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Is Grapefruit Juice Harmful?

ABSTRACT & COMMENTARY

Synopsis: *These studies suggest that even a small amount of juice can cause a significant drug interaction and, therefore, these drugs should not be ingested within 24 hours after ingesting grapefruit juice or eating a significant amount of the fruit.*

Source: Kane GC, Lipsky JJ. *Mayo Clin Proc* 2000;75:933-942.

The american public is consuming grapefruit juice in great quantities with 14% of men drinking the juice at least weekly.[1] Yet grapefruits, like prunes, have commonly been referred to as a "funny" fruit. Yet, there is nothing funny about the way grapefruit interacts with some drugs.

A possible drug interaction with grapefruit juice was first reported approximately 10 years ago when investigators at the University of Western Ontario were attempting to find an effective way of disguising the flavor of alcohol. They found that double-strength grapefruit juice best masked the taste of alcohol, but they also found the blood level of felodipine to be three times higher in those people who were taking that medication with alcohol that had been laced with grapefruit juice to mask the taste of the alcohol[2] than were the blood levels in subjects who had taken the medication without grapefruit juice. Bailey and colleagues at the University of Western Ontario tested this serendipitous observation by measuring drug blood levels after giving the felodipine on one day with water and comparing the observed blood levels to those obtained the next day when felodipine was given with grapefruit juice—the drug blood levels were found to be up to four times higher when grapefruit juice was ingested with the drug.[3]

The drug-food interaction observed when ingesting grapefruit juice appears to occur because of the inhibition by grapefruit juice of one of the intestinal cytochrome enzyme systems. The isoform known as cytochrome P-450 3A4 (CYP3A4) is well known because of its frequent involvement with drug-drug interactions. The largest concentration of this family of heme-containing proteins is found in the endoplasmic reticulum of cells located throughout the body—especially in the liver and in the intestinal wall where they play a

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role in the oxidative biotransformation of numerous endogenous substances and xenobitics. Wide variations exist in the expression of this enzyme in the liver and intestines; however, it has now been clearly demonstrated that patients with the highest intestinal CYP 3A4 concentrations display the greatest untoward effects when they ingest grapefruit juice.[4]

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Skeptical members of the medical community initially ignored the data; however, multiple studies have now clearly confirmed the interaction of grapefruit juice with felodipine as well as with other medications. The majority of the studies on pharmodynamic evaluations have been performed on relatively small numbers of healthy adult volunteers but more recently, an increasing number of case reports of adverse effects due to drug interactions of grapefruit juice with many medications have been published. These drugs are clearly tabulated in the Table.

Table

Grapefruit and Drug Interactions*

Drug	Interaction
Calcium-channel blockers	
Amlodopine (Norvasc)	Yes
Felodopine (Plendil)	Yes
Nifedipine (Procardia)	Yes
Nimodopine (Nimotap)	Yes
Nisoldipine (Sular)	Yes
Diltiazem (Cardizem)	No
Verapamil (Calan, Isoptin)	No
HMG-CO inhibitors (statin)	
Atorvastatin (Lipitor)	Yes
Cervastatin (Baycol)	Yes
Lovastatin (Mevacor)	Yes
Simvostatin (Zocor)	Yes
Fluvastatin (Lescol)	? No
Pravastatin (Pravacol)	? No
Others	
Sildenafil (Viagra)	Yes
Diazepam (Valium)	Yes
Buspirone (Buspar)	Yes
Quinidine	No
Prednisone	No
Quinine	No
Ethenil estradiol	No

*This is a partial list, many other medications are being investigated.

An argument can be made that if a patient has been taking medication with grapefruit juice for some time without ill effect, it is probably safe to continue to do so; however, the variability in the level of interaction with different types of juice would suggest that this approach may not be entirely safe. For example, felodipine blood levels have been demonstrated to increase 300-500% when taken with grapefruit juice and such elevations have led to symptoms of flushing, lightheadedness, and fainting in otherwise healthy research subjects. Obviously, an elderly person with significant coronary artery disease or hypertension might even have more significant symptomatology. Each patient's medical condition should be individually considered and advice regarding the use of grapefruit juice should be based on the specific medication involved; however, it would seem foolhardy not to recommend to patients that they use water rather than

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grapefruit juice for the ingestion of any of the many drugs tabulated in the Table. These drugs should not be taken with grapefruit juice until the drug-grapefruit juice interactions have been clarified. The spectrum of these drugs included many drug categories such as heart/high blood pressure agents, antihistamines, transplant rejection agents, cholesterol-lowering drugs, and other agents such as warfarin (Coumadin), cisapride (Propulsid), and even sildenafil (Viagra).

