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INTERNAL MEDICINE ALERT®

A twice-monthly update of developments in internal and family medicine

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INSIDE

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Folic Acid Supplements — Finally Here to Stay?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: Three years of folic acid supplementation improves information processing speed in older adults with raised total homocysteine blood levels.

Source: Durga J, et al. *Lancet.* 369:208-216.

It has been clearly demonstrated that cognitive function, especially in the domains related to memory and information processing speed, decline significantly with aging[1] and that these changes have been linked to the risk of developing dementia in older age.[2, 3] Modifiable risk factors for age-related cognitive decline have previously been identified[4] and, interestingly enough, an inadequate folic acid intake has long been suspected to be one of these risk factors.[5, 6]

Because previous studies[7, 8] yielded mixed results (possibly due to such factors as small study populations, short duration of folic acid supplementation, and/or inadequate cognitive function testing) as to the benefits of folic acid supplementation, Durga and his colleagues organized and performed the FACIT trial.[9] This randomized, double-blind, placebo-controlled study took place between November, 1999 and December, 2004. The 818 participants who were aged 50-70 years were randomly assigned to receive 800 mcg oral folic acid or placebo daily for 3 years. The effect on cognitive performance was measured as the difference between the two groups with respect to the three-year change in performance for memory, sensorimotor speed, complex speed, information processing speed, and word fluency using five separate tests which have been previously described.[10, 11] At the end of the three-year study period, serum folate concentrations increased by 576%, plasma total homocysteine concentration decreased by 26%, and both information processing speed, and sensorimotor speed had improved and were significantly better in the folic acid group than in the placebo group.

COMMENTARY

Being able to avoid the usual decline in cognitive function which occurs with aging is obviously an important goal for each and every

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one of us. The FACIT trial[9] is a very well designed randomized, double-blind, controlled trial which has yielded extremely important results. However, the possibly significant limitations of the trial deserve exploration. First, assuming that high plasma total homocysteine concentrations might be a causal risk factor for cognitive decline, 3044 out of 4200 participants were excluded from the study because of low total plasma homocysteine concentrations. Thus, the observed effect of folic acid supplementation on cognitive function might have been greater than would be expected in populations with lower plasma total homocysteine concentrations, for example, as in countries such as the USA where overall homocysteine levels are generally lower than they are in other countries (probably because fortification of flour with folic acid is mandated in the USA). It is important to also note that even though the prevalence of dementia was not measured at baseline, it is unlikely that the study population included many cognitively impaired or demented participants since the general performance on the dementia screening test (ie, the Mini-Mental State Examination) was quite high both at the beginning and at the end of the trial.

In summary, the basic question is whether or not folic acid supplementation will lead to a reduced incidence of cognitive decline and/or dementia. Some have argued that age-related cognitive decline is the beginning of a continuum leading to dementia[12] and others have argued that[13] it is not an early stage of dementia.[2] These quite complex issues and other factors such as the confounding effects of vitamin B12 deficiency and/or the clinical relevance of folic acid supplementation in populations already afflicted with mild cognitive impairment and dementia will have to be evaluated. However, at this time, it would appear safe to say that three years of folic acid supplementation improves information processing speed and memory in older adults with raised total homocysteine concentration and that, at this time, there appears to be little reason not to prescribe 800 mcg of folic acid orally for individuals over 50 years of age with elevated homocysteine levels. ■

References

1. van Boxtel MPJ, et al. *J Geront A Biol Sci Med Sci.* 1998;53:M147-154.
2. Lovden M, et al. *Psych. Aging.* 2005;20:303-316.
3. Peterson RC, et al. *Arch Neurol.* 1999; 56:303-308.
4. Fillit HM, et al. *Mayo Clin Proc.* 2002; 77:681-696.
5. Calvaresee E, et al. *J.Geront B Psychol Sci Soc Sci.* 2001;56:327-339.
6. Mattson MP, et al. *Trends Neurosci.* 2003;26:137-146.
7. Morris MC, et al. *Arch Neuro.* 2005;62:641-645.
8. Malouf M, et al. *Sys Review.* 2003;4:CD 004514.
9. Durga J, et al. *Lancet.* 369:208-216.
10. Jolles J, et al. Maastricht: Neuropsych publishers, 1995.
11. Durga J, et al. *Neurobiol aging.* 2006;27:334-343.
12. Brayne C, et al. *Lancet.* 1988;331:1265-1267.
13. Morrison JH, et al. *Science.* 1997;278:412-419.

