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A Modern Day Faustus: COX-2 Inhibitors—Are We Trading Gastric Protection for Cardiac Death?

ABSTRACT & COMMENTARY

Synopsis: *This study suggests that high-dose rofecoxib may increase the risk of cardiovascular events.*

Source: Ray WA, et al. *Lancet*. 2002;360:1071-1073.

THIS RETROSPECTIVE COHORT TRIAL ASSESSED THE RISK OF low- and high-dose COX-2 inhibitors (celecoxib and rofecoxib) for serious coronary heart disease defined as a new myocardial infarction or cardiovascular death. The Tennessee Medicaid program enrolled 202,916 subjects who were assessed for a 2-year period. Subjects currently taking COX-2 inhibitors (10,298 person years) were compared to nonusers (237,975 person-years) and to those taking nonsteroidal medications (ibuprofen, naproxen; 37,423 person-years). Eligible subjects were nonnursing home patients without a life-limiting illness, aged 50-84 years.

When compared to nonusers, patients taking high-dose rofecoxib (> 25 mg/d) had an adjusted risk ratio of 1.93 (95% CI, 1.1-3.4; P = 0.02). There was no statistical difference between nonusers and those taking other nonsteroidals, celecoxib or low-dose rofecoxib (< 25 mg/d). The event rate in patients not taking COX-2 inhibitors or NSAIDs was 1.3%; the event rate in the high-dose rofecoxib population was 1.1%. The absolute risk of harm was 0.2%; 500 patients would have to be treated with high-dose rofecoxib instead of no therapy before 1 additional cardiovascular event could be expected (number needed to harm = 500).

COMMENT BY JEFF WIESE, MD

The VIGOR trial found that subjects who took rofecoxib 50 mg/d were 5 times as likely to have a myocardial event as those who took 1000 mg of naproxen per day.[1] The initial explanation was that naproxen was cardioprotective, but this was discounted in subsequent studies that found no benefit of naproxen in preventing cardiac disease.[2]

INSIDE

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COX-2 inhibitors selectively inhibit the cyclo-oxygenase 2 enzyme, and in doing so, decrease inflammation without inhibiting the prostaglandins important for gastrointestinal protection. One potential complication of this selective inhibition may be an increase in arachidonic acid metabolites shunting down the thromboxane pathway, thereby increasing platelet aggregation. Bombardier and colleagues have suggested that COX-2 inhibition may affect nitric oxide synthetase, thereby increasing vascular tone and myocardial work. The observation of this study and the VIGOR trial may be the clinical manifestation of these physiologic postulates.[1]

The results of this study should be interpreted with caution. There are many potential confounders that may explain the results of this study. It is likely that most patients in this study began with a nonsteroidal such as ibuprofen, advancing to a COX-2 inhibitor if this failed. The patients in the rofecoxib group may therefore represent a patient population with a greater severity of inflammation and a greater risk of cardiovascular events. Furthermore, patients with comorbid diseases prohibiting nonsteroidal therapy such as renal insufficiency or gastrointestinal bleeding would have been excluded from the ibuprofen group but may have been included in the COX-2 group. These patients may have been disproportionately represented in the rofecoxib group.

This study suggests that high-dose rofecoxib may increase the risk of cardiovascular events. Further randomized trials will be required to eliminate the numerous potential confounders from interpretation of the results. Until that time, high-dose rofecoxib should be used with caution, especially in those with underlying cardiovascular disease. ■

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2. Ray WA, et al. *Lancet*. 2002;359:118-123.
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Valproate for Diabetic Painful Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *Sodium valproate appears safe and effective for the management of DPSN.*

Source: Kochar DK, et al. *Acta Neurol Scand*. 2002;106: 248-252.

Diabetic painful sensory neuropathy (DPSN) remains difficult to treat—witness the persistence of ongoing and upcoming clinical trials searching for the magic bullet and the large number of medication options available (none work superbly in all cases). In this randomized, double-blind, placebo-controlled trial, sodium valproate, 400 mg p.o. t.i.d., was administered to 30 patients with efficacy and safety compared to 30 placebo-controlled patients. All 60 patients were demographically matched with documented DPSN, and they were excluded if they demonstrated hepatic disease, TB, or other causes of neuropathy including uremia, vitamin deficiency, paraneoplastic or hereditary neuropathy, or alcoholism. Detailed clinical and neurological examina-

tions were performed and the short-form McGill pain questionnaire was used to quantify pain severity at study entry, week 1, and after 4 weeks of therapy. Motor and sensory nerve conduction studies were performed at study onset and after 4 weeks. Student's t-test provided statistical analysis.

Among 28 patients who completed 4 weeks of the active drug arm, 20 reported pain relief compared to 5 of 24 in the placebo arm. Pain severity was significantly decreased ($P < 0.05$) after 4 weeks on active therapy, though no significant change was appreciated after 1 week. Electrodiagnostic studies did not improve during this short study. Only 1 patient was withdrawn due to abnormal liver function tests while on valproate. Among the other patients who did not complete the study, 3 were for noncompliance (1 active arm, 2 placebo arm) and 2 due to lack of effect (placebo arm). Sodium valproate appears safe and effective for the management of DPSN.

