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INSIDE

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Is it Better to Prescribe a Cyclooxygenase-2 Inhibitor or Conventional NSAIDs to Prevent Adverse Gastrointestinal Events?

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

Professor, University of Texas Health Science Center, Houston; St. Luke's Episcopal Hospital, Houston

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

Synopsis: *Cyclooxygenase 2 (COX 2) inhibitors may not be as safe as previously thought. These agents have a considerable risk of adverse gastrointestinal events. The concurrent use of ulcer-healing drugs appears to decrease this risk.*

Source: Hippisley-Cox J, et al. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ*. 2005;331:1310-1316.

THIS BRITISH STUDY WAS AIMED AT EVALUATING THE RISK OF AN adverse upper gastrointestinal event among patients taking different cyclooxygenase-2 (COX 2) inhibitors and comparing it with those taking non-selective non-steroidal anti-inflammatory drugs (NSAIDs). The study was designed as a nested case-control analysis utilizing a large British database of 367 general practices. Analysis was done for those patients with an adverse upper gastrointestinal episode such as hematemesis, gastritis, or peptic ulcer disease. For each adverse episode, 10 controls were matched for age, gender, time of year, and type of practice.

Over the 4-year study period, 10,892 patients had a first-ever diagnosis of an adverse upper gastrointestinal event, with an overall incidence for all ages of 1.36 per 1000 person years. The incidence was higher in men than in women and increased with age. The incidence for patients aged 65 years and older was 4.03 per 1000 person years. After correcting for other variables, 9,407 patients were analyzed and compared with 88,867 controls. Of these 9407 patients,

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45.2% had been prescribed NSAIDs in the prior 3 years and 9.9% had been prescribed a COX 2 inhibitor. Odds ratios (OR) for the development of an adverse gastrointestinal event were adjusted for other medications, comorbidity, and smoking status.

Once adjustments were made, the highest OR was associated with current use of naproxen (OR, 2.12), followed by current use of diclofenac (OR, 1.96), other COX 2 inhibitors (OR, 1.72), other non-selective NSAIDs (OR, 1.67), aspirin (OR, 1.60), and ibuprofen (OR, 1.59). Previous utilization of diclofenac and aspirin was associated with significantly higher odds ratios. Among those patients taking ulcer-healing medications, current use of all NSAIDs showed no significantly increased risk of adverse gastrointestinal events. However, the risk remained elevated for those patients taking diclofenac despite the concurrent use of ulcer-healing medications.

COMMENTARY

The use of NSAIDs and COX 2 inhibitors has increased significantly over the past decade.[1] The increase in the use of COX 2 drugs, in particular, was attributed to the "lower risk" of adverse gastrointestinal events.[2]

The most important finding in this study was that the investigators found no strong evidence of enhanced safety with the newer COX 2 inhibitor compared with traditional non-selective NSAIDs. Moreover, the concurrent use of ulcer-healing drugs in patients taking COX 2 inhibitors appeared to reduce the risk for adverse gastrointestinal events.

This study suggests that COX 2 inhibitors may not be as safe as originally thought. One could even justify prescribing ulcer-healing medications to any patient that will require long-term use of COX 2 inhibitors. ■

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Questions & Comments

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Lamotrigine for Migraine with Aura

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, New York-Presbyterian Hospital, Cornell Campus

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *The strong correlation between reduction of aura symptoms and migraine attacks stresses the potential role of aura-like events and possibly cortical spreading depression as a trigger for trigeminal vascular activation, and subsequently the development of migraine headaches.*

Source: Lampl C, et al. Lamotrigine Reduces Migraine Aura and Migraine Attacks in Patients with Migraine with Aura. *J Neurol Neurosurg Psychiatry*. 2005:76:1730-1732.

