AMERICAN HEALTH CONSULTANTS

ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

Science-based Information for Clinicians

CME Test included with this issue

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Special Issue: Candy

Chocolate: Food, Drug, or Lifestyle?

By Charlea T. Massion, MD

Chocolate is great
Chocolate is grand
Melts in your mouth
Melts in your hand[1]

MANY WOMEN HAVE A PASSIONATE AND AMBIVALENT RELATIONship with chocolate. Chocolate is associated with romance (a seductive gift, a lover's apology) and solace (taking to bed with a box of tissues in one hand, a box of chocolates in the other). Many of us grew up believing chocolate consumption was associated with acne, obesity, and premenstrual binges. In recent years, chocolate has been recast as a benign, even healthful food. This article will explore some studies of chocolate and women's health.

As a taste of chocolate's past and future, the Swedish botanist Linnaeus titled the genus of cacao trees *Theobroma*, from *theo* for god and *broma* for food. *Theobroma cacao* has more than 20 types that are divided into three major groups: criollo (native); forastero (foreign); and a cross between the two, trinitario (sent from heaven).

Theobromas are small, rather delicate evergreens that thrive in hot, humid climates only if protected from direct sun. As a middlestory tree in Mesoamerican rain forests, wild cacao often grows under Madre de cacao (*Gliricidia sepium*), a larger tree that provides semi-darkness, nutrients from both leaf fall and the nitrogen-fixing bacteria in its roots, plus minute traces of coumarin that poison animals that crave cacao beans. However, the cacao depends on cacao-seeking vertebrates to reproduce, because its pods, even when fully ripe, do not drop off the tree.[2] In the rain forest, cacao seeds are dispersed by bats, rats, monkeys, and squirrels that gnaw through the pods to procure the sweet, mucilaginous pulp around the bitter seeds. (No studies have been done to ascertain if female, non-human vertebrates are more intense than males in their cacao bean-seeking behavior.)

Volume 3 • Number 12 • December 2001 • Pages 89-96

INSIDE

Cacao grows in a narrow band within 20 degrees of the equator, with the islands of Cuba at the northern boundary and Reunion at the southern boundary.[3,4] Cacaos begin to bear football-shaped fruit that are 7-10 inches long at four years of age. Fully mature at seven years, they can live up to 100 years, producing dozens of pods annually. Ripening pods change from green to red or purplish-yellow and are hand-harvested with a special machete. Each pod contains 20-50 seeds.[3]

Pharmacology

Please don't mention the chemical connection
Chocolate makes in my head
It's Swiss Miss I'm drinkin'
It's Hershey bars I'm thinkin'
If I can't be in love
I'll have a truffle instead[1]

Food or drug? Chocolate is the most commonly craved food in North America; one landmark study documents that chocolate accounts for almost half of all food cravings.[4] Is chocolate craving an indication of hypomagnesemia? If so, why don't millions of humans crave nuts and whole-grains instead? Is chocolate appealing simply because it is high in fat and sugar, or does it have drug-like effects? Chocolate does contain biologically active constituents; however, other pharmacologically related foods go unmentioned in art and science. Are chocolate cravings physiologically or psychologically based?

Pharmacological Effects

Chocolate's pharmacological components include biogenic amines, methylxanthines, and cannabinoid-like fatty acids. (Consider eating a piece of chocolate as you review these.)

Biogenic Amines

Several biogenic amines, notably tyramine and phenylethylamine (PEA), are present in chocolate. These amines have sympathomimetic effects, and, like nicotine, stimulate dopamine release in the brain. PEA, also known as the "love drug," is associated with various euphoric states, including the ecstasy experienced with cocaine, amphetamines, and occasionally, long-distance running.[5] PEA is distributed throughout the brain and is quickly metabolized by monoamine oxidase-β and aldehyde dehydrogenase to phenylacetic acid. PEA is a neuromodulator of mood, and depression is associated with reduced levels of PEA.[4]

Chocolate contains sufficient PEA (0.4-6.6 mcg/g) to convince some researchers that chocolate craving may be an attempt to increase the brain's PEA level and improve mood. However, certain cheeses and sausages contain much more PEA and tyramine, yet hardly have the following of chocolate. Also, since the half-life of PEA in serum is only 5-10 minutes, PEA ingestion may not raise systemic concentrations enough to influence the central nervous system level.[4]