COMMENT BY MICHAEL RUBIN, MD

Why do some diabetics develop painful sensory neuropathy while in others the neuropathy is painless? Ten painful sensory neuropathy diabetics were matched with 10 diabetics with nonpainful sensory neuropathy for age, diabetes duration, insulin regimen, duration of neuropathy, and HbA1c. All were fitted with a continuous glucose-monitoring system (MiniMed Inc., Sylmar, Calif, US) for 3 days to determine if a relationship existed between glucose fluctuations and painful neuropathy. Patients with other causes for foot pain, including arterial disease, skin ulcers, or arthritis were excluded. Daily pain scores were recorded by the patients on a horizontal 10-cm scale. Analgesics were allowed as needed. Glucose excursions were measured as a mean amplitude over 24 hours, and M-values, a quantitative measure of blood glucose deviations over a specified time period, were calculated.[1] Spearman's rank correlation coefficient and the Mann-Whitney U-test provided statistical analysis.

Frequency of glucose excursions, mean glucose value, and mean M-value were significantly greater in the painful neuropathy group compared to the painless group. However, the mean amplitude of glucose excursion did not differ between groups and no correlation was appreciated between episodes of pain and number or amplitude of glucose excursions. Greater glucose flux is associated with painful, rather than painless, neuropathy in diabetics. ■

Dr. Rubin is Professor of Clinical Neurology, New York Presbyterian Hospital—Cornell Campus.

Reference

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Helicobacter pylori Infection

ABSTRACT & COMMENTARY

Synopsis: Helicobacter pylori *is an exceedingly common inhabitant of the human stomach. The discovery of its role in the pathogenesis of peptic ulcer disease was revolutionary, but many questions remain about this organism and an appropriate medical approach to its presence.*

Source: Suerbaum S, Michetti P. *N Engl J Med*. 2002; 347(15):1175-1186.

HELICOBACTER PYLORI WAS FIRST CULTURED 20 years ago, and it was soon recognized that peptic ulcer disease might have an infectious pathogenesis. Presence of the organism is strongly correlated with socioeconomic conditions, ranging from 80% of middle-aged adults in developing countries to as little as 20% in industrialized countries. It seems likely that the decreased infection levels in the United States will eventually lead to the complete elimination of this infection from our society. *H pylori* in adults is usually chronic and resolves only with specific therapy, but children probably commonly spontaneously eliminate this infection. *H pylori* survives in the stomach using a number of protective mechanisms, including the production of urease-generated ammonia as a potent acid-neutralizing agent. Gastric inflammation is invariably produced by infestation with *H pylori*, and some infected patients have an autoantibody against the ATP-ase of parietal cells that may lead to gastric atrophy. Clinical outcome of infection is highly variable. Antral gastritis is associated with duodenal ulcers, and corpus gastritis seems related to gastric ulcers, gastric atrophy, intestinal metaplasia, and potentially gastric adenocarcinoma. MALT lymphoma is directly related to *H pylori* infection in genetically susceptible individuals. Incidence of cancer in Japan has been documented at 2.9% over 8 years. Nevertheless, it remains clear that most patients with *H pylori* infection never get ulcers, malt lymphoma, or gastric cancer. Controversy continues as to whether infection with *H pylori* protects against gastroesophageal reflux disease. Diagnostic tests for infection include the urea breath test, serological tests, and stool antigen testing. Serology cannot document either active infection or effec-

tive eradication. Trials have documented the substantial efficacy of triple therapy with PPI (b.i.d. except for rabeprazole that can be administered once daily) and 2 antibiotics (usually clarithromycin and amoxicillin) for *H pylori* eradication. Failure of eradication is common, often due to poor compliance with the initial regimen and may require quadruple therapy including a bismuth-based triple regimen plus a PPI or H2 receptor antagonist. Rifabutin plus amoxicillin and a PPI might be another option for second-line therapy. At the moment, the only completely accepted indications for *H pylori* eradication are ulcer disease and MALT lymphoma. Except in settings with a known high background prevalence of ulcer disease, empirical treatment of *H pylori* in dyspeptic patients is not recommended.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

This area remains confusing, partly because many medical payers have urged empirical treatment of *H pylori* for economic reasons. The strong epidemiologic data for an inverse relationship between the presence of *H pylori* and gastroesophageal reflux disease would certainly suggest that physicians avoid seeking to diagnose *H pylori* in patients with primary GERD symptoms.

Strong international recommendations for aggressive eradication of *H pylori* to prevent cancer probably do not apply to North America.

The Effect of the Amount and Intensity of Exercise on the Plasma Lipoproteins

ABSTRACT & COMMENTARY

Synopsis: *There were widespread beneficial effects of high amounts of exercise on plasma lipoproteins.*

Source: Kraus WE, et al. *N Engl J Med*. 2002;347: 1483-1492.

Increased physical activity is related to reduced risk of cardiovascular disease. This may be related to the improvement in plasma lipoproteins. However, the amount of exercise training required for optimal results is unknown. This randomized, prospective study investigated the effects of the amount and intensity of exercise on lipoproteins.

