Cyanide Poisoning, 2 Cases Report and Treatment Review

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Abstract

Two patients, a 4-year-old girl and her brother 1 $^{1}/_{2}$ year-old, with cyanide poisoning are reported. They vomited and became comatose 9 hours after ingestion of boiled cassava. At a community hospital, they were intubated and given ventilatory support. The girl was transferred to Ramathibodi Intensive Care Unit. At 19 hours after ingestion, sodium nitrite and sodium thiosulfate were given as well as other supportive treatment. She recovered with normal breathing on the next day. The boy was referred to Ramathibodi 4 hours later. On arrival, he appeared normal except for the bitter almond breathe. Only supportive treatment was given. Their blood cyanide levels on arrival were 0.56 and 0.32 μg/ml (normal value < 0.3 μg/ml) respectively confirming the diagnosis of cyanide poisoning. Other abnormal laboratory findings included metabolic acidosis and lactic acidemia.

The pathogenesis and management of cyanide poisoning are reviewed.

Key word : Cyanide Poisoning, Cassava Ingestion

Cyanide is one of the most potent intracellular and lethal poisons known to humans. The hydrocyanic acid is extremely volatile which is able to produce the deadly hydrogen cyanide gas causing the pathognomonic odor of bitter almonds. Cyanide intoxication can occur as a result of toxic gases initiated by the pyrolysis of plastics or nitrile-based polymer fibers. It can also be the result of administration of certain drugs such as sodium nitroprusside and laetrile; or ingestion of plants containing cyanogenic glycosides such as cassava which is the most common cause of cyanide poisoning in up-country agricultural part of Thailand. Here, we report two siblings of cyanide poisoning from cassava ingestion. The younger developed early serious symptoms with respiratory depression and cyanosis but recovered after life-saving supportive treatment without antidotal therapy. The elder sister showed

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good response to the administration of antidotal therapy of sodium nitrite and sodium thiosulfate. Since these 2 antidotes are not commonly available and their mechanisms of action are not well understood, the pathogenesis of cyanide poisoning and antidotal therapy are reviewed.

CASE REPORTS

A 4-year-old sister and one and a half year-old brother, were referred from Chachoengsao Provincial Hospital with the history of boiled cassava ingestion 19 hours prior to admission. Nine hours after ingestion, they woke up at midnight, vomited several times and became unconscious. They were brought to the community hospital where the boy was intubated because of stupor, spasticity and hypoventilation with cyanosis. Subsequently, both were referred to the Provincial Hospital while the boy required ventilatory assistance and the girl required only oxygen via nasal mask during transport. At the Provincial Hospital, the girl victim became stuporous but responsive to purposeful pain stimuli. Her blood pressure dropped and intravenous fluid was immediately loaded. She was intubated and ventilated with ambu bag, while being transferred to Ramathibodi Hospital. The boy was referred later because clinical manifestation was not stable enough for transfer. He needed mechanical ventilator with hyperventilation and circulatory support by intravenous fluid loading and dopamine ranging from 5 to 20 μg/kg/minute as well as dobutamine.

PICU course for the girl

Physical examination at Ramathibodi Hospital revealed an alert and ashen gray color girl on endotracheal intubation with mechanical ventilatory setting as follows: FiO_2 1, PIP/PEEP 18/2, IMV 20/min.

Arterial blood gas revealed hypocapnea with metabolic acidosis due to lactic acidemia (Table 1). Blood sample for cyanide was obtained and antidotes were started immediately as follows: 3 per cent sodium nitrite 4 ml intravenous drip in 4 minutes, 2.5 per cent sodium thiosulfate 150 ml intravenous drip in 30 minutes and another 100 ml intravenous drip in 20 minutes. After inserting a nasogastric tube, the first specimen of gastric fluid obtained was collected for determining the cyanide level. Gastric lavage was performed until clear, then activated charcoal 15 grams and emulsion liquid paraffin 15 ml were given for decontaminating the remained toxin. Post-antidotal therapy for 50 minutes, the arterial-venous blood gas analysis and lactic acidemia were simultaneously improved with the methemoglobin level of 3.95 per cent. Then, she was closely observed and additional symptomatic treatment was provided. The initial high blood cyanide level of 0.56 μg/ml was confirmed and subsequently reduced to 0.02 μg/ml.

