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INSIDE

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Very Close Veins Can Be a Pain

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus

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

Synopsis: *Symptoms of lower extremity venous disease are directly related to the degrees of visible and functional disease, but may occur even in legs that appear normal.*

Source: Langer RD, et al. Relationships between symptoms and venous disease: the San Diego population study. *Arch Intern Med*. 2005;165: 1420-1424.

LOWER EXTREMITY VENOUS DISEASE IS NOT GLAMOROUS OR straightforward. A variety of symptoms have been ascribed to venous disease. It can present as simply as spider veins, or as complicated as non-healing ulcers. Disease can be present without any visible signs. This study attempts to correlate symptoms of venous disease with signs and duplex ultrasonography.

The 2404 subjects were randomly selected from current and retired employees of the University of California, San Diego, along with their spouses and some volunteers who had heard about it. Women and minorities were oversampled. The age range was 29 to 91 years old with an average age of 59.7 for men and 58.4 for women.

Routine demographic data—medical history, family history, and lifestyle information—were obtained. Symptoms possibly related to venous disease (aching, itching, heaviness, tired legs, cramping, swelling, nighttime restless legs) were determined. A detailed physical examination of the lower extremities and a duplex ultrasound of the superficial and deep venous systems were performed.

For the purposes of this study, visible venous disease was divided into normal, telangiectasis or spider veins (TSVs), varicose veins (VVs), and trophic changes (TCs: hyperpig-

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mentation, lipodermatosclerosis, healed or active ulcers). The classification was hierarchical. Normal legs had no TSVs, VVs, or TCs. Legs with TSVs had no VVs or TCs. Legs with VVs could also have TSVs, but no TCs, etc. Patients with normal appearing legs, but a history of sclerotherapy or vein stripping, were classified as TSVs and VVs, respectively.

The duplex ultrasound exam determined functional classification. It, too, was hierarchical. Legs could be normal, have superficial functional disease (SFD), or have deep functional disease (DFD). SFD was defined as reflux or partial or complete obstruction of the long or short saphenous veins or another superficial vein. Similarly, DFD was defined as the same problems in the common femoral, superficial femoral, popliteal, posterior tibial, or peroneal veins or an abnormal Valsalva response at the common femoral vein or saphenofemoral junction.

Women (84%) had more visible disease than men (57%); this was true for TSVs (56% vs 44%) and VVs (28% vs 15%). However, men (8%) had more TCs than women (5%). Overall, functional disease was more common in women (30%) than men (24%), but while women held the edge in SFD (22% vs 13%), DFD was more common in men (11% vs 8%).

The most common symptom was aching (17.7%), followed by cramping (14.3%), tired legs (12.8%), swelling (12.2%), heaviness (7.5%), restless legs (7.4%), and itching (5.4%). Women were more symptomatic than men. The prevalence of all symptoms (except restless legs) was directly related to the severity of the functional disease. The same direct relationship existed for symptoms and visible disease.

Odds ratios (OR) for each symptom were calculated for each of the 12 combinations of visible and functional disease (eg, TSVs/normal, VVs/DFD, etc). Logistic regression adjusted for age, sex, body mass index, race/ethnicity, and educational achievement revealed several statistically significant associations. Aching (OR, 2.20) and swelling (OR, 2.99) were associated with DFD, even in people with no visible disease. Itching was associated with VVs across all degrees of functional disease. No symptom reliably distinguished normal from disease. For instance, although aching was the most common symptom, present in 17.7% of people overall, 15.5% of people with normal function complained of it (vs 27.2% with DFD). On the other hand, although swelling was present in subjects with normal function (9.5%), in individuals with DFD the rate almost tripled to 26.9%. Aching, itching, heaviness, and swelling were present in people without visible disease (14.2%, 4.0%, 4.4%, and 7.2%, respectively), but the rates were much greater in VVs (25.5%, 8.7%, 11.8%, and 19.1%, respectively) and TCs (29.1%, 13.1%, 16.0%, and 35.7%, respectively).

COMMENTARY

The take-away message here is the worse the symptoms, the worse the disease, both functionally and aesthetically. I've chosen my words carefully; the industry that has grown up around the elimination of visible venous disease is big business. Each morning, when I drive to work, I'm assaulted by a billboard that screams, "Do you have varicose veins?