A total of 111 sedentary, overweight men and women with mild-to-moderate dyslipidemia were randomly assigned to participate for 6 months in a control group or for approximately 8 months in 1 of 3 exercise groups: high-amount-high-intensity exercise, the caloric equivalent of jogging 20 miles per week at 65-80% of peak oxygen consumption; low amount-high-intensity exercise, the equivalent of jogging 12 miles per week at 65-80% of peak oxygen consumption; or low amount moderate-intensity, the equivalent of walking 12 miles per week at 40-55% of peak oxygen consumption. Subjects were encouraged to maintain their base-line body weight. The 84 subjects who complied with these guidelines served as the basis for the main analysis. Detailed lipoprotein profiling was performed by nuclear magnetic resonance spectroscopy with verification by measurement of cholesterol in lipoprotein subfractions.

Results

There was a beneficial effect of exercise on a variety of lipid and lipoprotein variables, seen most clearly with the high amount of high-intensity exercise. The high amount of exercise resulted in greater improvements than did the lower amount of exercise (in 10 of 11 lipoprotein variables) and was always superior to control conditions. Both lower amounts of exercise groups always had better responses than the control group.

The highest amount of weekly exercise, with minimal weight change, had widespread beneficial effects on the lipoprotein profile. The improvements were related to the amount of activity and not to the intensity of exercise or the improvements in fitness.

COMMENT BY RALPH R. HALL, MD, FACP

So! More is better! Although the majority of exercise studies have demonstrated that the greater amount of exercise the more improvement in cardiovascular risk factors, newspapers and even the American College of Sports Medicine have downplayed the benefits of greater amounts of exercise. They have emphasized that even a little exercise is better than none, hoping to get the most sedentary of us to do a little. Many of us have been concerned that those doing moderate amounts of exercise would do less as result of the media's emphasis on benefit of a small amount of exercise. The greatest benefit in the lipid profiles occurred in the high-amount high-intensity group. Tall in an accompanying editorial discusses the mechanisms that may influence these significant changes in the plasma lipids.[1] He points out that the increase in plasma lipoprotein lipase increases the metabolism of VLDL

and a decrease in hepatic lipase has a beneficial effect on HDL lipoproteins. This is a complicated process that we are just beginning to understand. It is illustrated by the recent work of Votruba and colleagues, which demonstrates exercise alters the way fat is metabolized and also that the change produced by exercise is dependent on the type of fat consumed.[2]

This study does not settle the argument about whether amount or intensity is more important in altering the plasma lipid levels. The low amount-high intensity group attained the same degree of fitness as the high amount-high intensity group. The low amount averaged the equivalent of 11 jogging miles per week while the large amount averaging 19 miles per week. One would expect the group exercising almost 2 times as much to attain the higher level of fitness. The fact that this did not happen implies that that there were nonresponders in the high amount-high intensity group or that there were actually errors in measuring the intensities between the groups. The authors corrected for the differences in fitness levels attained by men vs women by using peak oxygen consumption rather than the percent of maximum oxygen consumption. (Women attain lower levels of fitness, when fitness is measured by percent of maximum oxygen uptake—their percent of change is comparable to men when measured by peak oxygen uptake).[3] ■

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Pharmacology Update

Adefovir (Hepsera) for the Treatment of Chronic Hepatitis B Infection

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

THE FDA HAS RECENTLY APPROVED ADEFOVIR DIPIVOXIL for the treatment of chronic hepatitis B in adults. This prodrug of adefovir is a nucleotide analog that was originally developed for the treatment of HIV infections but has also been found to be active against the hepatitis B virus. Adefovir dipivoxil is marketed as Hepsera by Gilead Sciences.

Indications

Adefovir is indicated for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevation of serum aminotransferases (ALT or AST) or histological active disease.[1]

Dosage

The recommended dose is 10 mg once daily. It may be taken without regard to meals.

Dosage reduction is recommended in patients with renal impairment and it is dosed based on creatinine clearance.[1] The dose should be 10 mg every 2 days for patients with a creatinine clearance of 20-49 mL/min, 10 mg every 3 days for creatinine clearance 10-19 mL/min, and 10 mg every 7 days for patients on hemodialysis.[1]

Potential Advantages

Adefovir appears to be effective in treating lamivudine-resistant strains and wild type of hepatitis B virus.[1,2] A mean reduction in serum hepatitis B virus (HBV) DNA of 3.11 ± 0.94 $\log_{10}$ copies/mL were reported in 59 patients with clinical evidence of lamivudine-resistant HBV compared to no decrease in patients who remained on lamivudine alone.[1] Adefovir appears to have a low potential to be involved in drug interactions involving cytochrome P450 isoenzymes.[1]

Potential Disadvantages

Adefovir is potentially nephrotoxic. The effect appears to be dose-related and is more likely in patients who are at risk for renal dysfunction, are currently renal impaired, or are taking concomitant nephrotoxic drugs. All patients on adefovir should be monitored for changes in renal function.[1]

Exacerbations of hepatitis have been reported in up to 25% of patients who discontinue adefovir. This usually occurs within 12 weeks after discontinuation.[1] The dose of adefovir for HBV is subtherapeutic for HIV. Patients should be offered HIV antibody testing to avoid emergence of resistant HIV due to unrecognized or untreated HIV infection.[1] Lactic acidosis has been reported with the use of nucleoside analogs. Obesity, prolonged use, and female sex appear to be risk factors.[1]

