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TOXICOLOGY LETTER

COMPRISING THE NEW YORK CITY AND UPSTATE NEW YORK POISON CENTERS

When is "Enough" Actually "Enough"?

Resuscitation in the Acutely Poisoned Patient

Jeanna M. Marraffa Pharm.D., DABAT, Upstate NY Poison Center

We are often faced with a patient that has acutely overdosed that then has cardiovascular collapse requiring resuscitation efforts. During any resuscitation effort, the question is always asked....how long should these efforts be continued? Specific patient scenarios often dictate the time of resuscitative efforts. This is of particular importance in the acutely poisoned patient....what if we have an antidote or a specific therapy that we recommend during the cardiac arrest? How long should resuscitative efforts be continued until we know if an antidote is effective?

This will focus on a few antidotes that are given specifically during a code situation and how their administration may affect the duration of the code.

Case I:

A 17 year old female is found unresponsive in her bedroom after an apparent intentional ingestion of 60 tablets of amitriptyline. On arrival to the Emergency Department, she is unresponsive and has a systolic blood pressure of 50/palp mmHg, a heart rate of 115 beats per minute. Electrocardiogram reveals a QRS complex duration of 180 milliseconds. Shortly after arrival, she continued to deteriorate and was noted to be in PEA. What approach to specifically manage the toxin-induced cardiotoxicity should be done?

Sodium Bicarbonate

Sodium bicarbonate plays an important role in managing patients with cardiotoxic effects from TCAs and other drugs with sodium-channel blocking properties. The use of sodium bicarbonate was realized for drug-induced sodium channel blockade in the 1950s when it was given for quinidine-induced cardiotoxicity. It was quickly recognized as effective in treating TCA-induced cardiotoxicity and has been validated in many animal models as well as human case reports. Sodium bicarbonate in the setting of TCA-induced cardiotoxicity has been shown to decrease QRS complex duration and decreases life-threatening dysrhythmias and hypotension. It is believed to do this by providing sodium and increasing the availability of sodium influx in open sodium channels and by decreasing the amount of ionized drug and thereby decreasing the amount of sodium channel blockade. Sodium bicarbonate has been shown to be effective in human case reports in treating the cardiotoxicity from other drugs that are sodium channel blockers. Cocaine

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Program Announcements

UNY: Combined Medical Examiner/Toxicology Case Conference, Center for Forensic Science 1/10, 4/11,7/11, 10/10 1:30-3:30pm

Albany Medical Center ½ day in Toxicology April 2013, (WEBEX available) more information to follow.

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

Please call administrative telephone numbers for more information and to attend remotely.

Toxicology Advice Centers

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is a sodium channel blocker and causes widening of the QRS complex duration; 2mEq/kg of bicarbonate has been shown to effectively reduce cocaine-induced QRS prolongation in an animal model. The usual dose of sodium bicarbonate is 1-2 mEq/kg IV bolus over 1-2 minutes. However, in unstable patients (eg: the coding patient), higher doses should be used and are often necessary. The end point of therapy is narrowing of the QRS complex and improvement in vital signs. In the code situation, it is difficult to say 'how much bicarbonate is enough' but anectodal evidence shows that there have been cases of patients requiring 10-12 ampules of sodium bicarbonate in PEA arrest with return of pulses. The effect of sodium bicarbonate is rapid and therefore after IV bolus, the effects should be seen within 2-3 minutes. If a patient has a sodium channel blocker causing cardiac arrest and have not responded to 10-12 rapidly administered sodium bicarbonate boluses, rather than call the code, the next step would be administration of fatty acid emulsion.

Fatty Acid Emulsion 20% (IFE)

A novel use of fatty acid emulsion is its role as an antidote for drug-induced cardiovascular collapse. The first studies were laboratory studies and showed the successful use of fatty acid emulsion in increasing the lethal threshold in animal models with bupivacaine induced cardiac toxicity. Since those early animal models, there have been multiple case reports of successful resuscitation of cardiovascular collapse due to local anesthetic toxicity as well as other drug toxicities. The exact mechanism of action remains speculative at this point but the 'lipid sink' theory is foremost at this time; other actions that might contribute include direct activation of myocardial calcium channels; and modulation of myocardial energy by providing the heart with energy in the form of fatty acids. IFE should be considered a first line antidote to bupivacaine induced toxicity. And it should be considered in a patient with presumed toxin induced cardiovascular collapse who fails advanced supportive care measures including other accepted antidotal therapy. Potential toxins that should be considered amenable to IFE (in addition to local anesthetics) include those which are lipophilic and are toxic to the myocardium and have a high lethality. Specific toxins include tricyclic antidepressants, calcium channel blockers especially verapamil and diltiazem, beta blockers, bupropion, and propranolol.

Intravenous fat emulsion 20% (e.g.Intralipid® 20%) IV 1.5 mL/kg over 2-3 minutes and follow immediately with an infusion at a rate of 0.25 mL/kg/minute for 30-60 min. Continue chest compressions (lipid must circulate). Repeat the bolus twice every 3-5 minutes if asystole persists up to 3mL/kg. Continue the infusion until hemodynamically stable. Increase the rate to 0.5 mL/kg/minute if patient remains hemodynamically unstable. The maximum dose of IFE is unknown although one source suggested a total of 8 mL/kg. (*www.lipidrescue.org*) If asystole is still present after the total dose of 3 mL/kg and 3-5 minutes has gone by since the last dose, the fatty acid emulsion did not provide benefit and the resuscitation can be stopped.

