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# TOXICOLOGY LETTER

COMPRISING THE NEW YORK CITY AND UPSTATE NEW YORK POISON CENTERS

## Arsenic in Apple Juice

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### Introduction

Arsenic (chemical symbol As) is the twentieth most abundant mineral in the earth's crust, and trace amounts are found ubiquitously in the environment. The toxic and poisonous properties of arsenic have been well known for centuries, and it has a notorious reputation of being used frequently as a homicidal agent. Recent reports of arsenic found in apple juice have caused unnecessary fear regarding the safety of these products.

In Fall of 2011, Dr. Mehmet Oz, host of US talk show The Dr. Oz Show, announced that commercial apple juice brands like Juicy Juice contained 16 ppb of arsenic, while Gerber contained 36 ppb, but did not specify organic vs inorganic arsenic. In response to the consumer anxiety induced by this announcement, the FDA also tested apple juices, and found only trace amounts of inorganic arsenic in its samples. Specifically, only five percent of 160 samples exceeded the current FDA threshold for safety in juices of 23 ppb[1].

*Consumer Reports* magazine performed their own study, testing 88 samples of apple and grape juice found on grocery store shelves. They found that that 10 percent had total arsenic levels that exceeded US federal drinking-water standards of 10 parts per billion (ppb), the same threshold for the European Union. Specifically, 5 samples of apple juice and 4 of grape juice had total arsenic levels exceeding the 10 ppb federal limit for drinking water. Levels in the apple juices ranged from 1.1 to 13.9 ppb, and grape-juice levels ranged from 5.9 to 24.7 ppb. In this case, most of the arsenic detected was inorganic[2]. A juice industry group, The Juice Products Association, responded with a statement in early December 2011 that none of the magazine samples tested exceeded 23 ppb for inorganic arsenic and expressed confidence in the FDA's regulatory system.

### Arsenic

Arsenic has a molecular weight of 74.9 daltons, and is classified as a metalloid or transitional element, since it commonly complexes with other metals (eg, lead arsenate), but also with non-metals (oxygen, hydrogen, etc). It is estimated to be present at an average concentration of 5ppb in the earth's crust, making it the 33rd most abundant element. While there are three major groups of arsenic compounds: inorganic arsenicals, organic arsenicals, and arsine gas; this report discusses only inorganic arsenicals[3].

Inorganic arsenic (*i*As) compounds exist in three common valence states: the metalloid or neutral, elemental oxidation state ($As^0$), the trivalent arsenite ($As^{3+}$), and the pentavalent arsenate ($As^{5+}$). The toxicity of iAs compounds varies widely, but the trivalent arsenicals are several-fold more toxic than the pentavalent compounds. The most common trivalent *i*As compounds are arsenic trioxide, sodium arsenite, and arsenic trichloride. Common pentavalent *i*As compounds are arsenic pentoxide, arsenic acid, and arsenates such as lead arsenate[4].

### *i*As Absorption

The major routes of absorption of *i*As compounds are ingestion and inhalation. Soluble *i*As compounds [arsenates (III) and arsenites (VI)] are well-absorbed from the GI tract after oral ingestions, either from food or water supplies.(Dart) Most epidemiologic evidence of the long-term toxicity of *i*As compounds comes from studies of ingestion of *i*As compounds

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## Program Announcements

**UNY:** The 2012 Toxicology Teaching Day is Scheduled for 11/7/12. Please mark your calendars!!

**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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in drinking water supplies. Inhalation exposures in the industrial setting are usually to $As_2O_3$, and can be well absorbed, but depositions and amount of absorption is dependent on particle size. Many larger particles not absorbed in the lungs will be cleared by pulmonary mechanisms, only to be then coughed up and swallowed, allowing absorption from the GI tract. Significant dermal absorption has been documented only in rare industrial accidents involving splashes of high concentrations of *i*As compounds on worker's skin. It is unknown how much dermal absorption of *i*As compounds occurs from concentrations typically found in soil or water, or what type or concentration of *i*As compounds would lead to significant absorption.