MDMA (3,4 methylenedioxymethamphetamine, or Ecstasy) and PEA are structurally similar, and both are amphetamine analogs. One study of seven MDMA addicts noted that all had intense chocolate cravings and frequent chocolate binges. This study has led some experts to state, "This association of chocolate cravings with certain drug-induced psychoses suggests that the psychopharmacologic effects of chocolate deserve further attention."[4] However, as any intern who has been in emergency rooms between midnight and 5 am (possibly consuming machine-dispensed chocolate in large quantities themselves) knows, there are no chocolate overdose victims hooked up to respirators and no chocolate addicts in acute withdrawal screaming, cursing, and/or seizing as various intravenous drips modulate their central nervous system functions.

Methylxanthines

Chocolate also contains alkaloid methylxanthines, primarily theobromine (3,7 dimethylxanthine) and

Alternative Therapies in Women's Health, ISSN 1522-3396, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
MANAGING EDITOR: Paula L. Cousins.
GST Registration Number: R128870672.
Periodical rate postage pending at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Therapies in Women's Health***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $38. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

THOMSON
AMERICAN HEALTH

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcpub.com
Editorial E-Mail: paula.cousins@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$279 per year (Student/Resident rate: $110).
Multiple Copies
1-9 additional copies: $206 each; 10 or more copies: $183 each
Outside the United States
$309 per year plus GST (Student/Resident rate: $125 plus GST).

Accreditation

American Health Consultants (AHC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.
American Health Consultants designates this continuing medical education activity for up to 20 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity. This CME activity was planned and produced in accordance with the ACCME Essentials.
For CME credit, add $50.

Questions & Comments

Please call **Paula Cousins**, Managing Editor, at (816) 960-3730 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Education guidelines, physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. Cates, Dr. Fugh-Berman, Dr. Greenwood, Dr. Kronenberg, Dr. McPartland, and Dr. Massion have reported no relationships with companies related to the field of study covered by this CME program. Dr. Awang is a consultant for Leiner Health Products and Global Botanical/Health 4 All. Dr. Low Dog is a consultant for the Materia Medica Group. Dr. Pan is a researcher for Chitosan. Dr. Scialli has the following relationships: consultant for TAP and Merck; speaker for TAP; researcher for TAP, Wyeth-Ayerst, and Balance Pharma.

caffeine (1,3,7-trimethylxanthine). Both compounds are highly lipid-soluble and easily cross the blood-brain barrier. In the brain, methylxanthines are competitive inhibitors of adenosine. Caffeine also facilitates the release of epinephrine, amplifying its stimulatory effects.

Less research has been done on theobromine, which seems less stimulating and takes longer to reach peak pharmacologic effects than caffeine does. Administration of theobromine in capsules does not reduce chocolate craving symptoms, so it may have insignificant physiological and psychological effects. The presence of caffeine is unlikely to explain "chocolate addiction," since chocolate contributes little to most people's daily caffeine intake.[6] However, some speculate that caffeine and theobromine act synergistically, producing a greater effect than either alone.

Table

Mineral content for cocoa powder and chocolate liquor per 100 g

Nutrient	Cocoa Powder[a]	Chocolate Liquor[b]
Potassium	1495.50 mg	1023.80 mg
Iron	13.86[c] mg	13.52 mg
Magnesium	593.64 mg	314.17 mg
Zinc	7.93 mg	4.29 mg
Copper	4.61 mg	2.36 mg

[a] Cocoa powder, 10% fat.

[b] Chocolate liquor (unsweetened, bakers chocolate), 50% fat.

[c] USDA *Agriculture Handbook No. 8-19*: cocoa powder, unsweetened.

Source: Knight I, ed. *Chocolate and Cocoa: Health and Nutrition.* Oxford: Blackwell Sciences, Ltd.; 1999.

