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FAMILY PRACTICE ALERT™

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Obesity is a Problem!

ABSTRACT & COMMENTARY

Synopsis: *A BMI between 20-25 is optimal and is associated with the longest survival for any causes of death.*

Source: Calle EE, et al. *N Engl J Med* 1999;341:1097-1105.

The relationship between excessive body weight and mortality is problematic. In addition to the questions of the optimal weight at different ages and gender, there has been the suggestion of a U-shaped curve regarding body weight with respect to survival; the latter has stimulated much discussion regarding the potential downside of being underweight or lean, perhaps due to unrecognized medical conditions. The Cancer Prevention Study II, a prospective study of mortality among U.S. men and women, initiated in 1982 by the American Cancer Society, recently reported 14-year follow-up data. By 1996, 20% of the entire cohort of 457,785 men and 588,369 women had died. All participants were divided into 12 categories of body mass index (BMI). The primary end points were all-cause death as well as cardiovascular disease mortality. Smoking history, status of disease at entry, and race and gender were examined. The results indicate a relationship between increasing BMI and mortality that differed by smoking status and the presence of any disease. Obesity was more strongly associated with decreased survival in nonsmokers and in those without a disease history. Leanness was most strongly associated with decreased survival in smokers with a history of disease. Intermediate survival was noted for smokers without a history of disease and for nonsmokers with concomitant disease. At a BMI of 28 and higher, the relative risk of death began to increase most steeply for the nonsmokers without a history of disease. The highest mortality rates occurred in obese men, with a relative risk of 2.7 vs. 1.9 in women. There was a small increase in risk in the leanest men and women. The nadir of the BMI curves and mortality was at a BMI between 23.5 and 25 in men and 22.0 and 23.4 in women. In nonsmokers without a disease history, the association between a high BMI and increased mortality was stronger in whites than in blacks. BMI and cancer death demonstrated a positive relationship; there was no elevation in risk among lean individuals for cancer. The cardiovascular curves were U-shaped; there was no increased risk of dying in lean

men and women. A high BMI was predictive of death from cardiovascular disease; it was greater in men (relative risk 2.9) than in women; risk began to increase at a BMI of more than 25 in women and 26.5 in men. The relative risk associated with high BMI diminished with increasing age. Overall death rates increased throughout the range of moderate to severe overweight in both men and women, less so in blacks and particularly black women (about one-third lower than white women). Cancer deaths increased by 40-80% in the heaviest groups of men and women, without a concomitant increase risk in lean subjects. Calle and associates conclude that a BMI between 20 and 25 for men and women of all ages is optimal and is associated with the longest survival for any causes of death. "These data offer support for the use of a single recommended range of body weight throughout life."

COMMENT BY JONATHAN ABRAMS, MD

These data, while not surprising, are of great interest because of the enormous size of the study population (> 1 million) and the long-term (14-year) follow-up. That approximately one-third of American adults meet WHO criteria for a grade 1 overweight (BMI 25-30) and 22% are even more overweight confirms that obesity is a substantial health problem. Only 8% of the adults in the United States have a BMI less than 20. The health care burden of a high BMI is well demonstrated in this study. It is unclear why blacks carry a lower burden of mortality for comparable degrees of obesity; however, it must be stressed that moderate to high levels of BMI are adverse for all causes of death unrelated to age, gender, or ethnicity. This study did not include coronary artery risk factor measurements; one cannot conclude that increase in mortality among the healthy overweight was related to coronary events, although this is likely. Obesity is associated with insulin resistance or the "metabolic syndrome," which includes dyslipidemia, hypertension, impaired glucose tolerance, and overt diabetes. For high-BMI individuals, particularly nonsmokers without disease, the BMI curves in this study are truly alarming. (*Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.*) ❖

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Topical Vitamin E Application

ABSTRACT & COMMENTARY

Synopsis: *Investigators put to a brief test the hypothesis that vitamin E improves cosmetic appearance of surgical scars. They found that, in 90% of the cases in this study, topical vitamin E either had no effect on or actually worsened the cosmetic appearance of scars.*

Source: Baumann LS, Spencer J. *Dermatol Surg* 1999;25: 311-315.