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Questions & Comments

Please call **Robert Kimball**, Managing Editor, at (404) 262-5413 (e-mail: robert.kimball@thomson.com) between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Do you have 45 minutes? Walk home!" Google "varicose" and you'll discover myriad sites devoted to the treatment varicosities, along with some reputable patient information sites (for instance, the National Library of Medicine[1] and the Department of Health and Human Service's Office on Women's Health[2]).

One could question whether you can extrapolate the findings of this study to your patients, since the study population was derived from folks employed by a university. One question unanswered by this study is whether treatment affects symptoms, and if there are differences among various treatments. Available treatments include surgical stripping, sclerotherapy, phlebotonics (natural flavonoids such as grape seed oil), and VNUS® Closure®, which uses radiofrequency (RF) energy delivered intravascularly. Sclerotherapy is better than stripping in the short run, but stripping is better at 5 years.[3] Phlebotonics seem to help with edema.[4] RF endovenous occlusion may be a better tolerated surgical approach,[5] but at 3-year's follow-up stripping may have better outcomes.[6]

Swelling, aching, itching, and heaviness of the legs are vague symptoms and not limited to venous insufficiency. Indeed, physicians and their patients tend to associate swelling with congestive heart failure, aching with myositis or overuse, and itching with dermatitis or xerosis. However, these symptoms, especially if they occur together, should prompt us to consider venous disease. ■

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Treating Osteoporosis with Parathyroid Hormone: When and How to Do It

ABSTRACTS & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

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

Synopsis: *Two recent studies shed further light on the short-term use of parathyroid hormone (PTH) to enhance the treatment of osteoporosis. PTH is approved for use up to 2 years in patients with moderate-to-severe osteoporosis. The anabolic bone formation induced by PTH is largely lost after stopping therapy, but is well maintained by continued therapy with a biphosphonate. PTH may be given continuously or cyclically to enhance bone formation.*

Sources: Black DM, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med*. 2005;353:555-565; Cosman F, et al. Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med.* 2005;353:566-575.

Parathyroid hormone (PTH) is given by daily subcutaneous injection and is approved for up to 2 years in the treatment of moderate-to-severe osteoporosis. The reasons for the short-term use are twofold. First, the early studies of PTH in rats showed an increased risk of osteosarcoma with longer-term use, a finding which has been discounted by further analysis. More importantly, the benefits of PTH in causing bone formation appear to be short lived, mainly during the first 6-12 months of therapy, although some benefits have been shown for up to 2 years. The early increased bone formation with PTH before resorption has been called the *anabolic window*.

Previous research by Black and colleagues reported in 2003 showed that while PTH was highly effective in treating osteoporosis, concomitant therapy with a bisphosphonate offered little addition benefit.[1] In addition, this earlier research showed that the benefits of short-term PTH administration were diminished after therapy was discontinued. In the new study referenced here, Black et al showed that the benefits of PTH therapy are largely maintained by administering a bisphosphonate continuously after PTH therapy.

Cosman et al studied a new use of this novel therapy

for osteoporosis, by administering PTH in 3-month cycles for one year, comparing it with daily therapy with PTH, and comparing both regimens with a bisphosphonate. A control group took a bisphosphonate only. These researchers hypothesized that the enhanced anabolic effects seen with PTH in the first months of therapy might be repeated with the 3-month cycles. They found that PTH increased bone mineral density over bisphosphonate alone by 6.1% with daily PTH and 5.4% with cyclic PTH. While they did not find an enhanced benefit of the cyclic therapy, they confirmed the treatment value of PTH to increase bone mineral density.

It should be noted that the number of subjects in both of these studies was small, 119 in the Black et al study and 126 in the Cosman et al study. With these small numbers and the short term follow-up, no statement can be made to demonstrate that the PTH therapy prevented fractures.

COMMENTARY

While osteoporosis continues to increase among both men and women, major strides have been made in its treatment. The same issue of the *New England Journal of Medicine* which reported these studies has an excellent clinical review of postmenopausal osteoporosis.[2] Lifestyle and pharmacologic options are available for both prevention and treatment. Bisphosphonates have emerged as the preferred first-line agents for most postmenopausal women.

