Acute Selenium Toxicity Associated With a Dietary Supplement

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Background: Selenium is an element necessary for normal cellular function, but it can have toxic effects at high doses. We investigated an outbreak of acute selenium poisoning.

Methods: A case was defined as the onset of symptoms of selenium toxicity in a person within 2 weeks after ingesting a dietary supplement manufactured by “Company A,” purchased after January 1, 2008. We conducted case finding, administered initial and 90-day follow-up questionnaires to affected persons, and obtained laboratory data where available.

Results: The source of the outbreak was identified as a liquid dietary supplement that contained 200 times the labeled concentration of selenium. Of 201 cases identified in 10 states, 1 person was hospitalized. The median estimated dose of selenium consumed was 41,749 µg/d (recommended dietary allowance is 55 µg/d). Frequent reported symptoms included diarrhea (78%), fatigue (75%), hair loss (72%), joint pain (70%), nail discoloration or brittleness (61%), and nausea (38%). Symptoms persisting 90 days or longer included fingernail discoloration and loss (52%), fatigue (35%), and hair loss (29%). The mean initial serum selenium concentration of 8 patients was 751 µg/L (reference range, ≤125 µg/L). The mean initial urine selenium concentration of 7 patients was 166 µg/24 h (reference range, ≤55 µg/24 h).

Conclusions: Toxic concentrations of selenium in a liquid dietary supplement resulted in a widespread outbreak. Had the manufacturers been held to standards used in the pharmaceutical industry, it may have been prevented.

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Selenium is a naturally occurring mineral required for good health. It is obtained from food, and the recommended dietary allowance is 55 µg/d for persons 14 years or older, with a tolerable upper intake limit of 400 µg/d. The amount of selenium available in a diverse diet with meat, grains, vegetables, and nuts is typically sufficient to negate the necessity for supplementation. Selenium toxicity can occur with acute or chronic ingestion of excess selenium. Symptoms of selenium toxicity include nausea; vomiting; nail discoloration, brittleness, and loss; hair loss; fatigue; irritability; and foul breath odor (often described as “garlic breath”).

Selenium is found in the environment in soil. Soils of certain areas in the Great Plains and western United States as well as other parts of the world have high concentrations of selenium, which are taken up by plants. For example, chronic selenium toxicity was endemic in parts of China until recently. Outbreaks of acute selenium poisoning are rare, but have been reported.

In March 2008, a chiropractor in Florida noted common symptoms of gastrointestinal illness and hair loss among several of his patients. In response to their symptoms, these patients had doubled the dose of a dietary supplement they had purchased at the chiropractic office. The patients subsequently noted worsening symptoms, including nail discoloration. Two couples contacted the local health department, where investigators identified the common exposure and initiated an investigation. Active case finding was initiated by the local health department, including contacting the chiropractor, who provided a list of patients to whom the dietary supplement had been sold. These patients were interviewed. Simultaneously, the US Food and Drug Administration

See Invited Commentary at end of article
(FDA) initiated an independent investigation as a result of similar complaints, at which time other agencies, including the poison control center and state health department, were notified. The dietary supplement was identified as the common exposure among all affected persons.

METHODS

A case of selenium poisoning was defined as hair loss, nail discoloration or brittleness, or 2 or more of the following symptoms: muscle or joint pain, headache, foul breath, fatigue/weakness, gastrointestinal symptoms, or cutaneous eruption. Symptom onset must have occurred within 2 weeks after the person ingested a liquid dietary supplement manufactured by Company A, purchased after January 1, 2008.

Case finding was conducted on a national level through multiple mechanisms. Company A’s list of all retail locations and persons who had placed an Internet or telephone order for the implicated product was obtained. State health departments contacted retail outlets within their respective states and obtained lists of consumers known to have purchased the implicated product. A voluntary product recall and FDA and state press releases stimulated spontaneous self-reports of consumption and illness to state health departments, poison control centers, and the FDA’s Safety Information and Adverse Event Reporting System (MedWatch). Attempts were made to contact any person who reported consumption of the supplement, as well as those listed as product recipients with either the company or a retail distributor.