Vitamin e is a generic term for a group of tocol and tocotrienol derivatives. Since the discovery that vitamin E is the major lipid-soluble antioxidant in skin, this substance has been tried for the treatment of almost every type of skin lesion imaginable. Anecdotal reports claim that vitamin E speeds wound healing and improves the cosmetic outcome of burns and other wounds. Several physicians recommend topical vitamin E after skin surgery or resurfacing.

This study attempted to determine whether topically applied vitamin E has any effect on the cosmetic appearance of scars as suggested by multiple anecdotal reports. Fifteen patients who had undergone skin cancer removal through Mohs surgery were enrolled in the double-blinded study. All wounds were primary closed in two layers. After the surgery, the patients were given two ointments

labeled A (Aquaphor®, a regular emollient) or B (Aquaphor mixed with vitamin E, added at a concentration of 320 IU/g of d-alpha-tocopherol). The scars themselves were randomly divided into two parts, A and B. Patients were asked to put the A ointment on part A and the B ointment on part B twice daily for four weeks. Evaluation criteria were subjective, and the opinions of patients and treating physicians were recorded at weeks 1, 4, and 12. A third blinded investigator was shown photographs of the outcomes, and rated each side of the scar.

In 90% of the cases in this study, topical vitamin E either had no effect on or actually worsened the cosmetic appearance of scars; 33% of patients developed a contact dermatitis. We conclude that the use of topical vitamin E on surgical wounds should be discouraged.

COMMENT BY JOHN La PUMA, MD, FACP

These University of Miami investigators put to a brief test the hypothesis that vitamin E improves cosmetic appearance of surgical scars. But three of their 15 patients dropped out after 48 hours, and two of the 12 remaining dropped out after a week. A sharply marginated, pruritic, erythematous rash erupted on the vitamin E side of five patients' scars. After 12 weeks, most of the 10 remaining patients and the treating physicians felt that there was no difference in the sides of the scar. (*Dr. La Puma is Professor of Nutrition, Kendall College, Director, C.H.E.F. Clinic, C.H.E.F. Skills Research, Alexian Brothers Medical Center, Elk Grove Village, Ill.*) ❖

Diet and Ischemic Stroke

ABSTRACT & COMMENTARY

Synopsis: *Patients should focus on consuming fruit and vegetables and not try to replace them with dietary supplements.*

Source: Joshipura KJ, et al. *JAMA* 1999;282:1233-1239.

The nurses' health study continues to provide helpful data on women's health trends. In this prospective cohort study, Joshipura and colleagues from Harvard followed the dietary intake of 75,596 healthy nurses aged 34-59 from 1980 to 1994. (They also followed a similar male cohort from the Health Professionals' Follow-Up Study.) Both cohorts responded to surveys every two years to indicate their dietary and other health habits (with extensive food frequency questionnaires), as well as their incidence of cardiovascular disease and other health outcomes. For respondents who reported strokes, Joshipura et al reviewed medical records and imaging studies to verify the diagnoses.

Of the large cohort in the Nurses' Health Study, 366 women eventually suffered new ischemic strokes. It turned out that the women in the highest quintile for intake of fruit and vegetables (with a median of 5.8 servings daily) had a relative risk of ischemic stroke of 0.74 (95% CI 0.52-1.05) compared with women in the lowest quintile. Each daily serving of fruits or vegetables appeared to lower women's ischemic stroke risk by 7%, with the greatest effect seen with green leafy vegetables, cruciferous vegetables, and citrus fruit (including juices). Only legumes and potatoes appeared to confer no benefit. These statistically significant findings persisted after investigators controlled for smoking and other cardiovascular risk factors, for fat intake, and for use of multivitamins and other nutritional supplements. The men's cohort produced similar results.

COMMENT BY ELIZABETH MORRISON, MD, MSED

Stroke affects half a million people every year, many of them women. Fortunately, those of us who provide primary care have opportunities to counsel women about lifestyle modifications that can make a difference. I enjoy finding articles like this one by Joshipura et al because they give me interesting new perspectives to share with patients when discussing dietary recommendations for health maintenance.

