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Multivitamin Use, Folate, and Colon Cancer in Women in the Nurses' Health Study

ABSTRACT & COMMENTARY

This study asks about determinants of colon cancer. The data are the dietary reports from a cohort of the Nurses' Health Study. This subgroup was composed of 88,756 women followed since 1976. In 1980, Giovannucci and colleagues started tracking dietary habits at two-year intervals using a semiquantitative food-frequency questionnaire. Subjects also provided information about vitamin use, hormone use, smoking, physical activity, aspirin use, colonoscopy or sigmoidoscopy, and parental history of colorectal cancer. After controlling for an array of potentially confounding factors, Giovannucci et al found that those women who used multivitamins for more than 15 years showed a significant reduction in rates of colorectal cancer. Folate from dietary sources alone was related to a modest reduction in risk, whereas the benefits of long-term multivitamin use were seen at all levels of dietary intake. (Giovannucci E, et al. *Ann Intern Med* 1998;129:517-524.)

COMMENT BY SARAH L. BERGA, MD

Now we have folate and its sources to consider when advising women about the chemoprevention of aging. Folate might well be nominated as the vitamin of the year. Not only does its intake reduce the risk of neural tube defects in pregnant women, but its use also has been touted as a way to diminish the risk of cardiovascular disease due to elevated homocysteine levels.[1] Why might folate be so important? As Giovannucci et al point out, folate is essential for regenerating methionine, the methyl donor for DNA methylation. Also, it is needed for producing purines and pyrimidines for DNA synthesis. Inadequate availability of folate may contribute to aberrations in DNA methylation and may lead to abnormalities in DNA synthesis and repair. Hypomethylation of DNA is reported to be one of the earliest events in colon carcinogenesis. It is estimated that 88% of the population has folate intake of less than 400 g/d, the amount currently recommended and generally contained in multivitamin preparations. While foods naturally high in folate contain important micronutrients and the goal of obtaining most nutrients from food should not be abandoned, multivitamin use or increased

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INSIDE

intake of fortified foods is recommended to ensure adequate folate status.

COMMENT BY ELIZABETH MORRISON, MD, MSED

We already know that all American women of reproductive age should be taking supplementary folate because it prevents neural tube defects in their offspring.[2] Data from the Nurses' Health Study, published in the *JAMA* earlier this year,[1] indicate that women who take multivitamin supplements with folate may decrease their risk of coronary artery disease by up to 25%. Now, we have compelling evidence of yet another benefit of multivitamin supplements and folic acid for women—reducing the risk for colon cancer.

Giovannucci et al skillfully handled possible confounders. Women who take multivitamin and folate supplements are likely to pursue other "health-seeking behaviors" such as low-fat and high-fiber diets. Giovannucci et al searched for confounding ties between these behaviors and colon cancer risk but found none that altered the substantial relationship between folate, multivitamins, and colon cancer.

It is interesting that even high intake of dietary folate did not seem to decrease colon cancer risk, while folate and multivitamins in supplement form did. Giovannucci et al point out that dietary folate is not as bioavailable as folate supplements, which may account for this difference. One also wonders why no benefit resulted when women took the supplements for less than 15 years. Could other dosages or forms of these nutrients provide more rapid or more powerful benefits?

Giovannucci et al discuss the study's main flaw—its inability to separate the effects of folate from the multivitamins in the supplements. It is certainly possible that unknown nutrients in the multivitamin supplements, and not the folate, are ultimately responsible for the reduced risk of colon cancer. Clearly, we need to see data from a randomized, controlled trial, preferably one that separately analyzes folate and other nutrients contained in multivitamin supplements. Since such data will not be available any time soon, if ever, this study's meticulous analysis provides useful interim findings. I will add this study to my repertoire as I encourage women to pursue "health-seeking behaviors" that include daily folate-containing multivitamin supplements. *(Dr. Berga is Associate Professor, Departments of Obstetrics, Gynecology, Reproductive Sciences, and Psychiatry, University of Pittsburgh, PA.; and Dr. Morrison is Assistant Clinical Professor of Family Medicine, University of California, Irvine.)* ❖

