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INSIDE

Risk of Community-Acquired Pneumonia and Use of Gastric Acid-Suppressive Drugs

ABSTRACT & COMMENTARY

Synopsis: *Current use of gastric acid-suppressive therapy was associated with an increased risk of community-acquired pneumonia.*

Source: Laheij RF, et al. *JAMA*. 2004;292:1955-1960.

In a survey of 365,000 records of patients followed by general practitioners in Holland for at least 1 continuous year during 7 years, 5551 incident cases of pneumonia developed. Users of acid suppression, particularly proton pump inhibitors (PPIs), had a 4.5 fold increased unadjusted risk of pneumonia, compared to untreated controls. Laheij and colleagues believe that this increased risk can be attributed to the loss of the protective acid milieu of the stomach that normally serves as a barrier to pathogens. Current PPI users were at more risk than patients who had previously discontinued PPI use, and there was no increased risk of pneumonia for those with a distant past history of use of acid inhibiting drugs. Histamine-2 receptor antagonists (H2RAs) appeared to be associated with a similar unadjusted excess risk of pneumonia to that seen with PPIs, but numbers of patients using various H2RAs and various H2RA doses were too small to allow discrimination of risks beyond those for the entire population of H2RA recipients. Higher PPI doses seemed to produce a further elevation of pneumonia risk vs conventional daily doses. Laheij et al seem quite confident in the reliability of these results from such a large population in a country where follow-up of patients is virtually guaranteed by the national health system.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

This is not the first time that this attribution of pneumonia risk to use of acid suppressing drugs has been made. In an accompanying *JAMA* editorial, the actual described risk is placed at one case per 100 patient years (about the same as the risk of GI hemorrhage from use of NSAIDs). Nevertheless, the results of this study should

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not be accepted without reservation. For example, it is likely that much of the use of antisecretory medication is directed toward gastroesophageal reflux disease. GERD itself may represent an important contributor to the pathogenesis of pneumonia (eg, by aspiration). If so, the association of drugs used for treatment might be entirely spurious. Only a prospective study would sort this out, and such a study is quite unlikely to be done. In a marketing flurry based on competition between sucralfate and ranitidine, there was an attempt to demonstrate that ranitidine was associated with nosocomial pneumonia in the hospital. This concept was thoroughly discredited at that time. H2RAs do not produce achlorhydria or even profound hypochlorhydria, and even the much more potent PPIs do not eliminate stomach acid. Although there is a remote possibility that acid suppression may in some cases tilt the balance toward bacterial overgrowth in the stomach, this effect is likely to be counterbalanced by the dramatic decrements in gastric volume that also are associated with antisecretory agents (particularly PPIs). I am sure that we have not heard the last word in this area, but I would urge physicians to realize that the amazing efficacy of currently available H2RAs and PPIs should continue to be made available to all patients with diagnoses that demand acid suppressive therapy. ■

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Hemoglobin A1c: It's Not Just for Diabetics Anymore

ABSTRACT & COMMENTARY

Synopsis: *The relative risk for each 1% increase in hemoglobin A1c was 1.3 for CHD, 1.2 for CVD, and 1.2 for all cause mortality.*

Source: Khaw KT, et al. *Ann Int Med*. 2004;141:413-420.

THIS PROSPECTIVE COHORT TRIAL ASSESSED THE RISK OF cardiovascular disease in 25,623 patients with 6 levels of a hemoglobin A1c level obtained at baseline: < 5% (n = 2766), 5-5.4% (n = 3573), 5.5-5.9% (n = 2531), 6-6.4% (n = 813), 6.5 to 6.9%; n = 157), > 7% (n = 149). One percent (n = 243) of the study had been previously diagnosed with diabetes (mean HgbA1c = 8%). Participants were followed over 6 years for 3 end points: coronary heart disease events, cardiovascular disease events and all-cause mortality.

In men, all end points increased in frequency as the hemoglobin A1c increased, with the most significant jump occurring at the 6.5-6.9% category (RR = 3.4 CHD; 3.0 CVD; 3.5 all cause mortality). There was a progressive increase in events in women beginning at the 6-6.4% category (RR = 2.3 CHD; 1.6 CVD; 1.6 all cause mortality). There was a substantial increase in all events in both sexes at the > 7% category (men, RR = 7 CHD; 5 CVD; 3.4 all cause mortality; women, RR = 4.7 CHD; 8.0 CVD; 6.9 all cause mortality).