For prevention of coronary artery disease, the American Heart Association already recommends that all Americans consume a balanced diet emphasizing antioxidant-rich vegetables, fruits, and whole grains rather than specific antioxidant supplements.[1] We can now tell female patients that such a diet appears to prevent ischemic stroke as well. Current recommendations that patients consume at least five daily servings of fruit and vegetables appear to be right on the mark.

Joshipura et al discussed current evidence, they suggested mechanisms through which fruit and vegetables (particularly of the green, leafy, cruciferous, or citrus varieties) would prevent ischemic stroke—dietary flavonoids, folate and its effect on serum homocysteine, fiber, and potassium. They concluded that the data support no single mechanism. The important point from this study and others is that patients should focus on consuming fruit and vegetables and not try to replace them with dietary supplements.

Since this study is not a randomized, controlled trial, it is naturally subject to confounding factors. For exam-

ple, women who consume more fruit and vegetables might also exhibit other health-promoting behaviors that limit ischemic stroke. Yet, when Joshipura et al painstakingly controlled for a multitude of possible confounders, the apparent benefit of fruit and vegetable intake persisted. Joshipura et al also note that their cohorts are fairly homogenous in terms of occupation and socioeconomic status, minimizing the risk that socioeconomic factors confounded the results. However, it would be interesting in future studies to see how dietary factors interact with ischemic stroke risk among populations of lower socioeconomic status. (*Dr. Morrison is Director of Maternity Care Education, Assistant Clinical Professor of Family Medicine, University of California, Irvine.*) ❖

Reference

1. Tribble DL, et al. *Circulation* 1999;99:591-595.

Nursemaid's Elbow: Pronation or Supination?

ABSTRACT & COMMENTARY

Synopsis: *This study concludes that the pronation technique for reduction of radial head subluxation is a viable alternative to the classic supination method.*

Source: McDonald J, et al. *Acad Emerg Med* 1999;6:715-718.

The ed of a tertiary care children's hospital was the site for this prospective, randomized study. One hundred forty-eight patients younger than 7 years were enrolled and randomized to receive either rapid supination and flexion vs. rapid pronation and flexion for patients with a presumptive diagnosis of radial head subluxation. Failure after first attempt, defined as no resolution of spontaneous use of the affected arm within 30 minutes, led to repeating that maneuver; after two failures, the alternative method of reduction was attempted. Four-point ordinal pain scoring data were provided by both the parent and the physician performing the maneuver in an attempt to grade the discomfort associated with each method.

No significant difference was found between the two techniques on first attempt (69% success supination vs 79% success pronation, P = 0.19). In cases of unsuccessful reduction, however, repeat pronation was significantly more likely to result in success than was repeat supination (64% success vs 19% success, P = 0.009). The two methods were equally successful on the third (crossover) attempt. When the left arm was injured, the pronation technique was significantly more likely to be effective, but there was no difference when the right arm was affected. Physicians rated the pronation method to be significantly less painful on the first attempt only; parental perceptions of pain did not favor a method. McDonald and coworkers conclude that the pronation technique for reduction of radial head subluxation is a viable alternative to the classic supination method, highlighting both its effectiveness when the left arm is injured (reason unclear), and the perception by physicians that it may be less painful.

COMMENT BY RICHARD A. HARRIGAN, MD, FAAEM, FACEP

This paper adds support to advocates of the pronation technique for reduction of nursemaid's elbow, or radial head subluxation. This study did not find the statistical advantage found by Macias and colleagues.[1]

In their study, Macias et al found first-attempt pronation to be significantly more successful than first-attempt supination (success rate 95% vs 77%, respectively). Enrollment and exclusion criteria were similar for both studies. Advantages of the study by McDonald and associates include a larger sample size with a priori power calculations and an assessment of pain. Furthermore, an increase in the time of observation before a reduction attempt was judged to be unsuccessful to 30 minutes in the current study (vs 15 minutes in the study by Macias and colleagues) is attractive. The 15-minute time frame may be too brief; 30 minutes is consistent with the recommendations of others.[2] (*Dr. Harrigan is Assistant Professor of Medicine, Temple University School of Medicine, Acting Chief and Associate Research Director, Division of Emergency Medicine, Temple University Hospital, Philadelphia, PA.*) ❖