For the practicing physician, it is important to recognize that regular strength grapefruit juice has as much as 80-90% of the untoward effect of double-strength grapefruit juice and, in fact, whole grapefruits have almost the same effect. Therefore, it behooves all physicians to caution their patients about the use of any strength grapefruit juice as a liquid vehicle for the ingestion of any drug, but especially for those listed in the Table. Also, it should be noted that most studies examining the grapefruit-drug interactions have used a single 8-oz glass of fresh or reconstituted grapefruit juice. These studies suggest that even a small amount of juice can cause a significant drug interaction and, therefore, these drugs should not be ingested within 24 hours after ingesting grapefruit juice or eating a significant amount of the fruit. ❖

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Effectiveness and Cost-Benefit of Influenza Vaccination of Healthy Working Adults

ABSTRACT & COMMENTARY

Synopsis: *The study found that influenza vaccination in healthy working adults younger than 65 years of age can reduce the rates of influenza-like illness, lost work days, and physician visits during years when the vaccine and circulating viruses were similar, but vaccination was not cost effective.*

Source: Bridges CB, et al. *JAMA* 2000;284:1655-1663.

The cost effectiveness of influenza vaccination in reducing influenza illness, hospitalization, and death is well established in persons aged 65 years or older.[1-3] However, the benefit of annual influenza vaccination in healthy young adults is less clear. The purpose of this study was to determine the clinical efficacy and cost benefits of influenza vaccination in healthy young adults.

Bridges and colleagues conducted a double-blind, randomized, placebo-controlled trial of influenza vaccine among healthy working adults during the 1997-1998 and 1998-1999 influenza seasons. The primary outcome measures were clinically defined respiratory illness based on ICD-9 codes, associated physician visits, lost workdays during the influenza season, and the cost benefits.

Patients between the ages of 18 and 64 years were randomly assigned to receive either trivalent inactivated influenza vaccine or placebo. Study participants were sent follow-up surveys via e-mail twice monthly and information was obtained on respiratory illness and related physician visits, medications, hospitalization, and lost work days. During November through April of each study year, throat swabs, nasopharyngeal swabs, or both were collected from participants who notified the study nurse of an influenza-like illness (ILI) and who had been ill for four days or less. Specimens were sent for viral culture. Influenza isolates were sent to the Centers for Disease Control and Prevention (CDC) and antigenically characterized. A total of 1184 participants were randomized in the 1997-1998 and 1191 in the 1998-1999 seasons. Complete follow-up was available for 95% (1130/1184) and 99% (1178/1191) of participants in each period, with 23% in each year having serologic testing. In 1997-1998, when the vaccine virus was different from the predominant circulating viruses, vaccine efficacy against serologically confirmed influenza illness was 50% (P = 0.33). The vaccination did not reduce ILI, physician visits, or lost workdays; the net societal cost was $65.59 per person compared with no vaccination. In 1998-1999, the vaccine and predominant circulating viruses were well matched. Vaccine efficacy was 86% (P = 0.001), and vaccination reduced ILI, physician visits, and lost workdays by 34%, 42%, and 32%, respectively. However, vaccination resulted in a net societal cost of $11.17 per person compared with no vaccination.

Bridges et al thus conclude that in years in which there is a good match between vaccine and the circulating virus, vaccination against influenza can have substantial health benefits by reducing rates of ILI, physician visits, and work absenteeism. However, it

does not provide societal economic benefits for healthy young adults.

COMMENT BY DAVID OST, MD

The strategy for influenza vaccination in the United States has emphasized prevention of influenza in persons most likely to experience complications: those aged 65 years or older and younger individuals with cardiac, pulmonary, and other chronic conditions. Studies have shown that vaccination is cost effective in the elderly population.[1] Although vaccination of healthy adults is known to be effective in preventing clinical influenza, cost-effectiveness has not been demonstrated conclusively in this population.

