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## INSIDE



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# Esomeprazole in Patients with Upper GI Symptoms Taking NSAIDs, Including COX-2 Inhibitors

ABSTRACT & COMMENTARY

***By Malcolm Robinson, MD, FACP, FACG***

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***Synopsis:*** *Esomeprazole 20 mg and 40 mg daily improve upper GI symptoms occurring during NSAID therapy, including selective COX-2 inhibitors.*

**Source:** Hawkey C, et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiinflammatory drugs. *Am J Gastroenterol*. 2005;100:1028-1036.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) ARE widely used and clinically effective for control of musculoskeletal pain. However, up to 40% of NSAID recipients have any of a variety of upper GI symptoms such as dyspepsia, abdominal pain, and heartburn. These symptoms occur frequently with both conventional NSAIDs and the newer, selective, COX-2 inhibitors. There is clearly a need to prevent the noxious symptoms associated with NSAID therapy. Since gastric and duodenal mucosal lesions occurring during NSAID therapy are known to be acid-mediated, acid suppression with proton pump inhibitors (PPIs) has been used to avert such damage and improve symptoms thought also to be related to acid. Hawkey and colleagues comment that the 'greater' acid inhibition afforded by esomeprazole vs omeprazole, lansoprazole, pantoprazole, and rabeprazole might lead to particular efficacy in prophylaxis and treatment of NSAID symptoms. These 2 studies respectively involved 94 centers in 6 countries and 116 centers in 11 countries. Patients had to have a chronic condition such as osteoarthritis or rheumatoid arthritis which would require stable continuous NSAID therapy for ≥ 7 months.

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Endoscopy was done at baseline to rule out ulcerations in the esophagus, stomach, and duodenum and to check *H. pylori* status by histology. PPIs, H2RAs, and prostaglandins during the 2 weeks prior to endoscopy were forbidden; and other standard exclusions were applied. GI symptoms were recorded and quantified on a 6-point scale daily for 7-11 days at baseline. Patients with moderately severe symptoms (score of ≥ 3) on at least 3 of the last 7 days were enrolled. Daily diary cards (heartburn and regurgitation, upper abdominal bloating, and nausea—along with pain, discomfort or burning involving the upper abdomen) were continued during 4 weeks of therapy with esomeprazole 20 mg, 40 mg, or placebo. Quality of life was also assessed at baseline and at 4 weeks. Studies included 595 and 554 patients randomized in each of the 2 trials. Ten percent of patients were found to be *H. pylori* positive. COX-2 use was 30% in the first study and 38% in the second one. Completion rates were 94% and 90%. Both doses of esomeprazole were superior to placebo for upper gastrointestinal (UGI) symptom relief, but placebo recipients also had substantial improvement in their symptoms. Antacid use was lowered from 2.2 antacid tablets a day to 0.72 and 1.06 with esomeprazole compared to 1.22 tablets daily for placebo recipients. Symptoms responsive to esomeprazole included heartburn and acid regurgitation, but nausea and upper abdominal bloating were far less responsive. There was no obvious impact of *H. pylori* positivity on response to therapy. The minimum change in UGI symptom score thought to be clinically significant has been set at 0.4, and esomeprazole 20 mg attained a 0.60 change while esomeprazole 40 mg produced a 0.48 change in score.

## COMMENTARY

The use of PPI therapy for UGI symptoms occurring with NSAID therapy is well accepted, and this approach is widely used. Now that the safety of COX-2 selective NSAIDs has become highly questionable, it is likely that nonselective NSAIDs along with concomitant PPIs will be even more frequently prescribed. The results of these huge esomeprazole studies are far from compelling, both because of the unexpectedly high placebo response and the relatively modest amelioration of symptoms achieved. If the makers of esomeprazole wish to convince us that this PPI is superior to other available PPIs for this indication, comparative studies would have to be done. It seems likely to this writer that such studies will not be forthcoming since they would not be likely to demonstrate any measurable difference between the available PPIs. This study and many other PPI studies indicated an odd disconnect between dose and efficacy in that the 20 mg dose seemed to be superior to the 40 mg dose. Although not directly addressed in this paper, the explanation of this finding could lie in nonspecific GI symptoms that could occur with the higher esomeprazole dose (particularly likely in individuals who are slow metabolizers of omeprazole/esomeprazole). ■

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# Folate: An Under-Rated Vitamin!

