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INSIDE

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, is a consultant for Abbott, Amylin, Boehringer Ingelheim, Eli Lilly, Endo, Novartis, and Novo Nordisk. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

Salt! Bad for Slugs and Humans

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus, Huntsville

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

Synopsis: *Limiting dietary sodium can reduce blood pressure and morbidity and mortality from cardiovascular disease.*

Source: Cook NR, et al. *BMJ.* 2007;334:885-892.

The Trials of Hypertension Prevention phase I (TOPH I) and phase II (TOPH II) were conducted in the late 1980s and early 1990s, respectively. These studies investigated several hypertension treatments including weight loss, sodium restriction, stress management, and dietary supplements, such as minerals and fish oil. The two studies randomized a total of 3126 patients to a sodium intervention or control group. The enrollees in these studies had similarities, but also some differences. At the initiation of the studies, patients were 30-54 years old (average around 43), about two-thirds male, mainly white, and not on antihypertensive medications. Patients in TOPH I had mean diastolic blood pressures (DBP) of 84 mm Hg; in TOPH II, DBP averaged 86 mm Hg. Mean systolic blood pressure (SBP) in TOPH I was 125; in TOPH II it was 127. The average body mass index (BMI) in TOPH I was 27.1. TOPH II purposefully enrolled patients with weights 110-165% of desirable and the average BMI was 30.9. Both studies demonstrated modest reductions in blood pressure (SBP/DBP 1.7/0.8 in TOPH I and 1.2/0.7 in TOPH II) and urinary sodium excretion in the intervention groups.

From 2000 to 2005, the investigators followed the patients, collecting data on cardiovascular events (myocardial infarction, stroke, coronary artery bypass graft, coronary angioplasty, and cardiovascular death) and self-reported sodium intake. The follow-up rate was 77%. The overall rate of cardiovascular disease (CVD) in the restricted sodium groups was 7.5%, compared to 9.0% in the control groups. Overall mortality was 2.3% and 2.6%, respectively. The results were not affected when the data were analyzed by age, gender, race, BMI, and active weight loss intervention. Additionally, individuals in the intervention groups

VOLUME 29 • NUMBER 13 • JULY 15, 2007 • PAGES 97-104

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reported a dislike for salty food more often than those in the control groups (48% vs 32%), used low-sodium products more frequently (47% vs 29%), and read food labels for sodium more frequently (66% vs 44%).

COMMENTARY

"Hello, I'm Allan, and I'm a saltaholic." In fact, I'm eating cheese and crackers and dry-roasted peanuts as I write this. I'm not alone. According to the National High Blood Pressure Education Program, the average daily sodium intake in the US in 1999 was 4,000 mg; the recommended intake is 2,400 mg.[1] The good news is that, at least according to this study, I have a half-way decent chance of training myself to eat less salt-laden foods.

These individuals had prehypertension (120-139/80-89), which affects 45 million Americans.[2] Is a reduction in CVD from 9.0% to 7.5% and mortality from 2.6% to 2.3% over 10-15 years clinically significant? Traditional analysis would say that this translates into a number-needed-to-treat (NNT) of 67 for CVD and 333 for mortality. These are not the numbers that will likely change a patient's behavior, but when we are wearing our public health hats, it should change ours. For one thing, we should be pushing for more efforts to reduce the sodium content of processed food.

A Cochrane review[3] in 2004 concluded, "Intensive interventions, *unsuited to primary care or population prevention programmes* [my emphasis], provide only minimal reductions in blood pressure during long-term trials. Further evaluations to assess effects on morbidity and mortality outcomes are needed for populations as a whole and for patients with elevated blood pressure." TOPH I and II were included in this review.

When my residents ask about using the newest medication for disease X that they heard about from the pharmaceutical representative of company Y, I invariably will ask them (the residents and the drug reps) if there is any data on morbidity or mortality. The same standard must be applied to nonpharmaceutical interventions. For cardiovascular disease, it is not enough that blood pressure is lowered or cholesterol is reduced. Although I have recommended to them (the residents) that they advocate for salt restriction to reduce blood pressure, I haven't had much evidence to offer that it would do any good. Now I do. ■

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

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

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MANAGING EDITOR: Iris Williamson Young

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.