When patients have moderate-to-severe osteoporosis, the stakes are higher to protect bone and prevent fractures. For these high-risk patients, 1-2 years of therapy with PTH should be considered. As with the patients studied here, many of them have been taking a bisphosphonate and this should be continued while receiving the PTH although the additional benefit during combined therapy is small. There is no downside to combined therapy, and weekly or monthly use of a bisphosphonate is convenient. What is most exciting about these new data is that the benefits of administering PTH for 1-2 years are maintained when the bisphosphonate is continued. We may now with confidence give these high-risk patients a boost in bone mineral density which lasts. Admittedly, the data for fracture prevention with PTH are still lacking. ■

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Polycystic Ovary Syndrome: Changes in Glucose Tolerance

ABSTRACT & COMMENTARY

By Leon Speroff, MD

Professor of Obstetrics and Gynecology, Oregon Health & Science University, Portland

Dr. Speroff is a consultant for Barr Laboratories.

Synopsis: *Women with polycystic ovaries demonstrate a definite rate of worsening glucose tolerance and conversion to type 2 diabetes mellitus.*

Source: Legro RS, et al. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *J Clin Endocrinol Metab*. 2005;90:3236-3242.

Legro and colleagues followed 71 women with polycystic ovary syndrome and 23 normal women with regular menses for 2 to 3 years. Impaired glucose tolerance increased in prevalence during the follow-up period in the women with polycystic ovaries, from 37% with impaired tolerance and 10% with type 2 diabetes mellitus at baseline to 45% and 15%, respectively. Based on their results, Legro et al affirm the importance of periodic assessment of glucose tolerance, but they question whether this is necessary annually.

COMMENTARY

Although we know that there is a high prevalence of impaired glucose tolerance in adult women with polycystic ovaries, we have not known the rate at which individuals change from normal to abnormal. The changes in the women in this study were not dramatic. For example, the glycohemoglobin levels were in the range of normal in the group with polycystic ovaries, but the levels had increased to the upper range in the relatively short time of the follow-up. Nevertheless, the measurements indicated a worsening and conversion rate of about 2% per year to type 2 diabetes mellitus.

Another useful clinical finding in this study was the fact that fasting glucose levels did not change. Therefore, measurements of fasting glucose and glycohemoglobin levels will not detect the early worsening of insulin resistance and glucose tolerance. The proper method to evaluate insulin resistance and glucose tolerance has been somewhat controversial.

Interpretation of the 2-hour glucose response:	
Normal	less than 140 mg/dL
Impaired	140-199 mg/dL
Noninsulin-dependent diabetes mellitus	200 mg/dL and higher
Interpretation of the 2-hour insulin response:	
Insulin resistance very likely	100-150 U/mL
Insulin resistance	151-300 U/mL
Severe insulin resistance	greater than 300 U/mL

Because of the variability, the fasting glucose to fasting insulin ratio is no longer recommended; a 2-hour oral glucose tolerance test is now the preferred method of assessment.

All anovulatory women who are hyperandrogenic should be assessed for glucose tolerance and insulin resistance with measurement of 2-hour glucose and insulin levels after a 75 g glucose load.

In my view, periodic surveillance is necessary in women who continue to manifest this disorder. Until strong evidence emerges to the contrary, I believe an annual assessment with the 2-hour glucose tolerance test is appropriate, especially in women who fail to lose weight. ■

Pharmacology Update

Tigecycline Injection (Tygacil™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Associate 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 FDA HAS APPROVED TIGECYCLINE, THE FIRST OF A new class of antimicrobial agents. The drug is a novel parenteral antibiotic that is chemically similar to minocycline. It is active against a wide variety of bacteria that cause complicated intra-abdominal and complicated skin and skin structure infections including methicillin-resistant Staphylococcus aureus (MRSA). Tigecycline is marketed by Wyeth as Tygacil™.

