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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 AstraZeneca, 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.

Reynolds Risk Score: An Update to Cardiovascular Risk Assessment in Women

ABSTRACT & COMMENTARY

By Eileen C. West, MD

Director of Primary Care Women's Health, Clinical Assistant Professor of Internal Medicine, University of Oklahoma School of Medicine, Oklahoma City

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

Synopsis: *For women, up to 20% of all coronary events occur in the absence of traditional major risk factors, and many women with these risk factors do not develop coronary events. The Reynolds Risk Score adds high sensitivity C-reactive protein (hs-CRP) and family history to traditional cardiovascular risk factors in order to more accurately predict cardiovascular risk in women than the ATP-III model currently in use.*

Source: Ridker PM, et al. Development and Validation of Improved Algorithms for the Assessment of Global Cardiovascular Risk in Women: The Reynolds Risk Score. *JAMA*. 2007;297:611-619.

In the 1960s the Framingham Study helped to define hypertension, age, hyperlipidemia, smoking, and diabetes as the major factors in development of cardiovascular disease. These data were incorporated into global models for risk assessment which have received widespread attention in recent years. Unfortunately for women, up to 20% of all coronary events occur without these major risk factors, and many women with those risk factors never develop coronary events. Fifty years of research has helped hone our understanding of the biological processes of atherosclerosis. Concepts including hemostasis, endothelial dysfunction, inflammation, thrombosis and plaque instability are better defining the pathophysiology, but have not yet been incorporated into risk algorithms for women and heart disease.

Researchers from the Donald W. Reynolds Center for Cardiovascular Research at Boston's Brigham and Women's Hospital have developed a new algorithm for the assessment of global

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cardiovascular risk in women. Using data collected from 1992 to 2004 in the Women's Health Study (WHS), the researchers selected about 25,000 US women 45 years and older who were free of cardiovascular disease and cancer at the start of the study and followed them for an average of 10.2 years. They looked for incident myocardial infarction, ischemic stroke, coronary revascularization, and cardiovascular deaths. Plasma samples were measured for total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), lipoprotein (a), apolipoproteins A-1 and B-100, hs-CRP, sICAM-1, fibrinogen, creatinine, hemoglobin A1c and homocysteine.

Two different models for risk prediction (A and B) were defined at the outset and compared to a validation cohort. Model A was more detailed than Model B. Model B was designed for easy use in the clinical setting. What they found was that both models were superior to existing models because they narrowed the large group of women who fell into two "intermediate risk" categories. The 10-year risk groups used matched those of the ATP-III risk prediction model, namely less than 5% (low risk), 5% to less than 10% (low to moderate risk), 10% to less than 20% (moderate to high risk), and 20% or higher (high risk).

Actual event rates for model A matched well with predicted rates in nearly all groups studied. Using Model A, 50% of women who fell into the 5-20% intermediate categories were reclassified more accurately as lower or higher risk. Model B is a simplified version of Model A. It too withstood statistical testing and proved to be more accurate in determining who would develop disease than the most often used existing model.

COMMENTARY

So, what new information have we obtained, and how can we use it in clinic? The analysis supports the use of the inflammatory marker hs-CRP in calculating cardiovascular risk in women. It incorporates family history of heart disease before age 60 years. The traditional risk factors systolic blood pressure, total cholesterol, HDL, smoking and hemoglobin A1c (if diabetic) are included. The new model is called the Reynolds Risk Score, and an online calculator may be found at http://www.reynoldsriskscore.org.

What didn't help so much in creating a risk model were homocysteine, fibrinogen, sICAM-1, and serum creatinine. Homocysteine and sICAM-1 do appear to predict risk, but did not meet criteria for inclusion because there was a less clear correlation between lower values and lower risk. Of interest, it seems neither body mass index, alcohol use, nor exercise frequency improved the predictive power of the model. Also of note, there was no significant contribution from menopausal status or hormone therapy. Limitations of the study include the study population which consisted of relatively well off, primarily white women health professionals. But as the authors note, all components of the models presented have been found previously to predict cardiovascular risk in men.

I follow this data with great interest, as it helps to give a good reason to order inflammatory markers in assessment for cardiovascular disease risk. As yet, the role of imaging in prediction of cardiovascular disease has not been established. More research is needed. This analysis may have two benefits: it gives more accurate risk prediction, and it presents a framework to use when designing future research with imaging tests. Look for more information in the months and years to come on this pertinent and timely model. ■

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Score One for the Kidneys

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *A simple questionnaire can identify individuals at risk for chronic kidney disease.*

Source: Bang H, et al. SCreening for Occult REnal Disease (SCORED): a simple prediction model for chronic kidney disease. *Arch Intern Med.* 2007;167:374-381.