How Low Can You Go?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

Dr. Scherger reports no financial relationship to this field of study.

Synopsis: *A retrospective analysis of a large international trial of patients with hypertension and coronary artery disease (CAD) showed that lowering diastolic blood pressure (DBP) below 80 mmHg increased the risk of myocardial infarction and all cause death. Patients with a DBP below 70 mmHg had the same adverse outcomes as patients with a DBP over 100 mmHg.*

Source: Messerli FH, et al. Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med. 2006;144:884-893.

CORONARY ARTERY PERFUSION TO THE HEART MUSCLE mainly occurs during diastole. Research has suggested through the years that there may be a J-shaped

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response to lowering blood pressure in patients with CAD. Benefit occurs up to a point and if the blood pressure is reduced further, adverse events occur. Recent studies have suggested that lowering blood pressure even within normal ranges confers benefit in patients with coronary artery disease.[1] Ideal blood pressure is considered around 120/80 or lower and the category of prehypertension has been developed for the risk involved with blood pressures above 130/80 up to 140/90. The focus of recent research has mainly been on the systolic blood pressure (SBP) with is now felt to be the more important of the readings.

A team of investigators from St. Luke's-Roosevelt Hospital in New York looked at the data from an international study of blood pressure lowering in patients with CAD. Named the INVEST trial, and conducted between 1997 and 2003, it compared verapamil with a beta-blocker in 22,576 patients.[2] There were 862 study sites in 14 countries. They focused on blood pressure lowering and subsequent mortality, all cause and cardiovascular. The relationship between blood pressure and all cause death and myocardial infarction was J-shaped, particularly for DBP, with a lowest mortality at 119/84. Looking at each 10 mmHg increment, modest increased risk occurred in the group with DBP between 70 and 80 mmHg. The risk rose substantially with DBP below 70, with the same adverse outcomes as patients with DBP above 100.

COMMENTARY

I reported in *Internal Medicine Alert* in the December 15, 2004 issue[3] the study from *JAMA* which showed that reducing normal blood pressure benefits patients with CAD. Nissen, et al, showed that lowering SBP into the low 120s conferred benefit compared with patients with SBP 130 or above.[1] This large multicenter trial (CAMELOT) helped lead to the designation of prehypertension. Little attention was given to DBP levels.

Having graduated from medical school in 1975, I started my career with the teaching that DBP was more important the SBP. Subsequently, multiple studies have shown the important of SBP to the point that is now has superiority of concern in lowering blood pressure. Where is the balance? The fact that coronary artery perfusion occurs mainly during diastole grabs my attention. This study suggests that the current dogma to lower blood pressures as low as possible without causing symptoms is misguided, especially with respect to DBP.

So now we have a balanced consideration with respect to treating hypertension, especially in patients with CAD. Get the SBP down into the low 120s, but do not lower the DBP much below 80. Combining the CAMELOT data with this study from the INVEST trial allows us to fine tune patients' blood pressure therapy. DBP is vitally important, which validates the knowledge from the 1970s. ■

References:

1. Nissen, SE, et al. *JAMA.* 2004;292:2217-2226.
2. Pepine CJ, et al. *JAMA.* 2003;290:2805-2816.
3. Scherger JE. *Internal Medicine Alert.* 2004;24:178-179.

Risk of Statins

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

Dr. Crawford is on the speaker's bureau for Pfizer.

Synopsis: *Available statins are associated with a small increased risk of hepatotoxicity, but not muscle toxicity or drug discontinuation for adverse effects.*

Source: Kashani A, et al. Risks Associated with Statin Therapy. *Circulation.* 2006;114:2788-2797.

Despite well-proven effectiveness, statin therapy is underutilized. This may be due to perceived risks by physicians and patients. Thus, Kashani and colleagues prepared a meta analysis of 35 randomized controlled trials of 74,102 patients using 6 statins currently on the market. Four cerivastatin trials were analyzed separately, since it is no longer on the market. Study inclusion characteristics included documented hyperlipidemia, double-blind, > 100 patients per arm, statin monotherapy vs placebo, and full documentation of adverse events.