ABSTRACT & COMMENTARY

***By Barbara A. Phillips, MD, MSPH***

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***Synopsis:*** *Increased intake of folate in any form is associated with a reduced risk of developing hypertension for women.*

**Source:** Forman JP, et al. Folate intake and the risk of incident hypertension among US women. *JAMA*. 2005;293: 320-329.

This report comes from 2 different cohorts of women in the Nurses' Health Study (NHS): the older cohort (NH1) and the younger cohort (NH2). Together, these cohorts yielded 156,063 women aged 25-55 at intake who were followed for 8 years. Dietary folate consumption was assessed with a validated food frequency questionnaire; this instrument correlates well with measured folate.[1] Data were also collected about nondietary supplemental folate intake. Hypertension was defined as a diastolic blood pressure higher than 140 mm Hg, or a systolic blood pressure higher than 90 mm Hg, or a diagnosis of hypertension given by a physician. Women with hypertension at the time of enrollment were excluded from analysis. Total folate intake was categorized as less than 200 µg/d, 200-399 µg/d, 400-599 µg/d, 600-799 µg/d, and > 800 µg/d. Relevant confounders such as age, body mass index, smoking status, physical activity, baseline blood pressure, other dietary constituents (such as caffeine, alcohol, sodium, and potassium), analgesic and oral contraceptive use, family history and race were identified and controlled for in the statistical analysis.

During the 8 years of follow-up, 1.14% of the younger cohort and 3.84% of the older follow-up developed incident hypertension. There was an inverse relationship between folate intake and unfavorable lifestyles; eg, those who consumed more folate were less likely to smoke, be obese, drink excess caffeine and alcohol, be physically inactive, and consume inadequate diets. In this cohort, most of the total folate intake consisted of supplements, rather than dietary intake. In the younger (NHS2) group, women who consumed 1000 µg/d of total folate had a 45% reduction in the risk of developing hypertension after adjustment for confounders ($P < 0.001$) compared with those women who consumed < 200 µg/d. In the older women (NHS1), those who consumed more than 1000 µg/d of folate were 28% less likely to develop hypertension than those in the lowest intake group ($P = 0.05$). When the analysis was restricted only to those who consumed most of their folate as supplemental rather than dietary, the reduction in the risk of developing hypertension persisted but was statistically significant only for the younger women. When the analysis was redone comparing the risk of hypertension between those who consumed 400 µg/d compared with 1000 µg/d, the protective effect of increased folate persisted. However, the use of multivitamins was not associated with a reduced risk of hypertension, controlling for all other variables.

## COMMENTARY

Although there have been 2 small trials suggesting that folate intake is related to reduced risk of hypertension[2,3] this is the first prospective study to demonstrate a relationship between folate intake and the risk of incident hypertension. Possible biologic mechanisms for folate's effect on blood pressure include increased nitric oxide production in endothelial cells[4] or reduction of plasma homocysteine.[5]

The US recommended daily allowance for folate is 400 µg/d,[6] and there are probably few people in the United States who consume less than 200 µg/d.[7] However, the greatest protective effect in this study was with the highest levels of folate intake (> 1000 µg/d), and there was a significantly reduced chance of developing hypertension for younger women who consumed > 1000 µg/d compared with those who consumed the recommended daily allowance of 400 µg/d. In this population of nurses, few people consumed > 1000 µg/d (251/93,803 in NHS 2, and 240/62,260 in NHS 1). Since it is likely that nurses are somewhat more health-conscious than the US population at large, probably very few of our patients consume the amount of folate (> 1000 µg) that was associated with the greatest benefit in reducing incident hypertension in this study. This suggests that consuming the recommended daily allowance of folate does not provide as much benefit as exceeding it.