Cannabinoid-Like Fatty Acids

Chocolate contains biologically active compounds that target endogenous cannabinoid receptors in the human brain, causing effects similar to those of cannabinoid drugs (e.g., euphoria and heightened sensitivity). Anandamide, which means "internal bliss," is an endogenous brain lipoprotein that functions as an internal cannabinoid neuromodulator. Acting in the nucleus accumbens septi, cannabinoids increase activity of the mesolimbic dopamine reward system by potentiating endogenous opioid receptors, and possibly by altering the action of other neurotransmitters (e.g., dopamine, histamine, serotonin, acetylcholine, norepinephrine, and prostaglandins).[4]

Chocolate contains *N*-acylethanolamines, which may mimic or potentiate anandamide's activity, producing a sense of well-being.[7] Another group, however, disputed this theory,[8] which remains controversial *(see* Alternative Therapies in Women's Health, *March 1999)*.

Chocolate and Behavior

With all that in mind, which component of chocolate causes cravings, "chocolate addiction," and chocolate-induced behaviors? One study that attempted to separate chocolate's pharmacological activity from its sensory factors found no physiological basis for chocolate craving. This crossover study compared chocolate bars, cocoa in capsules, white chocolate (cocoa butter without chocolate's other components), white chocolate plus cocoa capsules, no chocolate, and placebo on the satiation of chocolate craving in 72 students.[9] Only 34 students completed at least one observation for each "treatment." (Apparently the appetite of this population for participation in scientific studies was very easily satisfied.) Milk chocolate, for better or worse, served as the standard for craving relief. Results: White chocolate received intermediate scores, and cocoa capsules brought no greater craving relief than placebo.

Anecdotally, many women report that their chocolate craving increases premenstrually. One placebo-controlled, double-blind, crossover study tested the effects of progesterone and alprazolam on premenstrual craving for chocolate or sweets.[10] Subjects in this study were in the Premenstrual Syndrome (PMS) Program at the University of Pennsylvania, were between the ages of 18 and 45, and had regular menses and no current major psychiatric diagnoses. Forty-four women met the criteria for cyclic chocolate craving and 44 met the criteria for cyclic sweet craving; 34 women satisfied criteria for both. Records were kept for two baseline cycles. During the third cycle, subjects were treated with placebo, alprazolam, or oral micronized progesterone. Treatments were administered from day 21 until the second day of menses. Results: Neither progesterone nor alprazolam decreased either chocolate or sweet craving. (Although progesterone has been used for many years to treat PMS, progesterone actually may cause or amplify premenstrual anxiety and depression, so the results of the progesterone arm of this study are hardly surprising.)

How about modulation of affect and craving in "chocolate addicts"? One study of 40 women explored the interaction of mood and chocolate intake.[11] Twenty self-identified "chocolate addicts" and 20 controls kept seven-day diaries of hunger, mood, craving intensity, and amount of chocolate consumed. The chocolate addicts ate significantly more chocolate more often than controls did. They also had higher guilt, depression, and craving scores; lower relaxation and contentment scores before eating chocolate; and more guilt without relief of

depressive feelings after eating chocolate. Chocolate addicts scored higher than controls on indices of depression and disordered eating. Consuming chocolate, unfortunately, did not improve their indices. All around, "chocolate addicts" were unable to enjoy eating chocolate, and their moods remained anxious and/or depressed, even with high chocolate intake.

Antioxidants and Nutrients

Cocoa is warm
Fudgsicles chill
Whatever the form
It's always a thrill
Chocolate is love[1]

Chocolate may be good for the heart both figuratively and literally. Do you know that if you found chocolate purchased by your mother during her childhood, you could use it to bake a cake today? And that bar of melted chocolate you found at the bottom of a backpack last used 10 years ago is still OK to eat? Chocolate doesn't spoil because it has very high concentrations of antioxidants, and it is possible that these antioxidants have beneficial cardiovascular effects.

Chocolate contains more catechins (polyphenolic flavonoids) than tea; dark chocolate contains 53.5 mg/100 g; milk chocolate contains 15.9 mg/100 g; and an infusion of black tea (1 g/100 mL water) contains 13.9 mg/100 mL. However, the catechin thought to have the most beneficial antioxidant effects, (-) epigallocatechin gallate (ECGG), occurs in tea but not chocolate.[12] *(See* Alternative Therapies in Women's Health, *October 1999.)*

Candy Bits

By Adriane Fugh-Berman, MD

"A spoonful of sugar helps the medicine go down."