A questionnaire was administered to 227 affected persons identified in 9 states: Florida, Georgia, Kentucky, Michigan, North Carolina, Pennsylvania, Tennessee, Texas, and Virginia. In addition, 5 states (Florida, Georgia, Michigan, North Carolina, and Tennessee) administered follow-up questionnaires approximately 90 days after the initial interviews.

Questions addressed demographics, amount of product consumed, symptoms, and dates of onset and resolution of symptoms. The selenium dose was calculated as grams of selenium consumed per kilogram of body weight, after the date on which the first bottle of contaminated product had been opened.

Seven affected patients in Tennessee provided 24-hour urine specimens for testing of selenium concentration at the time of initial interview and at 1 week and 1 month thereafter. Standard laboratory methods were used to determine urine selenium concentrations, compared with blank controls. Testing was performed at the Vanderbilt University Medical Center, Nashville, Tennessee. Eight patients provided results of serum selenium testing ordered by their physicians from commercial laboratories.

Information about the product was obtained from Company A. After the outbreak was recognized, the FDA conducted inspections of the manufacturing and supply plants and tested the product from the implicated lots to measure selenium concentration.

Data were analyzed by using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). This investigation was determined by the Centers for Disease Control and Prevention’s human subjects review to be a public health outbreak response.

RESULTS

The implicated product was marketed as a dietary supplement, as stated on the label and the Internet, suitable for the “entire family” to provide a balance of nutrients to “maintain energy and sustain health.” The product contained a blend of 16 vitamins, 12 elements with labeled concentrations and 58 “trace elements,” 18 amino acids, 3 essential fatty acids, Spirulina, coenzyme Q10, and antioxidants, suspended in an ionic colloidal liquid. The label instructions directed adults to take 1 capful (1 fl oz [30 mL]) of the supplement daily, or one-half teaspoon (2.5 mL) for each 20 lb (9.07 kg) of body weight daily for children 5 years or older. On the basis of the reported symptom complex and the laboratory test results of the implicated product obtained by the distributor, selenium was suspected to be the source of illness. The product was labeled as containing 200 µg of selenium per fluid ounce (30 mL) in the form of sodium selenite, an inorganic form of selenium. The FDA subsequently tested the product and determined the selenium concentration to be 40 800 µg/1 oz, approximately 200 times the labeled concentration. Chromium was also identified as being elevated at 17 times the labeled concentration of 200 µg/1 oz. This was less than the amount known to cause adverse health effects among either humans or animals. None of the affected patients reported symptoms typical of chromium toxicity (eg, gastrointestinal hemorrhage, liver dysfunction, renal failure). All other tested ingredients were within the labeled concentrations.

The incriminated lots of 1200 bottles of the product were manufactured in September 2007, and distribution began in January 2008. Product distribution was primarily in the eastern United States, with the highest concentration in the Southeast. This was reflected in the geographic distribution of cases (Figure 1). The product was recalled in late March 2008.

Structured telephone interviews were administered to all persons identified as having consumed the product. Of 227 consumers, 201 (89%) met the case definition for selenium poisoning. The remaining 26 consumers who did not meet the case definition reported no or mild symptoms. Illness onset extended from January 5 through June 11, 2008 (Figure 2). The median patient age was 54 years (range, 4-92 years) and 121 (60%) were female. One hundred forty-nine (74%) were white, and 15 (7%) were black. At the time of the initial interview, 118 (59%) of the patients had sought care at private physicians’ offices, clinics, or emergency departments; 83 (41%) had not brought their symptoms to medical attention. One patient was hospitalized; none died.

The median period over which patients had consumed the misformulated product was 29 days (range, 1-109 days). Among 156 patients with data available, the median estimated amount of selenium ingested was 989 mg (range, 41-5875 mg), for a median of 41 585 µg/d (range, 3400-244 800 µg/d; recommended dietary allowance, 55 µg/d). Among 98 patients with weight and dose available, the median dose ingested was 12.8 mg/kg (range, 0.5-115.4 mg/kg).