Hoping to increase the identification of patients with chronic kidney disease, Bang and colleagues used the National Health and Nutrition Examination Surveys (NHANES) dataset to develop a prediction tool. They combined data from the 1999-2000 and 2001-2002 surveys, identifying 10,291 subjects. Serum creatinine values and other covariates were missing on many, and after excluding them, the final dataset had 8,530 subjects. Glomerular filtration rate (GFR) was calculated with the abbreviated Modification of Diet in Renal Disease (MDRD) formula:

GFR (mL/min/1.73 m2) = 186 x Serum Creatinine $(mg/dL)^{-1.154}$ x Age $(years)^{-0.203}$ x 1.212 (if black) x 0.742 (if female).

They used GRF < 60 mL/min as the cutoff for chronic kidney disease (CKD). This is the value that the National Kidney Foundation uses as its definition of CKD and corresponds to Stage 3. Six hundred one of 8,530 (7%) had CKD. On multivariate analysis these variables were statistically significant: age, female gender, anemia, hypertension, diabetes, history of cardiovascular disease, history of congestive heart failure, peripheral vascular disease, and proteinuria. In developing the scoring system, the authors assigned 2 points for age 50-59, 3 points for age 60-69, and 4 points for age 70 or greater. All the other variables were assigned 1 point. They chose a score of 4 or greater as the cutoff for CKD because it had the best combination of sensitivity (92%) and specificity (68%). When they validated their rule on an independent dataset, the Atherosclerosis Risk in Communities (ARIC), a score of 4 or greater identified 36% of people with kidney disease. The positive predictive value (PPV) was 18% and the negative predictive value (NPV) was 99%.

COMMENTARY

It is estimated that there are 20 million people in the US with CKD.[1] In 2002, the National Kidney Foundation published clinical guidelines for the prevention, diagnosis, and treatment of CKD.[2] Authors of a study[3] done in Norway found a similar percentage of individuals with CKD (same definition as above) when they screened people with hypertension, diabetes mellitus, or age > 55. Of the people who screened positive, only 1% progressed to end-stage renal disease (CKD Stage 5).

You may be wondering where this rule would be used, since most laboratories will calculate and report back GFR on patients who have had a serum creatinine drawn. The authors envisioned the tool being used "to identify individuals with a high likelihood of CKD before any evaluation with a serum laboratory analysis." They suggest that this could occur at mass screenings or it could be used in primary care offices by intake staff. They also suggest it could be used by patients on interactive websites. The authors include a sample questionnaire for risk evaluation. If a patient scored 4 or more, then they would have a confirmatory serum creatinine drawn.

The equation for the abbreviated MDRD formula is not one that I can keep in my head, but that's why personal digital assistants were invented. The National Kidney Foundation (www.kidney.org/professionals) and Epocrates (www.epocrates.com/index.html) are sources for downloadable PDA programs that will do the math for you. Those of you who use one of these or who looked closely at the equation will note that race (specifically being African American) is a variable, but was not noted to be a risk factor in this study. The authors were not able to explain this. Using this tool with a cutoff of 4 puts everyone 70 years or older in the at-risk group. The implication is that there's no reason to use it in that age group, just get a serum creatinine on everyone.

It's been two decades since Frame set forth his criteria for a good screening test.[4] They are:

1. *The condition must have a significant effect on the quality or quantity of life.*
2. *Acceptable methods of treatment must be available.*
3. *The condition must have an asymptomatic period during which detection and treatment significantly reduce morbidity or mortality.*
4. *Treatment in the asymptomatic phase must yield a therapeutic result superior to that obtained by delaying treatment until symptoms appear.*
5. *Tests that are acceptable to patients must be available at reasonable cost to detect the condition in the asymptomatic period.*
6. *The incidence of the condition must be sufficient to justify the cost of screening.*

CKD is a condition and SCORED is a screening test that meets these criteria. I will be introducing it to our office. ■

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What is the Optimal Dosing for Unfractionated Heparin?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

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

Synopsis: *Patients at high risk for VTE should be treated with three times daily UH, while patients at lower risk may be treated with twice daily therapy.*

Source: King CS, et al. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a meta-analysis. *Chest.* 2007;131:507-516.

