A review of selected seafood poisonings

R. F. CLARK, S. R. WILLIAMS, S. P. NORDT, and A. S. MANOQUERRA

California Poison Control System, San Diego Division, Division of Medical Toxicology, Department of Emergency Medicine, and Department of Clinical Pharmacy; UCSD Medical Center, San Diego; and UCSF School of Pharmacy, San Francisco, California

Clark RF, Williams SR, Nordt SP, Manoguerra AS. A review of selected seafood poisonings. Undersea Hyper Med 1999; 26(3):175–185. Seafood poisoning has been recognized as a problem in both coastal and inland populations for millennia. Many types of sea creatures from shellfish to the largest fish have been implicated. Severe cases of many different types of seafood poisonings can result in fatalities. While the pathophysiology of the toxins is well known in some cases, others, like ciguatera, remain somewhat confusing. As a result, the treatment of these conditions remains controversial, although supportive care continues to be the mainstay of therapy. In this manuscript, we review the pathophysiology, clinical presentation, and treatment of some of the most common and toxic varieties of seafood poisoning resulting from toxins.

at least three quarters of the world's population lives within 10 miles of a coast. Although there are many reasons why populations congregate near the sea, one includes the abundance of food beneath the ocean's waters. Sea food provides a significant percent of the protein in diets of many cultures. Only the depth at which we can harvest seafood restricts the variety of organisms that are edible. Both fish and shellfish, the most popular staples from the sea, have poisonous representatives.

Toxic seafood was described in the Bible. Humans have recognized that toxic seafood has been associated throughout time with seasons of the year, phases of the moon, water temperature, weather conditions, waterfowl mortality, and the color of the waves that wash into shore, along with many other things. Unfortunately, none of these methods has proven entirely successful at predicting when seafood poisoning will occur.

In this review, we will discuss what we consider to be some of the most toxic conditions that can occur following the consumption of seafood. Topics will include paralytic shellfish poisoning, domoic acid poisoning, ciguatera poisoning, scombroid poisoning, and tetrodotoxin poisoning. We will not discuss the toxicity that can occur from the various potential viral and bacterial contaminants of fish and shellfish.

PARALYTIC SHELLFISH POISONING

Shellfish have been implicated in poisonings for centuries, if not millennia. Epidemics of shellfish toxicity have been linked during this time to the proliferation of dinoflagellates and other small marine organisms that are responsible for "red tides" or "blooms" in oceans around the world. The Bible references red tides in Exodus 7:20–21, where "the waters that were in the rivers were turned into blood, and the fish that was in the rivers died; and the river stank..." The Red Sea was so named by ancient Greeks for its red appearance in certain seasons when red tides occurred. Red tides are described in the Iliad, and were first recognized by North American Indians as luminescence or "flickering" of ocean waves (1).

The first published description in the Western World of a patient with clinical findings suggestive of paralytic shellfish toxicity probably dates back to 1689. An article from a French journal named Ephemerides des Curieux de la Nature described a young woman who had ingested mussels (2–4). The description notes that her symptoms included fever, chest pain, respiratory insufficiency, nausea, seizures, and tachycardia. Emesis was induced, bringing up the mussels, and she eventually recovered. For years after this report, the incidence and cause of paralytic shellfish toxicity were undocumented throughout the world, but epidemics were known to occur in certain seasons and under certain conditions. Improvements in monitoring and public health reporting have demonstrated patterns of occurrence. Gessner and Middaugh (5), for example, described 54 outbreaks of paralytic shellfish poisoning in Alaska occurring in 117 individuals between 1973 and 1992. Another example is the California Paralytic Shellfish Poisoning Prevention Program, which as the longest running program aimed at public protection from shellfish
toxins has been so successful that it has been used as a model of surveillance for many other countries (6).

Today, several types of neurologic diseases are recognized to occur after ingestion of shellfish. Paralytic shellfish poisoning is one of the most common. This syndrome is most frequently reported during the summer months when water temperature is highest, but has been recorded from May to November (4,7). Some authors suggest that the toxin responsible for paralytic shellfish poisoning may be of significant concentration in some shellfish in certain geographical locations year round, and that shellfish harvested from untested areas of these regions never be consumed (5). The most commonly implicated varieties of shellfish include mussels, clams, oysters, and scallops (4,5,8).