IN THE ORIGINAL BOOK, THE MAGICAL NANNY MARY POPpins broke off her fingers, which were made of different flavors of candy, as treats for the kids (I guess that wasn't a wholesome enough image to use in the movie). Candy has long been used as a delivery system for medicine; sweetened syrups and tablets have been used to encourage children to ingest antibiotics, antitussives, vitamins, etc., and in recent years, fentanyl lollipops have been used to administer opiates to children. Medicinal candy isn't just for children: Oral capsaicin, a topical analgesic agent from chili peppers, has been incorporated into taffy and used to treat oral mucositis pain secondary to chemotherapy or radiation.[1]

Everyone agrees that candy is bad for the teeth, and can pose an aspiration risk in young children, but here are some more unusual risks of candy: Lead poisoning has been associated with several types of imported candy. The culprit appears to be lead in the wrappers, which leaches into the candy. After elevated lead levels in a child was traced to tamarind candy, two types of tamarind candy were tested by the Oklahoma County Health Department; the investigation found that more than half of the tamarind suckers tested exceeded the Food and Drug Administration level of concern for lead in this type of product.[2] Printed cellophane candy wrappers imported from Mexico also may present a significant risk for lead exposure.[3]

Essential oils used in candymaking can pose risks; an accidental ingestion of oil of wintergreen caused salicylate poisoning in an infant;[4] cinnamon oil contains cinnamaldehyde, which can cause dermal and mucosal irritation; a second-degree burn was reported in an 11-year-old who broke a cinnamon oil vial in his rear pants pocket and left the area unwashed for 48 hours.[5]

Several confections can cause bezoars. Three cases of intestinal tract and esophageal obstruction have been reported in children who ingested chewing gum.[6] Seven cases of bezoars associated with candied ginger root have been reported in children and edentulous elders.[7] ■

References

1. Berger A, et al. Oral capsaicin provides temporary relief for oral mucositis pain secondary to chemotherapy/radiation therapy. *J Pain Symptom Manage* 1995;10:243-248.
2. Lynch RA, et al. Lead-contaminated imported tamarind candy and children's blood lead levels. *Public Health Rep* 2000 ;115:537-543.
3. Fuortes L, Bauer E. Lead contamination of imported candy wrappers. *Vet Hum Toxicol* 2000;42: 41-42.
4. Howrie DL, et al. Candy flavoring as a source of salicylate poisoning. *Pediatrics* 1985;75:869-871.
5. Sparks T. Cinnamon oil burn. *West J Med* 1985;142:835.
6. Milov DE, et al. Chewing gum bezoars of the gastrointestinal tract. *Pediatrics* 1998;102:e22.
7. Corrigan D. *Zingiber officinale*. In: De Smet PAGM, et al, eds. *Adverse Effects of Herbal Drugs*. Vol 3. Berlin: Springer-Verlag; 1997.

For those concerned about fat intake, cocoa powder is an option, containing almost no fat but retaining antioxidant effects. Cocoa is a good option because it has more phenols by weight than bakers (unsweetened) chocolate, which in turn has more phenols than milk chocolate. A 41 g (1.5 oz) piece of milk chocolate contains 205 mg phenol, equivalent to the 210 mg phenol found in a 140 mL (5 oz) serving of red wine. An in vitro experiment found that cocoa phenols inhibited human low-density lipoprotein (LDL) oxidation by 75%,[13] and a clinical study found that LDL oxidation lag-time increased in the blood of 12 male volunteers after ingesting 35 g of cocoa.[14] Cocoa also has been shown to inhibit platelet aggregation.[15]

Chocolate also contains significant amounts of potassium, iron, magnesium, zinc, and copper *(see Table)*; a study using three-day dietary records found that chocolate is the largest source of mean daily copper intake.[16] So if you are a chocolate lover, you can feel fine about keeping chocolate in your diet!