Clinical guidelines now recommend using prophylaxis against VTE in high risk hospitalized patients. Subcutaneous unfractionated heparin (UH) has become the treatment of choice due to its safety and ease of monitoring and administration. Patients who are commonly treated include any acutely ill patient confined to bed, such as one with heart failure, respiratory disease, and postoperative care. Patients with a previous history of DVT or PE are at particularly high risk and should be treated.

Dosage regimens of two times daily and three times daily are used and have never been compared according to these study authors, who did an extensive review of the literature from 1966 through 2004. Five thousand units subcutaneously is the usual dosage with both regimens. The authors from the Department of Medicine at Walter Reed Medical Center in Washington, D.C. performed the meta-analysis, looking at 447 articles over the 38 years. All but 12 of the articles were excluded, mainly because they studied surgical and postoperative patients. A total of 7978 patients were represented in these 12 studies, with 6314 receiving two times daily therapy and 1664 patients receiving three times daily therapy.

The patients receiving three times daily therapy had fewer episodes of VTE than those receiving twice daily therapy. Total VTE risk was not significantly different in the two groups (5.4 per 1000 patient days with twice daily compared with 3.5 in the three times daily patients, $p = 0.87$). The risk of PE was significantly lower in the three times daily group (0.5 per 1000 patient days compared with 1.5 in the twice daily group, $p = .09$). Also, the risk of proximal DVT and PE was significantly lower in the three times daily group (0.9 per 1000 patient days compared with 2.3 in the twice daily group, $p = .05$). This reduced VTE risk is offset some by a higher risk of bleeding complications in the three times daily group (0.96 per 1000 patient days compared with 0.35 in the twice daily group, $p = .0001$).

■ COMMENTARY

While a head-to-head study of these two dosage regimens is needed, this careful study indicated that three times daily dosing of UH is superior to twice daily dosing with some increased risk of bleeding complications. Note that the risk of bleeding in the three times daily group is lower than the risk of VTE, DVT or PE in the twice daily group.

So what should we do with this important study? A prudent recommendation would be to use three times daily therapy for all patients at high risk for VTE, such as patients with a past history of DVT or PE, and immobile patients in bed. In patients in which the risk of VTE is lower but prophylaxis is still warranted, twice daily therapy would be appropriate to reduce the risk of bleeding complications. We can all thank these authors for a painstaking analysis of 38 years of medical literature. I would hope that funding for a head-to-head study of these regiments is forthcoming since the differences here are small and a meta-analysis of studies in which none used both regimens is far from being definitive. ■

Pharmacology Update

Vorinostat Capsules (Zolinza™)

By William T. Elliott, 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. Chan and Elliott report no financial relationship to this field of study.

A NEW CLASS OF DRUG HAS BEEN APPROVED FOR THE treatment of cutaneous T-cell lymphoma (CTCL) such as mycosis fungoides. Vorinostat is an orally active histone deacetylase (HDAC) inhibitor. It is manufactured by Pantheon, Inc in Canada and marketed by Merck & Co as Zolinza.

Indications

Vorinostat is indicated for the treatment of cutaneous manifestation of T-cell lymphoma in patients who have progressive, persistent or recurrent disease on or following two systemic therapies.[1]

Dosage

The recommended dose is 400 mg once daily with food. Patients should drink at least 2 liters of fluid daily to avoid dehydration while taking vorinostat. Treatment may be continued until the disease progresses or the development of unacceptable toxicity. If the 400 mg dose is not tolerated the dose may be reduced to 300 mg once daily.[1]

Vorinostat is available as 100 mg capsules.

Potential Advantages

Vorinostat is the first HDAC inhibitor approved for CTCL providing a drug with a different mechanism of action for patients refractory to, or intolerant of, current therapy.

