INTERNAL MEDICINE ALERT

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INSIDE

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Acetaminophen and Hypertension

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *Acetaminophen is able to induce a significant increase in BP in ambulatory subjects with CAD.*

Source: Sudano I, et al. Acetaminophen increases blood pressure in patients with coronary artery disease. *Circulation* 2010;122:1789-1796.

THE UNITED STATES FOOD AND DRUG ADMINISTRATION HAS MANDATED THAT a "black-box warning" be circulated for cyclooxygenase-2 (COX-2) selective inhibitors and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) because of the demonstrated potential of these agents to increase adverse cardiovascular outcomes. Literally hundreds of millions of patients worldwide continue to require pain-relieving therapy to maintain an acceptable quality of life; therefore, the uncertainty about safely using NSAIDs and COX-2 inhibitors has created difficult management decisions for both physicians and patients. In fact, because of these uncertainties, current guidelines recommend using acetaminophen as the first-line analgesic of choice for the management of chronic pain, especially in patients at high cardiovascular risk or with established cardiovascular disease, even though its analgesic potency is weaker.[1]

Despite the fact that sporadic studies have actually linked acetaminophen to hypertension[2,3] or to an increased risk for cardiovascular events,[4] only a few interventional studies assessing the effects of acetaminophen on hypertension are available and the results have been inconsistent.[5-7] Therefore, Sudano and her associates decided to prospectively evaluate the potential impact of acetaminophen on ambulatory blood pressure (ABP) and ventricular function in patients with established coronary artery disease (CAD) in whom traditional NSAIDs and COX-2 inhibitors are contraindicated and for whom acetaminophen

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currently represents the treatment of choice.

Sudano and her colleagues recruited and placed 33 patients with CAD into a randomized, double-blind, placebo-controlled, crossover study using acetaminophen (1 g three times daily) on top of standard cardiovascular therapy for 2 weeks. They measured the ABP, heart rate, and a variety of serum biomarkers as well as measures of platelet and vascular function. They observed a small but significant increase in mean 24-hour systolic and diastolic BPs similar to those effects which have been observed with many of the NSAIDs. Acetaminophen was found to have no significant effect on platelet adhesion, endothelial cells, or the numerous metabolic parameters which were measured. They concluded that the study, for the first time, demonstrated that acetaminophen induced a small but significant increase in ABP but had no significant effect on vascular function in patients with CAD and recommended that the drug should be used with the same caution as is applied to traditional anti-inflammatory drugs, particularly in patients at increased cardiovascular risk.

■ COMMENTARY

The Sudano study was performed with only a very small number of patients; therefore, before drawing firm conclusions, a much larger randomized, double-blinded, and placebo-controlled study would have to be performed. The clinical status of acetaminophen will not be effectively changed in the short term because of the results of this very small new study; however, the results do suggest that acetaminophen should be used with caution in patients with cardiovascular disease. In addition, it should be recognized that acetaminophen, although relatively effective for some forms of minor pain, is quite ineffective for treatment of symptoms due to significant inflammatory diseases such as moderate to advanced osteoarthritis or rheumatoid arthritis[8] and that most clinical trials have not demonstrated it to be superior to placebo. In addition, the hepatic safety of acetaminophen, particularly in large doses has proven to be of major concern recently and, in fact, the drug has been implicated in a number of cases of hepatic failure requiring liver transplantation.[9]

In summary, because of the new findings demonstrated by the Sudano study, it is quite clear that a lot more may be unknown about acetaminophen from a cardiovascular safety point of view than about the conventional NSAIDs and selective COX-2 inhibitors. Before recommending widespread use of this drug, especially in patients at increased cardiovascular risk, randomized controlled clinical trials of significant power specifically addressing the safety of this agent would have to be conducted. ■

References

1. Antman EM, et al. Use of nonsteroidal anti-inflammatory drugs: An update for clinicians: A scientific statement from the American Heart Association. *Circulation* 2007:115:1634-1642.
2. Chalmers JP, et al. Effects of indomethacin, sulindac, naproxen, aspirin and paracetamol in treated hypertensive patients. *Clin Exp Hypertens A* 1984;6:1077-1093.
3. Chan AT, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation* 2006;113:1578-1587.
4. Forman JP, et al. Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med* 2007;167:394-399.
5. Montgomery B. Does paracetamol cause hypertension? *BMJ* 2008;336:1190-1191.
6. Radack KL, et al. Ibuprofen interferes with the efficacy of antihypertensive drugs. A randomized, double-blind, placebo-controlled trial of ibuprofen compared with acetaminophen. *Ann Intern Med* 1987;107:628-635.
7. Pavlicevic I, et al. Interaction between antihypertensives and NSAIDS in primary care: A controlled trial. *Can J Clin Pharmacol* 2008;15:e372-e382.
8. Towheed TE, et al. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006;(1):CD004257.
9. Reisch JS, et al; Acute Liver Failure Study Group. Acetaminophen-induced liver failure: Results of a United States multicenter, prospective study. *Hepatology* 2005;42:1364-1372.