In this controlled, 3-year, prospective, open study, 59 patients suffering from migraine with aura, or migraine aura without headache, for at least 1 year, received lamotrigine beginning at 25 mg/day for 1 month, and if needed, increasing by 25 mg/day each

month to a maximum of 300 mg/day. Entry criteria required at least 1 headache/month graded as moderate to severe on a 4-step scale, and exclusion criteria included prophylactic headache medication in the 3 months preceding enrollment, previous seizure history treated with lamotrigine, hepatic, renal, or cardiac disease, and pregnancy or possibility thereof. Drug efficacy was evaluated by the maintenance of headache diaries documenting frequency and duration of headache and/or aura. Primary outcome measure was percentage of patients with at least a 50% reduction of migraine aura frequency, and secondary outcome measures included reduction of migraine headache and migraine aura frequency per month and reduction of migraine aura duration. Paired t test and Pearson's correlation were used for statistical analysis.

Lamotrigine significantly reduced monthly migraine aura frequency and duration in 44 of 59 patients, and 77% of responders (34/44) further experienced significantly fewer migraine headaches per month (mean, 2.1 vs 1.1; $P < 0.001$). Mean dose was 166.94 mg/d, most responding to 75-150 mg/d, and mean time to reach primary end point was 4.8 months (SD, 2.3 months). Lamotrigine appears to be an effective prophylaxis for migraine with aura, and up to 6 months of treatment should be offered before considering it ineffective. Given the open nature of this trial, further study of this potentially beneficial medication is warranted.

COMMENTARY

First approved in 1994 as adjunctive therapy for adult onset focal epilepsy, lamotrigine acts primarily by blocking sodium, and to a lesser extent, calcium channels. As monotherapy for seizures, it is comparable to phenytoin and carbamazepine, with fewer side effects and lower withdrawal rates. Adverse events mandate its discontinuation in 10.2% of patients (n = 3501), most often due to rash (3.8%), which, however, may be prevented by lower initial dosage, slower titration schedule, and avoiding co-administration of valproate, which slows lamotrigine metabolism. Stevens-Johnson syndrome occurs less often with lamotrigine compared to phenytoin, carbamazepine, and phenobarbital and, as a further advantage, lamotrigine is only minimally sedating.

Lamotrigine is metabolized by the liver but has no effect on hepatic enzymes and, hence, no effect on the metabolism of oral contraceptives or other antiepileptic medication. In epilepsy, it provides the advantage of a broad-spectrum agent with minimal sedation or drug interactions. Ataxia, dizziness, diplopia, somnolence, and headache are the most frequently reported side effects, with additional adverse events including vomiting and tremor. Its most significant drawback is its slow titration schedule, requiring 2-3 months to reach a therapeutic maintenance dose, something that must be respected when used for migraine therapy as well. ■

Frequent Fliers

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *A very small group of patients consume a significant portion of outpatient primary care physician time.*

Source: Naessens JM, et al. Predicting persistently high primary care use. *Ann Fam Med*. 2005;3:324-330.

As physicians caring for patients in ambulatory settings, we all have people who seek our attention more frequently than others. Of course, these visits consume a great deal of our time, and we sometimes wonder if it is time well spent. Naessens et al sought to characterize these patients and to devise a prediction tool to identify individuals likely to use our services at higher rates than average. The study was conducted from 1997 through 1999 in a smallish Midwestern city, among a group of 58,000 continuously insured individuals in a fee-for-service health plan that did not require co-pays or referrals for specially care. After excluding patients who did not give permission for examination of their medical records, 54,074 charts were available for study. The authors used the following definitions:

- Primary care visits were ones made to family physicians, general internists, general pediatricians, or obstetricians.
- A patient was classified as a high primary care user (HPCU) if he or she made 10 or more visits to primary care annually.
- Patients who made more than 10 visits in 2 consecutive years were termed persistently HPCUs (PHPCUs). The visits were sorted into ambulatory diagnosis groups (ADGs).

The most frequent diagnoses were: routine child health examination, otitis media, acute upper respiratory infection, acute pharyngitis, hypertension, gynecologic examination, medical examination (administrative), asthma, pregnancy, dermatitis, depressive disorder, heart

valve replacement status, deep phlebitis, and atrial fibrillation.