On the next day, she was extubated but the complications of partial upper airway obstruction from vocal cord granuloma and pneumonia were found. She was treated accordingly and discharged home 2 weeks later.

PICU course for the boy

On his arrival, 23 hours after ingestion, he was alert, not pale, no cyanosis status on endotracheal tube with mechanical ventilatory setting as followed : FiO_2 1, PIP/PEEP 12/2, IMV 25/min, Ti 0.7, O_2 Sat. 100 per cent. His breathe had bitter almonds smelling.

Arterial blood gas revealed respiratory alkalosis with mild lactic acidemia. Since his con-

Table 1. Laboratory investigation of the two patients.

	Blood gas analysis				Lactic acid* (mmol/L)	Blood cyanide level** (μg/ml)
	pH	PO_2	PCO_2	CO_2		
Girl, 4 years old						
19 hour after ingestion	7.352	118	21	11.7	7.4	0.56
50 min after antidote	7.376	471	26.4	15.6	5.2	
48 hour after ingestion						0.02
Boy, 1 6/12 years old						
23 hour after ingestion	7.467	276	25.2	18.3	2.7	0.32

* Normal lactic acid level < 3.4 mmol/L

** Normal blood cyanide level < 0.3 μg/ml

Table 2. Toxic effects of cyanide poisoning.

Systems	Manifestations
Odor	Bitter almond breathe (60-80%)
Skin	Cherry red color or cyanosis
CNS disturbances	Headache, agitation, disorientation, lethargy, seizures, coma, cerebral death
Cardiovascular instability	Hypertension or hypotension, tachycardia or bradycardia, ST-T wave changes, dysrrhythmias, AV block, cardiovascular collapse
Changes in oxygenation	Tachypnea or apnea, venous hyperoxemia: red venous blood, increased mixed venous O_2 content and decreased O_2 consumption resulting in narrow arteriovenous oxygen difference (AVO_2 diff)[6]
Metabolic acidosis	pH - elevated blood lactate and/or elevated lactate : pyruvate ratio
Others	Nausea, vomiting, abdominal pain, increased salivation

dition was good, he was lavaged and supportively treated without cyanide antidotal therapy. His blood and gastric cyanide level at 23 hours after ingestion were 0.32 and 0.02 μg/ml, respectively (Table 1). On the next day, he was extubated and discharged home uneventfully.

DISCUSSION

Cassava or Manihot esculenta is one of the major economic crops of Thailand produced for the animal food industry. It has been commonly known among Thai people that fresh cassava root is toxic. However, cases of poisoning from ingesting fresh cassava is not uncommon. Most of the victims were children who did not recognize its toxicity. Cassava contains cyanogenic glycosides; linamarin and lotaustralin. Linamarin is the major component. Both linamarin and lotaustralin are enzymatically hydrolyzed to cyanohydrins which are eventually converted by non-enzymatic process to release hydrogen cyanide[1-3]. Exposure to cyanide salts such as sodium, potassium and calcium and cyanide gas from burning materials induces a rapid onset of clinical signs and symptoms. Its rapid onset after exposure to the substances is the pertinent feature and clue for making the diagnosis. Poisoning by ingestion of cyanogenic glycosides, however, usually takes 1 to 12 hours after ingestion before clinical toxicity, because it needs time for converting cyanogenic glycosides and releasing hydrogen cyanide.

Cyanide is directly combined to myoglobin and many enzymes such as the cytochrome oxidase, nitrate reductase, ribulose diphosphate carboxylase, and the catalase. Binding to the cytochrome oxidase, a mitochondrial enzyme responsible for cellular respiration, will result in the inhibition of aerobic metabolism and consequent histotoxic anoxia state. Unconsiousness, dyspnea and cyanosis are the three most frequently reported signs and symptoms of cyanide poisoning. The range of toxic effects is shown in Table 2[4-6].

