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ADVERSE EVENTS WITH DIETARY SUPPLEMENTS

by Emily Goldman, PharmD Candidate

Introduction

Dietary supplement use is widespread in the United States. During 2007, 17.7% of adults and 3.9% of children used some type of non-vitamin, non-mineral, natural product (e.g. fish oil, ginseng).[1] Due to a unique regulatory environment, the safety of these products has been poorly established and adverse effects often come to light after the supplement has been marketed. For example, the FDA has recently issued warnings about loss of smell with the use of Zicam®, a popular homeopathic cold remedy that has been on the market since 1999.[2] A number of unique concerns must be considered when evaluating adverse events in the context of dietary supplement use.

Regulatory Background

Passed in 1994, the original Dietary Supplement Health and Education Act (DSHEA) placed the burden of proof for the safety of dietary supplements on the Food and Drug Administration (FDA). This act also established passive reporting of adverse events, including those possibly related to supplement use.[3] Reporting became mandatory in December 2007 with the enactment of the Dietary Supplement and Nonprescription Drug Consumer Protection Act, which requires manufacturers, packers, and/or distributors of dietary supplements to report any serious adverse events associated with the use of their product.[4] In the same year, the FDA also began requiring Good Manufacturing Practice (GMP) compliance by dietary supplement manufacturers—a practice originally sanctioned by DSHEA 13 years earlier.[5]

The vast difference between the regulation of prescription or over-the-counter medications and the regulation of dietary supplements is not fully appreciated by the public. Fifty-nine percent of respondents on a 2002 nationwide poll believed that supplements were approved by a government agency prior to marketing, 68% thought manufacturers were required to include accurate warning labels about the possible side effects of the supplement and 55% thought all safety claims were backed by solid scientific evidence. None of these assumptions are correct.[6]

Accurate Drug Histories

The first roadblock in assessing adverse events due to dietary supplements is the omission of dietary supplements from patients' medication histories. In an extension of the widespread belief that supplements are "natural" and therefore incapable of harm, many patients do not think their health care provider needs to know about their supplement use. In addition, perceived or real antagonism between Western medicine and alternative medicine can make patients reluctant to disclose their supplement use. All healthcare providers need to consciously expand their effort to accurately define a patient's supplement use by directly but sensitively questioning all patients, especially when investigating a possible adverse drug event.

Known Adverse Effects & Interactions

All healthcare facilities should have access to accurate and up to date references describing the known adverse effects associated with specific dietary supplements. Excellent references are available in print and online. Suggested references include Natural Medicines Comprehensive Database (online and print versions available) and Natural Standard (online).[7] Healthcare workers should be familiar with the toxicity profiles of the most popular supplements in their area and those supplements with well described toxicity (e.g. ephedra). Healthcare organizations may want to begin by familiarizing their staff with supplements with established hepatic, renal or cardiac toxicity since these conditions are easily detected and inherently dangerous. It is also important to have a reliable method of receiving updates on dietary supplements including new reports of adverse effects or recalls of specific products. *(cont. on pg. 2)*

IN THIS ISSUE

PEDIATRIC MEDICATION OVERDOSES & EMERGENCY DEPARTMENT VISITS

Recent data from the Slone Survey indicates 82% of adults and 56% of children take at least one medication every week.[1,2] Approximately 50% of poison exposures in children less than 6 years of age reported to poison control centers involve medications. This high frequency along with the increasing number of medicines stored in the home is a formula for medication overdoses.

To explore this public health problem, researchers from the CDC used the National Electronic Injury Surveillance System (NEISS) characterized poisoning-related emergency department (ED) visits in children.[3] Of the estimated 103,441 ED visits for poisoning over a 2 year period, 68.9% were attributed to medication-related poisonings categorized as 1) unsupervised ingestions, 2) medication errors, and 3) misuse. The rate of ED visits was highest among children <3 years of age.

The most common medications involved in medication-related ED visits were: acetaminophen, cough and cold medications, antidepressants, and nonsteroidal anti-inflammatory drugs. Most (97%) ED visits in children 1-5 years were attributed to unsupervised ingestions. In infants less than 1 year of age, approximately 25% of medication-related ED visits were attributed to medication errors.

Incorrect dosing was the most common medication error, followed by use of incorrect formulation.

Most pediatric poisonings are preventable. Strategies to reduce poison exposures in young children include:

1. educating caregivers to keep medicine out of reach of children
2. using child-resistant packaging or single dose units
3. reviewing units of measure and proper dispensing devices with caregivers
4. reminding caregivers about products with similar ingredients
5. developing policies to enhance medication safety awareness

References

1. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, & Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA. 2002;287(3):337-344.
2. Vernacchio L, Kelly JP, Kaufman DW, & Mitchell AA. Medication use among children <12 years of age in the United States: results from the Slone Survey. Pediatrics. 2009;124(2):446-54.
3. Schillie, SF, Shehab, N, Thomas, KE, Bidnitz, DS. Medication Overdoses Leading to Emergency Department Visits Among Children. Am J Prev Med. 2009;37(3):181-187.