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Beauty Sleep: What Your Tired Face Says About You

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant for Cephalon, and serves on the speakers bureaus for Resmed and Respironics.

Synopsis: *Sleep-deprived individuals appear less healthy, tired, and less attractive to untrained observers than when they are rested.*

Source: Axelsson J, et al. Beauty sleep: Experimental study on the perceived health and attractiveness of sleep deprived people. *BMJ* 2010;341:c6614; doi: 10.1136/bmj.c6614.

In this study, investigators photographed the faces of 23 adults (mean age, 23 years; 11 women; mostly college students) in the middle of the afternoon under two conditions: 1) after a normal night's sleep (at least 8 hours between 11 pm and 7 am, thus after about 7 hours of wakefulness); and 2) after sleep deprivation (sleep between 2 and 7 am one night, and then an entire night of sleep deprivation, thus after about 31 hours of wakefulness). Smokers, recent alcohol drinkers, and people with sleep disorders and complaints were excluded.

Participants slept in their own homes, and sleep times were confirmed (and enforced) with sleep diaries and text messages. Participants were instructed not to nap. During the normal sleep condition, the participants' mean estimated duration of sleep was 8.45 hours. The sleep deprivation condition started with a night of sleep restriction, estimated to be 5.06 hours on average, followed by a night of total sleep deprivation, which was monitored in a sleep laboratory.

For the photo shoot, participants wore no makeup, had their hair loose (combed backwards if long), underwent similar cleaning or shaving procedures for both conditions, and were instructed to "sit with a straight back and look straight into the camera with a neutral, relaxed facial expression." They were kept indoors 2 hours before being photographed to avoid the effects of exposure to sunlight and the weather. The photographer was not blinded to the sleep conditions, but followed a highly standardized procedure during each photo shoot, including minimal interaction with the participants. Each participant had a series of 5-6 photographs taken in a well lit room, with a constant white balance under each condition. The focal length and the distance from camera to head were fixed. A blinded rater chose the most typical photograph from each series. This resulted in 46 photographs, one from each sleep condition of each of the 23 participants.

The photographs were presented randomly at a fixed interval of 6 seconds to 65 observers (40 women; mostly students; mean age, 30 years), who were unaware of the conditions of the study. They rated the faces for attractiveness, health, and tiredness on a 100 mm visual analogue scale (VAS). After every 23 photographs a brief intermission was allowed, including a working memory task intended to prevent memorization of the faces by the observers. To ensure that the observers were not primed to tiredness when rating health and attractiveness, they rated the photographs for attractiveness and health in the first two sessions and tiredness in the last.

When sleep deprived, people were rated by the observers as less healthy (mean, 63 vs 68), more tired (53 vs 44), and less attractive (38 vs 40) than after a normal night's sleep. Compared with the normal sleep condition, perceptions of health and attractiveness in the sleep-deprived condition decreased on average by 6% and 4% and tiredness increased by 19% (all statistically significant).

In addition, perceived attractiveness was positively associated with perceived health and negatively with perceived tiredness, and there was a strong negative association between the perceptions of tiredness and health.

■ COMMENTARY

About once a month, a writer for a women's magazine contacts me to find out "the truth" about beauty sleep. Thus, I have had occasion to pore over the internet, looking for peer-reviewed and/or scientific data on this topic. While it has been speculated that adequate sleep is part of good skin care,[1] this issue simply hasn't been studied. Until now. The current study confirms what we knew intuitively: We look better when we have slept enough. And it may be that sleep duration, while important, is not the complete recipe for a healthy appearance. Sleep quality may matter as well. Recent work indicates that the microvascular effects of obstructive sleep apnea may also contribute to premature aging.[2]

Most of us spend a large percentage of our time trying to get patients to eat less, exercise more, quit smoking, and generally change behavior. Getting adequate sleep should be on the list of behaviors that we include in our instructions about healthy living. And not just because we humans look better when we sleep well. Short sleep has been associated with everything from obesity to death.[3-5] Sleep deprivation also impairs judgment and cognitive function. Indeed, it has been recently suggested that surgeons who are sleep-deprived notify would-be surgical candidates of this fact to allow them to give well-informed consent;[6] the current study suggests that patients could simply tell by looking.