Vegetables, of course, are rich in folate. Vegetarian diets have been shown to reduce blood pressure,[8] and it is likely that the increased dietary folate of a vegetarian diet is at least part of the explanation for the beneficial effect of such diets on blood pressure. In this study, total intake of folate remained significantly associated with a reduced risk of developing hypertension even after controlling for other known dietary factors such as calcium, magnesium, potassium, and fiber.

This study adds reduced risk of developing hypertension to the list of benefits that have already been associated with increased folate intake. Other likely benefits of folate include improved cognitive function in the elderly,[9] reduced risk of cervical and colon cancer,[10,11] reduced risk of congenital abnormalities,[12] and reduced cardiovascular risk.[13]

A cautionary note is in order here. The promise of vitamin A reducing lung cancer didn't pan out,[14] and vitamin E has actually been shown to be associated with increased cardiovascular risk.[15] However, the current findings about the benefits of high amounts of folate in reducing the risk of hypertension come from a large, well-designed, carefully controlled, prospective trial. They are worth paying attention. For me, this means including increased folate intake along with the other behavioral interventions (weight loss, exercise, reduced sodium, reduced alcohol) that we recommend for hypertension control. Pass the spinach, please. ■

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# Is Long-Term Alendronate Treatment a Problem?

ABSTRACT & COMMENTARY


***By Leon Speroff, MD***

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***Synopsis:*** *This study emphasizes the need for increased awareness and monitoring for the potential development of excessive suppression of bone turnover during long-term alendronate therapy*


**Source:** Odvina CV, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab*. 2005;90:1294-1301.

ODVINA AND COLLEAGUES REPORT 9 PATIENTS (8 women and 1 man) who sustained spontaneous, atraumatic, nonspinal fractures while on alendronate treatment. One patient also had a lumbar spinal fracture, but almost all of the fractures occurred in skeletal sites rich in cortical bone. In addition, 6 of the 9 patients displayed either delayed or absent fracture healing. The patients received the standard dose of either 10 mg/d or 70 mg/wk for 3 to 8 years. Estrogen was administered with the alendronate in 3 of the women and fractures occurred within 3 years, and glucocorticoids were used by 2 of the women. Tetracycline labeling demonstrated severe depression of bone formation in all 9 patients.

## ■ COMMENTARY

There is no doubt that bisphosphonate treatment prevents bone loss and reduces the incidence of fractures in women who already have osteoporosis. The concern is the use of bisphosphonates in younger postmenopausal women to prevent osteoporosis, a treatment that must be prolonged in order to be effective. This is not the first

report of a possible adverse complication. Most impressive are the patients who developed osteonecrosis requiring removal of the jaw.[1]

Bisphosphonates (like estrogen and raloxifene) inhibit bone resorption, but inhibition of bone resorption also secondarily inhibits bone formation. The increase in measured bone density is because older bone is more dense than new bone. The potential risk that has been long recognized is that prolonged exposure to bisphosphonates or excessive dosage would oversuppress bone resorption, thus oversuppressing bone turnover and affecting the biomechanical strength of bone.

What are possible mechanisms for an adverse effect of long-term bisphosphonate treatment? Animal experiments indicate that alendronate inhibits the normal repair of microdamage, resulting eventually in the accumulation of microdamage and loss of bone strength. Another mechanism is chronic suppression of resorption and bone turnover allowing excessive mineralization and increasing brittleness of bone. The mechanism for overdosage can be the unique tight binding of bisphosphonates to bone causing this drug to remain in the body for decades. This is believed to be the explanation for why there is no rapid bone loss after discontinuing bisphosphonate treatment in contrast to the rapid loss that follows the termination of estrogen therapy. Thus, when bone remodeling releases bound bisphosphonate, it is free to be active again, and the result is the endogenous bisphosphonate is added to the administered bisphosphonate, raising dosage exposure. At this time, we don't know the lowest effective dose and the lowest effective duration of exposure.