After adjustment for age and risk factors, the relative risk for each 1% increase in hemoglobin A1c was 1.3 for CHD, 1.2 for CVD, and 1.2 for all cause mortality. In the known diabetic subgroup, the risk for CHD, CVD and mortality (RR = 2.4, 2.2, and 2.3) was reduced to 1.0 after adjustment for hemoglobin A1c.

COMMENT BY JEFF WIESE, MD

This study confirms previous trials that found a continuous risk of macrovascular disease as the hemoglobin A1c increases.[1,2] More importantly, this study suggests that the risk for cardiovascular events in diabetics is mediated entirely by the hemoglobin A1c. In the diabetic cohort in the study, the risk for all events was reduced to that of non-diabetics once the model was adjusted for hemoglobin 1Ac levels.

Hemoglobin A1c is a marker for systemic glycosolation due to elevated blood glucose levels over the previous 3 months. Previous trials have suggested that tight glucose control decreases the risk for complications from diabetes; this and other trials suggest that tight glucose control may also reduce the risk of cardiovascular events in non-diabetic patients (by 20 to 30% for each percent decline in the HgbA1c).[3]

The results of this study should be interpreted with caution; however, as the cohort design permits commentary on association of hemoglobin A1c with cardiovascular events, but not causation. The latter claim will require a randomized trial in which non-diabetic patients are randomized to tight glycemic control vs status quo. There are numerous confounders that may explain the increased risk of cardiovascular events as the hemoglobin A1c increases. For example, the percentage of patients who smoked cigarettes also progressively increased with each hemoglobin A1c tier, as did the body mass index, suggesting that obesity, tobacco or inactivity may have been responsible for the increased mortality. Although Khaw and colleagues adjusted for these risk factors, the tight relationship between obesity and hemoglobin A1c makes complete adjustment impossible. Physicians tempted to tightly control hemoglobin A1c levels in non-diabetics, while neglecting the obesity that caused the increase in hemoglobin A1c, may find the results to be less than desired. Nonetheless, should a causal link between hemoglobin A1c and cardiovascular mortality be established in non-diabetic patients, the implications could be huge. Khaw et al estimate that a society-wide reduction of hemoglobin A1c of 0.1% has the potential to reduce the total US mortality by up to 6 percent. ■

References

1. Coutinho M, et al. *Diabetes Care*. 1999;22:233-240.
2. Gerstein HC. *Diabetic Med*. 1997;14 (Suppl. 3):S25-S31.
3. Park S, et al. *Diabetes Care*. 1996;19:450-456.

Influenza A Resistant to Oseltamivir

ABSTRACT & COMMENTARY

Synopsis: *Oseltamivir treatment of children with influenza A virus infection was associated with the selection of resistant mutants in 18%.*

Source: Kiso M, et al. *Lancet*. 2004;364:759-765.

Kiso and colleagues in Japan collected serial upper respiratory tract samples from children receiving oseltamivir for treatment of influenza A (H3N2), for isolation of the virus.

Mutations in neuraminidase were identified in virus obtained from from 9 of 50 (18%) immunocompetent children treated with oseltamivir. Eight of the 9 contained mutations previously identified as conferring resistance to oseltamivir, while the ninth had a novel mutation. In vitro susceptibility testing demonstrated that all 9 were resistant to this neuraminidase inhibitor. Drug resistant mutants were detected as early as 4 days after the start of treatment.

COMMENT BY STAN DERESINSKI, MD, FACP

Treatment of influenza virus infections with M2 ion channel inhibitors, such as rimantidine, have at least 2 drawbacks: this class of drugs is only active against influenza A, and resistant virus is often rapidly selected during treatment. The neuraminidase inhibitors are active against all influenza virus types. For instance, the H5N1 avian influenza strains that emerged in 2004, while resistant to the M2 inhibitors, are susceptible to neuraminidase inhibitors. While emergence of resistance has not been reported during treatment with the topically applied neuraminidase inhibitor zanamivir, it has previously been reported with oseltamivir, but at a frequency of less than 1% in adults and 4% in children. Thus, the detection of resistance, occurring in 18% of children in this study, is disturbing.

