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COMPRISING THE NEW YORK CITY AND UPSTATE NEW YORK POISON CENTERS

Follow-Up from the New York City Poison Control Center Consultants' Conference of March 1, 2012

Are You What You Eat? Pica in Pregnancy

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Case

A 37 year-old woman from Kenya who gave birth to a child 2 months ago, presents to the ED with epigastric pain for one day. The patient reports that her abdominal pain started after she ingested several baked clay pellets that she had brought from Kenya and had been ingesting in low dose daily throughout her recent pregnancy. She denies any nausea, vomiting or diarrhea. Her vitals are: blood pressure, 106/71 mm Hg; heart rate, 72 beats/min; respiratory rate, 20 breaths/min; temperature, 97.8˚ F; oxygen saturation is 100% on room air. Her physical exam is only notable for mild epigastric tenderness without guarding or rebound. No abdominal masses are palpated.

What is pica and what is its epidemiology?

Pica describes a behavior of craving and subsequent purposeful ingestion of non-food substances.[1,2] Pica was documented as early as 400 B.C. by Hippocrates and continues to be practiced today. Pica is generally considered to be a chronic behavior (> 1 month).[1] There are three commonly described forms of pica, corresponding to three most frequently consumed non-food substances: geophagy – ingestion of earth (soil, clay or baked clay), amylophagy – ingestion of raw starch, and pagophagy – ingestion of ice.

Overall, geophagy occurs most often, especially among pregnant women and children, although the prevalence of pica and the non-food substances consumed vary geographically.[1-3] In Africa for example, geophagy is most common.[1,4] This may be related to the ready availability of soil and clay compared to ice and starch, which require financial resource and accessibility to commodities such as electricity and refrigeration. Overall, geophagy is practiced in approximately 50% of pregnant women in Africa, and in Uganda, up to 84% of pregnant women reported daily consumption of soil/clay.[4] In Latin America, the prevalence of pica ranges from 23 to 44% and in certain countries, pagophagy is more common than geophagy (e.g. Brazil – pagophagy: 70%; geophagy 18%).[1,5,6]

Pica in the U.S. has been traditionally described and studied in the Southern states.[1,5] However, the practice of pica can be found in all regions of the U.S., representative of the diverse demographic characteristic and socioeconomic background of the population. It is more commonly reported among socioeconomically disadvantaged women, living in rural and immigrant communities, and in women of African heritage.[3] The self-reported prevalence of pica was as low as 8% in a study of urban African-American women in Washington, DC, while up to 76% of pregnant African-American women in Houston,

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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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Are You What You Eat? Pica in Pregnancy

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Texas reported pica.[1,7] Although ice was the most common non-food substance reportedly consumed among women in the US, a significant proportion of women still reported ingesting soil and other substances.[1,2,5]

Deeper layer of the soil, obtained > 60 cm below the topsoil, is typically consumed by pregnant women and is less likely to be contaminated by metals and other chemicals compared to the topsoil. It should be noted that children tend to ingest the topsoil.[9] In regions such as Africa, soil or clay is often obtained from termite mounds, walls of houses made from clay, or purchased in local markets and shops. Often, clay and baked clay pellets are exported to Europe and North America and sold in immigrant community stores to be consumed by the local ethnic population.[8]

Overall, the true prevalence of pica is likely higher in developed countries such as the U.S. where women may keep their practice secret, since pica is often considered "abnormal" and discouraged. The prevalence of pica in children also varies widely around the world (e.g. Zambia and Kenya, > 70% vs. New York, 1.7%), similar to the trend observed in pregnant women.[1,4]

What is the underlying etiology of the practice of pica/geophagy?