References

1. Rimm EB, et al. *JAMA* 1998;279:359-364.
2. Czeizel AE. *Ann N Y Acad Sci* 1993;678:266-275.

Which of the following conditions has *not* been linked to inadequate intake of folate?

a. Neural tube defects
b. Osteoporosis
c. Colon cancer
d. Cardiovascular disease associated with elevated homocysteine levels

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DVT and Pulmonary Embolism with Low-Molecular-Weight Heparin

ABSTRACT & COMMENTARY

Synopsis: *In a tertiary care hospital, the use of nurses to either teach patients to inject or directly administer the low-molecular-weight heparin dalteparin (200 U/kg every 24 hours) for a minimum of five days resulted in 95% completion (194 patients) of home treatment for deep venous thrombosis or pulmonary embolism. Recurrent thromboembolism occurred in less than 4% and major hemorrhage occurred in 2%.*

Source: Wells PS, et al. *Arch Intern Med* 1998;158: 1809-1812.

Pulmonary thromboembolism is a common and potentially deadly illness. There is an estimated incidence as high as 5% in the general population with a mortality of at least 20,000 individuals per year in the United States. Until now, the management paradigm has involved admission of patients to receive intravenous heparin once the diagnosis of either deep venous thrombosis or pulmonary embolism had been made. Hospital stay has been generally 7-10 days after a switch to warfarin had been successfully made. Prolonged hospitalization was often the result of inability to establish appropriate dosing levels using partial thromboplastin time (PTT) for standard heparin therapy and the prothrombin time (PT) or, more recently, the International Normalized Ratio (INR) for warfarin. Low-molecular-weight heparin has greater activity against factor Xa than standard heparin resulting in less risk of hemorrhage. Prolonged bioavailability and longer half-life allow a more predictable response with once or twice daily subcutaneous injections without the need for laboratory monitoring. In several recent trials, the use of low-molecular-weight heparins resulted in outcomes similar to unfractionated heparin for prevention of venous thrombosis and treatment of pulmonary embolism.[1,2] This ability to be administered subcutaneously has raised the possibility that home treatment would be possible. In recent studies,[3,4] outpatient treatment was demonstrated to be safe and effective for deep venous thrombosis using low-molecular-weight heparin administered subcutaneously. The study of Wells and colleagues builds on this information by evaluating this modality outside a research setting. Low-molecular-weight heparin was given using two methodologies of care. In one, community-based homecare nurses gave the patients injections and in the second, patients learned to inject themselves under nurse supervision during the three months of treatment. Patients had objective evidence by ultrasonography or venography of deep venous thrombosis or pulmonary embolism. Exclusion criteria included the need for hospitalization due to other factors (i.e., active bleeding, inpatient status, hemodynamic instability, requirement for pain medication, or age younger than 18 years). Patients were given 200 U/kg of dalteparin for a minimum of five days or until the patient's INR was greater than 2.0 for at least two days on warfarin. A total of 194 patients over 10 months were studied with more than 95% receiving their entire treatment at home. Approximately one-half of the patients injected themselves and the others received injection by the homecare nurse. The average age was approximately 64 years. Thirty-four patients had pulmonary embolism and cancer was present in approximately one-third of patients. There was no significant difference in the rate of recurrence between nurse-injected (3.2%) or self-injected patients (4%). Overall recurrence rate was 3.6%. Also, there were no significant differences in the rates of major hemorrhage, minor hemorrhage, or death. Eleven deaths were due to metastatic cancer.