In a double-blind, placebo-controlled trial of vaccination against influenza done by Nichol and colleagues, vaccination resulted in substantial health-related and economic benefits with an estimated cost savings of $46.85 per person vaccinated for healthy working adults.[4] This current study differs from the Nichol et al study in several important aspects. It was conducted during two consecutive influenza seasons, it defined the influenza period based on virologic surveillance at the study site, and it used diagnostic testing to confirm influenza infection rates in a subset of participants unlike the previous study where influenza was defined by clinical features only. This study illustrates that the clinical efficacy and the cost benefit of vaccination depends on the match between vaccine virus and the circulating virus, thus the need to take a multiyear approach in evaluating influenza vaccine programs. The findings of Bridges et al regarding cost effectiveness is especially important this year, because there is limited availability of influenza vaccine in the United States. It provides important clinical and cost-benefit data to help in the development of strategies for preventing influenza in healthy working adults. In conclusion, influenza vaccine is effective in preventing serologically proven influenza infection in young, healthy adults and may reduce cumulative days of illness and absence. However, programs for vaccination in the workplace may not provide economic benefit in all years. ❖

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Smoking and Mental Illness

ABSTRACT & COMMENTARY

Synopsis: *This study found that people who smoke cigarettes are approximately twice as likely to have mental illness as people who do not smoke.*

Source: Lasser K, et al. *JAMA* 2000;284:2606-2610.

Lasser and colleagues used data from the National Comorbidity Survey (NCS), a congressionally mandated study of the prevalence of psychiatric disorders in the United States. Data for this paper were gathered from 4411 people aged 15-54 years, and included smoking histories and a modified version of the Composite International Diagnostic Interview, a well-validated structured psychiatric interview. Mental illness was defined as major depression, bipolar disorder, dysthymia, panic disorder, agoraphobia, social phobia, simple phobia, generalized anxiety disorder, alcohol abuse, alcohol dependence, drug abuse, drug dependence, antisocial personality, conduct disorder, or nonaffective psychosis. Smoking status was broken down into never smokers, "lifetime smokers," (those who had smoked for at least a month in the past, but not currently), and current smokers. Current smokers were further categorized as heavy smokers (> 24 cigarettes/d) or moderate and light smokers. Among the findings of interest are: 1) the prevalence of ever having mental illness by Lasser et al's definition was 50.7%; 2) those with a history of mental illness were twice as likely to be lifetime smokers as those without (odds ratio [OR] 2.1; confidence interval [CI] 1.9-2.4); 3) those with a history of mental illness were twice as likely to be current smokers as those without (OR 1.9, CI 1.7-2.2); 4) heavy smoking was rare in people with no history of mental illness; only 10% of such persons were heavy smokers; and 5) people with mental illness comprise 44.3% of the U.S. tobacco market.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Previous studies[1-5] have suggested that smokers are more likely than are nonsmokers to have psychiatric disorders, and many front-line internists undoubtedly suspect this relationship on the basis of their daily experiences. This study is the first to use a structured psychiatric interview and to estimate the proportion of the tobacco market comprised by smokers. Although intuition suggests that mental disturbance predisposes

to smoking and there is some evidence to suggest that RJ Reynolds Tobacco Company may have deliberately exploited that tendency,[6] the converse may be true. Several studies have suggested that smoking increases the risk of psychiatric disorders, and not vice versa.[7-9]

Thus, smoking cessation and prevention may prevent not only the well-known causes of more than 400,000 premature deaths per year, but also some of the terrible morbidity and mortality associated with psychiatric illness. We spend a lot of time bemoaning the lack of effect of anti-tobacco educational and awareness programs. In fact, there is some evidence that exposure to anti-tobacco advertisements results in an increased likelihood of adolescent smoking.[10] The latest data on intensive, pharmacologically supported smoking cessation are not encouraging, either—at 12 months, a combination of nicotine inhaler and nicotine patch resulted in a 19.5% abstinence rate.[11]

What does work? Cost, of course. Not only do we know that excise taxes result in reduced teen (and overall) consumption, we have precise data on how many lives are saved by each percentage increase in the price of a pack of cigarettes.[10,12] The data on the effectiveness of excise tax increases in reducing tobacco consumption are overwhelming. Physicians need to remember this! I personally believe I can save many more lives (and maybe even reduce the suffering associated with mental illness) by enlightening legislators about this issue than I can working in the intensive care unit. ❖

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Pharmacology Update

Tenecteplase Injection (TNKase—Genentech, Inc.)

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

The fda has approved tenecteplase, a new single bolus thrombolytic for the treatment of acute myocardial infarction (AMI). Tenecteplase is a modified tissue plasminogen activator produced by recombinant DNA technology using Chinese Ovary cells. Genentech has modified its other thrombolytic, human tissue plasminogen activator (tPA), to create the new agent. The changes result in a 527 amino acid glycoprotein with a lower plasma clearance and more fibrin specificity allowing it to be administered in a single bolus over 5 seconds.

