AN EPIDEMIC OF TETRODOTOXIN POISONING FOLLOWING INGESTION OF THE HORSESHOE CRAB *CARCINOSCORPIUS ROTUNDICAUDA*

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Abstract. At certain seasons of the year in Thailand, the horseshoe crab *Carcinoscorpius rotundicauda* may be toxic to human and fatal poisoning occasionally occur. Tetrodotoxin (TTX) and its derivatives were major toxins in the toxic eggs of the horseshoe crab. An epidemic of poisoning by eating toxic eggs of the horseshoe crab affected 71 persons in Chon Buri which located in the eastern coast of Thailand. Patients generally presented with neurologic symptoms such as paresthesia, vertigo, weakness, respiratory paralysis, altered consciousness with unreactive dilated pupils in addition to gastrointestinal symptoms such as nausea and vomiting. Nineteen patients required artificial ventilation and there were two deaths. This is the first large outbreak of tetrodotoxin poisoning recognized in Thailand.

INTRODUCTION

At certain seasons of the year in Thailand, the horseshoe crab *Carcinoscorpius rotundicauda* may be toxic to humans and fatalities occasionally occur (Trishnananda *et al*, 1966). Tetrodotoxin (TTX) and anhydro TTX were major toxins in the toxic eggs of the horseshoe crab (Kungsuwan *et al*, 1987). An epidemic of poisoning by eating toxic eggs of the horseshoe crab affected 71 persons. It caused characteristic neurological symptoms and there were two deaths.

In this paper we present our experience of horseshoe crab poisoning. To our knowledge, this is the first large outbreak recognized in Thailand.

MATERIALS AND METHODS

During the period January, 1994 to May, 1995; a total of 71 patients with varying degrees of horseshoe crab poisoning were admitted to the medical service of Chon Buri Hospital. The severity of the poisoning was classified into four stages based on clinical signs of human tetrodotoxication (Ogura, 1971): (1) Numbness of the lips and tongue and often of fingers occurs. (2) Numbness progresses markedly. Muscular paralysis of extremities occurs without loss of deep tendon reflexes. (3) Motor incoordination progresses and paralysis develops, but consciousness is maintained. Voice production is difficult because of bulbar muscle paralysis. (4) Consciousness may progressively deteriorate, and respiratory paralysis can cause death.

RESULTS

There were 71 patients, 52 were males and 19 were females. Most patients had the onset of their symptoms less than 12 hours after eating toxic eggs of the horseshoe crab. The severity of the poisoning was divided into four degrees according to the stages of progression as described above (Table 1).

Table 1

Clinical staging and result in 71 cases.

Stage	No. of cases	No. of deaths
1	40	0
2	9	0
3	3	0
4	19	2

The most common presenting complaints of these patients was paresthesia, consisting of either numbness or tingling circumorally or in the extremities. Weakness and vertigo were common neurologic complaints in addition to gastrointestinal symptoms of nausea and vomiting. Nineteen patients developed paralysis and respiratory distress requiring ventilatory support. Nine patients had acute generalized flaccid paralysis, respiratory distress, altered consciousness, dilated and fixed pupils and negative oculocephalic movements; two of them showed no improvement and eventually died 8 hours and 36 hours after admission to the hospital, and one of them suffered anoxic brain

Table 2

Frequency of certain symptoms and signs.

Symptom and sign	No. of cases	%
Circumoral paresthesia	67	94
Paresthesia of the extremity	62	87
Vertigo	30	42
Weakness	31	44
Nausea and vomiting	21	30
Respiratory failure	19	27
Altered consciousness with fixed dilated pupils	9	13

damage. Frequency of certain symptoms and signs was showed in Table 2.

