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Folate for the Prevention of Colon Cancer

By Michael F. Roizen, MD

ACCORDING TO FOOD AND DRUG ADMINISTRATION DAILY VALUE Guidelines,[1] most of us need folic acid supplements. The typical American diet has 300-400 mcg of vitamin B_9, or folate. That's more than Americans have been getting because the grain supply is now supplemented with 100 mcg of folate per 100 g of grain, yielding approximately 25 mcg in most servings of grain products in the United States. The intent of this fortification was to prevent birth defects, notably spinal cord malformations and nervous system deficits such as spina bifida.[2] Still, it's too little for optimal health in more than 75% of Americans.

Retrospective studies have shown a clear association between homocysteine levels and atherosclerotic disease. Dietary or supplemental folic acid can lower homocysteine levels by 5-6 micromol/L with a daily intake of 400 mcg.[3] Recent evidence indicates folic acid supplementation is also beneficial for men who wish to father children as it increases sperm count (by 40% in subfertile men).[4]

There is now substantial evidence that if we don't take folate for those reasons, we should take it to prevent colon cancer. We should make sure we and our patients get enough through diet *(see Table 1)* and supplementation (800 mcg/d) to enjoy the 40% reduction in clinical cases of colorectal cancer that folate affords.

Mechanism of Action

Folate and all its coenzymatic forms have one function in mammalian systems: to mediate the transfer of the carbon methyl units. Two major pathways are served—the production of S-adenosylmethionine and deoxynucleoside triphosphate synthesis. Methyl donation facilitators are necessary for normal synthesis of the pyrimidine thymdylate, and the purines, including cytosine.[5-8]

Deficiency of uracil and cytosine have been shown in in vitro systems to cause cancer by making DNA more fragile. Such deficiencies also cause cancers by making miscoding accidents more prevalent, inhibiting the *P53* tumor-suppressor gene, and promoting growth of already established cancers.

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Thus, methyl donor deficiency can cause DNA mutations, promote DNA mutations, and promulgate DNA mutations.[5-8] Whether folate deficiency starts a clinical cancer or just promotes the clinical evidence of already formed cancers is important, but we do not know which mechanism is at work in human cancer. All four possible mechanisms *(see preceding paragraph)* make it biologically plausible that folic acid supplementation may reduce the risk of clinically evident colon cancer.

Clinical Studies

Solid research studies, some published as long ago as 1991, indicate that increasing folate intake can prevent or reduce the risk of colon cancer.[9-14] *(See Table 2.)*

The strongest of these studies is the 1998 publication of the 15-year follow-up of the Nurse's Health Study.[11] In this study, the relative risk for colon cancer in the highest intake group (> 400 mcg/d) was 31% less than that of the lowest intake group (< 200 mcg/d). The longer the exposure to high-folate intake, the greater the risk reduction for colon cancer, reaching a 75% risk reduction after 15 years of high intake compared to the lowest intake.

This prospective cohort study is strong because of the large number (88,756) of nurses about whom data were collected, and because of its adjustment for alcohol intake, physical activity, age, family history, red meat consumption, aspirin use, fiber intake, and smoking history. Interestingly, more than 86% of the women who consumed more than 400 mcg/d took a multivitamin that contained large quantities of folic acid. This latter fact gives more evidence that supplementation is needed for most Americans to obtain the optimum intake of about 800 mcg/d.

In the NHANES Follow-up Study (NHEFS),[12] the relative risk for colon cancer of the men in the highest intake group (> 239 mcg/d in diet) was 60% less than those men in the lowest intake group (< 103.3 mcg/d). While the direction of change was the same for women (a 36% risk reduction), it did not reach significance, perhaps because of the smaller number of cases of colon cancer in this group of women. This study suffers from lack of accounting for vitamin use and smoking.

Table 1

Food Sources of Folate*

Food	Serving Size	Amount (mcg)	%Daily Value‡
Chicken liver	3.5 oz	770	193
Breakfast cereals	1/2 to 1 1/2 cup	100-400	25-100
Braised beef liver	3.5 oz	217	54
Lentils, cooked	1/2 cup	180	45
Chickpeas	1/2 cup	141	35
Asparagus	1/2 cup	132	33
Spinach, cooked	1/2 cup	131	33
Black beans	1/2 cup	128	32
Kidney beans	1/2 cup	115	29
Baked beans with pork	1 cup	92	23
Lima beans	1/2 cup	78	20
Tomato juice	1 cup	48	12
Brussels sprouts	1/2 cup	47	12
Orange	1 medium	47	12
Broccoli, cooked	1/2 cup	39	10

*Folic acid and folate are interchangeable terms. Folic acid is the synthetic form of folate, which is found naturally in some foods.