The most frequently reported symptoms included diarrhea (78%), fatigue (72%), hair loss (70%), joint pain (67%), nail discoloration or brittleness (61%), nausea (57%), and headache (45%) (Table 1). The proportion of scalp hair lost ranged from 10% to 100%, with a median of 50%. foul breath (37%) and cutaneous eruption (26%) were also commonly reported.

A follow-up questionnaire was administered to 104 of 150 patients (69%) in Florida, Georgia, and Tennessee, at a median of 106 days (range, 43-206 days) after...
Among patients originally reporting specific symptoms and who were interviewed 90 days or more after symptom onset, symptoms persisting 90 days or more included fingernail discoloration and loss (52%), fatigue (35%), hair loss (29%), joint pain (26%), memory loss (22%), and muscle aches (22%) (Table 2).

Of the 78 patients reporting hair loss, 14 (18%) reported complete loss of scalp hair. One patient (1%) reported total body hair loss. Of the 74 patients who reported fingernail discoloration or brittleness, 28 (38%) reported nail loss.

Initial serum selenium concentrations were obtained from 8 patients at a median of 1 day after cessation of product consumption (range, 0-33 days). Initial serum selenium concentrations ranged from 321 to 1500 µg/L, with a mean of 761 µg/L and a median of 664 µg/L; 3 were higher than 1000 µg/L (reference mean, 125 µg/L). Initial urine specimens from 7 patients were obtained at a median of 9 days after cessation of product consumption (range, 6-37 days). Initial urine selenium concentrations ranged from 55 to 227 µg/d, with a mean of 166 µg/d and a median of 179 µg/d (reference mean for Tennessee residents, 55 µg/d).

Table 1. Reported Symptoms of Selenium Toxicity After Consuming a Misformulated Dietary Supplement

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients, No. (%) (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>156 (78)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>144 (72)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>140 (70)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>135 (67)</td>
</tr>
<tr>
<td>Nail discoloration/brittleness</td>
<td>122 (61)</td>
</tr>
<tr>
<td>Nausea</td>
<td>115 (57)</td>
</tr>
<tr>
<td>Headache</td>
<td>90 (45)</td>
</tr>
<tr>
<td>Tingling</td>
<td>78 (39)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52 (26)</td>
</tr>
<tr>
<td>Fever</td>
<td>43 (21)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>27 (13)</td>
</tr>
</tbody>
</table>

Symptoms

Figure 1. Distribution of cases of acute selenium poisoning after ingestion of a misformulated dietary supplement

Figure 2. Epidemic curve by date of onset of illness after consumption of a misformulated dietary supplement. The arrow indicates date of voluntary product recall.

Product recall

No. of Cases

Month/Week (2008)

Diarrhea

Fatigue

Hair loss

Joint pain

Nail discoloration/brittleness

Nausea

Headache

Tingling

Vomiting

Fever

Ataxia

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The supplement was distributed by Company A, a small privately owned company in Atlanta, Georgia. The product had been on the market for 12 years without any reported problems. Company A received the finished product from a manufacturer in Arkansas, which in turn received ingredients from suppliers in Louisiana.

The FDA conducted inspections of the manufacturing and supply plants after the outbreak was identified. Company A had recently changed the manufacturer of the product, and the misformulated lots were the first lots produced after the change. Employee error at one of the ingredient suppliers was determined to be the cause of the increased selenium in the product.

A misformulated liquid dietary supplement resulted in 201 cases of selenium poisoning, but the actual number of affected persons was likely greater. Outbreaks of selenium poisoning are rare; the last occurred in 1983 and involved 12 persons who had consumed inappropriately potent selenium tablets as a dietary supplement.\(^7\,8\) A single case of selenium poisoning in 1996 was attributed to vitamins with elevated amounts of selenium.\(^9\) Occasional cases of acute selenium poisoning are caused by unintentional or suicidal ingestion.\(^3\) Most recently, 21 polo ponies died after receiving a supplemental injection containing toxic amounts of selenium.\(^13\) Collaboration among epidemiologists, clinicians, and toxicologists during this outbreak provided an opportunity to identify the circumstances that led to the event, describe the clinical manifestations and their duration, and observe the kinetics of serum and urine selenium concentrations among affected persons.