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1. Macias CG, et al. *Pediatrics* 1998;102e10. URL: http://www.pediatrics.org/cgi/content/full/102/1/e10.
2. McNamara R. Management of common dislocations. In: Roberts JR, Hedges JR, eds. *Clinical Procedures in Emergency Medicine*. 3rd ed. Philadelphia, Pa. WB Saunders; 1998:818-852.

Pharmacology Update

Rosiglitazone

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

The fda has approved smithkline beecham's rosiglitazone for the treatment of type 2 diabetes mellitus. The drug is the second thiazolidinedione to be approved by the FDA. The first drug of this class is troglitazone (Rezulin), which has recently been associated with rare, but highly publicized hepatotoxicity. In clinical trials in about 5000 patients, rosiglitazone has not been associated with drug-induced hepatoxicity or elevation of liver enzymes, but whether rosiglitazone represents a safer thiazolidinedione remains to be established.

Rosiglitazone is marketed as Avandia by SmithKline Beecham and Bristol-Myers Squibb. A third drug in this class, Lilly and Takeda's pioglitazone (Actos), has also been recently approved

Indications

Rosiglitazone is approved for monotherapy, as an adjunct to diet and exercise, to improve glycemic control in type 2 diabetes. It is also indicated for use in combination with metformin when diet, exercise, and either drug alone do not provide adequate control.[1]

Dosage

The recommended starting dose for rosiglitazone is 4 mg daily administered qd or bid. The dose may be increased to 8 mg if there is insufficient glycemic control after 12 weeks of therapy.[1] Higher doses of rosiglitazone tend to be more effective administered twice daily compared to once daily. The difference in glycosylated hemoglobin was significantly greater with 8 mg qd vs. 4 mg bid but not statistically different at 4 mg qd vs. 2 mg bid.[1]

Rosiglitazone may be taken without regard to meals. No dosage adjustment is required in patients with mild to severe renal impairment or in the elderly.[1]

Rosiglitazone is supplied as 2-mg, 4-mg, and 8-mg tablets.

Potential Advantages

Clinical trial results reported no significant difference between placebo in the frequency of ALT elevations more than three times the upper limits of normal (0.2% for both groups).[1] The manufacturer reported no evidence of drug-induced hepatotoxicity in 4598 patients (3600 patient years). However, due to the chemical similarity between rosiglitazone and troglitazone, the FDA is recommending that liver enzymes be checked prior to initiation of therapy and monitored every two months for the first 12 months and periodically thereafter.[1] *In vitro* data suggest that rosiglitazone does not inhibit any of the major cytochrome P450 enzymes.[1]

Potential Disadvantages

Edema has been reported in 4.8% of patients administered rosiglitazone; thus, the drug should be used with caution in patients with heart failure.[1] Dose-related decreases in hemoglobin (≤ 1.0 g/dL) and hematocrit (≤ 3.3%) have also been reported.[1] Anemia has been reported in 1.9% of patients compared to 0.7% for placebo and 0.6% for sulfonylurea.[1] Mean weight gains of 1.75-2.95 kg were reported in patients treated with 4-8 mg of rosiglitazone for 52 weeks.[1] Rosiglitazone increases LDL-cholesterol mainly during the first 1-2 months of therapy. HDL-cholesterol is also elevated and continues to rise over time. The net result is an increase in the LDL to HDL ratio, which peaks after two months and tends to decrease over time.[1] The FDA's analysis of the data showed an increase in VLDL-cholesterol of 11.5 mg/dL from a baseline of 20.6 after 26 weeks.[7] Contraception may need to be considered in premenopausal anovulatory women with insulin resistance as rosiglitazone may cause resumption of ovulation.[1]