‡based on Daily Value for folate of 400 mcg

Sources: Pennington, Jean AT, ed. *Food Values of Portions Commonly Used*. 16th ed. Philadelphia, PA: Lippincott Raven Publishers; 1994. Food and Drug Administration: www.fda.gov/fdac/features/796_fcht.html and USDA Nutrient Database for Standard Reference: www.nal.usda.gov/fnic/foodcomp.

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Table 2

Studies indicating that folate may reduce colon cancer risk

Study	Study Group	Patients	Relative Risk (Confidence Interval)	Limitations
Giovannucci et al[11]	Nurses' Health Study	88,756 women	0.69 (0.52-0.93) > 400 mcg vs. 200 mcg/d 0.25 (0.13-0.51) after 15 years	Prospective cohort
Su et al[12]	NHANES I Follow-Up	14,407	0.40 (0.18-0.88) males 0.74 (0.36-1.51) females > 239 vs. < 103.3 mcg/d	Cohort Did not account for vitamins or smoking
Giovannucci et al[13]	Health Professionals Follow-Up Study	47,931 men	3.3 (1.58-6.88) for low-folate, low-methionine, high-alcohol intakes	Prospective cohort

In the Health Professionals Follow-Up Study, the hypothesis was that alcohol, which antagonizes methyl group metabolism, and low dietary intake of factors (folate and methionine) that facilitate methyl group donation, would increase the risk of colon cancer.[13] The relative risk for these methyl donor-deficient conditions was 3.30, again supporting the indication that high-folate diets or supplement use can reduce the risk of colon cancer.

Other studies conducted for other purposes or that were less well-controlled support the indication that high-folate intake reduces the risk of clinically evident colon and rectal cancers.[9,10,14] Even a study of a genetic mutation that limits methyl group availability showed an increased risk of colon cancers in the presence of substantial alcohol intake.[15] Thus, it appears likely that obtaining folate at a level of about 800 mcg/d from diet or supplements for 15 years decreases the risk of clinically evident colon and rectal cancers by 30-60%.

Adverse Effects

Supplementation with folic acid is safe. Folate toxicity is so rare that I could not find case reports of such when folate is taken in concert with vitamins B_6 and B_{12}. No human toxicity has been reported with intakes of less than 2,000 mcg/d.

There have been rare cases of exacerbation of vitamin B_{12} deficiency reported with high doses of folic acid.[16] This may be a concern in the elderly patient: Some data suggest that many elderly people have evidence of early vitamin B_{12}, B_6, or folate deficiency despite having normal serum vitamin concentrations.[17] Folic acid supplementation may make it more difficult to diagnose vitamin B_{12} deficiency using screening blood cell panels.

Drug Interactions

There are several drugs that can interact with folic acid. Patients treated with the antiseizure medication phenytoin may have a decrease in phenytoin levels, although at supplement doses this is unlikely to increase seizure frequency.[16] Folic acid may reduce the efficacy of methotrexate used for rheumatoid arthritis and other medical conditions.

Conclusion

If reduction of arterial aging and homocysteine levels were not enough motivation to supplement the diet with 800 mcg of folic acid a day, reduced risk of clinical colon and rectal cancer should be. I believe these data support this level of supplementation, at least pending intervention studies that indicate risk greater than benefit.[18,19] The available data are strong enough to make the burden of disproving the hypothesis necessary before the recommendation to supplement with folate is withdrawn.

Recommendation

We should be taking and prescribing vitamin B_9 (folate), and vitamins B_6 and B_{12} to decrease homocysteine levels. Supplementation decreases the risk of all arterial aging-phenomena heart disease, stroke, memory loss, impotence, and probably wrinkling of the skin as well.[20-22] The recommended daily dose of folate from diet and supplements for this preventive benefit is about 800 mcg (plus about 5 mg of B_6 and at least 25 mcg of B_{12}). ❖

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Human Growth Hormone to Prevent Key Physiological Effects of Aging

PART 2 OF A SERIES ON HUMAN GROWTH HORMONE

By Dónal P. O'Mathúna, PhD

INTEREST IN HUMAN GROWTH HORMONE (HGH) THERAPY has recently shifted away from its use by athletes to enhance performance to its use by baby boomers to prevent and even reverse the effects of aging.[1]

A huge marketing campaign is promoting HGH therapy as the latest Fountain of Youth. Barrages of e-mail claim HGH will "stop aging" and "turn back your body's biological time clock 10-20 years." HGH is alleged to help you "lose weight while you sleep," "reduce body fat (without working out)," "increase energy levels," "restore youthful skin," "improve sleep," and "improve sexual potency."

