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INSIDE

More ZZZ's for Those Who Wheeze

ABSTRACT & COMMENTARY

Synopsis: *Melatonin improved subjective sleep quality in women with mild asthma.*

Source: Campos FL, et al. *Am J Respir Crit Care Med*. 2004;170:947-951.

THIS WAS A BLINDED, RANDOMIZED, PLACEBO CONTROLLED study of 22 young women with mild-to-moderate asthma. Those who smoked, had frequent asthma exacerbations, used sleeping pills, or had other significant confounding problems (including smoking) were excluded. Subjects underwent a 2-week stabilization and washout period, during which everyone took inhaled steroids. Beta agonists were used prn. At the end of the baseline stabilization period, baseline data, including the Pittsburgh Sleep Quality Index (PSQI),[1] the Epworth Sleepiness Scale,[2] and pulmonary function were measured. Then subjects took either 3 mg of melatonin or 3 mg placebo 2 hours before bedtime for 28 days. They recorded their morning and evening peak flows (PEFR), asthma symptoms, and use of rescue beta agonists every day. Measurement of PSQI, Epworth Sleepiness Score, and pulmonary function were repeated at the end of the study period.

Twelve women received melatonin and 10 got placebo, but one of the melatonin subjects was lost to follow-up. At baseline, subjects were not different with regard to baseline measures, and 8 patients in each group were characterized as "poor sleepers," based on PSQI scores of 6 or more.

After 28 days, the group that received melatonin had a significant ($P < 0.001$) improvement in PSQI scores (from 7.4 to 3.4), but those who got placebo had no improvement. There was a trend ($P = 0.05$) toward improved daytime sleepiness in the melatonin group. Spirometry did not change significantly, but PEFR's improved significantly for both groups. Adverse effects were minimal; 8 patients (5 from the melatonin group) had headaches, and one from the placebo group had epigastric pain.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

The fact that this smallish study of subjective sleep quality was published in a premier pulmonary journal speaks volumes about the

VOLUME 26 • NUMBER 24 • DECEMBER 29, 2004 • PAGES 185-192

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perceived importance of sleep disturbance in patients with lung disease. Sleep complaints are common among pulmonary patients, and this is particularly true of asthmatics.[3,4] Further, impaired sleep may adversely affect daytime function quality of life in asthmatics.[4] The statistically robust finding of improved subjective sleep *compared with placebo* in this small group of asthmatic women suggests that the relationship is real. Since asthma and its associated morbidity, including sleep disturbance, are prevalent, there are patients in most of our practices who are potential candidates for this treatment.

But first let's remember that melatonin is not FDA-approved or regulated. Those of use who lived through the tryptophan eosinophilic myalgia debacle[5] are loath to experience anything like it again! A careful review of the findings of this study and their potential applications is in order. First and foremost, asthmatic patients who are considering melatonin for improvement in sleep quality need to be advised that the drug is not FDA approved; for medico-legal purposes, it is probably wise to document the warning in the medical record.

The biologic rationale for the use of melatonin in asthma is that it may modulate immune function,[6] and help regulate smooth airway tone.[7] In this study, however, there was no difference in measured pulmonary function, respiratory symptoms, or peak flows between the placebo and the treatment groups. Both groups experienced modest improvement in PEFR, probably the result of the Hawthorne effect. Thus, melatonin should not be given with the expectation that it will improve asthma.

The patients studied in this report were relatively young women who did not have co-morbid psychiatric or medical illness. Women appear to experience a marked increase in melatonin availability compared with men.[8] Thus, it is probably not reasonable to extrapolate these data to men, to older women, or to patients who have psychiatric or medical conditions contributing to their insomnia. In truth, patients with insomnia who do not have underlying medical or psychiatric issues are the exception rather than the rule.[9]

The dose used here was 3 mg, which is probably industrial strength. There is no justification or rationale for using higher doses. Further, timing of melatonin administration is key; in this experiment, it was given 2 hours before bedtime.