Case 2:

A 31 year old male is removed from a fully involved house fire by the local fire department. He was unresponsive for EMS and had soot around his nose and mouth. He had second degree burns encompassing approximately 5% body surface area. He was intubated in the field for airway control. On arrival to the Emergency Department, he was in full cardiac arrest and CPR was being performed by EMS personnel.

Hydroxocobalamin (Cyanokit®)

Acute exposure to cyanide causes significant morbidity and mortality. Exposure occurs with house fires, industrial accidents, attempted suicides and is a potential agent of chemical warfare. Smoke inhalation is one of the more common sources of exposure to cyanide in the United States. Suicidal attempts have also been due to ingestion of commercially available cyanide salts. Cyanide overdose is specifically seen in gold, jewelry and textile industry workers where the salts are readily used. Cyanide exposure causes rapid, severe systemic toxicity and rapid, cardiovascular collapse. Although there is no rapidly available laboratory test to diagnose cyanide poisoning, an elevated lactate concentration >8 mmol/l (72 mg/dL) and a venous blood gas with a high PO_2 and a high oxygen saturation, in the appropriate clinical scenario, is highly suggestive for cyanide toxicity. Therefore, empiric therapy is warranted.

Because of its relatively low adverse event profile, sodium thiosulfate should be given to all patients with suspected cyanide toxicity, including those patients with smoke inhalation. The dose of sodium thiosulfate for an adult is 12.5 grams (50 mL of 25% solution) and the pediatric dose is 0.5 g/kg (2 mL/kg of 25% solution up to the adult dose) One half of this dose can be repeated if toxicity reappears or at 2 hours as prophylaxis. Hydroxocobalamin is an appealing cyanide antidote because it is relatively safe, does not compromise oxygen-carrying capacity and unlike the nitrites or sodium thiosulfate does not produce hypotension. These features make hydroxocobalamin an ideal agent for empiric use in smoke

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Oral Anticoagulation: Striking the Perfect Balance

Betty Chen, MD, and Lewis S. Nelson, MD

Though anticoagulants are life-saving drugs, cases in which reversal is imperative due to uncontrolled bleeding are not uncommon. How can the effects of anticoagulants be safely reversed, and what potential hazards does this corrective effort present?

A 77-year-old man taking an oral anticoagulant for atrial fibrillation presents to the emergency department after falling at home. On arrival, he complains of abdominal pain. His vital signs are as follows: blood pressure, 67/42 mm Hg; heart rate, 102 beats/min; respiratory rate, 20 breaths/min; temperature, 97.9˚F. His oxygen saturation is 95% on room air. On physical examination, the patient appears uncomfortable. He is pale and weak and has a tachycardic, irregular rhythm. His lungs are clear, but his abdomen is diffusely tender with rebound.

Large-bore intravenous access is obtained, and his blood pressure improves to 110/76 mm Hg after 3 L of normal saline are administered. Initial lab test results are significant for a hemoglobin of 10 g/dL, an international normalized ratio (INR) of 3.4, and an activated partial thromboplastin time (aPTT) of 45 seconds. His basic metabolic panel is notable for a creatinine level of 1.3 mg/dL. A CT scan of his abdomen shows a mesenteric hematoma and a retroperitoneal hematoma.

Which anticoagulants can be administered orally?

The vitamin K antagonist warfarin is the most frequently prescribed anticoagulant for prevention and treatment of thromboembolic diseases. The vitamin K antagonists inhibit vitamin K 2,3-epoxide reductase and vitamin K quinone reductase. Inhibition of these enzymes hinders the conversion of inactive vitamin K to vitamin K quinol, the active form of vitamin K. Without active vitamin K, activation of factors II, VII, IX, and X is interrupted. Because genetics, diet, and drug interactions affect the action of warfarin, patients must undergo frequent surveillance of coagulation parameters and dose titration to ensure therapeutic consistency.[1] As a result, maintaining therapeutic dosing with warfarin is complicated and inconvenient.

Newer synthetic oral anticoagulants are now available that target different clotting factors and inhibit the coagulation cascade in a manner distinct from that of warfarin. A benefit of these new anticoagulants is the convenience of fixed-dose administration without the requirement for frequent laboratory surveillance of anticoagulant effect. Although these agents have few drug interactions and no dietary interactions, the absence of an adequate mechanism to monitor effect may underlie the lack of an apparent need to monitor.

