TOXICOLOGY
LETTER

COMPRISING THE NEW YORK CITY AND UPSTATE NEW YORK POISON CENTERS

As of January 1st, 2011 New York State consolidated from 5 poison centers to two; one located upstate in Syracuse and the other located downstate in New York City. For those of you who are accustomed to working with us, nothing has changed. We will continue to offer you timely, state-of-the-art patient-specific recommendations on your cases and answer questions you may have related medications and toxins. For our new customers we welcome your calls and promise the same high-quality services we have always provided. We are also here to meet your educational needs and would be happy to provide on-site programs both for your professional staff and the patients you serve. Contacting the poison center in your area has not changed: 1-800-222-1222.

Cardiac Glycosides and Fab Fragments: Beyond Digoxin

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Digoxin is a drug manufactured from the extracts of a plant species known as Digitalis purpurea or, more commonly, foxglove.[1] Digoxin is used as an anti-arrhythmic agent in patients with atrial fibrillation to control their heart rate and to increase their cardiac contractility.[1] It exerts its action through inhibition of the sodium-potassium ATPase. This elevates the intracellular concentration of sodium and results in an increase of intracellular calcium by its secondary actions on the sodium-calcium exchanger of the cardiac sarcolemma.[1] Increased intracellular calcium provides a positive inotropic effect as well as a vagal effect on the parasympathetic nervous system which slows the ventricular rate.[1] Digoxin toxicity can lead to heart block and either bradycardia or tachycardia (excluding supraventricular tachycardia with a 1:1 conduction.[2] Corresponding symptoms can include fatigue, nausea, vomiting, visual disturbances, diarrhea, loss of appetite, changes in heart rate and rhythm, confusion, nightmares, dizziness, agitation and depression.[2]

The acceptable range for digoxin serum concentration is between 0.5 and 2 ng/ml, although the current accepted maximum is 1 ng/ml.[2] Patients presenting with digoxin toxicity – both from acute ingestion and chronic use – are common in the ED. Currently accepted treatment is Digibind® or Digifab® – fab fragment products designed to bind to digoxin. Digoxin immune Fab, is the primary treatment for digoxin toxicity.[2] It is derived from specific anti-digoxin antibodies produced by sheep that have been immunized with the drug[3]. These antibodies are then isolated and purified to their immunoglobulin Fab fragments. Digoxin fab adheres itself to the unbound digoxin and prohibits their action on target cell binding sites.[3] These bound complexes then accumulate

Program Announcements ◆◆

UNY: The 2010 Toxicology Teaching Day is Scheduled for 11/3/10. Please mark your calendars!!

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

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Toxicology Advice Centers ◆◆

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in the blood and are eventually removed from circulation by the kidney.[3] For a patient with an acute overdose where the ingested dose is known, the amount of fab fragments needed can be calculated by the assumption that one vial will bind to 0.5 mg of digoxin. Since oral digoxin has a bioavailability of ~80%, if the amount ingested is multiplied by 0.8 and then the product is divided by 0.5 mg/vial, a therapeutically appropriate amount of fab can be derived. In late-presenting acute patients without a known ingested amount, or in patients with chronic toxicity possessing an elevated concentration several hours after their last dose, the estimated amount of fab needed can be quickly determined by combining the patient's weight (in kg) with their digoxin concentration and then dividing by one hundred. Although the efficacy of fab fragments in treating digoxin toxicity is well-recognized, clinical data supporting the use of fab with other cardiac glycosides is still limited. Various plant and animal-derived cardiac glycoside substances and their origins are explored below.

Ouabain:

Ouabain is a poisonous cardiac glycoside found in the seeds of the plant Strophanthus gratus and in the bark of Acokanthera ouabaio and also exists endogenously as a human hormone synthesized in the adrenal gland.[4] Although its mechanism of action is similar to digoxin, uniquely it can alter the expression of several genes via a sustained increase in phosphorylated tyrosine in MDCK cells, affecting signal transduction in the Ras-ROS pathway.[4] Prior to the development of digoxin, ouabain was medicinally used to treat atrial fibrillation and congestive heart failure, due to its inotropic effects.[4] However, due to digoxin's enhanced lipophilicity and superior bioavailability, the clinical use of ouabain diminished to primarily in vitro research studies.[4] Current research regarding the incidence of ouabain toxicity and its clinical presentation is rather scarce, suggesting that its effect is a result of its influence on signal transduction rather than its membrane depolarization.[4]

