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Folic Acid for the Secondary Prevention of Heart Disease

By Matthew J. Sorrentino, MD, FACC

HOMOCYSTINURIA IS A RARE GENETIC DISEASE CAUSED BY THE deficiency of the enzyme cystathionine beta-synthase leading to significantly elevated levels of homocysteine. The condition is associated with serious thromboembolic complications at an early age. Myocardial infarction, pulmonary embolism, and stroke are the most common causes of death in affected individuals.

Study of individuals with this rare disorder has led to speculation that homocysteine and other sulfur-containing amino acids may be a cause of arteriosclerosis. The recognition that folic acid and other B vitamins can lower plasma homocysteine levels suggests that a simple treatment may be available to prevent vascular disease.

Biochemistry and Pathogenesis

Homocysteine is an amino acid produced in the metabolism of protein—usually dietary protein. It has been implicated in atherogenesis. Homocysteine levels are elevated after an acute coronary event. In addition, there is some evidence that endothelial dysfunction may raise homocysteine levels.[1] Administration of folic acid will reduce homocysteine levels by enhancing the remethylation of homocysteine to methionine.

Clinical Studies

Retrospective Analyses. An association between elevated plasma homocysteine levels and arteriosclerotic disease was first noted by retrospective case-control studies. Homocysteine levels are frequently elevated in adult patients with atherosclerotic disease. In 1990, Malinow summarized 11 series with more than 2,000 patients showing that homocysteine and other sulfur-containing amino acids values were higher in patients with coronary artery, cerebrovascular, and peripheral vascular disease.[2] There was no correlation between homocysteine levels and other cardiovascular risk factors such as cholesterol levels, cigarette smoking, or hypertension. A significant overlap of homocysteine levels was noted, however, with nearly 70-80% of patients having normal values.

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Boushey and colleagues extended Malinow's review with a meta-analysis of studies through June 1994.[3] Hyperhomocysteinemia was determined to be an independent risk factor for vascular disease with an odds ratio of 1.7 for coronary artery disease of a 5 µmol/L homocysteine increment. This risk is on the same order as risk for coronary disease by lipid factors.

The risk associated with hyperhomocysteinemia appears to be a graded risk without a threshold below which there is no risk. This suggests a causal relationship between homocysteine and vascular disease. More recently a multicenter case-control study in Europe showed that homocysteine concentrations greater than the 80th percentile for control subjects were associated with an increased risk of atherosclerotic disease.[4] Furthermore, low red cell folic acid concentration and low vitamin B_6 levels were associated with an increased risk.

Prospective and Additional Meta-Analysis. Results of prospective cohort studies of homocysteine and atherosclerotic disease have not been as conclusive as the retrospective case-control studies. The Atherosclerosis Risk in Communities (ARIC) study was a prospective trial designed to determine if homocysteine-related factors were associated with the incidence of coronary heart disease over a greater than three-year period.[5] After adjustment for other risk factors, homocysteine was not independently associated with coronary disease.

Genetic studies have also shown inconsistent results. Brattstrom and colleagues reported a meta-analysis of 13 studies that documented homocysteine levels in relationship to three genotypes and found that although the gene mutations caused a mild increase in homocysteine concentration, there was no increase in cardiovascular risk.[6]

Prospective vs. Retrospective Analyses. There are a number of reasons why the prospective studies may not have been as conclusive as retrospective analyses. Vascular disease itself may result in higher homocysteine levels. Vascular disease is an inflammatory process and a number of inflammatory markers are elevated in patients with atherosclerotic disease.

Prospective clinical data regarding the benefits of lowering homocysteine levels for the prevention of heart disease are not yet complete. In the European Concerted Action Project, use of vitamin preparations containing folic acid and B vitamins appeared to give protection against the development of vascular disease.[7] The Nurses Health Study demonstrated a similar observation.[8] Prospective randomized studies are needed to verify these preliminary observations.

Low levels of certain vitamins, such as folic acid, vitamin B_6, or B_{12}, may be the primary risk factor for vascular disease and homocysteine levels may be a marker of low vitamin levels. For example, the risk of fatal coronary heart disease was found to be associated with low serum folate levels in men and women in the Nutrition Canada Survey.[9]

Recent studies have implied that homocysteine may be a risk factor for thrombotic events. Patients with the rare genetic disease homocystinuria with high serum levels of homocysteine frequently have thromboembolic complications. Nygard and colleagues prospectively investigated the relationship between homocysteine levels and mortality in 587 patients with confirmed coronary artery disease and found a strong and graded relationship between homocysteine levels and total mortality.[10] This relationship was strengthened when the end point of coronary mortality was used. Acute coronary events are known to be associated with thrombus formation at the site of a ruptured plaque. This result was confirmed in the British United Provident Association Study where homocysteine levels were significantly higher in men who died of coronary heart disease with the association strongest in younger individuals.[11]

Fortification and Formulation

Homocysteine levels can be reduced by dietary or supplemental folic acid. A diet rich in fruits and vegetables

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

PUBLISHER: Brenda Mooney.

MANAGING EDITOR: Leslie G. Coplin.

ASSOCIATE MANAGING EDITOR: Paula L. Cousins.

GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail Address: customerservice@ahcpub.com

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World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States

$199 per year (Student/Resident rate: $95).

Outside the United States

$229 per year plus GST (Student/Resident rate: $110 plus GST).

Back Issues

$16 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 20 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials. This program has been reviewed and is acceptable for up to 20 Prescribed hours by the American Academy of Family Physicians. Term of approval is for one year from beginning of distribution date of July 1, 1998, with option to request yearly renewal.

