

Case Report

Tetramethylenedisulfotetramine Contaminated Milk Powder Induced Status Epilepticus in Two Siblings and Two Dogs

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A cluster of patients with tetramethylenedisulfotetramine (TETS) intoxication was reported in Thailand. Two siblings, a six-month-old boy and a four-year-old girl, and their domestic dogs presented with status epilepticus within 10 minutes after ingesting milk prepared from the same tin container of milk powder. Although the cases showed normal neurodevelopment at one-year follow-up, physicians should be informed of this lethal neurotoxic agent, especially in an era of terroristic activity.

Keywords: Bridged compounds, Infant formula, Milk, Neurotoxicity syndromes, Status epilepticus

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Tetramethylenedisulfotetramine (TETS, $C_4H_8N_4O_4S_2$) is an odorless, tasteless, white, crystalline powder that easily dissolves in water and its most common route of exposure is ingestion⁽¹⁾. TETS toxicity is most commonly reported in China^(1,2); there was only one reported case in the United States, which was traced to an illegally imported TETS-containing rodenticide from China⁽³⁾. To the best of our knowledge, this report is only the second reported case outside of China and the first reported case of TETS exposure in Thailand.

Case Report

A healthy, six-month-old Thai male was referred to the hospital with afebrile status epilepticus. He had a generalized, tonic, clonic seizure lasting more than 30 minutes which needed phenobarbitone sodium 20 mg/kg/dose and phenytoin 20 mg/kg/dose to cease the seizure. After the generalized tonic clonic seizure was controlled, multifocal clonic, intermittent blank staring and hypomotor seizures occurred and lasted for another 48 hours. The results of the routine

metabolic work-up (*i.e.* serum glucose, electrolytes, calcium, magnesium, and cerebrospinal fluid profiles) were normal. His ictal electroencephalogram showed 12 to 16 hertz- medium voltage spike-waves over the right temporal region time-locked with blank staring. Phenobarbital was continued for seizure control. At a two-month follow-up visit, the boy's mother informed us that her four-year-old daughter and her two dogs had shown similar symptoms about one week after the boy's seizure attack. Toxic substance exposure was suspected since the seizures occurred in a cluster; therefore, drinking water and other chemicals in their house were collected and sent for analysis. During this house visit the author was informed that the patient had drunk 3 ounces of milk before he had status epilepticus. While he and his mother had stayed in the hospital, his father had prepared a glass of milk from the powder in the same tin container used by the patient for his four-year-old daughter. Within a few minutes of finishing the milk, she developed unsteady gait followed by a generalized, tonic, clonic seizure. She was admitted to the intensive care unit at another hospital, from which her medical record revealed that she also had status epilepticus and needed a large dose of phenobarbital and phenytoin to end her convulsion. The father first thought that the girl had had a febrile

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convulsion as she had experienced when she was one year old, but then he suspected that there was something wrong with the milk. He subsequently tried to get rid of it by mixing the milk powder with water and gave to his two dogs. Both dogs developed a generalized tonic clonic seizure before they finished drinking the milk. One of the dogs had continuous convulsion for two hours and the other one had intermittent convulsive episodes lasting over two days. There was some milk powder left over in the suspected tin container source which the father could provide for investigation.

Because of the very rapid onset and marked severity of these seizures, TETS was likely concerned. Since Thailand has no laboratory test for the detection of TETS, the milk powder, drinking-water and other chemical specimen were sent to the Yunnan CDC Laboratory in China. TETS was detected in the milk powder through gas chromatography-mass spectrometry. Another sample of the milk powder was sent to Thailand's National Institute of Health to analyze for other substances that might cause seizures, such as strychnine, amphetamines, camphor, organochlorines, organophosphates; all results were negative. The other tin containers produced in the same lot by the same manufacturer were traced for investigation, but as considerable time had passed they had been sold and could not be located. Fortunately, there was no other case of status epilepticus reported from neighboring hospitals in the three months prior or following this serious event.