The oral direct thrombin inhibitor dabigatran etexilate binds bound and free thrombin and interrupts both conversion of fibrinogen to fibrin and platelet activation.[2] Dabigatran is approved in the United States for prevention of systemic thromboembolism and stroke in patients with nonvalvular atrial fibrillation. Dabigatran has few drug interactions, and hypersensitivity reaction to dabigatran and active pathologic bleeding are the only absolute contraindications. Dose adjustment may be required in patients with renal dysfunction since dabigatran is largely excreted by the kidneys.[3]

Rivaroxaban, another synthetic oral anticoagulant, inhibits factor Xa and thereby interrupts the coagulation cascade at the intersection of the intrinsic and extrinsic pathways. In addition, this medication interrupts tissue factor–induced platelet aggregation.[4] Rivaroxaban is approved for the prophylaxis of deep vein thrombosis and pulmonary embolism following orthopedic surgery and for prevention of stroke or systemic thromboembolism in patients with nonvalvular atrial fibrillation. Although not yet available in the United States, apixaban, another synthetic factor Xa inhibitor, is used for anticoagulation. Apixaban is eliminated both renally and fecally, which might increase safety for patients with renal dysfunction.[2]

How do you measure the anticoagulation effect of these medications?

The effect of the vitamin K antagonists is most frequently measured using prothrombin time (PT) and the INR. The PT is a measure of the extrinsic pathway as well as the common pathway of the coagulation cascade. The extrinsic pathway depends largely on factor VII, the vitamin K–dependent factor with the shortest half-life. However, because variations in reagents and laboratory

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Oral Anticoagulation: Striking the Perfect Balance

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Table

Recommendations for Management of Elevated INR in Patients Requiring Chronic Anticoagulation with Warfarin

INR	Recommendation
≥4.5-10; no evidence of bleeding	Omit next dose of warfarin No role for vitamin K or factor replacement
>10; no evidence of bleeding	Give oral vitamin K
Bleeding at any INR	Give vitamin K by slow intravenous injection Factor replacement with prothrombin complex concentrate or fresh frozen plasma

Adapted from Guyatt et al.6

equipment may change the PT result, the INR is more useful since it reports the PT as a ratio, comparing it to an international standard.[1] Factors II, IX, and X, part of the intrinsic or final common pathway, are also vitamin K–dependent. Therefore, warfarin may also increase aPTT, especially with supratherapeutic dosing.

There are no readily available tests to measure the degree of anticoagulation with the newer oral anticoagulants. Although the PT and aPTT increase with dabigatran use, there is not a linear relationship with the degree of anticoagulation.[5] The thrombin clotting time (TT) and the ecarin clotting time (ECT) do exhibit a linear relationship with the degree of anticoagulation achieved with dabigatran. The TT measures the time required for fibrinogen to convert into fibrin in a plasma sample, a surrogate for thrombin activity. ECT is a measure of the time required for a clot to form in the presence of ecarin, an extract derived from the venom of Echis carinatus, a viper found in the Middle East and Asia. Neither of these tests is widely and immediately available. The manufacturer of dabigatran has developed a test to rapidly determine the serum dabigatran concentration, but it has not yet been approved for clinical use and it does not necessarily reflect the degree of anticoagulation.

The factor Xa inhibitors increase the PT and aPTT in a dose-dependent fashion. A point-of-care assay that measures anti-Xa activity correlates well with factor Xa inhibitor dose. The factor Xa inhibitors have no effect on ECT or TT.

If the identity of an oral anticoagulant is unknown in the setting of abnormal coagulation parameters, it may be helpful to perform a mixing study. In this study, pooled plasma is mixed 1:1 with a sample of the plasma in question. If the INR, PT, or PTT are prolonged due to a deficiency in vitamin K–dependent clotting factors, the addition of an equal amount of normal plasma should lead to correction of these values, even in cases of severe vitamin K–dependent factor deficiency. Failure to correct in a mixing study suggests the presence of a coagulation inhibitor such as heparin or the lupus anticoagulant.[1]

How do you reverse anticoagulation in the setting of bleeding complications?

Vitamin K administration repletes the deficiency caused by the vitamin K antagonists. To assist in correction and prevent overcorrection of the INR, the American College of Chest Physicians published guidelines for management of elevated INRs in patients receiving vitamin K antagonists *(Table)*.[6] To decrease the incidence of anaphylactoid reactions associated with intravenous administration of vitamin K, the medication should be administered no faster than 1 mg/min, with close monitoring. Regardless of the route of administration, there is a delay of several hours in the onset of action of vitamin K.[7]

Because of the delay in vitamin K's effect, patients who are unstable or bleeding, or who have severe vitamin K deficiency, should receive direct factor replacement. Fresh frozen plasma, cryoprecipitate, recombinant factor VIIa, and prothrombin complex concentrate (PCC) are all methods of replacing deficient factors. Infusion of 15 mL/kg of fresh frozen plasma should be sufficient to reverse coagulopathy from the vitamin K antagonists, with the caveat that each unit of fresh frozen plasma does not have a standard amount of clotting factors. Repeat dosing of fresh frozen plasma may be required due to the short half-life of some of the clotting factors. In addition, fresh frozen plasma may cause volume overload, which can be problematic for patients with intracranial hemorrhage, renal failure, or congestive heart failure. PCCs are small-volume replacements for factors II, VII, IX, and X. Recombinant factor VIIa can also be used to reverse coagulation from the vitamin K antagonists, but thrombosis is a possible adverse effect.[1] The direct thrombin inhibitor dabigatran and the factor Xa inhibitor

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Fish "Sticks"

Nicholas Connors, MD, and Lewis S. Nelson, MD

A toxic exposure in a home aquarium results in sudden, excruciating pain for a 48-year-old man.