Potential Disadvantages

Common (> 20%) adverse events include increased serum glucose (69%), fatigue (52%), diarrhea (52%), proteinuria (51%), transient increase in serum creatinine (47%), nausea (41%), dysgeusia (28%), thrombocytopenia (26%), anorexia (24%), and weight loss (21%). Serious adverse events include pulmonary embolism (4.7%), squamous cell carcinoma (3.5%), and anemia (2.3%). Prolongation of QTc has also been reported. Vorinostat may be harmful to the fetus. Severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of vorinostat and other HDAC inhibitors such as valproic acid. Concomitant administration of vorinostat and warfarin can prolong prothrombin time and increase INR value.[1]

Comments

Vorinostat is an HDAC inhibitor. Histone deacetylases catalyzes the removal of acetyl groups from lysine residues of proteins (eg, histones). Overexpression of HDAC is observed in certain cancers. The accumulation of excess acetylated histones leads to cell death. The expedited approval of the drug was based on 2 open-label studies, one involving 74 patients with advanced CTCL who had progression, persistence, or recurrence on or following 2 systemic therapies. They were also intolerant to or not a candidate for bexarotene. All patients received vorinostat 400 mg daily. Efficacy was evaluated as complete clinical response (ie, no evidence of disease) or partial response (50% improvement in the disease). Complete or partial response needed to be maintained for 4 weeks. Overall all response was 29.5% with one complete response. Median times to response were 55 days. It may take up to 6 months in rare cases. In the second study (n = 33), 28 patients had advanced CTCL and were assigned to receive 400 mg daily, 300 mg twice daily for 3 days/week, or 300 mg daily for 14 days each 21 days. Response rates were 30.8%, 9.1%, and 33.3%. The estimated duration of response ranged from 84-168 days and time to disease progression, 202-211 days. The 300 mg twice-daily dose was associated with greater toxicity. Dose-related thrombocytopenia and anemia have been reported. Adverse events led to discontinuation of therapy in 9.3% of patients and 10.5% required dose modification after receiving 400 mg daily dosing. The median time to first adverse events was 42 days (17-253 days). Monitoring of blood cell counts, electrolytes, glucose, and serum creatinine should be done every 2 weeks for the first 2 months of therapy and monthly thereafter.[1] The 30-day cost is $7200.

Clinical Implications

CTCL is a rare cancer with an annual incidence of 3 per 1 million people.[2] The most common (44%) form is mycosis fungoides.[3] There is currently no cure for CTCL. Systemic therapy includes chemotherapy, inter-

feron, denileukin diftitox or bexarotene. An overall response of 48% has been reported with bexarotene.[4] Vorinostat provides an alternative to those who are intolerant of or not a candidate for bexarotene as well as other therapy. ■

References

1. Zolinza Product Information. Merck & Co. October 2006.
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4. Apisarnthanarax N, et al. *Am J Clin Dermatol.* 2002;3:193-215.

CME Questions

23. Which factor seems to add to existing models for prediction of cardiovascular risk in women?

a. Alcohol use
b. hs-CRP
c. hormone use
d. body mass index
e. all of the above

24. Risk factors for chronic kidney disease include all but one of the following. Choose the incorrect item.

a. age
b. female gender
c. anemia
d. history of peripheral vascular disease
e. family history of nephrolithiasis

25. Which statement about twice and three times daily therapy with unfractionated heparin in acutely ill hospitalized patients is true?

a. Twice daily therapy is safer than and just as effective as three times daily in preventing venous thromboembolism (VTE).
b. Three times daily therapy is preferred in high risk patients because there is no increased risk of bleeding complications compared with twice daily therapy.
c. Twice daily therapy is safer but less effective than three times daily therapy in preventing proximal DVT and PE.
d. Three times daily therapy should now be used in all patients at risk for VTE.

Answers: 23 (b); 24 (e); 25 (c)

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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.

Botulinum Toxin for Treatment of Hyperhidrosis

Persons who do not suffer hyperhidrosis (HID) may be surprised to learn that it has been associated with both occupational and physical impairment, as well as limitations in social interaction. Some success in managing primary axillary hyperhidrosis may be achieved with topical agents, systemic pharmacotherapies, and/or surgical intervention, but many patients continue to have inadequately controlled symptoms, or are dissatisfied with available methods.

The release of sweat from eccrine glands is mediated by acetylcholine through cholinergic neurons. Injected botulinum toxin type A (BTX) produces transient blockade of the cholinergic nerves that supply sweat glands.

Patients with primary axillary HID were randomized in a double-blind, placebo-controlled trial of treatment with BTX. Each subject received BTX or placebo and was followed for symptom control at weeks 1, 4, 8, and monthly thereafter. Subjects could elect an additional BTX injection, but not sooner than 8 weeks after the last injection.