Case reports and epidemiologic studies from previous poisonings, foreign and domestic, reveal a wide range of symptoms similar to those described herein.\(^1\,5\,8\,13\,14\) Notably, approximately one-fourth of the patients (23%) in this outbreak reported fever, a symptom not previously associated with selenium toxicity. Although only 3 patients had recorded their temperatures, they were substantially elevated at 38.4°C to 39.5°C. Whether fever can be attributed directly to selenium toxicity, represents a general sense of malaise, or is the result of concurrent infection could not be determined.

Persistence of symptoms was also notable; patients often continued to experience symptoms 90 days after the exposure to selenium had ended. This was true not only for the hair and nail changes, which are expected to require substantial time to return to normal, but also for constitutional symptoms, including memory loss, mood swings, fatigue, musculoskeletal complaints, and garlic breath.

Progression of symptoms with time often mirrors the distribution of selenium from its entry into the gastrointestinal tract to the well-perfused internal organs and to other less-perfused tissues.\(^1\,5\,14\,17\) Excessive amounts of selenium commonly cause gastrointestinal effects (eg, diarrhea and vomiting). Subsequent distribution of excessive amounts of selenium into musculoskeletal tissues has been reported to cause muscle pain and cramps as well as joint pain. There are no proven antidotes or curative treatments for selenosis. Treatment involves stopping the exposure and providing supportive care for symptoms.\(^1\)

The serum selenium concentrations in this outbreak were all substantially elevated and were comparable to or higher than values previously reported in association with selenium toxicity from dietary supplements.\(^5\,13\,18\) Although they were lower than values that have been reported after attempted suicides.\(^3\) The serum selenium concentrations reported during this outbreak are high for subjects ingesting inorganic forms of selenium. Ingestion of organic selenium in the form of selenomethionine is associated with much higher serum selenium concentrations than ingestion of inorganic forms.\(^10\) Biological samples (eg, urine and serum) correlate poorly with the degree of toxicity among humans. Selenium undergoes a unique concentration-dependent triphasic elimination. Depending on the actual dose ingested, different and unpredictable serum levels of selenium can result. As evidenced during this outbreak, selenium is sequestered in different organ tissues, and its slow metabolism accounts for the persistence of symptoms.\(^1\,5\,17\,20\,21\)

This episode of selenium toxicity caused by a misformulated commercially distributed dietary supplement presented unique clinical and public health challenges. Given the rarity of selenium toxicity, along with the array of nonspecific symptoms, recognizing the diagnosis can be difficult. Furthermore, a substantial proportion of patients had not yet sought medical attention at the time they were contacted by public health investigators. During interviews, patients often stated they had not suspected that a health product made them ill, and thus never mentioned to their health care providers that they were taking the implicated dietary supplement, despite experiencing weeks of unexplained symptoms. Patients even reported increasing their dose in an attempt to ameliorate symptoms. This highlights the importance of patients informing their health care providers about all dietary supplements, herbal remedies, and over-the-counter medications, in addition to prescription medications.

After recognition of the initial cluster, additional case finding was conducted by tracing sales of the product,
press releases to the general public, referrals from patients calling poison control centers, FDA field offices, and FDA’s MedWatch. Because of nonspecific symptoms and limited health care–seeking behavior among affected persons, the outbreak was probably even larger than recognized.

This investigation was limited by potential recall bias among patients and a limited number of clinical specimens available for laboratory testing. While the observation of fever in some patients is interesting, we were unable to determine conclusively that selenium toxicity was the cause. There were also substantial barriers to sharing proprietary or personally identifiable information among investigating agencies. Policy differences regarding the sharing of identifiable information among federal, state, regulatory, and nonregulatory agencies are complex and can impede the efficient flow of sensitive data, even during an acute outbreak investigation. In this case, for example, identifiable information from persons calling MedWatch was not shared directly with the health departments. Rather, FDA staff had to ask the callers to contact the health department themselves.