There is no clear unifying explanation to why pica occurs. Cultural beliefs, micronutrient deficiency – especially iron and calcium - hunger, and medicinal purpose may each play a role.[4,9] For example, among pregnant women in a coastal district of Kenya, 73% of the women ate clay regularly, a culturally accepted practice during pregnancy and practiced by women only, for its symbolic ties to fertility, reproduction, and ancestral blessing.[4] However, in the U.S. where pica is not culturally and medically accepted, it is still widely practiced by African-American women and women in both rural and immigrant communities.[3]

The most frequently cited hypothesis for pica is attributed to the concept of physiologic response – craving – due to the micronutrient deficiencies caused by pregnancy, especially iron. There is no evidence to suggest that micronutrient deficiencies can elicit a physiologic craving of pica substances. Several studies, in both developed and developing countries, have demonstrated that anemia and low hemoglobin concentration are commonly found in pregnant women who practiced pica.[1,3,4,6,7] However, a causal relationship remains unclear as studies of iron supplementation among children with anemia and pica failed to stop soil ingestion. Other micronutrient deficiencies, such as zinc and calcium, have also been investigated but the evidence is limited and the results, inconclusive.[1] Moreover, a large majority of the women who reported "craving" for the non-food substance cited an affinity towards the substance's taste, odor, and the texture as reasons for their ingestion.[2,3] Thus, practice of pica is most likely driven by a complex interplay of multi-factorial etiologies that warrant further investigation.

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Are there potential adverse consequences of pica to the mother and her fetus?

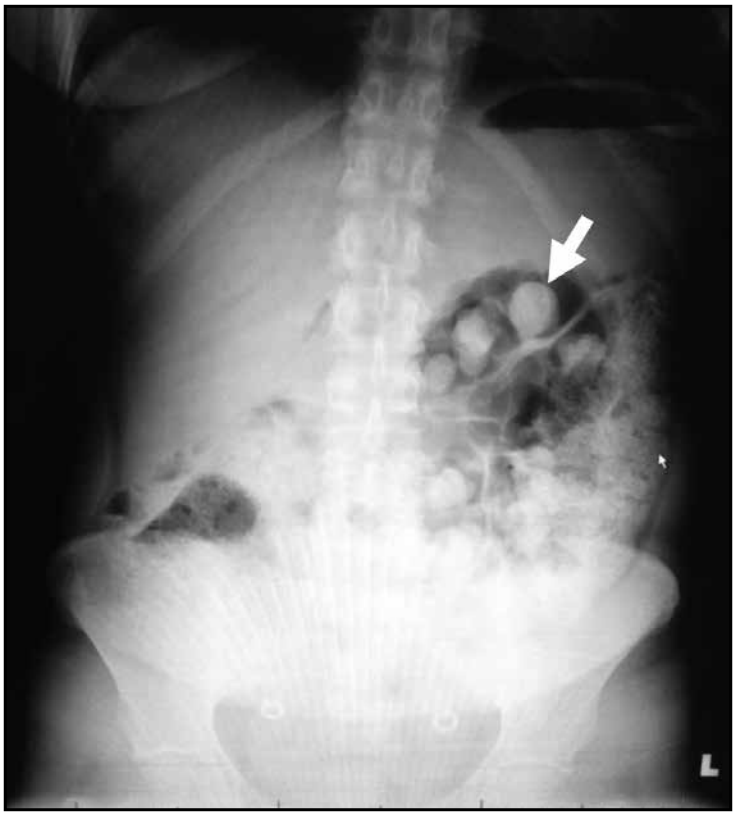
Depending on what is consumed, geophagy can result in exposure to metals, including lead, arsenic, mercury and cadmium, or other chemicals (such as pesticides). Some of these toxic chemicals may be naturally present or they may be due to environmental contamination by man. The most frequently concerning toxins are the metals, particularly lead, which is nearly all human derived. In one study, testing of the clay/soil samples from Africa, Europe, and the U.S. showed high mean lead concentration (40 mg/kg) compared to cadmium (0.053 mg/kg) and mercury (0.055 mg/kg).[8] Similarly, a UK study showed elevated concentrations of arsenic and lead in the imported baked clay from Bangladesh. It was estimated that daily clay ingestion could result in 3 and 6 fold greater exposure to arsenic and lead, respectively, compared to the WHO's recommended maximum daily intake.[10] Among pregnant women in New York City with elevated blood lead concentrations, geophagy (clay, brick or ceramic) was associated with significantly higher lead concentration and higher incidence of premature birth.[2]

In general, the effect on the fetus from maternal exposure to metals results in a wide spectrum of complications, including premature birth, spontaneous abortion, and permanent neurocognitive or neurodevelopmental deficits. Although the bioavailability of lead is limited compared to other heavy metals, it crosses the placenta readily and accumulates in the fetal tissues throughout gestation, potentially affecting neurodevelopment even at low exposure.