Risk of myalgias (risk difference / 1,000 patients = 2.7, 95% CI -3.2 to 8.7) creatine kinase elevation (RD = 0.2, CI -0.6 to 0.9) rhabdomyolysis (RD 0.4, CI -0.1 to 0.9) and drug discontinuation for any adverse event (RD -0.5, CI -4.3 to 3.3) were not significantly different between statin and placebo. However, the risk of transaminase elevations was higher on statins (RD 4.2, CI 1.5 to 6.9). Liver toxicity reached statistical significance in the fluvastatin and lovastatin individual trials. Individual comparisons showed a higher incidence of muscle toxicity with rosuvastatin, but this was not significant. Cerivastatin showed a significant increase in rhabdomyolysis (RD 12.4, CI 5.4 to 19.3, $p < 0.01$), but

not myalgias or creatine kinase elevations. The authors concluded that available statins are associated with a small increased risk of hepatotoxicity, but not muscle toxicity or drug discontinuation for adverse effects. Cerivastatin was the only agent that showed an increase in rhabdomyolysis and it has been withdrawn from the market.

COMMENTARY

This study is of particular interest to me because I have found considerable patient resistance to statin therapy. Maybe this is just another "California values" issue, but I suspect many have had the same problem. The internet must be full of horror stories about statins, and my patients tell me that their herbal medicine retailers rail against them in favor of the "natural" compoundsthey sell. Thus, this article is very reassuring and I can counter my reluctant patients with data in over 74,000 statin users. The muscle toxicity issue is really put to rest by this study; the available statins just don't significantly affect the muscles. Also, as they point out, rhabdomyolysis is rare and usually associated with drug-to-drug interactions. It was reassuring to see that cerivastatin did significantly increase rhabdomyolysis; justifying its withdrawal from the market. Transaminitis was increased to about 4/1,000 patients treated with statins, but this is most often asymptomatic and reversible. Liver failure is rare, if present. Therefore, this analysis supports the conclusion of the ACC / AHA / NHLBI guidelines that screening liver enzymes and creatine kinase only be performed if patients have symptoms.

There are some limitations to the study. Clinical trial populations are usually younger and healthier than the average patient populations. How the latter are affected by statins is unknown. There is limited data on rosuvastatin since it is relatively new. There is little data on drug-to-drug interactions such as statins and fibrates. Reports of statins causing memory loss and other neurologic symptoms could not be analyzed because of insufficient data. Finally, relative risk of adverse effects at different doses could not be evaluated. This is an important point because many believe from experience that adverse effects are more common with higher doses and often abate with dose reductions, without having to stop the statin completely. More data on this observation would be useful. In the final analysis, this study confirms the safety of these highly effective agents. ■

Osteoporosis and Depression

ABSTRACT & COMMENTARY

By Leon Speroff, MD

Professor of Obstetrics and Gynecology, Oregon Health and Science University, Portland

Dr. Speroff is a consultant for Warner-Chilcott.

Synopsis: *Women with fractures have a greater prevalence of clinical depression.*

Source: Silverman SL, et al. Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture: results from the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. *J Rheumatol.* 2007;34:140-144.

Silverman and colleagues reported the prevalence of depression in a cross-sectional subset of 3798 women in 6 English-speaking countries, who participated in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.[1] Depression was assessed by the Geriatric Depression Scale. Women with vertebral fractures recorded a greater number of depressive symptoms, accounting for a 6.6% prevalence and a 2.5% absolute increase compared with women without fractures. Women with 3 or more vertebral fractures had a 12.8% prevalence of depression.

COMMENTARY

Because there are so many women with osteoporosis, a greater prevalence of depression in this population would amount to a clinical problem of considerable proportions. According to the National Osteoporosis Foundation, 44 million people (55% of the people over age 50) have either osteoporosis or low bone mass, and it is predicted that this number will increase to 52 million (35 million women) by the year 2010 (www.nof.org/advocacy/prevalence).