In 1997 there were 987 HPCUs (1.8%), who accounted for 18% of all primary care visits; this group of patients was used to develop a tool to predict who would be a HPCU in 1998. Compared to the people who weren't HPCUs, these patients were more likely to be female (83.2% vs 53.0%), adults (86.0% vs 69.8%), and employed (61.9% vs 36.1%). By 1998, 58 HPCUs from 1997 were no longer in the plan, leaving 929. There were a total of 1,110 HPCUs in 1998. Of these, 173 were also HPCUs in 1997, and, thus, PHPCUs. Compared to non-PHPCUs, PHPCUs were more likely male (28.9% vs 13.9%) and pediatric (18.5% vs 13.5%). There were 4 ADGs which identified individuals at significantly increased risk of being a PHPCU. They were: ADG 11 (chronic medical-unstable), ADG 23 (psychosocial: time limited, minor), ADG 26 (signs/symptoms, minor), and ADG 30 (see and reassure). A fifth ADG, 33 (pregnancy), was negatively associated with being a PHPCU. The authors used these 5 ADGs to devise a clinical prediction tool that assigned a score of +1 (ADGs 23 and 26), +2 (ADGs 11 and 30), or -4 (ADG 33) to the patients visits. A score of ≥ 1 identified patients with future high use the next year (sensitivity 80.3%, specificity 62.7%). The model did not identify as well HPCUs who were persistently high uses over all 3 years of the study.

COMMENTARY

Many of us (especially if we've practiced hospital medicine) became familiar with DRGs (Diagnostic Related Groups) in the mid-1980s. ADGs are a similar concept applied to the outpatient setting. They are part of the Adjusted Clinical Group (ACG) case-mix system. International Classification of Diseases (ICD-9) codes are grouped into ADGs, based on clinical and expected utilization criteria: clinical similarity; likelihood of persistence or recurrence of the condition over time; likelihood that the patient will return for a repeat visit/continued treatment; likelihood of specialty consultation or referral; expected need and cost of diagnostic and therapeutic procedures for the condition; expected need for a required hospitalization; likelihood of associated disability; and likelihood of associated decreased life expectancy. The presence of 3 or more ADGs is a crude measure of significant morbidity burden.[1] To confuse matters further, ADG now stands for Aggregated Diagnostic Groups. It gets worse: ADGs are derived from ACGs (Adjusted Clinical Groups, née Ambulatory Care Groups). Blame all of this on the Johns Hopkins Bloomberg School of Public Health.[2]

Physicians are not likely to use ADGs any more than they use DRGs, so applying this clinical prediction tool to your patient list isn't going to happen. That in of itself does not invalidate the findings of this study. It does allow us to think about our "frequent fliers." They present with chronic, unstable diseases (think uncompensated congestive heart disease), low-level, short-term psychosocial problems (acute stress reaction), minor signs and symptoms (dyspepsia), or see-and-reassure concerns (benign nevi). This raises some uncomfortable questions. Are our patients with chronic, unstable diseases in frequently because we aren't providing them the best possible care? Should they be in a disease management program? Are our patients with minor, time--limited problems using these ailments as "the tickets" into our offices, when what they really need is attention to their psychosocial needs? Should they be referred for counseling or to support groups if we can't/won't delve into these concerns? If you do not practice in an area where patients have the insurance coverage that these folks had, finding the proper resources may not be easy.

This is not the first attempt to identify potential "overusers" of health care. An earlier study[3] found that gender, total number of visits, and percent of visits with "somatization potential" helped to distinguish chronic somatizing patients from other high utilizing patients. Naessens and colleagues characterizes these patients as "overserviced, but underserved."

Who has the problem here? A companion article in the *Annals of Family Medicine*[4] looked at frequent flying from the patients' perspective. It showed that patients who attend frequently do not have the ability "to reassure themselves that they are not ill" and do not share with physicians the same criteria for what constitutes "frequent." This leads to frustrations on both sides. The authors recommend that since frequent attendees need "consistent acknowledgement and legitimization of their perceived unique suffering," we need to be more aware of their perceptions and expectations. ■

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Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

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Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca, and Centocor.

Synopsis: *Infliximab, an antibody against tumor necrosis factor, is effective in ulcerative colitis.*

Source: Rutgeerts P, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462-2476.