A quarter of a century ago, credible reports linked cigarette smoking to ugliness,[7] and "smoker's face" is now a well-recognized clinical entity. Perhaps "sleepless face" will join the ranks of clinical findings that we can employ in our efforts to motivate behavior change in patients. ■

References

1. Kahan V, et al. Can poor sleep affect skin integrity? *Med Hypotheses* 2010;75:535-537.
2. Yim-Yeh S, et al. Obstructive sleep apnea and aging effects on macrovascular and microcirculatory function. *Sleep* 2010;33:1177-1783.
3. Gangwisch JE, et al. Short sleep duration as a risk factor for hypertension. *Hypertension* 2006;47:833-839.
4. Qureshi AI, et al. Habitual sleep patterns and risk for stroke and coronary heart disease: A 10-year follow-up from NHANES I. *Neurology* 1997;48:904-911.
5. Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. *Soc Sci Med* 2010;71:1027-1036.
6. Nurok M, et al. Sleep deprivation, elective surgical procedures, and informed consent. *N Engl J Med* 2010;363:2577-2578.
7. Model D. Smoker's face: An underrated clinical sign? *Br Med J (Clin Res Ed)* 1985;291:1760.

Incidentally, You Have a Tumor on Your Adrenals

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

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Dr. Wilke has no financial relationship to this field of study.

Synopsis: *Most adrenal masses found inadvertently as part of an investigation for another illness are benign. The work-up for an adrenal incidentaloma is presented.*

Source: Ng VW, et al. Evaluation of functional and malignant adrenal incidentalomas. *Arch Intern Med* 2010;170:2017-2020.

The term "adrenal incidentaloma" first appeared in the medical literature in 1982.[1] Since then, there has been considerable discussion as to the work-up of these coincidentally discovered masses. The current article describes the review that a tertiary endocrine center in Hong Kong undertook to study the clinical characteristics of their patients with adrenal incidentalomas (AIs). They retrospectively reviewed all of their cases from 2000 to 2007, which involved 139 ethnically Chinese patients, 53 men and 86 women, with an average age of 57 years. They gathered the usual demographic data and also looked for signs and symptoms related to hormonal hypersecretion, such as hypertension or diabetes mellitus, or malignant adrenal neoplasm. They followed a protocol for the work-up of these masses. Any mass that was initially detected by ultrasound was confirmed by computed tomography (CT) or magnetic resonance imaging. The hormonal evaluations included an overnight dexamethasone suppression test, 24-hour urine catecholamine collection, and, if the patient was hypertensive, the ratio of plasma aldosterone to plasma renin. If any of these tests were positive, they performed more selective follow-up studies. Patients determined to have benign nonfunctional incidentalomas were reevaluated every 6-12 months with laboratory and radiologic evaluations.

At baseline, the patients did not differ in terms of age, presence of hypertension or diabetes mellitus, or size of the lesions (median size, 2.5 cm; range, 0.8-19.8 cm). One hundred thirteen patients (82%) had benign lesions, 15 (11%) had malignant lesions, and the remaining 11 were uncategorized. Of the benign adenomas, 52 were functional with 27 excreting cortisol, 12 aldosterone, 12 catecholamines, and one that excreted a combination of cortisol and aldosterone. Only five of 27 patients with cortisol-excreting tumors had signs or symptoms of Cushing's disease. Only five of 12 patients with excess catecholamine excretion had hypertension and only six were symptomatic. Of the 15 malignant lesions, six were primary adrenal carcinomas (four nonfunctional, two secreting cortisol), eight adrenal metastases, and one adrenal lymphoma. Four of the six patients with primary adrenal carcinoma died, three related to their illness. Two patients had stage I disease and had been tumor-free for at least 5 years after adrenalectomy.

■ COMMENTARY

AIs are common. Recent prospective studies in Sweden[2] and Italy[3] estimate a prevalence of 4.5%. This is similar to the 3% rate of adrenal tumors noted on autopsy of people older than 50 years. The prevalence increases with age, reaching 7% in people older than age 70.[4]

This study has weaknesses. Foremost are its retrospective design and setting in a tertiary endocrine center in Hong Kong, whose clientele was entirely ethnically Chinese.