### Acute Toxicity

*i*As exerts its toxic effects in numerous organ systems via two main mechanisms. First, like other poisonous metals, it has an affinity for sulfhydryl groups (-SH), and binds irreversibly to these molecules commonly found in body proteins. When the binding occurs to sulfhydryl groups of numerous critical enzymes in the body, they are inactivated, and toxicity occurs. Trivalent *i*As compounds are particularly potent in this regard, and their toxicity is manifested as multisystem organ failure after acute poisonings. The second major mechanism of *i*As toxicity is the fact that pentavalent arsenicals competitively substitute for inorganic phosphate compounds when producing cellular energy, effectively uncoupling the cell's ability to perform oxidative processes. Both of these toxic mechanisms can lead to cell damage and multisystem organ damage and death. Main target organs are GI tract, and the neurologic, pulmonary, hematologic, cardiovascular and dermal systems. Survivors of acute poisonings can later develop chronic problems in the dermatologic, hematologic, and peripheral nervous systems (PNS) as well.

### Chronic Toxicity

Chronic *i*As toxicity is a significant public health problem in many areas of the world, mainly in third world countries. Historically, dysentery caused significant morbidity and mortality due to microbial contamination of surface drinking water supplies in many undeveloped nations, as well as pesticide runoff contamination of these surface water supplies in agricultural areas. Public health organizations (including WHO), recognizing the importance of clean, healthy drinking water supplies, sought practical solutions to this drinking water contamination. The availability of drilling technology allowed wells to be dug deep into the ground, tapping clean subterranean aquifers. While this eliminated the microbial contamination problem, it caused another, unforeseen problem. In certain areas of the world, the rock surrounding the aquifers contained high concentrations of *i*As, causing significant long-term exposures to *i*As-contaminated drinking water supplies. The *i*As contamination of the water supply was not discovered until epidemics of certain health effects known as arsenicosis began appearing. Investigators quickly recognized long-term exposures to *i*As contamination of the water supplies as the cause of these health effects. These long-term exposures to high *i*As-contaminated drinking water have since been linked epidemiologically to an increased risk of cancers of the skin, lung, bladder, prostate and kidney, in addition, several non-cancerous manifestations became evident, such as hyperpigmentation of the skin, hyperkeratosis, peripheral neuropathy, and peripheral vascular disease. Arsenic is classified as a definite carcinogen by the International Agency for Research on Cancer (IARC, Group 1) and the National Toxicology Program (NTP).

The international tragedy of *i*As-contaminated drinking water supplies underscores the importance of safe, healthful drinking water. Since the average daily water consumption is approximately 2 L (>2 quarts) of water per day, per adult, it is easy to see how contaminated water can adversely affect health. The US EPA reduced the maximum concentration level (MCL) from 50ppb in 2004 to 10 ppb.

### Acceptable and Toxic Levels

There are certain drinking water levels at which *i*As has been clearly shown in numerous epidemiologic studies to be associated with significant cancer and non-cancer effects. Studies from Argentina[5], Bangladesh[6], China[7], Chile[8], Mongolia[9], and Taiwan[10] have shown increased health risks for populations having levels in their drinking water in excess of 50 ppb, with most clearly increased risks being present when levels exceeded several hundred parts per billion (ppb)[11] . In fact, most of these studies show a dose-response relationship, with increased incidence seen in populations with higher levels of *i*As in their drinking water.

MCLs are generally set with a ten-fold margin of error, meaning that safe levels are usually set so that they are at least one tenth of the level where no observed adverse health effects are seen (NOAEL). The current available epidemiological evidence demonstrates adverse health effects in populations chronically exposed to drinking water As levels of several hundred mcg/L (i.e., 100's of ppb). Since the 50ppb was only about a 4-fold decrease from the known dangerous levels, it was felt that lowering it to a level more in line with the usual ten-fold safety margin would be more prudent. Therefore, the National Research Council (NRC) recommended in 1999 that the acceptable drinking water concentration be lowered from the standard 50 ppb (which was in place since the 1940's), since cancerous effects were found at As levels less than an order of magnitude greater than the 50ppb standard. The NRC met again in 2001 to consider new scientific evidence, and calculated cancer risks. In 2001, the EPA lowered the US maximum contaminant level (MCL) in municipal drinking water to 10 ppb , based largely on the findings and recommendations by the NRC. The regulated public water supplies had five years to comply, whereby the new standard became effective in 2006.

