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Supplements for Institutionalized Elderly Patients

ABSTRACT & COMMENTARY

Synopsis: *Low-dose supplementation of zinc and selenium provides significant improvement in elderly patients by increasing the humoral response after vaccination and could have considerable public health importance by reducing morbidity from respiratory tract infections.*

Source: Girodon F, et al. *Arch Intern Med* 1999;159:748-754.

Antioxidant supplementation is thought to improve immunity and thereby reduce infectious morbidity. However, few large trials in elderly people have been conducted that include end points for clinical variables. Girodon and colleagues sought to determine the effects of long-term daily supplementation with trace elements (zinc sulfate and selenium sulfide) or vitamins (beta-carotene, ascorbic acid, and vitamin E) on immunity and the incidence of infections in institutionalized elderly people. They conducted a randomized, double-blind, placebo-controlled intervention study including 725 patients older than 65 years (mean age 83.9), institutionalized in 25 geriatric centers in France. Patients received an oral daily supplement of nutritional doses of trace elements or vitamins or a placebo within a 2 × 2 factorial design for two years.

Correction of specific nutrient deficiencies was observed after six months of supplementation and was maintained for their first year, during which there was no effect of any treatment on delayed-type hypersensitivity skin response. Antibody titers after influenza vaccine were higher in groups that received trace elements alone or with vitamins. The vitamin group had significantly lower antibody titers ($P < 0.05$). The number of patients without respiratory tract infections during the study was higher in groups that received trace elements ($P = 0.06$). Supplementation with neither trace elements nor vitamins significantly reduced the incidence of urogenital infections. Survival analysis for the two years did not show any differences between the four groups.

Low-dose supplementation of zinc and selenium provides signifi-

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cant improvement in elderly patients by increasing the humoral response after vaccination and could have considerable public health importance by reducing morbidity from respiratory tract infections.

COMMENT BY JOHN La PUMA, MD, FACP

These French investigators assessed the prevalence of nutrient deficiency by assessing serum value and finding approximately 80% of patients to be deficient in selenium. Deficiencies were not significantly different across the groups. Supplemental zinc (20 mg) and selenium (100 mcg) were provided. Except for zinc, serum concentrations of vitamins reached a plateau after six months; zinc levels rose throughout the study, as zinc is absorbed slowly in older people. Adherence was very good—more than 85%.

Trace mineral supplementation was associated with fewer respiratory tract infections—markedly so.

Measuring mineral levels is not yet a standard assessment and, for this indication, seems unnecessary. The cost of the needed intervention is small, the side effect profile favorable, and the therapy efficacious. Compared with colds in nursing homes, zinc and selenium supplements look great.

All residents of long-term care institutions older than 65 years should take a trace mineral supplement of zinc and selenium, in addition to regular vitamins—about twice the U.S. RDI for vitamin C, beta-carotene, and vitamin E. (*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.*) ❖

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Depression and Platelet Reactivity

ABSTRACT & COMMENTARY

Synopsis: *This study provides direct evidence for enhanced in vivo platelet reactivity and platelet product release (e.g., PF-4 and B-TG) in depressed patients with ischemic heart disease.*

Source: Laghrissi-Thode F, et al. *Biol Psychiatry* 1997; 42:290-295.

Clinical depression has recently been recognized as an independent risk factor for cardiac mortality in patients 6, 12, and 18 months after myocardial infarction (MI).[1-2] This remains true even after controlling for other post-MI risk factors, such as left ventricular dysfunction, complex arrhythmias, and history of prior MI.[3]

The underlying mechanism(s) of this increased mortality in depressed patients post-MI have not fully elucidated. This study investigated the hypothesis that patients suffering from ischemic heart disease (IHD) and depression concurrently may have abnormal platelet activation resulting in an increased risk of thrombosis. Platelets activated at the interface with a vessel wall injury accelerate the local formation of thrombin and release a variety of endogenous products from their storage granules, including platelet factor 4 (PF-4), B-thromboglobulin (B-TG), and serotonin. PF-4, a protein synthesized by megakaryocytes, was originally recognized by its ability to neutralize the anticoagulant activity of heparin.