For CME credit, add $50.

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Conflict of Interest Disclosure

Physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. La Puma is Director of C.H.E.F. Skills Research. Dr. Hornig has the following relationships: Consultant for Forest Labs, Wyeth-Ayerst, Somerset Pharmaceuticals; Research for Dade-Behringwehrke, Pfizer Inc., and Wyeth-Ayerst; Speaker's Bureau for Forest Labs, Glaxo Wellcome plc., Eli Lilly & Co., Pfizer Inc., Pharmacia & Upjohn, SmithKline Beecham plc., Solvay Pharmaceuticals, Wyeth Ayerst. Dr. Ofman has the following relationships: Consultant for Zynx Health, Inc., Cedars-Sinai Health System; Research for Astra USA, Johnson & Johnson, Janssen. Dr. Barrette, Dr. deLeon, Dr. Dietz, Dr. Schiedermayer, Dr. Sorrentino, and Dr. Udani have no relationships with companies related to the field of study covered by this CME program.

should provide sufficient amounts of folic acid and other B vitamins. (*See Table 1 for food sources.)*

Unfortunately, the American diet is usually deficient in the foods needed to supply these vitamins adequately. It is estimated that if the American population increased intake of fruits and vegetables by two to three servings a day, folic acid intake would increase about 100 mcg/d with an average decrease in homocysteine levels of about 2 µmol/L.[3] Folic acid supplements can bring about further reductions in homocysteine levels. Supplementing the diet with 400 mcg/d of folic acid will decrease homocysteine levels by approximately 6 µmol/L.[3]

Recently the Food and Drug Administration began fortifying cereal-grain products with folic acid (140 mcg per 100 g of cereal) to help prevent neural tube defects. This fortification began January 1, 1999. Unfortunately, a recent study indicated that cereals fortified to this level would decrease homocysteine levels by only 3.7%, thought to be inadequate to make substantial impact on vascular disease,[12] but adequate to reduce the incidence of congenital neural tube defects in newborns.

Folate is commonly available in multivitamins, as part of B-complex supplements, and by itself in a capsule. It is water soluble, and may be taken at any time, once daily. The designation of the United States Pharmacopoeia (USP) on the label may indicate that the manufacturer believes the product meets USP standards for dissolution, purity, disintegration, and strength.

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. http://www.fda.gov/fdac/features/796_fcht.html and USDA Nutrient Database for Standard Reference, http://www.nal.usda.gov/fnic/foodcomp

Adverse Effects

Supplementation with folic acid is probably safe. There have been rare cases of exacerbation of vitamin B_{12} deficiency reported at high doses of folic acid supplementation.[13] This may be a concern in elderly patients, and especially elderly vegetarian patients, who may require B_{12} supplementation. There is some evidence to suggest that many elderly people have early vitamin B_{12}, B_6, or folate deficiency despite having normal serum vitamin concentrations.[14] Folic acid supplementation may make it more difficult to diagnose vitamin B_{12} deficiency, when it is present, by simple review of complete blood cell counts.

Drug Interactions

Several drugs may interact with folic acid. Patients treated with the anti-seizure medication phenytoin may have a decrease in phenytoin levels, although at supplement doses of 400 mcg/d, this decrease is unlikely to increase seizure frequency.[13] Folic acid may also reduce the efficacy of methotrexate used for rheumatoid arthritis and other medical conditions.

Conclusion

Retrospective studies have shown a clear association between homocysteine levels and atherosclerotic disease, and identified homocysteine as an independent risk factor for heart disease. Prospective studies have been less conclusive but there is growing evidence that homocysteine levels may correlate with the risk of thrombotic complications. In patients with known atherosclerotic disease the desirable homocysteine level is less than 11 µmol/L. Dietary or supplemental folic acid of 400 mcg can lower homocysteine levels 5-6 µmol/L.

Patients who have premature atherosclerosis or high homocysteine levels may require higher doses of folic acid to achieve a full beneficial effect. In these patients it may be desirable to remeasure homocysteine levels six to eight weeks after initiating therapy to see if an adequate reduction has been obtained.

Recommendation

Screening for increased levels of homocysteine is recommended in individuals with premature atherosclerosis or thrombotic complications without clear cause. Families of affected individuals should be screened as

well. Patients with known coronary artery disease should have adequate folate intake either through a diet rich in folic acid or with supplements.

Adequate folic acid intake can be achieved with a diet high in fruits and vegetables. Foods rich in folic acid include green leafy vegetables such as spinach and turnip greens; fruits such as oranges; beans such as pinto, garbanzo and kidney; and cereals such as wheat flakes and fortified bran flakes. The current USDA recommendation of five to nine helpings of fruits and vegetables daily should supply an adequate amount of folic acid.

If further supplementation is needed because patients do not eat the recommended number of fruits and vegetables, a capsule containing 400 mcg/d should be adequate for most individuals. In the elderly, supplementation of both vitamin B_6 and B_{12} should also be considered to avoid untoward neurologic reactions in patients with covert B_{12} deficiency. Higher doses of folic acid should be reserved for those individuals in whom very high homocysteine levels are documented. ❖

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Study Examines Homocysteine Levels in Adolescents

The April 7, 1999 issue of the *Journal of the American Medical Association* features a study that examined the cardiovascular health of adolescents and particularly, the association between homocysteine, folic acid, and increased risk of cardiovascular disease.