It is possible that this complication of bisphosphonate treatment is seen only in patients with concurrent diseases or in patients receiving concurrent estrogen therapy (combining the effects of 2 antiresorptive agents). But this is not known for certain, and our concern should not be limited to these instances. More importantly, how does this report jibe with the published results indicating long-term (10 years) safety of alendronate treatment?[2] It will be at least another 10 years before we know whether negative effects due to bisphosphonate treatment have the potential to outweigh the beneficial effects.

**It seems to me that several conclusions are warranted at this time:**

1. An increased susceptibility to nonspinal fractures may occur relatively early when bisphosphonate treatment is combined with another antiresorptive treatment, and this should be avoided because no additional benefit on fracture risk has been demonstrated with combined treatment.
2. Bisphosphonate treatment is best reserved for older postmenopausal women. It is not a drug of choice for the prevention of osteoporosis in relatively young postmenopausal women.
3. In all patients being treated with bisphosphonates, it would be wise to consider a time limit for duration of exposure, perhaps 5 years. ■

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## *Pharmacology Update*

# Exenatide Injection (Byetta™)


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

*Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Asst. 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.*


THE FIRST OF A NEW CLASS OF ANTIDIABETIC DRUGS has been approved for the treatment of type 2 diabetes mellitus. Exenatide is a polypeptide amide that mimics the action of the incretin hormone glucagon-like peptide (GLP)-1. It is manufactured by Amylin Pharmaceuticals, Inc and co-marketed by Amylin and Eli Lilly and Company as "Byetta™".

### Indications

Exenatide is indicated as adjunctive therapy in type 2 diabetics who have not achieved adequate glycemic control while taking metformin, a sulfonylurea, or a combination of the two.[1]

### Dosage

The initial recommended dose is 5 µg administered subcutaneously twice daily at any time within 60 minutes before the morning or evening meal. If the response is not adequate after one month of therapy, the dose may be increased to 10 µg twice daily. The recommended sites of injection are thigh, abdomen, or upper arm. If exenatide is added to a sulfonylurea, dose reduction should be considered to reduce the risk of hypoglycemia. Metformin dose reduction is not generally required.[1]

Exenatide is available as 5 µg and 10 µg per dose prefilled pens.

## Potential Advantages

Exenatide provides a drug with a different mechanism of action than existing drugs. It provides improved glycemic control in type 2 diabetics being treated with metformin, sulfonylurea, or a metformin-sulfonylurea combination.[1-4] Exenatide also produces weight loss.

## Potential Disadvantages

The most common adverse events associated with exenatide were gastrointestinal. Nausea is the most frequent, and is generally mild or moderate in severity, occurring during the initial weeks of therapy, and is dose dependent.[2,3] Exenatide must be administered by injection. It is currently not recommended for use in type 1 diabetes and is not a substitute for insulin in type 2 diabetes requiring insulin.[1]

## Comments

GLP-1 is a naturally occurring incretin hormone released in the gastrointestinal tract in response to nutrient stimulus. It is rapidly inactivated by dipeptidyl peptidase-4 in the plasma.[5] Exenatide effectively binds to the GLP-1 receptor but is resistant to degradation by dipeptidyl peptidase-4. It was first isolated from the salivary secretion of the Gila monster. The current preparation is synthetic 39-amino acid peptide with a 53% amino acid sequence overlap with mammalian pancreatic GLP-1. The drug's action includes glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, enhancement of beta cell mass, slowing of gastric emptying, and inhibition of food intake.[6,7] Results from 30-week studies showed a 0.4% to 0.6% reduction in HbA1c and 0.8% to 0.9% reduction in HbA1c when exenatide 5 µg twice daily and 10 µg twice daily, respectively, were added to patients on sulfonylurea, metformin or the combination of the 2 compared to a 0.1% to 0.2% increase with placebo.[1-3] The baseline HbA1c of these patients ranged from 8.2% to 8.7%. Patients with higher baseline HbA1c had greater reductions. Reduction of 0.58% and 1.22% were reported in patients with a baseline HbA1c 9%. Weight loss up to 2.8 kg in body weight has also been reported and larger loss tended to be associated with patients with a greater baseline BMI (≥ 30).[1,2] Exenatide appears to be generally well tolerated. The most common side effect is nausea (44% vs 18% for placebo), vomiting (13% vs 4%), diarrhea (13% vs 6%), feeling jittery (9% vs 4%), and dyspepsia 6% vs 3%).[1] Adverse event related withdrawal from clinical studies were 7% for exenatide vs 3% for placebo. Antiexenatide antibodies have been reported with a frequency of 43%. However the titers tend to be low and the clinical significance not clear.[2] The wholesale cost of exenatide is $147 for a 30-day supply of 5 µg twice daily and $172.50 for 10 µg twice daily.

