AN OUTBREAK OF HORSESHOE CRAB POISONING IN CHON BURI, THAILAND: CLINICAL, TOXICOLOGIC AND THERAPEUTIC CONSIDERATIONS

Jirasak Kanchanapongkul[1], Attaya Kungsuwan[2], Vorarit Tantisiriwan[1], Chirapa Punthawangkun[1] and Panida Krittayapoositpot[1]

[1]Department of Medicine, Chon Buri Hospital, Chon Buri 20000, Thailand; [2]Department of Fisheries, Bangkok 10120, Thailand

Abstract. In 1994-1996, an outbreak of horseshoe crab poisoning by eating toxic eggs of the horseshoe crab *Carcinoscorpius rotundicauda* affected over 100 persons in Chon Buri which located on the eastern coast of Thailand. We discuss clinical description and management of this first major outbreak. The responsible toxin has been partially purified by means of ultrafiltration and high performance liquid chromatography. The horseshoe crab toxin is identified as tetrodotoxin (TTX) and anhydro TTX.

INTRODUCTION

Horseshoe crabs are primitive marine invertebrates closely related to scorpions and spiders. Most species of horseshoe crab have disappeared through evolution except only four species remaining as live fossils in the world. Two species of horseshoe crab, *Carcinoscorpius rotundicauda* and *Tachypleus gigas* inhabit the Gulf of Thailand. Both of these are called mangda.

The eggs of horseshoe crab are commonly used as food among Thai people. While there is little available meat, the eggs form a considerable mass and are much esteemed. There were sporadic cases of food poisoning due to horseshoe crab ingestion (Smith, 1933; Trishnananda *et al*, 1966). The causative species was *C. rotundicauda* in all the cases reported. One of us (A.K.) found that tetrodotoxin (TTX) and anhydro TTX were major toxins in the toxic eggs of the horseshoe crab (Kungsuwan *et al*, 1987).

In 1994-1996, an outbreak of horseshoe crab poisoning by eating toxic eggs of the horseshoe crab *C. rotundicauda* affected over 100 persons in Chon Buri which located on the eastern coast of Thailand. This is the first large outbreak of horseshoe crab poisoning recognized in Thailand.

In this paper, we discuss the clinical features and management of horseshoe crab poisoning. We also report the toxin profile for horseshoe crab involved in this outbreak.

MATERIALS AND METHODS

During the period January, 1994 to March, 1996; we collected clinical information of 100 patients with varying degrees of horseshoe crab poisoning which were treated at the medical service of Chon Buri Hospital. The severity of the poisoning was classified into four stages based on clinical signs of human tetrodotoxication as previously described (Kanchanapongkul and Krittayapoositpot, 1995).

Monitoring for toxicity in two kinds of Thai horseshoe crabs, *C. routundicauda* and *T. gigas*, collected from Chon Buri province was performed between March 1995 to April 1996. Horseshoe crabs collected from the site of the outbreak were subjected to mouse bioassay and all toxic eggs of *C. rotundicauda* found were pooled and partial purification was done using activated charcoal treatment and ultrafiltration. The toxin profile of such partially purified toxin was done on a high performance liquid chromatography (HPLC) compared to the standard tetrodotoxin (TTX).

RESULTS

Clinical description

There were 100 patients, 78 were males and 22 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 classified into four stages based on clinical signs of human tetrodotoxication (Table 1).

The most common presenting complaints of these patients was paresthesia, consisting of either numbness or tingling of lip, tongue, around the mouth, hands and feet. Weakness, dizziness, and vertigo were common neurologic complaints in addition to gastrointestinal symptoms of nausea and vomiting. Twenty-nine patients developed total paralysis and respiratory distress requiring ventilatory support. Three patients died from cardiovascular collapsed and one patient suffered anoxic brain damage. Frequency of certain symptoms and signs was shown in Table 2.

Table 1

Clinical staging and result in 100 cases.

Stage	No. of cases	No. of deaths
1	48	0
2	20	0
3	3	0
4	29	3

Table 2

Frequency of certain symptoms and signs.

Symptom and sign	No. of cases	%
Circumoral paresthesia	95	95
Paresthesia of the extremity	89	89
Hypertension	55	55
Vertigo and dizziness	54	54
Weakness	53	53
Nausea and vomiting	44	44
Total paralysis and respiratory failure	29	29
Fixed dilated pupils	16	16

Toxicologic study

From the results of mouse bioassay, the highest toxicity of 230 mouse units per gram was found in the specimen of a horseshoe crab *C. rotundicauda* left by a patient admitted at Chon Buri Hospital after ingesting its eggs in May 1995. No toxicity was found in the eggs of all *T. gigas* specimens assayed. The results of HPLC confirmed that the toxin in horseshoe crab *C. rotundicauda* was TTX and anhydro TTX as previously reported (Kungsuwan *et al*, 1987).

DISCUSSION

The clinical pictures and the apparently seasonal appearance of horseshoe crab poisoning are similar to those of paralytic shellfish poisonings (PSP). PSP is caused by ingestion of bivalve molluscs contaminated with the neurotoxins of the toxic dinoflagellates *Gonyaulax catenella* or *Gonyaulax tamarensis*. The responsible toxin has been named saxitoxin (STX) because it has been extracted from the Alaska butter clam, *Saxidomus giganteus* (Hughes and Merson, 1976). STX, like TTX is a heterocyclic guanidine. The thermostable STX, like TTX, blocks voltage-dependent neural sodium channels (Catterall, 1980; Mills and Passmore, 1988; Watters, 1995).