Pathophysiology

The etiology of paralytic shellfish poisoning is several varieties of marine protozoa called dinoflagellates that range throughout most oceans of the world. Dinoflagellates are classified as Pyrrophyta under the Phytolankton, since they contain chloroplasts which have chlorophyll. These small organisms serve as food for many larger species of marine animals, including numerous shellfish, which filter and concentrate them in their digestive glands (9). The most commonly implicated dinoflagellate is *Alexandrium catanella* (formerly *Gonyaulax*), which produces a complex of compounds known as saxitoxin (8,10). Other related compounds such as neosaxitoxins and gonyautoxins may be found in addition to saxitoxin in affected seafood and may be responsible for the symptom diversity and the overlapping nature of clinical findings of paralytic shellfish poisoning. *Alexandrium tamarense* (also formerly *Gonyaulax*) and *Pyrodinium phoneus* can also concentrate saxitoxin leading to paralytic illness in humans (4,8,11).

Saxitoxin is water-soluble, base labile, and heat stable, and both raw and cooked shellfish have caused human cases of paralysis (10). Saxitoxin takes its name from the giant Alaskan butter clam, *Saxidomus giganteus*, from which it has also been extracted (11). Its molecular structure is that of a tetrahydropyrimine derivative. Saxitoxin, like some other neurotoxins, has its potency measured in terms of mouse units (mu/mg). A mouse unit is the amount of toxin required to kill a 20-g standard laboratory white mouse within 15 min of intraperitoneal injection. The amount of saxitoxin required to meet one mouse unit criteria is 0.18 μg. The potency of saxitoxin is therefore listed at 5,500 mouse units per milligram (8). It has been estimated that as little as 0.5–1.0 mg of saxitoxin can be fatal in humans (10).

Saxitoxin acts by blocking sodium channels in nerve and muscle cells (12,13). Inhibition of sodium flow in these cells arrests impulse conduction along neurons. In addition, saxitoxin may suppress AV nodal conduction, directly depress the medullary respiration center, and progressively reduce peripheral nerve excitability. During peak red tide seasons, mussels may accumulate up to 50,000 mouse units each of saxitoxin. Muscle concentrations of saxitoxin have been recorded to be too high for consumption when seawater dinoflagellate counts are as few as 200 • ml⁻¹ (10).

Neither steaming nor cooking effects the potency of the toxin. Commercial processing of shellfish does not eliminate the toxin or the potential for toxicity; therefore, public health agencies in the United States and Canada strictly monitor these canning industries.

Clinical Presentation

The onset of symptoms of paralytic shellfish poisoning is rapid. Within 30–60 min of ingesting toxic shellfish, victims complain of paresthesias, numbness, vertigo, and tingling of the face, tongue, and lips. Cranial nerve dysfunction, including dysarthria, dysphonia, dysphagia, and even blindness can occur (4,5,11,14). These feelings progress to involve the extremities and trunk over the first 1–2 h. Weakness of the limbs may begin anytime after the sensory changes and gradually progresses to ataxia, inability to use the extremities, and finally paralysis. Reflexes are frequently normal throughout progression of the disease, and patients remain awake and alert. Death results from respiratory failure with diaphragmatic and chest wall muscle paralysis.

The lack of gastroenteritis and thus early self-decontamination may in part explain why mortality from paralytic shellfish poisoning approaches 25% in some older series (8,15). More recent reports cite a lower incidence of fatalities, probably due to improvements in respiratory care. Other autonomic nervous system effects such as salivation, tachycardia, and diaphoresis may occur. Hypotension can result from direct action of the compound on vascular smooth muscle (13). Toxicity is never delayed more than 10–12 h, with a median onset of 3 h. Prognosis is good for individuals surviving past 12 h, but weakness can persist for weeks following recovery (16).

Treatment

There are no antidotes for saxitoxin or paralytic shellfish poisoning. Airway patency and respiratory support are of utmost importance, and even patients with severe symptoms of paralytic shellfish poisoning often do well if expeditiously supported with mechanical ventilation. Although gastric emptying has been advocated by some authors when shellfish suspected of containing saxitoxin
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are ingested (11), airway loss can be rapid and emesis should not be attempted in most cases. These toxins bind well to charcoal and an oral dose of charcoal should be administered if this can be done safely (17). Some authors suggest that atropine administration may worsen symptoms of paralytic shellfish poisoning and should be avoided because saxitoxin and its derivatives may have some antimuscarinic effects (18). Several studies have also suggested that acidity may enhance the potency of saxitoxin (4,19,20), leading some authors to speculate that serum alkalinization might be of benefit to victims (21,22), although the efficacy of this practice has yet to be established.

