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## INSIDE



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# Boning Up: Mortality Risk Associated with Fractures

ABSTRACT & COMMENTARY

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

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*Director, Sleep Disorders Center, Samaritan Hospital, Lexington*

*Dr. Phillips is a consultant to Cephalon and Ventus and serves on the speaker's bureau of Cephalon and Boehringer Ingelheim.*

***Synopsis:*** *In older women and men, all low-trauma fractures were associated with increased mortality risk for at least 5 years. Subsequent fracture increased that risk.*

**Source:** Bliuc D, et al. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;301:513-521.

THIS REPORT COMES FROM THE DUBBO OSTEOPOROSIS EPIDEMIOLOGY Study, which is a longitudinal population-based study of women and men aged 60 years and older living in Dubbo, Australia.[1] The study entire group was 2245 women and 1760 men who were mostly (98.6%) white. Over an 18-year period of follow-up, 952 of the women and 343 of the men had at least one low-trauma bone fracture. Of this group of individuals who had bone fractures, 452 of the women and 162 of the men agreed to participate in detailed, ongoing follow-up. From the time of recruitment, these individuals were studied every other year for an average of about 18 years. Data collected included physical activity, dietary calcium intake, cigarette smoking, alcohol consumption, number of falls in the last year, comorbid illnesses, medications, anthropometric measurements, bone mineral density (BMD), quadriceps strength, and sway.

Fractures were identified from X-ray reports obtained from the radiological services for the entire Dubbo area. Circumstances surrounding the fracture were obtained by personal interviews. The authors excluded from analysis high-trauma fractures, pathological fractures, and fractures of the head, fingers, or toes. Fractures were

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analyzed in 4 separate groups: hip, vertebral, major, and minor fractures. Major fractures included pelvis, distal femur, proximal tibia, 3 or more simultaneous ribs, and proximal humerus. Minor fractures included all remaining osteoporotic fractures.

Mortality status of all fracture participants was identified from systematic searches, including the Australian Bureau of Statistics for each year of the study.

**Fracture and Mortality Rates for the Entire Population.** There were 952 fractures in women and 343 in men for the Dubbo population aged 60 years and older during the period of observation. These equated to an average fracture incidence of 32 per 1000 person-years in women and 17 per 1000 person-years in men. During this same period of time, mortality rates were 4.3 per 100 person-years and 5.5 per 100 person-years for women and men, respectively. Among the study participants, 461 deaths were observed in women and 197 in men, yielding substantially higher mortality rates of 7.8 per 100 person-years and 11.3 per 100 person-years in women and men, respectively. Standardized mortality ratios for fracture type for the first 5 years after fracture are shown in the Table *(see right)*.

For each age group, mortality in the fracture participants was consistently higher than that in the general population. Mortality rates were higher for those sustaining hip, vertebral, major, and minor fractures, in that order. Mortality was higher for men than for women at all age groups, most markedly in the older age groups.

**Table**

**Standardized mortality ratio by fracture type for 5 years after fracture for the entire study population**

| | Women | Men |
|---|---|---|
| **Hip** | | |
| All Ages | 2.5 | 3.5 |
| 60-74 years | 8.3 | 2.4 |
| ≥75 years | 2.2 | 3.7 |
| **Vertebra** | | |
| All Ages | 1.8 | 2.3 |
| 60-74 years | 3.8 | 4.2 |
| ≥75 years | 1.5 | 1.9 |
| **Major** | | |
| All Ages | 1.6 | 2.0 |
| 60-74 years | 3.2 | 2.2 |
| ≥75 years | 1.3 | 1.8 |
| **Minor** | | |
| All Ages | 1.4 | 1.6 |
| 60-74 years | 1.4 | 0.9 |
| ≥75 years | 1.4 | 1.8 |

Absolute and standardized mortality rates were highest in the first 5 years following fracture, for all fracture types. Of the excess mortality in the first 5 years after a fracture, hip, vertebral, and nonhip, nonvertebral fractures were each associated with approximately one-third of deaths (37%, 35%, and 29%, respectively). For the 5- to 10-year postfracture interval, mortality rates remained elevated only after hip fractures. After 10 years, mortality rates were not different from that of an appropriately age-matched population, even for those who had experienced hip fractures.