Table

Complications of Outpatient Treatment

	Overall(%)
Bleeding	3.6
Minor	5
Major	7
Death	7

COMMENT BY ALAN M. FEIN, MD

The use of anticoagulation to treat thromboembolic disease is an important therapeutic modality but is also a major cause of morbidity and mortality in and out of the hospital. Heparin is among the major causes of drug-related complications in hospitalized patients, while the increased use of warfarin continues to result in major morbidity and mortality (in some studies up to 10% per year)—especially in older patients and those with malignancy. Therefore, the use of low-molecular-weight heparin that permits anticoagulation without the need for continued monitoring is a welcome addition to the therapeutic armamentarium. Several previous studies have demonstrated outpatient therapy with low-molecular-weight heparin to be safe with similar outcomes and complications to inpatient therapy. In this outcome study performed in a community setting, it was demonstrated that more than 80% of all patients could be treated at home using either self-injection or nurse supervised injection. In previous studies, 30-75% of patients with venous thromboembolism were excluded because of potential complications. Combining the results of both methods of treatment, overall rates of recurrence were low (less than 4%) and bleeding and death were similarly low (2% and 7%, respectively). Since none of the deaths occurred during the first two weeks of the study, it seems unlikely that these patients died of pulmonary embolism. Despite the overall positive results, the application of low-molecular-weight heparin therapy should be introduced cautiously to outpatients. As Wells et al point out, patients with hemodynamic instability or risk of bleeding were excluded. Based on my own practice, a much lower percentage than the 80% reported would have been able to be treated at home. My own comfort level with home treatment would need to be higher than it is currently to apply this to a broad range of patients. Still, the use of low-molecular-weight heparin for outpatient treatment of venous

thrombosis and pulmonary embolism should satisfy the need to reduce cost of care and improve patient satisfaction and needs to be further explored. ❖

References

1. The Columbus Investigators. *N Engl J Med* 1997; 337:657-662.
2. Simonneau G, et al. *N Engl J Med* 1997;337:663-669.
3. Koopman MMW, et al. *N Engl J Med* 1996;334:682-687.
4. Levine M, et al. *N Engl J Med* 1996;334:677-681.

In the low molecular weight heparin study, major hemorrhage occurred in:

a. 4% of patients.
b. 8% of patients.
c. 2% of patients.
d. 10% of patients.

Late-Breaking Lipid Trials

CONFERENCE COVERAGE

Synopsis: *Several studies were recently reported that should influence clinical practice.*

Source: American Heart Association Annual Scientific Sessions, November 8-11, 1998, Dallas, TX.

AVERT: Atorvastatin vs. Revascularization

This multicenter, nine-country study was designed to investigate the potential of aggressive, lipid-lowering strategy with atorvastatin vs. angioplasty in stable patients with CAD with few symptoms and single- or double-vessel disease with preserved left ventricular function. Mean LDL cholesterol was 140; patients had to be able to complete a four-minute exercise test without ischemia. Three hundred forty-one subjects were randomized to receive 80 mg of atorvastatin daily or the scheduled angioplasty that triggered the enrollment process. Follow-up was approximately 18 months. The primary end point was any major ischemic event, including death, nonfatal infarction, stroke, revascularization, or hospitalization for unstable angina. Secondary end points included the time to the first ischemic event as well as safety parameters. Because of the concern that the patient cohort treated with atorvastatin alone might have threatening episodes of ischemia, two interim analyses were scheduled. The patients were evenly matched; approximately 90% were male, with a mean age of 58; more than 50% had single-vessel disease, and 44% had two-vessel disease. The LAD was involved in more than one-third. More than 40% of these subjects had a prior infarction. Patients had angina class 1 or 2. Baseline LDL cholesterol was 140 mg/dL. The angioplasty group received the usual medical care, and at the end of the study, their LDL cholesterol had fallen by 18% to 119 mg/dL. The high dose of atorvastatin resulted in a 46% drop in LDL cholesterol, to a mean of 77 mg/dL. Atorvastatin subjects had less angina and experienced a 36% reduction in the combination of cardiovascular events (nonfatal myocardial infarction, revascularization, hospitalization for angina), compared with individuals treated with angioplasty and usual care. The actual overall event rate was 13% in the atorvastatin cohort and 21% in the angioplasty cohort (P = 0.048). The time to the first ischemic event was shorter in the angioplasty cohort than in the statin group, with major curve separation beginning at approximately 6-7 months (P = 0.027); the overall combined end point was relatively low overall—approximately 2% per year. Both angioplasty and coronary bypass surgery were decreased by lipid lowering, as was hospitalization for unstable angina; 87% of these individuals did not suffer an event by 18 months. Safety monitoring revealed a 2.4% incidence of increased liver enzymes. No patient had other adverse reactions and there were no elevations of creatine kinase.