It is well recognized that fractures secondary to osteoporosis are accompanied by a reduction in psychological and physical well-being. As far as depression goes, it is difficult to know which came first, depression or fractures leading to subsequent depression. It has been reported that depressed people have a greater incidence of falls,[2] and thus it is not unreasonable to consider that depression comes first in some people. Furthermore, depressed people are sedentary and eat poorly, factors that favor bone loss. The authors also speculate that increased cortisol levels associated with depression might lead to bone loss, similar to that observed with the

pharmacologic administration of glucocorticoids. On the other hand, the current study, as well as a cohort study of American women, despite finding a link between depression and fractures, failed to detect an increase in depression associated with lower bone density measurements.[2] However, other studies have reported increases in depression associated with lower bone densities.[3-5]

Bone loss has been documented in an established rodent model for stress-induced depression, characterized by a decrease in osteoblastic bone formation that can be attenuated by an antidepressant drug.[6] In this experimental model, osteoblastic inhibition was mediated by stress-induced stimulation of the sympathetic nervous system. Although this response is associated with an increased secretion of adrenal glucocorticoids, the evidence also indicates a direct role for sympathetic fibers in bone.

There are several clinical lessons to be derived from these reports. Older, depressed women should be assessed for potential pharmacologic treatment to prevent osteoporosis-related fractures. We need to be aware that women who have experienced fractures may have depressive symptoms, and appropriate interventions can have a beneficial impact on quality of life. The important point is that depression and fractures are linked; one may precede the other and vice-versa in different patients. ■

References

1. Silverman SL, et al. *Study. J Rheumatol.* 2007;34:140-144.
2. Whooley MA, et al. *Arch Intern Med.* 1999;159:484-490.
3. Robbins J, et al. *J Am Geriatr Soc.* 2001;49:732-736.
4. Milliken LA, et al. *J Gerontol A Biol Sci Med Sci.* 2006;61:488-494.
5. Kahl KG, et al. *Psychosom Med.* 2006;68:669-674.
6. Yirmiya R, et al. *Proc Natl Acad Sci.* 2006; 103:16876-16881.

Pharmacology Update

Panitumumab Injection (Vectibix)

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

PANITUMUMAB IS A HUMAN MONOCLONAL ANTIbody that is approved for the treatment of colorectal carcinoma. The drug binds to the human epidermal growth factor receptor (EGFR) in a way similar to cetuximab, which is a chimeric antibody (part mouse part human). Panitumumab is marketed by Amgen as Vectibix.

Indications

Panitumumab is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimdine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.[1]

Dosage

The recommended dose of panitumumab is 6 mg/kg, given over 60 minutes as an intravenous infusion, every 14 days. Doses higher than 1000 mg should be given over 90 minutes.[1]

Potential Advantages

Panitumumab prolongs progression-free survival by about 1 month (96 days vs 60 days) in patients with metastatic carcinoma of the colon or rectum.[1,3] Panitumumab is a fully human monoclonal antibody. It has been associated with less infusion-related reactions and a lower antibody formation against the drug than cetuximab, 1% vs. 3%.[2,3] Compared to cetuximab, panitumumab does not require premedication (eg, intravenous diphenhydramine).[3]

Potential Disadvantages

It is not certain if panitumumab improves overall survival compared to best supportive care (BSC).[1] Severe dermatologic toxicities have been reported in 12% of patients and severe infusion reactions in 1% of patients.[1] Other adverse events include fatigue, abdominal pain, paronychia, nausea, diarrhea, constipation, vomiting, and hypomagnesemia.[4]

Comments

Panitumumab is a fully humanized monoclonal antibody with high selectivity for EGFR (both normal and tumor cells). EGFR is overexpressed in 25-77% of colorectal cancers and is generally associated with poor prognosis. The efficacy of panitumumab was shown in an open-label, multinational, randomized controlled trial of 463 patients with EGFR-expressing metastatic carcinoma of the colon or rectum. Seventy-five percent had progressed on or followed a regimen(s) containing a fluoropyrimidine, oxaliplatin, and irinotecan.[1] Patients were randomized to panitumumab (6 mg/kg every 2 weeks or 2.5 mg/kg/week) plus BSC or BSC alone. Mean progression-free survival was 96 days for panitumumab and 60 days for BSC. Progressive free survival rates were 49% vs 30% at week 8, 18% vs 5% at week 24, 10% vs 4% at week 32, and 1% each at