## Clinical Implications

Exanetide provides a new therapeutic agent with the ability to stimulate insulin secretion in response to rising blood glucose. In addition, it slows gastric emptying thus slowing the absorption of glucose. The major disadvantage is that the drug must be given by injection. Its effectiveness has been demonstrated only in type 2 diabetics on a sulfonylurea, metformin, or the combination. GLP-1 agonist analogs are being studied in combination with insulin in type 1 diabetics.[8] Amylin is currently working on a longer-acting preparation.[9] ■

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# CME Questions

**29. Increased folate intake is associated with a reduced risk of developing hypertension:**

a. that is greater for older women than for younger women
b. only for dietary (not supplemental or nondietary) folate
c. and taking a multivitamin with folate reduces the risk of developing hypertension.
d. and taking more than the recommended daily allowance reduces the risk of developing hypertension.

**30. Esomeprazole produced which of the following results in these large studies of 20 mg and 40 mg in symptomatic chronic NSAID users?**

a. There was a dose-related efficacy with these doses of esomeprazole.
b. Results indicated minimal placebo response and considerable efficacy for the esomeprazole.
c. Patients who were H. pylori positive had markedly less response to both doses of esomeprazole.
d. Esomeprazole clearly had benefit for reduction of NSAID-related upper abdominal pain and heartburn/regurgitation.

**Answers:** 29 (d); 30 (d)

By Louis Kuritzky, MD

## Hemochromatosis and Iron-Overload Screening

Hemochromatosis (HCRM) is something of an enigma to clinicians, since despite being recognized as having a gene frequency more common than any other known heritable disorder (1/10), HCRM symptoms and target organ damage are often sufficiently subtle or non-specific that the disorder goes unrecognized. Because many of the clinical consequences of HCRM are able to be reversed, or at least halted by appropriate treatment (phlebotomy), it is important to heighten clinician awareness of the disorder.

The HEIRS study (Hemochromatosis and Iron Overload Screening study) has screened for the prevalence, genetic determinants, and clinical impact of HCRM in diverse populations from 6 metropolitan areas: Washington, DC, Birmingham, Alabama, Irvine, California, Portland, Oregon, Honolulu, Hawaii, and Ontario, Canada. The population screened was comprised of White, Native American, Hispanic, Black, Pacific Islander, Asian, and multiethnic individuals (n = 99,711). Laboratory data included serum iron, iron-binding capacity, ferritin, transferrin saturation, and the genetic mutation most commonly associated with HCRM (HFE C282Y) .

Overall, 3 persons per thousand were homozygous for the C282Y mutation; amongst persons homozygous for C282Y (who had not been previously diagnosed with HCRM), an elevated ferritin was found in 88% of men and 57% of women. The population most frequently affected was non-Hispanic whites, although all populations had some affected persons. There remains a substantial body of individuals with undiagnosed HCRM whose clinical syndromes could be prevented or at least modified by appropriate identification and treatment. ■

*Adams PC, et al. N Engl J Med. 2005; 352:1769-1778.*

## RSV Infection in Elderly and High-Risk Adults

Clinicians may think of respiratory syncytial virus (RSV) as a pathogen generally involved in infectious diseases of childhood. The first reports of RSV causing serious illness in older adults began in the 1970s, when RSV was recognized as the pathogen responsible for outbreaks in long-term care facilities. To obtain a clear assessment of the role of RSV infections, a population which included healthy community dwelling elders (n = 608), high-risk adults (eg, persons with underlying COPD or heart disease, n = 540), and adults admitted to the hospital for pneumonia (n = 1,388) was studied using multiple techniques (including PCR) to confirm the presence of RSV. For purposes of comparison, similar methods to identify influenza A virus were simultaneously used. The populations (in Rochester, MN) were prospectively followed for 4 winter seasons, 1999-2003.