COMMENT BY JONATHAN ABRAMS, MD

This long-awaited study, although modest in patient size, strongly suggests that aggressive lipid lowering in patients with stable CAD is beneficial and may avert or delay revascularization procedures. This is consistent with plaque stabilization and improvement in coronary endothelial function, as well as slowing of progression of coronary atherosclerosis. None of these putative mechanisms can be assessed in this trial. The LDL target achieved is the lowest in any reported statin trial to date; the potency of atorvastatin allows this to occur, and the final mean LDL cholesterol of 77 mg/dL appears to put downward pressure on what is the optimal target LDL for patients with vascular disease. The recently completed post-CABG trial also achieved an LDL cholesterol level of substantially below 100, and demonstrated a significant reduction in saphenous vein graft disease. Thus, it appears that a statin should be part of the therapy of most or perhaps all patients with CAD, with a target LDL cholesterol of less than 100 mg/dL. Whether the trial would have been less positive if the achieved LDL-C was 10 or 20 mg/dL higher can only be resolved by subsequent studies. At this time, it does appear reasonable to include as state-of-the-art medical therapy a statin, along with aspirin and anti-anginal drugs. AVERT results support an extremely aggressive approach to cholesterol lowering in patients with established coronary disease, and raise the possibility that such therapy may truly alter the natural history of coronary disease, and potentially decrease the need for revascularization while stabilizing coronary atherosclerosis to prevent

acute ischemic events.

VA-HIT Trial

HIT is a VA cooperative trial conducted at 20 centers that asked the question if individuals with low HDL and normal LDL cholesterol would benefit from raising HDL with a fibrate. This ambitious trial enrolled 2531 patients between 1991-1993 who had an HDL of less than 40 mg/dL and an LDL of less than 140, with triglycerides less than 300. Subjects were randomized to gemfibrozil 1200 mg daily in long-acting formulation or placebo. The primary end point was CAD death or nonfatal myocardial infarction. Mean follow-up was seven years. Secondary end points included all-cause of mortality, stroke, revascularization procedures, and nonfatal MI. The male patient cohort was 90% white, with a mean age of 64. Patients were overweight with an increased waist-hip ratio. Twenty percent were smokers, more than 50% had hypertension, and 25% had diabetes. Baseline lipids were: TC 175; LDL-C 111; HDL-C 32; and TG 161. The primary end point of CAD death or nonfatal MI was 21.6% in placebo subjects vs. 17.3% in gemfibrozil patients (RR = 22%, P = 0.006), with similar results on CAD death and nonfatal MI. Strokes and TIA were decreased. Unstable angina and revascularization were unaffected by therapy. Event curves began to separate by 18-24 months. Treatment lowered TC 28%; HDL increased 7.5%, LDL-C increased 4%, and TG decreased by 25%.

COMMENT BY JONATHAN ABRAMS, MD

Only the Helsinki Heart Study has demonstrated a benefit for HDL-C elevation in patients that had elevated TG, low HDL, and modest elevation of LDL-C. In the HIT population, baseline LDL levels were excellent, yet individuals taking gemfibrozil clearly benefited with respect to cardiac events. Thus, it appears that efforts to increase HDL cholesterol, even in individuals who have no other lipoprotein abnormality, are justified in secondary prevention CAD subjects. The HIT trial confirms the value of gemfibrozil. However, greater HDL elevations can be achieved with niacin, and this is a reasonable alternative for many individuals. Whether other fibrate drugs will have a greater or equivalent effect than gemfibrozil remains to be determined. At the present time, all patients with vascular disease who meet the lipid criteria in VA-HIT should be considered for gemfibrozil treatment. *(Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.)* ❖

The aggressive atorvastatin therapy vs. angioplasty trial showed that atorvastatin:

a. increased liver function tests in 24%.
b. increased creatine kinase in 15%.
c. reduced cardiac events by 36%.
d. reduced mortality.

How Do Physicians Communicate About Advance Directives?

ABSTRACT & COMMENTARY

Synopsis: *When primary care physicians discussed advance directives, conversations were brief (about 5 minutes), with the physician speaking two-thirds of the time, and the conversations rarely dealt with values or attitudes toward uncertain recovery.*

Source: Tulsky JA, et al. *Ann Intern Med* 1998;129: 441-449.