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Are Ureteral Stents More Trouble Than They're Worth?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Professor, University of California, San Diego
Dr. Scherger reports no financial relationship to this field of study.

Synopsis: *In a systematic review and meta-analysis of worldwide data on the placement of ureteral stents after ureteroscopy in patients with kidney stones, the authors found higher morbidity with lower urinary tract problems and no benefit on stone-free rate, rate of urinary tract infection, requirement for analgesia or long term ureteral stricture formation.*

Source: Nabi G, et al. *BMJ.* 2007;334:572.

URETERAL STENTS ARE COMMONLY PLACED BY urologists after ureteroscopy in patients with kidney stones. Using the Cochrane controlled trials registry, these authors from Scotland did a systematic review and meta-analysis of 9 identified randomized controlled trials looking at clinical outcomes with and without stenting after ureteroscopy. Eight hundred thirty-one patients were identified. The incidence of lower urinary tract symptoms was significantly higher in patients who had a stent inserted (relative risk 2.25). For dysuria, the relative risk was 2.00, and for frequency or urgency, 1.11.

Among patients with ureteral stents, there were no significant benefits, nor difference in postopera-

tive requirement for analgesia, urinary tract infections, stone free rate, or ureteral strictures. Costs were higher in the group with stents. None of the trials reported on health-related quality of life.

The authors point out that the quality of the trials was poor, with marked heterogeneity of study methods which limited the power of the systematic review. While these findings suggest that the complications of ureteral stents exceed any benefits in patients with uncomplicated ureteroscopy, the authors state that this area remains unclear and that better randomized controlled trials should be done.

COMMENTARY

This study caught my eye since my experience with ureteral stents has been consistently negative. First of all, the great majority of patients with kidney stones may be treated conservatively with analgesia, hydration, and observation. Time heals. A referral to a urologist in the acute phase may result in the patient undergoing ureteroscopy. As stents became common practice, I often asked why, especially when the patients came back with pain and dysuria. Did my patient really need to have this foreign body and when can we get it out?

Uncomplicated kidney stones should by managed by primary care physicians, emergency room physicians or hospitalists. Imaging can identify patients who are developing serious obstruction. A few more days of analgesia is usually better than a procedure with a high complication rate. Even if ureteroscopy is indicated, ask whether the patient really needs a stent before it is placed. By avoiding stents, we will not have to deal with their complications.

A Randomized Trial for Treatment of Chronic Constipation

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

Emeritus Clinical Professor of Medicine, University of Oklahoma College of Medicine Oklahoma City

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

Synopsis: *This study documents the safety and efficacy of oral polyethylene glycol for the long-term treatment of chronic constipation.*

Source: DiPalma JA, et al. *American Journal of Gastroenterology.* 2007;102:1-8

Fifty centers ultimately enrolled 304 evaluable patients with at least a 3-month history of constipation (609 screened). The study was designed to compare the effects of polyethylene glycol vs placebo for the treatment of chronic constipation over a period of 6 months. Chronic constipation was defined (using modified ROME criteria) as less than 3 satisfactory stools per week plus at least one of the following: straining at stool in more than 25% of defecations; lumpy or hard stools in more than 25% of defecations; sensation of incomplete evacuation in more than 25% of defecations. Patients had never taken any form of polyethylene glycol (PEG) for treatment of constipation, and constipation-producing concomitant medications were not allowed at baseline although these might be added if necessary during the course of the study. Other laxative preparations were not allowed except for rescue medication involving 10 mg of oral bisacodyl if severely uncomfortable or if no bowel movement had occurred in the past 4 days. PEG (MiraLAX™) or a matching maltodextrin placebo was given as a powder dissolved in 8 ounces of liquid daily. Treatment success required no use of rescue laxative, satisfactory stools at least 3 times weekly, and one or fewer of the modified ROME criteria outlined above. Data were collected using a telephone-based interactive voice response system. Super efficacy was defined as treatment success with none of the ROME criteria for constipation being present.

