

PUFFER FISH (TETRODOTOXIN) POISONING: CLINICAL REPORT AND ROLE OF ANTI-CHOLINESTERASE DRUGS IN THERAPY

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SYNOPSIS

Various species of the puffer fish are commonly found in the coastal waters of Singapore, but poisoning by their ichthyosarcotoxin, tetrodotoxin, from ingestion is rare. There is no known specific antitoxin or antidote and treatment has so far been purely symptomatic and supportive. A case report is presented and an observation was made that rapid recovery of muscle power was seen after administration of an anti-cholinesterase drug. The concept of a competitive reversible block of tetrodotoxin, not only at the motor axon and muscle membrane, but at the motor end-plate as well, is proposed.

INTRODUCTION

Puffer poisoning is the best known of all types of fish poisoning and has been recognised from ancient times. It is probably the most common fish poisoning along the coasts of Asia. The puffer fish is also variously known as toadfish, blowfish, globefish, swellfish and balloonfish. All belong to the Order Tetraodontiformes.

The poison is called tetrodotoxin (TTX) and poisoning is caused by ingestion of the flesh, viscera or skin of toxic tetraodontiform fishes. As there is a distinct relationship between gonadal activity and toxicity, the fishes are most dangerous to eat immediately prior to and during the reproductive season. Highest concentration of the toxin is found in the viscera (gonads, especially the ovaries; liver; intestines) and skin. The body musculature is usually free of poison (1, 2).

In spite of the toxic nature of the puffer fish and its recognised ill effects, "Fugu", a species of puffer fish, is a delicacy in Japan prepared by licensed puffer cooks. It is also eaten in other parts of Asia and Oceania. Furthermore, Halstead (1, 2) quoted from various Japanese sources of the medicinal value of the toxin. TTX was reported to be used with therapeutic value in the treatment of bronchial asthma, nocturnal enuresis, leprosy, gonorrhoeal arthritis, orchitis, tetanus, impotence, headaches, as well as paralysis agitans.

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CLINICAL REPORT

The patient, a 25-year old Thai immigrant worker in Singapore, caught a puffer fish off the western coast of the island State on 7 December 1982. He had cleaned the fish, gutted and fried it before eating it for dinner. (The fish was later identified as *Sphaeroides maculatus*).

Three hours after ingestion of the fish, he developed circumoral paraesthesia, spreading to involve the extremities and trunk. He also complained of progressive weakness of the lower limbs, after which he experienced difficulty with respiration. One hour later, he vomited. There was no abdominal pains.

Seven hours after taking the fish, he was admitted to hospital. On arrival, he was conscious but drowsy, with flaccid paresis and areflexia. He had a mask-like face, resembling that seen in patients with Parkinsonism. His speech was slurred with dysphonia. Palatal movement was impaired. Ophthalmoparesis with impaired ocular movements was present. His pupils were not dilated and reacted to light sluggishly. Motor power was Grade 2 in the upper limbs and Grade 1 in the lower limbs. Respiration was impaired with increased shallow inspiratory and expiratory effort. No cyanosis was present. The pulse rate was 72 per minute and regular. The blood pressure was 130/90 mmHg on admission, falling to 110/70 mmHg soon after admission. No bradycardia or arrhythmia was detected.

Electrolyte estimation showed mild hypokalemia (potassium 3.1 mmol/L). Blood gases showed p_{aO_2} 69.8 mmHg (decreased), p_{aCO_2} 36.8 mmHg, pH 7.451, Base Excess +1.8 mmol/L, Standard Bicarbonate 24.9 mmol/L and O_2 saturation of 97.4 per cent. Electrocardiogram was within normal limits with no evidence of bradycardia or arrhythmia. Serum cholinesterase level was 140 units. The spinal fluid was clear and colourless. There were no cells. The protein was 40 mg/dl, glucose 74 mg/dl, and chloride 720 mg/dl. The hemoglobin level was 14.9 gm/100 ml, and the white count 10,400/uI (73 per cent neutrophils).

He was immediately intubated via the nasal route with a cuffed polyvinyl chloride endotracheal tube. Respiration was assisted with a Bird Mark VIII respirator with 40 per cent humidified oxygen. Stomach washout was then carried out to remove remaining contents. Feeding was instituted through a Ryles' tube. Electrocardiography was monitored by oscilloscope. Potassium replacement was given by slow intravenous infusion.