Most of the BTX subjects (75%) reported a major improvement in HID symptoms (at least a 50% improvement in the Hyperhidrosis Disease Severity Scale). The median duration of positive effect was greater than 6 months. There were no significant adverse effects that differed between BTX and placebo (placebo was an injection of sterile saline). BTX has a favorable efficacy and tolerability profile, and should be useful in management of HID. ■

Lowe NJ, et al. J Am Acad Dermatol. 2007;56:604-611.

A Fish Story

Two major intervention trials have shown that consumption of fish (either in the diet, or by means of fish-oil supplement) is effective in secondary prevention of coronary events post-MI. Long-chain fatty acids in fish—specifically eicosapentanoic (EPA) and docosahexanoic acid (DHA)—have been shown to be inversely related to CAD mortality.

The population of Japan has a diet high in fish. Whether the addition of EPA to this diet would impact coronary events in dyslipidemic patients was the clinical question addressed by JELIS: The Japan EPA Lipid Intervention Study.

JELIS was a prospective randomized placebo-controlled trial in hypercholesterolemic men and women (n = 18,645), all of whom were already receiving statin treatment (specifically, pravastatin or simvastatin). Subjects were assigned to either EPA (1,800 mg/d) or placebo for 5 years. The primary endpoint was any major coronary event.

After a mean followup of 4.6 years, there was a statistically significant 19% relative risk reduction in the primary endpoint for persons on EPA compared to placebo. When the population was separated to look at effects in those with pre-existing CAD vs without, it was discerned that only the former group had a statistically significant benefit, although the trend for event reduction even in the primary prevention group looked promising (18% relative risk reduction). EPA/DHA supplements offer benefit even in persons with diets commonly high in fish, and already on a statin. ■

Yokoyama M, et al Lancet. 2007; 369:1062-1063

Diabetes Control: It's More Than Just A1c Control

In our zeal to refine glucose control in diabetes to attain microvascular risk reduction, we sometimes overlook an equally relevant attribute: better glucose control helps patients feel better! Quality of life (QOL) studies have generally demonstrated QOL improvements with better glucose control. Does it make a difference how you get better control? That question was addressed by Vinik and Zhang in their randomized trial of glargine (GLAR) vs Rosiglitazone (ROSI).

Subjects with uncontrolled type 2 diabetes despite full therapeutic doses of metformin and a sulfonylurea were randomized to add either GLAR or ROSI, and followed for 6 months. In addition to monitoring changes in control of diabetes (A1c), a health-related quality of life instrument was used to measure outcomes.

GLAR and ROSI provided similar improvements in A1c (1.5% - 1.66% reduction). Numerous differences in QOL were evident however, favoring GLAR: total symptom distress score, mood symptoms, ophthalmologic symptoms, fatigue, and perception of general health.

Clinicians have been sometimes reluctant to initiate insulin therapy for persons with uncontrolled diabetes. These data suggest that insulin treatment not only provides substantial A1c improvements, but—with comparable glucose control—resulted in better QOL improvements that ROSI. How we gain control of type 2 diabetes may make a difference. ■

Vinik AI, Ahang Q. Diabetes Care 2007;30(4):795-800.

Can It Wait until after X-Mas?

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*
Dr. Grauer reports that he is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

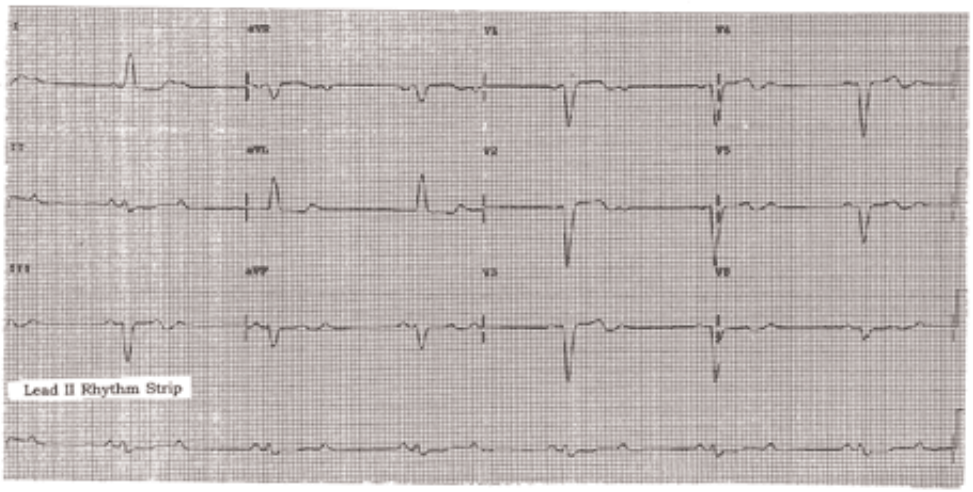

Figure. 12-lead ECG and lead II rhythm strip obtained from an older woman with weakness. Can treatment of this rhythm wait?