An *in vitro* experiment exposed oubain and fourteen other digoxin-like molecules (including bufalin and marinobufagenin) to digoxin-specific Fab, and the level of inhibition of their activity was measured. Schild analysis was utilized to determine the concentration of digoxin-specific Fab necessary to cause a shift in the cardiac glycoside inhibition curve and it was found that digoxin-specific fab were able to neutralize each of the agents to some extent. The potency of digoxin-specific Fab towards ouabain was similar to that of digoxin, and was found to be more than twenty-times more effective than with marinobufagenin (p<0.005).[5]

Oleander:

Nerium and yellow oleander are tropical flowering shrubs and small trees (respectively) found in the dogbane family Apocynaceae.[6] They are two of the most poisonous garden-variety plants, and are extremely toxic when a sufficient amount is ingested. Various deleterious toxins are derived from these plants, including the cardiac glycosides oleandrin and neriine in nerium oleander and thevetoxin, neriifolin, peruvoside, and ruvoside in yellow oleander.[6] Human exposure

commonly results from unintentional ingestion through its incorporation into food, drinks, and herbal medicinal products.[6] However, these same species have been used since antiquity for intentional poisoning. Toxicity from oleander poisoning results in nausea, vomiting, tachy- and bradyarrhythmias, and various types of premature ventricular beats.[6]

A trial was published in Lancet that described treatment of oleander poisoning with Fab fragments. Suicidal patients presenting to a Sri Lankan hospital with yellow-oleander ingestion were randomized to receive either 1200 mg of anti-digoxin Fab or a saline placebo. Participants were incorporated into the study if they presented with sinus arrest or block, sinus bradycardia, atrial tachyarrhythmias or second- or third-degree atrioventricular block. In total sixty-six patients were included in the study. Thirty-four patients received digoxin-specific Fab and thirty-two received the saline control. Prior to and throughout the duration of treatment, a 12-lead ECG, three minute rhythm strip and electrolyte and cardiac glycoside concentrations were obtained. In fifteen of the anti-digoxin Fab-treated patients, the presenting arrhythmia had diminished within two hours. In comparison, only two patients in the control group achieved similar results (p<0.001). Twenty-four patients receiving digoxin-specific fab obtained sinus rhythm with a heart rate greater than forty-four beats per minute within eight hours, compared to only five patients in the placebo group (p<0.001). Statistical analysis via a Kaplan-Meier test highlighted the effects of digoxin-specific fab in treating the patient's arrhythmias, as the overall results showed experimental subjects achieving a sinus rhythm earlier than those in the control group (p<0.001). Likewise, heart rates increased over the first two hours of treatment from baseline in the experimental group, but not in the control subjects (p<0.001). These results support the use of digoxin-specific fab fragments in cases of serious cardiac toxicity precipitated by the ingestion of yellow oleander.[7]

Another detailed case study described a chronically depressed forty-four year old man who ingested Nerium oleander leaves in an apparent suicide attempt. He presented to the emergency department four hours later with confusion, vomiting and bradycarida (25 bpm). He was treated with a single dose of digoxin-specific fab antibody. Shortly after initiating treatment, the patient's rhythm stabilized, his vomiting ceased, and his neurological symptoms diminished. Two days later the patient was completely asymptomatic and was discharged from intensive care.[8]

Bufalin (Toad Venom):

The skin, venom, and parotid glands of many toad species contain the cardioactive steroid bufotoxin or bufalin a more potent inhibitor of the sodium-potassium ATPase than ouabain.[5,9] Therapeutic use of this compound is widespread outside of the United States and in China and Japan, the dried extract of toad skin is used as a cardio-tonic agent. In the West Indies, toad venom is incorporated into aphrodisiacs and venomous secretions from toads are utilized as local anesthetics.[9] Appropriate use of these amphibian-derived compounds can

provide some clinical benefit, but unintentional exposure or purposeful ingestion will result in cardiac toxicity, signs and symptoms of which are similar to digoxin poisoning (including nausea, vomiting, dizziness, blurred vision, hypotension and, most seriously, sinus arrest with atrio-ventricular block).[9]

A 1996 report outlined six healthy men who ingested a cardio-toxic aphrodisiac and described their presentation with positive apparent digoxin concentrations and cardiac dysrhythmias. Although sold under different names, the toxic substance in each of the patient cases was chemically similar to Chan Su, a Chinese medication derived from the dried venom of the bufo gargarizans toad. The first four patients expired following only supportive care. The remaining two survived following treatment with digoxin-specific fab fragments. The patients are depicted in the following chart[9].

