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INSIDE

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Internal Medicine Alert's editor, Stephen Brunton, MD, is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and Astra-Zeneca, and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

Sudden Cardiac Death

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD

Synopsis: *The authors attempt to redefine SCD by concluding that it uncommonly or even rarely occurs "suddenly out of the blue" without any premonitory symptoms.*

Source: Zipes DP, et al. Neural modulation of cardiac arrhythmias and sudden death. *Heart Rhythm.* 2006;3:108-113.

Clinical Professor of Medicine, UCLA School of Medicine

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

SUDDEN CARDIAC DEATH (SCD) IS DEFINED AS UNEXPECTED death due to cardiovascular causes occurring in a person with or without pre-existing heart disease within one hour after onset of change in clinical status.[1] The mechanism of death in most episodes of SCD is due to ventricular tachycardia which degenerates into ventricular fibrillation (VF). Sixty to 80% of episodes of SCD occur in patients afflicted with coronary artery disease and most of the other cases are due to nonischemic cardiomyopathy, infiltrative and/or inflammatory cardiac diseases or acquired valvular heart disease.[2] Finally, a small number of episodes of SCD occur in individuals with genetic abnormalities such as hypertrophic cardiomyopathy, congenital heart defects such as anomalous coronary arteries, and rarely in patients with Brugada syndrome or catecholaminergic ventricular tachycardia.

Despite widespread advances in the diagnosis and treatment of ischemic heart disease, SCD remains the major cause of death in the industrialized nations. It accounts for more than 300,000 deaths per year in the U.S. alone, which is approximately 20% of all deaths.[2] Classically, SCD occurs quite suddenly, is unexpected and seemingly is random in nature and, as a result, early detection efforts have always focused on the individuals at highest risk (especially the subset of SCD patients without overt signs or symptoms of cardiac disease) looking for evidence of cardiac disease.[3]

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Searching for preventative measures for SCD, Muller and his colleagues[4] collected information on cases of out-of-hospital SCD in the Berlin, Germany, emergency medical system via a questionnaire. In addition, bystander interviews were performed by an emergency physician who was staffed in a physician-manned mobile intensive care unit or a rescue helicopter both of which were connected with a single central hospital (Universitatsmedizin Berlin) which serviced approximately 10% of the 3.5 million inhabitants of Berlin. For the present study, SCD was defined as sudden unexpected arrest of presumed cardiac origin in adults over the age of 18, such arrest having occurred within 24 hours after onset of any symptoms which could retrospectively be interpreted as being of cardiac origin. Patients with symptoms of longer duration or which were clearly of non-cardiac origin were excluded from the analysis. Of 5831 rescue missions, 406 involved patients with presumed cardiac arrest and 274 of these were witnessed. Typical angina was present for a median of 120 minutes in 25% of the witnessed SCD episodes and 33% of episodes during which patients had a symptom duration of less than one hour. SCD was found to occur more often at home in the presence of relatives and after a significant period of typical symptoms.

COMMENTARY

Muller's conclusion[4] that 72% of SCD events occurred at home is consistent with previous data reported from United States.[5] Although 25% of episodes occurred in totally asymptomatic patients, symptoms of angina followed by dyspnea, nausea/vomiting, and/or dizziness/syncope occurred for varying degrees of time in the remainder of the patients. Patients who suffered SCD at home tolerated the symptoms longer (75 minutes) than did those patients who were in public areas (20 minutes). Symptoms were tolerated for a median time of 60 minutes (range 10-380 minutes) before collapse occurred and the authors concluded that, in this particular study population, signs and symptoms which could herald the onset of SCD were present often for a significant period of time. As was noted in previous reports,[6] patients were more likely to survive when SCD occurred in public places where emergency medical services had faster access and where patients were more likely to receive bystander CPR. It should be recognized that the statistical conclusions of this study may be somewhat flawed because, in 148 of the 554 cases of nontraumatic episodes of SCD, the emergency physician was called off by first-arriving emergency medical technicians equipped with a defibrillator because of apparent signs of irreversible death, and only the age and sex of these patients were registered—no additional information was obtained on this group of patients. In addition, although they redefined SCD by allowing a long symptom duration of 24 hours, when they applied stricter definitions than those used in their study, the results apparently did not change significantly.