(cont. from pg. 1)

Dietary Supplements

Drug interactions must also be considered when evaluating a patient for possible adverse drug events associated with supplement use. Pharmacokinetic and pharmacodynamic interactions have been well characterized for a few supplements (e.g. St. John's Wort) but the majority of supplements have not been well studied in the context of drug interactions.[7]

Alternatively, the poison control center is an excellent resource for information on adverse effects and interactions due to dietary supplements. In addition to their access to and familiarity with established references, poison centers may consult on multiple patient cases involving specific dietary supplements allowing them to establish a knowledge base about those products. In 2007, US poison centers handled 21,687 cases related to dietary supplements. Adults over 19 years of age accounted for 15% of cases, 10% occurred in adolescents and remaining cases were in children less than 6 years old. Seven percent of these exposures were due to adverse reactions occurring with therapeutic use of the supplement.[8] Poison centers are accessible 24 hours a day and staffed by pharmacists and nurses who are trained in the evaluation of adverse events due to dietary supplement use.

Contamination & Adulteration

Supplements have been fraught with contamination and adulteration controversies. Unfortunately for consumers, one of the most prevalent forms of "adulteration" of dietary supplements is products that do not contain any of the stated ingredients. Patients should be advised to look for the United States Pharmacopeia (USP) seal on products to increase the chance the bottle contains what the label claims and does not contain any unwanted substances.[9]

In addition, unregulated plant growth and harvesting can lead to heavy metal contamination of plant products, as has been documented in patient case reports and laboratory analysis of randomly selected dietary supplements on the market. This problem is most common in supplements imported from Asia.[9] Increasing enforcement of "good manufacturing practice" requirements should decrease heavy metal contamination, however, safety cannot be guaranteed, especially with products ordered over the internet. Herbal supplements are also subject to errors of misidentification—a classic example being the substitution of Aristolochia (a known renal toxin) into a Chinese herbal supplement because its Chinese name is *(cont. on pg. 3)*

NATIONAL POISON PREVENTION WEEK MARCH 14-20, 2010

National Poison Prevention Week, established in 1961, provides an opportunity to heighten awareness to the poisoning problem. More than 2 million poisonings are reported to poison control centers in the U.S. each year. Poisonings are preventable. Help us celebrate National Poison Prevention Week by spreading the poison prevention message.

Visit our website for educational resources:
www.utahpoisoncontrol.org

(cont. from pg. 2)

Dietary Supplements

similar to another product.[9]

Dietary supplements can also be adulterated with prescription medications. The FDA has compiled a list of weight loss products found to be contaminated with prescription medications such as sibutramine and fluoxetine. Published in December 2008, the original list included 28 products and has since expanded to include 72 products by March of 2009.[10] Unfortunately, only 3 of those weight-loss supplements had been voluntarily recalled as of March 2009.[11]

Other Concerns

The widespread use of dietary supplements can complicate health care and the diagnosis and treatment of adverse events in more subtle ways as well. Members of the lay public are often confused when the FDA issues warnings about dietary supplements but those products are not removed from the market, as is the current case with Zicam® and the weight loss supplements mentioned above. This gives the illusion that the adverse events are not as serious as the FDA is stating and consumers continue to use the product.

In addition, carcinogenicity studies on dietary supplements are rare and there are products on the market, like DHEA, that have shown tumorogenesis in rats. There is also the concern that belief in the superiority of alternative medicine will lead to a delay of medical care. Dietary supplements, when labeled appropriately, are clearly not indicated for the treatment of disease and should not be used that way—especially when more effective options are available.[9]

One common factor between prescription medications and dietary supplements is patients' tendency to use multiple agents. Consider the challenge of evaluating a young adult woman who complains of abdominal pain, fatigue, weakness, shortness of breath, headaches, irregular menstrual cycles and odor sensitivity when the only notable history is the use of 15 different dietary supplements, 7 of which are combination products.[3] As with prescription drugs, the use of multiple products greatly complicates the ability to tease out the offending agent when a patient is experiencing an adverse effect. Unique to supplements, however, is the extensive use of combination products—many of which include "proprietary blends" where the manufacturer is not required to disclose specific ingredients.

The sheer number of dietary supplements on the market and the rate at which new products appear is a concern in itself. Staying abreast of all new products and their possible adverse effects is a monumental task simply not possible in most healthcare settings. Therefore, healthcare providers are better off focusing on building a basic general knowledge while keeping watch for new major adverse events in their patients or as announced by the FDA.

Most dietary supplements do not come with child resistant packaging and, those purchasing and using dietary supplements should be urged to keep them well out of the reach of children. All products should be assumed toxic until proven otherwise.[3]

Reporting Adverse Events

Manufacturers of dietary supplements are required to report adverse events associated with their products to the FDA but the enforcement and efficacy of this legislation is still unproven. All healthcare providers are encouraged to be proactive in reporting adverse events to the FDA through MedWatch (http://www.fda.gov/Safety/MedWatch/). The Natural Medicines Comprehensive Database website also recently launched a similar program in an attempt to increase knowledge of adverse events with dietary supplements.