At least one human case report and animal data have implied that dialysis or hemoperfusion may benefit some patients with severe paralytic shellfish poisoning (15,17). More recent reports are less optimistic (23), and other in vitro trials have demonstrated that dialysis is not effective in removing saxitoxin. Some authors have suggested enhancing renal clearance with diuresis (8), but again no study supports this practice. Maintaining urine output in normal quantities should suffice in most cases.

The most important aspect of managing paralytic shellfish poisoning is prevention. Most coastal agencies monitor dinoflagellate concentrations off the coasts of developed countries and restrict shellfish harvesting during high-risk periods. Many recent outbreaks of this illness have occurred on isolated islands where public health monitoring is infrequent and intensive care medicine resources are scarce.

DOMOIC ACID POISONING

Domoic acid is an excitatory neurotransmitter first described in Japan in 1958, isolated from the red algae Chondria armata (24). The first documented human outbreak of poisoning with this compound was in 1987 from Prince Edward Island, Canada, when more than 100 people became ill after ingesting cultured blue mussels, Mytilus edulis, later found to be contaminated with domoic acid (25–27). Three of these individuals died, and the clinical description of persistent memory impairment in many survivors prompted the nickname of “amnestic shellfish poisoning” (26). The source of the toxin in these cases was found to be Nitzschia pungens, a pennate diatom that had been ingested by the mussels before human consumption (28,29).

Epidemics of domoic acid poisoning have been more prominent in other marine life, especially sea birds (30–32). A large number of dead and distressed pelicans and cormorants were noted in Monterey Bay, California, in September 1991 (30,31). Autopsies performed on the dead birds demonstrated they had consumed large quantities of anchovies from the bay. Subsequent testing showed the anchovies contained high levels of domoic acid. This was the first report documenting the presence of domoic acid in the United States. Further studies of mussels taken during the same period from Monterey Bay also revealed the presence of domoic acid (32). Water samples taken in the area identified significant quantities of the diatom Pseudonitzschia australis, which when grown in a laboratory environment were able to produce domoic acid (31,33). Three species of Pseudonitzschia are now known to produce domoic acid.

In the fall of 1991, the latest reported epidemic of domoic acid poisoning occurred in Washington State (34). Over 20 people who consumed razor clams were involved in this incident. Subsequent testing confirmed the presence of domoic acid in razor clams along the coasts of both Washington and Oregon, although mussels tested in these areas were virtually free of toxin. Dinginess crabs collected from these waters were also found to be contaminated with domoic acid.

Pathophysiology

Following the 1987 epidemic of domoic acid poisoning, significant evaluation was undertaken of the surviving victims. Chemical analysis at various laboratories ruled out all other known toxic causes of the symptoms displayed by the patients (25). Intraperitoneal injection of extracts of the implicated mussels into mice produced a syndrome characterized by reproducible scratching followed eventually by death (26,27). The toxin was finally identified as domoic acid.

Domoic acid is a glutamate agonist. After its discovery in 1958, it was investigated for potential use as an antihypertensive in children in Japan at doses of about 0.6 mg·kg⁻¹, significantly lower than that ingested by effected individuals in Canada (25). In the following years, domoic acid was tested for its insecticidal properties, but results were disappointing.

Domoic acid is structurally related to kainic acid, a potent neurotoxic amino acid (25,26,35–37). This group of compounds is excitatory and acts on three types of receptors in the central nervous system, with the hippocampus being the most sensitive. Domoic acid seems to work by activating kainate receptors in the brain more potently than kainic acid itself. The result of this stimulation is extensive damage to the hippocampus in victims of the poisoning, as well as less severe injury to portions of the thalamic and forebrain regions (26,38,39).

It was estimated that mussels implicated in the Canadian outbreak of amnestic shellfish poisoning contained a total amount of domoic acid in excess of 6 kg, with most being
concentrated in the digestive glands (7,25). When the same toxic blue mussels were placed into tanks of clean water, they rapidly purged themselves of the toxin over several weeks. Other organisms known to produce domoic acid include the phytoplankton *Alistium corallinum* and *Chondria armata*. Subsequent research suggests that other phytoplankton such as *Amphora coffeaeformis* can also produce domoic acid. Scientists continue to monitor shellfish and marine microorganisms to determine the presence of other sources.

