Tetrodotoxin Poisoning : Field and Prehospital Management

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Tetrodotoxin (TTX) poisoning is one of the most well-known and commonest life-threatening natural marine poisonings acquired from consuming marine puffer fish which belongs to the family of Tetraodontidae (Picture 1) and this led to the name of this toxin. Not only the Tetraodontidae contain TTX, but other families including Diodontidae (porcupine fish) and Molidae (ocean sunfish) also contain TTX. TTX is known from almost 140 animal species which vary in classes and even phyla. More common in marine species such as goby fish, starfish, gastropod molluscs, blue-ringed octopus, xanthid crabs, mangrove horseshoe crabs, ribbon worms but also terrestrial animals such as frogs, toads, salamanders and newts that shown to have TTX[1].

Picture 1. blackspotted puffer (*Arothron nigropunctatus*) in Family of Tetraodontidae, Andaman Sea of Thailand (copyright Gridsana Pimpanon)

TTX (Chemical formula: $C_{11}H_{17}N_3O_8$) is a thermostable non protein biotoxin which will not be destroyed by most food processing including hot cooking, frozen storage, sun dry, salt curing and canning process. TTX blocks the propagation of nerve and muscle action potentials by a non-depolarizing blockade of sodium channels. Its potency has been demonstrated to be more potent than cyanide. Oral ingestion is the commonest route of TTX exposure followed by the injection route of TTX from bites of venomous animals. No known reports via route of exposure by inhalation and skin absorption. The median lethal oral dose (LD_{50}) for mice is only 435 µg/kg, but the parenteral

(subcutaneous injection) is much lesser at 8 μg/kg[2]. For an adult, the minimum oral lethal dose of only 1 mg of TTX may be required[3] and may be less from envenomed bite.

Over 40 species of puffer fish (order Tetraodontiformes) have been shown to have this toxin. Most of them contain in skin and visceral organs especially the liver, not in their flesh (muscle). Licensed chefs have been trained for proper technique of fish dissection in in Japan and it decreased the chance of contamination in proposed edible puffer fish (Fugu). Genus of *Lagocephalus* has been commonly found in the Gulf of Thailand and also had been found in the local fish market. The most common are *L.spaciceus, L.lunaris, L.inermis* and *L sceleratus* with varies of tetrodotoxin contamination in their visceral organs and skin[4]. *Lagocephalus lunaris* (green rough-backed puffer) has contained this potent toxin including in their flesh (muscle)[4,5] while *Lagocephalus spadiceus* (half-smooth golden pufferfish) which thought to be edible by having no known TTX component, but recently found detectable in one report (5). The level of toxins has been found to increase in spawning season. Thai freshwater puffer fish such as *Tetrodon fangi* and *Tetrodon palembangensis* which belonging to the family of Tetraodontidae did not contain TTX, but saxitoxin (STX) is the principal toxin and manifested as paralytic shellfish poisoning (PSP) which also share similar manifestation of TTX intoxication and have been reported in Thailand[6]. The mangrove horseshoe crab (*Carcinoscorpus rotudicauda*), marine and brackish arthropod of the family Limulidae have been described to have an epidemic outbreak of TTX poisoning by consuming their eggs in Thailand[7] and also other countries on both sides of Thailand. The first report of TTX poisoning associated with marine pufferfish and horseshoe crab in Thailand was in 1929[8] and 1966,[9] respectively. There were also documented human fatality and severe envenoming reports associated with blue-ringed octopus bites (*Hapalochlaena lunulata*; greater blue-ringed octopus and *Hapalochlaena maculosa*; lesser blue-ringed octopus)[10] which were mostly be accidentally bitten while handling the octopus with bare hands or shoulder. There were also reported cases of TTX poisoning by eating blue-lined octopus (*Hapalochlaena fasciata*) in Taiwan[11].

TTX poisoning in Thailand has been mostly reported and found to be related with consumption of puffer fish both intentional as underestimation of the toxicity of puffer fish and unintentional as fish derivatives such as fish ball, fish noodles and unidentified fish meat (called chicken-meat fish). TTX poisoning from mangrove horseshoe crab also shared similar events by unpredictable seasonal toxicity of this species or undifferentiated eggs from the edible one (*Tachypleus gigas*, Indo-Pacific horseshoe crab). A recent short

survey from the Ministry of Public Health (MOPH) has shown low incidence by the active search and routine surveillance system[12]. The case fatality rate (CFR) from puffer fish associated TTX poisoning varies depending on the diagnosis and life support and intensive care quality and capabilities. CFR reports from Japan is as high as over 50% in the 1940s, but after Japan's legislative regulation, CFR has been decreased to average 6.4%[13]. In Thailand, CFR from puffer fish was 13.7% (excluded fresh puffer fish)[6], but probably underestimated because fatal cases outside the hospital were not included and mild cases are undiagnosed. CFR from horseshoe crab associated TTX poisoning in Thailand is 1.75%[14]. The only rarely found species of blue-ringed octopus in both the Gulf of Thailand and Andaman Sea is *Hapalochlaena maculosa*[15] but no reports of envenomed bite or oral poisoning.