Sound too good to be true? One advertisement urges, "Don't believe the hype, read the science." The promoters claim "over 20,000 studies, abstracts and reports have documented these wonderful benefits."[2] Little wonder, then, that they claim, "Anyone over 35 who wants to have good health and longevity will need to be on an HGH program."[2]

Many of your patients will have encountered these advertisements. Some will be tempted to try oral supplements, but since they don't contain HGH, many will waste their time and money. They may even avoid good nutrition and healthy exercise in the misguided belief that these supplements are effective. They may neglect

high-quality medical care in the belief that these supplements will cure all their ailments. However, interest in these products—and in prescription HGH injections—provides a useful opportunity to educate patients on how to examine claims made for therapies and remedies.

Background

Part 1 of this article described the role of HGH in human physiology.[1] The amount of hormone produced by the body decreases with age, and has thus been associated with the effects of aging. Increased recognition of adult-onset forms of growth hormone deficiency (GHD) also have brought attention to this area.[3]

Many GHD symptoms resemble aging, and are reversed by HGH. These findings are used to claim that normal, older people can use HGH to overcome age-related changes such as reduced fat-free body mass, increased adipose tissue mass, irregular sleep cycles, and reduced bone density. Clinical studies with injectable HGH generally are positive for symptomatic relief and physiological changes. Although these results do not mean that aging has been stopped, these changes in body composition are highly desired by those attracted to anti-aging medicine.

Commercial Claims: HGH

Advertisements for commercial products claim that thousands of scientific studies support HGH's anti-aging and "youthing" effects. The 24-page brochure for one product specifies nine studies it claims "prove HGH's youthing effect."[2] Of the nine, four studies had nothing to do with HGH or aging (two were for herbal remedies, one for Ayurvedic medicine, and one for testosterone). Four "studies" were reviews of HGH treatment that uniformly concluded that it was premature to recommend HGH administration to adults except in clinical trials[4] or for those with demonstrated GHD.[3] One study did find that HGH produced beneficial changes in body composition and is reviewed below.[5]

Such misrepresentation of study results should lead to skepticism about the rest of the claims made throughout any advertisement. In addition, the citations of five of the nine articles above contained at least one error. Such inattention to detail, quickly revealed by a MEDLINE search, also should heighten suspicion about the accuracy of the remainder of the brochure.

Commercial Claims: Oral Supplements

Popular HGH products are marketed as oral supplements, even though the polypeptide hormone is not active orally. These oral formulations do not actually contain HGH. Therefore, studies involving injectable, prescription-only, FDA-approved HGH are irrelevant to the efficacy of these oral products.

These oral HGH products contain various combinations of amino acids said to boost endogenous HGH levels. These oral products are sometimes called "HGH secretagogues," which should not be confused with pharmaceutical HGH secretagogues currently being developed to overcome muscle wasting conditions associated with various diseases.[6]

Clinical Studies: HGH

The first study to examine the anti-aging effects of injectable, prescription HGH involved 21 healthy men ages 61-81.[5] Twelve men were randomly assigned to receive HGH (0.03 mg/kg subcutaneous three days/week) and the other nine men received no treatment. After six months, the treatment group had 8.8% more lean body mass, 14.4% less adipose tissue mass, and a 1.6% increase in lumbar vertebral bone density (all $P < 0.05$). No significant changes occurred in the control group.

Changes in body fat were examined in a double-blind, randomized study involving 110 healthy men and women (ages 65-88 years) given HGH (six months at 20 mcg/kg self-injected three times/week) with or without sex steroids.[7] In women, neither HGH, hormone replacement therapy, nor both altered abdominal fat distribution. In men, subcutaneous fat but not visceral fat was reduced significantly compared to placebo after HGH (14%, $P = 0.05$) and HGH plus testosterone (16%, $P = 0.0005$).

A similar study examined the effects of HGH (0.02 mg/kg subcutaneous three times/week) with or without sex steroids on bone metabolism in 125 healthy men and women (> 65 years).[8] Biochemical markers of bone metabolism had beneficial changes in women given HGH, but not in those given HGH plus hormone replacement therapy. In men, these markers showed small improvements with HGH and much larger ones with HGH plus testosterone. Bone mineral density did not increase in men or women given HGH alone.

A complex study divided 31 healthy men (ages 73-75 years) into four groups.[9] The interventions were: HGH alone, HGH plus resistance training, placebo plus resistance training, or placebo alone. HGH alone had no significant effect on muscle strength, size, power, or fiber size, but did produce changes in myosin heavy chain composition consistent with more youthful muscle. Resistance training produced significant muscular gains that HGH did not augment, just as was found with younger athletes.[1] HGH alone also significantly reduced

fat mass and increased fat-free mass, but did not change bone mineral content.