Under assisted respiration, he was given a slow intravenous injection of edrophonium 10 mg. Immediately afterwards, he was able to move all his limbs and gradually regained motor power. The following day he was extubated and his respiration was noted to be normal. Blood gases were within normal limits after extubation. On the third hospital day, he was given unrestricted oral fluids. He was allowed a free diet on the fourth day and was able to walk steadily unassisted. Since then, his convalescence was uneventful until his discharge from hospital on the eighth hospital day, completely recovered.

DISCUSSION

Toxicology

Although TTX is among the most toxic substances known among the non-proteins, little is known about the mechanism of its action. In 1969, Fuhrman et al (3) reported it to be an aminoperhydroquinazoline compound ($C_{11}H_{17}N_3O_8$) of proven structure. Cornish (4) suggested that man is particularly susceptible to TTX poisoning, and that an oral dose as low as 10 μ g/kg may be fatal. Isolated cases of puffer fish poisoning have been reported (5, 6, 7), but in Japan, the case fatality rate was 59.4 per cent over a 77-year period (2).

TTX is primarily a neurotoxin but has significant effects on the heart as well. Kao (8) believes that neuromuscular transmission is interrupted by TTX, not at the end-plates, but on the motor axons and on the muscle membrane. Conduction block of the nerve and muscle is carried out through its rather selective inhibition of sodium-conductance while keeping the potassium-conductance intact (9). The toxin has no demonstrable effect on the acetylcholinesterase level, as concluded by Golin and Larson (10) and Teravainen (11). Ogura et al (12) also reported that TTX possesses no anti-cholinesterase activity. TTX, in large doses, can cause bradycardia, hypotension and cardiac arrhythmia (12).

Clinical Presentation

In man, onset and types of symptoms vary greatly, depending upon the person and the amount of poison ingested. Symptoms usually appear from 10 to 45 minutes from ingestion, but may develop as late as 3 hours or more. Circumoral paraesthesia develops and spreads to involve the extremities and trunk. Malaise, dizziness, salivation, sweating, precordial pain and headache appear early. Nausea, diarrhoea, vomiting and epigastric pain may also be present. The pupils are constricted in the initial phase, but later become dilated, fixed, with loss of pupillary and corneal reflexes.

After the development of paraesthesia, respiratory symptoms and signs become prominent. Dyspnea, shallow rapid respiration and cyanosis have been observed. Muscular twitching, tremor, and incoordination progress to terminate in extensive muscular paralysis. The larynx and muscles of deglutition become paralysed first resulting in aphonia, dysphagia and aphagia. Paralysis of the muscles of the extremities then sets in and the patient is unable to move. Petechial hemorrhages, blistering and subsequent desquamation, as well as hematemesis have been reported.

Convulsions, cardiac arrhythmia and hypotension may occur. Consciousness is retained and mental faculties remain acute until shortly before death which usually occurs within the first 6 hours or within 24 hours at the latest. The prognosis is good if the patient survives for 24 hours (1).

Fukuda and Tani (13) divided the disease into four degrees according to the stages of progression:

- FIRST DEGREE** : Oral paraesthesia present, sometimes accompanied by gastrointestinal symptoms.
- SECOND DEGREE** : Advanced paraesthesia, motor paralysis of extremities, but reflexes still intact.
- THIRD DEGREE** : Gross muscular incoordination, aphonia, dysphagia, respiratory distress, precordial pain, cyanosis, drop in blood pressure, but victim is conscious.
- FOURTH DEGREE** : Mental faculties impaired, respiratory paralysis, extreme drop in blood pressure, heart continues to pulsate for a short period.

Management

The treatment of TTX poisoning is purely symptomatic and supportive. There is no specific antitoxin or antidote to TTX. Recommended use of emetics, apomorphine, analeptics, as well as intravenous calcium has been suggested (1). Golin and Larson (10) found that strychnine or pralidoxime combined with atropine to be an effective antidote on experi-

mental animals. Atropine is said to have a mild cerebral stimulatory effect as well as ameliorating the muscarine-like effects of the toxin (sweating, increased salivation and bronchial secretions). However, atropine, by itself, was found to increase the lethality of TTX (10).

Torda et al (5), in 1973, proposed a regime of treatment aimed at (i) maintenance of airway and ventilation (ii) maintenance of adequate circulation and renal function, and (iii) treatment of cardiac arrhythmia.

Vomiting should be induced if there is no difficulty in swallowing or weakness of the voice. Otherwise, gastric lavage can be carried out after intubation with a cuffed endotracheal tube. Gastric lavage is indicated even if it is more than 3 hours after ingestion, as TTX may delay gastric emptying.