DISCUSSION

Tetrodotoxin (TTX), a highly potent neurotoxin of puffer fish, is well known as a potential hazard to people who do not take necessary precautions before eating the fish (Ogura, 1971). It has also attracted the attention of scientists because of its unique chemical structure and its ability to block sodium ion influx through excitable cell membranes of nerve and muscle (Narahashi, 1972; Catterall, 1980; Fuhrman, 1986; Mills and Passmore, 1988). TTX is one of the most potent non-protein neurotoxins. It is a heterocyclic guanidine. The empirical formula of the molecule is $C_{11}H_{17}O_8N_3$. It is heat-stable so it cannot be destroyed by cooking (Narahashi, 1972; Catterall, 1980; Fuhrman, 1986).

TTX is highly concentrated in the skin and viscera (liver, gonads, gut) of puffer fish. Puffer fish poisoning is notorious in Japan, where it most commonly occurs from eating puffer fish, or *Fugu*. *Fugu* is considered a gourmet delicacy despite its toxicity and requires a special training and license to prepare (Ogura, 1971; Hashimoto, 1979; Mills and Passmore, 1988). In a 78-years period there were 6,386 cases of puffer fish poisoning in Japan, with a mortality rate of 59% (Sims and Ostman, 1986).

In addition to the public health aspect, the etiology of TTX has become an interesting topic, because of the wide distribution of the toxin among genetically unrelated animals and the marked variability of toxicity in a given species (Mosher and Fuhrman, 1984). TTX has been found in California newt (Mosher *et al*, 1964), atelopid frogs (Kim *et al*, 1975), blue-ringed octopus (Sheumack *et al*, 1978), goby (Noguchi and Hashimoto, 1973), Japanese ivory shell (Yasumoto *et al*, 1981), trumpet shell (Narita *et al*, 1981), starfish (Noguchi *et al*, 1982) and the horseshoe crab *Carcinoscorpius rotundicauda* inhabiting Thailand (Kungsuwan *et al*, 1987).

In the study on the mechanism of toxin accumulation by TTX-containing animals, Yasumoto *et al* (1986) detected TTX and its derivatives in herbivorous fish, crabs, their diet alga and finally, in culture broths of an epiphytic bacterium, *Alteromonas* sp, which was initially assigned to *Pseudomonas*. Noguchi *et al* (1986) had demonstrated that a *Vibrio* bacterium isolated from the intestines of a xanthid crab (*Atergatis floridus*) produced TTX and anhydro-TTX. Narita *et al* (1987) and Noguchi *et al* (1987) had isolated TTX-producing bacteria from a toxic starfish (*Astropecten polyacanthus*) and a puffer fish (*Fugu vermicularis vermicularis*), respectively, and identified dominant species as *Vibrio alginolyticus*. Yotsu *et al* (1987) identified TTX and its derivatives in culture broths of *Pseudomonas* sp isolated from skin of the puffer fish. These studies suggest that TTX-containing animals may accumulate TTXs produced by bacteria.

Kungsuwan *et al* (1987) reported that TTX and anhydroTTX were major toxins in the toxic eggs of the horseshoe crab *Carcinoscorpius rotundicauda* inhabiting Thailand. In an attempt to detect TTX-producing bacteria in the Thai horseshoe crab *Carcinoscorpius rotundicauda*, Kungsuwan *et al* (1988) showed that *Vibrio* sp, including *V. alginolyticus*, isolated from the intestines of the horseshoe crab, produce these toxins. The horseshoe crab is thought to accumulate the toxins which come from intestinal bacteria, consisting mainly of *Vibrio* sp. Part of the toxins may come directly via the food chain. The horseshoe crab may use TTX for a defence purpose, considering also that the lethal potency in this crab tends to increase in the breeding season (Kungsuwan *et al*, 1987).

Symptoms and signs of human tetrodotoxication usually appear within 30-60 minutes after ingestion. Symptoms include numbness and tingling of the face and limbs, weakness, nausea, vomiting, ataxia, dysphonia and dysphagia. Severe cases lead to paralysis of the whole body, respiratory failure, altered consciousness, fixed and dilated pupils, and variable

degrees of hypotension and bradycardia (Ogura, 1971; Sims and Ostman, 1986).