The authors have attempted to redefine SCD by concluding that it uncommonly or even rarely occurs "suddenly out of the blue" without any premonitory symptoms. If they are correct, the majority of episodes of SCD are avoidable or more likely to be resuscitated if premonitory symptoms are recognized and earlier treatment is initiated. Finally, and most important, because the majority of episodes of SCD occurred in domestic settings and in the presence of relatives, the authors stress the importance of training patients and relatives to recognize warning signs and symptoms and to react accordingly.

Relatives who are more likely to be witnesses of SCD should at least learn to perform basic life sup-

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port since most programs that aim to encourage the use of automatic defibrillators and early defibrillation focus mainly on public places. Of course, as the cost of automatic defibrillators decrease and efficiency/efficacy improve, it almost certainly would pay to consider installing AICD units in homes of patients who are at high risk of developing SCD. Appropriate training and recognition programs should be implemented in order to lead to earlier recognition of patients at risk of SCD, and thereby encourage more rapid contact of emergency medical services, all of which will result in a higher percentage of bystander CPR leading to a higher probability of survival in patients with SCD. ■

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Statins for Heart Failure

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speakers' bureau for Merck, Pfizer, and Parke-Davis.

Synopsis: *Among adults diagnosed with heart failure who had no prior statin use, incident statin use was independently associated with lower risks of death and hospitalization among patients with or without coronary heart disease.*

Source: Go AS, et al. Statin Therapy and Risks for Death and Hospitalization in Chronic Heart Failure. *JAMA*. 2006;296:2105–2111.

YET ANOTHER OBSERVATIONAL STUDY HAS BEEN published that strongly suggests the value of concomitant statin treatment in a medical condition that is not clearly related to dyslipidemia. Because of prior reports in the literature regarding the favorable effect of statin utilization in patients with heart failure (in non-randomized or prospective trials), Go and colleagues from the Kaiser Permanente of Northern California Group, initiated an elaborate observational protocol in an attempt to identify whether statin treatment in patients with congestive heart failure is or is not beneficial. The medical records of almost 10,000 patients were carefully reviewed and a wide variety of potential confounding factors, ie, drug therapy, socio-economic status, were collected. The study only utilized data regarding the incidence of statin use in patients who were not receiving a statin at the study entry date, and who were eligible for treatment based on the national guidelines. The authors controlled for a wide variety of medications used in the treatment of heart failure; data on race and ethnicity were included. Renal dysfunction and multiple other diagnoses were assessed using ICD-9 codes, laboratory data, etc. Left ventricular function was obtained from health plan databases. Reduced left ventricular systolic function was defined as an LV ejection fraction of < 40% or a designation of moderate or severely reduced systolic function; preserved LV function was defined by an LVEF of > 40% or a qualitative statement of "only mildly reduced systolic function." Enrollment in the database could occur at any time during the 9 year window. A wide variety of statistical techniques were utilized, and many baseline demographic characteristics were identified. Twenty-five thousand adults with CHF and no prior statin use were identified and considered eligible for lipid-lowering therapy. During follow-up, half of these individuals initiated statin therapy; these patients tended to be younger and male, but no other clinical differences were noted. There was a higher prevalence of coronary heart disease (CHD), diabetes, and hypertension in those individuals initiating statin therapy during the observational period. Baseline use of multiple drugs used for heart failure therapy and other lipid-lowering drugs were also higher among patients who initiated therapy during the study period.