**Clinical Presentation**

Rats injected with high concentrations of domoic acid develop hippocampal seizures and die within several days (27). Surviving rats exhibit difficulty in remembering maze pathways they had previously encountered, signifying retrograde amnesia. If rats are injected with domoic acid, prior maze learning skills are not retained, suggesting an additional effect on anterograde memory (26,27). These effects are similar to those of intraperitoneally injected kainic acid. Interestingly, pelicans reportedly poisoned by domoic acid-containing anchovies in 1991 exhibited the same “scratching behavior” demonstrated in laboratory rats after domoic acid injection (40).

Humans involved in the Canadian epidemic of amnestic shellfish poisoning were found to have initial symptoms of nausea, vomiting, abdominal cramps, and diarrhea 1–24 h after ingestion (26,27). Neurologic symptoms beginning with memory loss began within 48 h after ingestion, and progressed in some patients to seizures, hemiparesis, ophthalmoplegia, and coma. Some victims displayed purposeless grimacing and chewing. Follow-up neuropsychologic testing on affected patients displayed predominantly an anterograde memory disorder, with most other cognitive functions preserved (26). The most severely affected individuals also had some retrograde amnesia. A labile blood pressure and cardiac dysrhythmias were recorded in a few people. Elevations in blood urea nitrogen and creatinine phosphokinase were also noted in many victims and have been recorded in animals suffering domoic acid poisoning, proposed to have resulted from exertional myopathies or tremors (26,31).

The onset of symptoms in victims of the Prince Edward Island epidemic ranged from 15 min to 38 h, with the average approaching 5 h (26,27). Most fatalities occurred in the oldest victims, with postmortem findings suggesting neuronal loss or necrosis, accompanied by astrocytosis (26). The most severe damage was to the hippocampus and amygdala areas. Lesions were also noted in the claustrum, septal, and olfactory regions. No lesions were found in the motor nuclei of the brainstem. Hippocampal lesions in victims at autopsy resembled those seen in the brains of animals injected with kainic acid (26,38,39). A follow-up study done on patients from the Montreal area suggested that bronchial secretions became so profuse in the hours after mussel ingestion that half of the severely effected individuals required endotracheal intubation (26). Pupillary dilation or constriction and piloerection were also common findings. Approximately 10% of the involved patients demonstrated either persistent memory loss or other neuropathies. Of those patients exhibiting neurologic toxicity, maximal effects were noted within the first 3 days of mussel ingestion, and maximal improvement in the neurotoxicity occurred in 24 h to 12 wk after ingestion.

**Treatment**

As with most other shellfish toxins, no antidote exists for amnestic shellfish poisoning. Based on the alleged mechanism of action of both domoic and kainic acid, it is possible that benzodiazepines may be beneficial in controlling some of the excessive hippocampal activity and seizures (31,36). Animal studies have suggested a lowered mortality in groups in which benzodiazepines are used after domoic acid injection. Government agencies continue to observe coastal areas for outbreaks of domoic acid toxicity and for the presence of phytoplankton known to produce the compound. “Blooms” of organisms such as *Nitzschia pungens* and *Pseudoantizichtia australis* are closely monitored and reported.

**CIGUATERA POISONING**

Worldwide, ciguatera accounts for more cases of fishborne illness than any other type of ichthyosarcotoxocosis (41). Ciguatera is most commonly seen in the Indian Ocean, South Pacific, and the Caribbean. Outbreaks of ciguatera poisoning have been greatest between the months of April and August (42). In endemic areas the incidence is estimated to be between 500 and 600 cases per 10,000 people (43). The majority of cases in the United States occur in Hawaii and Florida, with the incidence in Florida estimated to be five cases per 10,000 people (44). Outbreaks of ciguatera poisoning have been associated with the ingestion of warm-water, reef-dwelling fish caught between +35° and −35° latitude; however, there have been recent reports of ciguatoxic fish being caught in waters at +33° latitude (45). In addition, the advent of flash freezing and shipping of fish around the world has accounted for several cases of ciguatera in non-endemic areas (46). Ciguatera poisoning has also been reported after the ingestion of farm-raised salmon (47).