INFLIXIMAB IS A HUMANIZED ANTIBODY AGAINST tumor necrosis factor (TNF) that has been widely utilized in the treatment of rheumatic disorders and Crohn's disease (CD). As is true in CD, large amounts of TNF are found in the blood, colonic lumen, and stools of ulcerative colitis (UC) patients. This international study (conducted in 2 nearly identical parts), authored by a virtual Who's Who in inflammatory bowel disease, involved a total of 728 patients with moderate-to-severe active UC (verified by biopsies). Disease was not controlled in these patients despite steroid and/or immunosuppressive therapy. Patients with positive TB skin tests were excluded. Infliximab was administered IV at weeks 0, 2, 6, 14, and 22 in the second study and also at weeks 30, 38, and 46 in the first of these studies. Combining data from the 2 sub-studies, 67% of patients had a sustained clinical response to 5 mg doses of infliximab vs 33.25% of placebo recipients. 10 mg doses produced sustained clinical response in 65.35% of patients. Remissions were attained in 13.15% of placebo recipients at week 30 compared to about 33% of pooled infliximab recipients. As expected, some patients developed antibodies to infliximab and there were some mostly mild infusion reactions. Mucosal healing occurred in about 60% of infliximab recipients vs about 30% of placebo recipients. Approximately 22% of patients were able to discontinue steroid therapy by the end of the respective study periods. One case of tuberculosis occurred, and one fatal case of histoplasmosis was noted in relation to infliximab treatment.

COMMENTARY

UC can be a dreadful disease with striking morbidity and significant mortality. However, unlike CD, UC can be permanently cured by proctocolectomy. Moreover, a large number of UC patients respond well to conventional therapy including topical and systemic aminosalicylates, topical corticosteroids, brief systemic steroid use, and immunosuppressive agents such as azathioprine and 6-mercaptopurine. There has been great enthusiasm for the use of infliximab in CD, and there is no doubt that it has proved extremely helpful in many seriously ill patients. However, the short and long-term complications of infliximab are still uncertain but nonetheless worrisome. In addition to infusion reactions and life-threatening infections, risk of future malignancy is suspected.

Infliximab therapy is extremely expensive, and it may be likened to having a tiger by the tail in that it may be difficult or impossible to discontinue infliximab therapy once initiated. So, in conclusion, it is good to have yet another option for the treatment of severe and refractory UC. However, let us hope that far better therapies are on the way. ■

Pharmacology Update

Mecasermin Injection (Increlex™)

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 relationships to this field of study.

A NEW DRUG HAS BEEN APPROVED FOR THE TREATment of children with below average height who are resistant to growth hormone. Mecasermin is a human insulin-like growth factor-1 (IGF-1) that is produced by recombinant DNA technology. This protein is marketed by Tercica, Incorporated as Increlex™.

Indications

Mecasermin is indicated for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (IGFD) or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone.[1]

Dosage

The recommended starting dose is 0.04 to 0.08 mg/kg

twice daily by subcutaneous injection. If the dose is well tolerated after at least one week it may be increased by 0.04 mg/kg per dose up to a maximum of 0.12 mg/kg administered twice daily. The dose should be given before or after (± 20 minutes) a meal or snack. The dose should be reduced if hypoglycemia occurs even with a meal or snack. The recommended sites of injection are the upper arm, thigh, buttock, or abdomen.[1]

Potential Advantages

Mecasermin has been shown to be effective in patients with extreme short stature with normal growth hormone secretion.

Potential Disadvantages

Adverse events associated with mecasermin include severe hypoglycemia, enlarged tonsils, intracranial hypertension, worsening scoliosis, slipped capital femoral epiphysis, and allergic reactions.[1] Long-term safety is not known as insulin-like growth factor signaling is implicated in cancer.[2] The IGF-1 receptor is a target of anticancer therapy. Mecasermin injection contains benzyl alcohol that has been associated with neurological toxicity in neonates.[1]