Table 3. Correlation between whole blood cyanide levels and symptoms.

Blood level (μg/ml)	Symptoms
< 0.03	Normal
0.5-1	Hyperventilation, tachycardia
1-3	Decreased mental state
> 3	Death

Hypoxic signs in the absence of cyanosis may be considered to be a diagnostic clue, but cyanosis may occur in a late state. The presence of a bitter almond odor is diagnostic, but it is possibly detected in only 60 to 80 per cent of victims, as shown in one reported case. The other signs and symptoms such as unexplained anion gap, metabolic acidosis and tachypnea in the absence of cyanosis with bright red blood is also highly suggestive of cyanide poisoning. Correlation between whole blood cyanide levels and symptoms has been established as shown in Table 3.

Although the determination of cyanide levels is necessary to comfirm the diagnosis and severity, unfortunately it is not available in most of the provincial hospitals in Thailand. Cyanide poisoning is a critical situation since early death may occur within minutes. In cases of emergency, decision to treat depends on clinical data. The prompt

Table 4. Suggested dose of sodium nitrite and sodium thiosulfate according to the patient's hemoglobin levels.

Hemoglobin level (g/dl)	Initial dose of 3% sodium nitrite (ml/kg)	Initial dose of sodium thiosulfate (ml/kg)
7	0.19	0.95
8	0.22	1.10
9	0.25	1.25
10	0.27	1.35
11	0.30	1.50
12	0.33	1.65
13	0.36	1.80
14	0.39	1.95

management is required for favorable outcome. The approach of treatment is divided into 2 mainareas including general supportive measures and specific antidotal therapy.

Supportive care

1. Establish airway, intubate patient and assist ventilation if necessary because respiratory arrest usually develops quite rapidly. Administration of 100 per cent oxygen may also be required even if the partial oxygen pressure is normal.

2. Correct acid-base imbalance by administering sodium bicarbonate if pH is < 7.16 and the patient does not respond to antidotal therapy.

3. Administer normal saline to provide volume support and to maintain blood pressure. Vasopressors, dopamine or preferable dobutamine may also be needed.

4. Seizures and arrhythmias should be immediately treated if occur.

5. In case of ingestion of alkaline cyanide salts, attempts of preventing gastrointestinal absorption with gastric lavage and the use of activated charcoal.

Specific treatment

Antidotal therapy is aimed to reduce the amount of free cyanide that can bind to cytochrome oxidase and to release already bound cyanide. There are several antidotes for cyanide poisoning. The first group is sodium nitrite and sodium thiosulfate. Sodium nitrite produces methemoglobin and sodium thiosulfate enhances the biotransformation of cyanide to thiocyanate which is a less toxic compound. For children, the dosage schedule in Table 4 is recommended[7-9].

In the past, the objective of treatment was to maintain methemoglobin levels of 25-30 per cent[7]. But this level is too high and may induce serious hypoxic states. The doses used induced less than 10 per cent of methomoglobinemia and proved to be effective[10].

Immediately before administration, the sodium nitrite is mixed with fluid and given slowly through the intravenous route over 20 minutes. The blood pressure should be closely monitored since sodium nitrite has a significant vasodilating effect and may cause severe drop in blood pressure if administered rapidly. If symptoms of cyanide poisoning persist, another half dose of sodium nitrite may be given 30 minutes later. Upon completion of the sodium nitrite infusion, then sodium thiosulfate is given. One of the disadvantages in using sodium nitrite is that the methemoglobinemia may reduce the oxygen carrying capacity of the red blood cell. Fatal methemoglobinemia has been reported with excessive administration of sodium nitrite. Under such circumstances, exchange transfusion is the preferred treatment modality.