Influenza hemagglutinin initiates infection by binding to the sialooligosaccharide receptors on the cell surface. Viral neuraminidase sialidase promotes the release of replicated virus from infected cell by removing sialic acid from the receptor. Blockade of neuraminidase thus prevents viral spread from infected to noninfected cells.

Of note, is that the doses of oseltamivir used to treat the children in this study were lower than is recommended in most countries, a factor which might explain the high rate of selection of resistant mutants.

We may, unfortunately, be heading toward a perfect storm. For the upcoming influenza season, we have the problem of an inadequate supply of vaccine. Furthermore, the reemergence of H5N1 avian influenza in poultry, and its spread to humans (and recently, possible human-to-human transmission of the virus) in the absence of a vaccine suitable for humans, raises the specter of a new influenza pandemic. In such a circumstance, the only available tool would be antiviral drugs. These, however, are produced in insufficient supply. In addition, this report of a high rate of resistance to oseltamivir only increases the concern. ■

Dr. Deresinski is Clinical Professor of Medicine, Stanford; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, Palo Alta, Calif.

Better Shoulder Outcomes with Spinal Manipulative Therapy

ABSTRACT & COMMENTARY

Synopsis: *Adding early manual manipulation of the cervicothoracic spine for shoulder pain or dysfunction disorders, in addition to regular care of information, advice and medications, produced much better recovery at both 12- and 52-weeks post treatments.*

Source: Bergman, GJ et al. *Ann Intern Med*. 2004;141: 432-439.

THIS PROSPECTIVE, RANDOMIZED CONTROLLED TRIAL from The Netherlands sought to test the contribution of spinal "manipulative therapy" to the standardized treatments currently employed by the Dutch College of General Practitioners. The annual incidence of shoulder symptoms in that country is estimated at 10-25 per 1000 enrolled patients.

Current Dutch treatment guidelines for "pain between the neck and the elbow at rest or during movement of the upper arm" recommend 2 weeks of information and advice about home exercises and limited daily use, along with oral analgesics and NSAIDs. This is followed when needed by up to 3 corticosteroid shoulder injections at 2 week intervals with Triamcinolone 40mg and Lidocaine 10 mg. After 6 weeks of persistent symptoms, physical therapy referral is made for exercises, massage and physical applications.

In this study, all 150 participants received the usual care noted above, and half were randomized to concurrently receive 6 spinal treatment sessions over 12 weeks by physiotherapists registered to provide orthopedic manipulative therapies. Cases of chronic pain, severe trauma and dislocations were excluded. Manipulative techniques were standardized and involved generally low-amplitude, high-velocity thrust techniques for all, and high-amplitude, low-velocity thrusts when indicated at specific locations to decrease any restrictions in movement in the spine and adjacent ribs. Direct shoulder therapy and massage/exercises were discouraged as being a protocol deviation.

Outcomes were measured primarily by patient surveys and secondarily by analyzing pain severity scores and functional disability. Improved scores at 6 weeks favored the manipulation group, but did not reach statistical significance for full recovery until 12 weeks (43% vs 21%). At the end of one year after therapy began, 52% of manipulated patients considered themselves recovered, vs 35% of the control group who received usual care.

COMMENT BY MARY ELINA FERRIS, MD

It's hard to interpret human studies that involve physical interventions, since the treatment group cannot be blinded and obviously know that they are specially selected for a desired improvement. Relying on the patient's perception as the outcome measure is open to bias, and this study does not have any objective measurement of improvement other than the patient's impression. The intervention group had traditional physical therapy *excluded* (possibly to control the number of variables), so it is impossible to determine if there was anything unique to spinal manipulation compared to early institution of other physical treatments.

Furthermore, numbers are small, definitions of specifically which shoulder disorders are being treated are lacking, and manipulative therapies varied depending on the nature of the complaint and the therapist involved. Recovery rates among the individual therapists ranged from 14% to 83%, and there still were almost half of the manipulated group that did not consider themselves completely recovered at the end of the study (compared to 65% of the control group).