In Sub-Saharan African countries, geophagy has been associated with a high prevalence of infection with *Ascaris lumbroides* that can contribute to malnutrition and the development of iron deficiency anemia (IDA) in pregnant women.[4] However, IDA associated with geophagy did not affect the obstetric outcomes such as birth weight and length, gestational age or head circumference.[3,6]

How should a patient with geophagy be managed in the emergency department?

There is no evidence-based approach to managing a patient with pica. However, patients who ingested clay pellets should be managed as those with the ingestion of any foreign body. Although, the risk of perforation and a need for emergent endoscopic removal is low, baked clay pellets can potentially cause obstructive symptoms. Radiologic imaging such as abdominal x-ray and CT scan of the abdomen should be considered as needed and can be helpful in efforts to assess size and location of the foreign body, and for signs of intestinal obstruction.



Abdominal x-ray showed multiple round foreign bodies (white arrow) were identified in several loops of colon.

Laboratory testing may be of limited utility. However, a low hemoglobin concentration may be suggestive of chronic lead poisoning, as may the presence of basophilic stippling in the peripheral blood. Anemia with a reduced mean corpuscular volume (MCV) and high red cell distribution width (RDW) can also be suggestive of iron deficiency anemia. Since the source of the soil is often unknown and the potential risk of harm to the fetus is high, a blood lead concentrations should be obtained in any pregnant woman performing geophagy and probably in all patients with geophagy.

Primary intervention for a patient with an elevated blood lead concentration is to stop further exposure. The patient should be given a gastrointestinal agent such as polyethylene glycol electrolyte solution to assist in evacuation of the GI contents to decrease further GI absorption. Chelation therapy poses a unique challenge in pregnant women due to the theoretical association with teratogenicity in early pregnancy. However, symptomatic pregnant women with elevated concentrations of lead or other metals should be considered for maternal chelation therapy although there are only limited data to suggest a benefit to the fetus. When considering chelation therapy for a pregnant woman, consultation with a medical toxicologist or regional poison center may help to

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A Strange Concoction: A Focus on Aspirin's Toxicokinetics

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Case

A 42-year old male presents to the emergency department after ingesting what he described as a concoction of crushed aspirin tablets and promethazine liquid two hours ago. The patient's mental status was alert but combative, requiring sedation with lorazepam and haloperidol. Vital signs included: temperature, 37.9˚C; blood pressure, 104/80 mmHg; heart rate, 99 beats per minute; respiratory rate, 22 – 28 breathes per minute; oxygen saturation, 100% on room air. Physical examination was remarkable for dilated, sluggish pupils, warm, flushed skin and negative bowel sounds. The initial basic metabolic panel returned with significant findings including a bicarbonate of 22 mEq/L and a calculated anion gap of 15. An initial arterial blood gas showed a pH of 7.37, a pCO_2 of 30 mmHg, a pO_2 of 177 mmHg, and a bicarbonate of 22 mEq/L. An initial salicylate level (drawn about two and half hours after the ingestion) was 53 mg/dL. The acetaminophen level was negative. Alkalinization with sodium bicarbonate was started.

What is the kinetics of aspirin at therapeutic doses?