Approximately 30% of women and 22% of men experienced another fracture during the study period over a median of 5.1 years. Of these, 49% of the women and 74% of the men died. Subsequent fracture was associated with an increased mortality hazard ratio (HR) of 1.91 in women and 2.99 in men. The 5-year mortality for those with a subsequent fracture was greater than for those who only had one fracture. Mortality risk following a subsequent fracture declined over time, but still remained higher than the general population, even after 5 years.

Overall, the major causes of death were cardiac (27%), respiratory (26%), cerebrovascular (15%), and malignancy (13%). Fracture was mentioned in only

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10.5% of death certificates, primarily hip and vertebral fracture. Osteoporosis without a fracture was mentioned in an additional 2.5% of death certificates.

**Fracture and Mortality Rates for the Detailed Follow-up Group.** For the subset of participants who agreed to detailed follow-up, those who died were older, weighed less, had lower bone mineral density (BMD), and had weaker quadriceps. Women who died also had higher sway. Among those who died, there was more cardiovascular illness in women and more neurological and respiratory illness in men.

After controlling for multiple confounders, age, subsequent fracture, and weaker quadriceps were associated with increased mortality for all participants. In women, lower bone mineral density, smoking, and sway predicted increased risk of death, while in men, decreased physical activity was an independent predictor of mortality.

A subanalysis to assess the relationship between fracture and mortality independent of low bone mineral density was performed for 347 female fracture and 129 male fracture participants with the same numbers of age- and BMD-matched controls. Over about a 5-year period, the mortality rates for women matched by BMD groups were higher than that of the general population, but were similar between those with and without fractures. In men, fracture participants had higher associated mortality rates than their BMD-matched, nonfractured counterparts.

## ■ COMMENTARY

The association between fracture and mortality is not new.[2-4] What is new in this study is the demonstration of increased mortality associated with all major fractures at all ages (older than age 60) and both sexes, and even with minor fractures in older age groups. Mortality was increased for the first 5 years following fractures for all fracture groups except for hip fractures, where mortality rates remained elevated for up to 10 years. In this current study, 30% of all post-hip fracture deaths occurred in the first 6 months and 21% in the next 18 months.

Of the outcomes of fractures, least is known about the relationship between nonhip fractures. This paper is the first report of an increased mortality associated with minor fractures in older people. These findings suggest that we should take nonhip, nonvertebral fractures more seriously. In this study, such fractures accounted for about half of all low-trauma fractures and were associated with more than 40% of all deaths. They are also associated with increased subsequent fracture risk.

Osteoporotic fractures in older people are a huge and growing public health problem, associated with significant cost in dollars, health, and lives.[5,6] The current report indicates that the cost of bone fractures is not limited to those of the spine and hip.

So, what to do for our patients, beyond the usual caveats about diet, sleep, exercise, alcohol, and tobacco? A recent randomized study of bisphosphonate treatment of men and women soon after a hip fracture reported significantly decreased mortality,[7] and might be worth considering. And we need to recognize that broken bones help identify patients that are at risk. ■

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# Priming the Pump of a Leaky Gut

ABSTRACT & COMMENTARY


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

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*Dr. Robinson reports no financial relationship to this field of study.*

***Synopsis:*** *This is the first study documenting that a PPI compromises the mucosal barrier function of the upper GI tract.*

**Source:** J Mullin, et al. Esomeprazole induces upper gastrointestinal tract transmucosal permeability increase. *Aliment Pharmacol Ther* 2008;28:1317-1325.