Nonfasting serum homocysteine concentration was used as the main outcome measure and was found to be higher in boys than in girls; higher in African-Americans than in Caucasians and Hispanics; higher in children not taking multivitamins than in those taking multivitamins; and higher in children who smoke than in children who do not smoke.

Researchers with the Child and Adolescent Trial for Cardiovascular Health determined that a significant inverse relationship exists between serum homocysteine and serum levels of folic acid, vitamin B_{12}, and vitamin B_6. Serum homocysteine was not significantly associated with serum lipid levels or family history of cardiovascular disease and was only weakly related to body mass index and systolic blood pressure. After multivariate adjustment, homocysteine remained independently associated with sex, race, serum folic acid and vitamin B_{12} levels, and systolic blood pressure.

Overall, the distribution of homocysteine levels was substantially lower in the children studied than that reported for adults. The study results, however, do indicate that a small percentage of children are potentially at elevated risk for future cardiovascular disease and that serum folic acid may be an important determinant of homocysteine levels in children. ❖

Lactobacillus Acidophilus to Prevent Traveler's Diarrhea

By Jay Udani, MD

TRAVELER'S DIARRHEA IS THE MOST COMMON MEDICAL condition affecting travelers to Latin America, Asia, and Africa. Between 20-50% of all travelers to these areas are affected.[1]

Pathogenesis

Eighty percent of these travelers' diarrheal illnesses are caused by bacterial enteropathogens, especially *Escherichia coli*.[1] Toxin-producing strains of *E. coli* are the single largest pathogen responsible for traveler's diarrhea.[2] The most common sources of infection are contaminated food and water.

Usual Prophylaxis

There are many options for the prophylaxis of traveler's diarrhea, none of which is ideal. Antibiotics such as doxycycline and trimethoprim-sulfa have prophylactic abilities, but also carry the risk of side effects ranging from rashes and photosensitization to Stevens-Johnson syndrome and anaphylaxis. Bismuth subsalicylate has some antimicrobial properties, but must be taken four times a day to be effective. Ciprofloxacin is also used, but this indication is off-label; the drug is expensive; and it may have untoward adverse effects. Prophylactic therapy may also give travelers a false sense of security and may decrease their vigilance in making food selections.[1]

Some patients are more likely to benefit from prophylaxis than others. On the one hand there are persons in poor health or at higher risk for serious medical problems (immunocompromised, frail elderly, patients with chronic diseases).[1] On the other hand, healthy patients may be loath to take any substance as daily prophylaxis.[3]

Overview

The World Health Organization has included bacterial interference or "Microbial Interference Treatment" (MIT) as part of its program to combat increasing resistance to antibiotics.[4] The ability of MIT to combat gram-negative bacteria may make it a useful alternative to antibiotic therapy in selected cases.

Of the more than 400 species of microflora in the human GI tract,[5] the most important "friendly" or "probiotic" bacteria are Lactobacilli.

Lactobacilli appear to be a convenient, safe alternative for the prophylaxis of traveler's diarrhea. In addition, Lactobacilli have been reported to decrease the incidence of colon cancer; restore equilibrium to gut flora after the use of antibiotics; treat candidal vaginal infections; lower serum cholesterol and triglyceride levels; prevent relapses of *C. difficile* infections; stimulate the immune system; and prevent radiotherapy associated diarrhea.[6]

Mechanism of Action

Lactobacillus acidophilus, an anaerobic gram-positive bacterium, is the most stable intestinal lactobacillus. It is found throughout the GI tract and requires folic acid, riboflavin, and other B vitamins and amino acids for growth.[6]

L. acidophilus competes for the same intestinal wall environment as gram-negative bacteria such as *E. coli*, salmonella, clostridium, shigella, and staphylococcus. Competitive inhibition of intestinal wall attachment sites by *L. acidophilus* may prevent colonization by these bacteria.[6]

L. acidophilus also has the ability to hydrolyze lactose rapidly and produce lactic acid.[6] This lowers the intraluminal pH and creates a hostile environment for other bacterial species. Lastly, *L. acidophilus* can produce bacterocins, which are reported to be proteins with antibiotic-like bactericidal properties.[6] These bacterocins appear to have specific activity against proteus, staphylococcus, streptococcus, escherichia, and bacillus.

Clinical Trials

The literature was searched using MEDLINE, PUBMED, the Alternative Medicine Literature CD-ROM, and bibliographies. Protection rates were calculated using the formula in Figure 1. Lower protection rates confer a higher rate of protection against diarrhea.

The earliest RCT involving Lactobacilli for traveler's diarrhea was conducted in 1978 and involved 50 American tourists traveling to Mexico.[7] Twenty-six subjects received Lactobacillus and 24 subjects received placebo preparations. The preparations were given for one week, and the incidence of diarrhea was recorded for four weeks. The two groups were similar in incidence of diarrhea for the one week of active treatment and the three weeks following treatment. No information was available on the exact strain used in the treatment or the freeze-drying or preparation process.

A 1990 Finnish study described 820 tourists traveling to Turkey; 418 were randomized to receive placebo and 402 were randomized to receive Lactobacillus GG powder containing 2 billion Lactobacilli.[2] The intervention began two days prior to departure. Only 756 patients completed the study, however, and an intent to treat analysis was not performed. Data were obtained from a

Figure 1

Protection Rate Calculation: Lactobacilli and Placebo

$$\text{Protection rate} = \frac{(\text{\% diarrhea placebo - \% diarrhea lactobacilli})}{\text{\% diarrhea placebo}}$$

questionnaire completed on the return flight. A total of 178 patients (46.5%) experienced traveler's diarrhea in the placebo group, and 153 (41.0%) in the Lactobacilli group. The overall protection rate was 11.8%. Analysis of variance showed no impact of gender, but travel destination did show significant differences. Of the two resort destinations in Turkey, subjects staying in Alanya showed significant protection ($P = 0.02$), and those staying in Marmaris showed no significant protection.