After oral administration, aspirin is rapidly absorbed via passive diffusion from the stomach and the small intestine.[1] A fraction of the parent compound undergoes pre-systemic and first-pass hydrolysis to salicylic acid, which is the metabolite responsible for the toxic effects of aspirin.[1, 2, 5] Absorption is delayed by modified-release formulations, such as enteric-coating, secondary to delayed disintegration.[3, 4] Once absorption occurs aspirin and salicylic acid distribute throughout the body.[5] Salicylic acid is highly protein bound and the bound fraction is dependent on concentration.[5-7] Biotransformation occurs via a variety of hepatic pathways including: 1) conjugation with glycine to form salicyluric acid; 2) conjugation with ether glucuronide to form phenolic glucuronide; 3) conjugation with ester glucuronide to form acylglucuronide; and 4) oxidation to form gentisic acid.[8] The conjugation reactions represent the major metabolic pathways and occur via a capacity-limited reaction.[9] At lower therapeutic doses metabolism is concentration-dependent and the half-life of salicylic acid is 2 to 4 hours.[10-12] At higher therapeutic doses (greater than 600 mg), the primary metabolic pathways become saturated and metabolism occurs at a fixed rate independent of concentration.[5, 13] As a result disproportionate increases in salicylic acid concentration and half-life occur.[5] Excretion occurs primarily via renal elimination as the following metabolites: 1) salicyluric acid (75%); 2) phenolic glucuronide (10%); 3) unchanged salicylic acid (10%); 4) acylglucuronide (5%); and 5) gentisic acid (1%).[8] The salicylate conjugates and salicylic acid are freely filtered through the glomerulus and secreted into the proximal tubule.[14] The salicylate conjugates do not undergo renal reabsorption due to their poor lipid solubility.[14] Salicylic acid, on the other hand, can be reabsorbed through the proximal tubule via passive processes.[14]

Case continuation

Approximately 5 hours later the patient's mental status was obtunded. Vital signs included: temperature, 36.6˚C; blood pressure, 99/51 mmHg; heart rate, 82 beats per minute; respiratory rate, 26 breathes per minute; oxygen saturation 97% on 3L nasal cannula. A repeat basic metabolic panel was within normal limits. A repeat salicylate level, drawn 4 hours after the first level, was 56.4 mg/dL. A repeat arterial blood gas showed a pH of 7.39, a pCO_2 of 36, and a bicarbonate of 22 mEq/L. Alkalinization and supportive care continued.

Two hours later mental status was unchanged. Significant findings on a repeat basic metabolic panel included a potassium of 5.0 mEq/L. A repeat salicylate level at this time was 103.1 mg/dL. Alkalinization continued and the patient underwent emergent hemodialysis.

Five hours later the patient was awake and conversing. Dopamine was started for low blood pressure. Vital signs were otherwise unchanged. A repeat arterial blood gas showed a pH of 7.5 with a bicarbonate of 23 mEq/L. A five hour post-hemodialysis salicylate level was 72.6 mg/dL. Alkalinization continued and the dialysis catheter was left in place. A repeat salicylate level several hours later was 84 mg/dL.

Why was an increasing salicylate level observed after hemodialysis?

Case reports of peak salicylate levels occurring 24 and 35 hours after overdose have been reported.[16, 17] Delays in absorption can be potentially explained by a variety of factors. Disintegration and dissolution must precede absorption. In overdose the sheer volume of drug per liquid substrate is increased and the time required for dissolution will likely be increased as well.[20] Modified-release formulations, such as enteric-coating, slow disintegration which minimizes surface area and slows absorption.[4, 5] However, delays in peak concentrations are seen with both immediate and modified-release preparations in overdose.[15, 19] Therefore, factors other than formulation must alter aspirin/salicylic acid absorption in overdose. Aspirin absorption is directly related to gastric/gastrointestinal residence time and factors that prolong residence time, such as food, co-ingestants that slow gastrointestinal motility (such as promethazine) and salicylate-induced pylorospasm, will likely also increase aspirin/salicylic acid absorption.[17, 18] Additionally, both aspirin and salicylic acid are weak acids. At gastric pH the fraction of unionized aspirin is increased and an increase in gastric residence time may occur due to slowed dissolution.[21] As a result there is an increased possibility of concretions, which have been identified with overdose.[22]

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What other kinetic factors are altered in an aspirin overdose? (What are aspirin's toxicokinetics?)

At therapeutic concentrations salicylic acid is highly protein bound and has a volume of distribution that ranges between 150 to 200 mL/kg.[23] However, with increasing doses saturation of protein binding occurs and its volume of distribution increases due to a higher unbound plasma fraction.[5] Conditions that lower serum pH, such as salicylate-induced metabolic acidosis, will also favor the formation of a higher fraction of unionized salicylic acid and enhance tissue distribution and concentration because non-polar molecules transverse biologic membranes more easily.[13] Additionally, hepatic enzymes are exposed to higher salicylic acid concentrations in overdose and saturation of the two primary glucuronidation pathways occur.[5, 13] As a result metabolism occurs at fixed rate independent of concentration.[9, 13] Disproportionate increases in plasma concentration and half-life occur with increasing doses.[12] Therefore, the half-life and overall exposure time is more pronounced at higher doses. As these hepatic pathways become overwhelmed the fraction of salicylic acid eliminated in the urine decreases while the fraction of unchanged salicylic acid increases.[24] Since salicylic acid can undergo renal reabsorption, elimination could be potentially slowed due to the renal reabsorption.