Clinical Manifestation[16-18]

TTX poisoning cannot be differentiated from other marine poisoning such as paralytic shellfish poisoning (saxitoxin) and ciguatera poisoning (ciguatoxin) by only the clinical manifestations. The onset of clinical manifestation varies from the amount of TTX consumed or envenomed, but most are rapid with symptoms that begin within 10-45 minutes due to rapid gastrointestinal absorption of TTX, but 3 or more hours delays had been reported. Envenomated bite from the blue-ringed octopus which is painless with small puncture wound and spotted blood, but manifest more rapid and reported development of within 5-10 minutes. The first manifestation of oral poisoning usually is paresthesia and numbness of the tongue and oral cavity then progress of numbness and muscle paralysis from distal part of extremities to the proximal and called ascending paralysis[18] then development of diaphragmatic muscle paralysis and respiratory depression with preserved consciousness before cardiopulmonary arrest. These manifestations are categorized in different stages by Fukuda and Tani in 1944[19] and is still used today (Table 1). Patients may develop transient mild hypertension but may cause severe hypertension in preexisting hypertensive patients that need emergent intervention and may later develop hypotension. Cardiac dysrhythmias such as bradycardia may occur, but rare to have high grade conduction abnormalities. The clinical manifestation of envenomation is muscle aches and paresthesia at the bite site and spreading to the entire limb after became systemic the manifestation will be the same as oral poisoning. Local erythema and swelling of the bitten limb may occur.

The prognosis of patients with TTX poisoning is favorable including reports from either marine puffer fish or mangrove horseshoe crab poisoning if life-support measures and care had been delivered and with no complications such as aspiration pneumonitis. The recovery was quick with an average mean of duration using ventilation support for just 24-48 hours and had complete recovery with no residual symptoms. Most cases had survived if 24 hours had passed. The duration of envenomation effect varies, but may be shorter within 10-12 hours when compared to the oral poisoning.

Table 1 Stage of TTX poisoning, clinical manifestations and symptom onset

Stages of poisoning	Clinical Manifestations	Symptom onset
Stage 1	Perioral numbness and paresthesia, with or without gastrointestinal symptoms	5 – 45 min
Stage 2	Progression of numbness and paresthesias such as lingual numbness, numbness of the face, and distal areas. Early motor paralysis. Slurred speech. Normal reflexes are reserved.	10 – 60 min
Stage 3	Progression of generalised flaccid paralysis and incoordination, respiratory depression, dysphonia, dysphagia, cyanosis, hypotension, fixed or dilated pupils. Consciousness are clear.	15 min – several hours
Stage 4	Progression of respiratory paralysis and hypoxia, bradycardia, dysrhythmias and may progress to cardiac arrest. Seems unconsciousness, but intact sensorium.	15 min – 24 hr

Adapted from Fukuda & Tani [19] and Isbister [17]

Field and Prehospital Management[17-18]

Systematic approach using mnemonic ABCDEs has been advised for prevention of cardiac arrest in TTX poisoning patients. Airway obstruction and respiratory arrest are common in unconscious poisoned patients without airway protection. The patients should be assigned to have nothing by mouth. Early endotracheal intubation in patients with alteration of consciousness, difficulty in breathing, and bulbar paralysis may prevent aspirations and their associated complications. Assisted ventilation are needed in inadequate and non-breathing patients with bag-valve mask (BVM) ventilation or rescue

breaths with barriers, but mouth-to-mouth may be helpful in the field. Recovery position may aid in the prevention of airway obstruction in early stage especially in the mild poisoning.

Patients may rapidly deteriorate. The patient should be intensive care monitored focused on neurological disabilities and compromised respiratory physiology. Care for all patients who are critically ill or under evaluation for toxin ingestion should begin in a monitored treatment area where the development of central nervous system depression, hemodynamic instability. Prolonged cardiopulmonary resuscitation effort may be required once there is favorable prognosis of the disease. If the patient does not have anoxic brain injury, fixed and dilated pupils should not be an indicator because it was the common finding of severe poisoning in survivors. Extracorporeal membrane oxygenation (ECMO) has a potential role in prolonged resuscitation[20], but no routine use is recommended.