Indications

Tigecycline is indicated for the treatment of complicated intra-abdominal infections (cIAIs) caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterobacter faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.[1]

Tigecycline is also indicated for the treatment of complicated skin and skin structure infections (cSSSIs) caused by *E. coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *S. aureus* (methicillin-susceptible and resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, and *Bacteroides fragilis*.[1]

Dosage

The recommended dose is 100 mg initially followed by 50 mg every 12 hours. The dose should be given by intravenous infusion over 30-60 minutes. The recommended duration of treatment is 5-14 days depending on the severity, site of infection, and patient response. No dosage adjustment is required for mild-to-moderate hepatic dysfunction, renal impairment, age, gender, or race. For patients with severe hepatic dysfunction, the maintenance dose should be reduced to 25 mg every 12 hours.[1]

Tigecycline is supplied as a 50 mg single-dose vial.

Potential Advantages

In vitro data indicate that tigecycline is generally not affected by resistance mechanisms associated with methicillin-resistant staphylococcus, glycopeptide-intermediate and resistant *S. aureus*, vancomycin-resistant enterococci, penicillin-resistant pneumococci, and β lactamase producing pathogens.[2]

Potential Disadvantages

Nausea and vomiting are the most common side effects, occurring in nearly 30% and 20% of patients respectively.[1]

Comments

Tigecycline is the first member of the glycycline class of antimicrobial agents. Its bacteriostatic action is based on binding to bacterial 30S-ribosome. This is similar to, but more effective than, the tetracyclines, including tetracycline-resistant ribosomes.[2] It has demonstrated in vitro activity against the most prevalent bacteria that cause cSSSIs and cIAIs.[3] In phase III studies tigecycline monotherapy was found to be similar to vancomycin/aztreonam in cSSSIs and to imipenem/cilastatin in cIAIs.[4,5] In cSSSIs studies, patients were treated with tigecycline (100 mg, followed by 50 mg twice

daily) or vancomycin/aztreonam (1 g and 2 g twice daily). Duration of treatment was up to 14 days. Clinical response based on clinical modified intent-to-treat was 79.7% for tigecycline and 81.9% for vancomycin/aztreonam ($P = 0.42$) (n = 1057). Microbiologically evaluable clinical response was 86.4% and 88.5% respectively ($P = 0.54$) (n = 540). For the treatment of cIAIs, tigecycline (100 mg followed by 50 mg) was compared to imipenem/cilastatin (500 mg/50 0 mg every 6 hours). The treatment duration was 12-42 days. Clinical cure based on clinical modified intent-to-treat was 79.8% for tigecycline and 82.0% for imipenem/aztreonam ($P = 0.29$) (n = 1601). Microbiologically evaluable clinical response was 86.1% and 86.2% respectively ($P = 1.0$) (n = 1026). Tigecycline appeared to be well tolerated with gastrointestinal symptoms (nausea, vomiting, anorexia, diarrhea, dyspepsia) as the most common adverse events. In vitro data indicate that tigecycline is active against glycoprotein-immediately resistant *S. aureus*, resistant strains of *E. faecalis* and *E. faecium*, penicillin-resistant *S. pneumoniae*. Tigecycline appears to be generally unaffected by the commonly prevalent resistant phenotypes.[2,6] Comparative clinical trials with other antibiotics are lacking (eg, vs daptomycin or linezolid in cSSSIs). The cost for a 10-day course of therapy is about $10,000.

Clinical Implications

Tigecycline is a member of a new class of antimicrobials. It appears to be an important addition as an agent against pathogens resistant to other antimicrobials. Judicious use of this new agent is paramount in order to minimized future development of resistant pathogens. ■

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CME Questions

9. For patients with moderate-to-severe osteoporosis, which statement regarding therapy is accurate?

a. If parathyroid hormone (PTH) is used, other therapies such as a bisphosphonate should be discontinued and not restarted until 1 year after PTH administration.
b. PTH therapy is given subcutaneously and may be used for no longer than 5 years.
c. In patients on a bisphosphonate, PTH may be administered for 1-2 years while continuing the bisphosphonate during and after hormone administration.
d. PTH is best used as monotherapy and its anabolic effects continue after treatment with or without a bisphosphonate.

10. The most common symptom of venous disease of the lower extremities is:

a. swelling.
b. heaviness.
c. cramping.
d. itching.
e. aching.