### Arsenic in Apple Juice

The recent publications by consumer advocacy groups mentioned in the beginning of this article have worried many consumers that our children are being poisoned by arsenic in apple juice. A close inspection of the levels found that the overwhelming majority of the samples were below the drinking water MCL of 10ppb; the small numbers that were

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## Case presentation

A 13 year-old girl with no prior medical history presents to the emergency department via ambulance with continuous vomiting and diarrhea. The patient recalls feeling ill after drinking a beverage with her mother the night prior to presentation. Shortly after, she developed uncontrollable vomiting and diarrhea and then passed out. The paramedics report that the girl's aunt heard the patient calling for help early the next morning and found her covered in her own emesis, feces, and urine.

In the ED, her vitals are: blood pressure, 120/77 mmHg; pulse, 71/min; respiratory rate, 24/min; temperature, 97.3˚F; $O_2$ saturation, 100% on high flow oxygen. On physical examination, the patient appears very ill and continues to gag. She is responsive to sternal rub, and her pupils are 2 mm and sluggishly reactive to light. She is diaphoretic and covered in her own excrements. The cardiac exam is unremarkable and her lungs are clear. Her abdomen is soft, non-distended and non-tender with normal bowel sounds. Her cranial nerves are intact and her muscle tone and strength are normal.

### What is the toxicological differential diagnosis for altered mental status with profound gastrointestinal hyperactivity?

The clinical signs and symptoms that this girl displays can be summarized as SLUDGE: salivation, lacrimation, urination, diarrhea, gastrointestinal upset, and emesis. Additional findings of this "syndrome" include the more life-threatening bradycardia, bronchorrhea, and bronchospasm, often deemed the "Killer B's." These clinical findings result from an excess of acetylcholine at postganglionic muscarinic receptors within the parasympathetic nervous system. Stimulation of nicotinic receptors at the autonomic ganglia and at the neuromuscular junction can cause mydriasis, tachycardia, hypertension (signs of sympathetic overactivity), and fasciculations, muscle weakness or paralysis, respectively. In reality, the clinical effects of excess acetylcholine can be variable because acetylcholine receptors are found in both the parasympathetic and sympathetic nervous system. The SLUDGE syndrome of muscarinic toxicity is a reflection of parasympathetic pathway activation, whereas nicotinic receptor activation causes sympathetic effects. Though the parasympathetic pathway is usually emphasized in classical "cholinergic" teaching, excessive sympathetic activity often predominates.

Some mushrooms, such as the ivory funnel (*Clitocybe dealbata*) and some *Inocybe* species contain muscarine and can cause a SLUDGE syndrome. Muscarine is a quaternary ammonium parasympathomimetic that does not readily cross the blood brain barrier.

Infectious food "poisoning" can cause severe gastrointestinal effects and is responsible for a significant number of hospitalizations and deaths in the United States. Certain bacterial food poisonings are due to liberated toxins. Examples include Staphylococcus spp, *Bacillus cereus*, *Escherichia coli*, *Salmonella spp*, *Vibrio cholera*, *Shigella spp*, *Yersinia spp*, and *Campylobacter jejuni*. Some echinoderms, such as the starfish, can cause vomiting due to asteriotoxin. Other foodborne toxins can cause gastrointestinal illness, but also cause neurological symptoms ranging from allodynia to life-threatening neurological issues such as paralysis. Ciguatoxin, found in dinoflagellate-consuming reef fish, classically causes vomiting and diarrhea and an unpredictable course of neurologic illness. Patients often complain of lasting paresthesias. Conversely, more serious food poisoning can occur after consumption of the Japanese pufferfish (Fugu). Specific organs harbor tetrodotoxin, and if prepared improperly, consumption can cause death due to paralysis.

Plants can also cause gastrointestinal symptoms following consumption and may occasionally be associated with systemic findings. Many plants, such as raw tomatoes and potatoes (both of the Solanaceae family, can cause direct irritation to the gastric and intestinal mucosa. Nicotine and related nicotine-like alkaloids nausea, vomiting, and diarrhea, due to stimulation of intestinal cholinergic receptors. Plants containing cellular toxins, such as *Colchicum autumnale* (autumn crocus; colchicine) or *Ricinus communis* (castor bean; ricin), most prominently affect the rapidly dividing cells of the gastrointestinal tract. *(Nelson 2007)* Other plants produce gastrointestinal effects only following systemic absorption. This includes *Cephaelis ipecacuanha*, from which ipecac is derived, which acts via the chemoreceptor trigger zone in the brain.