With those caveats, it might be reasonable to undertake a month's trial of 3 mg of melatonin, 2 hours before bedtime, in young, relatively healthy women with mild asthma who understand that it is not FDA approved and will most likely not improve their asthma. The time has probably come to pay as much attention to sleep problems as to pain in addressing quality of life. ■

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Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

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

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

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1 year *with* free AMA Category 1 credits: $319.
(Student/Resident rate: $125).

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The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.
This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

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Beware of Using Fibrates with Statins

ABSTRACT & COMMENTARY

Synopsis: *Combining a fibrate with a statin increases the risk of rhabdomyolysis by more than 10 times the use of a statin alone. A large study of more than 250,000 patients found that this combination had greater risk than the use of cerivastatin (Baycol), which was removed from the market. For patients needing intensive drug therapy for dyslipidemia, high-dose statins or other combination therapy should be used.*

Source: Graham DL, et al. *JAMA*. 2004;292:2585-2590.

THE NEW GUIDELINES FOR LOWERING LIPID LEVELS, especially in high risk patients, call for intensive drug therapy. While statins are the mainstay of treating dyslipidemia, another drug may be needed to achieve recommended lipid levels. This is especially true for patients with metabolic syndrome or genetic hyperlipidemias. Statins alone have limited value in lowering triglycerides and raising HDL cholesterol. Fibrates have a specific indication for elevated triglycerides and low HDL cholesterol, so combining either fenofibrate or gemfibrozil with a statin may seem like an attractive option.

Graham and colleagues studied a database of 252,460 patients in 11 managed care health plans that were treated for dyslipidemia with drug therapy for at least 6 months between 1998 and 2001. Patients were either on monotherapy with a statin, a fibrate, or a combination of both. 24 patients were hospitalized with rhabdomyolysis, a very low rate. However, among these patients, a much higher risk of rhabdomyolysis occurred in the patients receiving combination therapy.

The risk of rhabdomyolysis requiring hospitalization in patients taking atorvastatin, pravastatin, or simvastatin was found to be 0.44 per 10,000 person years, a very low risk. The risk in patients taking a fibrate as monotherapy was 2.82 per 10,000 person years. Since this study was started before the removal of cerivastatin (Baycol) from the market, a comparison with this agent was made. The risk of rhabdomyolysis with monotherapy with cerivastatin was 5.34 per 10,000 person years, more than 10 times higher than the other statins, and about 2 times higher than using a fibrate alone. The risk of combination therapy with a fibrate and one of the *safe statins* was 5.98 per 10,000 years. The risk of rhabdomyolysis in patients using cerivastatin and a fibrate was a whopping 1035 per 10,000 person years, or more than 1 in 10 persons.

COMMENT BY JOSEPH E. SCHERGER, MD, MPH

I have seen 2 patients disabled from rhabdomyolysis due to the use of a statin with a fibrate. This is a heavy price to pay for treating an asymptomatic, albeit important, disease. This study from a large population shows that combined therapy with a statin and fibrate is as dangerous as using a drug that has been withdrawn from the market. This combination therapy should only be used in clinical practice for patients with severe, genetic hyperlipidemia, especially with very high triglycerides and very low HDL cholesterol.

Niacin and ezetimibe are effective medications which can be used with a statin. Niacin has similar beneficial effects as fibrates, and while side effects may be troublesome in effective therapeutic doses, they are not as serious as rhabdomyolysis. Major lifestyle modification with very low fat nutrition may prevent the need for multiple drug treatment in some patients. We should treat dyslipidemia aggressively, but also as safely as possible.

PPIs are Associated with a Reduced Incidence of Dysplasia

ABSTRACT & COMMENTARY

Synopsis: *Examining data from a 20-year time period, correlations were sought between antisecretory drug therapy and cumulative incidence of dysplasia. Incidence of dysplasia was significantly lower in patients who had received PPI therapy vs no therapy or H2-receptor antagonists.*

Source: El-Serag HB, et al. *Am J Gastroenterol*. 2004;99: 1877-1833.