Comments

IGF-1 is the principal hormonal mediator of statural growth. Its synthesis and secretion is stimulated by the action of growth hormone. Some patients with growth disorders fail to respond to growth hormone due to IGF-1 deficiency. These patients have low IGF-1 serum levels but normal growth hormone secretion. Laron syndrome is a genetic disorder in which patients do not produce adequate amounts of IGF-1.[3] Mecasermin was studied in 5 clinical trials in 71 pediatric patients. A large percentage (87%) had Laron syndrome. Primary end points were height velocity, velocity standard deviation score, and height standard deviation score (SDS). These end points improved from pre-treatment values.[1] A subset of 58 patients had pre-treatment height velocity data and 11-13 patients were followed for 8 years. Most common adverse events include hypoglycemia (42%) and tonsillar hypertrophy (15%). Seven out of 11 had tonsillectomy or tonsillectomy/adenoidectomy.[1] Injection site reactions included pain, redness, bruising, lipoatrophy, and lipohypertrophy. The long-term effect of mecasermin therapy is not known as IGF-1 has an important role in a variety of cell function including proliferation, differentiation, and transformation.[4] IGF-1 is also implicated in signaling in cancer.[2]

Clinical Implications

Mecasermin is indicated for the treatment of patients with severe growth disorder characterized by ≤ 3 standard deviations in height SDS, basal IGF-1 SDS, and normal or elevated growth hormone levels. It is estimated that about 6,000 patients in the United States meet these criteria.[5] Tercica is also seeking FDA approval for patients with less severe growth disorders. ■

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CME Question

1. The use of repeated infliximab infusions in active refractory ulcerative colitis may be expected to produce remission in approximately what percentage of patients?

a. 75%
b. 50%
c. 40%
d. 30%
e. 20%

Answer: 1 (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; and
- to describe cost-effective treatment regimens.

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.

Risk of Death in Elderly Users of Conventional vs Atypical Antipsychotic Medications

ATYPICAL ANTIPSYCHOTIC MEDICATIONS (AAM) such as aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal) and ziprasidone (Geodon) are commonly prescribed for elders suffering dementia, delirium, psychosis, and affective disorders. Very recently (April 2005), clinicians have been advised that numerous placebo-controlled trials (n = 17) of AAM in elders indicate an increased risk—almost a doubling—of death. Additionally, despite common popular usage, AAM have never been indicated for treatment of dementia, and this 'non-approved' status has also been highlighted by inclusion in the 'black box' warning appended to all AAM.

This recent warning message might have led one to assume that the earlier 'conventional' antipsychotic medications (CAM) are not fraught with such risk. Instead, the issue has not been well studied. CAM include such medications as chlorpromazine (Thorazine), fluphenazine (Prolixin), mesoridazine (Serentil), perphenazine (Trilafon), thioridazine (Mellaril), trifluoperazine (Stelazine), and haloperidol (Haldol).

A retrospective cohort study (n = 22,890) of adults older than age 65 in Pennsylvania who had received a new antipsychotic prescription (AAM or CAM) was undertaken. Results were adjusted for confounding variables such as coexisting illness (eg, diabetes, arrhythmias, cardiovascular disease, cancer). The primary study end point was the relative risk of death for persons receiving a CAM versus an AAM.

Treatment with a CAM was associated with an overall unadjusted hazard ratio for death within 180 days of 1.51. These data suggest that CAM are associated with even greater mortality risk than AAM. ■

Wang PS, et al. N Engl J Med. 2005; 353:2335-2341.

Beta-Blockers to Prevent Gastroesophageal Varices in Cirrhosis Patients

IN PATIENTS WITH ESTABLISHED esophageal varices (ESV), non-selective beta-blockers (BB) are effective in reducing risk of hemorrhage. This may be a result of decreased portal pressure through a combination of decreased cardiac output—a beta-1 effect, and reduced splanchnic blood flow—a beta-2 effect. Hence, selective BB (which are beta-1 selective) may or may not provide similar benefit.

Theoretically, BB might be useful to prevent the development of ESV, not just reduce bleeding from them. Groszmann et al studied a population (n = 213) of high-risk individuals for development of ESV: cirrhotics with portal hypertension as demonstrated by an elevated hepatic venous pressure gradient. This placebo-controlled trial involved administration of timolol (Blocadren) titrated to up to 80 mg/d with followup every 3 months for 54.9 months (mean). Study subjects underwent, in addition to hematology monitoring, endoscopy and measurement of hepatic venous pressure gradient on an annual basis.

