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Utox Update

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BISMUTH

Case Study

A 54-year-old man presents with a 6-week history of progressive confusion and memory difficulty and a 2-3 week history of involuntary movements and gait impairment. He demonstrates marked multifocal myoclonic jerks, coarse postural tremors, postural instability, and gait ataxia. Spinal tap and brain magnetic resonance scan were normal. Extensive toxic, metabolic, and infectious workup demonstrates bismuth toxicity. He gradually improves. As his encephalopathy clears, he reports using bismuth subsalicylate long term (8 oz/day). Serum bismuth concentrations 5 weeks after cessation of bismuth were elevated but normalized after 12 weeks. He followed a typical course for bismuth toxicity with subacute progressive encephalopathy and gradual recovery.[1]

Introduction

Bismuth toxicity was common when soluble bismuth salts were used in the treatment of syphilis and amebiasis. Symptoms included fever, weakness, jaundice, diarrhea, stomatitis, and blackening of the oral mucosa.[2] Between 1973 and 1980 approximately 1000 cases of bismuth related neurotoxicity and over 70 deaths were reported in France.[3] Today bismuth salts are primarily used for the treatment of gastrointestinal (GI) illnesses. Toxicity is uncommon from oral administration of over-the-counter preparations (Table 1) but the potential still exists as is evident in the case study.

Table 1. Commercially available products in the US containing bismuth salts

Bismuth Salt	Product Name	Dosage Forms/Strength	Uses
Subsalicylate	Pepto-Bismol®	Susp. 262 mg/15 mL Tablet 262 mg	Upset stomach Diarrhea
	Pepto-Bismol Maximum Strength®	Susp. 525 mg/15 mL	Indigestion H. pylori
	Diotame®	Susp. 262 mg/15 mL Tablet 262 mg	Nausea
	Bismatrol®	Susp. 262 mg/15 mL Tablet 262 mg	
Subcitrate	Tritec®	Tablet 400 mg • Ranitidine 162 mg • Bismuth 128 mg • Citrate 110 mg	H. pylori infection Ulcer (gastric, duodenal) Gastritis

Pharmacology/Pharmacokinetics

The proposed mechanisms of action include gastroprotective effects through coating of the stomach, binding of ulcer bases and bile acid, and enhancing prostaglandin synthesis. Bismuth also inhibits *Helicobacter pylori* attachment to mucosal cells.

Bismuth compounds are insoluble salts (subsalicylate, subnitrate, subcitrate, and subgallate) that have limited absorption (<1%) in the GI tract.[2] Additional absorption can occur through mucosal surfaces (ostomies) and abraded skin. Absorbed bismuth has a large volume of distribution and a terminal half-life of 21 to 72 days. Elimination is primarily through urinary and biliary routes. It remains detectable in blood and urine up to 5 months after the last oral dose.

Clinical Toxicity

Acute bismuth subcitrate overdose has resulted in decreased renal function with severe nephrosis and acute tubular necrosis.[4] Acute oliguric renal failure was observed in a 2-year-old boy three days after ingestion of 8.4 grams of colloidal bismuth subcitrate. His renal function returned to normal 20 days after exposure.[5] Neurological signs and symptoms are more prominent after chronic exposures, but tremors, lethargy, and weakness may occur after acute ingestion.

Increased salivation, bluish or brownish discoloration of the gums (bismuth line), black spots in the mucosa and gums, mucous membrane edema, ulcerative stomatitis and loss of teeth have been observed with chronic ingestion. Nausea, vomiting, diarrhea, and abdominal pain, acute nephritis, acute tubular necrosis, and renal failure are also commonly observed. Encephalopathy is the main chronic toxicity of insoluble bismuth salts. The majority of cases are reports from Europe and Australia, where bismuth is used chronically for odor control in patients with ileostomies and colostomies and it is systemically absorbed via the mucosal surface. Initial symptoms include weakness, fatigue, tremor, ataxia, myoclonus, and poor concentration. These symptoms may be followed by memory loss, visual and auditory hallucinations, and confusion.[2,6] Bismuth toxicity should be included in the differential diagnosis of patients with slow-onset encephalopathy or dementia. It may mimic Creutzfeldt-Jakob disease, Alzheimer's disease, Ramsay-Hunt Syndrome, viral encephalopathy, dichlorodiphenyltrichloroethane (DDT) toxicity, alcohol withdrawal, or chronic salicylate intoxication.