Eighty-five percent of study enrollees were female and mean age was 53 years. An average duration of 23 years of constipation was reported by enrollees. Efficacy was demonstrated in 52% of PEG recipients vs 11% with placebo. Active treatment was statistically better than placebo for all of the secondary endpoints (eg, straining, hard stools, incomplete defecation). Super efficacy was achieved in only 9.2% of PEG recipients vs 2.2% with placebo. However, there were no significant differences between groups in the use of rescue bisacodyl tablets during the study. PEG recipients overall (40% vs 25%) were more likely to have treatment-related symptoms such as nausea, loose stools, abdominal distension, and flatulence although none of the individual symptoms reached statistical significance vs the same symptom in the placebo recipients. No laboratory abnormalities were treatment-related in this study; and, in particular, electrolyte balance was not disturbed.

COMMENTARY

Other authors have also recently published data on the use of tegaserod in chronic constipation that indicate some efficacy. However, DiPalma and colleagues have a pending manuscript for the *American Journal*

of Gastroenterology that found PEG to be superior to tegaserod in efficacy and in tolerability (pending publication this summer). Some years ago, a great many gastroenterologists discovered that regular self-administration of refrigerated liquid PEG-based colon-cleansing solutions could be very helpful in the management of chronic constipation. More recently, companies have developed more conveniently prepared packages of PEG for daily dissolution and consumption (eg, MiraLAX™). Studies like those of DiPalma have demonstrated that there is significant benefit associated with chronic PEG use in longstanding constipation. PEG also appears to be generally safe. However, it is important to note that almost half of the PEG recipients had inadequate clinical responses. Moreover, PEG seemed to cause significantly more GI side effects than placebo. Clearly, we need more and better treatments. This can only occur when constipated patients can be better categorized as to specific underlying pathophysiology, thus allowing treatment to be individualized to address the potentially unique complex of abnormalities in each patient. Clearly, constipated patients with pelvic outlet problems do not need the same treatment as those with colonic inertia, and constipation with irritable bowel syndrome requires yet other therapeutic regimens. For now, there are undoubtedly many patients who will benefit from one or another of the PEG-based regimens for chronic constipation. ■

Are Statin-induced Myopathic Symptoms Improved by Coenzyme Q10?

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: *Statin-treated patients who developed symptoms of myopathy should be treated with at least 100 mg daily of coenzyme Q10 for a minimum of 30 days (assuming CPK values and/or other liver function tests are not abnormal) before discontinuing statin therapy.*

Source: Caso G, et al. *Amer J Card.* 2007;99:1409-1412.

THE MOST COMMONLY USED METHOD FOR DECREASING cholesterol production is by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) using statin drugs which have proven to be extraordinarily effective and safe[1-3] and, in addition, outcome studies have clearly demonstrated their incredible effectiveness in both the primary and secondary prevention of myocardial infarctions and strokes.[4] Since the biosynthetic pathway inhibited by statin drugs is shared by ubiquinone (coenzyme Q10), this vital component of the mitochondrial electron transport system[5] is usually significantly reduced in patients receiving statin therapy[9-13] thereby affecting oxidative phosphorylation and mitochondrial adenosine triphosphate (ATP) production which may result in impaired muscle energy metabolism and contribute to the development of myopathy and muscle symptoms.[6,7]

Recognizing that the clinical studies determining whether or not coenzyme Q10 supplementation would improve muscle symptoms in patients receiving statin therapy had not been previously performed, Caso and his colleagues studied 32 patients before and after treatment with coenzyme Q10 or vitamin E (control group) for one month.[8] Myopathic symptoms were defined as the development of muscle pain alone or accompanied by other symptoms, such as muscle weakness and/or fatigue. In a double-blinded protocol, patients who had been treated with statins and who developed myopathic symptoms were randomly treated with either 100 mg per day of coenzyme Q10 or 400 IU of vitamin E orally. After coenzyme Q10 treatment for 30 days, pain severity decreased by 40% and interference with daily activities because of the pain decreased by 38% whereas no change in pain severity or interference with daily activities due to pain was noted to occur in the control group which had been treated with vitamin E.