week 48.[4] There was no difference in overall survival; however, this may be misleading as 75% of those randomized to BSC were allowed to receive panitumumab. The median time to crossover was 8.4 weeks.[1,3] Dermatologic toxicities are typically associated with EGFR inhibition (89%) and efficacy and toxicity may be related.[5] Nondermatologic adverse events (25%) include fatigue, diarrhea, abdominal pain, constipation, nausea, and hypomagnesemia. The incidence and severity of diarrhea increases when panitumumab is used with irinotecan. Grade 3 or 4 hypomagnesemia occurs in 2% of patients, usually occurring 6 weeks after initiation of therapy. Monitoring of magnesium and calcium levels should be done during and for 8 weeks after therapy. Pulmonary fibrosis has been reported in 2 of 1467 patients. There are currently no comparative trials between panitumumab and cetuximab. However, when studied in similar patients (disease resistant to irinotecan and/or oxaliplatin), both drugs produced response rates of about 10% and stable diseases of 30-40%.[5] Panitumumab and cetuximab are currently being studied as first line therapy. The wholesale cost for panitumumab is $800 per 100 mg. ■

Clinical Implications

Panitumumab is the first fully human monoclonal antibody against EGFR. It provides a better tolerated alternative to cetuximab in patients with metastatic colorectal cancer.

References

1. Vectibix Product Information. Amgen Inc., September 2006.
2. Cohenuram M, et al. *Anticancer Drugs.* 2007;18(10:7-15.
3. Erbitux Product Information. ImClone Systems Inc. and Bristol-Myers Squibb. March 2006.
4. Hoy S, et al. *Drugs.* 2006;66(15):2005-2014.
5. Van Cuisem E. *Oncologist.* 2006;11(9):1010-1017.

CME Questions

11. This article concludes that oral folic acid supplementation improves information processing speed and memory in:

a. patients with a low homocysteine level.
b. patients in all age groups.
c. in adults over the age of 50 with elevated total homocysteine concentration.
d. is of no value.

12. The following statements are true regarding depression and fractures except:

a. it is possible that depression causes bone loss in some men and women.
b. osteoporosis should be suspected in depressed individuals.
c. metabolic changes secondary to depression can cause bone loss.
d. when present, one can assume that depression preceded bone loss.

Answers: 11 (c); 12 (d)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Predicting Stroke Risk after TIA

Stroke remains the third leading cause of death in America. Risk of stroke after TIA is greatly magnified, such that as many as 20% will suffer a stroke within 90 days, disproportionately occurring within the first 48 hours post-TIA. Scoring systems to enhance prediction of stroke after TIA have been devised and validated, and include the ABCD score and the California score. These scores had different boundaries (the ABCD score predicted 7 day risk; the California score looked at 90 day risk), and because of questions about generalizability (the ABCD was validated on Greek and British populations, vs the California Score which was developed from an American cohort), it would be desirable to evolve a single score capturing the best aspects of both the ABCD and California scoring systems.

Based on logistic regression, the authors derived a "unified ABCD" score and validated it upon a large population of individuals (n = 4,809) from American and British populations. The new scale, which they term the ABCD2 is so-named because it predicts risk in the 2 days post-TIA. Components of the ABCD2 include age, diabetes, blood pressure, duration of TIA, speech impairment, and focal weakness. The new scale predicts high risk patients in the first 48 hours better than either of the component scores from which it was derived. The authors offer this scale as "a new standard of care" model for identifying highest risk TIA patients who may benefit from more intensive investigation and treatment. ■

Johnston SC, et al Lancet. *2007;369:283-292.*

Which is the Better Study in Acute Stroke: CT or MRI?

Common wisdom suggests that for acute stroke, MRI is preferred to CT. Sometimes, however, patients who present with neurologic syndromes may suffer disorders other than/in addition to stroke. Hence, clinicians would prefer to know which imaging modality provides best information about stroke (ischemic and hemorrhagic), as well as other cerebrovascular maladies.

It is already recognized that CT is less valuable for detecting ischemic stroke than ruling out hemorrhagic stroke. Yet, there has been little comparison to determine whether CT or MRI is actually superior to detect CNS hemorrhage.