Median follow-up was 2.4 years, during which time 8,200 patients died and 9,200 patients were hospitalized for CHF. Age- and gender-adjusted rate of death was substantially lower in the statin therapy group, 14.5 per 100 person years vs 25.3 per 100 person years. Known CHD did not affect the data. Rates of hospitalization for heart failure were lower in those who began statin therapy vs those who did not, 21.9 per 100 person years vs 31.1 per 100 person years, $P < 0.001$. In the primary analysis (inten-tion to treat analysis), incident statin use was associated with a 24% lower relative risk of death compared to patients not taking a statin, even after adjustment for multiple co-morbidities, socio-economic factors, etc. In a secondary, time-dependent, exposure analysis, the risk of death was even greater than in the primary analysis, with a hazard ratio of 0.66. Hospitalizations for CHF were 21% lower using the intention to-treat approach.

The authors comment on theoretical benefits as well as adverse effects of statins. Two studies are cited that come to the same conclusion. However, "the present study attempts to overcome many … methodological challenges" that are related to the wide variability of data collection in other reports. The authors emphasize that the Kaiser population was "large and socio-demographically diverse," including patients diagnosed with CHF in and out of the hospital. Efforts were made to improve the power of this observational study. "Overall, statin therapy remained a robust predictor of improved outcomes." The authors stress that they could not exclude residual confounding or selection bias, despite a wide number of adjustments for many population characteristics. They note that limited other experimental data are available, and that randomized trials have utilized relatively small sample sizes and had mixed results. They point out that several very large prospective randomized trials will be available in the future to resolve this issue and to "clarify the role of statins in the management of heart failure."

COMMENTARY

This study fits in with many reports in a variety of conditions that indicate individuals who are on a statin have lower morbidity and mortality rates than those not exposed to a statin. These data sets are observational in nature. It is unclear whether overall physician treatment in statin-treated patients is different (ie, better) compared to those not exposed to statins. The increased use of appropriate congestive heart failure therapy in the statin group suggests that this may be a factor; that is, that care in general was better and more evidence-based in the statin group. There are a variety of intracellular effects of HMG CoA reductase therapy, known a pleiotropic actions. Thus, endothelial funtion and nitric oxide availability are improved, cytokines and other inflammatory markers are diminished, and coronary plaque may be stabilized by statins. This report adds to a wide variety of data in the literature that come to the same conclusion, although with widely disparate diagnoses. Clearly, at the very least, physicians should pay particular attention to current lipid guidelines, and make sure that congestive heart failure patients are appropriately treated, particularly for LDL cholesterol lowering, and that individuals with heart failure should not to be considered ineligible, or poor statin candidates, because of their primary illness. ■

Influenza A Responds to Tamiflu® Better Than Influenza B

SPECIAL REPORT

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper reports no financial relationship relevant to this field of study.

Source: Kawai N, et al. *Clin Infect Dis.* 2006:43:439–444.

To evaluate the effectiveness of oseltamivir for influenza, it was administered to 1818 patients with Influenza A and 1485 patients with Influenza B, all of whom were being seen in an "usual clinical setting" in 9 different community clinics in Japan. The patients were grouped by age and by time of onset of fever to the time of administration of the first dose of oseltamivir. A small number of patients who did not take the drug was used as a comparator group.

Not surprisingly, patients who received no treatment had a significantly longer duration of fever compared with treated patients with Influenza A (82 hrs vs 48 hrs) or Influenza B (78 hrs vs 65 hrs, respectively) (both groups, $P < 0.001$). The duration of fever after receipt of the drug was similar regardless of age or the timing of the first dose of drug,

with one exception. Patients aged 7–15 years had a somewhat shorter duration of illness, although this difference was arguably not clinically significant (~4 hrs).

What was somewhat surprising was the finding that for those who received treatment, the duration of fever following administration of oseltamivir was significantly shorter for patients with Influenza A compared to those with Influenza B. This statistically significant difference was found for all age groups, regardless of the timing of administration. For example, comparing patients with Influenza A or B, the mean duration of fever after receipt of thefirst dose of oseltamivir was 32 hrs vs 48 hrs, respectively, for those who received the drug within 0–12 hrs. Similarly, the mean duration of fever after the 1st dose of oseltamivir in patients with Influenza A vs Influenza B was 32 hrs and 45 hrs, respectively, for those who received the drug within 27–48 hrs of onset of symptoms.