■ COMMENTARY

Only a small fraction of the millions of people in the United States who have been treated with statin drugs have developed severe myopathy which, in the worst cases, can lead to severe myoglobinuria, acute renal failure, and even death. In fact, this complication, although occurring in only a small numbers of patients, was also associated with a small number of deaths which led to the relatively recent withdrawal of cerivastatin from the US markets. Toxic myopathy occurs in only approximate 0.1% of statin users and, fortunately, the myopathy usually resolves when statin therapy is discontinued. In a small published study, patients could accurately identify blinded statin therapy by carefully assessing their functional capacity and muscle strength.[7] Most physicians have characteristically simply reassured their patients that their muscular aches and pains were most most likely not due to statin therapy (especially if serum CPK determinations proved to be normal) however, it should now be recognized that the Caso study[8] results suggest that deficiency of coenzyme Q10 resulting from statin therapy may be contributing to or even causing the myopathic symptoms. Their study was an extremely

small one utilizing a total of only 32 patients but the results reached statistical significance and therefore their conclusions should be carefully considered.

In summary, it is important to recognize that the vast majority of patients who report muscular symptoms while on statin therapy do not have chronic or subacute myopathy and therefore statin therapy should, in most cases, not be discontinued unless the CPK becomes elevated (although CPK elevation has not been clearly demonstrated to be a sensitive marker to detect or assess statin-related myopathies). Even though the results of the Caso study were so impressive, it must be recognized that it was an extremely small clinical study which hopefully will lead to a larger, double-blinded, well controlled study. However, for the time being, the proven efficacy of statin therapy for primary and secondary prevention of cardiovascular disease especially in high risk cardiac patients mandates that statins should not be discontinued in patients complaining of muscular aches and pains but rather, it would now appear to be appropriate to consider treating these patients with at least 100 mg of coenzyme Q10 daily for at least 30 days assuming that their CPK enzyme values and/or liver function tests do not become significantly abnormal. Of course, many physicians will already have elected to prescribe coenzyme Q10 prophylactically when prescribing statin drugs in order to hopefully avoid the development of myopathic symptoms but, for those statin-treated patients not already receiving coenzyme Q10, 100 mg of coenzyme Q10 daily for at least 30 days should be considered as a therapeutic option before the statin drug is discontinued in the patient who presents with new onset of myopathic symptoms and who does not have a significant increase in CPK values or liver function tests. ■

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Levonorgestrel and Ethinyl Estradiol Tablets (Lybrel™)

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

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.

THE FDA HAS APPROVED THE FIRST CONTINUOUS, low dose, oral contraceptive for the prevention of pregnancy. This new contraceptive contains levonorgestrel and ethinyl estradiol and is marketed by Wyeth Pharmaceuticals, Inc., as Lybrel .

Indications

Levonorgestrel/ethinyl estradiol (LNG/EE) is indicated for the prevention of pregnancy in women who choose an oral contraceptive as the method of contraceptive.[1]

Dosage

One tablet is taken daily without any interruption (no tablet-free days). If the woman is not on any current contraceptive, therapy should be started on Day 1 (within 24 hours) of the menstrual cycle. If the woman is on a cyclic combination oral contraceptive, therapy should be started on Day 1 of withdrawal bleeding and no more than 7 days after the last active tablet. Non-hormonal backup contraceptive method is not recommended. If the woman is on a progestin only pill, therapy should be initiated the day after taking the progestin pill and a backup method is recommended for the first 7 days of LNG/EE. A backup method is recommended for conversion from implants or injectable contraceptives.[1]

Lybrel is available as 28 day dispensing unit, each tablet containing LNG 90 mcg and EE 20 mcg.

Potential Advantages

Continuous delivery of hormones eliminates menstruation and associated symptoms. This may be prefer-

able for certain women.

Potential Disadvantages

Unscheduled bleeding and spotting is more likely with continuous LNG/EE. Without regular menstruation it may be difficult to recognize pregnancy. Amenorrhea is induced in about 60% of women. It is uncertain how long after discontinuation of LNG/EE that conception is possible.