Comments

The approval of adefovir for the treatment of HBV infections was based on the results of 2 double-blind, randomized, placebo-controlled studies in 507 adults. The indications were based on histological, virological, biochemical, and serological response in HbeAg positive and negative patients as well as lamivudine-resistant hepatitis B patients with either compensated or decompensated liver function.[1] In one study, 329 subjects had HBeAg-positive chronic HBV, a median total Knodell Histology Activity Index (HAI) of 10, median serum HBV of 8.38 $\log_{10}$ copies/mL, a median ALT level of 2.3 time upper limits of normal (ULN), and 24% had previous interferon alpha therapy. Histological response with adefovir was 53% at week 48 compared to 25% for placebo. Histological improvement was defined as 2 or more points decrease in the Knodell necro-inflammatory score with no worsening of the Knodell fibrosis score. Adefovir resulted in a mean reduction in HBV DNA of 3.57 ± 1.64 copies/mL compared to 0.98 ± 1.32 for placebo. ALT normalization was 48% vs 16%, and HBeAg conversion was 12% vs 6%. The second study included 184 patients with HBeAg negative/HV DNA positive chronic HBV infection with a median total Knodell Histology Activity Index (HAI) of 10, median serum HBV of 7.08 $\log_{10}$ copies/mL, a median ALT level of 2.3 × ULN, and 41% had prior interferon alpha therapy. Histological improvement was 64% vs 35%, and mean reduction in serum HBV DNA was 3.65 ± 1.14 copies/mL compared to 1.32 ± 1.25 for placebo. ALT normalization was 72% vs 29%. Open-label studies suggest that adefovir is effective in pre- and post-liver transplant patients and those with clinical evidence of lamivudine-resistant HBV. Limited data suggest that treatment with adefovir may not lead to emergence of resistant virus after up to 60 weeks of therapy.[3] The primary limitations of adefovir therapy are nephrotoxicity and exacerbation of hepatitis upon discontinuation of therapy. Patients should be monitored periodically after discontinuation of therapy. The wholesale cost for 30 days of therapy is $440.

Clinical Implications

Chronic hepatitis B infection can be a life-long disease that can lead to cirrhosis, liver cancer, liver failure and ultimately death. The CDC estimates that about 1.25 million Americans have chronic HBV infections. Long-term control of viral replication is problematic. Current therapy includes interferon alpha-2b and lamivudine. Interferon is limited by side effects, need for parenteral administration, and toxicity in decompensated patients.[4] While lamivudine is given orally, is generally well tolerated, and can be used with hepatic decompensation, emergence of resistant strains is a major drawback—occurring in 15-32% of patients by 6 months.[4-6] Adefovir provides an oral alternative for the treatment of chronic hepatitis B infections, even if they are lamivudine-resistant. ■

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CME Questions

29. Which of the following regimens is not satisfactory for *Helicobacter pylori* eradication?

a. Bismuth, tetracycline, and metronidazole twice daily for 2 weeks.
b. Rabeprazole daily or other PPIs twice daily along with amoxicillin and clarithromycin twice daily for 1 week
c. PPI b.i.d. plus clarithromycin b.i.d. for 14 days
d. Rifabutin plus amoxicillin plus a PPI twice daily
e. Ranitidine bismuth citrate, clarithromycin, and amoxicillin or metronidazole daily for 7 days.

30. Which of the following is true for a 55-year-old man being prescribed pain medication?

a. Either ibuprofen or rofecoxib can be used; neither therapy offers additional myocardial risk.
b. Ibuprofen should be prescribed because ibuprofen, but not rofecoxib, is cardioprotective.
c. Rofecoxib at doses greater than 50 mg/d should be prescribed with caution, as this may increase the risk of cardiovascular death.
d. Rofecoxib may increase the risk of cardiovascular death, and this is independent of the dose that is prescribed.

31. Which of the following four statements is *false*?

a. The high amount-high intensity group had improvement in all the lipid fractions measured.
b. Women attain lower levels of fitness than men when given the same exercise prescription if the results are measured by maximum oxygen uptake.
c. Some of the changes in lipid metabolism can be explained by increases in muscle lipoprotein lipase.
d. Changes in HDL-C occur a few days after exercise is started.

By Louis Kuritzky, MD

Effects of Long-Term Treatment With ACE Inhibitors in the Presence or Absence of Aspirin

Both angiotensin converting enzyme inhibitors (ACEI) and aspirin (ASA) have a proven valuable track record in a variety of cardiovascular preventive and therapeutic areas. One of the mechanisms by which ACEI are believed to confer benefit is the production of vasodilatory prostaglandins, including PGI-2 and PGE-3. Since ASA can blunt production of prostaglandins, it is conceivable that the combination of the 2 might "cancel out" beneficial effects. To date, evaluation of large clinical trials in which both ASA and ACEI were used have provided conflicting data. Hence, Teo and associates undertook a systematic review of long-term randomized trials in which ACEI and ASA were coadministered (n = 22,060) for meta-analysis.

ACEI treatment in these trials (including the SOLVD treatment, SOLVD prevention, SAVE, AIRE, TRACE, and HOPE studies) produced overall a 22% reduction in major clinical outcomes. Concomitant use of ASA was not associated with a statistically significant diminution of benefit. Based upon this information, Teo et al suggest that for persons who are receiving either ACEI or ASA, if the other agent is indicated, clinicians may feel confident that the combination will not reduce beneficial effects. ■

Teo Koon K, et al. Lancet. 2002;360: 1037-1043.