It's important to note that improvements in body composition do not mean that aging has been stopped or reversed.

Clinical Studies: Oral Supplements

Oral supplements to boost endogenous HGH production date back to a 1981 study using lysine and arginine. Ingestion of several amino acids, especially arginine, lysine, and ornithine, can elevate HGH levels, making this a popular practice with some athletes.[10] However, the response is transient and highly variable, and reduced with aging.[11] Among athletes, the increased HGH levels after oral amino acid intake did not lead to improved muscle mass or strength or any other beneficial changes in body composition.[10] A search of MEDLINE produced only one study involving older people and the administration of oral amino acids (3 g arginine plus 3 g lysine PO bid).[12] This double-blind, randomized study involved 16 men (mean, 68 years), and after 14 days no significant differences in HGH levels were observed between the amino acid group and those taking placebo.

Adverse Effects

Much remains unknown about the connections between HGH and aging. Animal studies consistently find that mice with genetically impaired growth hormone production are smaller, frail, and less fertile; however, they also tend to live longer.[13] Also, higher than normal HGH levels are associated with reduced life expectancy in mice and humans; acromegaly is characterized by this complex.[14] Adverse effects from subcutaneous HGH include carpal tunnel compression, arthralgia, fluid retention, and reduced HDL-cholesterol levels.[1] In one study reviewed here, 12 of the 15 subjects taking HGH reported such adverse effects.[9]

There is concern about the safety of HGH obtained from glandular or organ material derived from animals. In the early 1980s, several cases of Creutzfeldt-Jakob disease developed because of contaminated cadaveric HGH.[15] Although HGH commercially available in the United States is made via recombinant DNA technology, some countries still produce cadaveric HGH of questionable quality which may be available through illegitimate outlets.

Regarding oral supplements, no adverse effects were reported in the study involving older men taking 6 g amino acids bid.[12] Higher doses (20-30 g amino acids/d) are sometimes recommended, and can lead to dyspepsia, nausea, or diarrhea.[12]

Formulation

Numerous formulations are available. The most popular ones are capsules containing 2-3 g of amino acids, usually arginine, lysine, and glutamine. Other herbs and glandular extracts often are included in these preparations. A month's supply costs from $50 to $200. Injectable HGH is legally available only by prescription, but a black market makes it available, especially among certain athletes.

Conclusion

Although clinical studies have shown that some amino acid supplements, taken orally, will increase endogenous HGH levels, the results are inconsistent and the clinical significance unknown. Results with athletes show none of the desired benefits. The few studies with the elderly have not found HGH-boosting effects and instead suggest that the physiological impact of oral amino acid supplements diminishes with aging.

A small number of studies of subcutaneous HGH injections administered to elderly people do reveal, however, some beneficial changes in body composition. Although this is not evidence that any formulation of HGH stops or reverses aging, they are changes that are highly attractive and may provide protection against certain diseases.

The promotional campaigns for HGH oral supplements are based completely on studies that are irrelevant for the products being marketed. Even if the subcutaneous HGH studies were relevant, the changes in body composition do not support claims that HGH stops aging or causes "youthing." These advertisements may generate interest in HGH injections, but there is no evidence to support their use as anti-aging products.[16]

Recommendation

Physicians should take advantage of patient interest in these products to point out how these advertisements deceptively misuse scientific studies. Taking time to educate patients will help them avoid both wasting money on ineffective products and placing hope in false promises.

At the same time, HGH injections may produce beneficial changes in some older people's body composition. A trial period may be appropriate, but HGH should always be prescribed under the careful supervision of physicians. Adverse effects are relatively common, and there are theoretical concerns that higher than normal levels of HGH may shorten lifespan. Patients should be reminded that the best ways to increase their chances of living a longer, healthier life are to adhere to well-established advice on nutrition, exercise, and smoking. Some

patients also may need help in coming to accept that aging currently cannot be prevented. ❖

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Chelation Therapy for Coronary Artery Disease

By Robert J. Nardino, MD, FACP

"CHELATION" COMES FROM THE GREEK WORD FOR claw. That fits just right with the popular notion that chelation therapy can snatch bad molecules from clogged arteries. Established as a treatment for heavy metal poisoning, chelation has been postulated as an alternative to the existing standard of care for the treatment of coronary artery disease (CAD).

Testimonials of dramatic improvement following chelation therapy continue to fuel a demand from patients with all forms of vascular disease. Although the extent of its use is unknown, one estimate put the number in the vicinity of 500,000 people per year in the United States;[1] a Canadian study surveying patients who had undergone cardiac catheterization found that 8% had tried chelation.[2] Despite greater attention to risk factor modification, CAD continues to kill half a million people annually in the United States, and its prevalence continues to rise. Therefore, it is crucial to determine if chelation is a viable treatment option. Currently, that question remains unanswered.