The name ciguatera is derived from a Spanish cigu name for the sea snail *Turbo pica* (48). This neurotoxic
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syndrome has been recognized throughout history, with one of the earliest cases probably reported in the fourth century, when Alexander the Great refused to allow his soldiers to eat fish, and during the Tang Dynasty in China (49). One of the earliest written records of suspected ciguatera poisoning is from the journal of Captain William Bligh describing symptoms consistent with ciguatera on 10 June 1789, after eating dolphin fish (mahi-mahi) (49).

Pathophysiology

The blue-green algae and free algae dinoflagellate, Gambierdiscus toxicus, produce ciguatoxins. Gambierdiscus toxicus adheres to dead coral surfaces and marine algae, which are consumed by smaller herbivorous fish (43,50). Larger reef fish eat the contaminated smaller fish, thereby becoming vectors as ciguatoxin is bioconcentrated up the food chain. Larger fish have been shown to have more ciguatoxin than smaller fish (11). Over 400 species of fish have been associated with ciguatera; however, certain species have been classically and more commonly implicated including grouper, snapper, barracuda, amberjack, sea bass, parrot fish, mahi-mahi (dolphin). There is one report of ciguatera from the consumption of jellyfish (51).

“Ciguatoxin” is actually a broad term, which includes at least three separate toxins: ciguatoxin, maitoxtin, and scaritoxin (52). In vitro studies have shown ciguatoxins induce membrane depolarization as a consequence of increasing voltage-dependent sodium channel permeability. This influx of sodium is antagonized in the presence of tetrodotoxin (53). Maitoxtin stimulates cellular uptake of calcium and the release of norepinephrine. There may also be a stimulation of cholinergic receptors due to acetylcholinesterase inhibition (53–55). In vitro studies have also shown that scaritoxin causes the release of norepinephrine and acetylcholine and increases sodium channel permeability (56).

Other toxins such as okadaic acid and more recently prorocentrolide, also found in reef-dwelling fish, have been implicated in diarrhetic shellfish poisoning, another common fish-borne illness (57,58). Palytoxin, from the marine zoanthid Palythoa, is commonly found in these same fish in the Caribbean. Palytoxin has been associated with tumor promotion and one case of rhabdomyolysis in a 55-yr-old male. These toxins may account for some of the symptoms inadvertently attributed to ciguatera (59,60).

Ciguatoxins are heat stable, lipid soluble, acid stable fatty acids with a molecular weight of approximately 1,100 daltons (46). Neither cooking nor freezing seems to destroy the toxin. Ciguatoxin is excreted in bodily fluids, and toxicity can be transmitted by both semen and breast milk (61,62).

The diagnosis of ciguatera is made on the clinical symptoms. Ciguatoxin may be detected in the flesh of fish by two immunoassay techniques: a mouse bioassay where a sample of the fish is injected intraperitoneally into a mouse, and a “rapid” IgG assay (46). These tests are of limited clinical benefit as most institutions do not have the ability to perform either.

Clinical Symptoms

The meal containing ciguatera is generally unremarkable in taste and smell, and symptoms may develop within minutes of ingestion, although they generally occur within 2–6 h after the meal (44). Almost all patients develop symptoms by 24 h, and the toxicity can generally be ruled out if the onset is delayed longer than this time (44,48). The severity of symptoms follows a dose-dependent fashion, with patients eating larger portions of ciguatoxic fish experiencing more severe symptoms (44).

The initial symptoms reported in most cases of ciguatera poisoning include acute gastroenteritis, with abdominal cramps, nausea, vomiting, and diarrhea (48). These symptoms rarely persist for longer than 24 h but may require fluid resuscitation (44). Patients may also have a myriad of neurologic complaints. Headache is common and victims often complain of experiencing a metallic taste. Paresthesias of lips and tongue and ataxia, weakness, arthralgias, and myalgias have all been reported (42,44). These neurologic symptoms seem to develop after the initial gastrointestinal symptoms. The paresthesias and myalgias are seen within the first 24 h and usually resolve by 48–72 h after ingestion, although there have been reports of neurologic symptoms persisting for weeks to months (42,48). In addition, the literature on ciguatera classically describes symptoms such as a sensory perception of “hot and cold reversal”, and loose, painful teeth. While the presence of these symptoms is suggestive of ciguatera poisoning, their absence does not exclude the presence of the disease (48). There have also been reports of a paradoxical reversal to temperature only resulting in cold feeling hot rather than hot feeling cold (48). However, other reports demonstrated gross temperature perception remains intact and the description of paradoxical heat perception is misleading (41). These authors describe the symptoms as intense, painful tingling or “electric shock” rather than the true reversal of hot and cold perception (41). Pruritus is occasionally experienced and may require treatment with histamine receptor antagonists. The onset of pruritus may be delayed for more than 24 h but is rarely, if ever, seen in the absence of other symptoms (42,57). Delayed symptoms may also include hiccups. Dysuria and vaginal discomfort have been reported in women after intercourse with ciguatoxic males (54). There is one report of ciguatera being transmitted to an infant through breast
milk (58). Cardiac effects such as bradycardia and orthostatic hypotension have been reported and are felt to be the result of increased parasympathetic tone (59).