Long-Term Risks Associated with Atrial Fibrillation: 20-Year Follow-up of the Renfrew/Paisley Study

Most of the studies of atrial fibrillation (AF) that address cardiovascular (CV) consequences provide only short-term or intermediate-term insight (6 months-24 months). Long-term consequences of AF are much less studied. Simon and colleagues evaluated CV outcomes (including hospitalizations and deaths) over a 20-year follow-up in 15,000 persons enrolled in Renfrew and Paisley, Scotland. The population was middle-aged (45-64 years) at enrollment.

At entry enrollment (1972-1976), 100 persons had AF. During the extended follow-up, women manifest a 5-fold increase in cardiovascular hospitalization or death, and risk in men was 2-fold increased. Lone AF (AF in the absence of discernible cardiovascular disease) did not confer a statistically significant increase in cardiovascular risk. The increase in CV risk associated with AF was expressed primarily as stroke and heart failure. This new information indicates substantial long-term risk from AF. Simon and colleagues suggest that strategies to prevent CHF, as well as those already commonly practiced for stroke prevention, may be of benefit in persons with AF. ■

Simon S, et al. Am J Med. 2002;113: 359-364.

Olfactory Impairment in Older Adults

Despite widespread attention to the demographics and management of hearing and visual impairments in older adults, there has been little study of olfactory impairments (OLF). Olfactory impairment can results in aggravation of nutritional problems, inability to respond promptly to risk situations such as fire or gas leaks, and reduce quality of life. To better determine the prevalence of OLF, Murphy and colleagues examined data from participants in the Epidemiology of Hearing Loss Study (n = 2491), a cross-sectional study of adults aged 53-97.

Initially, self-report of OLF was assessed by asking the question, "Do you have a normal sense of smell (compared to other people)?" Then, testing for OLF was performed using the San Diego Odor Identification Test (SDOIT), which uses natural home odors such as coffee and chocolate. OLF was defined as inability to identify at least 6 of 8 odorants.

One fourth of the tested population manifested OLF by SDOIT. On the other hand, only 9.5% of the population self-reported deficits in smell. A multiple logistic regression model determined that smoking, nasal congestion, stroke history, and epilepsy were associated with increased risk of OLF. ■

Murphy C, et al. JAMA. 2002;288:2307-2312.

What's Going On? (Part II)

By Ken Grauer, MD

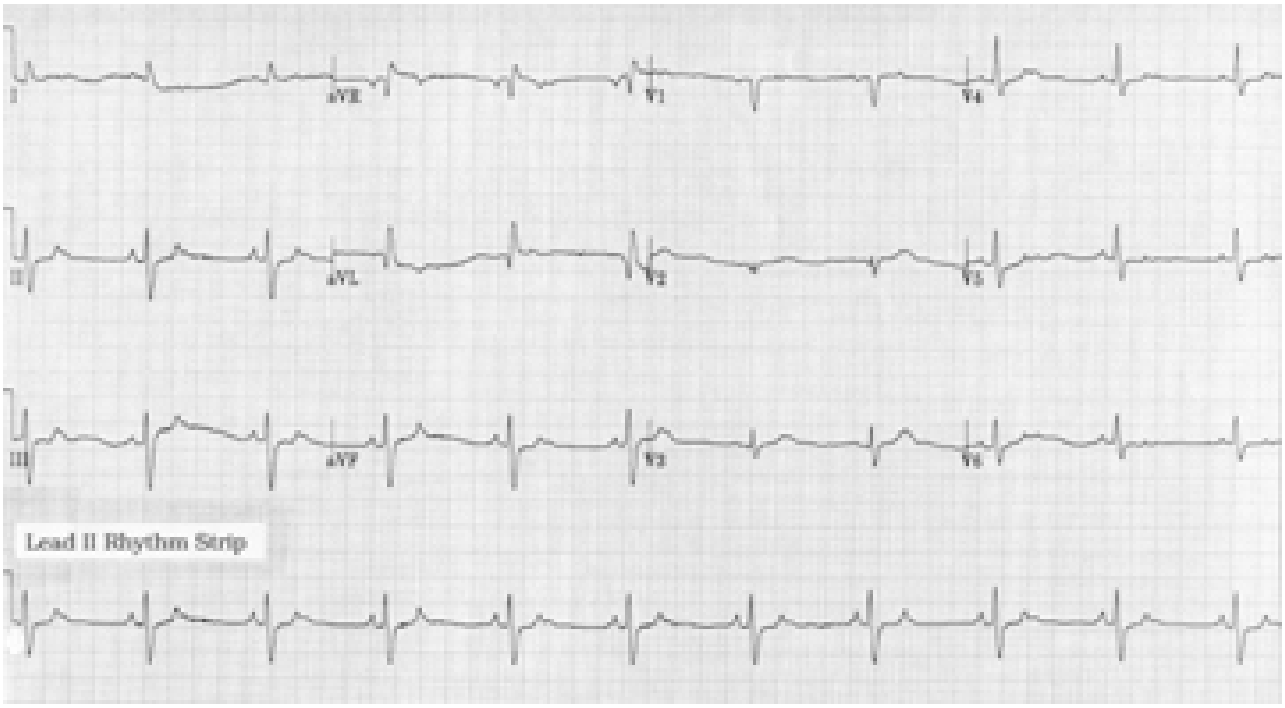

Figure. 12-lead ECG and lead II rhythm strip obtained from an 84-year-old man with acute dyspnea.