The primary care physician presented with the patient with an AI has two questions that must be answered: Is the tumor benign or malignant? Is the tumor functional? Tumors that are malignant or functional should be removed. A recent review recommends the following:[5]

1. Biochemical testing for pheochromocytoma with plasma or urinary catecholamine measurements,

2. Biochemical testing for hyperaldosteronism in hypertensive patients,

3. Biochemical testing for hypercortisolism in patients with glucose intolerance, weight gain, and unexplained osteopenia,

4. Annual or biennial imaging and biochemical re-evaluation for benign lesions, and

5. Repeat evaluation for growth after 3-12 months, with subsequent testing intervals based on the rate of growth, for more indeterminate tumors.

The determination of benign vs malignant tumors is more difficult. There are features on CT (Hounsfield units < 10, contrast washout > 50%, and size < 3 cm) that favor benignity. Lack of functioning does not, however, as was demonstrated in the current study. Intuitively, percutaneous adrenal biopsy would provide the answer. However, a recent review from a U.S. tertiary care center would suggest otherwise.[6] Of 30 biopsies performed for isolated adrenal incidentalomas that were radiographically suspicious, only five were malignant. The NIH consensus statement recommends surgical removal of lesions > 6 cm and close follow-up of those between 4 cm and 6 cm.

Some physicians (and, perhaps, their patients) might ask, "Is this trip necessary?" The authors of this review would answer, "Yes," and would cite primary aldosteronism as the most common cause of secondary hypertension and the improvement their patients with subclinical Cushing's syndrome and hypertension, diabetes, or obesity had with successful surgical treatment and weight reduction. They also cite the lethality of silent pheochromocytomas, especially during surgery or percutaneous biopsy. Operative mortality for adrenalectomy is low (2%). Of course, if the adrenal mass should prove to be a metastasis from a known or unknown primary cancer, there is no benefit to adrenalectomy. As always, a frank discussion between you and your patient, discussing what lies at the end of the work-up and weighing the risks and benefits of adrenalectomy, is paramount. ■

References

1. Geelhoed GW, Druy EM. Management of the adrenal "incidentaloma." *Surgery* 1982;92:866-874.
2. Hammarstedt L, et al. Adrenal lesion frequency. *Acta Radiol* 2010;51:1149-1156.
3. Bovio S, et al. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *J Endocrinol Invest* 2006;29:298-302.
4. NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("incidentaloma"). *NIH Consens State Sci Statements* 2002;19:1-25.
5. Nieman LK. Approach to the patient with an adrenal incidentaloma. *J Clin Endocrinol Metab* 2010;95: 4106-4113.
6. Mazzaglia PJ, Monchik JM. Limited value of adrenal biopsy in the evaluation of adrenal neoplasm. *Arch Surg* 2009;144:465-470.

Pharmacology Update

Saxagliptin + Metformin Extended-release Tablets (Kombiglyze XR™)

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

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

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

THE FDA HAS APPROVED A SECOND DIPEPTIDYL PEPTIDASE-4 (DPP-4) inhibitor and metformin combination. This follows the approval of sitagliptin/metformin in 2007. Saxagliptin and extended-release metformin XR (SAXA/MET XR) is manufactured by Bristol-Myers Squibb and marketed by Bristol-Myers Squibb and AstraZeneca as Kombiglyze™ XR.

Indications

SAXA/MET XR is indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.[1]

Dosage

The recommended dose is 1 tablet daily with the evening meal.[1] The dose should be individualized based on the patient's existing regimen and adjusted based on effectiveness and tolerability.

SAXA/MET XR is available as 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg.

Potential Advantages

SAXA/MET XR provides a once-daily regimen involving two agents with different mechanisms of action. A fixed combination reduces pill burden and may improve adherence in some patients.[2]

Potential Disadvantages

A fixed combination reduces the flexibility of dose titration.