Conclusion

Healthcare providers should have a basic understanding of dietary supplements and the special concerns that surround their use. Information about supplement use is an essential part of a thorough medication history—especially in the setting of possible adverse events or toxicities. Patients must be taught to treat these substances with the same respect as any medication while understanding that dietary supplements are not nearly as well studied.

References

1. Barnes PM, Bloom B, Nahin R. CDC National Health Statistics Report #12. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. December 10, 2008
2. Harris, G. FDA warns against use of popular cold remedy. The New York Times. June 17, 2009. Accessed online: http://www.nytimes.com/2009/06/17/health/policy/17nasal.html?_r=1&sq=zicam&st=cse&scp=1&pagewanted=print on 22 June 2009.
3. Woolf AD. Safety evaluation and adverse events monitoring by poison control centers: A framework for herbs and dietary supplements. Clin Toxicol 2006; 44:617-622.
4. Dietary Supplement and Nonprescription Drug Consumer Protection Act. Public Law 109-462. 2006.
5. FDA issues dietary supplements final rule. US Food and Drug Administration Press Release. 22 June 2007. Accessed online 10 June 2009 at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108938.htm.
6. Dangerous supplements: Still at large. Consumer Reports 4 May 2004.
7. Haller CA. Clinical approach to adverse events and interactions related to herbal and dietary supplements. Clin Toxicol 2006; 44:605-610.
8. Bronstein AC, Spyker DA, Cantilena LR, Green JL, Rumack BH, Heard SE. 2007 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25TH Annual report. Clinical Toxicology 2008; 46:927-1057.
9. Smolinske SC. Herbal product contamination and toxicity. J Pharm Prac 2005; 18:188-208.
10. FDA uncovers additional tainted weight loss products. US Food and Drug Administration Press Release. 20 March 2009. Accessed online 27 March 2009 at: http://www.fda.gov/bbs/topics/NEWS/2009/NEW01977.html
11. Singer N. Study urges more oversight of dietary items. The New York Times. March 4 2009.

POISON PEARLS

PROPOFOL ABUSE

Courtney Wilson, MD
Emergency Medicine Resident

Propofol is a sedative hypnotic medication that is widely used in anesthesia, long-term sedation, and conscious sedation. It is short acting, effective and safe when used appropriately. However, studies suggest that propofol is increasingly used as a recreational drug with deadly consequences. There is ample evidence supporting propofol's abuse potential from a biochemical and experiential standpoint. Multiple case reports describe tolerance and withdrawal phenomena, as well as dependence, abuse and even death from recreational use of this drug. After reviewing the literature of propofol's abuse potential, it is clear that it has alluring and addictive properties that can lead to misuse, dependence, and abuse. Moving propofol under the US DEA regulation as a controlled substance may be helpful to limit its availability and curtail the potential for propofol abuse.

TOXINS IN THE NEWS

- **Zinc-containing nasal cold remedies** have been associated with chronic and permanent **loss of smell.** Several products have been removed from the market.
- FDA issued a Boxed Warning for **IV promethazine**, due to **risk of severe tissue injury** following IV administration.
- **Sitagliptin** (Januvia®) has been associated with **acute pancreatitis**.
- **Exenatide** (Byetta®) has been associated with **acute renal insufficiency and failure.**

M-44 SODIUM CYANIDE

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Bureau of Wildlife Services would like us to remind you that the M-44 sodium cyanide device is used in Utah. The device is tubular and is placed in the ground with 1.5 inches sticking out of the ground baited with meat. This device is used in specific situations to control coyotes, redfox, gray fox and wild dogs. The purpose of the device is to protect livestock, poultry, and endangered species and to prevent the spread of disease. Although this device is primarily used on private lands, it may also be used on federal land in any county in the state. Areas where it is used are marked with signs. While human exposure to this device would be extremely unlikely, it is important to know that this device contains 91% sodium cyanide. Please report any exposure to this device to the Utah Poison Control Center at (800) 222-1222. We thank you in advance for your assistance.

MEET THE UPCC STAFF

BRENDA CLAUSING

came to the Utah Poison Control Center in July 2008 as the Administrative Assistant. She was born and raised in Utah. Never having lived anywhere else she loves to travel to different places. Some of her favorite places to visit are: Virginia, Georgia, Hawaii and New York. Brenda and some of her family traveled to Disneyland in 2008. The highlight of that trip was to be able to spend one night in the Disneyland's Dream Suite. She has traveled only in the U.S. but hopes to actually use her passport one day. Brenda loves to read, go shopping, watch movies, and spend time with family and friends. When she can find the time, she also likes to knit, crochet, take pictures and scrapbook. A favorite activity is to get away and go camping with her children and grandchildren. Brenda and her husband (of a whole lot of years) have 4 children and 6 grandchildren, with another one due in July. She loves spending time with and spoiling her grandchildren. Brenda was a little scared when she was faced with finding a new job and has learned a lot since starting at the UPCC. She feels very lucky to have found this job, that from the very beginning felt like she had "come home". She continues to enjoy her job and the great people she has had an opportunity to work with.

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*CSPI denotes Certified Specialist in Poison Information.

THANK YOU

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.

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POISON HELP 1-800-222-1222