In 1995, British soldiers deployed to Belize were randomized to receive *L. acidophilus* or placebo for three weeks.[8] Among 282 subjects, no significant difference was seen in the incidence of diarrhea episodes either during the three weeks of treatment or during the one week after treatment was discontinued. Subjects with greater than 90% compliance, whether on placebo or Lactobacilli, were found to have a significant ($P < 0.001$) decrease in diarrhea (15.4% for compliant, 52.9% for non-compliant). This suggests that good compliance may be associated with other risk-minimizing behavior.

In 1997, a trial was conducted of 245 American patients (126 on Lactobacillus GG and 119 on placebo) who were traveling to developing countries for one to three weeks.[3] Patients were instructed to drink only bottled water and to avoid salads, fruits, and fresh vegetables. The risk of having diarrhea on any given travel day was 7.4% for placebo and 3.9% for Lactobacillus GG patients ($P = 0.05$). The relative risk of diarrhea for patients on Lactobacillus GG was 53% with a protection rate of 47%. Age and gender did not impact the incidence of diarrhea as tested by analysis of variance. The protective effect was amplified (42%) in a subset of patients who had a prior history of traveler's diarrhea. In these patients, the risk of diarrhea was 29% for placebo and 16.7% for the group who had received Lactobacillus GG.

Lactobacilli have not been tested against standard treatments, noted above.

Adverse Effects and Allergy

To date, there have not been any serious side effects associated with the ingestion of *L. acidophilus*. Two patients receiving Lactobacillus GG in one of the RCTs[3] reported abdominal cramping, but did not stop taking the preparation. It is suggested to limit dosage to fewer than 10 billion viable *L. acidophilus* daily to decrease the risk of possible mild gastrointestinal disturbance.[6]

Lactobacillus GG has shown no invasive properties. Trials of over 2,000 healthy normal adult volunteers have shown no harmful effects of Lactobacillus GG.[9] Although it has been suggested that Lactobacilli may aggregate platelets, a 1996 study showed that Lactobacillus GG does not increase the risk of spontaneous or physiologically-induced platelet aggregation in vitro.[10] No reports of allergic reactions to *L. acidophilus* were found in the literature reviewed, but *L. acidophilus* preparations often contain lactose and milk proteins and these substances have an allergic potential in some people.[6]

Drug Interactions

L. acidophilus should be taken two to three hours after an antibiotic's dose to prevent killing the *L. acidophilus*. *L. acidophilus* has also been found to interfere with the metabolism of sulfasalazine, chloramphenicol, and palmitate by degrading them in the stomach if taken concurrently.[6] Lactobacilli are also negatively affected by alcohol, which should not be taken concurrently.[5]

Preparation

Aside from freeze-dried powder, there are many dietary sources of Lactobacillus. These include fermented milk products such as kefir, yogurt, and cheese, as well as miso and tempeh.[5] The pasteurization process kills Lactobacillus.[6] When buying milk products for their probiotic (such as *L. acidophilus*) content, make sure the probiotic bacteria were added after the pasteurization process.

A particular strain of *L. acidophilus*, the Lactobacillus GG strain, has been isolated from healthy humans because of its ability to resist acid and bile and adhere to human ileal cells.[3] The Lactobacillus GG strain has consistent adhesive properties that are independent of the freeze-drying process.[4] This strain is often used as the standard in traveler's diarrhea treatment.

Formulation and Dosage

When dosing *L. acidophilus*, the preferred species is Lactobacillus GG, which is supplied as a freeze-dried powder. The bacteria should be packaged moisture and

contamination free.[6] The bottle should be stored and transported at temperatures no greater than 60° F (15° C) or the bacteria will die.[6] In other words, it should be refrigerated at all times. Oxygen, moisture, and light are potentially harmful, and thus *L. acidophilus* should be stored in dark bottles.[6]

The minimum colony forming units (cfu) per weight in grams (g) should be 2 billion cfu/g.[6] Prophylaxis should begin on the day the person leaves the country and should continue for one to two days after returning. Lactobacilli are ingested by mouth in either freeze-dried powder form mixed with water or in capsules containing the freeze-dried form. There are no data to show that continued use beyond three weeks is detrimental, but it is not recommended.[1] *L. acidophilus* counts have been found to remain elevated for up to four weeks after the discontinuation of supplementation.[6]

Conclusion

The issue of prophylaxis for traveler's diarrhea is not clear cut, regardless of which drug or bug is used. The most effective prophylaxis for traveler's diarrhea still remains careful selection of food and beverage while traveling. Of the other choices available, *L. acidophilus* has the best side effect profile and the easiest dosing regimen, but highly challenging environmental conditions. Patients with a previous history of traveler's diarrhea may receive greater protection from Lactobacillus GG than do others. The literature on probiotics for the prevention of traveler's diarrhea is not conclusive, but the more recent and rigorous articles lean toward *L. acidophilus* as useful in preventing traveler's diarrhea.