Clinical Scenario: The 12-lead ECG and accompanying rhythm strip in the Figure were obtained from an 84-year-old man who presented to the Emergency Department with acute dyspnea from pneumonia and heart failure. Can you account for the relatively slow heart rate despite his acute shortness of breath? (Hint: As was the case for the ECG review from November 15, the key to interpreting this tracing lies within QRST morphology of the lead II rhythm strip.)

Interpretation: QRS complexes occur at a regular rate of about 60 beats/minute in the rhythm strip. However, this is not simply a sinus rhythm. Close inspection of each T wave in the rhythm strip shows variable T wave packaging. This variation in T wave morphology is not the result of artifact. Instead, it represents slight variation in the time of occurrence of premature P waves that deform each T wave. The rhythm is therefore atrial bigeminy, in which each premature P wave occurs so early in the cycle that it is blocked. Thus, the primary problem responsible for the relatively slow heart rate despite this patient's acute dyspnea is atrial bigeminy. Correction of hypoxia and treatment of his heart failure addressed the substrate producing the frequent PACs, and the normal sinus rhythm at a more appropriate rate was restored. ■

In Future Issues:

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PHARMACOLOGY WATCH

FDA Approves Generic Version of AstraZeneca's Prilosec

The FDA has approved the first generic version of AstraZeneca plc's blockbuster drug, omeprazole (Prilosec). KUDCO, a subsidiary of Germany's Schwartz Pharma was granted the approval in a court ruling in mid-October. The FDA has cleared a number of other generic versions of the drug; however, this is the first, in the eyes of the courts, that does not infringe on patents held by AstraZeneca. In a complicated set of deals, KUDCO is partnering with Andrix Pharmaceuticals and Genpharm Inc to bring the drug to market by early 2003. Prilosec, with worldwide sales of more than $4 billion a year, has been the focus of intense legal wrangling as AstraZeneca has pulled all the stops to prevent marketing of generic forms of the drug. Meanwhile, consumer groups hoping to bring down the cost of prescription medications have been urging the Bush administration to speed generics, such as omeprazole, to market. The FDA has approved omeprazole for over-the-counter use but is still working with AstraZeneca on labeling language. Consumers can expect OTC Prilosec in the second quarter of next year.

Pegasys Approved To Treat Hepatitis C

A second pegylated interferon has been approved for the treatment of chronic hepatitis C infection. F. Hoffmann-La Roche Ltd's peginterferon alfa-2a (Pegasys) will compete with Schering-Plough's peginterferon alfa 2-b (PegIntron) for this indication. It is estimated that nearly 4 million Americans have evidence of infection with hepatitis C, of which nearly 3 million have chronic hepatitis C infection. In the last few years, standard treatment has become interferon either standard or pegylated, alone or in combination with ribavirin. Standard interferon must be given 3 times a week. Adding polyethylene glycol (PEG) to the interferon molecule increases the elimination half-life, allowing for less-frequent dosing, generally once a week. Pegasys is approved only as monotherapy; however, Schering-Plough has applied for approval of combination therapy with Pegasys and ribavirin. The FDA has fast-tracked the application, with final approval expected before the end of year.

HRT Reduces Alzheimer's Risk, Study Says

Yet another study has weighed in on the issue of hormone replacement therapy and the risk of Alzheimer's disease (AD). This study of a population of older adults in Cache County, Utah showed that 10 years or more of HRT significantly reduced the risk of Alzheimer's disease. Importantly, the study also showed that once women are in the early stages of Alzheimer's disease, it is too late for HRT to have any benefit. The rate of AD was evaluated in 1357 men (median age, 73.2 years) and 1889 women (mean age, 74.5 years). After a 3-year follow-up, women who formerly used HRT or women who are currently using HRT for longer than 10 years had a statistically significant reduction in the rate of AD (HRT users represented 26 cases/1066 women, non

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HRT users represented 58 cases/800 women [adjusted HR, 0.59; 95% CI, 0.36-0.96]). Almost all the HRT-related reduction in the incidence of AD was among women who had formerly used HRT. A related editorial suggests that there may be a critical period soon after menopause, which is characterized by rapid estrogen depletion, where HRT may provide the most neuroprotective benefit for women (*JAMA*. 2002;288:2123-2129, 2170-2173). In mid-October officials from the National Institutes of Health announced that they would continue to study the effects of HRT or conditions such as osteoporosis and AD. This announcement was important in light of the early termination of the Women's Health Initiative study on hormone replacement in July. Currently, the National Institute on Aging is funding 3 studies that will compare how well HRT combination therapy or estrogen alone helps prevent memory loss and loss of cognitive function in women older than 65.

