CIGUATERA FISH POISONING

Marine toxins can be classified into three groups based on their origin. The toxin can be intrinsic to the organism, acquired by the organism from its environment or result from contamination by bacteria, viruses or parasites. Ciguatera poisoning results from toxins that occur in the environment and are subsequently acquired by reef fish. These fish are then consumed by humans to produce the poisoning syndrome.

The toxins associated with ciguatera poisoning originate in the dinoflagellate Gambierdiscus toxicus that is endemic near coral reefs. G. toxicus is consumed by herbivorous fishes, which are the food source of larger carnivorous fishes. The toxins are accumulated and concentrated in the carnivorous fish, rendering larger and older fish more toxic. Some of the predatory fish commonly associated with ciguatera toxin include amberjack, reef shark, moray eel, wrasse, red snapper, grouper and barracuda. Within a contaminated fish, the toxins are most highly concentrated in the viscera and flesh.

Though the actual incidence of ciguatera poisoning is not known, it is the most commonly reported non-bacterial food borne disease associated with fish in the United States. Data from 1978 indicate that ciguatera poisoning accounted for 12.3% of the food poisoning cases reported to the Centers for Disease Control. Endemic regions between the latitudes 35N and 35S have a high reported incidence of ciguatera intoxication due to the prevalence of G. toxicus. Although 90% of U.S. cases occur in Florida and Hawaii, ciguatoxin intoxications have been reported in North Carolina, Louisiana, Texas, California, Massachusetts, New York, Toronto, Vermont and Washington, D.C.. While ciguatera poisoning is common in the tropics, it is important to note that poisonings can occur in any area from transportation of toxic fish.

Clinical Pharmacology

Ciguatera fish poisoning is associated with multiple toxins. Toxic lipid extracts of the plancton G. toxicus have been designated GT-1, GT-2 and GT-3; a water-soluble component is designated GT-4. Toxins identified in the flesh and viscera of affected fish have been isolated and designated as CTX-1, 2 and 3. All toxins identified are unaffected by freezing, heat and gastric acid. Further, they are odorless and tasteless. Rates of absorption from the human gastrointestinal tract are unknown. The toxins associated with ciguatera poisoning are found in highly inconsistent ratios in predatory fish both within the same area and in fish from different areas. This observed variability might account for the highly variable clinical presentations.

The toxins that produce the ciguatera poisoning are divided into several different categories. The first group, the ciguatoxins, is very potent with an LD50 of 0.45 g/kg when injected into a mouse peritoneum. This correlates to about 2-5 g/kg of fish flesh. Ciguatoxin is a fat-soluble quaternary ammonium compound that activates voltage dependent sodium channels. This action may be mediated by the toxin binding at a calcium receptor site that modulates sodium entry. The effect of toxin binding to neuronal cells is to produce sustained depolarization. A study of ciguatoxin effect on frog neuronal cell membranes demonstrates that calcium antagonizes the effects of the toxin. This may represent competitive binding of the toxin and calcium to a cellular receptor. Another component of the ciguatera toxins, maîtotoxin is water soluble and associated with a hemolysin. This toxin has human erythrocyte anticholinesterase and neurotransmitter cholinomimetic activity. Palytoxin is a water-soluble polyether that may inhibit sodium-potassium ATPase and cause muscle contractions and rhabdomyolysis.

Clinical Toxicology

Onset of symptoms is usually rapid, with most patients symptomatic within 15 minutes to 4 hours after consuming contaminated fish. Later presentations are possible, but by 30 hours, 100% of patients will be symptomatic. Acute gastrointestinal symptoms (nausea, vomiting and diarrhea) are common and tend to occur early in the course of the illness. These symptoms usually resolve by 48 hours, although they have been noted to be more severe and of a longer duration in patients of Asian descent.

In a study of 3009 cases of ciguatera poisoning in the South Pacific the following symptoms and rates were observed: paresthesia of an extremity (89.2%), circumsoral paresthesia (89.1%), burning or pain on contact with cold water (87.6%), arthralgia (85.7%), myalgia (81.5%), diarrhea (70.6%), asthenia (60%), headache (59.2%), chills (46.5%), pruritus (44.9%), nausea (42.9%), vertigo (42.3%), ataxia (37.7%), vomiting (37.5%), perspiration (36.7%), tremor (26.8%), dental pain (24.8%), neck stiffness (24.2%), watery eyes (22.4%), skin rash (20.5%), dysuria (18.7%), salivation (18.7%), dyspepsia (16.1%), bradycardia (13.4%), hypotension (12.2%), paresis (10.5%).