Second, hydroxocobalamin (Vitamin B12a) is said to be one of the most promising antidotes available. Its advantage is the lack of adverse effects seen in nitrites such as methemoglobmemia and hypotenstion. It works by exchanging the hydroxy group for cyanide to form the non-toxic cyanocobalamin (vitamin B12). One molecule of vitamin B12a is needed to detoxify one molecule of cyanide. Thus, about 1400 mg hydroxocobalamin is required to detoxify 1 mmol of cyanide. Most common side effects observed with the use of hydroxocobalamin include an orange/red discoloration of the skin, mucous membranes and urine lasting about 12 hours.

Third, dimethylaminophenol (DMAP), another type of methemoglobinemia- forming antidote, produces more rapid methemoglobinemia within 12 minutes compared to that of sodium nitrite. Adjusting the dose, based on clinical sign such as the degree of brown-cyanotic discoloration of the skin, is often unreliable and very misleading since the same feature can be achieved by very low concentrations of methemoglobin.

Fourth, dicobalt edetate acts by chelating cyanide ions to form cobalt cyanide and monocobalt edetate. One concern, however, is that if it is administered to patient misdiagnosed as having cyanide poisoning, the patient may develop serious reactions.

Although recently hyperbaric oxygen, hemodialysis and hemoperfusion have become available, they are not the standard therapy for cyanide poisoning. At present, the favorable outcome of cyanide poisoning requires the prompt diagnosis and management including fully supportive treatment of ventilation, fluid and electrolyte balance as well as antidotal therapy if indicated.

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รายงานผู้ป่วยพิษจากซัยอาไนด์สองราย

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ได้รายงานผู้ป่วย 2 พี่น้อง พี่สาวอายุ 4 ปี และน้องชายวัย 1 ขวบครึ่ง ที่ส่งตัวมาจาก รพ.ฉะเชิงเทรา ด้วยอาการไม่รู้สึกตัว เนื่องจากกินมันสำปะหลังต้ม 9 ชั่วโมงหลังกินเริ่มมีอาการอาเจียนและไม่รู้สึกตัว รพ.ชุมชนส่งตัวไปรักษาต่อที่ รพ.จังหวัด ได้รับการใส่ท่อช่วยหายใจและช่วยหายใจ พบว่ามีความดันโลหิตต่ำร่วมด้วย พี่สาวได้รับการส่งตัวมาที่ รพ.รามาธิบดีก่อน และได้รับยาต้านพิษคือ sodium nitrite และ sodium thiosulfate ร่วมกับการรักษาอื่น ๆ อาการดีขึ้นสามารถถอดท่อช่วยหายใจ และหายใจเองได้ในวันรุ่งขึ้น ส่วนน้องชายเมื่อมาถึง รพ.รามาธิบดี อาการทั่วไปดี ลมหายใจมีกลิ่นถั่วไหม้ ๆ จึงรักษาประคับประคองโดยไม่ได้รับยาต้านพิษ อาการดีขึ้นในวันรุ่งขึ้นเช่นกัน ระดับซัยอาไนด์ในเลือดของเด็กหญิงและเด็กชาย เท่ากับ 0.56 และ 0.32 ไมโครกรัม/มล. ตามลำดับ (ค่าปกติ < 0.3) และมี metabolic acidosis ร่วมกับ lactic acidemia ซึ่งเป็นผลการตรวจพบที่ช่วยในการวินิจฉัยอีกทางหนึ่ง

เนื่องจากยาต้านพิษของซัยอาไนด์เตรียมยากและไม่อยู่ตัว กลไกการออกฤทธิ์ยังไม่เป็นที่รู้จักกันแพร่หลาย จึงได้ทบทวนกลไกการเกิดพิษของซัยอาไนด์และของยาต้านพิษ ตลอดจนขนาดของ sodium nitrite และ sodium thiosulfate นอกจากนี้ได้เสนอแนะยาต้านพิษชนิดอื่น เช่น hydroxocobalamin, dimethylaminophenol, dicobalt edetate เป็นต้น และแนวทางในการดูแลรักษาผู้ป่วยที่ได้รับพิษจากซัยอาไนด์

คำสำคัญ : พิษจากซัยอาไนด์, กินมันสำปะหลัง

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