To understand why advance directives do not work, Tulsky and colleagues audiotaped conversations between 56 primary care providers and established patients randomly selected from the office schedule. Patients were eligible for the study if they were at least 65 years old or had a serious medical illness (such as cancer, prior cardiac arrest, HIV infection, renal insufficiency, chronic obstructive pulmonary disease, or congestive heart failure), and had not previously discussed this topic with their physician.

The physician was asked to "discuss advance directives in whatever way you think is appropriate for this patient." Comments were coded and analyzed using standard techniques. The median age of the physicians was 37 years, and 56% were men. Ninety-five percent of the physicians said they were comfortable talking to patients about advance directives, although 61% said they rarely did this.

The median discussion lasted 5.6 minutes (range, 0.9-15.0 minutes), with the physician speaking for 3.9 minutes (range, 0.6-10.9 minutes) and the patient for 1.7 minutes (range 0.3-9.6 minutes). Most physicians (93%) discussed advance directives by posing hypothetical scenarios. The scenarios were typically dire (no hope of recovery) or completely reversible (no change in functional level). Relatively few of these scenarios (55%) had an unpredictable outcome. When the physicians discussed treatment options, such as cardiopulmonary resuscitation or mechanical ventilation, they rarely clarified what the patient knew about the treatment. Several patients expressed a desire not to be a "vegetable," but no physician asked what this meant to the patient. Patients overwhelmingly viewed these discussions as positive experiences. All stated they were glad to have

had the discussion, 96% felt it had been worthwhile, and all believed that their physician did a good job talking about these issues. Only 7% of the patients felt uncomfortable during the discussion.

COMMENT BY LESLIE A. HOFFMAN, PhD, RN

Numerous organizations, legislators, and the courts advocate use of advance directives to ensure that the patient's wishes are respected when making end-of-life decisions. Discussions regarding advance directives are supposed to introduce patients to the concept and elicit their preferences when they are competent and can provide input. Nevertheless, prior research indicates that advance directives rarely influence how care is provided at the end of life.

Findings from this study suggest that this outcome may be appropriate, rather than inappropriate. The study was conducted in five primary care medicine practices in two states (NC, PA), and involved 56 primary care physicians and 56 established patients, all of whom gave consent to participate. The physicians knew that they were being audiotaped, so the results presumably represent a best case scenario. Nevertheless, conversations were brief and infrequently included situations in which the outcome was uncertain. Most patients told their physicians they would reject treatment in the face of certain death and would desire aggressive treatment for reversible illnesses, an expected outcome.

Only 13% of physicians mentioned outcomes of life-sustaining treatment other than complete recovery or death, such as continued dependence on mechanical ventilation or impaired cognition. Physicians rarely asked patients to define what they meant by "a good quality of life" or "being a burden." Instead, they asked if they wanted specific interventions. The conversations accomplished the goal of introducing the topic of advance directives, but their usefulness in guiding future treatment decisions was unclear. Nevertheless, the patients valued these discussions.

Prior studies have examined a number of factors to explain why advance directives do not work as intended. Part of the explanation may lie in the findings of this study. We cannot be certain that a previously written directive accurately reflects the preferences of the patient in the current circumstances. Given this, it appears appropriate to reaffirm preferences, rather than simply follow the directive. It is not possible to know whether the prior discussion was of the quality necessary to accurately elicit preferences, or whether the patient understood all the implications. Rather than trying to increase the number of conversations about this topic, it would seem more important to attempt to increase the quality of communication and information shared during these conversations. ❖

When advance directives were discussed, most patients:

a. felt uncomfortable.
b. felt the discussion to be worthwhile.
c. wanted more time to talk.
d. felt it was a negative experience.
e. none of the above

Pharmacology Update

Estradiol/Norethindrone Acetate Transdermal Systems (CombiPatch)

By William T. Elliott, MD and James Chan, PhD

The fda has approved the first combination estrogen and progestin transdermal system for hormone replacement therapy. CombiPatch is an estrogen/progestin transdermal patch that uses a matrix patch technology that was developed by Noven Pharmaceuticals and marketed by Rhone-Poulenc Rorer. This system delivers 50 mcg of 17-estradiol and 140 mcg or 250 mcg of norethindrone acetate per day through the intact skin.[1] CombiPatch provides an alternative to oral estrogen and progestin or transdermal estrogen and oral progestin.