All family members insisted that no rodenticide was used and none of it was found in their house. From the interview, the family members showed no motivation to harm deliberately or intention to do a harmful act.

At one-year follow-up, the patient had normal development but was still being treated with phenobarbital because he had suffered a recurrent unprovoked seizure at one month following the first attack. His sister had normal development with no antiepileptic drug continuation. The two dogs were active and looked normal without further treatment.

Discussion

In such a situation, a toxic substance was likely to be the main suspect since the status epilepticus occurred in children and pets living in the same household. Seizures in all subjects came shortly after drinking reconstituted milk made from milk powder from the same container. Although other substances such

as strychnine⁽⁴⁾, amphetamine⁽⁵⁾, camphor⁽⁶⁾, cocaine⁽⁷⁾, or organochlorine⁽⁸⁾ could cause such a seizure, the strongly suspected TETS poisoning was primary because of the very rapid onset of seizure, which might not occur in the other neurotoxic agents.

TETS binds non-competitively and irreversibly to the chloride channel on the γ -aminobutyric acid receptor of the neuronal membrane, where it alters the intraneuronal potential and causes seizures⁽⁹⁾. Some studies have suggested that its poison can induce basal ganglion damage⁽¹⁰⁾ and monocyte dysfunction⁽¹¹⁾. Even a very small dose of TETS can be considered a lethal dose for human beings⁽³⁾ and it is in the list of extremely hazardous pesticides defined by the World Health Organization⁽¹²⁾.

Rapid onset-refractory seizures are the most recognizable clinical sign for TETS poisoning. Although laboratory identification can be accomplished by several methods, including gas chromatography (GC) with nitrogen-phosphorous detection, GC with flame photometric detection or GC-mass spectrometry⁽¹³⁾, laboratory identification of the compound is not practical for acutely poisoned patients because of the complexity of the analysis. Therefore, if poisoning is suspected, every attempt should be made to confirm subsequently the presence of this extremely toxic agent.

There has been no proven antidote for TETS poisoning. Management should follow standard guidelines for a poisoned patient showing signs of having alteration of consciousness⁽¹⁾. Gastric lavage may reduce the mortality risk⁽¹⁴⁾. The use of charcoal hemoperfusion or hemodialysis may provide extracorporeal TETS removal^(11,15) and intravenous pyridoxine and dimercaptosuccinic acid may also be effective⁽⁸⁾.

This is the first laboratory-confirmed report of TETS poisoning in Thailand. It is still unknown how this extremely hazardous substance was introduced into the milk powder since there is no TETS use in any known process of manufacturing. Although TETS has been banned in China⁽¹⁾, it still can be easily purchased in many areas and is very popular as an effective rodenticide. This incidence has been reported to the Thai Food and Drug Administration, and further probing of this banned rodenticide through Thailand's borders is under investigation.

Although the neurodevelopment of the two siblings was within normal limits and the dogs fully recovered at the one-year follow-up of their poisoning, this lethal neurotoxic agent usually causes severe

neurological damage. Awareness of it should be introduced to physicians, especially in an era of increased terrorist risk.

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การชักต่อเนื่องในเด็กสองพี่น้องและสุนัขสองตัวชักนำด้วยนมผงปนเปื้อนสาร *tetramethylenedisulfotetramine*

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เป็นรายงานกลุ่มผู้เกิดพิษจากสาร *tetramethylenedisulfotetramine* (TETS) ในประเทศไทย เด็กสองพี่น้องชายอายุ 6 เดือน หญิงอายุ 4 ปี และสุนัขเลี้ยงมีการชักต่อเนื่องภายใน 10 นาที หลังจากบริโภคนมที่เตรียมจากนมผงบรรจุกระป๋องเดียวกัน ถึงแม้ว่าผู้รับพิษเหล่านี้มีการพัฒนาทางระบบประสาทเป็นปกติใน 1 ปีต่อมา แพทย์ควรรับรู้ทราบเกี่ยวกับสารเป็นพิษถึงชีวิต โดยเฉพาะในยุคของการก่อการร้าย