Case

A 48-year-old man with a history of diabetes is cleaning his salt-water aquarium when he feels a sudden sharp pain in his right hand. He takes an over-the-counter nonsteroidal anti-inflammatory drug, which does not relieve his pain. He presents to the ED complaining of severe pain radiating from his right hand to his shoulder. On arrival, he states that the pain is constant and is among the worst he has ever experienced. Vital signs are: blood pressure, 172/93 mm Hg; heart rate, 94 beats/min; respiratory rate, 17 breaths/min; temperature, 98.1˚F. Oxygen saturation is 96% on room air.

On physical examination, the patient appears uncomfortable and is cradling his right hand. His cardiac, pulmonary, and abdominal examinations are normal. However, his right upper extremity is edematous and erythematous throughout the hand and fingers, with swelling extending to the wrist. There is a single puncture wound on the dorsum of the right hand but no visible matter or discharge from the wound.

What happened to this man?

While some people keep many types of exotic and dangerous creatures as pets, a limited number of toxic exposures are present in a home fish tank. For example,

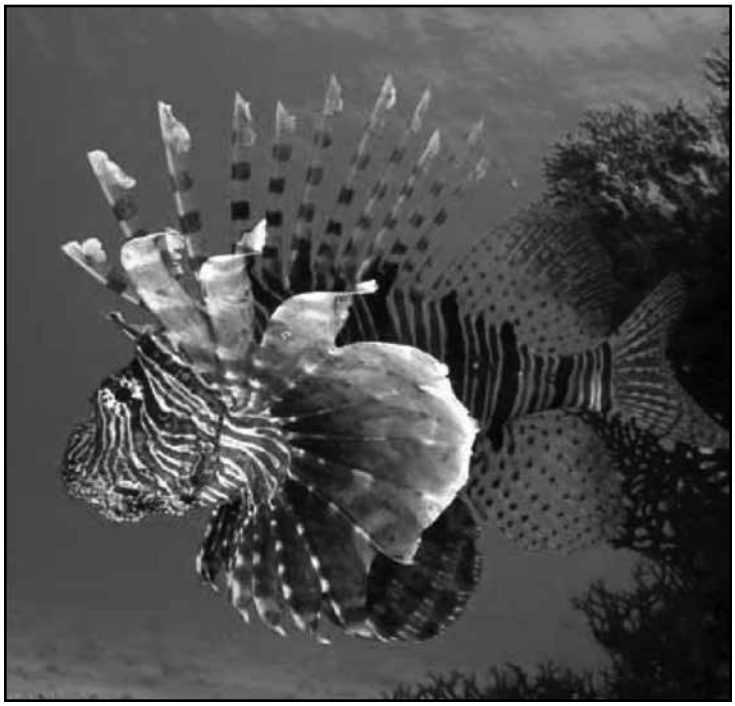

Figure 1: Lionfish - all bright colors and striping

Figure 2: Stonefish - Camouflage adds to the danger

while *Zoanthid* coral in home saltwater aquaria is known to cause serious palytoxin-induced illness through dermal or inhalational exposure,[1] envenomation by a member of the Scorpaenidae (scorpionfish) family of spiny fish is more common. Fish of the genus *Pterois* are brightly colored and striped; they are commonly known as lionfish *(Figure 1)*, but are also referred to as zebrafish, turkey fish, and red fire fish. Most spiny fish envenomations in the United States are caused by *Pterois volitans* and *Pterois lunulata*, the species commonly kept as exotic pets. One US poison center reports seeing an average of one or two cases of spiny fish-related envenomations a month.[2] Although their native range includes the Indian and Pacific Oceans, due to their release into the wild, these fish have become an invasive species along the American East Coast and the Caribbean.

There are other types of spiny fish that are not kept as home-aquarium pets but still pose an envenomation threat, specifically to bathers and fishermen. Stonefish are one such example. Unlike the beautiful lionfish, stonefish are rather hideous in appearance. Their coloring and appendages are more adapted for camouflage among rocks on the ocean floor, thus offering less of a warning to potential victims *(Figure 2)*. Among members of the genus *Synanceja*, the Australian estuarine stonefish *(S. trachynis)*, Indian stonefish *(S. horrida)*, and reef stonefish *(S. verrucosa)* pose the greatest envenomation threat to humans. Another threat is the California sculpin *(S. guttata)*,

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Fish "Sticks"

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which is native to the West Coast of the United States. In addition, the Trachinidae family of spiny fish, commonly known as weeverfish, is also known to envenomate humans; these fish are footlong and are found primarily in the European Atlantic Ocean *(Figure 3)*.

How is venom delivered? How does it work?