Comments

Rosiglitazone and troglitazone are both members of the thiazolidinedione class of antihyperglycemic drugs. These agents are thought to improve insulin sensitivity by acting as a potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARg). These receptors are expressed primarily in tissues such as liver, skeletal muscle, and adipose tissue and regulate the control of glucose production, transport, and use.[1] In animal adipose tissue models, thiazolidinedones may act by increasing the number of small adipocytes and decreasing the number of large adipocytes.[2]

Results from clinical trials on the drug have not been published and limited data are available from the manufacturer and/or in abstract forms only.[1,4,5,6,8] In placebo-controlled 26-week studies (n = 1400), rosiglitazone (4-8 mg daily) produced a reduction (difference from placebo) in fasting plasma glucose (FPG) of 31-76 mg/dL in patients with a baseline FPG of 220-229

mg/dL.[1] Corresponding reductions of glycosylated hemoglobin were 0.8-1.5% with baseline values of 8.9-9.0%. Rosiglitazone was generally more effective when administered twice daily compared to once daily.[1] In a 52-week comparative trial (n = 587) with glyburide (mean dose of 7.5 mg/d), rosiglitazone (4 mg bid) produced a mean change from baseline of 41 mg/dL vs. 30 mg/dL in FPG and 0.53-0.72% in glycosylated hemoglobin. Initial reductions in FPG and glycosylated hemoglobin were greater with glyburide; however, values at 52 weeks appeared to be comparable. In contrast to placebo-controlled trials, patients in the active-controlled trial had lower baseline FPG (190-196) and glycosylated hemoglobin (8.07-8.21). Unpublished data indicate that the addition of rosiglitazone to metformin, sulfonyurea, and insulin in type 2 patients has resulted in added improvement in glycemic control.[4-6] Currently, only the combination with metformin is FDA approved.

The daily cost of rosiglitazone (4-8mg) ranges from $2.50 to $5 per day. This compares favorably to troglitazone (200-800 mg/d), which ranges from $3 to $9.50 per day.

Clinical Implications

Thiazolidinediones are the newest class of antihyperglycemic agents approved for use in type 2 diabetics. Members of this class, which currently include troglitazone and now rosiglitazone, seem to work by increasing insulin sensitivity. These agents offer a different mechanism of action from the sulfonylureas, metformin, insulin, and acarbose. Thiazolidinediones also offer the potential for combination therapy with these other agents. Toxicity is a concern, with liver toxicity leading the FDA to recently change the labeling for troglitazone. On the other hand, animal studies have suggested that these drugs may protect the vasculature from diabetes-enhanced injury.[3] While clinical trial data are encouraging, whether rosiglitazone will be safer for the liver than troglitazone remains to be determined. ❖

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8. Grunberger G, et al. American Diabetes Association 59th Scientific Session. June 19-22, 1999. Abstract 0439.

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CME Questions

16. Nonsmoking, healthy, significantly overweight men and women have a lower mortality rate related to BMI than smokers.
a. True
b. False

17. In the Nurses' Health Study, daily intake of 5-6 servings of fruits and vegetables appeared to reduce women's risk of ischemic stroke by approximately:
a. 5%.
b. 15%.
c. 25%.
d. 35%.
e. 45%.

18. Which of the following is *not* an acceptable reduction method for radial head subluxation (nursemaid's elbow)?
a. Rapid alternating pronation and supination of the affected forearm with internal rotation of the elbow.
b. Rapid supination of the affected forearm with flexion of the elbow.
c. Rapid pronation of the affected forearm with flexion of the elbow.

19. Which of the following is *not* true for rosiglitazone?
a. It raises LDL and HDL cholesterol.
b. Higher doses are more effective administered twice a day.
c. It has not been associated with liver dysfunction in clinical trials.
d. The FDA is not recommending monitoring liver functions when the drug is started.

By Louis Kuritzky, MD

Acute Hyperhomocysteinemia and Reversal by Antioxidant Vitamins

Elevated levels of homocysteine (> 15 micromoles/L) are associated with increased risk of atherosclerotic cardiovascular disease. The mechanisms for this association are not fully understood, but endothelial dysfunction is felt to be a likely culprit.