CHRONIC ACID REFLUX IS THOUGHT TO UNDERLIE the pathogenesis of Barrett's esophagus (change from normal squamous mucosa to specialized columnar metaplasia). Barrett's esophagus (BE) underlies most or all cases of esophageal adenocarcinoma, and it is believed by many that continued acid exposure increases adenocarcinoma risk. It has been speculated that acid suppression might alter cancer risk in this setting, but results of studies have not been conclusive one way or the other.

This retrospective analysis of patients followed at the Tucson, AZ, VA hospital between 1981 and 2000 attempts to compare patients with BE who received acid suppressive therapy with those who did not. Two hundred-thirty six (236) patients who initially presented without dysplasia were analyzed. 155 patients (66%) received a PPI, and 149 patients got H2- receptor agonists (H2RAs), and 21 received neither. Fifty-six (56) patients developed dysplasia during a total follow-up of 1170 patient years creating an incidence rate of 4.7% per year. Dysplasia developed in 9 of 19 patients on neither medication, and in 25 of 64 patients taking H2RAs. PPI therapy given after diagnosis was associated with less dysplasia. At 5 years, dysplasia with PPI therapy was 11% vs 37%; at 10 years, results were 21% vs 58%. Time of diagnosis and length of Barrett's mucosa and grade of dysplasia did not alter these findings. El-Serag and colleagues believe that these data strongly suggest that potent acid suppression can alter the progression from metaplasia to dysplasia.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

El-Serag et al discuss some of the potential defects of the study. For example, prescriptions obtained outside of the VA system would not have been tracked. There were 2 cases of adenocarcinoma in patients who didn't demonstrate previous dysplasia. Both had received PPIs. El-Serag et al provide lots of useful information on the probable contributions of acid reflux and chronic inflammation to abnormal cellular proliferation. They mention the failure of prior studies of medical and surgical antireflux therapy to alter evolution to esophageal adenocarcinoma. Finally, they admit that prospective randomized data collection is necessary to confirm these findings. An accompanying editorial by Dr. Thomas Schnell outlines other potential flaws to the conclusions of the Tucson VA study. He points out that acid suppression itself has been *accused* of promoting cancer, and he reiterates the considerable existing data that negate any protective effect of acid suppression on cancer progression in Barrett's. This study and the editorial both mention the fact that there is poor inter-observer agreement regarding the presence or absence of low-grade or indeterminate dysplasia (vs no dysplasia). There is of course no data on what happened to these patients prior to study entry, and many factors could impact later cancer risk (toxin exposure, diet, etc). The relatively brief exposure to PPIs in this study (only 1-2 years generally) was described by Dr. Schnell as terribly brief to have an impact on years of carcinogenesis. Nevertheless, on balance, this article is certainly ammunition for those who urge that all patients with Barrett's esophagus be treated with PPIs (whether they have symptoms or not). I am not so sure about this conclusion, but I must admit that my doubt regarding PPI use in this setting has been shaken. We must all hope that well designed future prospective studies will provide an answer that all of us can accept in terms of the continued chronic and indefinitely prolonged use of expensive PPIs in any major subset of GERD patients. ■

Atherothrombosis and Atrial Fibrillation: Mixing Treatments to Match Pathophysiology

ABSTRACTS & COMMENTARY

Synopsis: *Current clinical trial evidence favors the use of aspirin or clopidogrel as first-line agents for the majority of patients with vascular disease.*

Sources: Tran H, et al. JAMA. 2004;292:1867-1874; Shireman TI, et al. *Stroke*. 2004;35:2362-2367.

Atherothrombosis, namely the superimposition of thrombus on preexisting atherosclerosis, is a pathophysiologic process that affects the cerebral, coronary, and peripheral arterial circulations. Oral antiplatelet drugs, because they prevent initiation and propagation of thrombus formation, are the drugs of choice to prevent ischemic events in patients with vascular disease. There is controversy, however, regarding the choice of oral antiplatelet therapy in patients with cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral arterial disease (PAD). Clinicians believe that each vascular condition is different: Neurologists tend to use aspirin (ASA) combined with extended-release dipyridamole (ER-DP) for patients with CVD. Cardiologists prefer ASA, clopidogrel, or their combination for patients with CAD, and the optimal antiplatelet treatment for PAD is uncertain.