Recommendation

Travelers at high risk for traveler's diarrhea, travelers whose health may be at risk if they contract traveler's diarrhea, and travelers who cannot take the time necessary to recover should they become ill with traveler's diarrhea should consider taking Lactobacillus GG in a dose of 2-10 billion cfu/g per day starting one day before departure and continuing up to two days after their return. ❖

Dr. Udani is a Fellow in Integrative Medicine and Health Services Research at Cedars-Sinai Medical Center in Los Angeles.

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Colonics for Maintaining and Enhancing Health

By Vance Dietz, MD, MPH, TM

"The serpent is in man. It is the intestine. The belly is a heavy burden; it disturbs the equilibrium between the soul and the body. It is the mother of vices. The Colon is King."

Victor Hugo

"The sins of the colon are its diseases. But I sometimes wonder whether it is not more sinned against than sinning, for what with attacks from above with purges, attacks from below with douches, and frontal attacks by the surgeon, its sorrows are numerous and real."

Arthur Hurst
BMJ 1922;1:941-943

ALTHOUGH BOTH ENEMAS AND COLONIC IRRIGATION ARE used for constipation and pre- and postoperatively, colonic irrigation (aka colonic hydrotherapy or detoxification) for maintaining health is poorly understood by the practicing physician. What is the evidence that the use of colonic irrigation promotes or enhances health?

Theoretical Bases of Colonics

Three theories are relevant: stasis, ptosis, and autointoxication. The theory of stasis holds that as humans began to walk on two instead of four legs, anatomical pressure was placed on the abdominal contents, resulting in "ptosis" of the intestines. The pressure on the tissue

holding the intestines in place produced thickening of these tissues and the creation of stress bands that narrowed the lumen of the gut. The advent of the germ theory of disease proposing that microorganisms, including those in the intestines, cause putrefaction and infection may also have helped to strengthen the argument that stasis and ptosis cause disease.[1] Important remedies for stasis were mechanical in nature and included massage to move the bowel contents, devices that "kneaded" the intestines, and colonic irrigation.

The theory of autointoxication had many early adherents but Charles-Jacques Bouchard received the Legion of Honor for his work in this field.[2] An early worker in what we now term biochemistry, Bouchard postulated that the body normally produces toxins from metabolism, from secretory organs, and from foodstuffs and putrefaction. Autointoxication occurs when the liver and kidneys cannot eliminate the toxins or when there is an increased production of toxins. Thus, "Man... is always working towards his own destruction; he makes continual attempts at suicide by intoxication."[3] Bouchard went on to postulate that, due to the slowness of peristalsis and subsequent movement of fecal material through the colon, toxins could have difficulty being eliminated and could be absorbed.

The theory of autointoxication was also promoted by Eli Metchnikoff who received a Nobel Prize in Medicine for his theory of phagocytosis. Metchnikoff later proposed a link between autointoxication, senility, and aging. He proposed colonic resection as an aid to general health. His name and Nobel Prize were widely used to promote the theory. However, by the early 1900s, colonic irrigation as a treatment to remove toxins and enhance health was under attack from conventional medicine and the American Medical Association and lost favor.

Historical Practice and Folklore

The use of enemas dates to antiquity. Records indicate that enemas or clysters were used as health practices by the Egyptians, Assyrians, Babylonians, Sumerians, Chinese, Hindus, Greeks, and Romans.[1] The Greeks believed that a putrefactive agent from feces was the cause of disease.[4] It was believed that the more effective enemas were those that used the more powerful means to administer the enema, i.e., more volume and more rapid administration led to better results. Ingredients used in enemas include honey, beer, and milk. Enemas with wine, urine, and tobacco smoke were said to be particularly useful for consumption, dropsy, and hernias.

Not true colonic irrigation since only the distal colon is affected—only removing fecal material without cleaning the colon—enemas rose again in the 18th century.[2] In medical practice and with the public, enemas became health interventions to rid the body of toxins. Enemas with mineral oil were felt to be ideal, as they both provoked elimination and prevented stasis by lubricating the intestines. Termed "lavages," enema use became widespread at fashionable spas in Europe. In the U.S., such spas were called "colon laundries."

In this century, colonic irrigation is said to be good for arthritis.[5] Autointoxication, for which colonic irrigation is prescribed, is said to cause fatigue, depression, anxiety, headache, and seizures,[6] and colonic irrigation may be prescribed for these complaints. Other "indications" include alcoholism, allergies, arthritis, asthma, colitis, hypertension, parasites, skin disorders, fevers, and ulcerative colitis.[6,7]

Colonic hydrotherapy is performed by inserting a sterile tube into the rectum connected to a machine that gently pumps water into the rectum. Most machines have light pressure, e.g., 1½ pounds, to ensure that the water enters the colon. Colonic hydrotherapy machines that are registered with the FDA come with a charcoal filter and a UV filter to remove bacteria from the water, which is generally municipal water. Repeated sessions of hydrotherapy are required to ensure that the entire colon is cleaned. The first sessions may only reach the sigmoid colon depending on the amount of fecal material present. Sessions are performed in hospitals as well in physicians' private offices or in colon hydrotherapy centers. According to the International Association for Colon Hydrotherapy (I-ACT), only water is used in colon hydrotherapy to cleanse the colon. However, physicians, particularly naturopaths, may add other substances such as medication or herbs. The I-ACT makes a clear distinction between colon hydrotherapy that is used to cleanse the colon with water and its use in conjunction with other alternative practices.

Data Analysis

To prepare this article, we performed a detailed search of the scientific literature and conducted a telephone interview with a representative of the International Association for Colon Hydrotherapy (I-ACT).