Pharmacology

The major active ingredient for chelation therapy is ethylenediamine tetraacetic acid (EDTA). EDTA comes in two forms—the disodium salt and the calcium disodium salt. The sodium salt chelates calcium—in fact, a rapid infusion may cause hypocalcemia, and is the form generally used for chelation therapy of atherosclerosis. It also chelates other polyvalent metals such as magnesium and zinc. The calcium disodium salt chelates divalent and trivalent metals, and is used predominantly for the treatment of acute and chronic lead toxicity. Both forms of EDTA are poorly soluble in water. After intravenous administration, EDTA has a half-life of 20-60 minutes. It is excreted predominantly by the kidney.

Mechanism of Action

The mechanism of action of chelation therapy for CAD remains controversial. Initially it was hypothesized that EDTA removed calcium from plaque. But

other mechanisms have been postulated, because atheromatous plaques are not simply calcium and bone preferentially may give up the calcium removed by EDTA.[3] These mechanisms include inhibition of platelet aggregation, free radical scavenging, and inhibition of matrix metalloproteinase activity, which may stabilize plaque.[4] EDTA may reduce the oxidation of LDL.[5] Finally, it also has been proposed that a reduction in serum calcium leads to vascular dilation.[6]

Technique

A single chelation treatment lasts from two to four hours. Anywhere from five to 30 treatments may be prescribed in the first month, with maintenance treatments recommended once monthly after this. The formulation recommended by the American College for Advancement in Medicine (ACAM) uses 50 mg/kg disodium EDTA with heparin, magnesium chloride, high-dose vitamin C, and additional B vitamins, along with lidocaine as a local anesthetic.[7] The ACAM's position paper on chelation therapy can be viewed at: www.acam.org/chelationtherapyinformation.php#intro.

Controversy

There exist some proponents of oral chelation therapy; however, no published data could be found to substantiate oral use, and the technique garners fervent criticism from many in the intravenous chelation therapy group.

Medicare and other health insurance providers do not reimburse for chelation therapy. In addition, in some locations, such as Oregon, insurance companies will not provide malpractice insurance for physicians who perform chelation therapy (www.acponline.org/journals/news/apr02/malpractice.htm).

It is clear that strong emotions surround the evaluation of chelation therapy. Proponents point to the uncontrolled, observational data they have accumulated and reported in the publication sponsored by the society that promotes chelation, the American College for Advancement in Medicine.[10,11] However, there may be significant placebo effects attributable to this treatment. With each recent controlled trial that has failed to show the superiority of chelation over placebo, there have appeared vociferous letters denouncing the findings as biased.[4,12-14] Remaining noticeably absent are studies conducted by chelation proponents appearing in peer-reviewed medical literature. Prior to the publication of the PATCH study (Program to Assess alternative Treatment strategies to achieve Cardiac Health), and because the previous randomized studies were not sufficiently powered to detect small differences, the National Institutes of Health, through the National Center for Complementary and Alternative Medicine (NCAAM), issued a request for grant proposals for a long-term study of chelation therapy.

Clinical Studies

Controlled trials concerning the efficacy of chelation therapy are few and far between. Ernst summarized the existing data on chelation for the treatment of CAD in 2000.[8] Many observational reports appeared in the 1960s and indicate subjective improvement. A placebo-controlled trial published in 1963 involving nine patients with a clinical diagnosis of CAD indicated initial improvement at 12 weeks, but no statistical analysis was performed. A German study appeared only in abstract form in 1997, showing that in 16 patients with angiographically proven CAD randomized to EDTA or placebo, no difference was observed in exercise performance.

More recently, Knudtson et al published the results of the PATCH study , a randomized double-blind, placebo-controlled trial of chelation therapy.[9] The investigators enrolled 84 patients with stable angina and CAD documented by cardiac catheterization. The intervention group received EDTA chelation therapy at a dose of 40 mg/kg for three hours, twice weekly for 15 weeks, followed by one treatment per month for three months. The control group received saline instead of EDTA with a similar treatment schedule. Both groups received oral multivitamins and treatment of risk factors according to American Heart Association guidelines. The main outcome measure was change in time to ischemia during treadmill testing done at baseline and again at 27 weeks. Secondary outcomes were exercise capacity by determination of anaerobic threshold and quality of life based on a series of validated instruments. In all three of these outcomes, chelation failed to produce a result that was superior to placebo.