Interestingly, platelets have been proposed as a model for central nervous system presynaptic nerve terminals, including serotonin terminals. Serotonin is a weak ago-

nist of platelet aggregation compared to thrombin, but markedly amplifies platelet reactions to other agonists (adenosine 5'-diphosphate, thromboxane A2, catecholamines, or thrombin).

In the current study, Laghrissi-Thode and colleagues evaluated three groups: healthy controls (n = 17), nondepressed patients with IHD (n = 8), and depressed patients with IHD (n = 21). Criteria for ischemic heart disease were defined by any of the following in the three months prior to the study: 1) MI; 2) coronary artery bypass graft; 3) angioplasty; or 4) angiographic evidence of luminal narrowing of a major coronary artery or one of its primary branches. Severity of IHD was assessed by the results of coronary angiography; cardiac function was assessed by the left ventricular ejection fraction. The Structured Clinical Interview for DSM-III-R was used to diagnose depression and exclude other diagnoses, and the Hamilton Depression Rating Scale was used to rate the severity of depression. PF-4 and B-TG were markedly elevated in the patients with both depression and IHD compared to the other groups. No association was found between measures of platelet activation and angiographic results, left ventricular ejection fraction, age, sex, or race.

COMMENT BY DONALD M. HILTY, MD

Further research is needed to investigate if alterations of the serotonin (5-HT) system in depressed patients with IHD contribute to PF-4 and B-TG elevations and if this phenomenon is reversed by successful treatment of depression. Unpublished data from the same author indicate that a selective serotonin reuptake inhibitor, paroxetine (Paxil), lowered similarly elevated levels of PF-4 and B-TG from four to eight times to approximately two times the level of controls and patients with IHD; interestingly, a tricyclic antidepressant, nortriptyline (Pamelor), did not lower the levels at all.

Depressed patients without IHD also appear to have abnormal platelet reactivity.[4] Depressed patients (n = 12), compared to healthy controls (n = 8), exhibited increased platelet activation at baseline and following orthostatic challenge, using monoclonal antibodies sensitive to detecting phase-specific stages of platelet activation.

Unquestionably, the evidence to date necessitates the screening for depression in patients with cardiovascular disease and implementing treatment if there is evidence of depression. To date, no single antidepressant or class of antidepressants has documented superiority in terms of efficacy in patients with cardiac disease. (*Dr. Hilty is Assistant Professor of Clinical Psychiatry, University of California, Davis, Sacramento, CA.*) ❖

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Good News for Marine Polyunsaturated Fatty Acids, but not so Good for Vitamin E

ABSTRACT & COMMENTARY

Synopsis: *Long-term polyunsaturated fatty acids but not vitamin E were beneficial for death and combined death, nonfatal myocardial infarction, and stroke due to the decrease in risk for overall cardiovascular death.*

Source: GISSI. *Lancet* 1999;354:447-455.

The latest contribution from the gissi investigators is a study of more than 11,000 individuals with a recent myocardial infarction (MI) (less than 3 months, mean time to study entry 12 days) who were randomized to fish oil, vitamin E, or both, in 2 × 2 factorial design study. There were approximately 2800 patients in each cell; supplements included N-3 polyunsaturated fatty acids (PUFA) 1 g daily; vitamin E 200 mg; the combination of the above; and neither. The study was open label and was carried out for an average of 3.5 years. The two primary end points were all-cause mortality, nonfatal MI (NFMI), and nonfatal stroke; and cardiovascular death, NFMI, and nonfatal stroke. A secondary analysis was performed for each individual event class. The trial was carried out from 1993-1995. The results were favorable for the fish oil supplement and neutral for vitamin E. Plasma lipids at six months demonstrated a decline in triglycerides from baseline in individuals taking PUFA, and an increase in LDL cholesterol in all groups, greater in the PUFA cohort. HDL and total cholesterol increased in all groups. The primary outcome demonstrated a decrease with PUFA for all-cause death, NFMI, and stroke (P = 0.053) of 10% (P = 0.048), with a similar decrease of 11% when cardiovascular death was included. Vitamin E resulted in no difference from control, and no further reduction of events when combined with PUFA. A four-way analysis of PUFA indicated a relative decrease of 15% in the combined end point, and 20% in the secondary combined