Tran and Anand have summarized the current state of evidence regarding oral antiplatelet treatment in various subgroups of patients with vascular disease. They searched the Medline database and the Cochrane Groups' trial register to identify studies published between 1960 and August 2004. They

concluded that the weight of current evidence supports the use of ASA or clopidogrel as first line therapy to prevent recurrent TIA or stroke. ER-DP combined with ASA is only a possible alternative because the evidence supporting its use comes from a single trial, The European Stroke Prevention Study 2 (ESPS 2)[1], and because dipyridamole has the potential to cause coronary artery dilatation that can divert blood flow away from stenosed coronary arteries and produce myocardial ischemia during exercise. Therefore, current ACC/AHA guidelines recommend that dipyridamole not be used in patients with stable angina.[2] This recommendation, however, was based on the short-acting form not ER-DP.[3] No increase in cardiac events from the use of ER-DP was observed in ESPS 2.[4]

Appropriate oral antiplatelet therapy is ASA for patients with ST-segment elevation myocardial infarction ASA, clopidogrel for those with chronic stable angina or peripheral arterial disease, and ASA plus clopidogrel for those with non-ST-segment elevation acute coronary syndrome.

Anticoagulation with warfarin is the most effective agent for stroke prophylaxis in elderly patients with atrial fibrillation (AF). Patients on warfarin commonly have concomitant conditions such as CAD, CVD, or PAD, for which antiplatelet drugs are indicated. Therefore, combined warfarin-antiplatelet therapy is common clinical practice.

Shireman and colleagues retrospectively studied elderly AF patients to determine the influence of patient-specific factors on concomitant warfarin-antiplatelet therapy, and the impact of combined therapy on major bleeding risk. They identified more than 10,000 patients, who were older than 65 years, in the National Stroke Project database, that had been discharged from hospital on warfarin. The cohort was divided evenly between men and women, and the mean age was 77 years. Approximately 20% of AF patients discharged on warfarin were simultaneously on an antiplatelet agent, principally ASA alone (90%), ASA plus clopridogrel or ticlopidine (6%), or clopidogrel or ticlopidine alone (4%). Antiplatelet use was less common among women, older persons, patients with terminal illness, cancer, dementia, and a history of bleeding. Patients with CAD were more likely to receive an antiplatelet agent. At 90 days after discharge, antiplatelet drugs increased major bleeding rates from 1.3% in the warfarin-only group to 1.9% in the combined therapy group (OR = 1.5, P = 0.052). Intracerebral hemorrhage was 3 times more frequent in the combined group, but the rates were 0.9% in the combined group vs 0.3% in the warfarin-only group.

After accounting for other risk factors, Shireman et al concluded that combined warfarin-antiplatelet therapy increased the risk of a major bleeding event by 50% during the 90-day follow-up period.

COMMENT BY JOHN J. CARONNA, MD

Tran and Anand summarized and critically reviewed the current evidence from clinical trials of antiplatelet drugs alone or in combination in patients with atherosclerosis of brain, heart, and limb arteries. On the basis of their analysis, they recommend ASA or clopidogrel for the majority of patients with vascular disease regardless of site. For patients who develop recurrent TIA or stroke while taking ASA or clopidogrel, an option for second-line therapy can be ASA combined with ER-DP, but only in the absence of symptomatic CAD.