In a prospective blind comparison of CT and MRI in presents presenting with suspected acute stroke, MRI was significantly more sensitive for both ischemic and hemorrhagic stroke detection. When assessed comparatively relative to the final clinical diagnosis, the sensitivity of MRI was substantially greater than CT (83% vs 26%). Unless cost or availability precludes its use, MRI should be the preferred study in patients presenting with symptoms suggesting acute stroke. ■

Chalela JA, et al. Lancet. *2007;369:293-298.*

Comparison of a DPP-4 and TZD for Monotherapy in Type 2 Diabetes

Glucagon-like peptide-1 (GLP) is one of a family of agents known as incretins (FYI, correctly pronounced in-KREE-tins, since your author has heard it repeatedly mispronounced "IN-creh-tins" at professional meetings of late). Incretins have numerous favorable physiologic effects in patients with type 2 diabetes (DM2), including enhanced glucose-dependent insulin secretion, activation of insulin biosynthesis and gene transcription, suppression of glucagon, slowed gastric emptying, induction of satiety, and inhibition of beta cell apoptosis. Until very recently, we have not been able to capitalize upon these physiologic attributes because the actions of GLP are very short lived. DPP4 inhibitors block the enzyme that degrades GLP, resulting in a prolonged GLP effect. Sitagliptin (Januvia) is the only currently approved DDP4 inhibitor, but others are pending FDA approval.

The potency of the DPP4 inhibitor vildagliptin (VIL) was compared in a double-blind fashion with rosiglitazone (Avandia) in type 2 diabetics. A population of newly diagnosed diabetics (n = 786) were randomized to VIL 50 mg b.i.d. vs rosiglitazone 8 mg qd and followed for 6 months. The primary outcome was change from baseline A1C (baseline = 8.7).

Both agents were similar in mean reduction of A1C at 24 weeks (1.1-1.3%), proving statistical noninferiority of vildagliptin to rosiglitazone. Additionally, amongst persons with higher baseline A1C (eg, > 9.0%), pharmacotherapy impact was correspondingly larger (A1C decrease 1.8%).

Because they are not associated with weight gain, and show similar potency to agents popularly used to treat DM2, the availability of this new class of oral agents is welcome. ■

Rosenstock J, et al Diabetes Care. *2007;30(2):217-223.*

How Many Findings?

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*
Dr. Grauer reports that he is sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

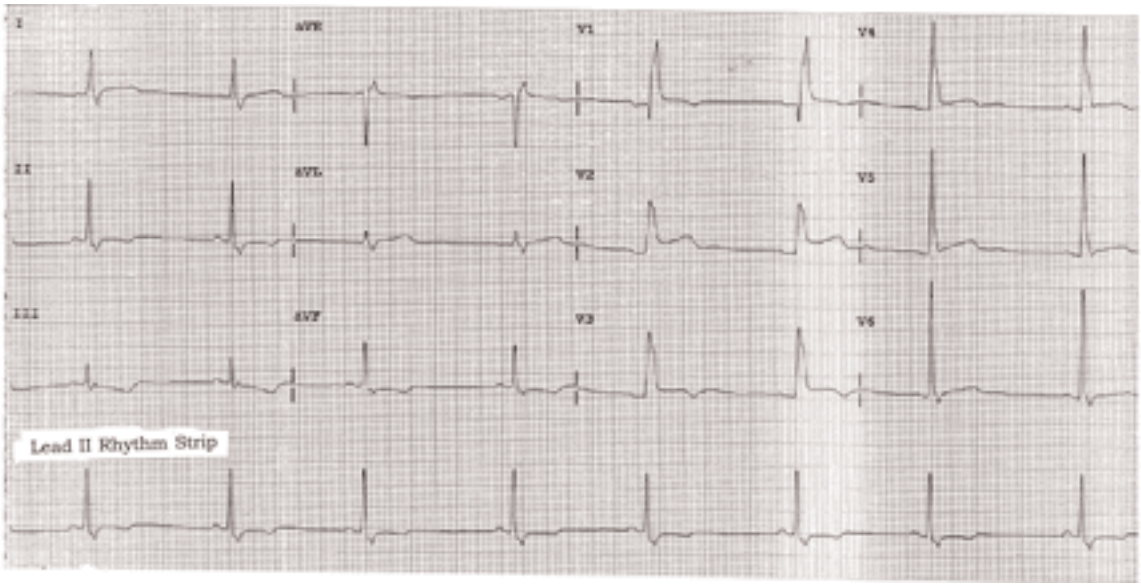

Figure. 12-lead ECG obtained from a 70-year-old man with chest pain for one day.