Nonetheless, more patients did feel better and considered themselves fully recovered in the intervention group, and isn't that what we are aiming for? Traditional allopathic medicine's disdain for unproven spinal manipulative techniques may change after the recent publication of 4 years of HMO claim data involving 1 million back pain patients, showing reduction in costs and radiology, surgery and hospitalization with access to chiropractic care.[1] An accompanying editorial, however, points out that lack of a

cause-effect relationship, especially since those with chiropractic insurance tended to be younger and healthier.[2]

My conclusion from both the study reviewed above and the new beneficial chiropractic economic analyses[1] is that there is an important role for "hands-on" treatments in musculoskeletal complaints, but for which treatments and for which conditions is far from clear. We should continue to work towards better definitions of these troublesome and pervasive problems, hopefully in collaboration with our physically inclined colleagues. ■

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1. Legorreta AP et al. *Arch Intern Med*. 2004;164: 1985-1992.
2. Ness J et al. *Arch Intern Med*. 2004;164:1953-54.

Pharmacology Update

Hydromorphone Extended-Release Capsules (Palladone) (C-II)

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

THE FDA HAS APPROVED A NEW FORMULATION OF hydromorphone for the management of pain. This extended-release formulation is designed to deliver hydromorphone over 24 hours with once daily dosing. It will be marketed by Purdue Pharma as Pallone.

Indications

Hydromorphone extended-release (ER) capsules are indicated for the management of persistent, moderate to severe pain in patients requiring continuous, long-term, around-the-clock analgesia with a high potency opioid analgesic. It should be used only in patients who are already receiving opioid therapy, have demonstrated tolerance, and who require at least a total daily equivalent of 12 mg of hydromorphone. Opioid tolerance is defined as at least 60 mg daily of oral morphine, 30 mg of oral oxycodone, or 8 mg of oral hydromorphone.[1]

Dosage

The initial dose of hydromorphone ER is based on the patient's prior opioid daily dose, potency, and type of opioid. To avoid overdose, conservative dose conversion is recommended. The dose should be titrated to adequate pain relief, and may be taken without regard to food. If cessation of therapy is indicated, the dose should be tapered gradually to prevent signs and symptoms of withdrawal in physically dependant patients. The capsules should be swallowed whole and not be broken, chewed, opened, dissolved, or crushed.[1]

Hydromorphone ER is available as 12 mg, 16 mg, 24 mg, and 32 mg capsules.

Potential Advantages

The extended-release formulation permits dosing every 24 hours, and significantly reduces fluctuation in steady-state peak and trough levels, compared to immediate release hydromorphone tablets.[1]

Potential Disadvantages

The long elimination of hydromorphone ER (18 hours) reduces dose adjustment flexibility. Adverse effects or overdosing will require monitoring and treatment for 18 hours or longer. It is not indicated as the first opioid product in patients who require treatment for a short period of time. The drug must be swallowed whole because chewing or crushing the capsule could result in rapid absorption of the full dose and a potentially fatal overdose.

Comments

One of the major disadvantages of previously available forms of hydromorphone is the short plasma half life (2-3 hours).[2] Hydromorphone ER is formulated in an oral extended release delivery formulation for once every 24-hour dosing. The extent of absorbed drug is the same as immediate-release hydromorphone, but with 2-3 fold reduction in fluctuation between peak and trough drug levels.[1] Hydromorphone ER is expected to be available the first half of 2005.

Clinical Implications

Opioids are the mainstay of therapy for moderate to severe pain and generally considered as first-line therapy in nocieptive, neuropathic, and mixed pain syndromes.[3] Hydromorphone ER provides a long-acting opioid in a defined role. It is only indicated in patients who are already receiving an opioid, have demonstrated opioid tolerance, who required an equivalent of 12 mg of oral hydromorphone, and required long term around-the-clock pain control not adequately achieved with immediate-release opioid formulations. ■

References

1. Palladone Product Information. Purdue Pharma L.P. September 2004.
2. Inturrisi CE. *Clin J Pain*. 2002;18:S3-S13.
3. Thomas JR, von Gunten CF. *CNS Drugs*. 2003; 17(9):621-631.