Clinical Scenario: The ECG in the Figure was obtained from an older woman who was seen in the Emergency Department with a chief complaint of weakness of several days duration. No chest pain. As it was "the season", she asked her physician, "Can it wait until after Christmas?" How would you respond?

Interpretation/Answer: Attention to the lead II rhythm strip at the bottom of this tracing shows an underlying sinus arrhythmia. Only every other P wave is conducted. That this rhythm is not 3° (complete) AV block is evident from the constant PR interval preceding each QRS complex. Thus, the rhythm is 2° AV block with 2:1 AV conduction.

There are three types of 2° AV block. Mobitz I (AV Wenckebach) is by far the most common form. This form of 2° AV block is often transient. It occurs at a higher level in the conduction system (usually at or around the AV node), and as a result the QRS complex most often is narrow. Because the right coronary artery is most often responsible for vascularizing the AV node, Mobitz I is usually seen in association with acute inferior myocardial infarction. Atropine may be helpful in improving AV conduction.

Mobitz II is a much more severe form of AV block than Mobitz I. This conduction defect usually occurs in association with acute anterior infarction, and generally occurs at a lower level in the conduction system. As a result, the QRS complex tends to be wide. The importance of recognizing this much less common form of 2° AV block is that a pacemaker will almost always be needed if the patient has Mobitz II.

The third form of 2° AV block is 2:1 AV conduction. Because you never see two beats conducted in a row, it is impossible to tell if the PR interval is increasing until the beat is dropped (as it would with Mobitz I) — or not increasing (as occurs with Mobitz II). This is the case for the rhythm seen here. However, the fact that the QRS complex in the Figure is clearly widened strongly suggests that the conduction defect is Mobitz II. Thus, this patient should not try to wait until after Christmas — but rather requires immediate evaluation to determine if a cardiac pacemaker is needed. ■

In Future Issues:

Omeprazole Before Endoscopy in Patients with Gastrointestinal Bleeding

PHARMACOLOGY WATCH

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.

Long-Awaited Torcetrapib Will Not Be Released, Too Risky

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, has been in development by Pfizer for nearly 15 years. The drug has been shown to elevate HDL levels while reducing LDL levels, prompting hopes that torcetrapib would be the first in a new class of important cholesterol medications. In December, Pfizer abruptly pulled the plug on further development of torcetrapib when the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial showed an increase in death from all causes associated with the drug, including an increased rate of cardiovascular events and hypertension. A new study points out a possible mechanism for the lack of cardiovascular benefit. In the international study, 1,188 patients with cardiovascular disease underwent intravascular ultrasonography. They then received atorvastatin and were randomized to receive 60 mg of torcetrapib daily or placebo along with atorvastatin for 24 months. Atorva/torcetrapib resulted in a 61% relative increase in HDL and a 20% further reduction in LDL, resulting in an average HDL higher than LDL. But the drug combination was also associated with an increase in systolic hypertension of 4.6mm Hg, and more importantly an increase in atheroma volume of 0.12%, compared to an increase of 0.19% in the atorvastatin alone group (P = 0.72). The authors conclude that treatment with the CETP torcetrapib was associated with improved lipid endpoints, but was also associated with an increase in blood pressure and no significant decline in coronary atherosclerosis (*N Engl J Med.* 2007;356:1304-1316.). In an accompanying editorial, Dr Alan Tall holds out hope that other CETP inhibitors may not show the same adverse effects but suggests that further development of this class of drugs needs to proceed with caution (*N Engl J Med*. 2007;356:1364-1366). ■

IBS-Drug Treatment Pulled, CV Side Effects

Tegaserod (Zelnorm), Novartis Pharmaceutical's drug for irritable bowel syndrome has been removed from the market by the FDA based on recent findings of increased risk of serious cardiovascular events associated with use of the drug. Tegaserod was approved in 2002 for women with irritable bowel syndrome whose primary symptom was constipation. It was given the additional indication in August 2004 for chronic constipation in men and women under the age of 65. Withdrawal was based on analysis of 29 studies involving more than 18,000 patients that showed a small, but statistically significant increase in the risk of cardiovascular side effects (0.1% serious adverse effects with tegaserod vs 0.01% with placebo). The FDA may allow continued use of the drug in a limited number patients for whom no other treatment options are available and the benefits of tegaserod outweigh the chance of serious side effects. The FDA may consider limited reintroduction of the drug at a later date if the population patients can be identified in whom the benefit of the drug outweighs the risk. ■