Patient Demographics	Serum Digoxin Concentration	Signs and Symptoms	Treatment	Outcome
26 yr old male	3.6 nmol/L (2.79 ng/ml)	Hypotension, ventricular fibrillation	Supportive Care	Death 20 hours post-ingestion
28 yr old male	2.0 nmol/L (1.6 ng/ml)	Hypotension, seizures, bradycardia, ventricular fibrillation	Supportive Care	Death within 2 hours of presentation to the ER
23 yr old male	1.2 nmol/L (0.9 ng/ml)	Diaphoresis, hypotension, cardiac arrest	Supportive Care	Death within one day of ingestion
40 yr old male	4.0 nmol/L (3.08 ng/ml)	Bradycardia, hypotension, vomiting, diaphoresis, ventricular tachycardia	Supportive Care	Death within a few hours following presentation to the ER
17 yr old male	5.0 nmol/L (3.9 ng/ml)	Sinus bradycardia, vomiting	10 vials of digoxin-specific fab fragments	Heart rate returned to normal within 1 hour
34 yr old male	2.3 nmol/L (1.8 ng/ml)	Peri-oral numbness, vomiting, prolonged PR interval	2 doses of 10 vials of digoxin-specific fab fragments	Full resolution of symptoms within a few hours

In 1999 an animal study described mice pre-treated with digoxin-specific fab fragments and then exposed to an extract of Chan Su. Forty-five mice were randomly divided to receive the digoxin-specific fab fragments or normal saline. Fifteen mice were in the experimental group, where they received 20 ml/kg of digoxin-specific fab fragments intraperitoneally followed by a 10 ml/kg intraperitoneal dose after thirty minutes. Thirty mice were in the control group and were administered equal volumes of normal saline via intraperitoneal injection at the same times. Following the injection at thirty minutes, both groups received a subcutaneous loading dose of Chan Su extract. The outcomes followed were seizures and death. Only eleven seizures and seven deaths were witnessed in the experimental group compared to seizures and fatality within four hours of administration in the entire control group (p=0.009 and p=0.00003 for seizures and mortality, respectively). In the treatment group, the mean time to seizure onset was increased (62 vs. 43 minutes, p=0.025) and the time to death was longer although not significant (99 vs. 81 minutes, p=0.065), indicating a benefit from treatment with digoxin-specific fab fragments.[10]

Conclusion:

Digoxin-specific Fab fragments, (Digifab® or Digibind®), decreases the cardio-toxic symptoms and mortality in patients suffering from digoxin toxicity. Through retrospective case studies, in vitro analysis and randomized controlled trials in humans and laboratory mice, digoxin-specific fab fragments are also effective in treating the signs and symptoms of toxicity associated with a variety of cardioactive steroidsderivatives similar to digoxin. While they have varied potency, ouabain, nerium oleander, yellow oleander, and bufalin from toad venom all affect the sodium-potassium ATPase in cardiomyocytes similar to digoxin. Their shared chemistry and pharmacologic effect likely permits digoxin-specific fab fragments to aid in the reversal of their toxic effects. Although not a panacea for all presentations of cardiac toxicity, digoxin-specific fab fragments appear to have a class-effect as a neutralizing agent, rather than as a specific treatment for a single drug.

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Baby Powder Inhalation

Fiona M. Garlich, M.D. & Lewis Nelson, M.D.

Case Summary:

A previously healthy, 11 month-old, boy is brought by his mother to the Emergency Department (ED) approximately 20 minutes after inhaling baby powder while he was having his diaper changed. The mother states that immediately after the exposure the infant had an episode of coughing during which he "turned blue," but then he rapidly improved. Upon arrival to the ED, he is noted to be tachypneic with a respiratory rate of 40-60/min. Oxygen saturation is 98% on room air, and the remainder of his vital signs include: BP, 90/55 mmHg; P, 104 / min; T 98.8˚ F. A radiograph of the chest is unremarkable. In the ED, the patient receives prednisone and is admitted overnight for observation on the pediatric ward. He is discharged well the next day.
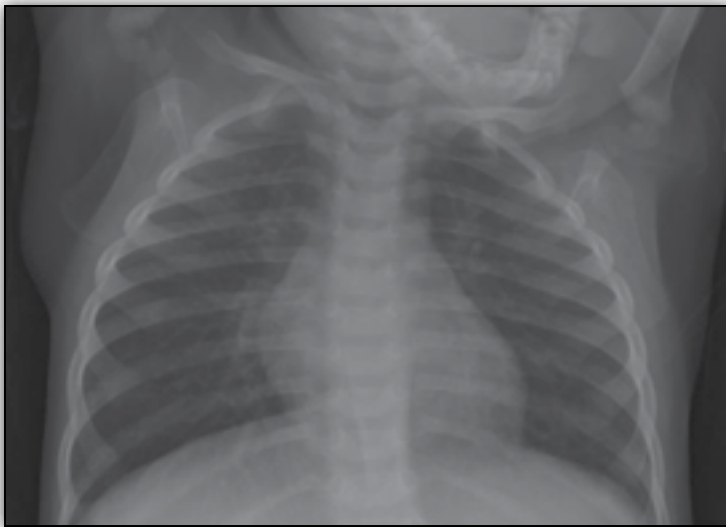
One day later the patient returns to the ED with grunting respirations, subcostal retractions, diffuse crackles, a respiratory rate of 60/min, an oxygen saturation of 92%, and a fever to 103˚F. Laboratory analysis of his blood is significant for a white blood cell count of $20 \times 10^3/mm^3$. An ABG reveals: pH, 7.4; PCO_2, 32 mmHg; PO_2 85 mmHg. A repeat chest radiograph (shown below) demonstrates increased bronchovascular markings and hyperinflation, suggesting a diffuse inflammatory reaction. No focal infiltrates are seen.

Upon the treating physician's request, the parents bring in the bottle of baby powder. It contains 81% talc.

What is talc?

Talc is a pearly white, naturally-occurring mineral composed of hydrated magnesium silicate ($Mg_3Si_4O_{10}(OH)_2$). It is found geologically in deposits around the world. The softest mineral on earth, its name is derived from the Arabic "talq," meaning "pure."[7] Talc has been used for millennia, and is currently used in a myriad of industrial and consumer products, including plastic, paint, cosmetics, lubricants, pharmaceuticals, gymnastic chalk, decorative soapstone, and talcum powder or baby powder. Talcum powder, which consists of finely ground talc, has soothing, lubricating, and absorptive properties when applied to the skin. For these reasons, talcum powder was first introduced for use as baby powder in 1893. Paradoxically, talc is used medically for to prevent recurrent pneumothorax, due to its ability to incite a localized inflammatory reaction on the pleural surfaces.

What are the symptoms and complications of acute talc inhalation?

In contrast to the benign nature of magnesium silicate when ingested, talc acts as an irritant after inhalation.[4] Findings can range from cough, sneezing, and transient dyspnea, to cyanosis, severe respiratory distress, respiratory failure, and even death.[4,5] Many cases of symptomatic talc inhalation are reported, primarily in infants and preschool-aged children. Most inhalation incidents occurred at the time of a diaper change, often with inadvertent inversion of the container of talcum powder by the child, or with older children mimicking the use of powder on a younger sibling.[6] The onset of symptoms is often delayed several hours from the time of inhalation, as in this case.[4] In cases of massive inhalational exposure, pneumonitis, bronchiolitis, diffuse pulmonary infiltrates, acute lung injury, bronchiolar obstruction, or pneumonia from bacterial superinfection can occur, leading to severe pulmonary compromise. The reported mortality in severe talc pulmonary toxicity ranges from 20% to 33% in case series.[3,4]

What is the pathophysiology of pulmonary injury in acute talc inhalation?

Talc is insoluble in water, causing drying of the mucus membranes of the tracheobronchial tree when inhaled. This results in impairment of the normal ciliary function that is required to clear particulate matter from the airways.[4] Inhalation of talcum powder can also cause complete obstruction of the small airways.[3] Mice that inhaled talcum powder were found on autopsy to have bronchioles obstructed with talc powder, associated histologically with hemorrhage, edema, and desquamation of the bronchial epithelium. Furthermore, adsorption of surfactant to the magnesium silicate powder may contribute to pulmonary injury.[4]

What therapeutic options are available to treat acute pulmonary injury due to talc inhalation?