(Thanks to Gary Ladd and Robert Steinberg, MD, for review of the manuscript.) ❖

References

1. "Chocolate is Love," a song by the Chenille Sisters.
2. Young AM. *The Chocolate Tree: A Natural History of Cacao.* Washington, DC and London: Smithsonian Institution Press; 1994.
3. Potts LK. Chocolate: Past, present and future of cacao. *HerbalGram* 1996;37:51-55.
4. Bruinsma K, Taren DL. Chocolate: Food or drug? *J Am Diet Assoc* 1999;99:1249-1256.
5. Ratey JJ. *A User's Guide to the Brain: Perception, Attention and the Four Theaters of the Brain.* New York: Pantheon Books; 2001.
6. Rozin P, et al. Chocolate craving and liking. *Appetite* 1991;17:199-212.
7. Di Tomaso E, et al Brain cannabinoids in chocolate. *Nature* 1996;382:677-678.
8. Di Marzo V, et al. Trick or treat from food endocannabinoids. *Nature* 1998;396:636.
9. Michener W, Rozin P. Pharmacological versus sensory factors in the satiation of chocolate craving. *Physiol Behav* 1994;56:419-422.
10. Michener W, et al. The role of low progesterone and tension as triggers of perimenstrual chocolate and sweets craving: Some negative experimental evidence. *Physiol Behav* 1999;67:417-420.
11. Macdiarmid JI, Hetherington MM. Mood modulation by food: An exploration of affect and cravings in 'chocolate addicts.' *Br J Clin Psychol* 1995;34:129-138.
12. Arts IC, et al. Chocolate as a source of tea flavonoids. *Lancet* 1999;354:488.
13. Waterhouse AL, et al. Antioxidants in chocolate. *Lancet* 1996;348:834.
14. Kondo K, et al. Inhibition of LDL oxidation by cocoa. *Lancet* 1996;348:1514.
15. Rein D. Cocoa inhibits platelet activation and function. *Am J Clin Nutr* 2000;72:30-35.
16. Joo SJ, Betts NM. Copper intakes and consumption patterns of chocolate foods as sources of copper for individuals in the 1987-88 nationwide food consumption survey. *Nutr Res* 1996;16:41-52.

Licorice and Women's Health

By Adriane Fugh-Berman, MD

Our audience is like people who like licorice. Not everyone likes licorice, but the people who like licorice really like licorice.

—Jerry Garcia

LICORICE CANDIES ARE VERY POPULAR IN MANY COUNtries, including Holland, Denmark, Finland, Sweden, Germany, Italy, and the United States. Licorice also is popular in beverages ranging from herbal teas to liqueurs (including arak, ouzo, and pastis); "brewer's licorice" may be added to porter and stout for both flavor and color.

Red or strawberry licorice (shudder) contains no licorice at all, and even black licorice in the United States usually is flavored with anise rather than licorice. Licorice from other countries is real licorice, and often is combined with salt, peppermint, or other flavors.

A perennial plant with sweet-tasting roots, licorice (*Glycyrrhiza glabra* L.) is native to Asia, Russia, the Middle East, and the Mediterranean, and is widely used as a flavoring, sweetener, and medicinal herb. Licorice root contains triterpenoid saponins, especially glycyrrhizin. Also called glycyrrhizic or glycyrrhizinic acid (GL), glycyrrhizin is 50 times sweeter than sugar, so licorice often is used as a natural sweetener, as well as a flavoring. GL is hydrolyzed to glycyrrhetinic acid (GA) in the intestine, apparently by intestinal bacteria.

Medicinal Use

Licorice and its derivatives were once used in conventional medicine in the United States for treating peptic ulcers, and numerous older studies found licorice and licorice compounds effective in ulcer treatment. However, the treatment fell out of favor because of side effects.[1]

The effect of licorice on cortisol levels once was exploited medicinally; licorice formerly was used to treat Addison's disease.[2] Licorice is one of the most common ingredients in traditional Chinese herbal mixtures, and also is used by Western herbal practitioners to treat mouth ulcers, peptic ulcers, cough, and respiratory infections, and as an anti-inflammatory and an immune system stimulant.

Licorice Toxicity

Reported cases of licorice toxicity have been associated with licorice-containing liqueurs, candies, chewing gum, laxatives, and chewing tobacco, not from the use of licorice in herbal medicine. Licorice is a very common component of Chinese and Western herbal medicines but almost always is used as part of a mixture (in addition to its therapeutic effects, the sweet taste of licorice may render some herbal mixtures more palatable). The synergistic effects of mixtures, as well as dose differences and short duration of use, may minimize adverse reactions.