end points. Furthermore, individual event end points demonstrated a decrease in total mortality by 20%, cardiovascular death at 30%, and sudden death at 45% with N-3 PUFA. These represent the major benefits of this trial. Vitamin E demonstrated no differences from control, except for a decrease in cardiovascular death, but not for any of the combined end points. N-3 PUFA plus vitamin E was no more beneficial than N-3 PUFA alone. Adverse effects were relatively minor. Approximately 27% of subjects had discontinued either study drug by the end of the trial. The GISSI investigators noted that the regimen of N-3 PUFA corresponds to a large fatty fish meal every day of the week.

The data are concordant with the DART Trial reported a decade ago that analyzed fish intake on cardiovascular death and reinfarction in post-MI patients. The GISSI investigators emphasize that the study population was relatively low risk, as most of them consumed a Mediterranean diet, and many were treated with aspirin, ACE inhibitors, beta-blockers, and statins. Therefore, this Italian post-MI population represents a model approach to therapy of MI. The GISSI investigators conclude that "long term N-3 PUFA, but not vitamin E . . . was beneficial for death and for combined death, non-fatal MI, and stroke. All the benefit . . . was attributable to the decrease in risk for overall cardiovascular death."

COMMENT BY JONATHAN ABRAMS, MD

This is certainly a "good news" story with respect to dietary supplementation with marine fish oils. There are considerable epidemiologic and research data in the literature, including fish oil and fatty fish consumption, that predicted this beneficial outcome. The vitamin E results are disappointing but are concordant with all reported large trials of vitamin E supplementation available today. The mechanisms of PUFA benefits are unclear, and these benefits include antifibrinolytic and lipid modification effects. Decreased oxidation of LDL cholesterol has been suggested for vitamin E. The GISSI investigators believe without good evidence that the major effect of fatty acids was on arrhythmogenesis—not on "atherosclerotic-thrombolic events." They further suggest that the relatively ideal profile of the study cohort with respect to the Mediterranean diet and high rates of use of proven post-MI therapies would make it difficult to demonstrate a major effect of either fatty acids or vitamin E. Nevertheless, the PUFA groups did demonstrate a major benefit.

In an accompanying editorial, Brown suggests that it may take a much larger study to demonstrate a favorable effect of vitamin E. He is less sanguine about the magnitude of PUFA benefit and points out that vitamin E did reduce risk by 11% when compared to no vitamin E, but this did not result in statistical significance. One can therefore conclude that benefit will accrue to post-MI patients who ingest marine fish oils, but not necessarily in the mega-amounts used in prior trials. The benefits of vitamin E remain unproven. Unfortunately, the recently released HOPE Trial of subjects with vascular disease and diabetes also did not show a benefit for vitamin E, although the ACE inhibitor ramipril was shown to be beneficial in reducing cardiovascular risk. Another effective agent, heretofore not proven to be effective, is the fibrate gemfibrozil, which was recently reported to reduce death, recurrent MI, and revascularization rates by 22-23% in a cohort of U.S. veterans with isolated low HDL cholesterol treated with this agent for a period of five years.[1] Mean total and LDL cholesterol were low. There was a decrease in triglyceride levels and a modest increase in HDL throughout the study.

In conclusion, recommendations for secondary prevention now include a statin if LDL cholesterol is elevated (more than 130-135 mg/dL). In individuals with aggressive or premature coronary disease, the use of N-3 polyunsaturated fatty acids should be considered, in addition to a diet high in fatty fish consumption. It remains to be convincingly demonstrated that vitamin E is of any benefit for primary or secondary prevention. In patients with established coronary disease who have a low HDL and otherwise normal lipids, a fibrate is clearly indicated. (*Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.*) ❖

Reference

1. Rubins HB, et al. *N Engl J Med* 1999;341:410-418.

Deep Brain Stimulation for Parkinson's Disease

ABSTRACT & COMMENTARY

Synopsis: *All patients sustained a dramatic benefit in motor performance, although the benefit was greater in the STN group.*

Source: Ardouin C, et al. *Ann Neurol* 1999;46:217-223.