Metal salts such as those of lithium, iron, arsenic, and mercury cause prominent and early nausea, emesis, and diarrhea. The directly oxidative effects of the metal ions damage the gastric mucosa, produce hematemesis and gastrointestinal bleed, and further increase absorption into the circulation to cause systemic toxicity. Iron ions, for example, can disrupt oxidative phosphorylation and cause metabolic acidosis following systemic distribution. Additional systemic symptoms include coagulopathy, hepatic dysfunction, myocardial depression, and neurotoxicity.

Features of the history and physical examination assisted in narrowing the differential diagnosis. For example, there was no history of plant or mushroom ingestion. Since the vomiting and diarrhea persisted for hours without metabolic acidosis or classic neurological findings, the likelihood of metal salt ingestion was unlikely. Furthermore, the combination of miosis, intractable vomiting, diarrhea, and urinary incontinence immediately raised the suspicion of cholinergic crisis. Although she did not have bronchorrhea, bradycardia, or bronchospasm in the ED, as suggested above, it is common to have incomplete findings.

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### What agents can cause cholinergic crisis?

Some insecticides are strong acetylcholinesterase inhibitors. The World Health Organization classifies insecticides into five groups, ranging from extremely hazardous to unlikely to present acute hazard in normal use. Parathion, for example, is a very hazardous cholinesterase inhibitor (organophosphorus or OP) insecticide that has resulted in numerous fatalities worldwide. Some countries, such as the United States, have banned pesticides deemed to be highly toxic, such as those with high potency or long duration of action. (Eddleston) However, "less toxic" cholinesterase inhibitors pesticides can be found in insect or roach baits, shampoos for head lice, or products for pets. (Roberts) Temephos, for instance, is widely available in the United States to control mosquito outbreaks. Hazardous pesticides remain available in other parts of the world due to their low cost and high effectiveness for agricultural purposes. Sometimes these compounds are smuggled into the United States for specific uses. For example, though prohibited for public use in the United States, aldicarb is imported from the Dominican Republic as Tres Pasitos. Cholinergic crisis following exposures was noted in New York City's Dominican population starting in the 1990's. Aldicarb is one of many carbamate insecticides; other common ones include carbaryl, carbofuran, and methomyl. Their mechanism of action is nearly identical to that of the OP insecticides. Generally, cholinergic crisis from carbamate poisoning may be indistinguishable from that of the OPs. However, the duration and severity of clinical poisoning tends to be less. The reduced impact of poisoning from carbamates is a result of spontaneous and rapid hydroxylation of the carbamate-cholinesterase bond, thereby releasing the esterase to metabolize acetylcholine. This contrasts with the OP insecticides, whose spontaneous hydrolysis of the enzyme-OP bond is slow and incomplete. To make OP poisoning more difficult to treat, after an initial reversible period, some OP compounds can become irreversibly bound to the acetylcholinesterase enzyme ("aging"), making it impossible to reverse, even when appropriate antidotes are administered.

Several therapeutic medications are cholinesterase inhibitors. When administered in excess, they can cause cholinergic symptoms. Examples include medications used to treat myasthenia gravis (pyridostigmine) or Alzheimer's disease (donezepil). Prescribers should be aware that their overuse can precipitate cholinergic crisis.

### What are the most important steps in caring for the patient?

Caregivers should protect themselves from contamination if OP or carbamate poisoning is suspected. Donning personal protective equipment, including impermeable gowns and gloves, is wise. Patients with dermal exposures should be undressed and thoroughly washed with soap and water. Healthcare personnel can become poisoned by inhaling or dermal contact with insecticide on the surface of a contaminated patient.

Addressing airway, breathing and circulation should be the first priority. The most common cause of death in cholinergic crisis is respiratory failure secondary to bronchorrhea. Early intubation is indicated for patients who exhibit neuromuscular paralysis, respiratory failure, or severely altered mental status. Orogastric lavage can be attempted if early after ingestion. Lavaged contents and emesis may contain the toxic substance and should be handled cautiously.