The primary goal in the treatment of patients with acute talcum powder inhalation is the maintenance of adequate ventilation and oxygenation. Supplementary oxygen should be administered as needed; intubation and mechanical ventilation may be required. A trial of inhaled bronchodilators is reasonable as appropriate, though there is no data to support their use. Corticosteroids, either orally or parenterally, are frequently administered in an attempt to mitigate the local inflammatory response. While the benefits of steroids have not been confirmed in clinical trials, there was a trend towards a mortality benefit in one retrospective review.[2] Accepted regimens include methylprednisolone 0.5-1 mg/kg intravenously every 6 hrs, or prednisone/prednisolone 1-2 mg/kg/day orally, both for a total of 3-5 days. Bronchoalveolar lavage may be of

benefit in the setting of massive talc inhalation, but its use is anecdotal. [3,4]

Is talc still used in baby powder?

Due to public awareness of the dangers of lung injury from talcum powder, cornstarch-based baby powder has been introduced. These products are non-inflammatory and of substantially lower risk if inhaled. Many parenting guides recommend against the use of talcum powder in infants. However, talc-containing products are still readily available, and are often found side-by-side with cornstarch-based diaper powder in baby care aisles (see photo below). Some bottles of talcum powder, labeled simply as "baby powder," have warnings cautioning against the dangers of inhalation, but many do not. The labels on these various powders may be confusing, misleading, or readily overlooked, prompting interchangeable use of the two quite distinctive products. Thus, although the incidence of talcum powder inhalation has decreased, it still poses a significant public health risk. In 2008, the American Association of Poison Control Centers reported 2,526 exposures to powders made of talc, 87% of which occurred in children under the age of 6 years. [2]

What are other causes of talc-related pulmonary toxicity?

The chronic inhalation of talc dusts in talc miners or industrial workers has long been associated with chronic pulmonary disease. When mined, naturally-occurring talc often contaminated with minerals such as crystalline silica and tremolite asbestos, which can lead to pulmonary damage in miners. The resulting conditions, termed talcosilicosis and talcoasbestosis, are clinically similar to silicosis and asbestosis respectively, both pathologically and radiographically. Chronic inhalation of talc dust in the industrial setting can lead to talcosis, a condition characterized by chronic bronchitis, interstitial fibrosis, and/or granuloma formation. [4]

Pulmonary toxicity is also described with the intravenous injection of talc-containing xenobiotics. One form of drug abuse involves the crushing, solubilizing, and filtering of oral medications, followed by intravenous injection. Talc is a common component in many of these tablets, and thus can be inadvertently injected if the filtering step is inadequate. The talc crystals become retained in the pulmonary capillary bed and produce angiothrombosis, granulomas, and interstitial fibrosis, which may lead to pulmonary hypertension and cor pulmonale. [1,4]

Case conclusion:

The patient is treated with intravenous methylprednisolone, along with ceftriaxone as empiric coverage for possible bacterial pneumonia. He is admitted to the Pediatric ICU, where he clinically improves over of the next two days and is transitioned to oral prednisolone. He does not require intubation or advanced ventilatory support. He is discharged on hospital day 3 to complete a five day course of corticosteroids.

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Talc-containing

Cornstarch-containing

WARNING: Keep powder away from child's face to avoid inhalation, which can cause breathing problems. Avoid contact with the eyes. For external use only.

To Use:
1. Shake powder directly into your hand, away from the face, before smoothing onto the skin.
2. Close tightly after use, store in a cool, dry place.

SAFETY TIP: Keep out of reach of children. Do not use if quality seal is broken.

Ingredients: Talc, Fragrance

Follow-Up from the New York City Poison Control Center Consultants' Conference of August 5, 2010

Inadvertent Intravenous Epinephrine Administration

Fiona M. Garlich, M.D. & Lewis Nelson, M.D.

Case Summary:

A 2 year-old girl with a history of mild, intermittent asthma is brought to the Emergency Department via ambulance with difficulty breathing and hives after eating a cashew. She vomits once and has a near syncopal episode en route. Upon arrival to the ED, she is in acute respiratory distress, with wheezing, stridor, and tachypnea to a respiratory rate of 40/min. An urticarial rash is noted. The remainder of her vital signs include: HR, 130/min; BP, 90/62 mm Hg; T, 99°F oxygen saturation, 98% on 4L O$_2$ via facemask.

Epinephrine 0.15 mg of 1:1,000 concentration is prepared for intramuscular administration for a diagnosis of anaphylaxis. However, the epinephrine is inadvertently administered intravenously. The patient subsequently develops tachycardia (heart rate in the 180s/min) and hypertension (blood pressure of 120/70 mmHg).