The last three years have seen an explosion of interest in deep brain stimulation for Parkinson's disease. Of the possible targets, only pallidal and subthalamic nucleus (STN) stimulation address the major cardinal symptoms of bradykinesia, rigidity, and tremor. Although implantation of a deep brain stimulator into

the internal pallidum or STN is not currently approved in the United States, these procedures, and in particular STN stimulation, are being performed at academic centers and in clinical practice. Ardouin and colleagues' review of the effects of bilateral stimulation on memory and executive functions is particularly important as neurologists struggle with the question of who should and who should not undergo these procedures.

Pooling patients implanted with bilateral STN or pallidal stimulators in Grenoble and Paris, 62 consecutive Parkinson's patients underwent a battery of neuropsychological tests before and after bilateral implantation of electrodes. Patients who underwent implantation were relatively young (average age < 55), with at least 12 years of Parkinson's symptoms. All responded to levodopa, with characteristic severe motor fluctuations. In the "on" state, patients were independent, and in the "off" state they were incapacitated (Hoehn and Yahr > 4/5). Electrodes were implanted in a single operative sitting using neuroradiologic landmarks and an intraoperative microelectrode recording to define placement. All patients sustained a dramatic benefit in motor performance, although the benefit was greater in the STN group. Patients implanted with STN stimulators were also able to substantially reduce their daily requirement for levodopa to assess the late effects of bilateral stimulation.

COMMENT BY STEVEN FRUCHT, MD

Patients with prior cognitive disturbance or hallucinations should probably not be considered as candidates. The conservative view would hold that STN stimulation should be performed in academic centers where resources are available for continuous neurological followup. The desperation of certain patients to undergo the procedure and the opportunity for considerable financial reimbursement in surgical fees may derail these plans. (*Dr. Frucht is Assistant Professor of Neurology, Movement Disorders Division, Columbia-Presbyterian Medical Center.*) ❖

Pharmacology Update

Zaleplon Capsules—Sonata (Wyeth Ayerst)

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

The fda approved wyeth ayerst's zaleplon (Sonata) for the short-term treatment of insomnia in adults. Zaleplon represents the first in a new class of nonbenzodiazepine hypnotics, the pyrazolopyrimidines. The drug is characterized by rapid absorption, rapid elimination, rapid onset, and short duration of action.

Indications

Zaleplon is indicated for the short-term treatment of insomnia. As with other hypnotics, zaleplon should generally be limited to 7-10 days of therapy.[1]

Dosage

The recommended dose of zaleplon is 10 mg, although a 20-mg dose may benefit certain patients. For the elderly, patients with low body weights, or patients with mild to moderate hepatic impairment, the dose should be reduced to 5 mg. No dose adjustment is necessary in patients with mild to moderate renal impairment. The drug should be taken immediately before bedtime or after the patient has gone to bed but failed to fall asleep, but it should not be taken if there are less than four hours left before the patient needs to be active. Zaleplon should not be taken with a heavy, high-fat meal as the absorption of the drug is significantly delayed.[1]

Zaleplon is supplied as 5 mg and 10 mg capsules. The FDA has given the drug a schedule IV classification similar to the benzodiazepines.

Potential Advantages

Zaleplon has a short half-life of elimination (0.9-1 hour); therefore, there is generally no next-day hangover or grogginess. The drug may be taken late into the night without risk of daytime sleepiness, as long as the patient has at least four hours left in bed. The metabolites of zaleplon do not appear to be active.