Comments

SAXA/MET XR was approved based on the bioequivalence of this combination with coadministered saxagliptin and metformin HCl extended release. Clinical evidence of efficacy of this combination was based mainly on saxagliptin and immediate-release metformin.[1] In a short-term, 4-week study, saxagliptin 5 mg or placebo was added to a stable dose of metformin XR in patients with type 2 diabetes (n = 93) inadequately controlled on metformin alone.[3] The 24-hour mean changes in weighted glucose from baseline were 13.8 mg/mL for saxagliptin and 3.0 mg/mL for placebo. The addition of saxagliptin (5 mg) or sitagliptin (100 mg) to a stable daily dose of metformin (1500-3000 mg) resulted in similar (non-inferior) reduction in HbA1c in type 2 diabetics with baseline HbA1c between 6.5% and 10% (n = 801).[4]

Clinical Implications

SAXA/MET XR is the second DPP-4 inhibitor/metformin combination to be approved for marketing. The efficacy appears to be similar to sitagliptin and metformin. Metformin is considered the cornerstone of dual therapy by a consensus panel of the American Association of Clinical Endocrinologist/American College of Endocrinology.[5] The DPP-4 inhibitor metformin combination is the preferred oral combination due to safety, lower risk of hypoglycemia, and weight gain relative to a sulfonylurea/metformin or thiazolidinedione/metformin combination.[5] ■

References

1. Kombiglyze XR prescribing Information. Princeton, NJ: Bristol-Myers Squibb Company; November 2010.
2. Xhernthaner G. Fixed-dose combination therapies in the management of hyperglycaemia in Type 2 diabetes. *Diabet Med* 2010;27:739-743.
3. Stenlof K et al. Saxagliptin and metformin XR combination therapy provides glycemic control over 24 hours in patients with T2DM inadequately controlled with metformin. *Curr Med Res Opin* 2010;26:2355-2363.
4. Scheen AJ. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev* 2010;26:540-549.
5. Rodbard HW et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus. *Endocr Pract* 2009;15:540-559.

CME Questions

1. **In the Sudano study, acetaminophen in doses used in daily clinical practice:**
   a. had no significant effect on BP in patients with CAD.
   b. may increase BP but had no effect on vascular function in patients with CAD.
   c. may increase BP and significantly affect vascular function in patients with CAD.

2. **Compared to the rested state, sleep-deprived individuals appear:**
   a. less healthy.
   b. more attractive.
   c. no different.
   d. stronger.

3. **Choose the correct statement. In the study of adrenal incidentalomas:**
   a. Most patients discovered with pheochromocytomas were symptomatic.
   b. Most patients discovered with cortisol-excreting adenomas were asymptomatic.
   c. More than half of the lesions were malignant.
   d. All of the patients with primary adrenal carcinoma died of their disease.
   e. All nonfunctional tumors were benign.

Answers: 1. b, 2. a, 3. b.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Daiichi, Sankyo, Forest Pharmaceuticals, Lilly, Novo Nordisk, Takeda.

Immunochemical FOBT and low-dose aspirin

Source: Brenner H, et al. Low-dose aspirin use and performance of immunochemical fecal occult blood tests. *JAMA* 2010;304:2513-2520.

Immunochemical fecal occult blood testing (i-FOBT) is becoming increasingly popular as a screening tool for colorectal cancer (CRC). At the same time, the number of persons taking long-term low-dose aspirin (ASA) for CV disease risk reduction is also increasing. Concern has been expressed that the predictable increase in GI bleeding associated with ASA would decrease the specificity of i-FOBT by increasing false positives. At the same time, it has been suggested that consequences of i-FOBT to detect upper GI bleeding may have been overestimated, since the globin chains detected by i-FOBT typically are degraded progressively during passage through the GI tract, and are hence less available for i-FOBT identification than more distal bleeding in the GI tract. Finally, utilization of ASA might also increase the risk of bleeding of CRC, thus enhancing likelihood of detection.

To assess the relationship between ASA, i-FOBT, and results of CRC screening, Brenner et al reported on almost 2000 adults who underwent CRC screening, 12% of whom were regular ASA users.

Sensitivity (the number of positive tests in persons confirmed to have advanced GI neoplasms) of i-FOBT was greater in ASA users than non-users. i-FOBT specificity (the number of negative tests in persons without advanced GI neoplasms) was minimally reduced.

Chronic low-dose ASA does not appear to compromise the ability of i-FOBT to detect advanced GI neoplasia, with a modest decrease in specificity. ■

Capitalizing on the second-meal effect in type 2 diabetes

Source: Chen JM, et al. Utilizing the second-meal effect in type 2 diabetes: Practical use of a soya-yogurt snack. *Diabetes Care* 2010;33:2552-2554.

It is probably not widely known that Mom was right — at least as it pertains to diabetes — that you should NOT skip breakfast. Why? Because of the "second-meal effect," a little-recognized physiologic response that can have a potentially favorable effect on glucose.