Amongst high-risk adults, 4-10% incurred RSV infection annually. Similarly, in community dwelling elderly, 3-7% developed RSV infection annually. Overall, RSV was responsible for 10.6% of hospitalized pneumonias, and was identified in 11.4% of COPD admissions; 5.4% of CHF admissions, and 7.2% of asthma admissions were attributed to RSV. On a comparative basis, influenza A and RSV were responsible for essentially equivalent impact upon hospital expenditures and overall mortality.

The substantial epidemiologic burden of RSV has been insufficiently recognized. An RSV vaccine could provide an important public health benefit. ■

*Falsey AR, et al. N Engl J Med. 2005;352:1749-1759.*

## BNP, CRP, and Urinary Albumin as Predictors of Mortality and Cardiovascular Events in Older Adults

Traditional risk factors for mortality and cardiovascular events such as blood pressure, lipids, and glucose provide excellent stratification opportunities for general populations. Unfortunately, not all important endpoints are directly attributable to currently recognized risk factors, and even when risk factors are effectively modified, the at-risk population is not returned to the same level of risk as persons without these same risk factors. Hence, so-called 'novel' risk factors have been sought to enhance the predictive value of available risk stratification tools.

C-reactive protein (CRP), brain natriuretic peptide (BNP), and albumin-to-creatinine ratio (ACR), have each demonstrated some predictive value in specifically defined populations. BNP levels have predictive ability even in healthy individuals.

A Danish population of 764 ostensibly healthy adults aged 50-89 was followed for 5 years, after obtaining baseline BNP, CRP, and urinary albumin-to-creatinine ratio.

Mortality risk was best predicted by BNP, with a hazard ratio of 1.96 (vs 1.88 for ACR, and 1.46 for CRP); similarly, BNP was more strongly associated with the first cardiovascular event, followed by ACR and then CRP.

Although CRP has enjoyed much more current popular discussion amongst clinicians, in healthy populations BNP and ACR provide better prognostic information. ■

*Kistorp C, et al. JAMA. 2005;293: 1609-1616.*

# Too Irregular for VT?

*By Ken Grauer, MD*

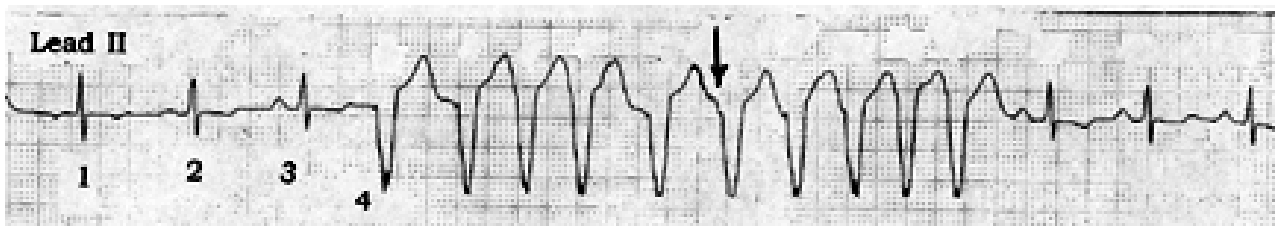


**Figure.** Lead II rhythm strip from a patient with ischemic cardioyopathy.

**Clinical Scenario:** The lead II rhythm strip shown in the Figure was obtained from an older man with ischemic cardiomyopathy. This asymptomatic 10-beat run of anomalous complexes was felt to be too irregular for VT (ventricular tachycardia). Do you agree?

**Interpretation/Answer:** The underlying rhythm in this tracing appears to be sinus, based on the presence of three consecutive similar-appearing upright P waves at the end of the tracing. A P wave of similar sinus morphology immediately precedes the tachycardia (beat #3). However, the first two QRS complexes in the tracing (beats #1 and 2) are preceded by different appearing P waves.