Potential Disadvantages

Due to its short duration of action, zaleplon is effective in inducing sleep rapidly, but may not be effective in sleep maintenance. Even though zaleplon is not a benzodiazepine, its behavior pharmacologic profile has been reported to be similar to that of triazolam when administered to subjects with a history of drug abuse.[3] Same-day and next-day subject-rated measures suggesting abuse potential were similar for the two drugs.[3]

Cytochrome P450 inducers such as rifampin decrease the zaleplon plasma concentration by 80%. Coadministration of zaleplon with rifampin and other inducers such as phenytoin, carbamazepine, and phenobarbital should be avoided. Cimetidine increases the bioavailability by 85% due to the inhibition of the

major (aldehyde oxidase) and minor (cytochrome P450 isoenzyme 3A4) pathways. A 5-mg dose should be used if zaleplon is coadministered with cimetidine.[1]

Comments

Zaleplon is a pyrazolopyrimidine that binds selectively to the BZ1 (omega 1) subtype of the GABA benzodiazepine-receptor complex.[2] In animal studies, zaleplon demonstrated a similar pharmacologic profile to zolpidem.[2] Its pharmacokinetics properties suggest that the drug may be most useful for insomnia characterized by difficulty falling sleep. Zaleplon does not appear to benefit patients with frequent awakenings or waking too early in the morning. Zaleplon does not appear to affect sleep duration. Clinical trials indicated that zaleplon reduced sleep latency by 10-20 minutes (15-30%) less than placebo.[1] Daytime anxiety was not observed in the clinical trials and rebound insomnia was reported to resolve by the second night following withdrawal.[1]

The cost of zaleplon is $1.72 and $2.12 per day for the 5 mg and 10 mg, respectively. It costs the same as 5 mg and 10 mg of zolpidem.

Clinical Implications

Insomia is the most common sleep disorder characterized by one or more of the following: difficulty falling asleep, difficulty maintaining sleep, and early awakening. The daytime consequences of insomnia include tiredness, difficulty concentrating, lack of energy, and irritability.[4] About 30-40% of adults have some form of insomnia per year and 10-15% consider the problem serious.[4] Insomnia is more prevalent in women and increases with age and socioeconomic class.[5] There are many causes of insomnia including environmental or situational factors, medication side effect, substance abuse, or medical and/or psychiatric conditions.

Insomnia can be categorized as transient and intermittent or chronic. Treatment should be directed toward correcting any underlying conditions and improving sleep hygiene. Short-term pharmacologic management has included benzodiazepines (e.g., temazepam, triazolam) as well as nonbenzodiazepine (zolpidem). Due to its short elimination half-life compared to other drugs, zaleplon is probably most useful for the short-term treatment of patients whose primary complaint is difficulty in falling asleep. ❖

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CME Questions

22. Which of the following supplements was shown in GISSI to reduce cardiovascular events?
a. Vitamin E
b. N-3 polyunsaturated fatty acids (fish oil)
c. Vitamin C
d. All of the above

23. Depression is associated with:
a. increased platelet reactivity.
b. decreased platelet reactivity.

24. Elderly institutionalized patients had increased humoral response after vaccination with:
a. mineral supplementation.
b. vitamin supplementation.
c. a combination of vitamins or minerals.
d. None of the above

25. Treatment of Parkinson's disease with deep brain stimulation:
a. is an improved procedure in the United States.
b. is more effective in the internal pallidum.
c. results in improved motor performance.
d. required patients to increase the dosage of levodopa.

26. Which is *not* true about zaleplon?
a. It is not affected by cytochrome P450 inducers.
b. It has a short duration of action.
c. It is not a benzodiazepine.
d. It is most effective for inducing rapid onset of sleep.

By Louis Kuritzky, MD

The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure

Despite the salutary effects of ACE inhibitors in heart failure, the effect of this class of agents on aldosterone appears to be transitory. Since aldosterone may affect magnesium and potassium excretion, sympathetic and parasympathetic activation, myocardial and vascular fibrosis, and arterial compliance, interruption of such effects could be of benefit in heart failure. In this trial, Pitt and associates tested the hypothesis that adding an aldosterone antagonist (25 mg spironolactone) to 'traditional' heart failure treatment (ACE inhibitor) would reduce mortality. All patients in this trial (n = 1663) suffered systolic dysfunction.