Adverse Effects

The most common side effect of intravenous chelation therapy is burning at the infusion site. In fact, one report characterized the inability to undertake a blinded study of chelation therapy because of this side effect. Recent studies have used lidocaine at the infusion site to prevent this symptom and preserve blinding.[15] Renal failure has been reported; renal tubular damage can result from high doses of EDTA, but not at the doses typically used for chelation therapy. If recognized early, the effects on the kidney are reversible. Only one patient in the Knudtson study dropped out because of a rise in serum creatinine (1.5 to 2.1 mg/dL).[9] Hypocalcemia appears to be rare with the currently used protocol.

Prolonged bleeding time, bone marrow depression, hypoglycemia, and death have been reported in association with chelation therapy.[8]

Contraindications include hypersensitivity to EDTA and anuria. Relative contraindications include pregnancy (potential teratogen) or existing hypocalcemia and hypokalemia, which can be worsened. Caution must be observed in patients with renal insufficiency or impaired myocardial contractility.

Other Effects

Calcium disodium EDTA is used to treat lead poisoning and intoxication by other heavy metals, and has been demonstrated to be effective in this regard.

Dosage and Formulation

EDTA is stored at room temperature, and must be diluted before use. The dose according to the ACAM protocol is calculated with consideration of creatinine clearance, but usually is 3 g. The infusion also includes: 20 meq sodium bicarbonate; 3 g vitamin C; 2.5 g magnesium sulfate; 2,500 units heparin; 2.5 mg folic acid; 100 mg pyridoxine; 1,000 mcg cyancobalamin; 1 mL B-complex-100 (optional, not always available); and lidocaine to relieve pain at the infusion site.

The infusion typically requires three hours and costs between $50 and $100. In the first month, patients usually receive from five to 30 treatments. Patients often are advised to continue preventive treatment once a month.

There is no specific licensure required to administer the therapy; because EDTA is approved by the Food and Drug Administration (FDA) for other indications, it can be employed for off-label uses. The ACAM provides training and essentially credentials practitioners for chelation therapy.

Conclusion

There are no data from properly controlled trials supporting the benefit of chelation therapy for patients with atherosclerotic diseases. The American Medical Association, the American Heart Association, the American College of Physicians, the American College of

Clinical Trials Harmed by Lack of Informed Consent

The mention of clinical trials often triggers a silence between physician and patient, usually because neither one knows much about the subject. Nearly 80% of physicians admit they would like to know more about clinical trials so they can help their patients make an informed decision before volunteering to participate.

"Most subjects enrolled in clinical studies have a meager understanding of what they have gotten into," says Alan Sugar, MD, chairman, New England Institutional Review Board, Professor of Medicine, Boston University School of Medicine, Boston. "Informed consent has largely focused around the signed form and has not practically become the continuous process that it needs to be. As a result, a subject's misunderstandings largely go unchallenged."

Properly informing patients is not only ethically necessary, say clinical trials experts, but it also ensures better trials and data. Last year more than 17 million people thought seriously about participating, but only a few million actually completed their trials, and many gave consent without a thorough knowledge of the facts.

"There's a simple ethical mandate that you don't ordinarily do dangerous things to people without their knowledge and consent," says Dale E. Hammerschmidt, MD, FACP, associate professor of medicine and director of Education in Human Subjects' Protection for the University of Minnesota Medical School in Minneapolis. "From a more pragmatic perspective, a well-informed subject is likely to cooperate better with the trial and is more likely to report potential problems. The quality of the data and the safety of the trial are both enhanced when the subjects really know what's going on."

Indeed, patients can be so daunted by questions and lack of information that they simply decide not to volunteer.

A new resource, written for doctors and clinical trial participants, can help answer some of these tough questions. Boston-based CenterWatch, the leading publisher of clinical trial news and information, now offers "Informed Consent," a consumer's guide to the risks and benefits of volunteering for clinical trials. The book is a practical guide through the confusing world that patients perceive clinical trials to be.

"Informed Consent" is a step-by-step guide that begins with a history of the clinical trials industry, and explores the drug development process and how a new drug makes its way to the marketplace. The book goes into detail about why people decide to participate, how to find clinical trials, how to research clinical trials and evaluate their risks, how to ensure proper informed consent, who the vulnerable populations are, and what to do when things go wrong.

Cost is $16.95 and it can be ordered from CenterWatch at (800) 765-9647, or by faxing your request to (617) 856-5901. It can also be ordered through centerwatch.com, Amazon.com, and barnesandnoble.com.

Cardiology, and the FDA have published statements recommending against the use of chelation therapy, citing no proven benefit.

A large NCCAM-sponsored study is planned, which should erase criticism about the insufficient power of prior studies.[16] Definitive evidence of efficacy and safety would benefit millions of individuals, and additional evidence from a large randomized trial would help to answer these questions.