In addition, isolation of virus at the completion of treatment was significantly more frequent in patients with Influenza B than Influenza A (52% vs 16%, $P < 0.001$).

These data confirm that oseltamivir is more effective against infection with Influenza A vs Influenza B, although the difference may not be especially clinically meaningful. ■

Pharmacology Update

Arformoterol Tartrate Inhalation Solution (Brovana™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

Arformoterol (R,R-formoterol) is a single isomer form of racemic (RR, SS) formoterol approved for the treatment of chronic obstructive pulmonary disease (COPD). This isomer shows high selectivity for the Beta 2-adrenergic receptor relative to Beta 1-adrenergic receptors. Arformoterol is administered twice a day and is characterized as a long-acting beta2 agonist (LABA). It is marketed by Sepracor, Inc as Brovana.

Indications

Arformoterol is indicated for maintenance therapy of bronchoconstriction in patients with COPD,including chronic bronchitis, and emphysema.[1]

Dosage

The recommended dose is 15 mcg administered twice daily (morning and evening) by nebulization using a standard jet nebulizer connected to an air compressor.

Arformoterol is supplied as 2 ml vials each containing 15 mcg of arformoterol.

Potential Advantages

Arformoterol has greater selectivity for Beta 2 adrenergic receptors than the other isomers or the racemic mixture. The inactive (S,S) isomer has been reported to paradoxically increase airway reactivity.

Potential Disadvantages

Arformoterol requires administration through a nebulizer machine. As with other long-acting beta agonist, arformoterol may increase the risk of asthma-related deaths. Decrease in bronchodilatory effect (tachyphylaxis) has been observed after 6 weeks of therapy.[1]

Comments

Arformoterol is the first long-acting beta agonist to be approved as a solution for administration by a nebulizer machine. Efficacy of the 15 mcg dose was demonstrated in two, 12-week, double-blind, placebo-and-active controlled, randomized parallel groups studies in the United States (n = 581). Eighty percent of these study subjects had bronchodilator reversibility as defined by a 10% or greater response in FEV^1 to albuterol. Arformoterol at 15 mcg twice daily significantly improved bronchodilation (FEV1) compared to placebo.[1] Over the first 6 hours the placebo-subtracted change in FEV^1 was approximately 0.2L. Effect was maintained over 12 weeks; however, the difference declined to 0.15L. Peak effect occurs at 1-3 hours. Even though salmeterol was included as an active comparator, comparative data were not reported. Adverse events that exceeded placebo included pain (8% vs. 5%), back pain (6% vs. 2%), diarrhea (6% vs. 4%), dyspnea, rash,

leg cramps (each 4% vs. 2%), and flu-like syndrome (3% vs. 1%). Dose-related events included asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor.[1] Currently there are no published clinical studies on arformoterol. The product is expected to be available the 2nd quarter of 2007 and cost is not available at the time of this review.

Clinical Implications

COPD is the fourth most common cause of death in the U.S.[3] In 2004, 11.4 million U.S. adults were estimated to have the disease. Bronchodilators are the mainstay of therapy. These include short-acting beta2 agonists, anticholinergics (ipratropium, tiotropium), and long acting beta2 agonists. While none of these affect disease progression, they reduce symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve quality of life.[4] There are no published comparative trials among different LABAs. Arformoterol is the first LABA approved as a solution for nebulization for the treatment of COPD. Clinical benefits directly related to the pure (R,R) isomer remains to be determined. ■

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CME Questions

1. **Sudden cardiac death (SCD) as defined by Muller and his colleagues:**
   a. Occurs uncommonly or even rarely "suddenly out of the blue" without any premonitory symptoms.
   b. Occurs predominantly in public areas.
   c. Were more likely to survive if SCD occurred at home rather than in public areas.
   d. Typical angina pectoris occurred only infrequently

2. **Statins may reduce mortality in patients with:**
   a. ischemic cardiomyopathy.
   b. idiopathic dilated cardiomyopathy.
   c. hypertrophic cardiomyopathy.
   d. A and B

Answers: 1 (a); 2 (d)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Lumbar Disk Herniation: Is Surgical Treatment Superior to Conservative Management?