Diagnostic Tests

A complete blood count, serum creatinine, blood urea nitrogen (BUN), and urinalysis should be measured. Frequent bismuth determinations are not necessary. There are no bismuth concentrations that are absolute indications for instituting chelation or hemodialysis.

Chronic toxicity has been associated with a wide range of blood (50-1600 mcg/L) and urine (150-1250 mcg/L) bismuth concentrations.[7] The median concentration in patients with encephalopathy ranges from 680-700 mcg/L. Patients with concentrations greater than 100 mcg/L should stop therapy with bismuth salts.[8] Undissolved Pepto Bismol® tablets are radiopaque. Computed tomography brain scans may reveal an increased density in the cerebral cortex and basal ganglia. Hyperdensities in the basal ganglia, cerebellum, and cerebral cortex are most marked when bismuth blood concentrations exceeded 2000 mcg/L. Ventricular dilation may also be present.

Treatment

Treatment of overdose is largely symptomatic and supportive. A single dose of activated charcoal may be useful in preventing absorption shortly after ingestion. Dehydration may predispose the patient to renal injury and adequate hydration is necessary.[9] In general, spontaneous recovery from the encephalopathy and renal failure occurs weeks to months after cessation of exposure. Even after large overdoses, the prognosis is good.[1,4] Although enhanced elimination of bismuth has been demonstrated with chelation in animals and humans, treatment has not been shown to improve clinical outcome or limit toxicity.

Summary

Bismith toxicity is a very rare occurrence. It is worthwhile considering it in the differential diagnosis of patients with new-onset encephalopathy, dementia or delirium.

Martin Caravati, MD, MPH, FACMT

Ben Gebhhart, PharmD

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2C-B: Another Hallucinogenic Amphetamine

"Ecstasy" (MDMA) is a well-know hallucinogenic amphetamine often used at "raves" and clubs. Another lesser known compound is 4-bromo-2, 5-dimethoxyphenethylamine, which is structurally related to mescaline. It is also known as 2C-B, Nexus, Bromo, Afterburner, Spectrum and Eve. It is supplied as a powder, in a capsule or as a pressed tablet. It is much more potent than Ecstasy and may be sold under that name. Since 1995, 2 C-B has been classified as a schedule I drug. There is little overdose experience to date. Based on its pharmacology it may cause mydriasis, tachycardia, delirium, hallucinations, seizures and rhabdomyolysis. It may mimic anticholinergic poisoning. The onset of action is 20-90 minutes with a duration of 4-8 hours. It is not detected on common urine toxicology screens. Treatment is supportive with intravenous fluids for dehydration or rhabdomyolysis, and benzodiazepines for seizures and agitation.

Martin Caravati, MD, MPH, FACMT

The Utah Poison Control Center expresses its sincere thanks to

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UPCC Update Ephedra

On December 30, 2003, the Food and Drug Administration (FDA) announced its plan to ban the sale of dietary supplements containing ephedrine alkaloids. On February 6, 2004 the FDA issued regulation prohibiting sale of dietary supplements containing ephedrine alkaloids. This ban will go into effect 60 days after the initial rule is issued. The FDA has also issued a consumer alert that states that these products present an unreasonable risk of illness or injury.

There are several Ephedra species in the plant family Ephedraceae that contain the ephedrine and related alkaloids. The most common species is Ephedra sinica, also known as Ma Huang. The most common alkaloid found in ephedra sp. is ephedrine. Other alkaloids found include pseudoephedrine, norpseudoephedrine (a schedule IV controlled substance) and norephedrine (phenylpropanolamine). Not all species of Ephedra contain ephedrine and related alkaloids. Ephedra nevadensis, also known as Mormon tea is devoid of ephedrine and related alkaloids.

Ephedrine is a sympathomimetic amine with both alpha and beta adrenergic effects. It is a central nervous system stimulant. Agitation and insomnia are common adverse effects. Seizures and both hemorrhagic and ischemic strokes have been reported. Elevations in heart rate and blood pressure are common. Myocardial infarctions and cardiomyopathies have been reported.