### What are the antidotes for cholinergic crisis?

Atropine competitively inhibits acetylcholine binding at the muscarinic receptors in the central and peripheral nervous systems. Atropine has no effect at the nicotinic receptors and will not reverse muscle weakness or paralysis. Atropine should be given intravenously, and the dose should be titrated in relation to bronchial secretions. Adults dosing can start at 1 mg, whereas children can receive 0.02 mg/kg, with a minimum dose of 0.1 mg. Rapid escalation by doubling the previous dose every two to three minutes may be necessary to control bronchorrhea, and this is one of the primary endpoints of therapy. *(Howland A34, Holstege)*

Pralidoxime releases the cholinesterase inhibitor and restores the ability of cholinesterase to metabolize acetylcholine. In adults, dosing regimens vary, but it is usually administered as a 2 gram loading dose over 30 minutes, followed by a continuous infusion at 500 mg/hr. Children should receive a 20-40 mg/kg loading dose over 1 hour followed by an infusion of 20 mg/kg/hr. Rapid administration of pralidoxime can cause cardiac and respiratory arrest. Ideally, if organophosphate toxicity is suspected, pralidoxime should be administered early, prior to aging of the OP-cholinesterase bond. *(Howland A33, Holstege)* Use of pralidoxime in carbamate poisoning is controversial since spontaneous hydrolysis is expected. However, the clinical differentiation of carbamate and OP poisoning is very difficult, and empiric therapy is reasonable.

## Case conclusion

The patient received atropine 3 mg intravenously and rapidly improved. Shortly after the patient arrives to the ED, her mother is arrived in the ED with similar but more severe findings. She is intubated and received antidotal therapy. The daughter recovers and the mother is extubated approximately 1 week later and states she has Tres Pasitos in the home. Laboratory analysis of the serum of both patients, sent at the time of admission, confirms the presence of aldicarb.

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# Diffuse Muscle Weakness in an Elderly Woman

*Colleen Rivers, M.D. and Lewis Nelson, M.D.*

## Case Presentation

An 81 year-old woman presents to the ED with five days of generalized weakness and dyspnea. She denies sensory symptoms, diplopia, dysarthria, and dysphagia. Her past medical history includes hypertension, hyperlipidemia, and atrial fibrillation. Her surgical history is notable for a remote thymectomy. Her medications include warfarin, digoxin, and simvastatin.

On physical examination, her vital signs are within normal limits. She is awake, alert, and cooperative. Her cardiac, pulmonary, and abdominal exams are all unremarkable. On neurological examination, her cranial nerves II-XII are intact. She has bilateral upper extremity weakness (4/5) that is slightly worse proximally compared to distally. She has bilateral lower extremity weakness (2/5) that is also slightly more pronounced in the proximal muscle groups. Her neck flexion is weak (3/5), deep tendon reflexes are absent throughout, and she is unable to walk. Perception of light touch is intact throughout.

### What is the toxicological differential diagnosis for diffuse muscle weakness?

There are a wide variety of etiologies for muscle weakness including those that are infectious, metabolic, autoimmune, endocrine, and toxicological in origin. One approach to this daunting differential considers whether the pathology originates within the peripheral motor neuron, at the neuromuscular junction, or within the muscle itself. This framework subsequently allows the history, physical examination, and clinical progression to further narrow the list of likely causes.

Neuronal dysfunction is typified by a demyelinating syndrome, and the most common cause is Guillan-Barre syndrome (GBS). This typically presents as an ascending motor weakness in the two to four weeks following a viral illness or a *Campylobacter jejuni* infection. Symptoms often begin with paresthesias of the distal extremities, followed by weakness that may progress to involve the trunk, upper extremities, cranial nerves or the diaphragm over the course of days to weeks. Deep tendon reflexes tend to be absent early in the disease course and objective sensory deficits are rare.[2] Toxicological mimics include diphtheria (a toxin released by the bacteria *Corynebacterium diphtheriae*) and buckthorn (from the fruit *Karwinskia humboldtiana*).

Tick paralysis and botulism both result from the inhibition of acetylcholine (ACh) release at the neuromuscular junction. Tick paralysis is rare in humans, but most commonly affects girls five to six days after the tick has embedded in their scalp (gender preference presumably due to long hair).[5] Botulism involves the absorption of botulinum neurotoxin (BoNT), an endopeptidase that cleaves essential polypeptides of the SNARE apparatus responsible for ACh exocytosis.