What is the mechanism of action of epinephrine?

Epinephrine, or adrenaline, is a catecholamine that is produced endogenously in the adrenal medulla. As a medication, epinephrine is administered parenterally as treatment for anaphylaxis and cardiac arrest. Its clinical utility is based on its activity at alpha- and beta- adrenergic receptors (beta >> alpha). Alpha-1 agonism in the peripheral vasculature results in vasoconstriction. Stimulation of beta-1 receptors in the myocardium increases chonotropy and inotropy, leading to increased heart rate and contractility, respectively. Stimulation of beta-2 receptors causes smooth muscle relaxation that in the peripheral vasculature induces vasodilation, and in the bronchioles causes bronchodilation. This forms the basis for the use of nebulized or aerosolized epinephrine as treatment for bronchoconstriction.

How is epinephrine dosing calculated?

Injectable epinephrine is available in two concentrations, 1:10,000 for intravenous use and 1:1,000 for intramuscular use. Epinephrine is unusual in its labeling because it is formulated as an unconventional dilution ratio of one thousand instead of as the more conventional percent (per one hundred) concentration. Since epinephrine was introduced before the enactment of the 1938 Food, Drug and Cosmetic Act, it does not fall under current FDA labeling standards.[4] The antiquated dilution formulation represents the volume of aqueous solution in milliliters into which 1,000 mg of epinephrine is dissolved. For example, a solution labeled as 1:1,000 represents 1,000 mg / 1,000 mL or 1 mg/mL, of epinephrine. Thus, the formulation intended for intravenous use is 10 fold more dilute than that intended for IM administration.

What are the indications and recommended doses for epinephrine administration?

According to the American Heart Association Guidelines, anaphylaxis should be treated by administration of epinephrine, 0.3 to 0.5 mg of the 1:1000 concentration IM in an adult (0.3 to 0.5 mL), and 0.01 mg/kg of 1:1000 IM in a child (up to

the adult dose).[1] Subcutaneous epinephrine administration is no longer recommended due to the achievement of more rapid peak plasma concentrations of epinephrine when administered intramuscularly in the thigh.[8,9] This can be repeated every 5-15 minutes until clinical improvement is demonstrated. For patients who do not respond, and who demonstrate evidence of anaphylactic shock, with refractory hypotension and signs of hypoperfusion, epinephrine should be administered intravenously at a dose of 0.1 mg (adults) or 0.01 mg/kg (children; up to the adult dose) of the 1:10,000 concentration via slow IV infusion over 5 minutes. During cardiac arrest, epinephrine is administered via IV bolus at a dose of 1 mg (adults) or 0.01 mg/kg (children; up to the adult dose) of 1:10,000 concentration (up to adult doses). Epinephrine can also be administered continuously via intravenous infusion at doses of 2-10 mcg/min as a second-line therapy for shock or unstable bradycardia.

Indication	Epinephrine Dose
Anaphylaxis (see below)	**Adult** 0.3 to 0.5 mg of 1:1,000 IM in thigh **Child** 0.01 mg/kg of 1:1,000 IM in thigh (up to 0.3 mg if not using autoinjector)
Anaphylactic shock (refractory)	**Adult** 0.1 mg of 1:10,000 IV over 5 minutes **Child** 0.01 mg/kg 1:10,000 IV over 5 minutes (up to 0.1 mg)
Cardiac arrest	**Adult** 1 mg of 1:10,000 IV push **Child** 0.01 mg/kg of 1:10,000 IV push
IM Autoinjectors for Anaphylaxis	**Epinephrine Dose**
Adult (e.g., EpiPen)	0.3 mg (0.3 mL of 1:1000)
Child (e.g., EpiPen Jr)	0.15 mg (0.3 mL of 1:2000)

What are the factors that contribute to dosing errors with epinephrine?