Licorice inhibits 11β-hydroxysteroid dehydrogenase, which converts cortisol to cortisone. Cortisol has the same binding affinity as aldosterone, whereas cortisone has a lower binding affinity to mineralocorticoid receptors. In the kidney, inhibition of 11β-hydroxysteroid dehydrogenase produces high renal levels of cortisol, resulting in a state of apparent mineralocorticoid excess that resembles 11β-hydroxysteroid dehydrogenase deficiency.[3]

In 10 healthy volunteers, GL 500 mg/d produced marked glucocorticoid activity, elevating urinary excretion of free cortisol, decreasing urinary free cortisone, and decreasing plasma cortisone (plasma cortisol was unchanged).[4] Eleven volunteers given licorice for 10 days experienced decreased plasma renin activity and decreased urinary aldosterone, indicating significant suppression of the renin-angiotensin-aldosterone system. Urinary free cortisol rose in all subjects.[5] Suppression of the renin-angiotensin-aldosterone system may last for several months.[3] In men, licorice (7 g, containing 500 mg GL daily for a week) significantly decreased testosterone and 17-hydroxyprogesterone levels.[6]

Cardiovascular Effects

Many people, including myself, consume licorice incessantly with no problems. While the prevalence of licorice toxicity is unknown, it is not common. In Denmark, the average licorice consumption per person is 2 kg/yr, and no epidemics of licorice toxicity have been reported. One study of Danish school children between 6 and 18 years of age found no linear relationship between licorice consumption and blood pressure.[7]

Some individuals, however, are susceptible to licorice toxicity, and women seem more susceptible than men. The classic picture of licorice toxicity is pseudoprimary aldosteronism; symptoms may include edema, hypertension, and hypokalemia.[8,9] Cardiac arrest, including two deaths, have been associated with excessive licorice use. Cardiomyopathy also has been reported.[10]

Excessive acute use of licorice also can cause adverse effects. A case of hypertension encephalopathy was reported in a 15-year-old three hours after eating 0.5 kg licorice;[11] ingestion of 1 kg licorice by a 25-year-old woman with myeloid leukemia caused decerebrate rigidity, tetraparesis, and coma.[12] Pulmonary edema was reported in a previously healthy, 64-year-old man who had eaten four packages (1,020 g) of Twizzlers (one of the few American "licorice" brands that contains real licorice) over three days; total GL consumed was approximately 3.6 g.[13]

Ingestion of 100 g licorice daily for four weeks in 30 normotensive subjects resulted in a significant (6.5 mm Hg) increase in systolic blood pressure, which had not returned to baseline 2-4 weeks after licorice consumption ended.[14] Diastolic blood pressure did not change significantly. Serum potassium decreased 0.24 mmol/L.

This experiment found that women were more sensitive to licorice than were men; blood pressures were slightly higher for women and 14 of 19 women gained weight (mean 0.59 kg; one women gained 6.8 kg); there was no significant weight gain in men. The experiment was repeated in 13 women who had been in the original study. With a lower dose of 50 g licorice, systolic blood pressure rose 5.6 mm Hg and diastolic blood pressure rose 3.4 mm Hg.

Hypokalemia

An analysis of 59 cases of licorice-associated hypokalemic myopathy noted that many patients had additional risk factors for hypokalemia, including alcoholism, diarrhea, or diuretic use.[15] Severe hypokalemia may result in rhabdomyolysis. Several cases of licorice-associated rhabdomyolysis have been reported, including the case of a 62-year-old Muslim man on diuretic therapy who developed weakness and pain during the holy month of Ramadan, during which observers fast during the day and often consume a licorice-containing soft drink during the evening meal. Apparently the fasting, diuretic use, and licorice consumption proved synergistic for hypokalemia.[16]

Licorice and Preterm Birth

A survey of 1,049 Finnish women who gave birth to singleton infants in 1998 examined the effect of

licorice on birth outcome.[17] Almost half of the mothers surveyed (46%) reported weekly licorice consumption, and only 2.3% of respondents never consumed licorice during pregnancy. The women were grouped by glycyrrhizin exposure (low: < 250 mg/wk; moderate: 250-499 mg/wk; and heavy: > 500 mg/wk).