THE SPORT (SPINE PATIENT OUTCOMES Research Trial) trial enrolled over 1,000 adults with lumbar disk disease-herniated disk, spinal stenosis, or spondylolisthesis-to compare outcomes between persons who were assigned to surgical treatment vs medical therapy. All study subjects underwent imaging to confirm pathology consonant with symptoms (97% had MRI).

The surgical intervention performed was open discectomy; medical therapy included exercise, education, and use of NSAIDs. The primary outcome measures were body pain and physical function (as measured on the SF-36) and degree of disability (as measured by the American Academy of Orthopedic Surgeons Oswestry Disability Index). End points were assessed at baseline, 3 months, 1 year, and 2 years.

For primary end points (by intention-to-treat analysis) there was no statistically significant difference between groups at any point during the study period. Although this would seem to confirm that surgery does not have advantage over conservative treatment, it must be recognized that the intention-to-treat analysis used in this trial does not necessarily function well because a large number of persons (40-45% in either group) originally assigned to one intervention ultimately crossed over to receive the other; ie, many patients randomized to surgery did not ultimately receive it, and vice versa. If one just looks at the data from the perspective of dividing the population into the treatment they actually received, outcomes favored surgery, but this does not reflect the original randomization process, and is hence subject to confounding. ■

Weinstein JN, et al. JAMA. 2006;296:2441-2450.

Rimonabant: An Answer to Obesity in Diabetes?

OBESITY IS A CAUSE, CONCOMITANT, and consequence of diabetes. Clearly, overweight status increases the likelihood of developing diabetes, and is present at the time of diagnosis in most type 2 diabetics. Similarly, pharmacotherapy is often associated with weight gain, and diabetic consequences such as painful neuropathy may result in reduced activity levels, further exacerbating weight control dilemmas. Some weight loss agents such as orlistat (xenical) have shown favorable effects in diabetic subjects, but may be limited by tolerability.

Rimonabant (RBT) has been shown to produce statistically significant weight loss in non-diabetic overweight and obese subjects. Additionally, the weight loss has been noted to impact the critical abdominal visceral fat compartment. Scheen, et al, investigated the impact of RBT in overweight diabetic subjects.

Overweight/obese subjects with type 2 diabetes (n = 1,047) were randomized to receive RBT or placebo. All subjects were counseled in regard to diet and exercise, and followed for 1 year.

RBT at 5 mg/d or 20 mg/d was superior to placebo for weight loss at 1 year (2.3 kg or 5.3 kg vs 1.4 kg, respectively). RBT has shown a statistically significantly greater weight loss than diet and exercise alone in type 2 diabetics. ■

Scheen AJ, et al. Lancet. *2006;368:1660-1672.*

Renin Inhibitors: A new Class of Antihypertensive Agents

DESPITE A DIVERSE ARRAY OF ANTIhypertensive agents, less than half of Americans with hypertension (HTN) are aware of their condition, on treatment, and controlled to a BP of less than 140/90. New treatments, hence, are welcomed.

Aliskiren (ALISK) is the first potential member of a new class of oral agents: renin inhibitors. Although drugs like ACE inhibitors and ARBs impact the renin-angiotensin-aldosterone system, they typically induce a compensatory increase in renin. Combination of ACE/ARB and ALISK, on theoretical grounds, is sensible and appealing. Vaidyanathan et al report on four open-label studies (n = 87) evaluating the efficacy, safety, and tolerability of ALISK in combination with a representative agent from each of the 4 most commonly used antihypertensive classes: calcium channel blocker (amlodipine), ARB (Valsartan), diuretic (HCTZ), and ACE inhibitor (ramipril). It was anticipated that ALISK was unlikely to have significant drug interactions, since it is hepatically eliminated unchanged (ie, no p450 interactions), does not inhibit p450 enzymes, and is not highly protein bound.