PROTON PUMP INHIBITORS (PPIs) ARE AMONG THE MOST widely utilized of all drug classes (more than $2 billion spent annually on PPIs in the United States), and they are generally presumed to be as safe as they are effective. The authors of this paper had previously documented that Barrett's esophagus (BE) patients had "leaky" upper gastrointestinal (GI) mucosa as assessed using the widely accepted sucrose permeability test (SPT). Many pharmacological agents that damage the mucosa (e.g., NSAIDs) are known to enhance mucosal permeability. The authors initially hypothesized that the leakiness found in upper GI mucosa in BE might actually be improved by therapy with PPIs (just as PPIs heal damaged esophageal mucosa when used to treat erosive esophagitis or resolve mucosal damage in many gastric and duodenal disorders). Oral sucrose can only be absorbed paracellularly in its disaccharide form (i.e., intact sucrose must pass through leaky intercellular junctions or through actual breaks in the mucosa as would be present in erosions or ulcerations). In the usual digestive setting, sucrose is absorbed through the intestinal mucosa after being enzymatically hydrolyzed to glucose and fructose by sucrase, an enzyme found on the surface of the duodenum. If sucrose as an intact molecule is absorbed through areas of damaged mucosa of the upper GI tract, this undigested sucrose passes unchanged into the urine. An overnight urine specimen after bedtime consumption of 100 g of sucrose in a concentrated sucrose solution can be quantitatively assessed for sucrose as a marker for upper GI mucosal leakage.

In the current study, mucosal permeability was measured in untreated GERD patients at baseline and after 8 weeks of esomeprazole 40 mg daily before breakfast. Eleven of 37 patients screened had > 200 mg of sucrose leak at baseline. This was thought to indicate the likelihood of alternative ongoing pathology, and these patients were excluded. Of the remaining 26 patients, 21 (84%) showed an increased sucrose leak by SPT after 8 weeks of esomeprazole. In this post-treatment group, 14 of the patients had more than 200 mg of sucrose leak, a level others have thought to be indicative of pathophysiology. The average baseline sucrose leak was 72 ± 9 mg vs a mean final sucrose leak of 325 ± 56 mg. This is a 351% increase ($P$ = 0.001). After this group of patients had been studied, a follow-up study of normal healthy individuals was initiated. Volunteers received 1, 2, 3, 5, 7, or 9 days of esomeprazole after a baseline SPT. The final SPT was done on the night following the last dose of esomeprazole. Results indicated a progressive rise in SPT values with increasing duration of esomeprazole therapy (reaching statistical significance after 3 days of therapy). By day 9 of therapy, the SPT was almost 400 mg greater than baseline. By day 4 after the completion and discontinuation of esomeprazole dosing, a follow-up SPT test had returned to baseline. The authors felt that gastric mucosal permeability should be measured after intravenous PPI therapy. It was also mentioned that animal studies had confirmed PPI-enhanced upper GI permeability. It was speculated that PPIs might affect the integrity of the cellular cytoskeleton since they may inhibit other phosphatases in addition to H,K-ATPase. Phosphatases have been implicated in control of tight junction permeability.

## ■ COMMENTARY

Astra Zeneca, maker of esomeprazole, was undoubtedly unhappy about the results of this study. Undoubtedly, they had been hoping to show that their drug led to improvement of pathological upper GI permeability. Instead, a multibillion dollar product has been shown to cause what could be a significant pathophysiologic abnormality of the upper GI mucosal barrier. Although there are no definite clinical abnormalities that can be ascribed to increased mucosal permeability, a number of disease states are apparently related to enhanced mucosal permeability. For example, as already mentioned, NSAIDs cause a quite reproducible increase in upper GI mucosal permeability that can be quantified by the SPT as used in these PPI studies. Crohn's disease is associated with more than normally permeable intestinal mucosa, and healthy relatives of Crohn's disease patients also have statistically increased intestinal mucosal permeability vs healthy control subjects. Defective intestinal barrier function has been linked to such disparate disorders as rheumatoid arthritis and a variety of systemic allergies.

Clearly, the finding of this mucosal effect of esomeprazole may or may not be generalized to other PPIs, but this certainly needs to be explored. More to the point, the clinical implications of dramatically enhanced intestinal permeability need to be carefully analyzed. Pharmaceutical companies seldom fund studies that backfire in the way that seems to have occurred in the present scenario, but there could be a number of valuable consequences that develop in the light of these quite unexpected data. ■

*Pharmacology Update*

# Eltrombopag Tablets (Promacta®)

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

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

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

ELTROMBOPAG IS A THROMBOPOIETIN (TPO) RECEPTOR agonist approved by the FDA for the treatment of thrombocytopenia. It is the second agent, after romiplostim, approved to stimulate the thrombopoietin receptor and the first in oral form. Eltrombopag is marketed by GlaxoSmithKline, Inc., as Promacta®.