Compared to babies exposed to the lowest levels of maternal licorice, babies exposed to the highest levels were significantly more likely to be born before 38 weeks gestation (odds ratio 2.5, 95% confidence interval 1.1, 5.5, P = 0.03). Adjustments were made for sex, maternal age, parity, smoking, coffee consumption, and systolic blood pressure. Heavy licorice consumption was associated with a mean shortening of gestation of 2.52 days. The researchers suggest that possible mechanisms include inhibition of cortisol metabolism (cortisol stimulates corticotropin-releasing hormone from the placenta, and is thought to be a parturition trigger) or possibly increased uterine prostaglandin levels through inhibition of 15-β-hydroxyprostaglandin dehydrogenase (a homologue of 11-β-hydroxysteroid dehydrogenase).

Drug Interactions

Licorice potentiates corticosteroids; oral administration increases the plasma concentration of prednisolone and topical GL potentiates the action of hydrocortisone.[18]

Oral Contraceptives

Combined oral contraceptives may increase sensitivity to GA. Two cases of hypokalemia and hypertension were reported in oral contraceptive users who used licorice chewing gum; one consumed about 120 mg GL daily, and another consumed 50 mg GL daily (this is notable because these are low levels of consumption; most reports of adverse effects occur with consumption of ≥ 400 mg GL per day).[19]

Advising Patients

So what is a safe range for licorice ingestion? There is clearly significant individual variation; 100 mg GL daily (about 50 g or 1.75 oz of candy) can produce adverse effects in some people, and most people who consume more than 400 mg GL daily will experience symptoms.[3] Some individuals, however, are hypersensitive to glycyrrhizin; doses as low as 20 mg/d GL have produced severe hypokalemia.[20]

A no-effect level study in 39 healthy women tested the effects of orally administered GL (1, 2, and 4 mg/kg body weight) for eight weeks.[21] The authors proposed a no-effect level of 2 mg/kg, and extrapolated an acceptable daily intake of 0.2 mg/kg body weight. Assuming that licorice contains 0.2% GL, a 60 kg person should ingest no more than 6 g (one fifth of an ounce) of licorice (containing 12 mg GL) daily. ❖

References

1. Schambelan M. Licorice ingestion and blood pressure regulating hormones. *Steroids* 1994;59:127-130.
2. Groen J, et al. Extract of licorice for the treatment of Addison's disease. *N Engl J Med* 1951;244:471-475.
3. Størmer FC, et al. Glycyrrhizic acid in liquorice—evaluation of health hazard. *Food Chem Toxicol* 1993;31: 303-312.
4. MacKenzie MA, et al. The influence of glycyrrhetinic acid on plasma cortisol and cortisone in healthy young volunteers. *J Clin Endocrinol Metab* 1990;70: 1637-1643.
5. Stewart PM, et al. Mineralocorticoid activity of liquorice: 11-beta hydroxysteroid dehydrogenase deficiency comes of age. *Lancet* 1987;2:821-824.
6. Armanini D, et al. Reduction of serum testosterone in men by licorice. *N Engl J Med* 1999;341:1158.
7. Ibsen KK. Liquorice consumption and its influence on blood pressure in Danish school-children. *Dan Med Bull* 1981;28:124-126.
8. Farese RV Jr, et al. Licorice-induced hypermineralocorticoidism. *N Engl J Med* 1991;325:1223-1227.
9. Epstein MT, et al. Effect of eating liquorice on the renin-angiotensin aldosterone axis in normal subjects. *BMJ* 1977;1:488-490.
10. Chandler RF. *Glycyrrhiza glabra*. In: De Smet PAGM, et al, eds. *Adverse Effects of Herbal Drugs*. Berlin: Springer-Verlag; 1997.
11. Van der Zwan A. Hypertension encephalopathy after liquorice ingestion. *Clin Neurol Neurosurg* 1993;95: 35-37.
12. Hupperets P, et al. Reversible coma due to hypokalaemia in a patient treated for acute leukaemia. *Neth J Med* 1983;26:21-22.
13. Chamberlain JJ, Abolnik IZ. Pulmonary edema following a licorice binge. *West J Med* 1997;167:184-185.
14. Sigurjonsdottir HA, et al. Is blood pressure commonly raised by moderate consumption of liquorice? *J Hum Hypertens* 1995;9:345-348.
15. Shintani S, et al. Glycyrrhizin (licorice)-induced hypokalemic myopathy. Report of two cases and review of the literature. *Eur Neurol* 1992;32:44-51.
16. Achar KN, et al. Severe hypokalemic rhabdomyolysis due to ingestion of liquorice during Ramadan. *Aust N Z J Med* 1989;19:365-367.
17. Strandberg TE, et al. Birth outcome in relation to licorice consumption during pregnancy. *Am J Epidemiol* 2001;153:1085-1088.