The primary end point, development of ESV or ESV bleeding, was no different in the timolol group than placebo. Disturbingly, there were more serious adverse events in the timolol group than in the placebo group. Nonselective beta blockers are not effective for preventing the development of ESV in high-risk patients. ■

Groszmann RJ, et al. N Engl J Med. 2005;353:2254-2261.

Effects of Protein, Monounsaturated Fat, and Carbohydrate Intake on Blood Pressure and Serum Lipids

IDENTIFICATION OF THE 'BEST DIET' remains an elusive target. Cardiovascular disease (CVD) remains the #1 cause of death in the United States, and reduction in saturated fat (SAT) is commonly suggested as a tool for CVD prevention. If one is to reduce the amount of SAT, unless the total number of calories are also reduced, some other nutrient category must be correspondingly increased. Whether substituting carbohydrate, protein, or unsaturated fat for the omitted SAT provides better impact upon blood pressure (BP) and lipids is the object of this study.

Adults (n = 164) with either prehypertension or stage 1 hypertension were randomized to 3 periods of dietary management, in each of which SAT was substituted: protein-enriched, carbohydrate enriched, and unsaturated fat-enriched. Weight was maintained constant throughout each 6-week feeding.

Using the carbohydrate-enriched diet for comparison, both protein-enriched and monounsaturated fat-enriched diets resulted in favorable, very similar changes in lipids and blood pressure. Although the impact of dietary change upon BP and lipids was small, it was sufficient to reduce estimated 10-year CHD risk (Framingham scoring). ■

Appel LJ, et al. JAMA. 2005;294: 2455-2464.

ECG Review

Abnormal ECG in a 35-Year-Old Man

By Ken Grauer, MD

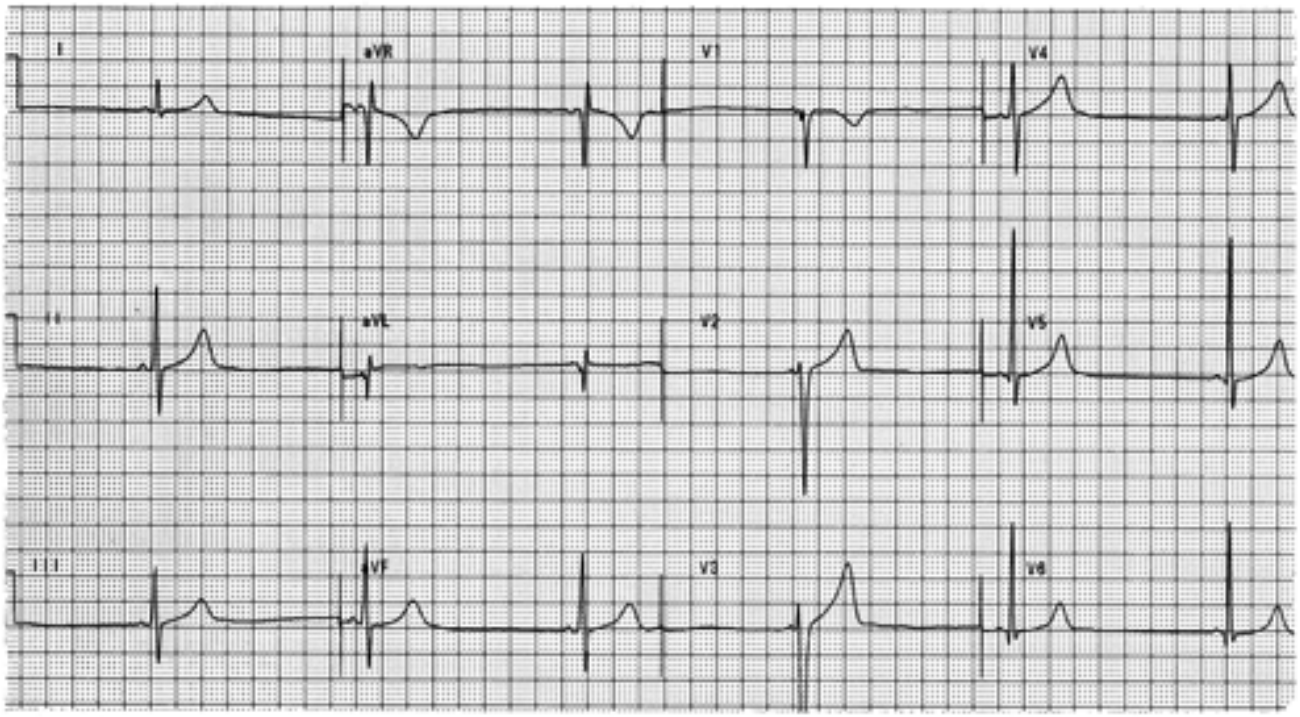

Figure. 12-lead ECG recorded from a 35-year-old man.