The way the "second-meal effect" works is like this: When breakfast is eaten, the degree of hyperglycemia seen after lunch is less than if the same amount of calories are given without having eaten breakfast. It has been suggested that the improved glucose level is related to a reduction in preprandial free fatty acids, which allows for greater storage of muscle glycogen during a second meal (and hence a greater disappearance of glucose from the plasma). This phenomenon occurs in both diabetic and non-diabetic individuals. Based upon this observation, Chen at al hypothesized that perhaps providing a pre-breakfast snack would reduce post-breakfast hyperglycemia.

Diabetic subjects (n = 10) were administered a snack of soya beans and yogurt 2 hours before breakfast. For scheduling convenience, the snack was administered at 8 am, and breakfast at 10 am.

Plasma glucose 2 hours after breakfast was significantly lower in the group who received the snack. Since postprandial glucose levels have been associated with adverse cardiovascular outcomes in diabetics, it might be both desirable and possible to manipulate post-meal hyperglycemia without using medications. ■

Aerobic vs resistance exercise for type 2 diabetes

Source: Church T, et al. Effects of aerobic and resistance training on hemoglobin A1c in patients with type 2 diabetes. *JAMA* 2010;304:2253-2262.

Most persons with type 2 diabetes (DM2) are overweight or obese. Exercise is routinely advised for DM2, although whether a particular method of exercise has an advantage for optimization of glycemic control is not well defined.

Church et al compared the effects of aerobic exercise (AER), resistance training (RES), or the combination (AER + RES) vs placebo in previously sedentary mid-life DM2 adults (mean age = 56 years). Participants engaged in the prescribed activities for 9 months. The primary outcome was change in A1c from baseline.

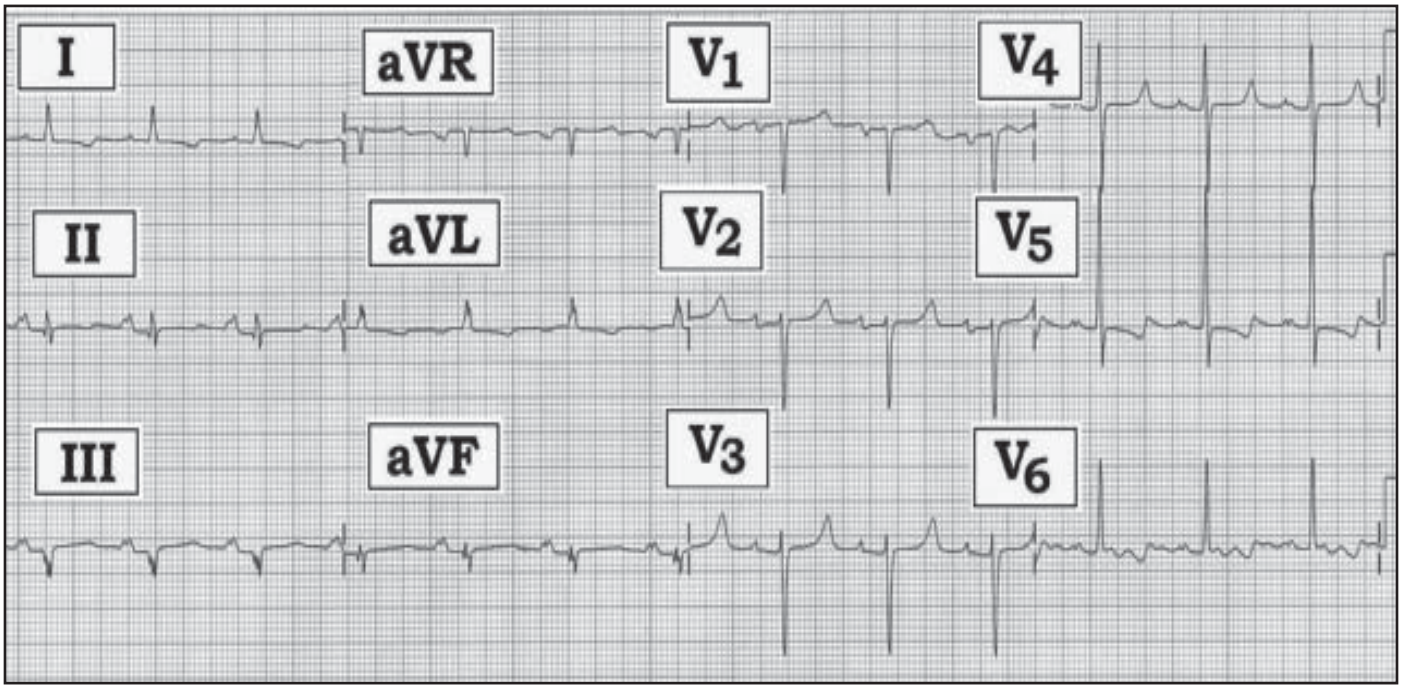
At the conclusion of the trial, only the AER + RES provided statistically significant reduction in A1c compared to placebo; AER alone or RES alone did not.