Comments

The efficacy and safety of continuous LNG/EE was shown in 2 one-year studies involving healthy women ages 18-49. One study which was done in Europe (n = 641) used a formulation that contained 100 mcg of LNG compared to 90 mcg in the second study which was done North America (n = 2134)[1,2] and is the same dose marketed in the US. The primary efficacy endpoint was the number of unintended pregnancies during treatment which was measured as the number per 100 women-years of use (Pearl Index). The overall Pearl Indices in the North American study were 2.38 (95% CI: 1.51, 3.57) among women 35 years or less in all users and 1.55 (95% CI: 0.87, 2.56) in women who took the tablets as directed.[2] About ¾ and ½ of women respectively, experience spotting only or bleeding by the second month. Bleeding and spotting tend to decline with continual use. However, 21% of women experienced uterine bleeding after 12 cycles of use with a median of 4 days of bleeding and 3 days of spotting per 28 days (2). Uterine bleeding was the primary reason for discontinuing therapy (18%). Amenorrhea was induced in 59% of women and absence of bleeding in 79%. Cost was not available at the time of this review.

Clinical Implications

Oral contraceptives have evolved from monthly regimens to every three months (ie, Seasonale® and Seasonique™) and now to continuous use (Lybrel™). These formulations give women the choice of monthly menstruation, 4 periods per year, or none per year. Women who have menstruation associated symptoms such as dysmenorrhea, menorrhagia, pelvic pain, migraine headaches, and even seizures may welcome a continuous oral contraceptive and consider these regimens an improvement in quality of life.[3,4] Long-term safety and the return of fertility, after discontinuation of continuous regimens are not known. ■

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CME Questions

34. Choose the one incorrect answer. Reducing sodium in diet can result in:

a. impotence in men.
b. lower blood pressure.
c. reduced cardiovascular disease.
d. reduced mortality.
e. a dislike for salty food.

35. Which statement about ureteral stents in patients with kidney stones is true:

a. Ureteral stents are associated with an increased rate of lower urinary complications without measurable benefit.
b. Ureteral stents reduce the pain of a kidney stone but increase the number of urinary tract infections.
c. Ureteral stents reduce the number of ureteral strictures but increase the number of urinary tract infections.
d. Ureteral stents improve outcomes in patients with kidney stones by facilitating stone passage and reducing the number of urinary tract infections.

Answers: 34 (a); 35 (a)

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.

Metabolic Effects of Topiramate in Obese Diabetics

Almost 90% of persons with type 2 diabetes (DM2) are overweight. Weight loss in DM2 consistently results in meaningful favorable changes in lipids, glucose, and insulin resistance, so the clinical community embraces tools to enhance weight loss in this population.

Unfortunately, currently available weight-loss tools (eg, orlistat, sibutramine) are limited by modest long-term impact, tolerability, and cost. Diet and exercise are highly effective as demonstrated in clinical trials, but most patients do not enjoy the "team" approach available in such trials, resulting in failure to achieve and maintain weight loss goals.

In clinical trials of immediate-release topiramate (TOP-IR) for migraine, weight loss has been consistently identified, in the absence of any dietary or exercise intervention. Similarly, TOP-IR has demonstrated weight loss in trials of DM2, but has had tolerability issues. Controlled release topiramate (TOP-CR) has been developed for greater ease of administration (qd vs b.i.d.) and lesser adverse effect profile.

DM2 subjects (n = 111) were randomized to diet and exercise with or without TOP-CR; approximately ¾ of both groups were also on metformin. At 16 weeks, endpoints favored the group with TOP-CR: weight loss (6.0 kg vs 2.5 kg), A1C (6.7 vs 7.1), and BP (117/74 vs 124/77). But because of the profile of adverse events (43% of participants on TOP experienced central nervous system or peripheral nervous system effects) it is unlikely that current formulations of TOP will have a role in metabolic management of diabetes. ■

Rosenstock J, et al. Diabetes Care. 2007;30(6):1480-1486.

Clues that Differentiate Toenail Onychomycosis from Look-alikes

It is tempting to initiate pharmacotherapy when the appearance of a pathologic nail suggests onychomycosis (ONYC). However, systemic treatments for ONYC require a protracted course of therapy, at substantial expense, with potential toxicity, leading to expert advice which suggests not initiating treatment unless the presence of fungus has been confirmed, eg, by KOH examination, fungal culture, or both.

A variety of other disorders may mimic ONYC, including psoriasis, lichen planus, and post-traumatic dystrophy. Seeking to discern factors which correlate with the presence of ONYC, Walling et al reviewed characteristics of 150 cases of ONYC confirmed by PAS staining.