Dietary supplements containing ephedrine alkaloids have been the center of controversy for many years. As early as 1995, the FDA formed a special working group on foods containing ephedrine alkaloids to discuss concerns about adverse health effects. In 1997, the FDA proposed a rule that would limit the amount of ephedrine alkaloids per serving and to strengthen the warning on the labels. After widespread industry opposition, the proposed rule was withdrawn in 2000. Several investigators evaluated data submitted to the FDA's adverse event monitoring system and the Government Accounting Office commissioned the Rand Corporation to formally study the health risks with ephedrine. The recent deaths of two high profile professional athletes highlighted the controversy. The National Football League has banned dietary supplements containing ephedrine alkaloids.

Other considerations that have increased the controversy concerning these agents are the promotion of some dietary supplements as alternatives to street drugs, the finding of synthetic ephedrine fortifying some dietary supplements containing ephedrine alkaloids and the inconsistencies in the alkaloid content versus label claims.

It appears inevitable that dietary supplements containing ephedrine alkaloids will be removed from the market in 2004. However, like the FDA ruling on phenylpropanolamine and droperidol, there will remain controversy as to what is absolute risk of adverse effects in the general population.

Many dietary supplements are already marketing "ephedra-free" products. In addition to containing caffeine, many of these products contain other sympathomimetic agents. Citrus aurantium, which contains the alkaloid synephrine, is a common substitute for Ephedra. While it is too soon to tell whether the same adverse health effects will be reported with these products, they are likely to occur based on the pharmacology of these substitutes.

Barbara Insley Crouch, PharmD, MSPH

News from the UPCC

The UPCC is now settled in at its new location. Please be sure to make note of our new address and phone number. As we mentioned last quarter, we also have a new phone system. We welcome your feedback on the new phone system and other aspects of the UPCC service.

In December 2003 President Bush signed into law the Poison Center Enhancement and Awareness Act Amendments of 2003. This law reauthorizes limited funding for poison centers. Funding is provided to poison control centers through a grant process with the Health Resources and Services Administration. This funding, approximately 7% of the UPCC's budget supports medical direction and outreach education activities.

The UPCC is very proud of the editorial activities of Dr. Caravati. Dr. Caravati was one of the lead authors for the third edition of Medical Toxicology released this fall. In addition he continues to maintain his activity as an Associate Editor for *Annals of Emergency Medicine*. Dr. Scott Marshall, Pharmacist-Specialist in Poison Information also contributed to the new edition of Medical Toxicology in the Poisonous Plants chapter.

Employment Opportunities

The UPCC has open positions available. You can find out more about these positions on our website at http://uuhsc.utah.edu/poison/employment.

Meet the UPCC Staff

Heather Bennett

Heather joined the UPCC as Assistant Director in January 2003. She was previously the software support team supervisor for AgencyWorks, a local software development company. After

completing an eight month management internship with the UPCC in 2002, Heather graduated with her Masters of Public Administration from the University of Utah. She is married with no children, but is currently raising and training an active beagle puppy. Hobbies include reading, scrapbooking, camping, hiking and traveling abroad.

Utah Poison Control Center Staff

Please send comments and suggestions for future articles to the editor of
UTOX Update at:
585 Komas Dr., Suite 200
Salt Lake City, Utah 84108
Or send e-mail to poison@hsc.utah.edu

*CSPI denotes Certified Specialist in Poison Information.

Poison Prevention Week

Each year National Poison Prevention Week is designated by Presidential proclamation and occurs during the third full week of March. It was authorized by Congress and the President in 1961. This year National Poison Prevention Week is March 21-27, 2004. The theme is "Children Act Fast, So Do Poisons."

In 2003, over 60% of the calls to the Utah Poison Control Center (UPCC) involved poison exposures in children less than 6 years of age. Many of these happen when adults are distracted for just a few moments, such as by the telephone or doorbell. Poison Prevention Week is a great opportunity to raise awareness of the dangers of unintentional poisonings and provide information on what steps can be taken to prevent unintentional poisonings.

Please call the UPCC at 1-800-222-1222 to request brochures, stickers, posters and magnets to distribute to your patients.

Intravenous N-Acetylcysteine

Intravenous N-Acetycysteine has been approved by the FDA. It is expected to be released in May. The product will be distributed by Cumberland Pharmaceuticals under the brand name Acetadote®. The generic name is registered as acetylcysteine. It will be supplied as a 20% solution in 30 mL single dose vials. It is approved for intravenous administration within 8-10 hours of potentially toxic acetaminophen ingestion. Stay tuned for additional information about this important addition to the treatment of acetaminophen

Utah Poison Control Center
585 Komas Dr., Suite 200
Salt Lake City, UT 84108

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