How can understanding the toxicokinetics of aspirin improve patient care?

Understanding a drug toxicokinetics can greatly impact patient management. As absorption is impacted by gastric/gastrointestinal residence time, interventions that reduce gastrointestinal transit time, such as activated charcoal and whole bowel irrigation, may limit absorption.[25] Additionally, a higher fraction of salicylic acid is ionized when the pH is more alkaline, reducing distribution into tissues.[26] Serum alkalinization with intravenous sodium bicarbonate is an effective option that reduces tissue penetrance and concentration.[26] It is important to understand that orally administered alkalinization has no therapeutic benefit and can actually be potentially harmful. Increased ionized gastric fractions secondary to gastric alkalinization will increase dissolution and, therefore, absorption.[27] Urinary alkalinization with intravenous sodium bicarbonate also increases the urinary ionized fraction, improving renal salicylate elimination by reducing renal reabsorption and increasing free salicylate secretion in the proximal tube.[14, 28] Finally, xenobiotics cleared via hemodialysis typically are water soluble, have low molecular weights, and are not highly protein bound.[29] Thus, in overdose the fraction of protein bound salicylic acid decreases and the fraction available for elimination via hemodialysis increases.

Case conclusion

Based on the increasing salicylate level observed after hemodialysis it is reasonable to assume that this patient still had a significant gut burden. Factors that prolong gastrointestinal residence time such as the anticholinergic promethazine, salicylate-induced pylorospasm and delays in dissolution could have contributed to this patient's prolonged absorptive phase. The patient acutely decompensated in the face of the rising salicylate level and expired prior to another session of hemodialysis could be initiated. An understanding of factors that influence aspirin's toxicokinetic behavior, particularly absorption, may have reenforced the potential negative implications with an increasing salicylate level after extracorporeal removal. An appreciation of a xenobiotic's kinetic behavior and the changes that occur in overdose can have a substantial impact on patient management and should be considered in potentially toxic patients.

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clarify the risks and benefits of maternal chelation therapy. Once postpartum, the blood lead concentration of the neonate should be checked and managed according to accepted guidelines.

Case resolution

An abdominal x-ray showed multiple foreign bodies in several loops of colon without radiologic signs of intestinal obstruction. Large amount of stool was also noted. (Image) Patient's laboratory evaluation showed hemoglobin of 9.7 g/dL, decreased MCV of 62.6 fL, and elevated RDW of 24%, suggestive of underlying iron deficiency anemia. Remaining laboratory evaluation was unremarkable. The lead concentration was undetectable. During her ED course, the patient remained in stable condition with improvement of abdominal pain. She was subsequently discharged with PEG to facilitate the passage of the baked clay pellets and given instruction to discontinue her pica habit and follow up with her primary care doctor.

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Select FDA Recalls July-October 2012