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Drug Combo Better for Migraine Treatment

Naprosyn plus sumatriptan is better than either drug alone for the treatment of acute migraine according to a new report. In 2 studies, nearly 3,000 patients with a history of migraine were randomized to sumatriptan 85 mg plus naproxen sodium 500 mg, both drugs alone, or placebo to be used after the onset of a migraine with moderate to severe pain. The primary outcome was headache relief at 2 hours, absence of photophobia, absence of phonophobia, absence of nausea, and sustained pain-free response. Sumatriptan plus naproxen was superior to placebo in all measures and was superior to either drug alone in sustained pain-free response. The incidence of adverse effects was the same for the combination as for the individual medications. The authors conclude that sumatriptan 85 mg plus naproxen 500 mg as a single pill for acute treatment of migraine is more effective than either drug as monotherapy (*JAMA*.2007; 297:1443-1454.). Pozen Pharmaceuticals/ GlaxoSmithKline is developing the combination pill, which is expected to be approved later this year under the trade name Trexima. ■

Pergolide Off the Market, Heart Disease Risk

Pergolide (Permax) is being withdrawn from the market after reports of serious valvular heart disease associated with the drug. Pergolide is a dopamine agonist used for the treatment of Parkinson's disease, hyperprolactinemia and pituitary tumor (?). The action was prompted by 2 reports in the January 4, 2007, *New England Journal of Medicine* that showed increased rates of valvular dysfunction in Parkinson's patients who were taking the drug. These findings coupled with the availability of other dopamine agonists prompted the FDA's action. Valeant Pharmaceuticals is removing Permax brand pergolide as are all generic manufacturers. ■

Hormone Treatment, Does Timing Matter?

Further analysis of the Women's Health Initiative suggests that the timing of the initiation of hormone therapy may have an effect on the risk of cardiovascular disease. The analysis looked at postmenopausal women who had undergone a hysterectomy and were randomized to conjugated estrogen or placebo and women who had not had a hysterectomy who were randomized to conjugated estrogen plus medroxyprogesterone or placebo. The main outcomes were coronary heart disease (CHD) and stroke. Women who initiated hormone therapy within 10 years of menopause had a lower incidence of CHD (HR 0.76 [95% CI, 0.50-1.16]), which equates to 6 fewer events per 10,000 person-years. For women who initiated therapy 10-19 years after menopause the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for women who initiated therapy 20 years after menopause the hazard ration was 1.28 (95% CI, 1.03-1.58) or 12 excess events per 10,000 person years. CHD risk increased when patients were stratified by age as well. Hormone therapy increased the risk of stroke with no significant difference based on time since menopause or age. There was a non-significant trend for improved overall mortality in younger women. The authors conclude that women who initiated hormone therapy closer to menopause had a reduced risk of CHD, with an increase risk among women more distant from menopause although the trends did not meet their criteria for statistical significance (*JAMA*. 2007:297;1465-1477.). ■

FDA Actions

The FDA has approved Cangene's immune globulin to prevent reinfection with the hepatitis B virus in certain liver transplant patients. The product was previously approved for preventing hepatitis B infection after exposure in 2006. It is marketed as HepaGam B.

The FDA has banned rectal suppositories that contain trimethobenzamide due to lack of efficacy in preventing nausea and vomiting. The popular suppositories have been marketed under various trade names including Tigan, Tebamide, T-Gen and others. The drug will still be available as oral and injectable preparations. The evaluation which eventually led to the withdrawal is part of the FDA's ongoing Drug Efficacy Study Implementation (DESI) which evaluates older drugs previously approved based on safety data to make sure that they are also effective.

The FDA has approved Merck's combination diabetes drug Janumet, which combines sitagliptin with metformin. Sitagliptin, which is a dipeptidyl peptidase-4 inhibitor, has been marketed by Merck since last October under the trade name "Januvia." The combination is approved for the treatment of patients with type 2 diabetes; it should be dosed twice daily with meals with gradual dose escalation. ■