Indications

CombiPatch is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, treatment of vulvar and vaginal atrophy, and treatment of hypoestrogenism due to hypogonadism, castration, or primary ovary failure.

Dosage

CombiPatch is available as a transdermal system that delivers 50 mcg of 17-estradiol or 140 mcg (9 cm^2) or 250 mcg (16 cm^2) of norethindrone acetate. For continuous combined therapy: CombiPatch 50 mcg/140 mcg should be worn continuously for 28 days. A new system should be applied twice a week during the 28-day cycle.

For continuous sequential therapy: CombiPatch 50 mcg/140 mcg should be worn for the last 14 days of the

28-day cycle following a 14-day estrogen regimen. Should a greater progestin dose be desired, CombiPatch 50 mcg/250 mcg is available.

The system should be appled on a smooth (fold-free), clean, dry area of the skin on the lower abdomen. The sites must be rotated with an interval of at least one week between sites. The patch should not be applied to or near the breast, oily areas, or areas where clothing may rub the system or modify its delivery (e.g., waistline).[1]

Potential Advantages

CombiPatch provides an alternative to oral estrogen/progestin therapy. This transdermal system provides consistent delivery of 17-estradiol, estrone, and norethindrone over the application interval. Mean serum concentrations at steady-state with application of the 50 mcg/140 mcg patches are 45 pg/mL (27-71) for estrogen, 54 pg/mL (49-72) for estrone, and 489 pg/mL (386-617) for norethindrone. Twice-weekly administration may improve medication adherence. CombiPatch has been reported to reduce triglyceride levels by 4.6% to 14.1% from baseline when measured after one year.[1] Oral hormone replacement therapy tends to increase triglyceride levels.[2]

Potential Disadvantages

Transdermal estradiol bypasses the first past metabolism seen with orally administered estrogens and appears to have less favorable effects on the liproprotein profiles. Reductions in total cholesterol and LDL-cholesterol are less than that reported for oral estrogens.[1-3] CombiPatch also reduced HDL-cholesterol, although most of the decrease was attributed to the HDL3 subfraction—not the HDL2 subfraction.[1] Oral hormone replacement tends to increase HDL-cholesterol levels.[2] Application site reactions have been reported at a rate of up to 21%.[1]

Comments

CombiPatch is the first transdermal product to combine estrogen and a progestin in a single patch for hormone replacement therapy. It is the transdermal counterpart to Prempro tablets (conjugated estrogen and medroxyprogesterone acetate) marketed by American Home Products and the recently approved Activelle tablets (estrogen/norethindrone acetate) marketed by Novo Nordisk. Clinical study results indicated that the product reduced the number and daily intensity of hot flushes compared to placebo.[1] Trial results also indicated that norethindrone acetate as formulated in CombiPatch was effective in reducing the incidence of estrogen-induced endometrial hyperplasia.[1] Transdermal estrogen appears to be effective in preventing osteoporosis; however, its potential favorable effect on cardiovascular disease risk is less certain. CombiPatch is about $0.90 per day compared to $0.65 per day for oral therapy with Prempro.

Clinical Implications

Oral hormone regimens are generally considered as first-line therapy for most postmenopausal women. Transdermal formulations may be considered for women in whom oral estrogen therapy does not relieve symptoms, is not tolerated, or women who have hypertriglyceridemia. The benefits of hormone replacement therapy include symptomatic relief, prevention of osteoporosis, and reduction of cardiovascular events. The latter has been an important reason for postmenopausal women to initiate hormone replacement therapy. Recently, the role of hormone replacement therapy in secondary prevention of CAD events and death has been questioned.[4] However, most women use hormone replacement in the role of primary prevention and data from observational studies tend to support this use. Randomized trials are underway to study the effect of estrogen replacement therapy and hormone replacement therapy both in secondary prevention and primary prevention. Results are expected in 2000-2005.[5]

References

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5. Petitti DB. *JAMA* 1998;280:650-651.