ALISK therapy was not associated with any clinically relevant tolerability or safety issues. Mild headache, dizziness, and GI symptoms were reported, but differed minimally from adverse effect profiles seen with the other classes of agents when used as monotherapy. ALISK is currently pending FDA approval. ■

Vaidyanathan S, et al. Int J Clin Pract. *2006;60:1343-1356.*

Why is the QRS Changing?

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*
Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.
Dr. Grauer reports no financial relationship to this field of study.

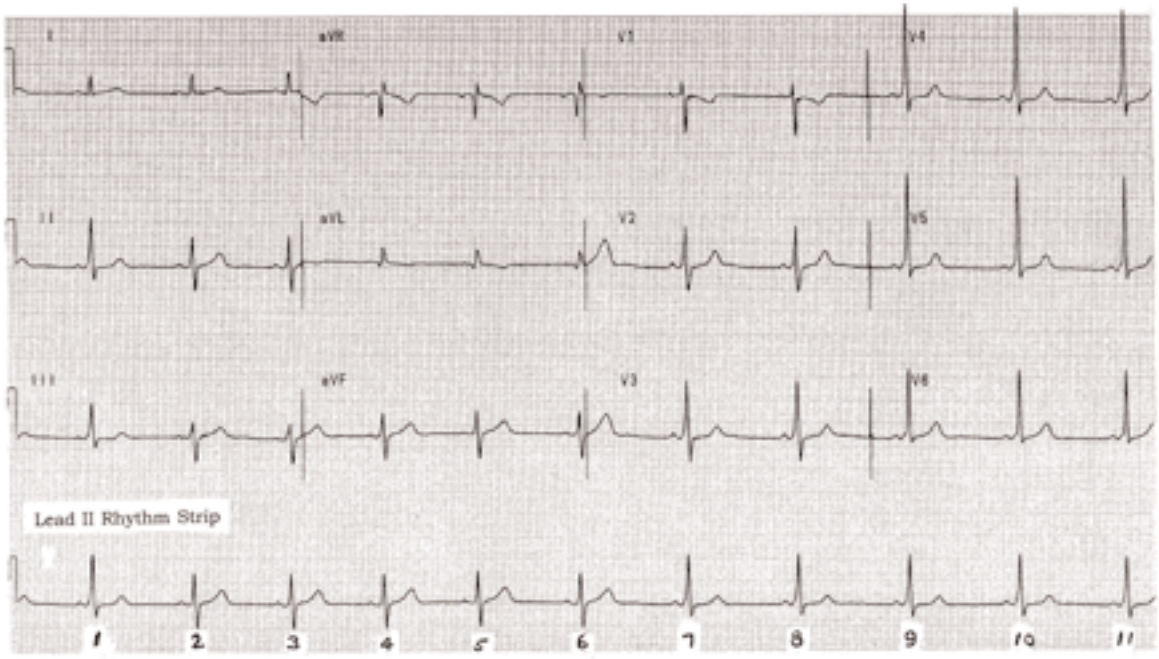

Figure. 12-lead ECG and lead II rhythm strip obtained from a mentally challenged 37-year-old prior to exercise testing.

Clinical Scenario: The ECG in the Figure was obtained from a mentally challenged 37-year-old man, who had been complaining of atypical chest pain. He was scheduled for an exercise treadmill test (ETT). Can you explain the "changing QRS" in the lead II rhythm strip of his pre-test baseline ECG? Will a stress test provide useful information?

Interpretation/Answer: As per the title of this ECG Review, the morphology of the QRS complex in the lead II rhythm strip at the bottom of the tracing is clearly changing! The QRS complex of beat #1 is predominantly positive (an Rs complex). It is biphasic (an RS complex) for beats #2 through 6, and then again becomes predominantly positive (Rs) for the rest of the tracing. Although there is slight variability in the P-P interval, consistent with sinus arrhythmia — the remarkable finding is the change in the PR interval. Slurring of the initial portion of the QRS complex of beats #7 through 11 results in PR interval shortening. The picture becomes clearer with inspection of simultaneously recorded leads V4 through V6. Thus, the patient has WPW (Wolff-Parkinson-White) syndrome, with intermittent conduction down the normal pathway (beats #2 through 6), alternating with conduction down the accessory pathway. Within the first 3-minute stage of exercise testing, the patient developed consistent conduction down the accessory pathway. This invalidated interpretation of any subsequent ST segment changes with exercise. The test was therefore stopped, and the patient referred for stress echocardiography to better assess the likelihood of coronary disease. ■

