later. Tetramine was detected in vomitus and blood (0.54  $\mu$ g/mL) on day 7. She was confused but experienced no further seizures. She was discharged on day 10 having made a full recovery.

### Discussion

Tetramethylene disulphotetramine (TETS), commonly called tetramine, is an odourless and tasteless small molecule with MV 248. It binds to the gamma-aminobutyric acid (GABA) receptor on the neuronal cell membrane and blocks the chloride channels.<sup>1,2</sup> Available pharmacokinetic data are incomplete and sometimes contradictory. Both reversible<sup>2</sup> and irreversible binding<sup>3</sup> to the GABA receptors have been described. The TETS can be absorbed through the gastro-intestinal tract and respiratory system. Thereafter, it is rapidly distributed to various body tissues and organs. It has a high volume of distribution, a slow metabolism, and is excreted unchanged in the urine and stool. It can remain in the body for up to 6 months. The lethal dose 50% for humans is 0.1 mg/kg and there is no specific and effective antidote reported in the literature at the time of writing.<sup>2,3</sup>

The quoted toxic and lethal ranges for tetramine are 0.002 to 0.369  $\mu$ g/mL and 0.64 to 5.49  $\mu$ g/mL, respectively.<sup>4</sup> In mild-to-moderate poisoning, symp-

toms include headache, dizziness, nausea, vomiting, abdominal pain, bradycardia, tachycardia, twitching, agitation, and visual and auditory hallucinations. In severe cases, status epilepticus, coma, and multi-organ failure can occur. Electroencephalography demonstrates generalised slow waves and spikes. Onset time is rapid and occurs within 30 minutes of exposure and may last up to 13 hours. A fatality rate as high as 3.67% has been reported.<sup>5</sup> Diagnosis depends principally on history and clinical presentation. Detection of tetramine in blood or the excreta by gas chromatography/mass spectroscopy is confirmatory.

Dimercaptopropanesulphonate may have an antidotal effect. Animal and human studies reveal that it prolongs the latent period of convulsions and reduces convulsive time and mortality.<sup>6,7</sup> Binding of GABA in the brain is also enhanced. The anticonvulsant effect is increased by high-dose vitamin B6 and diazepam.<sup>7-9</sup> Dimercaptopropanesulphonate is available in some major hospitals in Hong Kong.

Extracorporeal toxin removal has been frequently performed in China by plasma exchange, HP, and haemodialysis with variable results.<sup>2,4,10,11</sup> Plasma exchange is reported to be more successful in cases of severe intoxication. Haemoperfusion is nonetheless more common and is associated with less rebound phenomena and stable haemodynamics. Haemodialysis is least useful unless the patient is in renal failure.

The efficacy of ketamine in prolonged status epilepticus has been demonstrated in both animal models and humans.<sup>12,13</sup> It decreases the excitatory effects of glutamate and other excitatory neurotransmitters through blockade of the N-methyl-D-aspartate-gated calcium channel. Ketamine and conventional anticonvulsants may have synergistic or additive effects when prescribed together.

Haemoperfusion is the standard treatment in China for severe tetramine poisoning. An intoxicated patient with plasma tetramine level of 70 µg/L excreted only 60 µg after 24 hours and a total of 80 µg after 48 hours.<sup>14</sup> Nonetheless one session of HP removed up to 1 mg of tetramine when the initial plasma level was 100 µg/L.<sup>14</sup> There was no demonstrable difference in plasma tetramine level before and after HP: this was attributed to redistribution of tetramine from the body store.<sup>15</sup> Abnormalities of EEG have been reported to persist for up to 1 year in patients not receiving HP.<sup>15</sup> Earlier resolution of EEG abnormalities has been observed in patients who receive more sessions of HP.

High-volume haemofiltration may be an alternative to HP since the charcoal cartridge for the latter is not readily available in most ICUs and its shelf-life is limited. Although the success of haemofiltration has not been extensively evaluated, the number of successful case reports is increasing. Its use in tetramine poisoning has not been reported.

In the first patient reported here, the plasma tetramine level was decreased by both HVHF and HP. The drop in plasma tetramine level was greater following HVHF (63%) than charcoal HP (25%). The increase in tetramine level from 0.35 µg/mL to 0.53 µg/mL 12 hours after HVHF was compatible with the rebound phenomenon and redistribution of the toxin from tissue stores to plasma. The difference in plasma level reduction following HVHF and HP may have been due to different treatment durations and the mechanisms involved. It is difficult to compare the efficacy of toxin removal by HVHF and HP if the amount of tetramine removed cannot be quantified.

As there is limited immediate access to charcoal HP in most ICUs, HVHF can be considered an alternative treatment for tetramine poisoning.

## Conclusion

Early and adequate resuscitation combined with seizure control are crucial to the management of acute tetramine poisoning. Ketamine and conventional anticonvulsant drugs may have synergistic and additive effects in the management of refractory status epilepticus. High-volume haemofiltration may be an alternative to charcoal HP in tetramine poisoning.

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