11. The following statements are true regarding polycystic ovaries and glucose tolerance *except*:

a. A fasting glucose level as part of an annual evaluation is an adequate screen for impaired glucose tolerance.
b. Active intervention by clinicians can prevent the onset of overt diabetes mellitus in women with polycystic ovaries.
c. The rate of conversion to type 2 diabetes mellitus in women with polycystic ovaries warrants periodic assessment of glucose tolerance.
d. Fasting insulin levels reliably establish the presence of insulin resistance.

Answers: 9 (c); 10 (e); 11 (a)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances; and
- to describe cost-effective treatment regimens.

Clinical Briefs

By Louis Kuritzky, MD

Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Staphylococcal Toxins in Patients with Psoriasis, Atopic Dermatitis, Erythroderma, and in Healthy Control Subjects

THE ROLE THAT MICROBES PLAY IN some dermatoses is not always immediately evident. For instance, the yeast *Pityrosporum orbiculare* is etiologic in some cases of seborrheic dermatitis; hence, even though topical steroid treatment can control symptoms by reducing inflammation, antifungal treatment may also resolve seborrheic dermatitis.

Staphylococcus aureus (SA) is found on the skin or nares of up to 30% of healthy individuals. In skin lesions of atopic dermatitis (AD) or psoriasis (PSO), colonization with SA is found even more often (46-93%). Additionally, SA is cultured disproportionately more frequently in active skin lesions of AD and PSO than in uninvolved skin, giving credence to a potential etiologic role.

Patients (n = 75) with AD, PSO, and controls were evaluated for the presence of SA; additionally, SA subtyping was performed to determine the presence of Staphylococcal enterotoxin. More AD patients (88%) than PSO (60%) were lesion-positive for SA. In both disorders, there was a correlation between the presence of SA enterotoxin and disease severity. The authors posit that SA enterotoxin may induce or aggravate skin lesions of psoriasis and atopic dermatitis, and that methods to reduce SA colonization might be beneficial in both disorders. ■

Tomi NS, et al. J Am Acad Dermatol. 2005;53:67-72.

Insulin Resistance and Risk of Congestive Heart Failure

HEART FAILURE (CHF) IS MOST COMmonly caused by hypertension and coronary artery disease. Framingham data from as far back as 1974 have shown an association between diabetes and CHF. Only recently has a relationship between obesity and CHF been described. A variety of mechanisms by which diabetes or obesity might increase risk for CHF has been offered, but the insulin resistance (IR) shared by both maladies appears a likely culprit.

The Uppsala Longitudinal Study of Adult Men is a prospective observational study intended to investigate metabolic risk factors for cardiovascular disease in Uppsala, Sweden; between 1970-1974, all men age 50 were invited to participate (n = 2322), and the population was re-investigated in 1990-1995; these data provide the baseline information for this study. Baseline data included BP, smoking status, waist circumference, BMI, oral glucose tolerance test, insulin resistance (by euglycemic insulin clamp method), plasma insulin, plasma proinsulin, and lipids.

The population selected for study was free of CHF or valvular disease at baseline. During a mean follow-up of 8.9 years, 104 men developed CHF.

The presence of IR was found to be a predictor of CHF, independent of diabetes, and other known CHF risk factors. The association between obesity and CHF, which held true whether waist circumference or BMI was used as the metric, was mitigated when IR was included in the multivariate analysis, suggesting that IR is, to some degree, causal in the relationship. ■

Ingelsson E, et al. JAMA. 2005;294:334-341.

Ciprofloxacin Interacts with Thyroid Replacement Therapy

A NUMBER OF COMMONPLACE MEDications have been shown to interfere with absorption of orally administered thyroid hormone (levothyroxine), including aluminum-containing antacids, iron, cholestyramine, sucralfate, and calcium carbonate. Such interactions can be problematic on a large epidemiologic scale since, for instance, many of the middle-aged women who are taking thyroid hormone replacement (TH) are also taking calcium carbonate for bone health.

Two case reports highlight the potential of ciprofloxacin (CIP) to impede TH absorption. In Case 1, an 80-year-old woman who had been stable on 125 µg/d TH reported fatigue after 4 weeks treatment with CIP for osteomyelitis. Lab evaluation showed marked decreases in T4 and T3, with corresponding elevation in TSH (up to 44 mIU/L). Increasing the TH had no effect.