Heparin Plus Alteplase More Effective

Patients with submassive pulmonary emboli (PE) will fare better treated with heparin plus alteplase compared to heparin alone, according to a new study. Alteplase, a thrombolytic agent, is commonly used in the treatment of massive PE. This study seeks to define the drug's role in submassive PE in hemodynamically stable patients. Two hundred fifty-six patients with PE and pulmonary hypertension or RV dysfunction but without arterial hypertension or shock were evaluated. One hundred thirty-eight received heparin plus alteplase 100 mg and 118 received heparin plus placebo. The primary end point was in-hospital death or treatment escalation (pressors, repeat thrombolysis, intubation, CPR, or emergency embolectomy). The primary end point occurred nearly 3 times as often in the heparin plus placebo group, all due to treatment escalation. In-hospital death was nonsignificantly higher in the heparin group, 3.4%, vs 2.2% for the alteplase group ($P = .71$). However, 30-day event-free survival was higher with heparin vs alteplase ($P = .005$). The authors conclude that thrombolytic therapy with alteplase plus heparin should be considered in patients with submassive PE (*N Engl J Med*. 2002;347:1143-1150).

Digoxin Effects Differ By Sex

Digoxin should be used with caution in women with heart failure and may even be associated with an increase in mortality, according to a new study. The Digitalis Investigation Group looked at 6800 patients on digoxin therapy with the primary end point being mortality from any cause. While there was no increased mortality in men on digoxin, women on the drug had a higher rate of death compared to the placebo group (33.1% vs 28.9%, respectively; 95% CI,-0.5-8.8). The authors conclude that the effect of digoxin therapy differs between men and women. Women with congestive heart failure of a higher mortality rate associated with use of the drug, while the same is not seen with men (*N Engl J Med*. 2002;347:1403-1411).

McClellan Named FDA Commissioner

The Food and Drug Administration finally has a commissioner, after 2 years of vacancy in the position. The new commissioner, Mark McClellan, MD, was approved quickly and unanamously. He has a background in both medicine and economics, and has been an advisor to both Presidents Clinton and Bush. He has most recently been a professor of medicine and economics at Stanford University. Dr. McClellan joins the FDA at a time of unprecedented change and turmoil. There is high turnover at the agency, and criticism from consumer groups that drug approvals take too long on the one hand, and are too cursory on the other. President Bush has recently backed removing legal obstacles to the approval of generic drugs, a move meant to reduce prices for consumers, and a move that is not popular with Pharma.

FDA Actions

The FDA has approved 2 formulations of buprenorphine, a new schedule III narcotic for treatment of patients with narcotic addiction. Buprenorphine will be marketed as Subutrex by Reckitt Benckiser pharmaceuticals, while the second preparation, which combines buprenorphine with naloxone, will be marketed by the same company as Suboxone. The combination with naloxone is intended for maintenance therapy since naloxone will safeguard against intravenous abuse. The FDA took the unusual step of putting buprenorphine into the schedule III category rather than schedule II to allow easier prescribing in compliance with recent congressional legislation making maintenance narcotics more available to patients.

Bristol-Myers has received approval to market Metaglip, a new combination drug for treatment type 2 diabetes. Metaglip combines gliptizide and metformin in a single tablet for initial therapy of type 2 diabetes. ■

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By Louis Kuritzky, MD

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Daily Vitamin E and Multivitamin-Mineral Supplementation and Acute RTI in Elderly Persons

Source: Graat JM, et al. *JAMA*. 2002;288:715-721.

Vitamin supplementation has been shown to improve cellular immune parameters, but whether vitamin E or multivitamins/minerals (MVIM) have an effect on clinical events has not been clearly elucidated. Since respiratory tract infections (RTI) may become especially consequential for senior citizens, the question of whether vitamin E or MVIM alter the frequency, severity, or duration or such infections is of great clinical relevance.

Graat and associates studied the effect of MVIM, containing traditional RDA levels of multiple vitamins and minerals, including zinc, selenium, iron, magnesium, copper, iodine, calcium, manganese, chromium, molybdenum, and silicium, as well as a separate vitamin E supplement of 200 mg. Study subjects (n = 652) were comprised of noninstitutionalized persons older than age 60 who were followed for 15 months. At baseline, a very small proportion of individuals had suboptimal serum levels of either ascorbic acid (6%) or alpha-tocopherol (1.3%).

MVIM supplementation demonstrated no clinically or statistically significant effect upon RTI incidence, severity, duration, number of symp toms, or restriction of activity. Vitamin E supplementation demonstrated worse outcomes than placebo in reference to illness severity, duration, symptoms, fever, and restriction of activity. Graat et al caution that not only do their data discourage employment of MVIM due to lack of efficacy, but also due to a deleterious effect of vitamin E. ■

B-Type Natriuretic Peptide Levels and Outcome in Patients with Heart Failure

Source: Bettencourt P, et al. *Am J Med*. 2002;113:215-219.

Brain natriuretic peptide (BNP) levels reflect the degree of cardiac ventricular wall stress and are useful to diagnose chronic heart failure (CHF), as well as differentiate other dyspnea syndromes (in which BNP levels are not elevated) from CHF. BNP levels correlate with severity of CHF, hence, in any one episode of CHF, their degree of elevation might provide prognostic information. Bettencourt and colleagues examined the relationship between hospital BNP levels (on admission and discharge) in persons with acute decompensation of CHF, and subsequent hospital CHF readmission or death.

All subjects (n = 43) received "standard" CHF treatment, including diuretics (furosemide, and in some cases, spironolactone) and ACE inhibitors. Subjects were followed for 6 months.