PSP occurs when toxic dinoflagellates increase in number and are ingested by filter-feeding bivalve molluscs. The molluscs concentrate the neurotoxin in their tissues but are not affected. When the dinoflagellates proliferate or "bloom", they often impart a red or reddish-brown discoloration to the water, giving rise to a "red tide". However, red tides can be caused by nontoxic dinoflagellate species, and shellfish may become toxic in the absence of a red tide. (Hughes and Merson, 1976; Mills and Passmore, 1988). These blooms of toxic algae have recently become more prevalent, posing a greater threat to human and marine health. Outbreak of PSP affected more than twice as many areas in 1990 as they did in 1970. Coastal pollution and shipping practices are believed to have contributed to the expansion (Epstein *et al*, 1993; Anderson, 1994).

Initially, the responsible toxin of the horseshoe crab *C. rotundicauda* was supposed to be STX (Trishnananda, 1966; Warrell, 1990). Toxicity of the horseshoe crab and the chemical and pharmacological properties of the toxin remain puzzling for a long time until Kungsuwan *et al* (1987) first demonstrated that the toxicity of the horseshoe crab *C. rotundicauda* was mostly accounted for by TTX and anhydro TTX, and only partly by STX and neo STX. In an attempt to detect TTX-producing bacteria in the Thai horseshoe crab *C. rotundicauda*,

Kungsuwan *et al* (1988) showed that *Vibrio* spp. including *V. alginolyticus*, isolated from the intestines of the horseshoe crab, produce TTX and anhydro TTX. The horseshoe crab is supposed to accumulate the toxins which come from intestinal bacteria, consisting mainly of *Vibrio* spp. Part of the toxins may come directly via the food chain.

Onset time of the symptoms after horseshoe crab ingestion ranged from 30 minutes, in severe cases, to a few hours, in most cases, but seldom exceeded 12 hours. Of those dying most will do so within the first few hours. According to the family members, some victims of horseshoe crab poisoning died before reaching the hospital.

Paresthesia is the first and most common symptoms of horseshoe crab poisoning. Paresthesia, consisting of either numbness or tingling, is frequently localized to the lip, tongue, and around the mouth. The palms of hands and soles of feet are also commonly affected. Weakness, dizziness and vertigo were common neurologic complaints. Motor weakness most commonly involving the extremities. Severe cases lead to total paralysis of the whole body and respiratory paralysis requiring ventilatory support. Fixed dilated pupils usually developed in totally paralyzed patients with or without altered consciousness. Pupils may remain fixed and dilated for a short time after clinical recovery. This suggest that TTX has direct local effects on sphincter muscles.

Although hypotension is the classically described blood pressure reaction of human tetrodotoxication (Ogura, 1971), 55 patients of horseshoe crab poisoning developed hypertension. Hypertension may be mild, moderate or severe. Hypertension was found in every stage of poisoning. It was usually transient and required only modest dose of antihypertensive drugs or no treatment. The degree of hypertension does not correlate with clinical severity. Hypertension in a patient with total paralysis, fixed dilated pupils and negative oculocephalic movement may make the clinical picture look like intracerebral hemorrhage with irreversible brain damage. There were two reports of hypertension in human tetrodotoxication following consumption of unidentified species of fish and gastropod mollusc (Deng *et al,* 1991; Yang *et al,* 1995). Hypertension may come either from an exaggerated response to sympathetic stimuli or due to various responses of the vasomotor center to TTX. Some patients may have pre-existing hypertension and some may also ingest alcoholic beverages. Further studies are required to elucidate the mechanism of hypertension in horseshoe crab poisoning.

In myelinated nerve fibers, sodium channels are primarily located at the nodes of Ranvier (Waxman and Ritchie, 1985). Both TTX and STX are neurotoxins that block these sodium channels. Electrophysiological studies of two patients poisoned with either TTX (Oda *et al*, 1989) or STX (Long *et al*, 1990) shown prominent slowing of motor and sensory conduction velocities, and prominent prolongation of distal motor and F wave latencies. Muscle action potentials were moderately decreased in amplitude initially, without temporal dispersion or focal conduction blocks. Sensory nerve action potentials were small or absent. All electrophysiological parameters returned to normal over 4-6 days and neurological recovery occurred over approximately one week. The rapid recovery of conduction slowing and the known effect of the two toxins on sodium channels make demyelination unlikely in these cases. The marked reversible slowing in conduction was, instead, due to slowed saltatory conduction resulting from lower conductance of sodium currents at the nodes of Ranvier.

Treatment is symptomatic and supportive. There are no known antidotes to TTX. Gastric lavage and administration of activated charcoal are recommended, but vomiting produced by the toxin itself may make the procedure unnecessary. Because the toxin is less stable in an alkaline environment, gastric lavage using 2-5% sodium bicarbonate may be effective if used within the first hour of poisoning (Ogura, 1971; Sims and Ostman, 1986). A cathartic should be administered in an effort to remove unabsorbed toxin from the lower intestinal tract. Mortality from horseshoe crab poisoning is related to respiratory failure and cardiovascular collapse, therefore ventilatory and circulatory support are the mainstay in the management of horseshoe crab poisoning. 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 cardiorespiratory arrest. If respiration and circulation is supported for 12-24 hours after ingestion, many patients, seemingly dead or near death, can be revived. Therefore, artificial respiration must be employed even in advanced cases. Severe cases with hypotension should be treated with in-

travenous dopamine or adrenaline. We emphasize that resuscitation attempts in patients with horseshoe crab poisoning should not be prematurely abandoned even in the presence of signs suggestive of extensive brain damage.

Cholinesterase inhibitors are of no practical use in human tetrodotoxication from puffer fish poisoning (Ogura, 1971). However, there are case reports of their effectiveness (Torda *et al*, 1973; Chew *et al*, 1984). In our experience, the drugs are ineffective.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the team of dedicated nurses and physicians who care for the patients on a day-in, day-out basis.

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