Etiologies of botulism include foodborne botulism (preformed BoNT), wound botulism (growth of Clostridium in injection sites of drug users), and iatrogenic botulism (following administration of high concentrations of therapeutic or cosmetic BoNT). Clinically, patients with both syndromes initially complain of diplopia, dysphagia, and other manifestations of cranial nerve dysfunction. These symptoms are followed by a descending paralysis with consequential involvement of the respiratory musculature.[6]

A variety of toxic-metabolic derangements also affect transmission at the neuromuscular junction through a variety of mechanisms. Hypermagnesemia, for example, interferes with presynaptic calcium entry and causes a blockade of ACh release. While this toxicity is classically associated with obstetrical patients receiving intravenous magnesium for pre-eclampsia, iatrogenic hypermagenesmia is also reported following large quantities of magnesium containing antacids.[9] Hypokalemia, resulting from a variety of etiologies including decreased oral intake, gastrointestinal losses, renal losses, and processes that shift potassium intracellularly (e.g., poisoning with soluble barium salt) can result in flaccid paralysis. In these cases, hypokalemia alters the electrochemical potential of excitable cells, blocking repolarization, and rendering them unexcitable.[3] In all cases of severe electrolyte abnormalities, alterations in cardiac conduction can also occur.

Finally, myopathies are a group of disease processes that affect the muscle fibers themselves, resulting in weakness that is symmetrical in nature and tends to involve the more proximal muscle groups. Patients may complain of muscle pain and are noted to be tender on exam. Although congenital disorders are a common cause in infancy (Duchenne's muscular dystrophy), acquired myopathies in adults are commonly drug related. Etiologies include corticosteroids, zidovudine, colchicine, or statins. *(see Table 1)*

## Case continuation:

The patient's initial laboratory values were notable for the following: CPK, 3513 IU/L (normal <40); BUN, 68 mg/dL; Cr, 2.3 mg/dL. A lumbar puncture returned with no cells and normal protein and glucose measurements. The patient was admitted to the hospital and underwent nerve conduction studies (NCS) that were unremarkable and electromyography

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(EMG) that was abnormal and consistent with the diagnosis of myopathy.

### How does one differentiate these potential etiologies?

Clinical features of the history and physical examination assist the differentiation. For example, in this patient the weakness is localized to her limbs and trunk with no cranial nerve abnormalities, lowering the likelihood of botulism and myasthenia gravis.

Secondly, initial laboratory studies from the emergency department including electrolytes, cerebrospinal fluid (CSF), and CPK can help differentiate these causes. In this case, normal serum potassium and magnesium concentrations essentially rule out hypermagnesemia or hypokalemia as a cause of weakness. A lumbar puncture was performed to evaluate for GBS looking for "cytoalbumin dissociation." This classic CSF finding of elevated protein and a normal white blood cell count suggests GBS, but is not always present in the first few days of this disease process. Still, normal CSF protein and cell count as in this case make GBS an unlikely etiology. Additionally, this patient had an elevated serum CPK at 3513 IU/L, reflecting muscle breakdown and release of myocyte contents into the systemic circulation, suggests myopathy as an etiology. This is sometimes coupled with a reddish discoloration of urine and a positive urine dipstick for blood in the setting of a negative urinalysis for red blood cells, both pointing to the presence of urinary myoglobin.

Lastly, a number of studies can be obtained in the hospital to further narrow the differential diagnosis. Nerve conduction studies, for example, may be helpful to diagnose diseases of neuronal transmission such as GBS. In this test, a peripheral nerve is electrically stimulated and the time it takes the impulse to travel to the motor end plate is measured. NCS may be coupled with EMG, a test that evaluates the electrical activity of muscle cells by generating electrical impulses at the muscles and measuring the resulting action potentials. In the case of a myopathy, for instance, one would expect to see a decrease in the duration of the action potential of the muscle cells. In this case, a normal NCS with an abnormal EMG also points toward myopathy.

### Many patients in the ED take statins for management of hyperlipidemia. Are particular statins more likely to cause a myopathy?

Statins are the most widely prescribed of lipid-lowering drugs largely due to their outstanding efficacy and favorable safety profile.[7] They work by inhibiting HMG-CoA reductase, the ratelimiting enzyme in the chemical synthesis of mevalonic acid and subsequently endogenous cholesterol. Though generally safe when taken at low doses, they can cause elevated liver enzymes and muscle breakdown in susceptible individuals. One possible mechanism for these unintended effects is that inhibition of HMG-CoA reductase also leads to decreased levels of ubiquinone, also known as coenzyme Q (CoQ). This chemical is a key-player in the electron transport chain and intracellular signaling as well as an intracellular anti-oxidant. *[Hargreaves]* As a result, CoQ supplementation has been studied as a treatment for statin associated myalgias with some success.[1]