Clinical and Laboratory Studies

No clinical or laboratory studies assessing the impact of colonic hydrotherapy or irrigation on general health could be found.

Anecdotal Data

Discussions with the medical director of an Atlanta wellness center that specializes in colonic hydrotherapy indicate other claims and theories. Because the body

must exert energy to eliminate waste and neutralize toxins, colonic hydrotherapy "frees energy" that would have been used and strengthens the liver and kidneys by decreasing their exposure to toxic substances. As a negative pressure balance supposedly develops inside the lumen, the colon acts as a "sponge" to draw in toxins that have leaked to surrounding tissues. The net effect, it is claimed, is fewer toxins in the body, more energy to fight infection, and five to 10 pounds less fecal material (some persons have been said to lose 20-30 pounds). This loss also relieves distention, bloating, and other sensations associated with constipation.

Unfortunately, there are no empirical data to support or refute this concept. Those who claim enhancement of health from hydrotherapy may be reacting to a placebo effect induced by their belief that toxins are eliminated from the body.[8] Of course, the elimination of 5-10 pounds of fecal material could indeed make one feel better.

I-ACT has about 3,000 members and promotes the safe use of colonic hydrotherapy equipment that has been approved by the FDA as safe for colonic irrigation. The organization issues a certificate in colonic hydrotherapy. The I-ACT representative in our interview stated that colonic irrigation was indicated for constipation and pre- and postoperative treatment. The representative also stated that many practitioners make claims as to the effect of colon hydrotherapy on the treatment of a variety of disorders for which there is no evidence of effectiveness. He stated that colon hydrotherapy was indicated to cleanse the bowels of those individuals who suffered from poor bowel habits for medical, physiologic, or nonmedical reasons. He knew of no controlled trials that had been conducted to assess effectiveness. I-ACT is interested in identifying research centers to collaborate in the design and implementation of such studies.

Adverse Effects

Colonic irrigation has been associated with at least one outbreak of amebiasis in Colorado.[9,10] Investigation of the outbreak revealed that the colonic-irrigation machine had heavy contamination with fecal coliform bacteria. Elsewhere, other cases of enteritis associated with colonic irrigation have been reported.[11] Two deaths associated with the receipt of coffee enemas as a form of therapy for cancer have also been reported.[12] The cause of death was attributed to sodium and chloride depletion and fluid overload.

Some have postulated that colonic irrigation could disrupt the normal bacterial flora of the gut, thereby leading to disease.[13] This has not been documented. Frequent use may be associated with loss of both intestinal muscle tone and normal defecation reflex.[14] Concern has been expressed over the risk of "water intoxication" and hypokalemia; these risks are logical but remain unproven.[7] Colonic perforation is a potential complication but no reports were located.

Contraindications

Colon hydrotherapy is contraindicated in persons with diverticulosis, intestinal bleeding, intestinal neoplasm, hemorrhoids, or enteritis.

Formulation/Dosage

Different practitioners use differing procedures to perform hydrotherapy. The center we visited recommends five to 10 procedures that each last 30 to 45 minutes. I-ACT stated that generally 10-12 sessions are performed depending on the amount of fecal material and the rapidity of the patient's response. Generally, two procedures are performed during the first week of therapy; the next week is skipped; then two more procedures are performed in the third week; and procedures are performed once weekly thereafter. Sessions range from $30-$120 each and often cost more in large metropolitan areas. Some practitioners combine colon hydrotherapy with diet and herbal therapy.

Conclusion

In summary, no studies have been conducted that assess the claim that colonic hydrotherapy enhances health. There is no medical reason to perform or prescribe colonic irrigation other than for constipation or pre- and postoperative indications. Occasional, very serious adverse effects have been reported.

Recommendation

Physicians should discourage the use of colonics for general health enhancement, and should point out that colonics have been evaluated only for the treatment of constipation and pre- and postoperatively and that theories on enhancing health from colonics have not been validated. Physicians should determine whether a patient's interest indicates a need for nutritional counseling and attention to bowel function.

If patients proceed to undergo colon hydrotherapy, they should be advised to determine if the hydrotherapy center has staff accredited by I-ACT and if they use equipment recommended by I-ACT and registered by the FDA. Patients should be cautioned that transmission of parasitic and bacterial infections have been reported from the use of contaminated equipment. ❖

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CME Questions

26. Patients with the genetic disease homocystinuria have elevated levels of homocysteine and are at increased risk for thrombotic events such as pulmonary embolism.
a. True
b. False

27. High levels of homocysteine and low levels of folic acid, vitamin B_6 and vitamin B_{12} have been associated with an increased risk of myocardial infarction and fatal coronary heart disease.
a. True
b. False

28. Dietary sources of Lactobacillus include:
a. fermented milk products.
b. tempeh.
c. miso.
d. All of the above.

29. A patient complains about frequent respiratory infections and feeling poorly for several months. He asks about the value of colon irrigation to improve his health. What do you tell him?
a. Colon irrigation removes toxins from poorly processed food stuffs in the intestines and can result in more energy.
b. There is no evidence that colonic irrigation has any impact on enhancing health.
c. This a harmless procedure without risk so it is acceptable to proceed and have a session of hydrotherapy.

30. A patient has decided to go to a Wellness Center and receive a colonic irrigation. He asks you for any advice on choosing a center. What do you say?
a. Centers providing colonics are generally regarded as safe and there is nothing to worry about.
b. Colonic irrigation is quackery and patients should not receive such therapy.
c. Patients should be aware that improperly maintained equipment has been associated with the spread of parasitic infections and should verify whether the center uses approved equipment.