Poisoning by one of these toxic species can be differentiated from tetrodotoxin (from puffer fish), scombroid (from tuna-type fish), and ciguatoxin (from reef fish), in that clinical effects occur as a result of envenomation rather than ingestion. Fish in the *Scorpaenidae* and *Trachinidae* families have spines along their dorsum, pelvis, and

Figure 3: Weeverfish

anus, with small venom ducts at the base. Lionfish have long, delicate spines with small venom glands, whereas stonefish have short, thick spines with very well developed venom glands. Stonefish and weevers rest on the bottom of the sea, partially buried in the sand, awaiting prey. Their spines and venom may also serve as a defensive measure against larger fish predators. Since some species prefer very shallow water, bathers are at risk of foot envenomation.

As with most types of venom, those from poisonous fish consist of a milieu of peptides with varying actions. The most concerning is stonefish envenomation, which has been compared to that of a cobra and can be lethal. This type of venom contains hyaluronidase, which breaks down connective tissue and allows wider dispersion of venom. Stonustoxin, trachynilysin, and verrucotoxin, each specific to a different species, act directly on cardiac, skeletal, and involuntary muscle to cause dysfunction or paralysis. Stonefish venom has also been reported to have hemolytic properties.[3] Venom from lionfish *(P. volitans)* and from stonefish *(S. trachynis)* cause increases in neuronal intracellular calcium, either by opening existing ion channels or creating new pores formed by the toxin. This results in the severe neuropathic pain and muscle dysfunction characteristic of envenomations.[4]

How do patients present after marine envenomations?

In an analysis of 51 cases of Scorpaenidae envenomation, 88% were caused by lionfish and were aquaria-related.[5] Six of the 51 patients were envenomated by the California sculpin while scuba diving or fishing.5 In all 51 victims, severe pain in the envenomated region was the typical presenting symptom. Without treatment, pain generally abated approximately 30 to 90 minutes post-envenomation and resolved completely by 24 hours. A small percentage of patients experienced sensory deficit in the affected extremity for several days post-incident. In this analysis, all envenomations occurred on the upper extremity, with the vast majority to the hand. Almost 60% of patients had local swelling and approximately 20% had radiation of the pain up the arm to the shoulder. Systemic symptoms of nausea, diaphoresis, dyspnea, chest or abdominal pain, weakness, hypotension, and syncope were noted in about 10% of the cases.[5]

Stonefish venom can cause similar—albeit more—severe reactions, which include hallucinations and delirium, both of which can last for days. Edema, ischemia, and then cyanosis of the tissue around the wound occur prior to necrosis of the site. Severe systemic symptoms such as dysrhythmia, hypotension, seizures, respiratory depression, and acute respiratory distress syndrome can develop, and rarely, death may occur.[3,6]

How are patients with marine envenomations treated?

As the toxins found in the various forms of spiny fish are heat labile, the mainstay of treatment involves exposure of the wound to warm, nonscalding water (urine also has been used) to denature the toxin and reduce associated pain.[6] This practice is supported by animal models, in which heating stonefish venom to 122˚F for 5 minutes was shown to prevent hypotension and wound necrosis.[7] In the largest study to date of human envenomation from spiny fish, 80% of patients describe relief from this intervention5; however, it is possible that the toxin simply distributed or was metabolized. Although local anesthetics (eg, subcutaneous lidocaine) can be used, patients generally require no more than a nonprescription analgesic upon discharge from the ED.

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Fish "Sticks"

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In Australia, an equine-derived stonefish antivenom (IgG against the venom of *S. trachynis*) has been used in over 200 cases, with a successful reduction of pain and improvement in systemic symptoms.[8] There is anecdotal evidence that stonefish antivenom is also effective in treating exposures to other fish venoms of the Scorpaenidae family, but no trials exist to support this. The antivenom is administered intramuscularly and is based on how many puncture wounds are present. For example, if one or two punctures exist, treatment requires one ampule of antivenom; three or four punctures require two ampules; and more than four punctures require three ampules.[8]

Regarding wound care, normal principles apply. A careful examination should be performed, with consideration of a radiograph to assess for any retained foreign body, especially pieces of a broken fish spine. The envenomation site should be examined for the total number of puncture wounds, as an increased number suggests greater potential venom burden. Of note, in one cohort, 10% of wounds sustained from the spine of lionfish or scorpionfish became infected, with one patient requiring admission for intravenous antibiotics.[5] Typical organisms found in infected wounds include skin flora as well as serious pathogens such as Vibrio vulnificus.[9]

Case Concluded

The patient in this case was envenomated on his right hand when he inadvertently brushed against a pet lionfish while cleaning its tank. In the ED, the affected hand was immersed in warm, nonscalding water for about 60 minutes, and subcutaneous lidocaine was administered for additional pain control at the wound site. His tetanus immunization was updated, and no fish spine was noted subcutaneously on a plain film. Because this patient had a medical history significant for diabetes, he was discharged with oral antibiotics to cover typical skin flora and Vibrio species. He was instructed to return in 2 days for a wound check.

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Smoking Cessation Can Be Toxic to Your Health

Lauren Shawn, MD, and Lewis S. Nelson, MD, FACEP, FACMT

Is the patient's examination consistent with a particular toxidrome?