Tenecteplase is marketed as TNKase by Genentech.

Indications

Tenecteplase is indicated for use in the reduction of mortality associated with AMI.[1]

Dosage

The dose of tenecteplase is based on body weight: 30 mg for patients less than 60 kg; 35 mg for those 60 kg or more, but less than 70 kg; 40 mg for patients 70 kg or more, but less than 80 kg; 45 mg for patients 80 kg or more, but less than 90 kg; and 50 mg for those 90 kg or more. The single intravenous bolus dose should be administered over 5 seconds and should be initiated as soon as possible after the onset of AMI symptoms.[1]

Tenecteplase is supplied as 50 mg lyophilized powder with 10 mL sterile water for injection.

Potential Advantages

The primary advantage of tenecteplase is its ease of administration. It can be given as a single bolus dose over 5 seconds compared to alteplase (rtPA), which requires a loading bolus and infusion over 1.5 hours, and reteplase, which requires two bolus doses 30 minutes apart. In a large (n =16,949), multicenter comparative trial, Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2), the frequency of noncerebral major bleeding was lower with tenecteplase compared to alteplase (4.68% vs 5.94%; $P = 0.0002$).[2] The frequency of transfusion was also lower (4.25% vs 5.49%; $P = 0.0002$).

Potential Disadvantages

As with other agents, the primary disadvantage of thrombolytic therapy is the risk of stroke. In the ASSENT-2 trial, the stroke rates were 1.78% with a rate of 0.9% for intracranial hemorrhage. These rates were comparable to that seen with alteplase, 1.66% and 0.94%. The rate of ischemic stroke was slightly higher with tenecteplase but not statistically different from altepase (0.72% vs 0.64%).[2]

Comments

Tenecteplase is a mutant of human tissue plasminogen activator. The alteration by recombinant DNA technology results in a molecule with a longer plasma half-life (20 min vs 4 min), greater fibrin specificity, and more resistance to inhibition by plasminogen-activator inhibitor-1 compared to alteplase.[3] In the ASSENT-2 trial, tenecteplase was comparable to alteplase in 30-day mortality. ASSENT-2 was a multicenter, double-blind, randomized, controlled trial involving 16,949 patients with AMI of less than six hours with a median time of onset to treatment of 2.8 hours. Patients received 30-50 mg of tenecteplase over 5-10 seconds, depending on weight, or up to 100 mg of alteplase by rapid infusion. All patients received aspirin and heparin. Heparin was titrated to a target activated partial thromboplastin time of 50-75 seconds for 48-72 hours. The 30-day mortality was 6.18% with tenecteplase and 6.15% with alteplase. The overall rate of mortality or nonfatal stroke was 7.11% with tenecteplase and 7.04% with alteplase (relative risk of 1.01 [95% CI 0.91-1.13]). Subgroup analysis revealed that patients whose time to treatment was longer than four hours seemed to fare better with tenecteplase than alteplase (7.0% mortality vs 9.2%; $P = 0.018$). The ASSENT-2 investigators suggest that the higher fibrin specificity of tenecteplase may lead to better dissolution of older fibrin clots.[2] However, this subgroup represented only 22% of the study population. Overall, there was no difference in 30-day mortality. Patients who received treatment within 2-4 hours, representing the largest subgroup at 47%, fared numerically but not statistically better with alteplase (5.5% vs 6.3%; $P = 0.106$).

Clinical Implications

Tenecteplase appears to be comparable to alteplase in 30-day mortality. Its primary advantage is the ease of administration. It also appears to have a slightly lower incidence of major bleeding and need for transfusion. The ease of administration may shorten the time between the onset of AMI symptoms and thrombolysis. A course of treatment for tenecteplase is about $2000, which is comparable to the cost of alteplase. ❖

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CME Questions

1. Which one of the following statements is correct?

a. Grapefruit juice, even in small amounts, can cause significant drug interactions.
b. Physicians should caution their patients about the use of any strength grapefruit juice as a liquid vehicle for the ingestion of any drug.
c. Certain drugs should not be ingested within 24 hours after ingesting grapefruit juice or eating a significant amount of grapefruit.
d. All of the above

2. The use of influenza vaccine in healthy adults younger than 65 years of age (matched virus vaccine) results in:

a. increased ILI related physician visits and work absenteeism.
b. decreased societal economic costs.
c. decreased ILI related physician visits and work absenteeism but increased societal cost.
d. a and b
e. None of the above

3. Which one of the following is true?

a. People who smoke cigarettes are approximately twice as likely to have mental illness as people who do not smoke.
b. People who smoke cigarettes are approximately half as likely to have mental illness as people who do not smoke.
c. There is no relationship between cigarette smoking and mental illness.
d. Mental illness causes cigarette smoking.