Antiplatelet therapy remains central to the treatment of CAD because the pathophysiology of acute coronary artery occlusion often involves plaque rupture or fissure with platelet aggregation.[5] Therefore, it is not surprising that Shireman et al found that one-fifth of AF patients were discharged on combined warfarin-antiplatelet therapy, usually because of concomitant CAD. The bad news is that combined therapy resulted in an increase in major bleeding risks, especially for ICH. The good news is that the absolute rates remained low. Therefore, the clinician must carefully consider both the potential cardiac benefit and the bleeding risk in a particular elderly patient with AF before recommending combined warfarin-antiplatelet therapy. ■

Dr. Caronna is Vice-Chairman, Department of Neurology, Cornell University Medical Center; Professor of Clinical Neurology, New York Hospital, NY, NY.

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Perspective

Flu Shortage—Who Cares?

By Carol Kemper, MD

Isn't it amazing how people don't want something until they cannot have it. This year's nationwide shortage of flu vaccine, caused by manufacturing problems at the Chiron facility in England, has generated more bellyaching, finger pointing, and outright panic than is justified—it makes one almost wonder if the shortage was just an attempt to get people to want the flu shot. Let's put this in perspective. Every year, hundreds of thousands of doses of flu vaccine go unused and are destroyed, as the Public Health Service and healthcare providers urge patients to get vaccinated. At best, ~65% of the elderly and at risk patients receive the flu vaccine. Last year, when flu vaccine was offered free of charge to patients in our hospital, about 30% refused.

People need to understand some basic information about the flu shot: vaccination against the flu offers only partial (~70%) and temporary protection against a few flu viruses. In contrast, the natural immunity one develops from actual infection is much broader and more durable, lasting an estimated 3 to 5 years following infection. Every year, influenza experts meet to determine the composition of the following year's influenza vaccine, which amounts to little more than a crapshoot. The vaccine usually contains 3 strains of virus: 2 type A strains and 1 type B strain. For the 2003-2004 flu season, the trivalent influenza vaccine included A/Panama/2007/99 (H3N2)-like antigen, A/New Caledonia/20/99(H1N1)-like antigen, and B/Hong Kong/330/2001-like antigen. Last year, it was estimated that only 10-14% of those who received the flu vaccine were protected against the strain of flu they were exposed to. This year's vaccine is identical.

I've overheard perfectly healthy 30-year olds complaining they cannot get vaccine—although they look puzzled when you ask them if they've ever received one before. One mother was furious that her 4- year-old was denied a vaccine by her pediatrician—until I pointed out to her that that was a good thing; it meant her child was healthy and not at high risk for complications of the flu. Interestingly, the mother desperately explained the child really need the vaccine because she'd had the flu last year—and did not understand the child probably already had much better immunity than any vaccine could provide.

Most likely, there will be enough vaccine for those high-risk patients who may benefit the most from vaccination. The print and mogul media have a responsibility to quell peoples' fears of epidemics and shortages, provide the public with accurate information about the flu shot, and encourage healthy people to pass on vaccination. ■

Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center, Calif.

Pharmacology Update

Omega-3-Acid Ethyl Esters Capsules (Omacor)

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

The FDA has approved a new lipid regulating agent—the ethyl esters of omega-3 fatty acids for the treatment of high triglyceride levels. Marketed under the trade name "Omacor," the drug is a combination of eicosapentaenoic acid and docosahexaenoic acid. The Ross Division of Abbott Laboratories will market Omacor™.

Indications

Omega-3-acid ethyl esters (OAEE) are approved as an adjunct to diet to reduce very high (500 mg/dL) triglyceride levels in adult patients. Diseases and/or drugs that may be contributory to hypertriglyceridemia should be evaluated and adequately treated.[1]

Dosage

The daily dose of OAEE is 4 g per day taken as a single 4 g dose or 2 divided 2-g doses. In clinical trials OAEE was taken with meal(s).[1] Each 1-gram capsule contains approximately 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid as ethyl esters (a total of at least 900 mg).

Potential Advantages

OAEE has been reported to reduce triglyceride levels by a median value of 44.9% and a difference of 51.6% compared to placebo. In addition high density lipoprotein cholesterol (HDL-C) was increased by a median value of 9.1%, non-HDL-C was reduced by 13.8%, and very low-density lipoprotein cholesterol (VLDL-C) was reduced by 41.7%.[1] Drug interaction involving CYP isoenzymes are not expected with OAEE.