The trial had been designed to last for up to three years; however, mortality reductions achieved by 24 months dictated early closure of the trial. Spironolactone recipients had enjoyed a 35% reduction in risk of death, attributed to reduced mortality from both progressive heart failure and sudden death. Additionally, worsening of heart failure resulting in hospital admission was 35% lower in persons receiving spironolactone. Spironolactone is well known to cause gynecomastia at high doses, but at 25 mg, only 10% of men reported this symptom; hyperkalemia occurred with no greater frequency in the spironolactone group, though the selection criteria for the study did exclude patients with creatinine greater than 2.5—thereby reducing the likelihood of this adversity. Pitt et al conclude that the addition of aldosterone to traditional ACE inhibitor therapy reduces mortality in heart failure patients. ❖

Pitt B, et al. N Engl J Med 1999;341: 709-717.

Hypoglycemia and the Decision to Drive a Motor Vehicle by Persons with Diabetes

The ability to safely operate a motor vehicle is significantly compromised when blood sugar drops to levels of less than 65 mg/dL. When type 1 diabetics have undergone driving performance testing with simulators, literally half of persons with glucose levels sufficiently low to be associated with sub-par driving performance did not recognize that they were at a level of hypoglycemia that should prompt consideration not to drive.

In two separate study populations, Clarke and colleagues queried type 1 diabetics on whether they felt safe to drive, at the same time having obtained a blood glucose level. With each blood sugar measured (3-6 times daily), subjects rated on a 6-point scale their perceived level of autonomic activation (e.g., sweating, rapid heart rate) and symptoms of neuroglycopenia (e.g., poor concentration, lightheadedness, lack of coordination). Subjects were also asked to perform and self-evaluate two cognitive function tests and estimate what each of their measured blood glucose results would be. Finally, subjects were asked if they would drive at each time blood sugar was measured.

As many as 47% of subjects whose measured blood glucose was less than 40 mg/dL still felt fine to drive. Even more subjects (60%) stated they would drive when measured glucose was 60-70 mg/dL. Surprisingly, almost 45% of the time when diabetics self-estimated glucose to be within a range they knew to be potentially deleterious to driving performance, they still decided to drive.

Fortunately, type 1 diabetics have not been found to be responsible for any disproportionate segment of auto accidents. Nonetheless, such data should prompt clinicians to reinforce the necessity for close adherence to avoidance of driving during times when hypoglycemia is present. ❖

Clarke WL, et al. JAMA 1999;282: 750-754.

Sunscreen, Beta-carotene, and the Prevention of Skin Cancer

Although there has been the suggestion that sunscreen prevents the development of solar keratoses, there has been, as yet, no proof that sunscreen prevents skin cancer. Intellectually, the concept that beta-carotene might reduce skin cancer risk is appealing since it reduces free radical-induced cellular DNA damage consequent to UV light and has been demonstrated to effectively decrease UV-induced skin tumors in animal studies.

The Nambour Skin Cancer Prevention Trial investigated the effect of sunscreen, beta-carotene, or the combination vs. placebo on skin cancer. The trial enrolled 1621 individuals who were followed for 4.5 years—all residents of Queensland, Australia, an area considered high risk due to its subtropical location. Sunscreen (SPF-16) was applied once daily; 30 mg beta-carotene was administered once daily orally. Study end points were incidence of squamous cell and basal cell carcinoma; each patient was examined on multiple occasions by a dermatologist blinded to study-arm allocation.

The study found a significant 39% decrease in the incidence of squamous cell carcinoma among users of sunscreen but no change in frequency of basal cell carcinoma by any intervention. Overall, there was no skin cancer reduction afforded by beta-carotene; to the contrary, there was a trend toward increase in squamous cell carcinoma with beta-carotene (nonsignificant). ❖

Green A, et al. Lancet 1999;354: 723-729.

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: Exercise and Coronary Heart Disease