CME Questions

21. Which of the following are initial primary treatments for shoulder pain in the Guidelines of the Dutch College of General Practitioners?

a. Corticosteroid shoulder injections
b. Physical Therapy
c. Oral Analgesics and NSAIDs
d. Spinal Manipulative therapies
e. All of the above

22. The Dutch study correlating use of acid suppression with community-acquired pneumonia supports the following statement:

a. Pneumonia invariably follows use of potent acid suppression.
b. PPIs, but not H2RAs, seem to be associated with an increased risk of community-acquired pneumonia.
c. Both current PPI use and recent use are associated with increased likelihood of pneumonia although current use has the higher risk.
d. There is no relationship between GERD and pneumonia.
e. The risk of pneumonia associated with the use of acid suppression is 10 times greater than the risk of GI hemorrhage associated with the use of NSAIDs.

23. Which of the following is true for a 55 year-old non-diabetic man?

a. His risk of cardiovascular disease events is increased once his hemoglobin A1c is greater than 7%.
b. His risk of cardiovascular disease events is increased only if he meets the criteria for diabetes.
c. His risk of cardiovascular disease events is increased by 20% for every 1% increase in his hemoglobin A1c, even if he is not diabetic.
d. He should receive oral hypoglycemics regardless of his diabetic status in an effort to decrease his hemoglobin A1c to as low a level as possible.

Answers: 21 (c); 22 (c); 23 (c)

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By Louis Kuritzky, MD

Erythromycin and the Risk of Sudden Death

AGENTS WHICH ALTER CARDIAC repolarization have been associated with torsades de pointes. Although erythromycin (ERY) is a generally safe and efficacious medication, it does have the potential to prolong cardiac repolarization, especially when drug levels are elevated. Because ERY is metabolized through the CYP-450 3A system, substances which block CYP3A (such as antifungal agents, diltiazem, and verapamil) can have a potent effect upon raising ERY levels, resulting in at least a doubling of ERY plasma levels when coadministered.

To evaluate whether coadministration of ERY with CYP3A blockers is associated with any meaningful risk of cardiac adversities, data from a Tennessee Medicaid cohort (n = 1,249,943 person-years of follow-up) was examined to identify persons who had received ERY, CYP3A inhibitors, or both. As a control, persons who had not received antibiotics, as well as a comparator control of persons who had received amoxicillin (which has no measurable effect upon cardiac repolarization), was included.

Persons who had used ERY had twice as high a death rate from cardiac causes than persons who had not used antibiotics. Amoxicillin was not associated with an increase in cardiac deaths. Although ERY in the absence of a CPY450 3A inhibitor was not associated with an increase in sudden death, concomitant administration was associated with a greater than 5-fold increase.

Coadministration of ERY with CYP3A inhibitors is associated with a meaningful increase in risk of adverse cardiac events, and should be avoided. YP3A inhibitors which fall into this risk category include (but are not limited to) ketoconazole, itraconazole, fluconazole, diltiazem, verapamil, troleandomycin, nefazodone, and protease inhibitors. ■

Ray W, et al. N Engl J Med. 2004;351: 1089-1096.

Acute Hyperglycemia, Mood, and Cognitive Performance in People with Type 2 Diabetes

HYPERGLYCEMIA IN DIABETES IS associated with increased incidence of neuropathy, nephropathy, and retinopathy. Data about the effects of hyperglycemia upon cognitive function have been conflicting, however. To test whether hyperglycemia impacts cognitive function in type 2 diabetics, a study was performed by maintaining glucose levels using the glucose clamp method over brief, monitored time intervals.

Study subjects underwent cognitive testing after a sustained period of blood glucose levels maintained at either 81 mg/dL or 297 mg/dL. Testing modalities included complex visual scanning, motor performance, speed of coding, reaction time, auditory verbal learning (intermediate and delayed), visual memory, attention, digit span, and letter/number sequencing. The University of Wales Institute of Science and Technology mood checklist was also administered.

Although not all metrics registered significant impairment during hyperglycemia, complex visual scanning, coding performance, and reaction time were significantly decremented. Digit Span and Letter/number sequencing were also impaired. For mood, decreased happiness and alertness were found, as well as an increased sense of agitation during periods of sustained hyperglycemia.

Because this study evaluated persons during a very brief window of observation (80 minute intervals), it is impossible to ascertain the long-term effect of hyperglycemia upon cognitive and mood function. Nonetheless, these data support energetically seeking euglycemia in an effort to maintain best cognitive function and mood. ■

Sommerfield AJ, et al. Diabetes Care. 2004;27(10):2335-2340.