Clinical Scenario: The ECG in the Figure was obtained from a 35-year-old man. Is it abnormal? What do you want to know?

Interpretation/Answer: There are a number of remarkable findings on this tracing. The rhythm is fairly regular but quite slow. The R-R interval is at least 8 large boxes, corresponding to a heart rate of less than 40/minute. An upright P wave is seen for the single beat that is recorded in lead II, but the PR interval is very short. QRS voltage criteria for LVH (left ventricular hypertrophy) are present, and Q waves are seen in the lateral leads. There are no acute ST-T wave changes.

The key to interpreting the clinical significance of this ECG lies with the history. The patient in question is an otherwise healthy 35-year-old man who is on no medications, and who is completely asymptomatic. He obtained this ECG as part of an ETT (exercise treadmill test) that he wanted done as an indicator of his fitness level. His exercise capacity on ETT was excellent as expected, and he had a completely normal blood pressure and ST segment response to exercise. Rhythm strips obtained before and after exercise demonstrated sinus bradycardia and arrhythmia, intermittently with a normal variant wandering atrial pacemaker. The 12-lead ECG shown here shows one of the atrial foci from his wandering pacemaker that happens to have a short PR interval. Echo demonstrated a normal heart in this athletic young adult. Conclusion: Clinical correlation is everything, and remember to insist on having a rhythm strip before concluding that an ECG rhythm on a 12-lead tracing is abnormal. ■

In Future Issues:

In Search of the Healthy Diet

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.

FDA Recommends Approval of Muraglitazar, But May Need To Reconsider

In September of 2005, an FDA advisory committee recommended approval of muraglitazar for the treatment of type 2 diabetes. However new review of the data presented to the FDA challenges the safety of the drug, and suggests that compared with placebo or standard treatment, muraglitazar is associated with excess mortality.

The drug is a peroxisome proliferator-activated receptor (PPAR) that has both alpha receptor activity (similar to fenofibrate and gemfibrozil) and gamma receptor activity (similar to pioglitazone and rosiglitazone). Muraglitazar has been widely anticipated because of its dual effect of improving lipid profiles and increasing insulin sensitivity in patients with type 2 diabetes.

In the new study, researchers from the Cleveland clinic reviewed the data submitted to the FDA from phase 2 and 3 clinical trials. The combined studies included 3725 patients who were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo in combination with metformin or glyburide in trials ranging from 24 to 104 weeks. The primary end points were death, nonfatal MI, or nonfatal stroke and a more comprehensive composite outcome, which included those 3 outcomes plus incidence of CHF or TIA. The primary outcome (death, MI, or stroke) occurred in 35 of 2374 (1.47%) of muraglitazar treated patients and in 9 of 1351 (0.67%) of patients in the combined placebo and pioglitazone treatment groups (RR 2.23; 95% CI, 1.07-4.66; *P*. = .03). The more comprehensive outcome occurred in 2.11% of muraglitazar treated patients and 0.81% of control patients (RR, 2.62; 95%CI, 1.36-5.05; *P* = .004). Incidence of CHF was 0.55% muraglitazar and 0.07% controls (*P* = .053).

The authors conclude that compared with placebo or pioglitazone, muraglitazar was associated with increased risk of death, major adverse cardiovascular events, and CHF. They also recommend the FDA not approve the drug until safety can be documented (Nissen SE, et al. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes Mellitus. *JAMA*. 2005;294: 2581-2586).