Light sedation may be desirable. Oral intake should be suspended if there is difficulty in swallowing, and intravenous hydration instituted.

Endotracheal intubation is indicated if there is respiratory tract obstruction from saliva and respiratory secretions, increasing dyspnea, or progressive elevation of carbon dioxide arterial tension. Nasal intubation is preferred because of its advantage in causing less discomfort, is less liable to be dislodged, and is easier to fix firmly in place. Ventilatory insufficiency is an indication for assisted or controlled ventilation.

Plasma expanders may be indicated to maintain urine output above 40 ml/hour as TTX causes vasodilation and hypotension. Inotropic agents (isoprenaline) is indicated if the central venous pressure rises without restoration of urine output. 2 litres of dextrose-saline over 24 hours has been recommended for maintenance fluid when urine output is satisfactory. Potassium supplement may be required. Electrocardiogram is monitored to detect bradycardia or cardiac arrhythmia. Atropine is said to be ineffective in preventing TTX-induced bradycardia. The effect of cardiac glycosides on the cardiotoxicity of TTX is yet unknown. A temporary pacemaker may be necessary when complete atrio-ventricular dissociation occurs.

Supportive measures from good nursing care are necessary. These included hourly turning of the patient, protection of eyes and oral-tracheal toilet.

TABLE I

CASE REVIEWS WITH USAGE OF ANTICHOLINESTERASE DRUGS

AUTHOR	PATIENT	CLINICAL	TREATMENT
Torda et al 1973 (5)	14-year old boy	generalised paralysis, areflexia, flaccid, intubated	iv edrophonium 10 mg followed by neostigmine 2.5 mg and atropine 1.2 mg. (given during recovery phase)
Tan 1980 (7)	21-year old man	generalised paralysis, areflexia, flaccid, intubated	iv neostigmine 1.5 mg and atropine gr 1/100. (given during acute phase)
Our patient	25-year old man	generalised paralysis, areflexia, flaccid, intubated	iv edrophonium 10 mg only. (given during acute phase)

Role Of Anti-cholinesterase Drugs In Treatment

Anti-cholinesterase drugs have been used in two case reviews in the literature as well as in our patient (See Table I). Torda et al (5) gave a slow intravenous dose of edro-

phonium 10 mg in their patient who developed respiratory difficulties after extubation. The patient's vital capacity improved from 0.8 L to 1.0 L soon after. A dose of atropine and neostigmine was then given, and 2½ hours later, the patient's vital capacity increased to 2.4 L. Tan (7) reported a case of a patient with puffer fish poisoning who responded to atropine and neostigmine.

In our patient who had symptoms and signs of TTX poisoning of third degree (Fukuda and Tani classification (13)) described above, intravenous edrophonium 10 mg was given as a test dose. Interestingly, immediately after injection was given, there was significant increase in the motor power followed by gradual improvement subsequently, even though he was not maintained on long-acting anti-cholinesterase drugs.

Anti-cholinesterase drugs given early and during recovery appeared effective in accelerating the return of muscle power and the improvement appeared to be maintained. This is contrary to reports by Kao (8) that TTX blockade is not antagonised by neostigmine or edrophonium. Kao further added that neuromuscular transmission is interrupted by TTX, not at the end-plates, but on the motor axons and muscle membrane. He also indicated that in complete TTX block, no neural stimulation is effective, nor can acetylcholine depolarisation of the end-plate lead to excitation of the muscle membrane.

It was also reported that TTX does not interfere with the release of acetylcholine from nerve endings nor with its local action on the muscle fibre (10). It must, however, be emphasized that these were findings from animal experiments.

In view of the clinical response of these three patients with TTX poisoning to anti-cholinesterase drugs, it is likely that TTX causes a competitive reversible block at the motor end-plate as well as at the motor axon and muscle membrane. This blockage can be reversed by increasing the quantal release of acetylcholine at the neuromuscular junction by anti-cholinesterase drugs. Teravainen (11) has indicated that TTX did not cause ultrastructural alternations in the pre- or post-synaptic parts of the myoneuronal junction (in rats) and that this absence of alternations could not contribute towards explaining the action of TTX. Perhaps further studies into this aspect could be forthcoming from bioscientists. Meanwhile, we suggest that anti-cholinesterase drugs should be given early in cases of TTX poisonings in view of its recognised beneficial clinical effects.

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