- **New England Compounding Center (NECC) Potentially Contaminated Medication: Fungal Meningitis Outbreak** [UPDATED 10/06/2012] Recall from NECC with full list of products is now linked. CDC and FDA recommends all health care professionals cease use and remove from their pharmaceutical inventory any product produced by the NECC. Originally Posted 10/05/2012
- **Hospira Lactated Ringer's And 5% Dextrose Injection, 1000 Ml, Flexible Containers: Recall - Mold Contamination** Voluntary Nationwide Recall Of One Lot. Injections of mold could potentially lead to septicemia, which in a worst-case scenario may have the potential to progress to septic shock, which may be life threatening. Posted 10/06/2012
- **Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/500 mg (Watson Laboratories): Recall - Potential for Oversized and Superpotent Tablets** Ingestion of excessive amounts of acetaminophen may result in liver toxicity, severe liver damage, or death. Posted 09/24/2012
- **Mojo Nights and Mojo Nights for Her: Recall - Undeclared Drug Ingredient** Product marketed as dietary supplement contains drug ingredients tadalafil and sildenafil, which may interact with nitrates found in some prescription drugs and lower blood pressure to dangerous levels. Posted 09/21/2012
- **Mirapex (pramipexole): Drug Safety Communication - Ongoing Safety Review, Possible Risk of Heart Failure** FDA currently evaluating analysis of randomized clinical trials and epidemiologic studies. Posted 09/19/2012
- **Intestinomicina (contains chloramphenicol) by Laboratorios Lopez: Safety Alert - Contains Drug Ingredient Withdrawn from US** Intestinomicina contains chloramphenicol, drug ingredient withdrawn from the US due to the risk of serious and life threatening injuries. Posted 09/18/2012
- **ACTRA-Sx 500 Capsules by Body Basics Inc.: Recall - Undeclared Drug Ingredient** The active drug ingredient, Sildenafil, may interact with nitrates found in some prescription drugs and lower blood pressure to dangerous levels. Posted 09/18/2012
- **Over-The-Counter Topical Muscle and Joint Pain Relievers: Drug Safety Communication - Rare Cases of Serious Burns** Some of the burns had serious complications requiring hospitalization Posted 09/13/2012
- **EphBurn 25 Dietary Supplement by Brand New Energy: Recall - Undeclared Drug Ingredient** Adverse effects associated with ephedrine alkaloid-containing supplements may include elevated blood pressure, rapid heartbeat, nerve damage, muscle injury, psychosis, memory loss, heart attack, stroke, seizure and death. Posted 08/31/2012
- **Revatio (sildenafil): Drug Safety Communication - Recommendation Against Use in Children** Recent long-term clinical pediatric trial showed children taking a high dose of Revatio had a higher risk of death than children taking a low dose. Posted 08/30/2012
- **Reumofan Plus: Recall - Undeclared Drug Ingredient** UPDATED 08/28/2012. The FDA has received dozens of additional adverse event reports, including death and stroke, associated with the use of Reumofan Plus since the agency issued its first warning about the product. Originally posted 06/01/2012.
- **Hospira Propofol Injectable Emulsion: Recall - Glass Vial Defect** Risks associated with this defect could include tissue necrosis in one or more organs that could result in stroke, myocardial infarction, respiratory failure, and loss of renal and hepatic function. 08/16/2012
- **Hospira Hydromorphone Hydrochloride Injection 2 MG/ML, 1 mL fill in 2.5 mL Carpuject: Recall- May Contain More Than The Intended Fill Volume** Opioid pain medications such as hydromorphone have life-threatening consequences if overdosed. Posted 08/16/12
- **Codeine Use in Certain Children After Tonsillectomy and/or Adenoidectomy: Drug Safety Communication - Risk of Rare, But Life-Threatening Adverse Events or Death** Ultra-rapid metabolizers are more likely to have higher than normal amounts of morphine in their blood after taking codeine. High levels of morphine can result in breathing difficulty, which may be fatal. Posted 08/15/2012
- **Benzalkonium Chloride Antiseptic Wipes by Dukal: Recall - Potential Microbial Contamination** Use of contaminated wipes could lead to infections, some of which pose health risks in immune-suppressed patients. Posted 08/01/2012
- **X-ROCK 3 Day Pill For Men and Z-ROCK: Recall - Undeclared Drug Ingredient** Undeclared active ingredient may interact with nitrates found in some prescription drugs (such as nitroglycerin) and lower blood pressure to dangerous levels. Posted 07/24/2012
- **Ampyra (dalfampridine): Drug Safety Communication - Seizure Risk for Multiple Sclerosis Patients** Patients with kidney impairment may develop higher blood levels of the drug, thereby increasing their seizure risk. Posted 07/23/2012
- **iFlora Kids Multi-Probiotic and iFlora 4-Kids Powder Dietary Supplements: Recall - Possible Salmonella Contamination** Consumers possessing these products should immediately discontinue their use. Posted 07/10/2012
- **Leucovorin Calcium Injection (Bedford Laboratories): Recall - Visible Particulate Matter** Particulate matter has been recognized as a potential health hazard causing numerous adverse reactions. Posted 07/06/2012

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