Recommendation

Current data do not support the use of chelation therapy for the treatment of atherosclerotic disease. In the hands of experienced practitioners, it appears to be relatively safe; however, patients with renal disease or congestive heart failure should proceed with caution. Patients wishing to try chelation therapy should be should be encouraged not to abandon proven therapies when indicated. ❖

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CME Questions

15. Which of the following is *false*?

a. Folate is consumed at a level below that recommended by the FDA by more than 75% of Americans.
b. High intake of folate increases sperm count by 40% or so in subfertile men.
c. Folic supplementation decreases heart attack risk.
d. The FDA required supplementation of all grains in the USA with 45 mcg of folic acid per serving.

16. The evidence that folate in diet and folic acid supplementation can reduce colon cancers is supported by all of the following types of studies *except*:

a. Patients with high alcohol use rates have higher rates of colon cancer.
b. Nurses with increased intake of folic acid have reduced rates of colon cancer that become more prominent the longer they have supplemented with folic acid.
c. More folic acid in diet correlates with fewer rectal cancers.
d. Two randomized blinded intervention studies of more than 5,000 volunteers each for more than seven years have demonstrated a 55% and a 70% reduction in colon cancer rates.

17. Products marketed as human growth hormone (HGH) therapy to prevent or reverse aging most commonly contain:

a. human growth hormone.
b. pharmaceutical drugs which stimulate growth hormone production.
c. selected amino acids.
d. androgenic steroid hormones.

18. The thousands of studies reported to support the use of HGH:

a. do not exist.
b. are irrelevant for the oral products marketed.
c. produced no beneficial results.
d. support the use of HGH as an anti-aging medicine.

19. The most common types of adverse effects reported in patients taking large doses of amino acids to boost HGH levels are:

a. heart attacks.
b. excessive muscular growth.
c. allergic reactions.
d. gastrointestinal disturbances.

20. The most common side effect of intravenous chelation therapy is:

a. local pain and hemorrhage.
b. hypercalcemia.
c. burning at the infusion site.
d. renal failure.

Clinical Briefs

With Comments from John La Puma, MD, FACP

Homeopathic Immunotherapy and Asthma

Sources: Lewith GT, et al. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: Double blind randomised controlled clinical trial *BMJ* 2002;324:520.

Feder G, Katz T. Randomised controlled trials for homoeopathy. Who wants to know the results? *BMJ* 2002;324:498-499.

TO EVALUATE THE EFFICACY OF homeopathic immunotherapy on lung function and respiratory symptoms in asthmatic people allergic to house dust mite, a double-blind randomized controlled trial was conducted in 38 general practices in Hampshire and Dorset.

Of 242 people with asthma and positive results to skin prick test for house dust mite, 202 completed clinic-based assessments, and 186 completed diary-based assessments. After a four-week baseline assessment, participants were randomized to receive oral homeopathic immunotherapy or placebo and then assessed over 16 weeks with three clinic visits and diary assessments every other week. The following clinic-based assessments were conducted: forced expiratory volume in one second (FEV_1), quality of life, and mood. Diary-based assessments included: morning and evening peak expiratory flow, visual analogue scale of severity of asthma, quality of life, and daily mood.

There was no difference in most outcomes between placebo and homeopathic immunotherapy. There was a different pattern of change over the trial for three of the diary assessments: morning peak expiratory flow ($P = 0.025$), visual analogue scale ($P = 0.017$), and mood ($P = 0.035$). At week three there was significant deterioration for visual analogue scale ($P = 0.047$) and mood ($P = 0.013$) in the homeopathic immunotherapy group compared with the placebo group. Any improvement in participants' asthma was independent of belief in complementary medicine.

Homeopathic immunotherapy is not effective in the treatment of patients with asthma who are allergic to house dust mite. The different patterns of change between homeopathic immunotherapy and placebo over the course of the study are unexplained.

COMMENT

This confusing and criticized study has ignited a pollen cloud of inner sanctum disagreement, confusing many clinicians further. An editorial didn't help much: Both editorialists had been paid by companies invested in manufacturing or advancing homeopathy, and found, in part, that "randomization and blinding of participants substantially distorts the context of homeopathic prescribing, potentially weakening its effect."

Designed to replicate the landmark, positive study by Reilly et al of the homeopathic treatment of asthma with larger numbers, more power, and broader outcome variables, the investigators actually tested effectiveness of placebo vs. (nontraditionally prepared) homeopathic preparation. Both groups improved symptomatically and in FEV_1, but because no third arm of active, conventional treatment was tested, it's impossible to know how they compare with prescription medication.