Potential Disadvantages

OAEE may increase LDL-C levels and non-HDL-C in some patients.[1,2] An increase in LDL-C of 44.5% has been reported. Periodic monitoring of LDL-cholesterol is recommended.[1] Short-term increases in fasting glucose levels have been reported.[3] However no alteration in glycemic parameters were detected at 6 months at dose of 2 g per day in a large (n = 935) study that included patients with type 2 diabetes and glucose intolerance.[4] Adverse events associated with OAEE compared to placebo were flu symptoms (3.5% vs 1.3%), infection (4.4% vs 2.2%), eructation (4.9% vs 2.2%), and taste perversion (2.7% vs 0%).[1]

Comments

OAEE appears to be effective in lowering high triglyceride levels. Its approval was based on 2 randomized, placebo-controlled, double-blind studies in 84 adults.[1] In 10 studies cited in a systemic review, 5 involving Omacor, omega-3 fatty acid at doses 3 g or higher showed mean reduction in triglycerides of 29%, VLDL of 30.2%, and a 10% increase in HDL-C although the authors cited methological flaws in these studies.[2] Only 3 of 10 studies found significant increases in LDL-C. The mechanism(s) of action of OAEE is/are not clear. Inhibition of acyl-CoA:1,2-diacylglycerol acyltranferase, increased peroxisomal -oxidation in the liver, and inhibition of esterification of other fatty acids has been proposed.[1] The addition of OAEE (4g daily) to patients (n = 59) with coronary heart disease and on simvastatin therapy resulted in additional 20-30% reduction in triglycerides (mean baseline of 406 mg/dL) with no adverse effect on LDL-cholesterol.[5] In another small study (n = 28), OAEE (4 g/d) was found have a similar reduction in triglyceride levels to gemfibrozil (1200 mg/d).[6] In addition reduction in VLDL and increase in HDL-C and LDL-C were also similar. Increase in LDL-C was due to increase in cholesterol contents in the more buoyant LDL subfractions compared to the more dense subfractions. However, OAEE appears to increase the susceptibility of LDL-C to oxidative modification in vitro compared to gemfibrozil. The clinical relevance of this observation in not known. Adverse effects appear to be minimal. The cost of Omacor was not available at the time of this review.

Clinical Implications

Epidemiological evidence has suggested cardiovascular benefit of omega-3-acids.[7,8] However, randomized controlled trials are less convincing.[9] Omega-3-acid supplements were considered food supplements prior to the approval of Omacor. This concentrated preparation now provides an alternative to fibrates or niacin in the treatment of high triglycerides particularly those that cannot tolerate these agents or due to adverse events or drug-drug interactions. It may also be a possible add on to statin therapy as low HDL-cholesterol and high triglycerides may modulate the capacity of statins to decrease cardiovascular risk in primary and secondary prevention.[10] ■

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CME Questions

32. Which of the following treatments carries the highest risk for rhabdomyolysis?

a. atorvastatin and niacin
b. simvastatin and ezetimibe
c. pravastatin and gemfibrozil
d. a statin and a very low fat diet

33. The Tucson VA study describes a population of patients with Barrett's esophagus who were treated with PPIs, H2RAs, or neither. What was the risk of developing dysplasia or adenocarcinoma of the esophagus in PPI recipients over 10 years of follow-up?

a. 5% of patients developed adenocarcinoma of the esophagus
b. 2 patients developed adenocarcinoma of the esophagus
c. 75% of Barrett's esophagus patients got cancer over 10 years
d. 21% of patients developed dysplasia
e. 11% of patients developed dysplasia

34. In women with mild-to-moderate asthma, 3 mg of melatonin at night improves which of the following compared with placebo?

a. spirometry
b. morning peak flow measurements (PEFR)
c. subjective respiratory complaints
d. polysomnographically measured sleep quality
e. subjective sleep quality

Answers: 32 (c); 33 (d); 34 (e)

By Louis Kuritzky, MD

Antioxidant Supplements for Prevention of Gastrointestinal Cancers: A Systematic Review and Meta-Analysis

CLINICIANS AND PATIENTS HAVE hoped that antioxidants might prevent cancer. Since oxidant stress may be one of the culprits in gene mutation that leads to carcinogenesis, it was logical to entertain the therapeutic potential of antioxidant supplements. Observational studies have been generally supportive of potential benefits from antioxidants, but of course randomized interventional trials trump observational data as an evidence source.