Case

An 18-month-old girl is found drinking approximately 2 mL of a liquid from a small container she found on her father's nightstand. She begins to vomit and subsequently becomes ataxic and lethargic. She is brought to the emergency department by her parents, and her vital signs on presentation are as follows: blood pressure, 129/89 mm Hg; heart rate, 190 beats/min; respirations, 24 breath/min; afebrile. Her physical exam is significant for pale, diaphoretic skin; pupils approximately 2 mm in size without nystagmus; clear lungs; and increased bowel sounds but no focal tenderness on palpation. Although it is difficult to do a complete neurologic exam on the patient due to her depressed mental status, her exam is significant for a slight tremor with movement.

The patient is relatively hypertensive and tachycardic for her age. Sympathomimetics can cause these vital sign changes but should not cause lethargy or small pupils. Although phencyclidine (PCP) is a dissociative anesthetic that can cause hypertension and tachycardia, other physical findings should include nystagmus, normal or increased muscle tone, purposeless movements, and potentially agitation during recovery. Sedative hypnotics like gamma-hydroxybutyrate (GHB) and ethanol can cause ataxia and lethargy, but not the vital sign abnormalities. Antimuscarinics/anticholinergics can produce tachycardia, but the blood pressure is generally normal, the skin dry, and the pupils large. The patient is vomiting and diaphoretic and has small pupils and increased bowels sounds, findings suggestive of the cholinergic toxidrome.

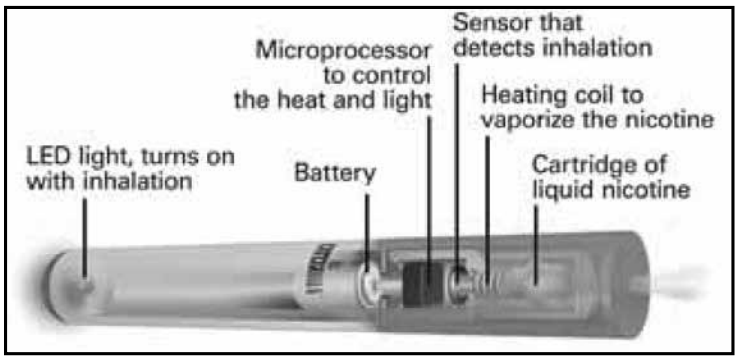

Figure: Tip to tip, how an electronic cigarette works to simulate smoking

How can her vital signs and examination abnormalities be explained?

The acetylcholine receptor is found in both the central and peripheral nervous system. Acetylcholine is a key neurotransmitter in the autonomic and somatic nervous system that affects nearly every organ system in the human body. There are two broad classes of acetylcholine receptors: nicotinic and muscarinic. The nicotinic receptor is primarily found in the preganglionic synapses of both sympathetic and parasympathetic neurons, the postganglionic neurons of the sympathetic nervous system, and in the neuromuscular junction. The muscarinic receptors are found in the brain and in the postganglionic parasympathetic nerve endings that synapse on various organs.

Stimulation of the muscarinic receptors causes the classic cholinergic toxidrome of salivation, lacrimation, urination, diaphoresis, gastrointestinal distress (vomiting and diarrhea), miosis, and the "killer B's": bronchorrhea, bronchospasm, and bradycardia. This toxidrome is expected following exposure to a toxin such as an organophosphorus insecticide. Stimulation of preganglionic nicotinic receptors, found in both sympathetic and parasympathetic ganglia, increases outflow of both branches of the autonomic nervous system and produces findings consistent with both parasympathetic and sympathetic excess (sympathetic generally wins!). These findings are typical of nicotine, the receptor's namesake, and account for the physiological effects that cigarette smokers achieve. In addition, central nervous system acetylcholine effects produce euphoria at low doses (which causes nicotine addiction) and altered mental status, vomiting, and seizures as the dose increases. Stimulation of nicotinic receptors in the neuromuscular junction by drugs such as succinylcholine and nicotine can cause fasciculations, tremor, weakness, and subsequent paralysis secondary to excessive, continued stimulation.

Could this be nicotine poisoning?

Nicotine is a familiar drug available in the form of tobacco products such as cigarettes and cigars. It is one of the most addictive substances known and causes a

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Smoking Cessation Can Be Toxic to Your Health

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significant health burden from cancers and pulmonary disease in the United States as well as worldwide. There is 10 to 30 mg of nicotine in a standard cigarette, but the average smoker actually inhales only 0.05 to 3 mg per cigarette.[1] There are reports of significant acute nicotine toxicity from cigarettes when small children ingest a cigarette or butt. The median lethal dose in an adult is approximately 1 mg/kg, and a fatal case in a child involved as little as 2 mg of nicotine. Children under the age of 6 generally become symptomatic after ingesting one whole cigarette or three butts.[1]

Nicotine patches are a common form of replacement therapy for those desiring smoking cessation. In a case series of adults who intentionally applied excessive nicotine patches in suicide attempts, the most common findings were dizziness, hypertension, diaphoresis, and altered mental status.[2] Most of the cases were complicated by co-ingestants, and none involved unintentional exposures in children. In one case, an 11-year-old boy placed two of his mother's patches on his arm, resulting in nausea, vomiting, dizziness, and diaphoresis, which resolved within a few hours after the patch was removed.[3]

Nicotine has been used as an insecticide for centuries. Although nicotine is rarely used for this purpose in the United States today, it is still used in many other countries and can be obtained over the Internet. Farmers and gardeners may seek it out because it is a natural pesticide and could therefore satisfy requirements for growing organic produce. Green tobacco sickness is an occupational exposure in which workers who are harvesting tobacco plants develop acute nicotine toxicity as moisture from the plants allows transfer of nicotine onto their skin. A case of fatal poisoning occurred when a 15-year-old boy ingested several milliliters of concentrated nicotine sulfate, which was available decades ago as a household insecticide and has since been discontinued.[4] The patient suffered cardiac arrest and catastrophic brain injury despite return of spontaneous circulation.