Homocysteine levels rise after a load of oral methionine in healthy individuals. This study evaluated healthy young men, age 25-45 (n = 20), for the effect of an acute elevation of homocysteine upon endothelial function, as measured by vascular response to L-arginine (the immediate precursor to nitric oxide); endothelial responses were also measured after administration of antioxidants (vitamin E 800 IU and vitamin C 1000 mg) to see whether pretreatment with antioxidants affected outcomes. In addition to vascular responsiveness, plasma lipids, glucose, coagulation profiles, and adhesion molecules were monitored.

Methionine loading produced a change of mean plasma homocysteine from 10.5 to 27.1, unaltered by administration of antioxidants. Coagulation parameters increased significantly upon homocysteine elevation, but this increase was abolished by pretreatment with antioxidant vitamins; the same profile was seen with adhesion molecules. L-arginine normally produces a reduction in blood pressure, platelet aggregation, and blood viscosity. Elevation of homocysteine significantly altered these responses, and the deleterious alterations seen were favorably modified by pretreatment with antioxidant vitamins.

Nappo and associates conclude that acute elevations of homocysteine produce adverse changes in cardiovascular risk profiles, including blood pressure, coagulation parameters, and response to L-arginine. Antioxidant vitamins prevent acute endothelial dysfunction produced by elevation of homocysteine. ❖

Nappo F, et al. JAMA 1999;281: 2113-2118.

Inflammation and Prediction of Diabetes Mellitus in Adults

Macrovascular disease remains the no. 1 cause of mortality in diabetics. Inflammatory processes are felt to play a role in atherosclerosis, and mediators of inflammation such as tumor necrosis factor alfa and interleukin-6 are elevated in type 2 diabetes. The purpose of this study was to determine whether inflammatory markers predict the development of type 2 diabetes in nondiabetic participants in the Atherosclerosis Risk in Communities study (n = 15,792). In this study group, approximately 80% were caucasian and 20% African-American. Inflammatory markers surveyed included fibrinogen, white blood cell count (WBC), sialic acid, orosomucoid, alpha-1-antitrypsin, and haptoglobin, at levels below that which would be considered indicative of an acute inflammatory reaction.

Individuals in the highest WBC quartile had 50% higher odds of developing diabetes. Persons with sialic acid, orosomucoid, and haptoglobin levels higher than the median also had a 1.7-7.9-fold odds ratio for developing diabetes.

Proinflammatory cytokines (e.g., tumor necrosis factor alpha) may affect insulin sensitivity or secretion; it has been theorized that tumor necrosis factor alpha produces insulin resistance by decreasing autophosphorylation of the insulin receptor, in addition to other mechanisms.

Schmidt and colleagues believe that although the pathophysiologic mechanism remains incompletely explained, inflammatory mediators are etiologically involved in the development of type 2 diabetes. ❖

Schmidt MI, et al. Lancet 1999; 353: 1649-1652.

Coffee Consumption and the Risk of Symptomatic Gallstone Disease in Men

Numerous aspects of the physiologic effects of coffee and caffeine suggests that coffee ingestion might have some effect on gallstones. Stimulation of cholecystokinin release and enhanced gallbladder contraction are effects of coffee; bile cholesterol concentrations may be affected by cafestol, a component of coffee beans. Caffeine affects bile flow, gallbladder fluid absorption, and tendency to bile crystallization all in an anti-stone-forming fashion.

The cohort evaluated were participants in the Health Professionals Follow-up Study (n = 51,529). Coffee consumption was evaluated on the basis of a 131-item questionnaire in 1986. At the same time, a baseline assessment for presence or absence of gallstones was performed, and surveillance continued through 1996.

More than 1000 cases of gallstone disease were discovered. Intake of regular coffee had a strong inverse relationship with gallstones. For instance, men who drank at least four cups of coffee daily had a 33% lower relative risk of gallstones than those who drank no coffee. No statistically significant relationship was found between consumption of tea, decaffeinated coffee, or caffeinated soft drinks and gallstones. In this population, higher intake of regular coffee in men older than age 40 is associated with reduced incidence of gallstone disease. ❖

Leitzmann MF, et al. JAMA 1999; 281:2106-2112.