## Indication

Eltrombopag is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura who have had insufficient response to corticosteroids, immunoglobulin, or splenectomy.[1]

## Dosage

The recommended starting dose is 50 mg once daily taken on an empty stomach (1 hour before or 2 hours after a meal as food reduces the absorption). A 4-hour interval should be allowed between other medications, foods, or supplements containing cations (e.g., calcium, iron, zinc). The starting dose is 25 mg once daily for patients with East Asian ancestry or with moderate-to-severe hepatic insufficiency. The daily dose may be adjusted to achieve and maintain a platelet count of $\geq 50 \times 10^9$/L to prevent bleeding. The dose should not exceed 75 mg daily. Eltrombopag should be discontinued if the platelet count does not increase after 4 weeks of therapy or if the platelet count exceeds $200 \times 10^9$/L.[1]

Eltrombopag is available as 25 mg and 50 mg tablets.

## Potential Advantages

Eltrombopag is effective orally. The other thrombopoietin receptor agonist, romiplostim, is given by subcutaneous injection. Approximately two-thirds of patients respond to eltrombopag.[1]

## Potential Disadvantages

Eltrombopag increases the risk for development or progression of reticulin fiber deposits within the bone marrow. The risk of hematologic malignancies may be increased. Excessive production of platelets may lead to thrombotic or thromboembolic complications and discontinuation of the drug may result in worsening of thrombocytopenia. Eltrombopag may increase the risk of hepatotoxicity. Serum liver tests should be done at baseline, every 2 weeks during dose titration, and monthly after establishing a stable dose.[1] Inducers and inhibitors of CYP1A2 and CYP2C8 may affect the plasma levels of eltrombopag. The drug is an inhibitor of the organic anion transporting polypeptide (substrates include atorvastatin, rosuvastatin, rifampin, methotrexate). Polyvalent cations reduce the absorption of eltrombopag. Other adverse events associated with eltrombopag include nausea, vomiting, menorrhagia, myalgia, paresthesia, cataract, dyspepsia, ecchymosis, increased ALT/AST, and conjunctival hemorrhage.[1]

## Comments

Acting as a thrombopoietin receptor, eltrombopag stimulates megakaryocyte proliferation and differentiation, resulting in increased platelet production. Its efficacy and safety was shown in 2 randomized, double-blind, placebo-controlled studies.[1,2] Study subjects had platelet counts of $< 30 \times 10^9$/L and at least one prior therapy for ITP. In study 1, subjects (n = 114) were randomized to eltrombopag 50 mg daily or placebo at a 2:1 ratio. In study 2 (n = 117), subjects were randomized to 30 mg, 50 mg, 75 mg, or placebo at a 1:1:1:1 ratio. Subjects were treated for a maximum period of 6 weeks followed by 6 weeks off therapy. Seventy percent of patients had at least 2 prior ITP therapies (e.g., corticosteroids, immunoglobulin, rituximab, cytotoxic therapies, danazol, and azothiaprine) and 40% had splenectomies. The primary endpoint was achieving platelet count of $\geq 50 \times 10^9$/L. The response rates for the 50 mg dose were 59% (43/73) in study 1 and 70% (19/27) in study 2. Response was similar in subjects regardless of whether they had a splenectomy. Response was detected 1 week after initiation of therapy and maximum effect after 2 weeks of therapy. The incidences of bleeding during treatment were 17% for placebo and 7% for 50 mg of eltrombopag.[2] Bleeding and platelet counts gradually return to baseline or near baseline during the 6-week follow-up. The drug is also being studied in thrombocytopenic patients with cirrhosis associated with hepatitis C.[3]