The factors that best correlated with confirmed fungal infection included male gender, age over 64, concurrent tinea pedis, and involvement of the third or fifth digit. Dystrophic changes of the great toe were the most commonly noted finding, but only in half of cases of dystrophic changes of the great toe was fungus confirmed. Female gender was a negative predictor.

Because current methodologies for confirmation of fungal infection are imperfect, cases which test negative for fungi but are associated with positive correlation factors should be considered for repeat testing. ■

Walling HW, Sniezek PJ. Am Acad Dermatol. 2007;56:945-948.

Comparing Medical and Surgical Management of Sciatica

Low back pain (LBP) remains one of the most commonplace and costly disabilities affecting working Americans. Although there is some controversy about appropriate indications for surgery, the presence of persistent sciatica (SCI)—peripheral pain that is indicative of a lumbar or sacral nerve compression—is commonly used as a selection criterion for consideration of surgical intervention. There is little data to compare outcomes for persons with SCI treated with conservative treatment versus surgery. Some guidelines suggest that surgical treatment be considered for persons with SCI persistent after 6 weeks of conservative therapy.

Subjects (n = 283) with SCI rated as severe due to incapacitating pain were enrolled in this trial if symptoms persisted 6-12 weeks, and were randomized into early surgery (within the next 2 weeks) or conservative management. A small percent of persons assigned to surgery (11%) experienced resolution within the 2-week waiting period for surgery. Because of persistent or worsening symptoms, 39% of the group randomized to conservative treatment underwent surgery. Outcomes of the trial included degree of functional disability, intensity of leg pain, and overall perceived degree of recovery, as assessed periodically over 1 year.

Symptom relief was more prompt in the surgical group. However, at 1 year the degree of functional recovery, as well as the other outcomes measured were the same in both groups.

Rapid pain relief may be critical in some cases. If pain management can be satisfactorily achieved without surgical intervention, it appears that conservative treatment offers similar overall outcomes. ■

Peul WC, et al N Engl J Med. 2007;356:2245-2256.

Guess What the Cath Shows?

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.*

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

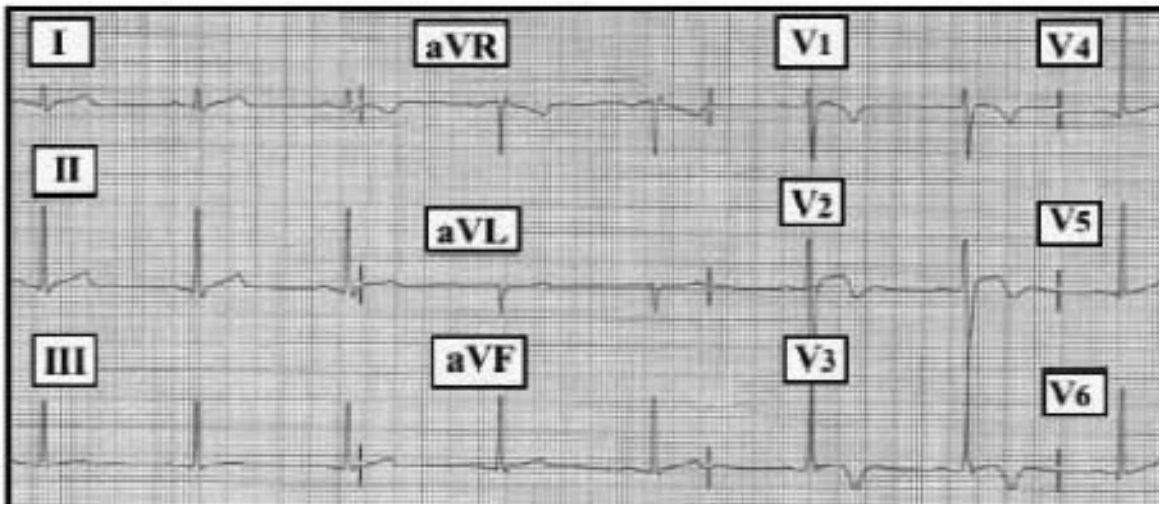

Figure. 12-lead ECG obtained from a 33-year old man with atypical chest pain.