18. Teelucksingh S, et al. Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. *Lancet* 1990; 335:1060-1063.
19. de Klerk GJ, et al. Hypokalaemia and hypertension associated with use of liquorice flavoured chewing gum. *BMJ* 1997;314:731-732.
20. Chubachi A, et al. Acute renal failure following hypokalemic rhabdomyolysis due to chronic glycyrrhizic acid administration. *Intern Med* 1992;31:708-711.
21. van Gelderen CE, et al. Glycyrrhizic acid: The assessment of a no effect level. *Hum Exp Toxicol* 2000;19: 434-439.

CME Questions

23. Chocolate contains significant amounts of:
a. calcium.
b. magnesium.

24. Premenstrual chocolate craving can be reduced with:
a. progesterone.
b. alprazolam.
c. both progesterone and alprazolam.
d. None of the above

25. Heavy licorice consumption during pregnancy has been associated with:
a. birth at or before 38 weeks gestation.
b. low birthweight.

26. Licorice consumption can cause:
a. hypertension.
b. hypokalemia.
c. edema.
d. All of the above

27. Cannabinoid-like substances cross-react with cannabinoids from *Cannabis* in urine immunoassays.
a. True
b. False

Clinical Abstracts

With Comments by Charlea T. Massion, MD, and John McPartland, DO, MS

The Chocolate Defense

Source: Tytgat J, et al. Cannabinoid mimics in chocolate utilized as an argument in court. *Int J Legal Med* 2000;113:137-139.

CHOCOLATE CONSUMPTION HAS BEEN used as a creative defense in a drug case. A 46-year-old prisoner whose urine tested positive for cannabinoids was accused of smoking and dealing marijuana. The defendant's lawyer argued that the accused had supposedly eaten a massive amount of chocolate, causing a false-positive test for *Cannabis* in the urine immunoassay. To investigate this possibility, *N*-oleoyl- and *N*-linoleoyl-ethanolamide (cannabinoid-like substances in chocolate) were synthesized and spiked together with the endogenous cannabinoid anandamide (*N*-arachidonoylethanolamide) in urine. At concentrations of 300 µmol and 1 mmol, immunoassay for cannabis was negative, indicating that no cross-reactivity occurs between cannabinoids in *Cannabis* and cannabinoid-like substances in chocolate. As a result, the lawyer's claim could be refuted and the accused was convicted.

Comments: "Cannabinoids" come in two varieties: the "exogenous" kind produced by marijuana plants, such as tetrahydrocannabinol (THC), and the "endogenous" cannabinoids, including anandamide. The two compounds are structurally dissimilar—THC is a tricyclic compound, while anandamide is a fatty acid derivative of arachidonic acid. It astonishes scientists that both compounds can activate the same brain receptors.

The lawyer's suggestion that an immunoassay would cross-react between the two compounds is really a stretch, similar to saying chocolate would cross-react with capsaicin (chili peppers). But then again, there are lots of stretches in the cannabinoid field: Saying anandamide is found in chocolate (even cocoa) is amazing, because its metabolic source, arachidonic acid, is not produced by plants. And *just* when you think you have it figured out: Scientists have discovered that vanilloid receptors, the receptors that are activated by capsaicin, also are activated by anandamide.[1] Keep tuned to these pages for updates! ❖

Reference

1. Szallasi A, Di Marzo V. New perspectives on enigmatic vanilloid receptors. *Trends Neurosci* 2000;23:491-497.

In Future Issues:

Pilocosanol

Marital Stress and Cardiovascular Disease

Breast Cancer, Night Work, and Melatonin