## Clinical Implications

Idiopathic thrombocytopenia purpura is an acquired

autoimmune disorder characterized by antibody-mediated destruction of platelets and impaired platelet production.[4,5] The most serious consequence of the disease is risk of bleeding, particularly intracranial hemorrhage. Treatment has generally been targeted at the antibody-mediated platelet destruction with splenectomy, corticosteroids, IVIG, rituximab, and cytotoxic agents. It appears that the underlying immune defect may vary between patients and no single therapy is effective in all patients.[6] There are now 2 TPO receptor agonists that target platelet production and provide options for patients who have not responded to corticosteroids, immunoglobulin, or splenectomy. Eltrombopag is available only through a restrictive distribution program, PROMACTA CARES. Prescribers, pharmacies, and patients must register with the program to prescribe, dispense, or receive the drug. ■

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## CME Questions

**12. Death rates following fractures in older people:**
a. are increased for women, but not for men.
b. are highest for hip fractures.
c. are increased significantly for the remainder of the person's lifetime.
d. are not influenced by the number of fractures experienced.

**13. Which of the following was an independent predictor of mortality among men but not women?**
a. Lower bone mineral density
b. Smoking
c. Decreased physical activity
d. Sway

**14. Esomeprazole 40 mg daily before breakfast for 8 weeks led to what degree of enhancement of baseline mucosal permeability in the study of GERD patients?**
a. Approximately 1,000 %
b. Approximately 750%
c. Approximately 350%
d. Approximately 200%
e. Less than 25%

**Answers:** 12. b, 13. c, 14. c.

## CME Objectives

The objectives of *Internal Medicine Alert* are:
- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

# Clinical Briefs

*By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville*
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## Estrogen + Progesterone and Breast Cancer

**Source:** Chlebowski RT, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009;360:573-587.

THE WOMEN'S HEALTH INITIATIVE (WHI) provided convincing evidence that the use of estrogen plus progesterone (E+P) in postmenopausal women is associated with an increased risk of breast cancer. The outcomes of this clinical trial motivated large numbers of women and their clinicians to rethink the risk-benefit balance of hormone replacement therapy, evoking a sea-change in prescribing habits.

Despite the acknowledged association between E+P and breast cancer in WHI, a concomitant decline in use of mammography after the breaking WHI news invited the possibility that during post-WHI years, less screening for breast cancer might be influencing the observed breast cancer decline rather than simply less E+P use. To study this issue further, WHI investigators evaluated two data sets: the original WHI population (n = 16,608 women without breast cancer at baseline) and a second observational study population (n = 41,449 without breast cancer at baseline). The observational study group did not receive advice about whether to use E+P, but were informed about the results of the interventional WHI when it became available. In the observational WHI population, more than 16,000 women were taking E+P at baseline.

Long-term follow-up of the observational WHI population showed an increased incidence of breast cancer in women who had used E+P. Breast cancer incidence in this population declined subsequent to hormone discontinuation. This suggests the possibility that some early breast cancers may regress or disappear if hormone therapy is stopped. The data did not, however, provide a meaningful association between less use of mammography and reduced breast cancer. ■

## Prostate Cancer Risk with Testosterone Replacement

**Source**: Shabsigh R, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: A systematic review. *Int J Impot Res* 2009;21:9-23.

GROWTH AND DEVELOPMENT OF THE prostate is recognized to be testosterone (TST)-dependent. Clinicians have long held concerns that TST therapy might not only worsen symptoms of benign prostatic hyperplasia (BPH), but also stimulate the development, growth, proliferation, or aggressiveness of prostate cancer. Some of this concern stems logically from the observation that testosterone deprivation has salutary effects on prostate cancer growth.

This systematic review of 44 articles using FDA-approved agents (see concerns below with regard to other agents) was unable to directly provide a definitive answer to the question of whether TST replacement increases risk of prostate cancer, but provides other interesting insights.

First, trials of hypogonadal men treated with testosterone have not evidenced an increased risk for prostate cancer; if anything, a protective effect may occur. Second, TST-treated men with a history of prostate cancer did not experience more recurrences or metastases. Third, TST did not appear to influence Gleason scores when prostate cancer was detected.