Treatment

The treatment of ciguatera poisoning is primarily supportive. Intravenous hydration with crystallloid and electrolyte replacement may be necessary for dehydration. Antiemetics such as droperidol, prochlorperazine, and metoclopramide may be beneficial. Atropine has been shown to be effective in patients with symptomatic bradycardia or excess cholinergic stimulation (63). Activated charcoal may bind some of the toxin in the gastrointestinal tract but is rarely useful given the expected time of presentation.

Many traditional remedies have been used for centuries in the treatment of ciguatera poisoning, although more recently mannitol has become one of the most widely applied therapies in severe cases (64). Most of the reports of success in the use of mannitol for ciguatera poisoning are based on limited data with small numbers of patients (65–68). One series described 24 patients with ciguatera poisoning treated with mannitol. All received a maximum of 1 g · kg⁻¹ of 20% mannitol administered over 30 min. None of the victims received more than 250 ml of 20% mannitol (65). The mechanism by which mannitol might be effective in abating the neurologic symptoms from ciguatera poisoning is unknown. Several theories have been suggested, including acting as a free radical scavenger, acting as a competitive inhibitor of ciguatoxin at the cell membrane, and promoting a decrease in Schwann cell edema. It is also possible that the osmotic action of mannitol may render ciguatoxin inert (65,66). One concern with the administration of mannitol in the setting of ciguatoxin is that patients may be clinically dehydrated and therefore should be adequately rehydrated before its administration.

Local anesthetics (e.g., lidocaine, tocaid) have also been used in the treatment of ciguatera (69,70). These agents are effective blockers of sodium influx and may antagonize the effects of ciguatoxin. In addition, amitriptyline has been used for its sodium channel-blocking effects as well as its potent antimuscarnic effects (54,71,72). Nifedipine, a dihydropyridine calcium channel antagonist, has been used to counteract the cellular uptake of calcium caused by maitotoxin (54). Although there is limited experience with most of these therapies, they may be beneficial in cases refractory to supportive care alone.

For travelers, common sense dictates avoiding any fish the local fishermen and residents do not eat. Internal organs of implicated fish seem to concentrate the toxin, and should therefore be avoided. Natural events such as hurricanes and earthquakes have been associated with an increased incidence of ciguatera, presumable due to reef disturbance. The recent “el niño” storms may also affect the incidence of ciguatera in the Pacific.

SCOMBROID POISONING

Scombroid fish poisoning, the most commonly reported seafood poisoning in the United States, occurs when certain species of fish are improperly handled and stored after catch. These most commonly include fish from the family Scombridae that includes the many tuna species, Albacore, bonito, and mackerel. Ingestion of sea perch, mahi-mahi, sprat, saury, striped marlin, swordfish, and others have also been implicated. When stored for as little as 2–3 h at temperatures above 20 °C, certain enteric bacteria, most commonly Proteus morgani, P. vulgaris, Clostridium sp., Escherichia coli, Salmonella sp., and Shigella sp., act on the flesh of the fish to produce a toxin or toxins.

Pathophysiology

The “scombrotoxin” was initially thought to be histamine, produced by decarboxylation of histidine, which is commonly found in large amounts in the flesh of these fish. However, the syndrome of scombroid cannot be reproduced solely by the administration of equal or even massive doses of histamine by the oral route. Histamine is rapidly inactivated by enzymes in the gastrointestinal tract and upon first pass through the liver, and very little becomes available in the systemic circulation to produce a pharmacologic effect. Therefore, it has been speculated that some other compound is also present in the decomposed fish flesh that either facilitates the absorption or inhibits the gastrointestinal or hepatic degradation of histamine (73,74). The toxin is heat stable and not destroyed by cooking. The fish most often appears normal and no untoward odor is present.