In Future Issues: Antipsychotics in Alzheimer's Patients

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This issue of your newsletter marks the start of a new continuing medical education (CME) or continuing nursing education (CNE) semester and provides us with an opportunity to review the procedures.

Internal Medicine Alert, sponsored by AHC Media LLC, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

Upon completing this program, the participants will be able to:

1. describe new findings in differential diagnosis and treatment of various diseases;
2. describe controversies, advantages, and disadvantages of those advances;
3. describe cost-efficient treatment regimens; and
4. describe the pros and cons of new screening procedures.

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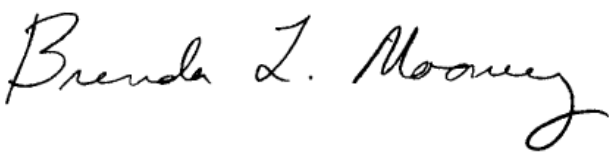

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Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Study: Long-Term Use of Clopidogrel for DES Patients

Patients with coronary artery disease who have received intra-coronary, drug-eluding stents (DES) may benefit from longer courses of clopidogrel than is currently standard. Researchers at Duke looked at 4,666 patients undergoing percutaneous coronary interventions with bare metal stents (BMS) (n = 365) or DES (n = 1501). Patients were followed up at 6, 12, and 24 months with the main outcomes being death, non-fatal MI, and the composite of death or MI at 24-month follow-up. For patients who received DES and were event free at 6 months, use of clopidogrel was a significant predictor of fewer events at 24 months (death rate 2.0% with clopidogrel vs 5.3% without , P = 0.3; death/MI 3.1% vs 7.2%, P = 0.02). However the same was not seen for BMS patients, with no significant difference in death rate or death/MI in the patients who took clopidogrel. For DES patients who were event free at 12 months, use of clopidogrel continued to improve outcomes (death rate 0% with clopidogrel versus 3.5% without, P = .004; death/MI 0% versus 4.5%, $P <$ 0.001). For patients with BMS who were event free at 12 months, use of clopidogrel was still not associated with any change in death rate (3.3% vs 2.7% P = 0.57) or death/MI (4.7% 3.6%, P = 0.44). The authors conclude that extended use of clopidogrel in patients with drug-eluding stents may reduce the rate of death and MI. However the appropriate duration of clopidogrel administration has not yet been determined. (*JAMA* early release article posted 12/05/06). Implications of the study are significant in that current recommendations following PCI with drug eluting stents is for 3 to 6 months of clopidogrel. Several studies have shown that these stents have increase risk of catastrophic stent thrombosis, higher than bare metal stents, months after the procedure. This has led some experts to recommend long-term use of clopidogrel, perhaps even lifetime use in patients who have received a DES. While the study does not make recommendations, it does confirm the fact that clopidogrel is beneficial for patients who received a DES for up to 2 years.

Drug Labels — A Prescription for Misunderstanding?

Prescription drug labels are commonly misunderstood according to a new study in the *Annals of Internal Medicine*. Nearly 400 English-speaking patients were enrolled in the study to assess their understanding of 5 different medication labels, all had relatively common instructions. Patients with low literacy, defined as 6th-grade level or less, were less likely to understand all 5 labels. Patients with low literacy read the instruction, "Take two tablets by mouth twice daily," but only 35% could demonstrate the number of pills to be taken daily. Patients who had multiple prescriptions were significantly

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more likely to misunderstand prescription labels. The authors admit that the patient's actual drug-taking behaviors were not observed, so authors could not demonstrate a link between misunderstanding the labels and actual medication errors. Still the authors suggest that patients of all ages would benefit from additional efforts to improve the clarity of prescription labels and suggest that the text and format of existing prescription containers should be redesigned and standardized (*Ann Int Med*. 2006;145: Epub ahead of print).