4. Tenecteplase:

a. is indicated for use in the reduction of mortality associated with acute myocardial infarction.
b. is easier to administer than alteplase and may shorten the time between the onset of AMI symptoms and thrombolysis.
c. appears to have a slightly lower incidence of major bleeding and need for transfusion.
d. is comparable to the cost of alteplase.
e. All of the above

5. What factor has been proven to greatly reduce tobacco consumption in the United States?

a. Anti-tobacco campaigns
b. Peers
c. Excise taxes
d. Mental illness
e. None of the above

By Louis Kuritzky, MD

Individual Cholesterol Variation in Response to a Margarine or Butter-based Diet

Reduction in cholesterol through diet is a tool commonly used in persons who suffer stroke, myocardial infarction (MI), or peripheral vascular events, as well as in those persons felt to be at risk of such end points. Nonetheless, not all persons respond well to dietary intervention. Indeed, as many as 15-20% of persons counseled on diet do not demonstrate significant cholesterol reductions, despite adherence. This study investigated familial differences on effect of cholesterol-lowering diet upon LDL over two five-week periods.

Of the 56 initial families selected from the Dallas-Ft. Worth area, 46 completed the trial during which subjects used either butter (80% fat by weight) or margarine (since regular commercial margarine contains 60% fat by weight, subjects consumed specially compounded 80% fat by weight margarine). Family compliance to monitored ingestion of butter or margarine was excellent.

On average, adults experienced an 11% reduction in LDL by margarine substitution for butter. In concordance with earlier data, 19% of subjects experienced no LDL lowering. No single genetic factor was determined to account for individual variability in response to diet. Clinicians may anticipate that despite dietary compliance, a substantial minority of individuals will not enjoy cholesterol lowering. ❖

Denke MA, et al. JAMA 2000;284: 2740-2747.

A Prospective Study of Back Belts for Prevention of Back Pain and Injury

Low back pain (lbp) and its consequent disability have been our nation's single largest source of disability dollar expenditure for many years. Numerous avenues of investigation seek to find effective tools to prevent, treat, or shorten the disability related to LBP. Wassell et al investigated the effect of low back support belts (BSB) in reducing the incidence of back injury claims or LBP among 110 supermarket-merchandise stores of a single corporation.

Of 144,469 corporate employees, 10% were identified as involved in "material handling tasks." Study data come from those individuals who successfully completed baseline interviews, divided equally among stores that required belt use for material handlers, compared to those in which belt use was voluntary.

There was no discernible effect of using a BSB. This same nil effect persisted in a variety of subgroups, including persons with or without history of previous back injury, persons with highly consistent belt wearing habits, and employees with the most strenuous jobs. This study demonstrates that BSB use does not favorably affect LBP. ❖

Wassell JT, et al. JAMA 2000;284: 2727-2732.

Stratified Care vs. Step Care Strategies for Migraine

There is, as yet, no clearly defined evidence-based path for best acute management of migraine. Lipton and colleagues describe "step care" as a process in which the patient usually initiates treatment with a nonspecific treatment such as simple analgesics; if resolution is inadequate, treatment escalation is used. In their description of "stratified care," the choice of initial treatment is based upon headache-related disability (i.e., activity limitations in various domains of function). Lipton et al compared step care with stratified care (n = 1062).

Step care treatment began with aspirin (800-1000 mg) plus metoclopramide (10 mg); unsatisfactory resolution indicated escalation to a triptan (zolmitriptan 2.5 mg). Patients with Migraine Disability Assessment Scale (MIDAS) scores of I-II were treated initially with the same aspirin plus metoclopramide regimen; MIDAS scores II-IV received the triptan as initial therapy.

The proportion of responders was significantly greater in the stratified care than in the step care groups. Lipton et al conclude that the stratified care strategy is superior to step care, suggesting that the patient's headache disability score may be used to enhance the likelihood of success of initial therapy. ❖

Lipton RB, et al. JAMA 2000;284: 2599-2605.

