Tetrodotoxin poisoning: a clinical analysis, role of neostigmine and short-term outcome of 53 cases

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ABSTRACT

Introduction: Puffer fish (tetrodotoxin) poisoning is now a common form of poisoning throughout coastal countries, but its diagnosis and management are still unclear. In this paper, we aim to share our experience and to find out the toxic manifestations, lag period between ingestion of fish and development of symptoms, the short-term clinical outcome, and value of neostigmine in its management.

Methods: The study was carried out in the Department of Medicine and Paediatrics, Khulna Medical College Hospital, Khulna, Bangladesh, from May 1, 2001 to May 1, 2006. A total of 53 patients were admitted with the history of puffer fish ingestion. All the cases were clinically analysed from admission to discharge, for the following variables: Onset of symptoms in minutes after the ingestion of fish, toxic manifestations that developed after ingestion, relation of clinical outcome with approximate amount of fish ingested, and the role of neostigmine.

Results: All patients developed toxic manifestation. Important symptoms were perioral paraesthesia (38), weakness of all limbs (33), paraesthesia all over the body (34), headache (25), and difficulty in respiration. Eight patients died, probably due to respiratory muscle paralysis, of which five patients died immediately after admission. We used neostigmine in those patients who developed respiratory failure. 13 patients improved significantly (p-value is less than 0.5), while only three patients died.

Conclusion: Because of the availability and affordability of puffer fish, the occurrence of tetrodotoxin poisoning throughout coastal countries is very likely. Therefore, health personnel should have enough knowledge regarding its toxic manifestations and management.

Keywords: neostigmine, perioral paraesthesia, poisoning, puffer fish, tetrodotoxin

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INTRODUCTION

Toxic exposure has become one of the most common cases of acute medical illness in many countries.[1] The magnitude of the problem, the circumstances of exposure and the types of poisoning vary from country to country.[2] In the UK, it accounts for 10%–20% of all acute medical admissions.[3] In developing countries, pesticide poisoning is far more common with one million cases of serious unintentional pesticide poisoning annually and two million cases of hospitalised deliberate pesticide ingestion.[4] A recent study showed that poisoning was the commonest cause of injury-related death, accounting for 60% of all injury deaths and 14% of all deaths in Bangladesh.[5] Puffer fish (tetrodotoxin) poisoning is an unsual form of poisoning that is sporadically encountered in Bangladesh throughout the year. This is not a common form of poisoning, but its high incidence of neurological complication and fatality need attention, hence its medical interest.

METHODS

All the patients in this study were admitted to the medicine and paediatrics department of Khulna Medical College Hospital, Khulna, Bangladesh from May 1, 2001 to May 1, 2006. They were included irrespective of their age and gender. A presumptive diagnosis was made on the basis of history of recent consumption of puffer fish and classical clinical presentation of the cases.[6,7] A total of 53 cases were selected. All the cases were clinically analysed for the following variables: onset of symptoms in minutes after the ingestion of the fish, toxic manifestations that developed after ingestion, relation of clinical outcome with approximate amount of fish ingested, and role of neostigmine in those patients developing respiratory failure. All data were

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analysed manually. Descriptive statistics with percentage and various tables were applied. To determine the significance of the use of neostigmine regarding recovery from respiratory failure, we used the Fisher's exact test.

RESULTS

The study covered a total of 53 cases of puffer fish poisoning. In Bangladesh, puffer fish is popularly known as "potka fish". Because of its low cost and availability, potka fish is popular, particularly among people in poor rural communities.[8] Out of 53 patients, 28 were female and 25 were male. The highest number of affected patients were in the 11–20 years age group, and the lowest number was in the 31–40 years age group. The lag period in minutes between the time of ingestion and onset of symptoms is shown in Table I. 15 patients developed symptoms within 30 minutes, while eight patients were affected after 121 minutes. The highest number (18) of patients developed toxic manifestation within 91–120 minutes.

The toxic manifestation that developed after ingestion of puffer fish is shown in Table II. On admission, the most common symptom was perioral paraesthesia that developed in 38 patients, and the least common symptom was cramping pain in the lower limb, difficulty in speech and salivation that developed in only four patients. Other observed symptoms were paraesthesia all over the body (34), weakness of both upper and lower limbs (33), headache (25), nausea and vomiting (24), difficulty in respiration (16), weakness of jaw muscles (16), vertigo (16), blurring of vision (12), abdominal pain (9) and dizziness (7).

According to the patients' statements, the amount of fish ingested varied from less than 50 g to more than 200 g. Out of 53 patients, 45 patients improved, while eight patients died (Table III). All the patients received gastric lavage treatment, fluid and electrolyte imbalance maintenance, and maintenance of breathing by O_2 inhalation. Regarding the use of neostigmine, we categorised the patients into group A and group B (Table IV). Group A consisted of 37 patients, of which five patients died immediately after admission. The remaining 32 patients did not have clinical features of respiratory failure and so did not receive neostigmine.

Table I. Onset of symptoms in patients with puffer fish (tetrodotoxin) poisoning (n = 53).