It would be unfortunate if clinicians were to interpret this trial as indicating a lack of value of either AER or RES alone. All exercise groups had favorable changes in anthropomorphic metrics, and exercise has been shown to be associated with a favorable impact upon cardiovascular risk in large population studies, an effect that may be independent of glycemic effects. ■

Competing Conditions

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.



Scenario: The ECG shown above was obtained from a dialysis patient with a long cardiac history, but no acute chest pain. Why did we select the title of "Competing Conditions" for this ECG Review?

Interpretation: The surface ECG shows the net result of electrical forces that are operative. This concept is important to remember when potential "competing conditions" are operative. The rhythm in this tracing is sinus. There is generalized low voltage in the limb leads. The PR interval is upper normal (0.21 second), the QRS is narrow, and the QT appears prolonged. There is left axis deviation (LAD), as suggested by the predominantly negative QRS complex in lead aVF. Prior inferior infarction is suggested by the small q wave in leads II and aVF, and a "forme fruste" Q in lead III. Interplay of electrical forces from probable left anterior hemiblock (LAHB) and presumed prior inferior infarction is the first set of competing conditions that appear to be present in this tracing.

Multichamber enlargement in the form of a notched and peaked P wave in the inferior leads and a deep negative component to the P in lead V_1, with a small peaked positive P in leads V_2,V_3 suggest that combined left and right atrial enlargement is the second set of competing conditions. We suspect underlying cardiomyopathy given this patient's long cardiac history, left and right atrial enlargement, and a precordial lead pattern suggestive of left ventricular hypertrophy (LVH).

The final set of competing conditions most probably accounts for the unusual ST-T wave morphology in the precordial leads. The long QT with T wave peaking in leads V_2,V_3,V_4 suggests hyperkalemia in this patient on dialysis. In contrast, the sagging ST segment in lead V_5 suggests "strain" from probable LVH. Especially in view of terminally T wave peaking in lead V_5, it is impossible to know how much ST-T depression there would be if opposing forces from hyperkalemia were no longer operative. Morale: Always repeat the ECG after correction of hyperkalemia. ■

In Future Issues:

Alcohol Use in Older Women

PHARMACOLOGY WATCH

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

Statin Use in Patients with Abnormal Liver Function

In this issue: Statins and liver function; dosing timing for thyroxine; rivaroxaban for VTE, DVT, and stroke; echinacea and the common cold; and FDA actions.

Statins and liver function

Most physicians are hesitant to use statins in patients with abnormal liver function tests (ALT or AST less than three times the upper limit of normal). A new study suggests that not only are statins safe and effective, they may improve liver abnormalities in patients with fatty liver. In a study recently published in the *Lancet*, 437 patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation study population were noted to have moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease. Of that group, 227 were treated with a statin (atorvastatin) and 210 were not. Patients treated with a statin had substantial improvement in liver tests ($P < 0.0001$), whereas the group not treated with a statin had further increases in liver enzyme concentrations. Cardiovascular events occurred in 10% of atorvastatin-treated patients vs 30% of the non-statin group (60% relative risk reduction; $P > 0.0001$). This was a greater improvement in benefit than seen in patients with normal liver function tests. Fewer than 1% of the participants who received a statin had to discontinue statin treatment because of transaminase concentrations more than three times the upper limit of normal. The authors concluded that "statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease" (*Lancet* 2010;376:1916-1922). ■

Dosing timing for thyroxine

When is the best time to take thyroxine? Patients are generally told to take it on an empty stomach in the morning and wait at least 30 minutes before eating. A new study suggests that taking thyroxine at bedtime might be a better option. Over 6 months, 105 patients were randomized to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Taking levothyroxine at bedtime lowered thyrotropin levels and increased free thyroxine and total triiodothyronine levels (the primary outcome). Treatment did not change secondary outcomes including quality of life. The authors concluded that taking levothyroxine at bedtime is a good alternative to morning intake (*Arch Intern Med* 2010;170:1996-2003). This would likely benefit patients who find it difficult to wait 30 minutes to eat after taking their thyroxine each morning. ■