Clinical Presentation

The effects of scombroid fish poisoning occur within minutes of the consumption of the fish with victims often relating that the fish tasted “peppery.” Although not an allergic reaction, the symptoms are similar. The initial symptoms typically include headache, diffuse erythema, nausea, vomiting, diarrhea, abdominal cramps, and a burning sensation in the mouth and oropharynx. Flushing of the head, neck, and upper torso is characteristic. Severe effects such as bronchospasm, generalized urticaria, hypotension, palpitations, and arrhythmias have been reported but are not frequently seen (11,75). In most healthy victims the syndrome is self-limited, but in patients with preexisting respiratory or cardiac disease, the effects of the poisoning can precipitate a more severe illness (76,77).
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Treatment

If left untreated, symptoms of scombroid poisoning usually subside in 8–12 h. The use of emesis is not indicated as symptoms occur rapidly; vomiting is a primary effect of the toxin, and induced emesis has not been demonstrated to be helpful. The oral administration of activated charcoal may be beneficial although this has not been studied. Symptoms can be lessened or controlled with the administration of histamine-1 (H-1) receptor antagonists such as diphenhydramine. The use of histamine-2 (H-2) receptor antagonists (cimetidine, famotidine, etc.) has also been shown to relieve most of the symptoms (78) and perhaps a combination of H-1 and H-2 receptor antagonists may be most effective. Intravenous fluids and inhaled bronchodilators should be used as needed.

Scombroid fish poisoning is a preventable illness and can be avoided if the offending fish species are promptly refrigerated or iced after catch and maintained until the fish is cooked or processed for storage.

TETRODOTOXIN

Tetrodotoxin (TTX) is a potent neurotoxin found in a variety of creatures and has been isolated from animals of four different phyla, including puffer fish, the California newt, the blue-ringed octopus, poison dart frogs, the ivory shell, and trumpet shell. The puffer fish, also known as the blowfish or globefish, is one of the better-recognized species that contains TTX. These species of fish can be found in both fresh-water and salt-water environments (80). In humans, the most common exposure to TTX is the ingestion of fugu, a specially prepared species of puffer fish. Human TTX poisonings have also occurred after consumption of gastropod mollusks (81). Envenomation from the blue-ringed octopus is rare (82).

Puffer fish poisoning has been recognized for millennium. Ancient oriental literature documents the dangers of eating puffer fish (80). References to puffer fish are found in the hieroglyphics of the ancient Egyptian dynasty of 2700 BC. Scholars suggest the puffer fish was known to be poisonous during Egyptian times. Mosaic sanitary laws against eating fish without fins and scales may have been derived to avoid fish containing TTX. The tetrodotoxin-containing fish in the region inhabited by the Israelites were scaleless (80).

On 7 September 1774, Captain Cook recorded his experience after eating a piece of liver from a puffer fish purchased from a native fisherman. Before preparing the fish for eating, it was described and drawn. As a result of the delays in completing the description, only the roe and liver were prepared for supper. Cook tasted the liver and described a vivid feeling of extraordinary weakness and numbness (80).

Tetrodotoxin was named around 1911 after searching for the active ingredient in fugu ovaries (83). Isolation of the chemical was achieved in the 1950s. In 1964, tarichatoxin, the non-protein neurotoxin found in the California newt, was confirmed to be the same molecule as TTX (84). In the 1970s, the major toxin in certain poison dart frogs was identified as TTX. The Australian blue-ringed octopus was known at that time to have a toxin from its salivary glands that resembled TTX. In 1978, isolation of crystalline TTX was performed. Later, certain species of gastropod mollusks, a type of crab, and several starfish were also found to contain TTX (83).

Fugu

In Japan, fugu is considered a delicacy even though its ingestion is responsible for a number of deaths each year. Chefs must undergo a rigorous certification process before they are allowed to prepare fugu. The filet of the puffer fish contains very minute concentrations of TTX. Fugu is served raw with paper-thin slices placed into an ornate configuration. The presence of small quantities of TTX gives the desired effect of slight oral tingling. Importation of fugu into the United States is illegal; however smuggling has resulted in cases of poisoning (85).

The toxin is concentrated in the liver, viscera, gonads, and skin of puffer fish. Female fish are considered more toxic than males especially since there is high concentrations of TTX in ovaries. Musculature is less toxic but still may contain a significant amount of TTX. The toxin is heat stable and is not inactivated by freezing. Seasonal variation of TTX concentration occurs, with peak levels during spawning season.