The 10-beat run of anomalous (widened) QRS complexes is clearly irregular. Despite this irregularity, it is highly unlikely that this represents a run of atrial fibrillation with QRS widening from aberrant conduction. The WCT (wide-concept tachycardia) begins late in the cycle after beat #3. Its onset is not preceded by a premature P wave, and the WCT occurs at a time in the cycle (ie, well after the T wave of beat #3) when there should not be any reason for aberrant conduction. QRS morphology during the tachycardia is markedly widened and dramatically different from that of the supraventricular complexes seen on this tracing. The clinical setting (older patient, history of ischemic cardiomyopathy) is consistent with VT, and statistically VT is a much more common cause of new-onset tachycardia than atrial fibrillation with aberrant conduction.

Although VT is usually a regular or at least fairly irregular rhythm, it may be irregular as shown here. At times, sustained VT manifests either a "warm up" or "cool down" period prior to establishment of a near regular rhythm. Gradual acceleration and regularity of the last few beats of the WCT seen here may represent such a "warm up" phenomenon. We suspect there is ongoing AV dissociation *during* the WCT shown here, as part of a sinus P wave appears to be present under the arrow at the midpoint of the tachycardia. The hint of deformity in various parts of other wide QRS complexes before and after this arrow at a rate that approximates the sinus rate suggests possible ongoing atrial activity, but the fact that underlying sinus rhythm was not consistently present before the tachycardia and the indistinct nature of the above noted deformities make our hypothesis of ongoing atrial activity with AV dissociation difficult to prove. Regardless, the irregular WCT seen here is almost certainly a 10-beat run of VT. ■

**In Future Issues:** Cardiac Resynchronization Therapy in CHF

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.

# Is Nesiritide Associated with a Higher Death Rate?

Nesiritide, Scios' intravenous recombinant form of human B-type naturetic peptide, has been widely used for the treatment of congestive heart failure in hospitalized patients. On Scios' website, nesiritide is touted as the "best-selling IV cardiovascular drug ever brought to market." All that may change with the publication of a new study that suggests that patients with acutely decompensated heart failure (ADHF) treated with nesiritide have a higher death rate at 30 days compared with patients who are not treated with the drug. The study was a pooled analysis of 12 randomized, controlled trials, of which 3 met all inclusion criteria. In those 3 trials, 485 patients with ADHF were randomized to nesiritide and 377 to control therapy which was noninotrope-based treatment. Thirty-day death rate was higher among the nesiritide group (7.2% vs 4.0% for placebo, 1.74 risk ratio; 95% CI [0.97-3.12]; *P* = .059). The authors conclude that therapy with nesiritide may be associated with increased risk of death after treatment for acutely decompensated heart failure, and suggest that an adequately powered, controlled trial should be undertaken (*JAMA*. 2005;293:1900-1905). This follows an earlier study that suggested nesiritide may worsen in renal function in patients with ADHF. In that study, which was also a pool analysis from 5 randomized studies, 1269 patients with ADHF were reviewed. Nesiritide was associated with a significantly increased risk of worsening renal function, compared with noninotrope control therapy (RR, 1.52; 95% CI, 1.16-2.0; *P* = .003) or any control therapy, including noninotrope and inotrope based therapies (RR, 1.54; 95% CI, 1.19-1.98 ; *P* = .001). Even low-dose nesiritide was found to worsen renal function. The authors conclude that nesiritide significantly increases the risk of worsening renal function in patients with ADHF, but suggests further investigation to determine the prognostic importance of this finding (*Circulation*. 2005;111:1487-1491).