The authors conclude, "There is no evidence that TST increases risk of prostate cancer in hypogonadal men." Of some concern, however, are the case reports of aggressive prostate CA in recipients of a non-FDA-approved supplement containing TST, estradiol, chrysin, and elk velvet antler. ■

## The Suicidal Process: Time to Intervene?

**Source:** Deisenhammer EA, et al. The duration of the suicidal process: How much time is left for intervention between consideration and accomplishment of a suicide attempt? *J Clin Psychiatry* 2009;70:19-24.

SUICIDE HAS BEEN AMONG THE MOST common causes of death in the United States for more than 20 years, usually ranking among the top 10. Clinicians would like to play a useful role in suicide prevention, yet data are sparse to inform about the interval between first suicidal ideation and the ultimate carrying out of a suicide attempt. Deisenhammer et al attempted to bridge this knowledge gap with a study of persons with failed suicide attempts, all of whom (n = 82) were interviewed within 72 hours of their attempted suicide.

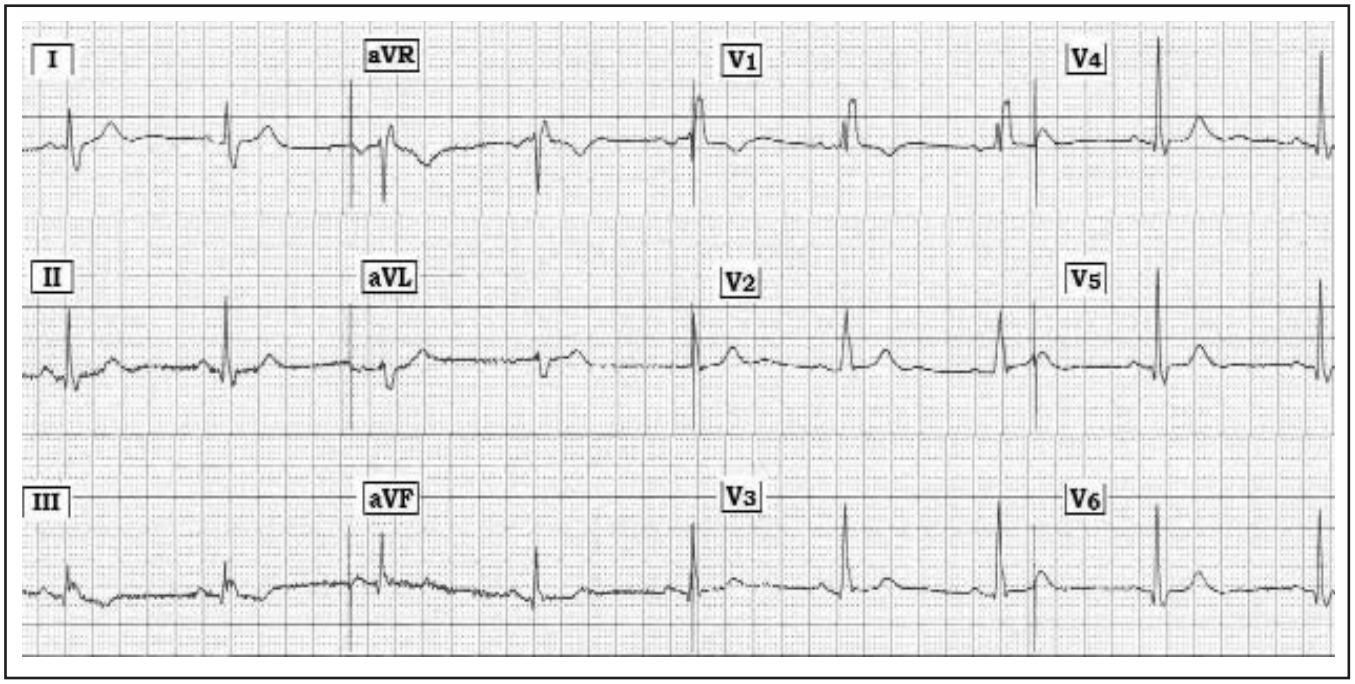
Most (83%) subjects were alone at the time of conceptualization of suicide, and almost half reported that the time interval from first conception of suicide to attempt was 10 minutes or less. Nonetheless, during this brief interval, most (77%) had had some contact (usually via telephone) with friends or family, and the majority either indicated their wish to die, or (according to their subjective report) hinted at their death wish.