A constellation of classic neurologic symptoms may provide the best indication that an individual has been exposed to ciguatera toxin. The reversal of temperature sensation is often cited as pathognomonic, however this symptom may be observed in association with shellfish toxins as well. The neurologic symptoms may be present for months following exposure and are exacerbated by emotional and physical stress, severe illness, malnutrition and alcohol consumption. Symptoms related to the nervous system are thought to arise from the increased permeability of neural cells to sodium. Electrophysiologic studies in the sural nerves of patients with neurologic symptoms of ciguatera poisoning demonstrate prolongation of the absolute and relative refractory, as well as supernormal periods, suggesting prolonged sodium channel opening. It is postulated that this increase in cellular activity results in cell edema that causes further neurologic dysfunction. A study of explanted frog nerves exposed to ciguatoxin demonstrated that there was an increase in the nerve cell volume at the nodes.
of Ranvier. Pretreatment with tetrodotoxin, a known inhibitor of the sodium channel inhibited the cellular edema effect of ciguatoxin

Cardiovascular effects are uncommon, but may include severe hypotension and bradycardia. Ciguatoxin has mild adrenergic agonist effects that may result in hypertension and tachycardia. However, in most cases, the cardio-depressive effects of maitotoxin predominate, resulting from direct depressive effects on myocardial chronotropy and inotropy. In a report from Toronto, Canada, several fish imported from Florida were consumed by three individuals. On presentation the first patient had a systolic pressure of 50 mmHg and a heart rate of 27 that required atropine, dopamine and a seven-day hospitalization. Another patient had a blood pressure of 88/50 mmHg and a heart rate of 48. After two liters of normal saline his blood pressure rose to 100/60 mmHg with a heart rate of 47. Both patients were discharged with stable hemodynamics. A third patient was identified as exposed to the toxin by history, but did not seek medical attention. All three of these patients reported paresthesias as well as diarrhea.

Observations of increasing severity of symptoms in individuals repeatedly exposed to the toxins suggest that the toxin may accumulate in humans. It is unknown if the toxin crosses the placenta.

**Laboratory**

Diagnosis is based on clinical findings. Any patient who presents with gastroenteritis and a constellation of neurologic complaints should have a dietary history taken. If the presentation and history are consistent with ciguatera poisoning, treatment should be initiated. If any un-consumed fish remains, it should be collected for possible analysis. A monoclonal antibody test for ciguatoxin is available for use on suspected fish. Alternatively, HPLC can identify ciguatoxin after lipid extraction. Previously, the diagnosis was made by injecting a lipid extract of suspected toxic fish tissue into mice to observe for limb flexion, weakness, ataxia, coma or death. Previously used methods of toxin identification include feeding the viscera of suspected fish to a cat in a dose of 10% of the test animal's weight and then observation for neurologic symptoms or death. Folklore regarding the detection of ciguatoxin is colorful, but unreliable. Anecdotal signs of contamination include: different coloration of the flesh, peppery taste (especially the viscera) or aversion of flies and ants to toxic fish. Fish which are separated from the rest of a school are likely poisonous and should not be eaten.

**Treatment**

Treatment of ciguatera poisoning is supportive and based on symptoms. However, the evidence for most interventions is case reports. Gastrointestinal decontamination with charcoal and a cathartic is reasonable. Administration of magnesium containing cathartics may augment calcium channel blockade and are best avoided. Nausea and vomiting should be treated with an antiemetic.

Cardiovascular effects are treated based on clinical presentation. While hypotension associated with volume depletion from vomiting and diarrhea will readily respond to fluid replacement, cardio-depressive effects of the ciguatoxins are best treated pharmacologically when the patient is symptomatic. Atropine for brady-cardia and dopamine for hypotension are recommended first line agents.

A large body of anecdotal data exists to support the use of mannitol in diminishing or preventing neurologic symptoms. There has been one controlled study suggesting that mannitol is superior to a mixture of vitamins B6 and C given with calcium gluconate. A dose of 1mg/kg of 20% mannitol given over 30 minutes once a day for five days has been shown to be safe and effective. The efficacy of mannitol is most dramatic when given within the first 24 hours. The mechanism of action is unclear, but may be related to reduction of nervous cell edema or by acting as a free radical scavenger.

Paresthesias and dysesthesias have been treated with amitriptyline (25 mg orally twice a day). Pruritus usually responds well to H1-blockade. Long-term management should include educating the patient to the etiology of the toxin and avoidance of foods that may lead to exacerbations, such as fish, alcohol and nuts. There is no immunity to the toxin and repeated exposures are associated with increasing severity of symptoms.

**Prevention**

The only reliable way to prevent ciguatera poisoning is to never eat tropical reef fish. It is advisable to avoid both high-risk fish as well as the viscera, which may have high concentrations of toxins. Smaller and younger fish are generally safer than larger fish of the same species. Finally, in the near future an immunoassay for ciguatoxin may become commercially available to provide immediate detection.

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**References**