Rivaroxaban: an oral, factor Xa inhibitor

Rivaroxaban is an oral, direct factor Xa inhibitor that is approved in several countries for the prevention of venous thromboembolism (VTE) after orthopedic surgery. It is currently being evaluated by the FDA for this indication. Based on the findings of the EINSTEIN study, it appears the drug is also effective for the treatment of acute deep vein thrombosis (DVT). EINSTEIN consists of three randomized trials of rivaroxaban, one for the treatment of acute DVT, one for treatment of acute pulmo-

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nary embolism, and one for continued, long-term treatment in patients who have received treatment for acute DVT or pulmonary emboli. The results of the first and third wings of the study were recently reported in the *New England Journal of Medicine*.

In the DVT treatment arm, 3449 patients with acute DVT were randomized to rivaroxaban (50 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. In the continued treatment wing of the study, patients were randomized in a double-blind fashion to rivaroxaban 20 mg once daily or placebo for additional 6 or 12 months after completion of 6-12 months of treatment for VTE. The primary outcome for both studies was recurrent DVT. For the treatment of acute DVT, rivaroxaban was non-inferior to enoxaparin-vitamin K antagonist (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; $P < 0.001$). In the continued treatment study, rivaroxaban had superior efficacy compared to placebo (8 events [1.3%] vs 42 events [7.1%] with placebo; HR 0.18; 95% CI, 0.09-0.39; $P < 0.001$). There were four patients in the rivaroxaban group with non-fatal major bleeding vs none in the placebo group. The EINSTEIN authors concluded that "Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation" (*N Engl J Med* 2010;363:2499-2510).

Rivaroxaban is also being evaluated for the prevention of stroke in patients with nonvalvular atrial fibrillation based on the ROCKET AF study, which was presented at the American Heart Association meetings in November 2010. If approved, it will join the recently approved direct thrombin inhibitor dabigatran (Pradaxa®) for this indication. Both drugs have the advantage over warfarin of not requiring ongoing lab monitoring. ■

Echinacea and the common cold

The National Center for Complementary and Alternative Medicine (NCCAM), a division of NIH, has been in existence for nearly 20 years, much of the time under the intense scrutiny of the mainstream medical community. Despite NCCAM's attempts to verify the effectiveness of alternative healing practices, most if not all rigorously studied modalities have been shown to be ineffective. The benefit of another alternative staple, echinacea, is questioned with the publication of a NCCAM-sponsored study testing the benefit of the herbal remedy for treating the common cold. More than 700 patients in Wisconsin with new-onset common cold were assigned to one of four groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded). The primary outcome was severity of the cold by self reporting with secondary outcomes of interleukin-8 levels and neutrophil counts from nasal washes. The comparison of the two blinded groups showed a trend toward benefit for the echinacea group (an average decrease in duration of cold of 7-10 hours out of 1 week; $P = 0.089$), but no difference in mean illness duration. There were no differences in the secondary outcomes. The authors concluded that the differences in illness duration and severity were not statistically significant with echinacea compared to placebo (*Ann Intern Med* 2010;153:769-777). ■

FDA Actions

The FDA is removing the breast cancer indication for bevacizumab (Avastin-Genentech). The somewhat unusual move was made after an FDA advisory panel suggested last summer that the drug did not provide a survival benefit for patients with breast cancer and at the same time caused serious side effects. The drug is still approved for treating cancer of the brain, colon, kidney, and lung.

The **FDA advisory panel is recommending approval for the first new diet pill in a decade. Orexigen Therapeutics' Contrave® is a combination of the antidepressant bupropion and the opioid antagonist naltrexone.** The drug was recommended for approval by a vote of 13-7, with some committee members voicing concern about potential side effects of the drug and recommending close post-marketing follow-up and studies to assess the risk of major cardiac events. The recommendation to approve the drug was based on studies that show an average weight loss 4.2% greater than placebo.

The **FDA has approved denosumab for the prevention of skeletal related events (fracture and bone pain) in patients with bone metastases from solid tumors.** The drug, which is given as a once monthly injection, was approved after a 6-month priority review. Denosumab is a monoclonal antibody to RANKL, a protein essential for the formation, function, and survival of osteoclasts. Denosumab in a lower-dose formulation was recently approved for the treatment of osteoporosis under the trade name Prolia™. Amgen Inc. will market the drug for this new indication under the trade name Xgeva™. It is expected to compete strongly with Novartis Pharmaceutical's zoledronic acid (Zometa®), which is approved for the same indication. ■