### *Stopping Aspirin Before Surgery*

A new study suggests that stopping aspirin 5 days prior to surgery is optimal. Researchers from Ireland recruited 51 volunteers who were randomly assigned to 3 groups: placebo, aspirin 75 mg per day, or aspirin 300 mg per day. Utilizing template bleeding times and specific platelet function testing, all bleeding times normalized within 96 hours and all platelet function test normalized within 144 hours after discontinuing aspirin. By day 6, there was no demonstrable hemostatic defect in any of the volunteers. There was also no difference between the 75 mg or 300 mg dose of aspirin. The authors conclude the data sup-

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ports withholding aspirin for 5 days with elective surgery been performed on the sixth day (*J Am Coll Surg*. 2005;200:564-573). This study is important because of recent data that cardiovascular events are much more likely to occur in patients who had recently withdrawn from aspirin—with the peak of events occurring at 10 days (*Pharmacology Watch*. March, 2005). Safely stopping aspirin for 5 days prior surgery, with reinstitution as soon as possible after surgery, makes good clinical sense.

### The Sponge Returns

The Today Sponge contraceptive device is returning to the US market this summer. Last marketed more than 10 years ago, the sponge was removed from the market because of manufacturing problems. It is being brought back by Allendale pharmaceuticals, whose manufacturing facility met FDA standards. The sponge, which was made infamous by a memorable *Seinfeld* episode, is an over-the-counter, round, disposable, soft sponge that is impregnated with spermicide. It is inserted vaginally, and can be kept in place for 24 hours and for multiple sexual encounters. When it was taken off the market in 1994, the sponge was the most popular over-the-counter female contraceptive available, with 250 million of them sold in the 11 years it was available.

### Preventing Metabolic Syndrome

Metformin and intensive lifestyle intervention both help prevent metabolic syndrome in patients who have impaired glucose intolerance. In a study derived from the Diabetes Prevention Program, 1711 patients with impaired glucose tolerance (defined by World Health Organization criteria plus fasting glucose level < 95) were evaluated. More than half the participants (53%) had metabolic syndrome at the baseline. In patients who did not have metabolic syndrome, metformin 850 mg twice daily or intensive lifestyle intervention designed to achieve and maintain 7% weight loss and 150 minutes of exercise per week were both effective in preventing metabolic syndrome. Lifestyle intervention was the more effective intervention with a 41% reduction in the incidence of metabolic syndrome ($P < .001$) while metformin reduced the incidence by 17% ($P = .03$) compared to placebo. Three-year cumulative incidences of metabolic syndrome were 51%, 45%, and 34% in the placebo, metformin, and lifestyle groups, respectively. The authors conclude that both lifestyle intervention and metformin are effective in reducing the development of metabolic syndrome in patients with glucose intolerance, although the impact of lifestyle intervention was more marked than that of metformin (*Ann Intern Med*. 2005;142:611-619).

### FDA Actions

The FDA has approved exenatide for the treatment of type 2 diabetes in patients who have not responded to other treatments. The drug was derived from lizard saliva, and represents a new class of antidiabetic agents known as incretin mimetics—which mimic the effect of GLP-1, a naturally occurring incretin hormone found in human gut. Exanatide normalizes postprandial physiology by stimulating beta cells to secrete insulin in glucose dependent fashion. In alpha cells, the drug normalizes the pathologic hypersecretion of glucagon in a glucose dependent fashion. It also slows gastric emptying and improves satiety, all which serve to reduce postprandial hyperglycemia. There is some evidence that the drug may also attenuates weight gain seen with other hypoglycemic agents and may even be associated with weight loss. The drug will be marketed by Eli Lilly and Amylin Pharmaceuticals under the trade name Byetta.

Ropinirole (Requip) has been approved for the treatment of moderate-to-severe restless leg syndrome (RLS), the first US medication to be approved for this indication. The drug has been available for the treatment of Parkinson's disease since 1997. The approval was based on 3 randomized, double-blind, placebo-controlled trials in adults diagnosed with moderate to severe RLS. All 3 studies demonstrated a statistically significant improvement in the treatment group receiving ropinirole. Side effects include nausea, extreme drowsiness, and dizziness, and the drug will be labeled to warning about the possibility of falling asleep while engaged in activities of daily living including driving. GlaxoSmithKline is enthusiastic about the prospect of treating the estimated 1 out of 10 adults in this country with restless leg syndrome, the most common cause of insomnia. ■