When patients were hospitalized for CHF, BNP levels typically decreased with treatment. After hospital discharge, in the group that remained event free during follow-up, the decline in BNP during hospitalization (47%) was much more substantial than the decline in persons who required readmission (17%). Patients whose BNP increased during the index admission were more than 3 times more likely to require readmission or die during follow-up. BNP, and its response to treatment, provides important prognostic information in persons with CHF. ■

Companion Influence During Primary Care Medical Encounters

Source: Schilling LM, et al. *J Fam Pract*. 2002;51:685-690.

It is commonplace in primary care settings for patients to be accompanied by family, friends, or caretakers in the examining room during some portion or all of the clinician-patient interaction. The effect of the "third person" (3P) has received little literature scrutiny. Schilling and colleagues studied 226 adult medical encounters, approximately half of which included another accompanying adult who spent any portion of the visit in the examining room. Patients, companions, and clinicians rated the influence of the companion upon the visit. Aspects of the clinical encounter that were monitored included physician understanding, patient understanding, counseling time, length of visit, treatment, referrals, and number of tests ordered.

Physicians reported that having a companion present generally was either neutral to or increased physician and patient understanding. Almost universally, physicians perceived no effect upon treatments, referrals, or number of tests ordered whether a companion was present. On the other hand, 25-32% of physicians felt that the 3P caused an increase

in the length of visit or time spent counseling. Although overall the presence of an adult companion may enhance physician and patient understanding, it appears to be potentially at the expense of greater time required for counseling and the visit itself. ■

Efficacy of Handrubbing with Alcohol-Based Solution vs. Standard Handwashing with Antiseptic Soap: Randomized Clinical Trial

Source: Girou E, et al. *BMJ*. 2002; 325:362-365.

Handwashing (HWS) is generally recognized as the single most influential factor to reduce transmission of nosocomial infections. Unfortunately, studies indicate that half or less of clinicians comply with appropriate HWS recommendations. Despite interventions to increase adherence with handwashing (eg, more sinks, educational programs), results have been disappointing. Although handrubbing with alcohol (HRA) is suggested as an alternative to HWS, its acceptance has been impeded by lack of clinician confidence that an alcohol based, waterless hand antiseptic is sufficiently effective in reducing bacterial contamination.

Girou and associates performed a prospective, randomized, blinded trial in 3 intensive care units. Subjects (health professionals) were randomly assigned to chlorhexidine 4% (Hibiscrub) or handrubbing with an alcohol- based solution. Hand cultures were performed immediately before, and 1 minute after cleansing.

Both maneuvers were effective in reducing bacterial contamination, but HRA was substantially more effective (83% vs 58% reduction in contaminating bacteria). HWS and HRA occupied essentially the same mean amount of time (about 30 seconds). Previous in-vitro studies have shown that HRA is more effective than soap. Incorporation of HRA may enhance control of nosocomially transmitted infections but may require enhanced clinician education for endorsement. ■

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A Program To Prevent Functional Decline in Physically Frail, Elderly Persons Who Live at Home

Source: Gill TM, et al. *N Engl J Med*. 2002;347:1068-1074.

Most literature that addresses restoration of function in elders focuses upon rehabilitation of persons who have recently suffered a morbid event, such as a stroke or hip fracture. Whether other frail elders might benefit from 'prehabilitation' strategies is little studied. To that end, Gill and colleagues recruited a population (n = 188) of seniors (> age 75) who were defined as "frail" by means of a rapid-gait test and a mobility test (ability to rise from a chair with arms folded).

The intervention program included instructions in safe techniques for moving in bed and outdoors, gait training, removal of environmental hazards (eg, loose rugs, cords, clutter) and installation of adaptive equipment in bathrooms. Interventions were monitored for 16 visits over 6 months, with last follow-up at 12 months.

The recipients of the home intervention had significantly less disability and less admission to a nursing home. Interventions included the service of a physical therapist, but the entire mean cost of intervention, including equipment and supplies, was $1998 per participant. The subjects who suffered severe disability at baseline continued to experience deterioration over time, despite receiving the same interventions. Gill et al comment that though the frequency of physical therapy visits is in excess of that allowed for reimbursement by Medicare, the overall cost-per-patient is comparatively moderate. ■

Treatment of Chronic Painful Diabetic Neuropathy with Isosorbide Dinitrate Spray

Source: Yuen KCJ, et al. *Diabetes Care*. 2002;25(210):1699-1703.

Painful diabetic neuropathy (PDN) is a troublesome and often refractory clinical dilemma. Nitric oxide (NO) production is impaired in PDN and is suspected of playing a pathogenetic role in producing pain and burning. All clinical formulations of nitrates are NO donors. Based upon anecdotal observations that individual PDN patients reported a favorable effect of isosorbide dinitrate (ISDN) spray on pain symptoms, Yuen and colleagues initiated a formal clinical trial.

Patients (n = 22) had all suffered chronic PDN and had failed traditional treatments, such as acetaminophen, amitriptyline, or gabapentin, either due to lack of efficacy, intolerance, or both. The trial was structured such that patients received either 40% propylene glycol (placebo) or 30 mg isosorbide dinitrate (1 spray) QHS in a double-blind crossover fashion for 2 sessions of 4 weeks each, punctuated by a 2-week washout period.

Use of ISDN spray produced a statistically significant reduction in pain and burning. Side effects (transient headache) were mild. ISDN may be of value in treatment of PDN, perhaps through a mechanism of increased delivery of NO. ■