Unfortunately, examples abound in which dietary supplements have been associated with toxicity. Human error during manufacturing resulted in toxic concentrations of selenium in this dietary supplement. Dietary supplements such as vitamins, minerals, and herbal products are not subject to premarket review or approval for safety, efficacy, or Good Manufacturing Practices (GMPs). Under the Federal Food, Drug, and Cosmetic Act, the manufacturer of a finished dietary supplement product is responsible for ensuring the safety and the quality of the final product, which includes all ingredients received from suppliers. That responsibility includes testing of received ingredients, including premixed ingredients and the final product, for compliance with predetermined specifications for identity and composition. In September 2007, the FDA issued guidelines for the gradual implementation of GMPs on the basis of the number of employees of a manufacturer of dietary supplements. However, the GMP regulations, which govern the manufacturing process but not necessarily the outcome, were not required of all suppliers and final manufacturers at the time of processing the product implicated during this outbreak. Had the manufacturers been held to standards used in the pharmaceutical industry, this outbreak may have been prevented. Gaps in existing regulations present a significant public health risk, and attention should be directed at correcting them to prevent recurring outbreaks such as this.

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**The Dietary Supplement Health and Education Act**

**Time for a Reassessment**

In 1994, Congress enacted the Dietary Supplement Health and Education Act (DSHEA), a law that dramatically changed the way in which supplements are regulated. In addition to broadening the definition of a dietary supplement to include vitamins, minerals, herbs or botanicals, amino acids, and any combination of these substances, the DSHEA allowed manufacturers to market their products without submitting proof of efficacy or safety to the Food and Drug Administration (FDA). Dietary supplements were assumed to be safe unless proven otherwise by the FDA through postmarket surveillance. In addition, under the DSHEA, manufacturers and distributors of dietary supplements were not required by law to record, investigate, or forward to the FDA any reports of illnesses that may have resulted from the use of their products. In response to a number of serious adverse events linked to the supplement epidemics and the disclosure of such events by manufacturers, Congress passed the Dietary Supplement and Nonprescription Drug Consumer Protection Act in 2006, which mandated reporting of serious adverse events. Then, given a significant number of reports of product contamination and false or incomplete labeling, the FDA released its final rule for Current Good Manufacturing Practices (cGMPs) for the supplement industry in 2007, stating that manufacturers are required to evaluate the identity, purity, strength, and composition of their dietary supplements. By June 2010, all domestic and foreign companies that manufacture, package, label, or hold dietary supplements must be in compliance with the 2007 rule. MacFarquhar and colleagues deftly walk through the epidemiologic investigation that resulted in identification of a dietary supplement containing toxic levels of selenium. Their detailed description of the investigative process and the barriers to efficient root cause analysis is laudable. While the human error in the manufacturing process of the source ingredients occurred before the deadline of the cGMP phase-in period, the error may not have been prevented even if cGMPs had been in place. As the authors note, only firms that manufacture, label, or hold dietary supplements are subject to cGMP regulations and that firms making or supplying the source ingredients—as was the case here—are not subject to these regulations.

In addition to manufacturers of dietary supplement source ingredients being exempt from cGMP regulations, there are additional loopholes that undermine the reach and effectiveness of the existing dietary supplement regulations. For example, the final rule requires that manufacturers, not the FDA, determine the quality specifications for their products. Companies that want to use less stringent specifications can do so without penalty. More importantly, the FDA has scant resources for dietary supplement oversight, which makes enforcement of cGMPs unlikely. Only approximately 4% of the FDA’s Center for Food Safety and Nutrition resources is dedicated to dietary supplements.

While the legislative remedies undertaken in recent years have served to address discrete issues and strengthen the DSHEA, an evaluation of this controversial legislation, 15 years after its passage, is warranted to determine whether it has served in the spirit with which it was intended. Congressional support for the passage of the DSHEA essentially revolved around 4 main points. First, it was designed to allow consumers access to safe dietary supplements. Second, it was intended to improve the health of Americans. Third, it was favorably viewed as a means of empowering consumers to make choices...