Homeopathic physicians have a different and sometimes effective way of diagnosing and treating patients, and may easily, much to the puzzlement of allopathic and osteopathic physicians, come up with 100 different prescriptions for 100 different patients with the same biomedical condition. But a well-known meta-analysis of four years ago showed a greater-than-placebo effect in a number of conditions, including asthma. And homeopathy is popular: Two in five adults in Australia, one in 12 adults in the United Kingdom, and one in 25 in the United States use homeopathy.

The argument that this current trial tested isopathic preparation ("the use of homeopathically prepared allergens to treat allergies" and absent molecules) not homeopathy (with its focus on long, deliberate visits, multifaceted history and assessment, and few molecules of active ingredient in its dilutions) is probably correct, though this is certainly particle splitting in the world of the randomized controlled trial.

Recommendation

Asthma has effective conventional treatments. Offer them first to patients with moderate-to-severe disease. Homeopathic treatment may not be better than placebo, but both consistently result in symptomatic improvement. Asthmatic, allergic patients who want to try homeopathy can be encouraged: A visit to a homeopathic physician for a long, attentive visit may in itself be helpful. ❖

Adverse Reactions Associated with Echinacea Use

Source: Mullins RJ, Heddle R. Adverse reactions associated with echinacea: The Australian experience. *Ann Allergy Asthma Immunol* 2002;88:42-51.

FIFTY PERCENT OF AUSTRALIANS USE complementary and alternative medicines (other than vitamins) in any 12-month period, of which echinacea-containing products are increasingly popular. Recent reports have highlighted the risk of allergic reactions to complementary medicines in atopic patients.

To determine the characteristics of adverse reactions linked to use of the popular herbal remedy echinacea, five privately referred patients were evaluated by the authors in their office practice via skin prick testing (SPT) on the volar aspect of the forearm and radioallergosorbent test after adverse reactions to echinacea. As there was little published information on adverse reactions to echinacea, reports to the Australian Adverse Drug Reactions Advisory Committee were reviewed. Those suggestive of possible allergic reactions were evaluated in greater detail by anonymously surveying the health care professionals who had reported the cases and from one unreported case. Serum was collected for further analysis where possible.

Five cases of adverse reactions to echinacea were personally evaluated by the authors. Two patients suffered anaphylaxis and a third had an acute asthma attack 10 minutes after their first ever dose of echinacea. The fourth patient suffered recurrent episodes of mild asthma each time echinacea was ingested, and the fifth developed a maculopapular rash within two days of ingestion, which recurred when rechallenged. Three of the patients had positive SPT results. Three reported repeated spontaneous "challenges" and symptoms after further ingestion of echinacea.

Fifty-one Australian adverse drug reports implicating echinacea also were reviewed. There were 26 cases suggestive of possible immunoglobulin E-mediated hypersensitivity (four anaphylaxis, 12 acute asthma, 10 urticaria/angioedema). Of these 26 patients, age ranged from 2 to 58 years, 78% were female, and more than 50% were known to be atopic. Four were hospitalized, four reacted after their first known exposure, and one patient suffered multiple progressive systemic reactions. Twenty of 100 atopic subjects who had never taken echinacea also had positive SPT results to this substance when tested by one of the authors in his office practice.

Some atopic subjects have positive SPT results to echinacea in the absence of known exposure. Atopic subjects also are over-represented in those experiencing reactions to echinacea. The possibility that cross-reactivity between echinacea and other environmental allergens may trigger allergic reactions in "naïve-naïve" subjects is supported by the Australian data. Given its widespread (and largely unsupervised) use, even rare adverse events become inevitable. Atopic patients should be cautioned appropriately.

COMMENT

An earlier summary of the Australian registry of adverse reactions to echinacea, referred to in the *Annals of Internal Medicine* this year, indicated only very mild concern about adverse reactions to echinacea. But either because of increasing usage or allergenicity, or both, frightening atopy seems to be emerging. Recurrent erythema nodosum associated with echinacea herbal therapy also was reported last year by Soon and colleagues.[1]

Practical dosing difficulties with echinacea include the usual recommendation of three times daily dosing, with either pressed juice or tincture, and variability of supplement reliability and purity. But the appearance of such specific and clear allergy, including anaphylaxis, is worrisome.

Recommendation

Patients with atopic conditions and environmental allergies should avoid echinacea; if they want to take it, they should be warned about the identified and increased incidence of reaction to it. ❖

Reference

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In Future Issues:

Natural Immunomodulators for the Treatment of Cancer

Role of Huperizine A in Alzheimer's Disease

Nuts for the Treatment of Hypercholesterolemia: Seeds of Change?

Resveratrol and Cancers of the Prostate and Breast

Cranberry (*Vaccinum macrocarpon*) and Urinary Tract Infection