A "Sited" Tachycardia

By Ken Grauer, MD

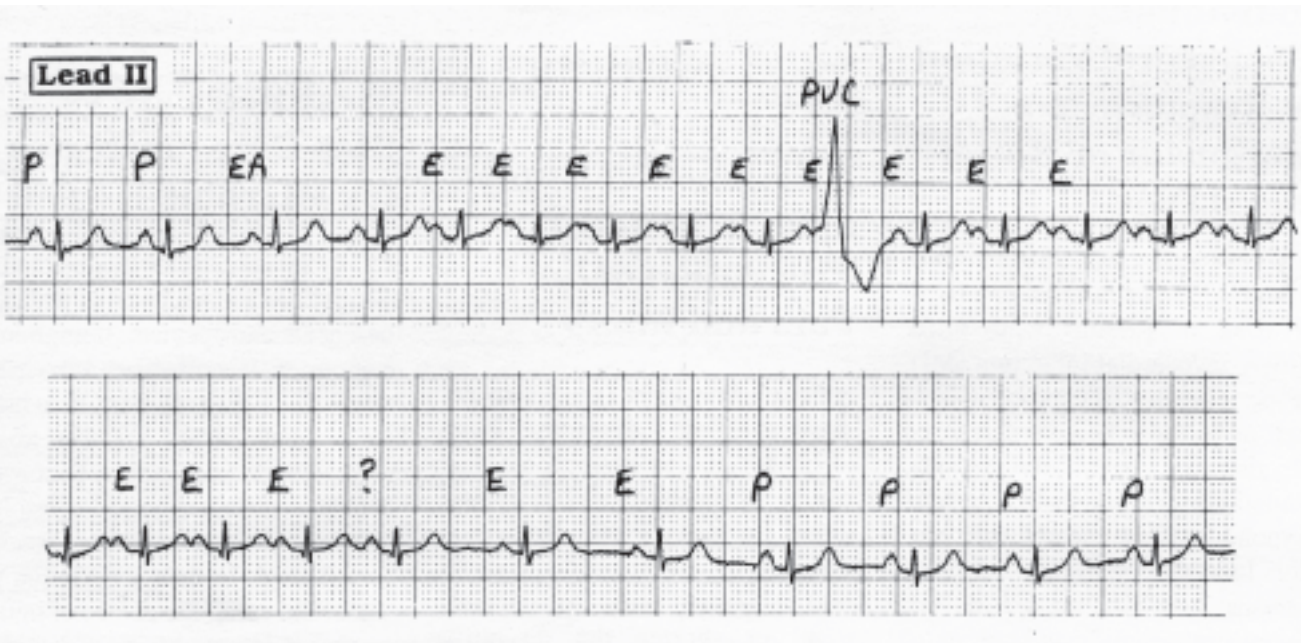

Figure. Telemetry rhythm strips showing the onset and resolution of this patient's tachycardia.

Clinical Scenario: The tachycardia shown in the Figure was obtained from an older woman who presented with shortness of breath and a recent history of "irregular heart beat" episodes. The top strip shows the onset of one such episode, and the bottom strip shows its resolution. What is the probable mechanism of this patient's arrhythmia? Is the premature ventricular contraction (PVC) seen in the top strip supportive of this diagnosis? How might you treat this patient's rhythm disorder?

Interpretation: The underlying rhythm is sinus, as suggested by the two normal beats that initiate the top tracing. P wave morphology changes with the third beat, which most likely arises from an ectopic atrial site (EA). Acceleration of the rhythm follows, with development of a tachycardia that manifests an upright but different (ectopic) appearing P wave (E) compared to the sinus-conducted beats. The rate of the tachycardia is approximately 135/minute, and the occurrence of the PVC does nothing to terminate the episode. Gradual slowing is seen in the bottom strip, with conversion of P wave morphology back to the sinus-initiated (P) focus.

The features described and illustrated in the above tracings are characteristic of an ectopic atrial tachycardia (gradual onset and offset of the rhythm with ectopic P wave morphology). Unlike the overwhelming majority of supraventricular tachycardia (SVT) rhythms in adults which are AV-nodal "dependent," ectopic atrial tachycardia arises from an *ectopic* atrial site that gradually accelerates and is independent of the AV node for its continuation. As a result, neither PVCs nor vagal maneuvers are likely to terminate the rhythm. Treatment consists of correcting the underlying cause (most likely heart failure, pulmonary disease, electrolyte disturbance, digitalis toxicity); AV nodal blocking drugs (for rate control); and occasionally antiarrhythmic agents (to suppress the ectopic atrial site), though the response to such treatment is highly variable. ❖

In Future Issues:

Hope For the Calorically Challenged