Confusion concerning the appropriate dose, formulation, and route of administration of epinephrine is common. Many hospital "crash carts" stock epinephrine in the intravenous formulation that is only appropriate for cardiac arrest, causing confusion or delay when a patient with anaphylaxis requires the more concentrated formulation for intramuscular delivery. Furthermore, many physicians understandably have difficulty with complex dose calculations and conversions, and this may be magnified under stressful conditions. In a survey of 150 hospital physicians, half were unable to correctly convert doses of epinephrine from a dilution to mass concentration.[6] Physicians may not have adequate insight into the appropriate dose and concentration for anaphylaxis . In another survey of 253 radiologists in 26 U.S. and Canadian hospitals, no physician was able to give the correct dose, concentration, and route of epinephrine administration. Of those surveyed, 17% would have administered an epinephrine overdose.[6]

Inappropriate route of administration (IV vs IM) can occur when there is miscommunication between team mem-

bers caring for a critically ill patient. A retrospective review of patients admitted with anaphylaxis at a single institution over a 5 year period identified a 2.4% incidence of potentially life-threatening complications from inappropriate epinephrine administration.[4] Two of their reported cases involved the inadvertent intravenous administration of a dose and concentration of epinephrine intended for IM use. The causes of these errors were multifactorial, and were attributed to inadequate physician knowledge, lack of IM doses in emergency crash carts, complicated dose calculations involving ratios and decimal points, and lack of adequate communication between physicians and nurses. In a survey of inpatient pharmacies, only 1 of 7 responding hospitals had epinephrine available in prefilled syringes for IM administration, as is appropriate for anaphylaxis.[4] Inappropriate intravenous epinephrine administration can also occur with infusion pump malfunction in the setting of continuous infusion.[5]

What adverse effects are associated with inadvertent overdose of epinephrine?

Tachycardia and hypertension occur following intravenous administration of inappropriately high doses of epinephrine. In many patients with acute exposures, these effects can resolve spontaneously without evidence of end-organ effects. Epinephrine is rapidly metabolized and has a short half life of approximately two minutes. However, prolonged cardiovascular toxicity has been described in both adult and pediatric populations, especially when exposure is prolonged by continuous infusion.

Case examples from the literature:

A 23 year-old woman presented with anaphylaxis and was erroneously given two doses of epinephrine 1 mg (1:10,000) as an IV bolus, instead of by slow infusion. She developed cardiogenic shock with severe left ventricular dysfunction (ejection fraction of 15%) and pulmonary edema requiring intubation. She returned to normal cardiac function after four days.[4]

A 33 year-old woman was erroneously given epinephrine 0.3 mg (1:1,000) IV instead of IM. She subsequently developed a right coronary artery dissection that required intracoronary stenting.[4]

A 5 year-old boy developed acute myocardial ischemia, as evidenced by elevated cardiac enzymes, ECG changes, decreased left ventricular systolic function, and pulmonary edema, after epinephrine was erroneously given intravenously instead of subcutaneously.[2] Ventricular dysrhythmias in children receiving excessive doses of subcutaneous epinephrine as treatment for asthma are described.[3]

An 18-year-old man receiving continuous epinephrine infusion for septic shock developed tachycardia to 198 beats/min, hypertension to 250/188 mm Hg, pulmonary edema, and myocardial damage as evidenced by ECG changes and elevated cardiac enzymes. It appears that electromagnetic interference from a nearby cell phone caused a malfunction of the infusion pump, resulting in the delivery of 10.5 mg of epinephrine over a period of 1.4 minutes.[5]

What are the therapeutic considerations for iatrogenic epinephrine overdose?

Management priorities in epinephrine overdose, as with any critically ill patient, are control of airway, breathing, and circulation. Continuous cardiac monitoring and frequent blood pressure measurements should be instituted. An ECG should be examined for myocardial ischemia. For patients with evidence of myocardial ischemia, end-organ hypoperfusion, cardiac failure, pulmonary edema, or persistent severe hypertension or tachycardia, the administration of an antidote should be considered. Phentolamine, a non-selective alpha-antagonist, can be administered intravenously at doses of 5 mg for adults and 1 mg for children to reverse peripheral and coronary artery vasoconstriction. A short-acting, cardioselective beta-1 adrenergic antagonist such as esmolol may be considered for refractory tachycardia, though this should be rarely needed. Beta blockade should be avoided without the concomitant administration of phentolamine or another vasodilator to avoid the dangers of unopposed alpha adrenergic agonism.

Case Conclusion:

An ECG shows sinus tachycardia with normal intervals without evidence of ischemia. Throughout this time, the patient receives IV diphenhydramine and methylprednisolone as secondary treatment for anaphylaxis, along with normal saline. Her stridor and respiratory distress improve rapidly, and over a four hour observation period her tachycardia and hypertension resolve. She is admitted overnight for observation, and is discharged the following day without sequelae.

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