Combipatch (estrogen/progestin transdermal patch) is associated with:

a. frequent episodes of breakthrough bleeding.
b. increased HDL levels.
c. reduced TG levels.
d. minimal impact on vasomotor symptoms.
e. None of the above

Attention CME Subscribers

CME Question #30, which appeared in the December 15, 1998 issue of *Internal Medicine Alert*, will be thrown out because there was not an accompanying arti-

By Louis Kuritzky, MD

cle. CME subscribers may leave question #30 blank on their Scantron form.

Use of Colchicine to Treat Severe Constipation in Developmentally Disabled Patients

The developmentally disabled often suffer some of the worst difficulties with constipation, since they more commonly also experience hypotonia, autonomic dysfunction decreasing bowel motility, physical inactivity, and polypharmacy. Based upon an n = 1 experience with a person suffering chronic constipation refractory to traditional measures, Frame and colleagues successfully managed this patient with colchicine 0.5 mg tid. Following this success, Frame et al performed a prospective double-blind crossover study of colchicine vs. placebo for eight weeks in developmentally disabled patients who required three or more laxatives to manage chronic constipation.

As defined by an increased number of bowel movements and/or decreased requirement for laxatives, Frame et al found that eight out of 11 patients were improved while on colchicine, and no clinically important side effects occurred.

Colchicine is known to stimulate gastrointestinal activity through neurogenic stimulation. In these patients, treatment produced an average of 4.27 more bowel movements per patient over eight weeks time.

Colchicine can cause adverse effects, but serious toxicity is rare and usually confined to those with renal or hepatic insufficiency. Frame et al suggest that although colchicine is not suggested as a first-line laxative, persons with refractory constipation to standard methods, as are commonly found among the developmentally disabled or nursing home populations, may merit consideration for this intervention. ❖

Frame PS, et al. J AM Board Fam Pract 1998;11:341-346.

Sinusitis in the Common Cold

Bacterial sinusitis is generally treated with antibiotics. Sinusitis, as determined, may be of diverse origin. During the common cold, if symptoms suggest sinusitis and sinus films are obtained, sinusitis seen on such films might prompt antibiotic use, as differentiation of bacterial from viral sinusitis is difficult. As part of a trial of fluticasone propionate in treatment of the common cold, Puhakka and associates studied sinus radiographs of 197 young healthy adult men and women on days 1, 7, and 21 of a common cold, and followed patients for three weeks clinically beyond that time.

Radiographs showed sinusitis in 14.2% of patients on day 1, 38.8% on day 7, and 11.3% on day 21. Common radiographic findings included mucosal thickening greater than 5 mm, air-fluid levels, and total opacification.

Overall, 57% of study subjects had sinus abnormalities during the first 21 days. All patients made full clinical recoveries, and no patient with radiologic sinusitis was treated for it with antibiotics.

Sinusitis is common, as defined radiographically, during the common cold. Puhakka et al suggest that, with few exceptions, sinus films should not be obtained during the typical evolution of the common cold, as such films lead to unnecessary irradiation, cost, and likelihood of superfluous antibiotic therapy. ❖

Puhakka T, et al. J Allergy Clin Immunol 1998;102:403-408.

Potassium Supplementation on BP in patients with Essential Hypertension

A variety of diverse pieces of information suggest that potassium (K) status is related to blood pressure (BP). Dietary K intake correlates inversely with BP, and meta-analyses show significant BP reduction with supplementation.

Kawano and colleagues studied, in a randomized crossover design method, 55 hypertensive Japanese men and women given 2500 mg/d K supplementation divided in four doses for four weeks by office BP measurement, home self measurement, and 24-hour ambulatory measurement. Serum K, though not deviating from normal, increased from a mean of 4.15 to 4.42. Similarly, urinary potassium excretion increased from 54 to 96 mmol/d. All BP measurement techniques showed lower BP during K supplementation periods, to a highly statistically significant degree. Overall decreases in BP were modest: home BP decreased 3.6/1.6, 24 hr BP 3.4/1.2, and office BP 2.9/1.3. These changes were consistent whether the patient was receiving pharmacotherapeutic treatment and did not differ by class of antihypertensive agent.

Supplementation of K for hyperten-

In Future Issues:

Smoking as a Risk Factor for End-Stage Renal Disease

sive patients produces small but significant changes in BP. ❖

Kawano Y, et al. Am J Hypertens 1998;11:1141-1146.