Psychosocial Risk Factors and Risk of Acute MI

STUDIES IN NORTH AMERICA, Europe, and Japan have provided some support for the concept that emotional stress is a risk factor for coronary heart disease (CHD), but there is scanty information about other populations. In addition to limited information, defining what actually constitutes stress, and how to measure it, has been elusive.

This study of 12,461 cases of acute MI in 52 countries included an assessment of psychological stress by means of questions about stress at home and at work. Stress was defined as "feeling irritable, filled with anxiety, or having sleeping difficulties as a result of conditions at work or at home." Patients were also asked to quantify their stress by indicating whether it was present never, some periods, several periods, or permanently.

All measurements of stress were more prevalent in persons who had suffered an acute MI. Confounders to the association included the fact that those who reported more stress also had a higher BMI and a greater incidence of smoking. According to this analysis, stress accounts for as much as 33% of the population attributable risk for MI, and hence may have been somewhat neglected as a an important modifiable risk factor. ■

Rosengren A, et al. Lancet. 2004;364: 953-962.

A Most Common Oversight

By Ken Grauer, MD

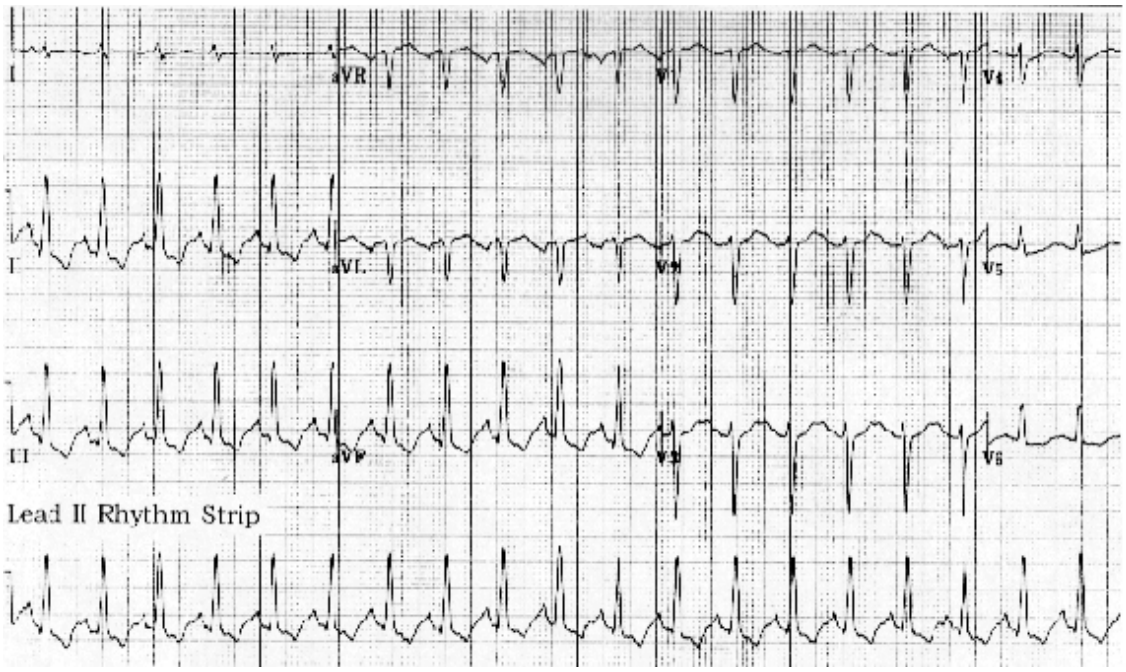

Figure. 12-lead ECG and rhythm strip recorded from an older man with shortness of breath.

Clinical Scenario: The ECG in the Figure was interpreted as showing sinus tachycardia with non-specific ST-T wave abnormalities. Do you agree?

Interpretation/Answer: The rhythm is regular at a rate of about 140 beats/minute. The QRS complex is narrow. Upright P waves appear to precede each QRS complex with a fixed PR interval in lead II. Alas, this is not what is really occurring.