Clinical Scenario: The ECG in the Figure was obtained from a 70-year-old man who presented with a history of chest pain for one day. How would you interpret his ECG? How many remarkable findings do you see on this tracing?

Interpretation/Answer: The lead II rhythm strip at the bottom of the tracing shows the rhythm to be sinus bradycardia and arrhythmia, with the rate at times dropping below 50 beats/minute. The PR interval is normal. However, the QRS complex is clearly wide. QRS morphology is most consistent with a RBBB (right bundle branch block) pattern. Instead of the usual rSR' pattern that is typical of RBBB, a QR pattern with a prominent Q wave is seen in lead V1. In addition, there is ST segment elevation which is subtle in lead V1, but more obvious in leads V2 through V4. The ST segment is covered in leads I, aVL, V5, and V6—and there is T wave inversion in the inferior leads, as well as in lead V3. Taken together, these findings are strongly suggestive of recent (possibly ongoing) acute anterolateral infarction.

Finally, R wave amplitude is markedly increased in leads V5 and V6. Even though amplitude criteria for ventricular enlargement are clearly less reliable in the setting of conduction disturbances such as RBBB, the degree of amplitude increase (especially in lead V6) makes it likely that the patient has LVH (left ventricular hypertrophy). ■

In Future Issues:

MRSA Decolonization

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Higher HDL Cholesterol in Statin Therapy, Key to Slowing Atherosclerosis?

Aggressive statin therapy is associated with slowed progression and even regression of atherosclerosis. A new study suggests that, when monitoring statin therapy, increases in HDL cholesterol may be as important as decreases in LDL cholesterol in preventing disease progression. Researchers from the Cleveland Clinic reviewed 4 large studies from United States, North America, Europe and Australia in which 1,455 patients with angiographic coronary disease underwent serial intravascular ultrasonography while receiving aggressive statin therapy for 18 or 24 months. During therapy, mean LDL levels dropped from 124.0 mg/dl to 87.5 mg/dl, and mean HDL levels increased from 42.5 mg/dl to 45.1 mg/dl, and LDL to HDL ratios were reduced from a mean of 3 to 2.1 ($P < 0.001$ for all). These changes were accompanied by a small, but statistically significant decrease in atheroma volume as measured by intravascular ultrasound. The largest decrease in atheroma volume was associated with patients with LDL cholesterol less than the mean of 87.5 mg/dl, and percentage increases in HDL cholesterol of greater than 7.5%. The authors conclude that when treating with statins, decreases of LDL cholesterol and increases in HDL cholesterol are independently associated with regression of atheroma volume. They also note that these changes were not associated with reductions in clinical events or improved clinical outcomes and that more research is needed (*JAMA*. 2007; 297:499-508).

Citalopram Useful for Depression in CDA Patients

Major depression affects up to one quarter of patients hospitalized with coronary artery disease and these patients have a worse prognosis than non-depressed patients. A new study from Canada compares the efficacy of citalopram vs interpersonal psychotherapy in reducing depressive symptoms among these patients. The study randomized 284 patients with CAD and major depression to 12 weeks of interpersonal psychotherapy plus clinical management vs clinical management only, and a second randomization compared 12 weeks of citalopram 20-40 mg/day vs placebo. The main outcomes were scores on objective depression scales. Citalopram was superior to placebo in reducing depression scores ($P = 0.005$), but interpersonal psychotherapy was ineffective, being no better than clinical management. The authors conclude that citalopram administered in conjunction with weekly clinical management was effective in treating depression whereas there was no evidence of value for interpersonal psychotherapy. The authors suggest that citalopram or sertraline (based on previous studies) should be considered as first-step treatment for patients with CAD and major depression (*JAMA*. 2007;297:367-379). An accompanying editorial agrees that citalopram and sertraline are safe and effective for treatment of depression in patients with coronary heart disease, and suggests physicians should actively screen for signs and symptoms of depression in these patients. However, there is not yet

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any evidence that treating depression in this patient population reduces subsequent cardiac events (*JAMA*. 2007;297:411-412).