Although some patients developed altered consciousness with fixed and dilated pupils corresponding to the 4th stage, prompt initiation of respiratory support allowed them to recover without any sequelae. Torda *et al* (1973) reported a 14-year-old boy with tetrodotoxication who was admitted to hospital apnoeic and with dilated, fixed pupils. The resuscitation team expected anoxic brain damage, but the boy recovered and described vividly his helpless state of paralysis, which the physicians regarded as coma but in which he could hear their conversation. Totally paralysed patients with dilated unreactive pupils can retain consciousness. This must make tetrodotoxication a terrifying experience. According to old Japanese accounts, some victims of puffer fish poisoning were pronounced dead and subsequently recovered in the morgue or on the way to the crematorium (Anonymous, 1984).

Serial nerve conduction studies of human tetrodotoxication were carried out by Oda *et al* (1989). There were reduced amplitudes of compound muscle action potential and sensory nerve action potential, slowing of conduction velocities, and prolongation of distal and proximal (F waves) motor latencies on the initial examination, with rapid return to normal values in parallel with clinical recovery and decreased urinary excretion of TTX. Neither temporal dispersion nor focal conduction block occurred. The authors conclude that TTX equally and reversibly affects myelinated nerve fibers throughout the entire length of the axon by lowering the conductance of sodium currents at nodes of Ranvier.

There is no specific antitoxin or antidote to TTX. Treatment is symptomatic and supportive, including active airway management, ventilatory support as needed, and circulatory support with intravenous fluids, atropine and pressor agents as required. Artificial respiration must be initiated as quickly as possible by any available artificial respiration apparatus, and the treatment must be powerfully and continuously practiced to prevent respiratory arrest. If respiration is supported for 8-9 hours after ingestion, many patients, seemingly near death, can be revived. Therefore, artificial respiration must be employed even in advanced cases (Ogura, 1971). Gastric lavage and use of activated charcoal may be effective, but vomiting produced by the toxin itself may make the procedure unnecessary. Symptoms generally resolve over a period of 24-72 hours. There are case reports of successful reversal of respiratory and motor paralysis with anticholinesterase inhibitors such as edrophonium and neostigmine (Chew *et al*, 1984). The clinical responses to anticholinesterase drugs also suggest that TTX causes competitive reversible block at the motor end plate.

The incidence of poisoning can be decreased by horseshoe crab surveillance. However, specimen collection and transportation, public and private sector coordination, and the bioassay cost may pose problems. With the help of radio and television it may be possible to institute control measures very promptly.

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REFERENCES

Anonymous. Puffers, Gourmands, and zombification. *Lancet* 1984; 1 : 1220-1.

Catterall WA. Neurotoxins that act on voltage-sensitive sodium channels in excitable membranes. *Ann Rev Pharmacol Toxicol* 1980; 20 : 15-43.

Chew SK, Chew LS, Wang KW, Mah PK, Tan BY. Anticholinesterase drugs in the treatment of tetrodotoxin poisoning. *Lancet* 1984; 2 : 108.

Fuhrman FA. Tetrodotoxin, tarichatoxin, and chiriquitoxin: historical perspectives. *Ann NY Acad Sci* 1986; 479 : 1-14.

Hashimoto Y. Marine toxin and other bioactive marine metabolites. Tokyo: Japan Sci Soc Press, 1979.

Kim YH, Brown GB, Mosher HS, Fuhrman FA. Tetrodotoxin: occurrence in atelopid frogs of Costa Rica. *Science* 1975; 189 : 151-2.

Kungsuwan A, Nagashima Y, Noguchi T, *et al*. Tetrodotoxin in horseshoe crab *Carcinoscorpius rotundicauda* inhabiting Thailand. *Nippon Suisan Gakkaishi* 1987; 53 : 261-6.

Kungsuwan A, Noguchi T, Arakawa O, *et al*. Tetrodotoxin-producing bacteria from the horseshoe crab *Carcinoscorpius rotundicauda*. *Nippon Suisan Gakkaishi* 1988; 54 : 1799-802.

Mills AR, Passmore R. Pelagic paralysis. *Lancet* 1988; 1 : 161-4.