Case 2 was a 79-year-old woman treated with CIP (500 mg b.i.d. × 3 weeks) for a wound infection. Thyroid function tests and symptoms been previously stable on 150 mg/d of levothyroxine. Testing after 3 weeks of CIP indicated a decline in free T4 (from 22 to 13 picomoles/L) and an elevation in TSH (from 1.6 to 19 mIU/L). Providing an interval of 6 hours between CIP and TH produced normalization of thyroid function tests.

Other data have shown that providing a gap between calcium carbonate administration and TH resolves the medication competition. For patients who take TH, administration of CIP should be separated by at least several hours. ■

Cooper JG, et al. BMJ. 2005;330:1002.

Premature Ischemia?

By Ken Grauer, MD

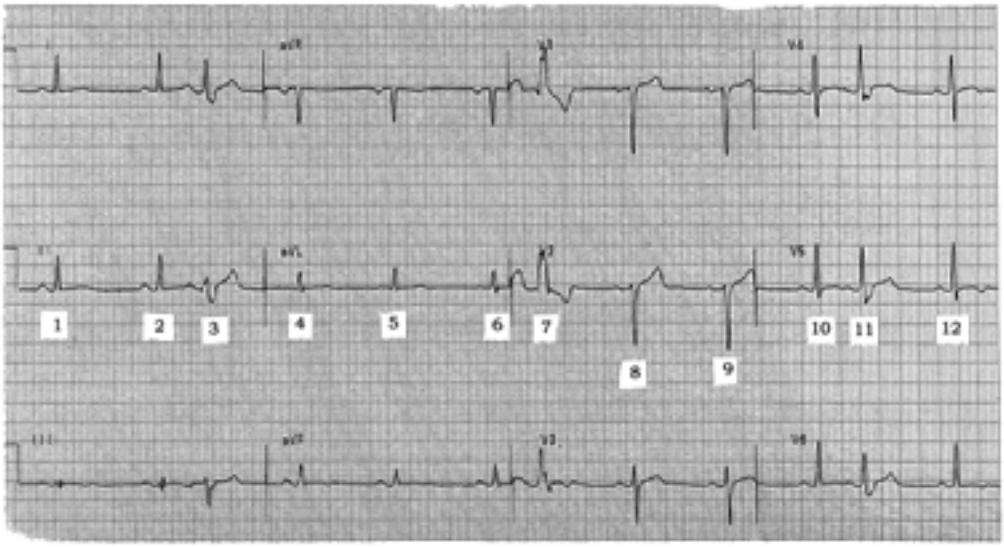

Figure. 12-lead ECG obtained from a 57-year-old man with intermittent episodes of atypical chest discomfort.

Clinical Scenario: The 12-lead ECG in the Figure was obtained from a 57-year-old man who presented with intermittent episodes of atypical chest pain, most often of short duration. The tracing was interpreted as showing PVCs, but without acute changes. What two amendments to this interpretation should be made?

Interpretation/Answer: Although no single lead rhythm strip is shown, the underlying rhythm in this tracing appears to be of sinus origin, since upright P waves with a constant PR interval are seen for the first 2 beats in lead II. Thereafter, there is obvious irregularity. The third beat in lead II (labeled #3) occurs early and is widened, however it is not a PVC. Instead, a "telltale" notched *premature* P wave is seen to precede beat #3, identifying this beat as a PAC (premature atrial contraction). QRS widening is the result of aberrant conduction.

Consecutive beats have been labeled in the figure under the middle row of complexes (ie, in leads II, aVL, V_2, and V_5). Following beat #3, the pattern of an early, widened beat is again seen for beats #7 and 11. Although a longer rhythm strip would be needed for confirmation, it appears that a pattern of "quadrigeminy" is present. It is likely that *each* of the premature, widened complexes (ie, beats #3, 7, and 11) are PACs conducted with aberration. We say this because two of these complexes are clearly preceded by premature P waves (beats #3 and 11), and QRS morphology for each of the widened complexes in the various leads is consistent with a RBBB (right bundle branch block) and LAHB (left anterior hemiblock) pattern. QRS morphology for aberrantly conducted premature beats most often manifests some pattern of bundle branch block, reflecting the fact that a PAC arrives at the AV node at an early enough point in time when a portion of the ventricular conduction system has not yet recovered. Thus, the wide terminal S wave seen in the early beats shown in leads I and V_6, in conjunction with the tall widened qR pattern seen in lead V_1 is consistent with RBBB morphology; and the deep negative S wave in lead II is consistent with LAHB. The rhythm in this tracing is therefore atrial quadrigeminy (ie, every fourth beat is a PAC), with QRS widening due to aberrant conduction (in which widened beats manifest a bifascicular block pattern of RBBB with LAHB).