When to Stop Anticoagulation Before Surgery?

For patients on warfarin who have been bridging therapy with low molecular weight heparin (LMWH) prior to surgery, when is the best time to stop anticoagulation? A new study suggests that the evening before surgery is too late. Researchers in Ontario, Canada, looked at 80 patients who were scheduled for surgery or invasive procedures and were bridged with LMWH. All 20 patients had normal renal function and were given enoxaparin 1 mg/kg of body weight twice daily with the last dose administered the evening before surgery. Blood anti-factor Xa heparin levels were measured shortly before surgery, an average of 14 hours after the last dose. Two-thirds of patients had anti-Xa heparin levels of 0.5 U/ml or higher shortly before their invasive procedure. Patients with higher BMIs were more likely to have higher levels as were patients with lower creatinine clearances. The authors conclude that preoperative bridging with twice daily enoxaparin results in high residual anti-Xa heparin levels if the last dose is given the evening before surgery. They recommend that the last dose be given the morning on the day prior to surgery (*Ann Int Med.* 2007;146:184-187).

Drug Warnings: Ranibizumab and Bevacizumab

Both of Genentech's anti-angiogenic agents, ranibizumab (Lucentis) and bevacizumab (Avastin), have been the subject of new warnings from the company and the FDA. Ranibizumab, which is used for the treatment of neovascular (wet) macular degeneration, has been associated with increased risk of stroke in elderly patients. The drug, which is administered as an monthly intraocular injection, was found to be associated with a 1.2% risk of stroke at the recommended dose of 0.5 mg compared to a 0.3% risk associated with the lower-than-recommended 0.3 mg dose ($P = 0.02$) at an average follow-up of 230 days. Patients who had a history of stroke were at the highest risk. Bevacizumab, which is approved for treatment of non-small cell lung cancer and metastatic colorectal cancer, was recently found to be associated with increased risk of gastrointestinal perforation and potentially fatal pulmonary hemorrhage. Gastrointestinal perforation was seen as a complication of patients treated for colorectal cancer, while pulmonary hemorrhage was seen in patients receiving chemotherapy plus bevacizumab for lung cancer. Other bleeding complications seen in bevacizumab-treated patients including GI hemorrhage, subarachnoid hemorrhage and hemorrhagic stroke.

Growth Hormone Treatment, More Harm Than Good

The January 16, 2007, *Annals of Internal Medicine* includes a review of the safety and efficacy of growth hormone in the healthy elderly. The review was undertaken because growth hormone is widely recommended and sold as an anti-aging agent in this population. The authors reviewed 31 articles, which included a total of 220 participants who received growth hormone. The mean age was 69 and patients were generally overweight. Treatment duration mean was 27 weeks. Growth-hormone-treated patients compared to placebo- treated patients were noted to have decreases in overall fat mass and increases in overall lean body mass, but weight did not change significantly. Total cholesterol decreased, although not significantly, after adjustment for body composition changes. Bone density and other lipid levels did not change. Those treated with growth hormone were significantly more likely to experience soft tissue edema, and arthralgias, carpal tunnel syndrome, and gynecomastia as well as a slightly increased rate of diabetes and impaired fasting glucose. The authors conclude that growth hormone use in the elderly is associated with small changes in body composition and an increased rate of adverse events and cannot be recommended (*Ann Int Med*. 2007; 146:104-115).

FDA Actions

The FDA has warned against unsupervised use of topical anesthetic products for cosmetic procedures. The agency has received multiple reports of adverse events associated with patients applying excess amounts of topical agents containing lidocaine, tetracaine, benzocaine, and prilocaine. Two women who used topical anesthetics with lidocaine and tetracaine died after applying the creams to their legs and wrapping their legs in plastic to increase absorption. Healthcare professionals are cautioned to prescribe topical anesthetics with caution in the lowest concentration consistent with pain relief goals and to advise patients in their safe use.

The FDA has approved Roche's orlistat for over-the-counter use to facilitate weight loss. The drug, available in prescription form under the trade name "Xenical," blocks absorption of fat by inhibiting pancreatic lipase thus preventing triglyceride absorption in the small bowel. The over-the-counter version will be available as a 60 mg dose, half the prescription dosage. Orlistat over-the-counter will be marketed as "Alli." ■