Why would liquid nicotine be kept in the home?

The patient's father had recently started using electronic cigarettes in an attempt to prevent second-hand smoke in his home. He had left a 10-mL bottle of liquid nicotine on his nightstand. The entire bottle contained 10 mg of nicotine.

Electronic cigarettes using liquid nicotine have become increasingly popular. First mass-produced in China in 2004, the growing number of manufacturers and Web sites selling the products has expanded the worldwide market.[5] Many view the electronic cigarette as inherently safer because its use does not involve the inhalation of tobacco smoke and therefore poses less risk of cancer and pulmonary disease. Others may view it as a more socially acceptable form of smoking since it is odorless and does not produce second-hand smoke. Recently, it has been marketed as a smoking cessation tool with the idea that the concentration of nicotine can be titrated down while the patient still gets the physical sensation of smoking (as opposed to chewing gum or using a patch).

When a person takes a drag from an electronic cigarette, it triggers a heating coil to vaporize liquid nicotine, and that vapor is then inhaled (see the Figure, page 8).5 The liquid nicotine is contained in a cartridge that is either fully replaced or can be refilled. The nicotine is usually dissolved in vegetable oil or propylene glycol.5 Furthermore, many websites that sell liquid nicotine allow purchasers to customize the liquid nicotine to be of specific strength and flavor (that ranges from menthol to various fruits to mocha). Although it usually takes as little as 1 mL of liquid nicotine to refill a cartridge, it is possible to buy a 5-L container online. Given the ease of purchase, the exotic flavors, and large quantities that can be obtained, there are significant public health concerns with this product. Teenagers may be able to access electronic cigarettes more easily than traditional tobacco products and could be susceptible to acute and chronic effects of nicotine exposure. Small children are at risk for oral and dermal exposure from large quantities of nicotine that potentially smell or taste appealing to the exploring toddler. Given the relatively large amounts of nicotine contained in a small volume, morbidity and mortality concerns are significant.

Currently, the Food and Drug Administration's (FDA) Center for Tobacco Products regulates cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco, but not non–tobacco-based nicotine products.[6] Although the FDA's Center for Drug Evaluation and Research regulates electronic cigarettes specifically marketed for therapeutic purposes, manufacturers not making such claims are not subject to FDA regulations. The FDA is attempting to gain regulatory authority over nicotine products like electronic cigarettes, and they caution that the safety of these products, even when used as intended, has not been fully evaluated.[6]

There is no practical antidote for nicotine poisoning. Supportive care is the mainstay of treatment. The most consequential effect, paralysis, requires respiratory support. Benzodiazepines should be given for seizures.

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inhalation victims suspected of cyanide toxicity. The empiric adult dose of hydroxocobalamin is 5 grams. Cyanokit® is currently available as a single vial containing 5 grams hydroxocobalamin. The 5 gram dose should be administered intravenously over 15 minutes. In an adult patient, the 5 gram dose can be repeated once and can be given within minutes if the first dose is ineffective. The pediatric dose of hydroxocobalamin is 70 mg/kg. A sufficient period of time after hydroxocobalamin administration during a code is approximately 15 minutes after the end of drug infusion.

Case 3:

A 75 year old male presents to the Emergency Department after an intentional overdose of an unknown quantity of digoxin 0.25 mg tablets. The ingestion occurred approximately 12 hours prior to presentation. The patient presented to the Emergency Department with a heart rate of 30 beats per minute and blood pressure of 70/30 mmHg. Initial electrocardiogram revealed peaked T waves and a wide complex. The patient rapidly deteriorated in the Emergency Department and had cardiac arrest. Resuscitative efforts using ACLS were unsuccessful and digoxin-specific FAB fragments were administered.

Digoxin-Specific FAB Fragments (Digibind® or Digifab®)

Digoxin specific antibody fragments (Fab) are lifesaving in the management of toxicity associated with digoxin as well as other cardioactive steroids including digitoxin and those derived from oleander and toad venom. They are safe and effective in both adults and children with both acute and chronic toxicity. Cardioactive steroids act on the heart to enhance contractility, on the conduction system of the heart to produce a variety of effects and on the autonomic nervous system. Toxicity is related to an exaggeration of these effects and often involves increasing intracellular calcium. Electrocardiographic changes secondary to digoxin toxicity can be vast and include anything with the exception of a rapidly conducted atrial fibrillation. In patients acutely poisoned with digoxin, empiric administration of 10-20 vials of Digoxin-specific Fab fragments should be administered to any patient demonstrating the following: consequential rhythm or conduction disturbances including symptomatic bradycardia or progressive heart block unresponsive to atropine; ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation; or in any patient with a serum potassium > 5.0 mEq/L without another cause. Other considerations for administration include a firm history of ingestion of greater than 4 mg in a child or more than 10 mg in an adult since these total body loads of digoxin will almost certainly cause significant cardiac toxicity as the digoxin moves from the blood compartment to the heart. The indications to initiate treatment in the chronically poisoned patient are less clear but should generally follow the same guidelines as for the acutely poisoned patient and include any patient with a life-threatening or potentially life-threatening dysrhythmias.