Time (minutes)	No. of patients
< 30	15
31–60	7
61–90	5
91–120	18
≥ 121	8

Table II. Toxic manifestations in patients with puffer fish (tetrodotoxin) poisoning (n = 53).

Clinical manifestations	No. of patients
Perioral paraesthesia	38
Weakness of both upper and lower limbs	33
Paraesthesia over the entire body	34
Headache	25
Nausea and vomiting	24
Vertigo	16
Abdominal pain	9
Cramping pain in the lower limbs	4
Blurring of vision	12
Difficulty in respiration	16
Dizziness	7
Weakness of jaw muscles	10
Difficulty in speech	4
Salivation	4

Table III. Relation of clinical outcome with amount of fish ingested (n = 53).

Amount of fish ingested (g)	Total no. of patients	No. of patients who improved	No. of patients who died
< 50	32	31	1
51–100	15	11	4
101–150	2	1	1
151–200	2	1	1
> 200	2	1	1
Total	53	45	8

Table IV. Role of neostigmine in patients who developed respiratory paralysis.

Group		Total	Died	Survived
A	Without neostigmine	37	5	32
B	With neostigmine	16	3	13
Total		53	8	45

$p \leq 0.5$

Group B comprised patients who developed clinical features of respiratory failure, and were treated with neostigmine.

16 patients developed clinical features of severe respiratory failure, such as tachypnoea, difficulty speaking in complete sentences, bounding peripheral pulse, laboured breathing, cyanosis and exhaustion. We administered injections of neostigmine 0.05 ml/kg body weight along with atropine 0.025 ml/kg body weight six hourly for one day. Atropine was used to mitigate the hypersecretory condition that develops because of neostigmine. Only three patients died and 13 improved significantly ($p \leq 0.5$) within 24–48 hours. All the clinical features of respiratory failure resolved and patients became completely stable. Out of the 53 patients, 45 patients were discharged with consultation. All the patients were well on follow-up.

DISCUSSION

Puffer fish is a very popular dish throughout the world, particularly in coastal regions. Tetrodotoxin poisoning is probably the most common poisoning along the coasts of Asia.[9] The fish is called "puffer", because when predators approach or a threatening situation arises, it can puff its throat with water or air. This inflation causes the fish to take on a puffy appearance. In different parts of the world, it has different names, such as blow fish, swell fish, balloon fish, toadfish and globefish.[10] In Japan, it is popularly known as "fugu". Fugu flesh is edible and is a delicacy in Japan, costing about US$400 per meal.[11] In Japan, licensed puffer fish cooks prepare this fish for consumption. Despite its careful preparation, the number of annual deaths in Japan from puffer fish poisoning is about 50.[10] In our study, out of 53 patients, eight patients died, giving a death rate of approximately 15% in total and only 3% per year. This is probably due to early diagnosis and prompt management. Deaths have also been reported in Singapore, Hong Kong and Australia.[10]

Fugu fish belongs to the order *Tetraodontoidea* which also includes ocean sun fish and porcupine fish.[11] It contains a neurotoxin named tetrodotoxin, and the liver, gonads, intestine and skin of the fish contain the highest concentration of tetrodotoxin.[6] This powerful neurotoxin can cause death in approximately 50%–60% of persons who ingest it.[10] As there is a distinct relationship between gonadal activity and toxicity, the fishes are most dangerous to eat in the immediate period prior to and during their reproductive season.[10] Tetrododoxin is a heat-stable, water-soluble and a non-protein quinazoline derivative neurotoxin.[12] It competitively blocks the post-synaptic acetylcholine receptor and sodium conductance with neuronal transmission in skeletal muscle, and thus, all the toxicity is secondary to blockage of action potential.[13,14] Neostigmine can dramatically restore transmission. If a large proportion of the receptors are blocked, the majority of acetylcholine molecules will normally be encountered, and destroyed by an acetylcholine esterase molecule before reaching a vacant receptor. Inhibiting acetyl cholinesterase will thus increase the number of acetylcholine molecules that will find their way to a vacant receptor, and thus increase the endplate potential so that it reaches the threshold.[15] It also acts on the central and the peripheral nervous systems, the autonomic motor and sensory nerves.[12] It also stimulates the chemoreceptor trigger zone in the medulla oblongata, causing vomiting, and depresses the respiratory and vasomotor centres.[10]

In puffer fish poisoning, tetrodotoxin-induced respiratory muscle paralysis is the predominant cause of death. Proper ventilatory support may reduce the mortality rate. It has no specific antidote. But its paralysing effect can be antagonised by judicious administration of neostigmine ($p \leq 0.5$) along with atropine.[9] Acute poisoning is an important clinical emergency and contributor to morbidity and mortality.[16] Because of its availability and affordability, there is an every chance of puffer (potka) fish (tetrodotoxin) poisoning throughout coastal countries, such as Bangladesh. Puffer fish poisoning should be included in standard medical textbooks so that every health personnel can acquire adequate knowledge and be prepared for medical emergencies such as this.

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