The second important finding to note on this tracing is the ST-T wave change seen in the lateral precordial leads. Interpretation of ST-T wave changes is often a challenging task when a 12-lead ECG is marked by frequent ectopy. One needs to avoid using the ST segments not only of the premature widened beats, but also of normally conducted beats that immediately precede widened complexes, since the PACs may distort the ST segments of these normally conducted beats. We therefore focus our attention on the ST segments of beats #1, 4, 5, 8, 9, and 12 in this figure. Subtle but definite shallow symmetric T wave inversion is seen in leads V_{4-6}. In view of the history of chest discomfort, these lateral precordial ST-T wave changes may reflect ischemia. ■

In Future Issues:

Barrett's Esophagus and Insurance

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.

Beta-Blockers May Be Useful for Noncardiac Surgery

High risk patients benefit from perioperative beta-blockers when undergoing major noncardiac surgery according to new study. Researchers from Tufts University reviewed the records of 782,969 patients in 2000 and 2001 at 329 hospitals throughout the United States. Patients were graded with the Revised Cardiac Risk Index (RCRI), which takes into account high-risk surgery, ischemic heart disease, cerebrovascular disease, renal insufficiency, and diabetes. The RCRI is graded on a 0-5 point scale, with 5 representing the highest risk. High risk surgery included all intrathoracic, intraperitoneal, and superinguinal vascular procedures. Patients with contraindications to beta blocker therapy were excluded. Over 660,000 patients had no contraindications to beta-blockers, and 120,338 patients received beta-blocker treatment during the first 2 hospital days. The relationship between perioperative beta-blocker treatment and the risk of death varied directly with cardiac risk. Patients with an RCRI of 0 or 1 were found to have no benefit from beta-blocker treatment, whereas for patients with an RCRI of 2, 3, or 4, or more the adjusted odds ratio for death in the hospital, were 0.88 (95% CI, 0.80, 0.80-0.98), 0.71 (95% CI, 0.63 - 0.80) and 0.58 (95% CI, 0.50-0.67), respectively. The authors conclude that perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk patients undergoing major noncardiac surgery. They also noted that there was no benefit for low risk patients (Lindenauer PK, et al. Perioperative Beta-Blocker Therapy and Mortality After Major Noncardiac Surgery. *N Engl J Med*. 2005;353:349-361). An accompanying editorial points out that perioperative beta-blocker therapy has been somewhat controversial because of conflicting data in recent years. The current study shows an apparent benefit in high-risk patients, but they also look forward to the results of 2 ongoing randomized trials that will help clarify the role of beta-blockers for low-risk and intermediate-risk patients (Poldermans D, et al. Beta-Blocker Therapy in Noncardiac Surgery. *N Engl J Med*. 2005;353:412-414).

Promising New Weight Loss Drug?

More data shows that topiramate (Topamax) is associated with weight loss and, in this latest study, may also lower blood pressure in obese, hypertensive patients. In a study from Norway, 531 obese patients with hypertension were randomized to placebo, topiramate 96 mg/day, or topiramate 192 mg/day. All patients received the same diet, exercise, and behavioral modification advice. Patients were followed for 28 weeks. Mean weight loss was 1.9% for placebo and 5.9% and 6.5% for the 96 mg and 192 mg doses, respectively ($P < 0.001$ for each compared with placebo). Diastolic blood pressure was reduced 2.1, 5.5, and 6.3 mm Hg, respectively ($P < 0.015$ vs placebo). Systolic blood pressure was reduced 4.9, 8.6, and 9.7 mm Hg, respectively (P = NS). Paresthesia occurred in 33% of the active treat-

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ment group. The authors conclude that topiramate produced clinically relevant effects in reducing body weight and BP, with generally mild to moderate adverse effects (Tonstad S, et al. Efficacy and Safety of Topiramate in the Treatment of Obese Subjects with Essential Hypertension. *Am J Cardiol.* 2005;96:243-251).