Clinical Briefs

With Comments from John La Puma, MD, FACP

T'ai Chi to Treat Hypertension

Young DR, et al. The effects of aerobic exercise and T'ai Chi on blood pressure in older people: Results of a randomized trial. *J Am Geriatr Soc* 1999;47:277-284.

IN A SUBURBAN BALTIMORE CLINIC, 62 sedentary older adults (45% black, 79% women, aged > 59 years) with systolic blood pressure 130-159 mm Hg and diastolic blood pressure < 95 mm Hg were randomized to a 12-week, moderate-intensity aerobic exercise program and a T'ai Chi program of light activity. The goal of each condition was to exercise four days per week, 30 minutes per day.

Blood pressure was measured during three screening visits and every two weeks during the intervention period. Estimated maximal oxygen uptake and measures of physical activity level were determined at baseline and at the end of the intervention period.

Mean BMI was 30.6 kg/m^2; mean age was 66.7 years. Nearly half of the population met criteria for systolic hypertension. Mean (SD) baseline systolic and diastolic blood pressures were 139.9 (9.3) mm Hg and 76.0 (7.3) mm Hg, respectively. For systolic blood pressure, adjusted mean (SE) changes during the 12-week intervention period

were -8.4 (1.6) mm Hg and -7.0 mm Hg in the aerobic exercise and T'ai Chi groups, respectively (each within group P < 0.001; between group P = 0.56).

For diastolic blood pressure, corresponding changes were -3.2 (1.0) mm Hg in the aerobic exercise group and -2.4 (1.0) mm Hg in the T'ai Chi group (each within group P < 0.001; between group P = 0.54). Body weight did not change in either group. Estimated maximal aerobic capacity tended to increase in aerobic exercise (P = > 0.06) but not in T'ai Chi (P = 0.24). Programs of moderate intensity aerobic exercise and light exercise may have similar effects on blood pressure in previously sedentary individuals.

COMMENT

The value of physical activity in reducing hypertension is not in question, but the intensity and type of activity is. Can T'ai Chi work as well as aerobics in older adults?

These Johns Hopkins investigators excluded patients on antihypertensives and insulin and patients with cardiovascular symptoms, and measured fitness using VO2max before randomly assigning subjects to a 1-hour group exercise conducted twice weekly, supplemented by home-based exercise.

The aerobic exercise increased progressively from 20-40 minutes by the ninth week. The goal of exercise was 40-60% of heart rate reserve (estimated maximum heart rate minus resting pulse rate).

The T'ai Chi intervention was taught in the Yang style (13 movements practiced in sequence in a slow fluid and continuous manner). According to those subjects returning exercise logs (mean 59% of the aerobic group; 45% of the T'ai Chi group), 96% practiced T'ai Chi four or more sessions per week but only 58% practiced aerobic activity that often.

Udani writes, "The three basic principles of T'ai Chi are: 1) the body should be extended and relaxed; 2) the mind must be alert but calm; and 3) all body movements require a well-coordinated sequencing of segments. This stance is combined with deep diaphragmatic breathing, which is common among the martial arts and many forms of meditation." (See *Alternative Medicine Alert*, October 1998, p. 116.)

To their credit, these investigators did not try to prescribe exercise times in Workout World settings, and recognized that most adults prefer light and moderate activity to vigorous exercise (for better or worse). Similarly, T'ai Chi does not require a specific set of clothes, special shoes, a particular setting or new equipment—all of which can be barriers to people who are not used to exercising.

The problems in this study are those the authors recognize: no no-exercise group; a widely variable adherence to prescribed regimens (average 65%); reliance on a seven-day physical activity recall (often inaccurate); and likely selection bias. Adverse events are not reported, but T'ai Chi is safely practiced by literally tens of millions of Chinese daily. Musculoskeletal injuries from aerobic exercise, conversely, are well-documented.

Recommendation

Much better studies need to be done before we can say with surety that T'ai Chi lowers blood pressure. But this promising pilot deserves a longer trial with better controls and adherence. ❖

Steroids in Chinese Herbal Creams

Keane FM, et al. Analysis of Chinese herbal creams prescribed for dermatological conditions. *BMJ* 1999;318:563-564.

To determine whether Chinese herbal creams used for the treatment of dermatalogical conditions contain steroids, 11 herbal creams obtained from patients attending general and pediatric dermatology outpatient clinics were analyzed with high resolution gas chromatography and mass spectrometry. Eight creams contained dexamethasone at a mean concentration of 456 mcg/g (range 64-1500 mcg/g). All were applied to sensitive skin areas such as face and flexures, sometimes several times daily. Greater regulations should be imposed on Chinese herbalists to prevent illegal and inappropriate prescribing of potent steroids.

COMMENT

People gravitate to Chinese herbalists for a cure, just like they come to primary care physicians for an itchy, scratchy rash that just won't go away. This report, from the Departments of Dermatology and Clinical Biochemistry at King's College Hospital in London, arose from the clinical observation that patients with eczema often reported improvement with Chinese herbal creams. These same patients returned to the National Health Service clinic after seeing the herbalist "when they could no longer afford the herbs (the cost was up to 35 pounds per week)"—approximately $45.

Sadly, seven of these patients were children, one only four months old and the one who received the greatest amount of steroid. The indications for prescription were eczema in seven cases, scaly scalp in two cases and eczema herpeticum in one case. All the bottles prescribed for eczema contained dexamethasone. Of the two bottles that were labeled (in Chinese), none contained dexamethasone; 456 mcg/g of dexamethasone is roughly equivalent to 0.05% betamethasone valerate.