Pathophysiology

Tetrodotoxin has a unique, non-protein structure and is widely used as a research tool to study sodium channels. Mouse bioassays demonstrate the minimal lethal dose of TTX by intraperitoneal injection is 8–20 μg · kg⁻¹ (84). Comparatively, cyanide has a minimal lethal dose of 10,000 μg · kg⁻¹ (84). Tetrodotoxin blocks sodium channels during the rising phase of the action potential (13). The interaction of TTX with the sodium channel is thought to be stoichiometric with each TTX molecule interfering with one channel. Tetrodotoxin affects the spike-generating process of sodium channels, not the resting or steady state voltage (13).

The etiology of hypotension caused by TTX has also been studied. Animal studies demonstrate that the profound hypotension is not explained solely by the axonal blockade of vasomotor nerves. Initial theories speculated that TTX stimulated the medullary vasomotor nerves; however,
subsequent studies demonstrated the effect was peripheral to the central nervous system. Tetrodotoxin also has minimal effect on the myocardium unless exposed to very large concentrations. Animal studies suggest that TTX has a peripheral effect that results in vasodilation independent of alpha- or beta-receptors (13,86). Further studies suggest a dose-dependent action. At low doses, systemic blood pressure is lowered although the perfusion pressure is initially maintained. Higher doses of TTX result in a profound fall in blood pressure (13). Experiments with animal models using TTX from blue-ringed octopi demonstrate a similar profound hypotension. Alpha agonists were the most effective agents in raising blood pressure (82).

Clinical Presentation

The onset of symptoms usually occurs within 30 min of ingestion, although death within 17 min has been described. The extent and type of symptoms vary according to the individual and the amount of TTX ingested. Oral paresthesias of the lips and tongue initially occur, and gastrointestinal symptoms of severe nausea, vomiting, and abdominal pain soon follow. Paresthesias advance to the extremities often with severe numbness that gives a feeling of the body “floating”. Hypersalivation with diaphoresis are commonly described. Motor paralysis affects the musculature with the onset of weakness, incoordination, hyporeflexia, and cranial nerve dysfunction. Fasciculations and paralysis progress over the next few hours. Hypotension is profound and may be refractory to treatment. Respiratory distress and insufficiency progress to cyanosis. Bradycardia and atrioventricular node conduction abnormalities may occur. Complete cardiovascular collapse with respiratory paralysis precedes death. Consciousness may be maintained until shortly before death (83).

Treatment

No antidote is currently available to treat TTX poisoning. Unfortunately, tolerance does not develop with repeat exposures and immunity is not acquired after TTX poisoning. Treatment is primarily supportive, with aggressive management of airway and assisted ventilation. Decontamination should be considered with a dose of activated charcoal given early. Atropine may be used to treat bradycardia in conjunction with adequate oxygenation. Intravenous fluid resuscitation should be initiated for hypotension; however, use of inotropic agents may be required to maintain perfusion. Alpha agonists are more likely to be effective.

Anticholinesterase agents have been used with mixed success to treat victims of TTX poisoning. There have been case reports that suggest subjective improvement in the neurologic symptoms after administration of anticholinesterase agents (87,88). Other case reports noted no improvement after infusion of these compounds (89,90). A review of earlier studies shows that TTX is not antagonized by anticholinesterase agents since the toxin interrupts neuromuscular transmission on the motor neurons and muscle membrane and not the motor endplate (91). Antihistamines and steroids have also been used with no clear benefit (90).

The worldwide distribution of the puffer fish and the attraction of fugu as a delicacy will continue to provide human exposures to TTX. Aggressive supportive care remains the cornerstone of treatment.

CONCLUSION

Seafood poisoning remains a significant health risk for much of the world’s population. In this manuscript, we have presented a review of some of the most common and interesting seafood toxins and their clinical manifestations. As we forage deeper into the ocean’s depths, it is likely that new poisons will emerge as previously unidentified organisms are discovered. Improved techniques of examining these known poisons and monitoring their concentration in coastal marine life have advanced our understanding of these compounds. Although, no antidotes exist to treat patients suffering from seafood poisoning, most patients will recover with supportive care.

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Address for correspondence: Richard F. Clark, M.D., UCSD Medical Center, 200 W. Arbor Dr., #8676, San Diego, CA 92103-8676, fax 619/543-3115 —Manuscript received September 1998; accepted July 1999.

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