Seeing the Clue to Bradycardia

By Ken Grauer, MD

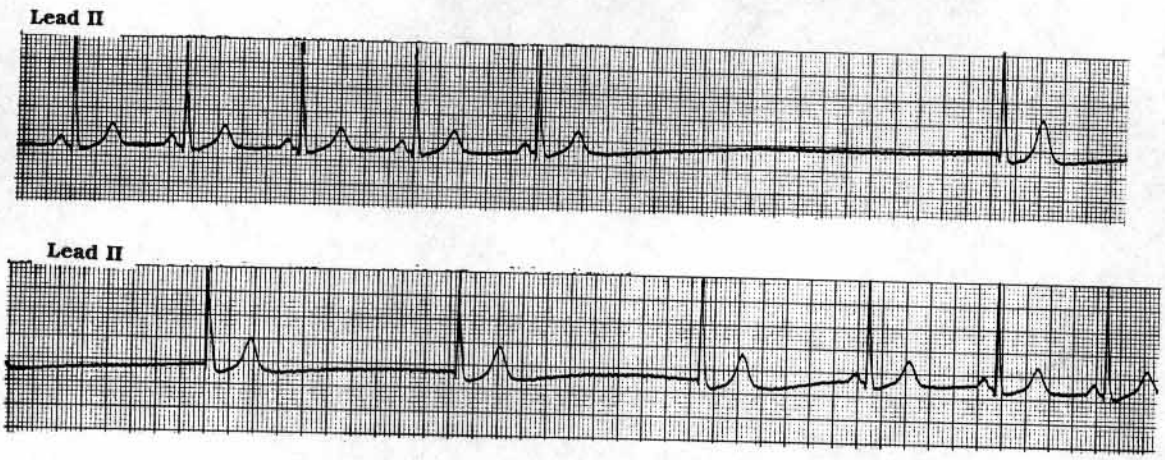

Figure. Telemetry strips from an elderly man taking lots of pills

Clinical Scenario: The continuous telemetry strips shown here were obtained from an elderly man who was taking multiple medications. Digoxin, verapamil, diltiazem, and beta-blockers were not among the pills he was taking. How would you interpret the rhythm? Clinically, what would you do?

Interpretation: The tracing begins as a sinus rhythm that slows and then abruptly stops. The worrisome pause in the top tracing is just under four seconds long. Asystole is prevented by a junctional escape rhythm that itself is inappropriately slow (although much preferred to the alternative). Sinus node activity finally resumes with the last three beats on the tracing.

The first priority in management is to assess the patient and address immediate treatment needs of the rhythm disturbance. The patient in this case felt faint momentarily, but thereafter was not symptomatic. Recurrence of marked bradycardia to the degree shown in these tracings was not seen. Were bradycardia to recur, treatment with atropine and/or pacing would clearly be indicated.

Clinically, one should assess for potential causative factors. The rhythm strips seen in these tracings could result from a marked vagal response, as might occur after an episode of severe vomiting, or in an elderly patient following prolonged straining at stool. As noted in the history, the patient in this case was not taking any of the *pills* that are usually associated with drug-induced bradycardia. However, no mention is made of a number of other substances that may also produce rate slowing (e.g., clonidine, beta-blocker *eye drops* that are at least to some extent systemically absorbed, and certain herbal medicines such as cardioactive glycoside derivatives and veratrum). Finally, a 12-lead ECG should be obtained to rule out myocardial infarction as a possible cause of the bradycardia. If the above evaluation does not suggest a reason for bradycardia, the patient most likely has sick sinus syndrome that will probably require permanent pacing. In this particular case, further questioning revealed the patient was using beta-blocker eye drops for treatment of glaucoma. Episodes of bradycardia resolved completely once this medication was stopped. ❖

In Future Issues: **Effect of Aspirin Dosage on Stroke Risk in Women**