The empiric dosing for acute toxicity is 10-20 vials for adults and children and 3-5 vials for adults and 1-2 vials for children with chronic toxicity. The prescribing information contains more precise information for infants. 105. To calculate a dose for a known serum digoxin concentration: Number of vials = [serum digoxin concentration (ng/mL) X Pt weight (kg)]/100 {round up}. This dose is generally infused IV over 30 minutes however in a critically ill patient, the dose should be administered as an IV bolus.

The mean time to initial response from the end of the Digibind® infusion has been reported to be 19 minutes (with a range of 0-60 minutes) and the time to complete response is 88 minutes (range: 30-360 minutes). Due to these pharmacokinetic properties and experience in patients with cardiovascular collapse, resuscitation efforts should be continued for at least 30 minutes after the administration of digoxin specific antibodies.

Conclusion:

Early recognition and management of the acutely poisoned patient is essential. Once patients are acutely decompensating and experiencing cardiovascular collapse from a toxin, it is imperative that antidotal therapy, when indicated, is provided in addition to advanced cardiac life support measures. Knowledge about the onset of effect of antidotes will aid in the determination of how long aggressive resuscitative efforts be continued.

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Oral Anticoagulation: Striking the Perfect Balance

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rivaroxaban have no definitive antidotes to reverse their anticoagulant effects. Dabigatran's manufacturer recommends fresh frozen plasma for volume resuscitation in cases of severe bleeding. PCC is also suggested, despite lack of substantial proof of efficacy. A study in mice given a single supratherapeutic dose of dabigatran noted a dose-dependent benefit from PCC in limiting surgically induced intracranial hematoma expansion. However, tail vein bleeding time remained prolonged despite PCC administration.[8] In healthy humans administered dabigatran for 2 days, there were no changes in aPTT, TT, or ECT after administration of PCC, as anticipated, since dabigatran inhibits thrombin, which is located at the end of the coagulation cascade. Upstream factor replacement should not change these measurements because the final common pathway is still interrupted.[9] Recombinant factor VIIa does not appear to be effective as an antidote, as measured in mice studies.[8]

Hemodialysis as a means to remove dabigatran has been suggested, although the data are limited. Preclinical studies show that hemodialysis extracts 62% to 68% of a single subtherapeutic dose of dabigatran administered to hemodialysis-dependent patients immediately prior to hemodialysis.[3] There have been no studies to evaluate the use of hemodialysis in overdose or the actual effect on coagulation parameters, bleeding, morbidity, or mortality. Hemodialysis may be risky in severely coagulopathic and unstable patients since catheter placement may cause bleeding.

Rivaroxaban is not amenable to dialysis due to its high protein binding. Appropriate volume resuscitation with factor replacement is the mainstay of care. Few studies have evaluated the efficacy of PCC in reversing rivaroxaban-induced anticoagulation. However, a single study suggests that PCC may be helpful. In healthy volunteers given rivaroxaban, administration of PCC normalized PT at a standard dose of 50 U/kg.[9]

Packed red blood cells can replace lost volume in hemorrhagic shock. However, red blood cells do not correct the underlying coagulopathy. In fact, transfusion of red blood cells alone can exacerbate coagulopathy by causing hypocalcemia due to the citrate anticoagulant they contain and by worsening factor dilution. Therefore, close monitoring of serum calcium and repletion of vitamin K–dependent factors are imperative.

Case Conclusion

The patient was intubated and admitted to the intensive care unit. He developed recurrent hypotension and was given 8 units of packed red blood cells as well as fresh frozen plasma after serial labs showed a falling hemoglobin.The surgery team did not take him to the operating room because he had been anticoagulated with dabigatran. Instead, the nephrologist performed hemodialysis based on the degree of coagulopathy and the severe nature of his illness. After two hemodialysis sessions, his hemoglobin stabilized. His INR and aPTT improved but did not normalize. The patient remained intubated for 3 days due to poor respiratory function, but he was subsequently extubated and discharged home.

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Smoking Cessation Can Be Toxic to Your Health

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Atropine can limit bradycardia and bronchorrhea, and hypertension can be managed with short-acting antihypertensives. If there is concern for dermal exposure, the patient should be decontaminated with soap and water. Activated charcoal can be administered if the patient presents immediately following exposure, but its use is generally limited by vomiting.

Case concluded

The child vomited several times in the emergency department and was not given activated charcoal. She received intravenous fluids and was monitored closely for 24 hours, during which time her tachycardia and hypertension resolved. The patient became more awake and alert, was able to eat and drink, did not develop any seizures, and was subsequently discharged home. The parents were educated about safe storage of the liquid nicotine refills.

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