Treating Shift-Work Disorder

Modafinil (Provigil) may be of some value for people with excessive sleepiness associated with shift-work sleep disorder. Researchers from Harvard randomized 209 patients with shift-work sleep disorder to receive either 200 mg of modafinil or placebo before the start of each shift. Modafinil resulted in modest improvement in nighttime sleep latency (1.7 ± 0.4 vs 0.3 ± 0.3 minutes, respectively; $P = 0.002$). More patients also had improvement in their clinical symptoms based on multiple objective tests and patients diaries (74% vs 36%, respectively; $P < 0.001$). Patients taking modafinil also had reduction in frequency and duration of lapses in attention during nighttime testing of performance, and proportionally fewer patients reported having had accidents or near accidents while commuting home (both $P < 0.001$). These benefits, however, were mild, and patients treated with modafinil continued to have excessive sleepiness and impaired performance at night. The authors conclude that modafinil 200 mg at the beginning of a shift may improve shift-worker's performance as compared to placebo, although the benefit is modest (Czeisler CA, et al. Modafinil for Excessive Sleepiness Associated with Shift-Work Disorder. *N Engl J Med*. 2005;353:476-486). An accompanying editorial urges caution when interpreting these results and suggests "the current study does not adequately assess the clinical value of this particular drug in shift-work sleep disorder, nor does it justify writing more prescriptions for modafinil." The authors do note that up to 20% of workers in industrialized nations are shift-workers and calls for "further scientific studies to address in a cohesive manner the serious health and safety issues that surround us by virtue of us having become, to a large extent, a shift-working society" (Basner RC. Shift-Work Sleep Disorder--The Glass is More Than Half Empty. *N Engl J Med*. 2005;353:519-521).

Another Flu Vaccine Shortage?

With the flu season looming, Chiron Corp. is again having difficulty with flu vaccine production. Last year the company found contamination at its Liverpool production plant, a situation that cause severe shortages of vaccine in the United States. This year, the company has discovered contamination at a German plant and is stating that it can only provide vaccine for the US market. The German plant was primarily the source of the Begrivac flu vaccine, which was sold on the world market. The company is making "substantial progress" in fixing problems at the Liverpool plant where the US vaccine is made. Meanwhile, Acambis plc is working on a universal flu vaccine that could offer permanent protection against all types of influenza. The company hopes to generate a universal vaccine that would not require annual changes in formulation and would protect against both influenza A and B including avian strains. The company, however, states that it may require years of clinical trials before earning approval. Fears of avian influenza pandemic have prompted the French company Sanofi-Aventis to work on a vaccine for the avian H5N1 strain that has killed millions of birds and 50 people in Asia. Preliminary results are promising, however, full-scale production could take months, according to Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases.

FDA Actions

The FDA has approved the first of the new class of drugs for the treatment of insomnia characterized by difficulty with sleep onset. Takeda Pharmaceutical's ramelteon (Rozerem) is a selective agonist at 2 melatonin receptors in suprachiasmatic nucleus, receptors that are thought to regulate circadian rhythm and sleepiness. Recently marketed sleeping medications target GABA receptors (ambien, lunesta) and, although these drugs are associated with less addiction and sleep latency then benzodiazepines, they are still designated as Schedule IV drugs. Ramelteon has shown no evidence of abuse or dependence potential and will, therefore, be marketed as a unscheduled drug. It is also approved for long-term use and has not been associated with memory impairment or impairment of motor ability. The most common adverse events associated with ramelteon were somnolence, fatigue and dizziness (> 2% over placebo).

Plan B, Barr Pharmaceutical's "morning-after pill" is being considered for over-the-counter approval by the FDA. The issue has become a political hot potato, and even briefly held up the Senate's confirmation of Lester Crawford, MD, as Commissioner of the FDA. It is expected that decision will be made by September. ■