Clinical Scenario: The ECG in the Figure was obtained from a 33-year old man who was admitted to the hospital with atypical chest pain because of this tracing. Guess what troponins and his cardiac catheterization report showed?

Interpretation/Answer: The rhythm is sinus bradycardia at 55/minute. All intervals are normal. The mean QRS axis is +75°. Voltage is probably normal given the patient's young age. The most remarkable part of the tracing is the ST-T wave morphology in the anterior precordial leads. Although the appearance of the ST-T wave in lead V1 is not by itself abnormal, it occurs here in the context of coved ST segment elevation and T wave inversion in lead V2. The abnormality continues in lead V3. Admittedly, the ST segment is not significantly elevated in lead V3, however it remains coved with accompanying T wave inversion. ST segment coving resolves between leads V4 to V5.

This is an obviously abnormal ECG. If the clinical setting was the occurrence of this tracing in an older patient with risk factors and the sudden onset of crushing chest pain, one would strongly suspect acute evolving myocardial infarction. However, the patient in this case was relatively young with no history of cocaine abuse, and his chest pain was atypical. In the absence of a prior ECG for comparison, the prudent course of action was still to admit the patient to the hospital to rule out acute infarction. Serum troponins were all normal. Cardiac catheterization showed completely clean coronary arteries with normal ventricular function.

There are a number of normal variant repolarization patterns that are commonly seen in otherwise healthy individuals. Although most often seen in athletic, young adult African American males, similar ECG patterns may also be seen in sedentary, older, Caucasian men or women. Because the normal variant repolarization pattern in this case manifests ST segment coving with elevation and T wave inversion, it would be easy in a patient with chest pain to mistake this tracing for acute evolving infarction. This healthy 33-year-old man was given a miniaturized wallet copy of his ECG, and told to show it if ever he again presented to an ED with chest pain. ■

In Future Issues:

Tadalafil (Cialis) Improves BPH Symptoms

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.

Avandia, Risk of Congestive Heart Failure Significant Safety Risk

GlaxoSmithKline's rosiglitazone (Avandia) will receive a black box warning by the FDA because of concerns over heart failure associated with use of the drug. Pioglitazone (Actos) will also be subject to a black box warning for the same reason. The drugs, used for treatment of type 2 diabetes, have been scrutinized because of a recent meta-analysis that suggested that rosiglitazone was associated with a significant- increase risk of myocardial infarction and a borderline significant-increase risk of death from cardiovascular causes. (published www.NEJM. org on June 21, 2007 [10.1056/NEJMoa 072761]). Soon on the heels of the publication of this study, Glaxo rushed an interim analysis of its own trial to press. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was published online in the *New England Journal of Medicine* on June 5, 2007. In the RECORD study, 4,447 patients with type 2 diabetes who had inadequate control with metformin or a sulfonylurea were randomized to receive add-on rosiglitazone or a combination of metformin and a sulfonylurea. The primary endpoint was hospitalization or death from cardiovascular causes. After mean follow-up of 3.75 years, 217 patients in the rosiglitazone group and 202 patients in the control group had the primary endpoint (hazard ratio 1.08), and after adding in pending primary end points the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There was no statistically significant difference between either group with regard to myocardial infarction or death from cardiovascular causes or any cause. There was a significantly higher rate of heart failure in rosiglitazone group (HR 2.15; 95% CI, 1.30 to 3.57). The authors conclude that the study was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes, as there was no evidence of an increased death rate of cardiovascular causes or all causes associated with the drug, but there was a significantly higher rate of heart failure. There was insufficient data to determine if there was an increase risk of myocardial infarction (published at www.NEJM.org June 5, 2007 [10.1056/NEJMoa 073394]). The study was accompanied by 3 editorials that recommended caution in use of rosiglitazone and similar drugs especially in patients at risk for congestive heart failure. And while GlaxoSmithKline sees the study as vindication of the safety the drug, others, including the FDA, see the risk of congestive heart failure as a significant safety risk. Soon after publication of the RECORD study, a congressional hearing was held to discuss the safety of rosiglitazone and within days the FDA issued the black box requirement for rosiglitazone and pioglitazone. During the hearing, it came to

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light that at least one official at the FDA had suggested stronger warnings on rosiglitazone nearly a year ago, but her recommendation was ignored; she was reassigned and subsequently left the agency. Within several days of the rosiglitazone hearing, legislation was introduced to bolster the FDA's ability to monitor prescription drug side effects, a bill which also includes many of the Institute of Medicines recent recommendations on drug safety, and also included limiting direct-to-consumer advertising for newly approved medications.