The most commonly overlooked sustained cardiac arrhythmia in our experience is atrial flutter. The 12-lead ECG shown here illustrates why. There certainly does appear to be an upright P wave preceding each QRS complex in each of the inferior leads in this tracing. However, this peaked upright deflection that precedes each QRS deflection is only one of two flutter waves that are seen to occur between each R-R interval. The second flutter wave is hidden and very easy to overlook unless carefully searched for. In fact, T waves are subtly notched in several leads (intermittently in each of the inferior leads, as well as in leads V_1 and V_2). Use of calipers allows one to precisely march out regular atrial flutter activity at twice the ventricular rate (ie, at 280/minute).

The easiest way to avoid overlooking the diagnosis of atrial flutter is to maintain a high index of suspicion for this arrhythmia. Practically speaking, the differential diagnosis of a regular SVT (supraventricular tachycardia) will most often consist of 3 entities: i)sinus tachycardia; ii) PSVT (paroxysmal supraeventricular tachycardia; and iii) atrial flutter. Because the atrial rate of untreated flutter in adults is almost always close to 300/minute and the AV conduction response is most commonly with a 2:1 ratio, any regular SVT at a rate between 140-160/minute should be thought of as a possibly due to atrial flutter until proven otherwise. Subtle notching in the T waves of several leads in this tracing is suggestive of this diagnosis. Equally suggestive is the unusual sharpness of inferior T waves and the downward deflection that follows the T wave in leads aVR and aVL. Application of a vagal maneuver may prove to be diagnostic (as it was here) by transiently slowing the AV response enough to allow clear visualization of underlying atrial flutter activity at a regular rate of 280/minute. ■

In Future Issues: Obesity and CV Risk Factors

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.*

The FDA and Merck Fielding Concerns About Vioxx

Merck announced on September 30th that it is voluntarily withdrawing rofecoxib (Vioxx) from the worldwide market. The decision was based on data from the APPROVe (Addenomatous Polyp Prevention on Vioxx) trial, a company sponsored perspective randomized, placebo-controlled trial designed to assess whether the drug reduces the risk of colorectal polyps in patients with a history of colorectal adenomas. However, after 18 months of the study, patients on 25 mg of rofecoxib were noted to have an increased risk of cardiovascular events such as myocardial infarction and stroke, compared to those patients taking placebo. The FDA supported Merck's action and acknowledged that, while the risk to any individual on rofecoxib is small, the risk increases with continued use. The APPROVe trial showed that the risk of cardiovascular events with rofecoxib was twice that of placebo, according to information published on the FDA News website (fda.gov/bbs/topics/news/2004/NEW01122.html). Previous studies, including a recently reported Kaiser Permanente/FDA retrospective trial, showed the risk to be 3 times that of placebo. The FDA is investigating whether cardiovascular risk may be a class effect of COX-2 inhibitors (coxibs), and is reviewing data from similar trials with celecoxib (Celebrex) and valdecoxib (Bextra). Meanwhile, Merck is initiating a buy-back program for unused Vioxx prescriptions, reimbursing patients for their unused prescriptions. The withdrawal has enormous implications for the company and its shareholders, not only from the loss of nearly $2 billion in revenues from drug, but lost share value for the company stock and the risk of future legal action. It is estimated that 2 million patients in the United States were taking Vioxx at the time of the withdrawal, and over 84 million people worldwide have taken drug at some point since its approval in May 1999. The October issue of the *New England Journal of Medicine* has 2 scathing reviews of Merck and the FDA with regard to the approval and marketing of rofecoxib. Dr. Eric Topol of The Cleveland Clinic, who was one of the first to raise concerned about rofecoxib, calls for a full Congressional review of this case. The senior executives at Merck, and the leadership of the FDA, share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health (*N Engl J Med.* 2004;351:1707-1709). Dr. Garrett FitzGerald of the University of Pennsylvania suggests evidence has been there all along that coxibs, including celecoxib and valdecoxib, may promote cardiovascular disease by blocking prostaglandin I2, which inhibits platelet aggregation, promotes vasodilation, and prevents the proliferation of vascular smooth muscle cells in vitro. At the same time, coxibs have little effect on thromboxane A2, which is responsible for platelet aggregation.