This meta-analysis reviewed trials of antioxidants for prevention of GI cancer. Inclusion criteria required that the trials be randomized and placebo controlled. Trial quality was ranked overall as high (n = 14 trials, study subjects = 170,525). Antioxidants addressed included beta-carotene, selenium, and vitamins A, C, and E.

In the overall analysis, none of the nutrients favorably impacted cancer incidence, although in 4 trials (3 of which are quoted as having unclear or inadequate methodology), selenium favorably affected GI cancer. Disturbingly, there were several trials that showed either increases of cancer, mortality or both. Despite our commonsense attraction to use antioxidants, convincing beneficial effects remain to be demonstrated. ■

Bjelakovic et al. Lancet. 2004;364: 1219-1228.

Imiquimod 5% Cream for the Treatment of Actinic Keratosis

RECENT CHANGES IN DERMATOLOGIC nomenclature classify actinic keratosis (AK) as keratinocytic intraepidermal neoplasia, or carcinoma in situ. A variety of treatments provide destruction and resolution of AK. Most of the time, biopsy is not performed, but rather, topicals like 5-fluorouracil are applied until a typical inflammatory cutaneous response exfoliates the lesions. Because the adverse effects of traditional treatments may be problematic, and the efficacy of standard therapies is imperfect, additional modalities are welcome.

Imiquimod 5% (Aldara™) is a commonly used topical immunomodulator for treatment of genital warts. It is also no approved for the treatment of AK. This investigation studied the efficacy of imiquimod (compared to placebo vehicle cream) applied 3 times weekly for 16 weeks to biopsy-proven AK in 286 patients.

Complete clearance of AK was seen in 57.1% of imiquimod patients, vs 2.2% of the placebo group. The most common adverse events associated with treatment were local cutaneous reactions of burning, erythema, itching, pain, and soreness. One or more of these adverse events were seen in the majority of patients, and essentially all patients experienced erythema. No serious adverse effects were attributed to imiquimod. Imiquimod may be considered a reasonable topical treatment for patients in primary care settings presenting with AK. ■

Saeimies RM, et al. J am Acad Dermatol. 2004;51:547-555.

Two 8-month Regimens of Chemotherapy for Treatment of Newly Diagnosed Pulmonary Tuberculosis

THE EPIDEMIOLOGIC PRESENCE OF tuberculosis has grown greater to some degree because of the sustained and evolving population of HIV-infected individuals worldwide. Standard therapy (as per the World Health Organization) for newly diagnosed smear positive tuberculosis has been a 6-month course of isoniazid (I) and rifampicin (R). Short course regimens are usually structured to include a 2 month intensive phase during which 4 drugs are given [ethambutol (E), isoniazid (I), rifampicin (R), and pyrazinamide (P)], followed by a 4-6 month 2 drug phase (I + R) .

This trial compared an 8-month regimen based upon ethambutol (E) and isoniazid with standard 6 month therapy. Two different 8-month regimens were used: Daily E+I+R+P for 2 months followed by E + I, or thrice weekly E+I+R+P for 2 months followed by E + I. The outcome of culture negativity was monitored at 2 months and 12 months.

Neither of the 8-month regimens provided superior outcomes to the traditional 6 month regimen. Thrice weekly multi-drug administration was less efficacious than daily. The stanard 6-month regimen should remain preferred. ■

Jindani A, et al. Lancet. 2004;364: 1244-1251.

In Future Issues:

Changing Face of Bacterial Meningitis