Aspirin, Higher Doses No More Effective, Risky

What is the best dose of aspirin for prevention of cardiovascular disease? More than 50 million people take aspirin regularly in doses that range from 50 mg to over 1000 mg per day. The most commonly used doses are 81 mg and 325 mg per day. A recent systematic review of the English-language literature revealed that doses as low as 30 mg/day are effective at fully inhibiting platelet thromboxane production and preventing platelet aggregation. Despite this, higher doses are frequently used. The available evidence, primarily from secondary prevention trials, suggest that doses greater than 81 mg do not enhance efficacy, but do increase risk of GI bleeding and other toxicities. The authors conclude that aspirin doses of 75 mg to 81 mg/day are optimal for the indication of cardiovascular disease prevention, and higher doses are no more effective but are associated with higher risk (*JAMA* 2007; 297:2018-2024).

Subclinical Hypothyroidism Treatment Benefits

Subclinical hypothyroidism is defined as raised TSH levels with circulating thyroid hormones within the normal range. A new study suggests that treatment of subclinical hypothyroidism improves cardiovascular risk factors and quality of life. One hundred patients with a mean TSH of 6.6 mIU/l who had never received thyroid treatment and did not have cardiovascular disease were enrolled in a randomized, double-blinded crossover study of 100 µg of l-thyroxine or placebo daily for 12 weeks. Treatment with L-thyroxine reduced total cholesterol from an average of 231.6 to 220 mg/dl (P <0.001), LDL cholesterol from 142.9 to 131.3 mg/dl (P < 0.05), and waist to hip ratio from 0.83 to 0.81 (P < 0.006). Treatment also significantly improved endothelial function based on brachial artery flow mediated dilation, an early marker of atherosclerosis. Patients also reported decreased tiredness in the active treatment group, and there was a trend towards improvement in the perceived negative impact of hypothyroidism on sexual function. The authors conclude that treating subclinical hypothyroidism with l-thyroxine lead to significant improvements of cardiovascular risk factors and symptoms of tiredness (*J Clin Endocrinol Metab* 2007; 92:1715-1723).

FDA approvals

The FDA has approved a new transdermal patch for the treatment of early stage idiopathic Parkinson's disease. Rotigotine transdermal is a once-daily patch that is available in 2, 4 and 6 mg strengths. The drug is a dopamine agonist that affects D3/D2/D1 receptors and is thought to exert its effect via stimulation of dopamine D2 receptors. In clinical trials the patch was shown to improve scores on standardized rating scales for daily living and motor components in Parkinson's disease. The most common side effects are site reactions, dizziness, nausea, vomiting, somnolence and insomnia. Rotigotine transdermal will be available by the end of 2007 and will be marketed by Schwartz Pharma under the trade name Neupro.

The FDA has approved a new continuous contraceptive for women that is designed to eliminate menstruation. Wyeth pharmaceuticals Lybrel is a 28-day pill pack of levonorgestrel and ethinyl estradiol (90 µg/20 µg) that does not contain a placebo or pill-free interval. In clinical trials 59% of women achieved amenorrhea without bleeding or spotting, while 20% experienced spotting but did not require sanitary protection, and 21% required sanitary protection due to breakthrough bleeding. There was also no delay to return of menses after discontinuing the product nor any significant delay in fertility. Lybrel is scheduled to be available by July 2007.

Risedronate (Actonel) has received approval for a new once-a-month dosing schedule for the treatment of osteoporosis. The dose regimen requires patients to take 75 mg tablets on 2 consecutive days each month. The approval was based on a study that compared the monthly regimen with a daily regimen of 5 mg per day and showed no significant difference in efficacy for increasing bone mineral density at the lumbar spine, total hip, and hip trochanter. Risedronate is marketed by Procter & Gamble pharmaceuticals. ■