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Traditional NSAIDs and aspirin block thromboxane production, accounting for their cardioprotective effects. Dr. FitzGerald states, "It is essential to determine whether cardiovascular risk is or is not a class effect." The burden of proof now rests with those who claim that this is a problem for rofecoxib alone, and does not extend to other coxibs." (*N Engl J Med*. 2004;351:1709-1711).

Erythromycin and the Risk of Sudden Death

Erythromycin may be associated with an increased risk of sudden death, according to new study in the *New England Journal of Medicine*. Oral erythromycin, which is extensively metabolized by cytochrome P-450 3A (CYP3A), prolongs cardiac repolarization, and has been associated with reports of torsades de pointes. Commonly used medications that inhibit CYP3A may increase plasma erythromycin levels, increasing the risk of ventricular arrhythmias and sudden death. Researchers from Vanderbilt reviewed data from a Tennessee Medicaid cohort that included more than 1.2 million person-years of follow-up and 1476 confirmed cases of sudden death from cardiac causes. The patients in the study were relatively young, with a mean age of 45. Seventy percent were female, and 58% were white. The multivariate adjusted rate of sudden death from cardiac causes among patients using erythromycin was twice as high as that among those who had not used any of the study antibiotic medications (incident-rate ratio 2.01; 95% CI, 1.08-3.75; $P = 0.03$). There was no increase in sudden death among patients using amoxicillin, or former users of erythromycin. For patients who were taking erythromycin with concurrent use of a CYP3A inhibitor (nitroimadazole antifungal agent, diltiazem, verapamil, or troleandomycin), the adjusted rate of sudden death was 5 times as high (incident rate ratio 5.35; 95% CI, 1.72-16.64; $P = 0.004$). The authors conclude that erythromycin should be avoided in patients who are taking CYP3A inhibitors (*N Engl J Med.* 2004;351:1089-1096).

Vaccine Shortage Putting Americans At Risk

Just as healthcare providers are about to start their annual flu vaccination program, British regulators have shut down Chiron Corporation's Liverpool flu vaccine manufacturing plant due to sterility problems. Chiron was expected to supply nearly 50 million doses of vaccine this year, half of the hundred million doses health officials expected to be administered to Americans this fall. Aventis, the other major supplier of vaccine, has told health officials that he could produce an additional million doses this year, but no more. Compounding the shortage, is the addition of 2 groups of patients recommended to receive the vaccine this year—children between the ages of 6 and 23 months (who require 2 doses 1 month apart) and pregnant women (or women who anticipate being pregnant during the flu season). Other high-risk patients include people over age 65, people in nursing homes, people with chronic illnesses, and those caring for people in these groups. Healthcare workers are also considered the highest priority for vaccination. The nasal flu vaccine, FluMist, does little to alleviate the shortage since it is only indicated for healthy children and adults between the ages of 5 and 49 years.

FDA Actions

The FDA will move ahead with warnings for many antidepressants stating that the drugs sometimes raise the risk of suicidal behavior in youth. The recommendation comes after an agency advisory panel, on a split vote, recommended a Black box warning. The agency may not go that far, however, since some advisors were concerned that warnings may discourage treatment of depressed children and teens who can benefit from antidepressants medications. The drugs subject to the warning are those with the brand names Prozac, Paxil, Wellbutrin, Zoloft, Celexa, Effexor, Luvox, and Remeron.

The recently approved antidepressant duloxetine (Cymbalta) has received FDA approval for treatment of pain associated with diabetic neuropathy. This is the first drug approved for this indication in this country. In 2 studies submitted to the FDA, the drug reduced 24-hour average pain levels, compared with placebo, in patients who had diabetes for an average of 11 years, and had neuropathic pain for average of 4 years.

The FDA has approved a new extended release formulation of hydromorphone for the management of persistent moderate-to-severe pain in patients requiring continuous, round-the-clock opioid pain relief for extended periods of time. The product is an extended release formulation that can be dosed once a day, and will be available in 12, 16, 24, and 32 mg capsules. The drug is only recommended for patients already receiving opioid therapy who have demonstrated opioid tolerance, and who require a minimum total daily opioid dose equivalent to 12 mg of oral hydromorphone. It will be marketed by Purdue pharmaceuticals with the trade name Palladone.