Osteonecrosis of the Jaw — New Side-Effect to Bisphosphate Use

With the widespread use of bisphosphonates for the prevention and treatment of osteoporosis, a new side effect, osteonecrosis of the jaw, has emerged as a concern. A new "Perspective" piece in the *New England Journal of Medicine* (November 30) helps answer the question, "Osteonecrosis of the Jaw—Do Bisphosphonates Pose a Risk?" Osteonecrosis of the jaw is characterized by exposed bone in the mandible, maxilla, or palate, and is often associated with dental disease, dental surgery, oral trauma, periodontitis, and poor dental hygiene. The author points out that the first case of osteonecrosis associated with bisphosphonates was reported in 2003, nearly 10 years after the drugs were first approved. Most reported cases are associated with high-dose intravenous bisphosphonates given to control metastatic bone disease where the rate is reported from 1.3% to 7%. The average patient with osteonecrosis had been receiving intravenous bisphosphonate therapy for 1.5 to 3 years. Use of oral bisphosphonates to treat osteoporosis involves doses that are often 10 times lower than intravenous doses. Fewer than 50 cases of osteonecrosis of the jaw have been associated with oral bisphosphonates, or approximately 1 in 100,000 patient years. There is concern that with long-term use of oral bisphosphonates, the rate of osteonecrosis may increase in the future. Some have even suggested that osteoporosis patients take a "drug holiday" after 5 years of therapy to reduce the risk; however, the benefit of the strategy is unclear at this time. A routine dental evaluation is reasonable prior to starting bisphosphonates; however, there is no reason to stop the drugs prior to dental treatment. Some oral surgeons advocate temporarily withholding drugs if invasive dental care is needed, but given the very long half-life of these drugs, it is unclear whether temporary cessation will have any effect on reducing the risk of osteonecrosis, and more research is needed (*N Eng J Med*. 2006; 355:2278-2281).

Beta-Blockers and Depression — Unlinked?

Many physicians are cautious about the use of beta-blockers after myocardial infarction because of the risk of depression. A new study suggests that this concern may be unwarranted. Researchers from the Netherlands looked at 127 patients who had a myocardial infarction and were not taking beta-blockers versus 254 MI patients who were taking beta-blockers at 3, 6, and 12 months post MI. Outcomes were scores on 2 commonly used depression scales. No significant differences were found between beta-blocker users and non-beta-blocker users regarding the presence of depressive symptoms or depressive disorder, although a trend towards more depression was seen in patients with long-term use of beta-blockers and patients on higher doses. Use of a hydrophilic versus lipophilic beta blocker made no significant difference. The authors conclude that in post MI patients, use of beta-blockers is not associated with an increase in depressive symptoms or depressive disorders in the first year (*J Am Coll Cardio*. 2006;48:2209-2214).

FDA Actions

The FDA has approved telbivudine for the treatment of chronic hepatitis B virus (HBV) infections in adults. The drug is approved for patients with evidence of viral complication in either persistent elevations in serum transaminases or histologically active disease. The approval was based on a one-year study, and more than 1,300 patients showed significant decreases in HBV-virus DNA levels compared with lamivudine. Telbivudine, which is given as a 600 mg oral daily dose, will be marketed by Idenix Pharmaceuticals and Novartis as "Tyzeka."

FDA has approved the first generic version of ondansetron injection (Zofran) for the prevention of nausea and vomiting associated with chemotherapy and prevention of postoperative nausea and vomiting. The generic product will be manufactured by Teva and SICOR Pharmaceuticals. GlaxoSmithKline, which previously held the patent for Zofran, had 2005 sales of nearly $850 million.

The FDA has approved expanded use of Herceptin for HER2-positive, early-stage breast cancer after mastectomy or lumpectomy. Previously, the drug was only approved for HER2-positive, metastatic breast cancer. ■