Mosher HS, Fuhrman FA, Buchwald HD, Fischer HG. Tarichatoxin-tetrodotoxin: a potent neurotoxin. *Science* 1964; 144 : 1100-10.

Mosher HS, Fuhrman FA. Occurence and origin of tetrodotoxin. In: Ragelis EP, ed. Seafood toxins, ACS symposium series no. 262. Washington DC: American Chemical Society, 1984: 333-44.

Narahashi T. Mechanism of action of tetrodotoxin and saxitoxin on excitable membranes. *Fed Proc* 1972; 31 : 1124-32.

Narita H, Matsubara S, Miwa N, *et al. Vibrio alginolyticus*, a TTX-producing bacterium isolated from the starfish *Astropecten polyacanthus*. *Nippon Suisan Gakkaishi* 1987; 53 : 617-21.

Narita H, Noguchi T, Maruyama J, *et al.* Occurrence of tetrodotoxin in a trumpet shell "Boshu bora" *Charonia sauliae*. *Bull Japan Soc Sci Fish* 1981; 47 : 935-41.

Noguchi T, Hashimoto Y. Isolation of tetrodotoxin from a goby, *Gobius criniger*. *Toxicon* 1973; 11 : 305-7.

Noguchi T, Hwang DF, Arakawa O, *et al. Vibrio alginolyticus*, a tetrodotoxin-producing bacterium in the intestines of the puffer *Fugu vermicularis vermicularis*. *Marine Biol* 1987; 94 : 625-30.

Noguchi T, Jeon JK, Arakawa O, *et al.* Occurrence of tetrodotoxin and anhydrotetrodotoxin in *Vibrio* sp isolated from the intestines of a xanthid crab, *Atergatis floridus*. *J Biochem* 1986; 99 : 311-4

Noguchi T, Narita H, Maruyama J, Hashimoto K. Tetrodotoxin in the starfish *Astropecten polyacanthus*, in association with toxification of a trumpet shell, "Boshu bora" *Charonia sauliae*. *Bull Japan Soc Sci Fish* 1982; 48 : 1173-7.

Oda K, Araki K, Totoki T, Shibasaki H. Nerve conduction study of human tetrodotoxication. *Neurology* 1989; 39 : 743-5.

Ogura Y. Fugu (puffe fish) poisoning and the pharmacology of crystalline tetrodotoxin in poisoning. In: Simpson LL, ed. Neuropoisons, their pathophysiological actions, vol 1. New York: Plenum Press, 1971 : 139-58.

Sheumack DD, Howden MEH, Spence I, Quinn RJ. Maculotoxin: a neurotoxin from the venom glands of the octopus *Hapalocchlaena maculosa* identified as tetrodotoxin. *Science* 1978; 199 : 188-9.

Sims JK, Ostman DC. Puffer fish poisoning: emergency diagnosis and management of mild human tetrodotoxication. *Ann Emerg Med* 1986; 15 : 1094-8.

Torda TA, Sinclair E, Ulyatt DB. Puffer fish (Tetrodotoxin) poisoning: clinical record and suggested management. *Med J Aust* 1973; 1 : 599-602.

Trishnananda M, Tuchinda C, Yipinsoi T, Oonsombat P. Poisoning following the ingestion of the horseshoe crab (*Carcinoscorpius rotundicauda*): report of four cases in Thailand. *J Trop Med Hyg* 1966; 6 : 194-6.

Yasumoto T, Nagai H, Yasumura D, *et al.* Interspecies distribution and possible origin of tetrodotoxin. *Ann NY Acad Sci* 1986; 479 : 44-51.

Yasumoto T, Oshima Y, Hosaka M, Miyakoshi S. Occurrence of tetrodotoxin in the ivory shell *Babylonia japonica* from Wakasa Bay. *Bull Japan Soc Sci Fish* 1981; 47 : 929-34.

Yotsu M, Yamazaki T, Meguro Y, *et al.* Production of tetrodotoxin and its derivatives by *Pseudomonas* sp. isolated from the skin of a puffer fish. *Toxicon*; 1987: 225-8.