Interviews with subjects did not provide any insight as to what might have deterred the suicide attempt. Nonetheless, the fact that most suicidal subjects did make contact with others leaves open the possibility that some component of interpersonal communication has the potential to change the course of suicide attempts. ■

# What Happened in the Past?

***By Ken Grauer, MD,*** *Professor, Department of Community Health and Family Medicine, University of Florida*

*Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.*




**Clinical Scenario**

The ECG shown above was a baseline tracing obtained during the initial visit with a new primary care provider. How would you interpret the tracing? What do you suspect happened in the past?

**Interpretation**

The rhythm is sinus bradycardia with a rate in the low 50s. The PR interval is normal, but the QRS complex is widened. QRS morphology is consistent with complete right bundle branch block (RBBB). The finding of note is the presence of multiple narrow q waves in the inferior and antero-lateral precordial leads. While small, narrow q waves may be a common normal finding in lateral precordial leads $V_5$ and $V_6$ (even in the presence of RBBB) — they are much less commonly seen in lead $V_4$, and usually won't be seen in lead $V_3$ or in the inferior leads in the presence of this conduction disturbance.

Thus, prior inferior and possibly also antero-lateral infarction should be considered in this patient with underlying RBBB. ST-T wave changes are consistent with RBBB, and do not suggest acute ischemia. However, the bradycardia should be explained, as to whether it is due to medication effect, sick sinus syndrome, or the patient's presumed underlying coronary artery disease. ■

## In Future Issues:

**Statins in Primary Prevention of Cardiovascular Disease: Are We Ready Yet?**

**Sleep to Your Heart's Content**

**Effects of Body Mass Index and Exercise on Risk of Heart Failure**

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*.

# Warning Regarding Topical Anesthetics

***In this issue:*** FDA warning on topical anesthetics; antipsychotics increase sudden cardiac death; the step up vs step down debate; treating pain, fatigue, mood, and sleep in fibromyalgia; FDA Actions.

## Something for your pain?

The FDA has issued a warning regarding topical anesthetics and the risk of life-threatening side effects. This is the second warning in 2 years regarding this issue, the first coming in February 2007 following the deaths of two women who used extensive topical anesthetics in preparation for cosmetic procedures. The latest warning was prompted by a study published in *Radiology*, which compared oral acetaminophen or ibuprofen vs lidocaine gel applied to the skin of the breasts to reduce discomfort during mammography. In the study, 4% lidocaine gel was applied by a nurse from the clavicles to the inferior costal margins and laterally to the mid axillary lines and then covered with plastic wrap to ensure consistency of application. Discomfort from mammograms was significantly lower in the lidocaine gel group and the authors postulate that decreased discomfort may improve the likelihood of future mammographic screening (Lambertz CK, et al. *Radiology* 2008;248:765-772). The FDA's previous warning in 2007 followed on the heels of two reports of young women undergoing laser hair removal who applied either lidocaine or tetracaine topical preparations to the lower extremities and then covered the application with plastic wrap. Both women developed seizures, fell into a coma, and eventually died due to excessive blood levels of the topical anesthetic. Many of these topical products are available over the counter. The FDA strongly advises consumers not to: make heavy application of topical anesthetics over large areas of skin, use concentrated formulas, apply to broken or irritated skin, wrap the treated skin with plastic wrap or other dressings, or apply heat to skin treated with these products.