Other pharmacological properties of statins place them at higher risk for causing myopathy when given with certain drugs. First, statins undergo glucuronidation and co-administration of other drugs that undergo glucuronidation such as gemfibrozil may increase statin concentrations.[8] Additionally, most statins are metabolized by CYP 3A4. Concurrent administration of drugs such as macrolide antibiotics, nondihydropyridine calcium channel blockers, and protease inhibitors that are also metabolized by this enzyme may increase statin levels via competitive inhibition of the enzyme.[8]

While severe myopathy and rhabdomyolysis as in this case are relatively rare occurrences given the large number of patients on statins, statin-related complications occur on a spectrum and should be considered in all patients presenting to the ED with weakness or muscle pain. Some patients have only muscle pain without an observable rise in their CPKs while others have mild CPK elevations at baseline or following vigorous exercise that do not reach the level of rhabdomyolysis (>10 times the upper limit of normal.) Other patients may have clinically important muscle weakness with little or no elevation of their CPK.[10] Little consensus exists on how to screen for this complication beyond clinical monitoring.

Recent data suggests that while all statins may cause myopathy, high dose simvastatin (80 mg) is associated with particularly high rates of statin induced myopathy. Following an extensive review of the safety and efficacy data, the FDA recently required changes in safety labeling for simvastatin. In these changes, they specified that the 80mg dose of simvastatin be restricted to persons who have taken the medication for more than twelve months without complications.

Additionally, they placed absolute and relative contraindications for the prescription of simvastatin in the setting of CYP3A-4 interacting drugs such as ketoconazole, diltiazem, and amlodipine.[4]

### Case conclusion:

Given that the patient's medications included high does simvastatin (80 mg daily), simvastatin was presumed the cause of the myopathy and the medication was discontinued. The patient was managed supportively, her CPKs trended down, and she was ultimately discharged to a rehabilitation facility.

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### Table 1: Non-toxicological Causes of Diffuse Muscle Weakness

| Etiology | Mechanism | Clinical Presentation |
|---|---|---|
| Lambert-Eaton Syndrome[12] | Pre-synaptic voltage-gated calcium channels blocked by auto-antibodies | * Starts with proximal leg weakness<br>* Slowly progressive<br>* Improves with exertion<br>* Possible diaphragm involvement |
| Myasthenia Gravis[12] | Post-synaptic nicotinic Ach receptors blocked by autoantibodies | * Starts with diplopia, cranial neuropathies<br>* Worsens with repeated effort<br>* Possible diaphragm involvement |
| Primary Periodic Paralyses (Hyperkalemic or Hypokalemic)[11] | Alterations in L-type calcium channel or skeletal muscle sodium channel subunits | * Attacks of flaccid paralysis sparing facial muscles<br>* Rare diaphragm involvement<br>* Common after exercise or large carbohydrate meal |
| Myopathies | Infection (e.g; Influenza)<br>Autoimmune (e.g; lupus)<br>Endocrine (e.g; hypothyroidism) | * Muscle pain<br>* Proximal limb weakness<br>* Elevated CPK |

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## Follow-Up from the New York City Poison Control Center Consultants' Conference of September 1, 2011

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## Arsenic in Apple Juice

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above the drinking water standard samples were at or near the current drinking water standard of 10ppb, the maximum being 13.9 for apple juice and 24.7ppb for grape juice. None were anywhere near the old safe MCL of 50ppb. It should be reiterated that ***no good reliable epidemiological studies have demonstrated adverse health effects from drinking water at or below the previous drinking water standard of 50 ppb***[15]. Therefore, no adverse health effects would be expected when drinking apple juice with these low levels that may exceed the new drinking water standard by a few parts per billion.

The new As drinking water standard was lowered to add a safety factor for drinking water. One cannot compare drinking water standards to other beverages, since drinking water standards assume a certain amount of water intake (in drinks, food, etc) on a daily basis for many years in a row, and calculate risks from that intake. This amount of water intake would exceed the amount of apple juice, even in children who drink apple juice as their preferred beverage (since they would get water from other food and drink). We should strive to have the lowest amount of As in all of our food and drink, but since As it is an abundant element occurring naturally in the earth's crust, it cannot be eliminated completely. However, striking unnecessary fear in consumers regarding insignificantly elevated As levels in apple juice is certainly not in the interest of public health.

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