The authors could not discover the original source of the creams, but speculate that individual mixing occurred at different shops, and that "personalized, unlabeled, unstandardized preparations" were given to patients. They note the "inadvertent use of topical steroid can cause severe exacerbation of eczema herpeticum" and denounce the use of steroids in "concentrations inappropriate for use on the face or in children." Like in the U.S., the source and quality of ingredients in the U.K. is not standardized, and hepatotoxicity has been reported from oral preparations for eczema.

Eczema (atopic dermatitis) usually spontaneously subsides by the time infants become toddlers. Though steroids suppress the itching, so do hydrating emollients, and the use of even topical steroids remains controversial. Schiedermayer writes, "Clinical trials are notoriously difficult to perform,

because of the inherent variability of the clinical state, the subjective nature of the assessment, and a large placebo response." (See *Alternative Medicine Alert*, January 1999, p.9.)

Recommendation

Patients who use individually prepared Chinese herbal creams for skin disorders have a good chance of receiving steroids—in this case, high-powered dexamethasone. Until such creams are manufactured, labeled, and regulated like the powerful medications they are, no parent should apply these creams to the face of a child, and no physician should recommend them. ❖

PENS for Relief of Low Back Pain

Ghoname EA, et al. Percutaneous electrical nerve stimulation for low back pain: A randomized crossover study. *JAMA* 1999;281: 818-823.

LOW BACK PAIN (LBP) CONTRIBUTES TO considerable disability and lost wages in the United States. Commonly used opioid and nonopioid analgesic drugs produce adverse effects and are of limited long-term benefit in the management of this patient population.

The effectiveness of a novel nonpharmacologic pain therapy, percutaneous electrical nerve stimulation (PENS), was compared to transcutaneous electrical nerve stimulation (TENS) and flexion-extension exercise therapies with long-term LBP. We used a randomized, single-blinded sham-controlled crossover design from 3/97-12/97 in an ambulatory pain management center at a university medical center.

Twenty-nine men and 31 women with LBP from degenerative disk disease of at least three months duration were randomized to four administered therapeutic modalities (sham-PENS, PENS, TENS, and exercise therapies) for 30 minutes three times a week for three weeks, with one week off between therapies. PENS was significantly more effective in decreasing visual analog scale (VAS) pain scores after each treatment than sham-PENS, TENS, and exercise therapies.

After treatment, mean +/- SD VAS scores for pain were 3.4/1.4 for sham PENS, 5.5/1.9 for PENS, 5.6/1.9 for TENS, and 6.4/1.9 for exercise therapy. The average +/- SD daily oral intake of nonopioid analgesics (2.6/1.4 pills daily) was decreased to 1.3/1.0 daily with PENS ($P < 0.008$) compared with 2.5/1.1, 2.2/1.0, and 2.6/1.2 daily with sham-PENS, TENS and exercise, respectively. Compared with the other three modalities, 91% of the patients reported that PENS was the most effective in decreasing their LBP. The PENS therapy was also significantly more effective in improving physical activity, quality of sleep, and sense of well-being ($P < 0.05$ for each). The SF-36 survey confirmed that PENS improved post-treatment function more than sham-PENS, TENS, and exercise.

In this sham-controlled study, PENS was more effective than TENS or exercise therapy in providing short-term pain relief and improved physical function in patients with long-term LBP.

■ COMMENT

This well-designed Dallas study has some flaws: the exercise prescribed was a simple spine flexion-extension repeated 30 times in 30 minutes; follow-up was limited to 72 hours; patients using opioids for LBP were excluded; how many patients had radiculopathy, if any, is not stated; and a double-blind design was not possible. Overall, its results are impressive in a notoriously difficult-to-treat population, albeit over the short-term.

PENS produced an acute analgesic effect immediately after each treatment, though it took three to four treatments to change their VAS scores for pain, activity, and sleep, and to decrease the consumption of oral analgesics, significantly beating TENS treatment alone.

PENS combines TENS with electroacupuncture to stimulate peripheral sensory nerves at the dermatomal levels corresponding to the local pathology. Ten 32 gauge stainless steel probes were connected to five bipolar leads connected to a small, non-FDA-approved electrical generator. The probes were placed deliberately into soft tissue or muscle from T12 to S2 and were stimulated at a frequency of 4 Hz for 0.5 milliseconds. In contrast, TENS used 4 one-inch cutaneous electrode pads, stimulated at 4 Hz for 0.1 milliseconds.

A recent randomized controlled trial with two-year follow-up comparison of chiropractic, physiotherapy, and an educational booklet for LBP showed approximately equivalent effectiveness (*N Engl J Med* 1998;339:1021-1029) with highest patient satisfaction for chiropractic and least cost for the educational booklet.

A new field of medicine—perhaps called "musculoskeletal medicine"—is emerging from between the cracks of rheumatology, physiatry, orthopedics, sports medicine, and anesthesiology. Physicians seriously interested in these patients approach their diseases from a multimodal rehabilitative perspective rather than a curative one. The main barriers to their success will be the time required to establish a therapeutic alliance.

Recommendation

As part of a multimodal approach to back pain, PENS warrants serious consideration in longer trials to test whether it can improve short- or long-term pain or improve function in a lasting fashion. ❖

In Future Issues:

Carnitine for Congestive Heart Failure
Guarana for Treating Obesity
Vitex for Perimenopausal Symptoms
Use of Guided Imagery in Cancer Treatment