## Increase in sudden cardiac death

Antipsychotics, both typical and atypical, are associated with a dose-related increase in sudden cardiac death according to a new study. Typical antipsychotics such as thioridazine (Mellaril®) and haloperidol (Haldol®) block repolarizing potassium currents and prolong QT intervals. Multiple studies have shown a dose-related increased risk of sudden cardiac death associated with these drugs. Less is known about the atypical antipsychotic drugs although many have similar cardiovascular effects. Researchers from Nashville reviewed the records of Medicaid enrollees in Tennessee including the records of 44,218 and 46,089 baseline users of a single typical and atypical antipsychotic, respectively. These were matched with 186,600 nonusers of antipsychotic drugs. Thioridazine and haloperidol were

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the most frequently prescribed typical agents, while clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), and risperidone (Risperdal®) were the most commonly used atypical agents. Both users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers with adjusted incident rate ratios of 1.99 (95% CI, 1.68-2.34) and 2.26 (95% CI, 1.8-2.72), respectively. There was a higher rate for users of atypical antipsychotic drugs vs typical antipsychotics with an incident rate of 1.14 for the comparison (95% CI, 0.93-1.39). For both classes of drugs, the risk for current users increased significantly with increasing dose. The authors conclude that current users of typical and of atypical antipsychotic drugs had similar, dose-related increased risk of sudden cardiac death and that atypical antipsychotic drugs are no safer than the older drugs (Ray WA, et al. *N Engl J Med* 2009;360:225-235). An accompanying editorial suggests that children and the elderly are particularly vulnerable to these drugs and their use in these populations should be "sharply reduced" (Schneeweiss S, Avorn J. *N Engl J Med* 2009;360:294-296).

### Step up vs step down

Which is more effective for treating dyspepsia: Starting with aggressive therapy and tapering down, or starting with antacids and progressing to more aggressive therapy depending on symptoms? The so called step-up vs step-down debate has raged for years, particularly in managed-care settings. In a new study from the Netherlands, patients with dyspepsia were randomized to treatment with an antacid, H2-receptor antagonist, and proton pump inhibitor (step up) vs the same drugs in reverse order (step down), with each step lasting 4 weeks. Primary outcome was symptom relief and cost-effectiveness of initial management at 6 months. Treatment success after 6 months was achieved in 72% of patients in the step-up group and 70% of patients with step-down group. The average medical costs were lower for patients in the step-up group (€228 vs €245; $P$ = 0.0008) mainly because of the cost of medication. The rate of adverse effects was the same in both groups and were generally mild. The authors suggest that treatment success is similar in both groups but the step-up strategy was more cost-effective for patients with new onset dyspeptic symptoms (van Marrewijk CJ, et al. *Lancet* 2009;373:215-225). An accompanying editorial suggests that the degree of cost difference between the two groups was overestimated because costs were based on brand name drugs and generics are now available. It furthers suggested that the study may not change practice in primary care as the author recommends a 4-8 week course of a proton pump inhibitor for patients with symptoms of the upper gastrointestinal tract with discontinuation of treatment if patients remain asymptomatic (van Zanten SV. *Lancet* 2009;373:187-189).

### Pain, fatigue, mood, sleep and fibromyalgia

Tricyclics work better than other antidepressants for the treatment of fibromyalgia according to new study from Germany. In a meta-analysis of 18 randomized controlled trials of antidepressants for the treatment of fibromyalgia, researchers reviewed studies utilizing tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAO). All antidepressants were associated with a reduction in pain, fatigue, depressed mood, and sleep disturbances. Pain reduction was particularly good for tricyclic antidepressants, while MAO inhibitors showed modest effect and SSRIs and SNRIs showed a small effect. TCAs were effective in low doses of 12.5-50 mg, far below the doses commonly employed to treat depression, and were very effective for reducing pain, fatigue, and sleep disturbance (*JAMA* 2009;301:198-209). Currently duloxetine (Cymbalta®), pregablin (Lyrica®), and milnacipran (Savella™) are the only FDA-approved drugs for the treatment of fibromyalgia.

### FDA Actions

The FDA is launching a program to improve the safety of imported drugs to the United States. The pilot program would allow manufacturers of drugs outside United States to apply for 1 of 100 certifications, which would require that companies have a secure supply chain for their product. Criteria would include holding an FDA-approved drug application, guaranteeing that active pharmaceutical ingredients would be imported only to make FDA-approved drugs, complying with Good Manufacturing Practices, and guaranteeing that their drug products use a secure supply chain. This program is in response to concerns about manufacturing processes outside the United States and the embargoing of several foreign manufactured drugs in the last year. ■