In a related, provocative editorial, James Brophy MD from McGill University suggests tactics that pharmaceutical companies use to "foster an allusion of safety" when presenting data as part of a FDA application including selecting study populations unlikely to have adverse outcomes, conducting under powered studies that are unable to detect meaningful safety differences, reporting individual rather than composite safety outcomes, and others. He poses the question "which safety message will the FDA buy?" (Brophy JM. Selling Safety—Lessons From Muraglitazar. *JAMA*. 2005;294:2633-2635).

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Which Antipsychotics Are More Dangerous?

Newer atypical antipsychotic drugs have been associated with higher death rates in elderly patients. Now, a new study shows that conventional antipsychotics are at least as dangerous as the newer drugs. In a retrospective cohort study, nearly 23,000 patients age 65 and older who had received conventional or atypical antipsychotic medications between 1994 and 2003 were studied. Conventional antipsychotic medications were associated with a significantly higher adjusted death rate then atypical antipsychotic medications for all time intervals studied up to 180 days (relative risk 1.37; 95% CI, 1.27-1.49). The relative risk was also higher for less than 40 days (RR, 1.56), 40-79 days (RR, 1.37), and 80-180 days (RR, 1.27). The greatest risks were for death occurring within the first few weeks after initiation of medication especially higher doses of conventional antipsychotics drugs.

The authors conclude that conventional antipsychotic medications are least as likely as atypical agents to increase the risk of death among elderly patients, and that conventional drugs should not be used to replace atypical agents if they were discontinued because of recent FDA warnings (Wang PS, et al. Risk of Death in Elderly Users of Conventional Vs. Atypical Antipsychotic Medications. *N Engl J Med*. 2005;353:2335-2341).

Should CPOE Undergo Evaluation?

Physicians who use computerized physician order entry (CPOE) systems often report that it is not a panacea for saving time and preventing medication errors. A new study raises concerns about an increase in adverse outcomes associated with CPOE. Researchers from Children's Hospital of Pittsburgh reviewed demographic, clinical, and mortality data before and after implementation of a commercially sold CPOE. Mortality rates were significant higher after implementation (75 deaths among 1942 children, 3.86% after implementation vs 39 of 1394, 2.80% prior to implementation, odds ratio: 3.28; 95% CI; 1.94-5.55). The authors suggest that while CPOE may hold great promise, "Institutions should continue to evaluate mortality effects, in addition to medication air rates. . ." They also suggest that CPOE should undergo rigorous review and evaluation, similar to drugs, to assess safety prior to implementation (Han YY, et al. Unexpected Increased Mortality After Implementation of a Commercially Sold Computerized Physician Order Entry System. *Pediatrics*. 2005;116:1506-1512).

New Treatment for Tennis Elbow

Botulinum toxin may be effective for treating tennis elbow, according to new study. Sixty patients with lateral epicondylitis were randomized to injections of 6 units of botulinum toxin type A or normal saline placebo injections. Subjective pain was significantly reduced in the botulinum group at 4 weeks (visual analog scale 25.3 mm botulinum vs 50.5 mm placebo [$P < 0.001$]) and was sustained at 12 weeks. Grip strength was not statistically different between the 2 groups, although mild paresis of the fingers occurred in 4 patients in the botulinum group at 4 weeks, but none of the patients in the placebo group. In only one patient did the symptoms persist until week 12. More patients in the botulinum group experience weak finger extension at 4 weeks as well (10 patients botulinum vs 6 patients placebo).

The authors conclude that botulinum toxin may be effective in treating pain over 3-month periods in patients with lateral epicondylitis, but the injections may be assisted with digit paresis and weakness of finger extension (Wong SM, et al. Treatment of Lateral Epicondylitis with Botulinum Toxin: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Int Med*. 2005;143: 793-797).

FDA Actions

Moxifloxacin (Avelox-Bayer) has been approved for the treatment of complicated intra-abdominal infections including polymicrobial infections. The approval was based on a study which showed that intravenous or oral moxifloxacin was as effective as IV therapies such as piperacillin/tazobactam (Zosyn) followed by oral amoxicillin/clavulanic acid (Augmentin). In a separate study, moxifloxacin was found to be equivalent to ceftriaxone plus metronidazole followed by oral amoxicillin/clavulanic acid for treating complicated intraabdominal infections. Moxifloxacin is also approved for treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, and skin and skin structure infections caused by susceptible organisms. ■