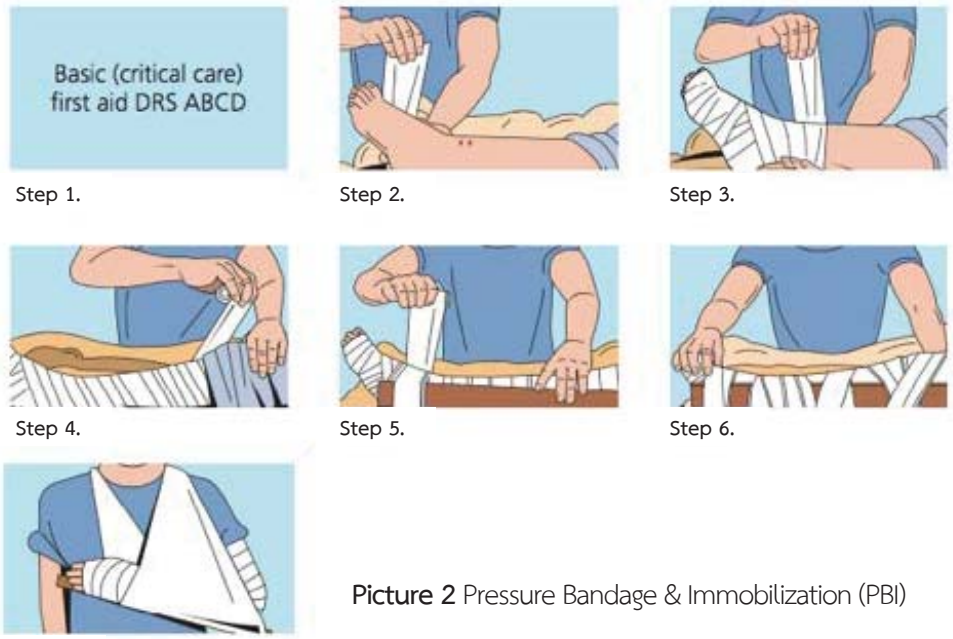
Monitoring of an electrocardiogram is warranted. Atropine should be given to rare cases, but serious case unstable bradycardia and temporary pacemakers may be required in severe conduction problems. Anticholinesterase drugs such as neostigmine and edrophonium are controversial as TTX does not interfere with acetylcholine release at nerve endings[21] and the recent systematic review concluded insufficient evidence to support or against uses[22]. Monoclonal antibodies have been developed and tested in animals, but further human studies are required. Intravenous isotonic fluids administration may enhance early TTX elimination by excretion unchanged form by the kidneys and support hemodynamics in the compromised patients which sometimes vasopressor preferably norepinephrine may be added. Keep samples of blood and urine for future analysis.

Gastric decontamination of TTX poisoning by ingestion

Gastric lavage and whole bowel irrigation has no role in field and prehospital care and are no longer recommended as routine in emergency department setting since TTX has rapid absorption and syrup of ipecac administration is contraindicated because of it increases the risk of aspiration later in the clinical progression. Inducing gag for vomiting by using finger down the throat may be safely used if early in the stage. There is no specific TTX antidote, the administration of single-dose activated charcoal (SDAC) 1 gm/kg body weight (maximum 50 gm) to adsorb TTX is recommended when the charcoal can be administered within 1 hour of poisoning in alert and cooperative patients with intact airways or optimal airway protection with advanced airways such as endotracheal intubation before SDAC would be given.

Retardation systemic TTX envenomation by envenomated bites

Lymphatic system has the role of venom delivery to the systemic circulation at the interstitium of the subcutaneous tissue at the site of venom injection. Pressure bandage & immobilization (PBI) has been developed and advocated for field first aid snake bites in Australia.[23] It has 2 components; pressure and immobilization, which are required for retardation of lymphatic flow and muscle pumping, respectively. After washing the wound to prevent further envenomation, place a cloth pad or rubber pad if available without harming the local tissues, such as surgical excision. Reassure the patient and completely immobilize the patient at the whole (lie down and no movement) and the bitten extremities (splinting) then consider Pressure bandage & immobilization (PBI) (Picture 2). But time is critical and should not delay in transportation to the ACLS capabilities. This technique may be suitable for elapid snakebites including sea snake, but has controversial issues for snake bites with local tissue damage such as viper snakes. Blue-ringed octopus bites have no or minimal local tissue damage and the role of PBI may apply and has been recommended in Australian guidelines[24]. This technique also requires skill and consistency. Pressure at the PBI on the extremities should be around 50-70 mmHg. Elasticized bandages are preferred over a crepe bandage, but improvisation using clothes may be appropriate in the field. Local compression with rubber pad and immobilization has been advocated in Myanmar for Russel's viper bites[25] and also shown to retard the systemic envenomation. Local application of nifedipine and lignocaine were also shown to have additional retardation,[26] but future studies are needed.



Picture 2 Pressure Bandage & Immobilization (PBI)

Diagnosis

Diagnosis is based on clinical manifestations described above and a history of exposure by ingestion of TTX containing marine animals especially the puffer fish and mangrove horseshoe crab in Thailand or be bitten by blue-ringed octopus bite. The definite diagnosis relies on the detection of TTX in poisoning sources and in the patients such as urine, but not routinely available in the field and probably not helpful in the acute care setting.

Field observation and disposition

Patients who presented with mild symptoms may rapidly deteriorate, so no field observation and disposition should be allowed. Patients should be evacuated to the definite healthcare facility preferably with intensive care unit capabilities. Patients who have no symptoms, but consume intoxicated food should be monitored for signs and symptoms arising during the evacuation.

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