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INSIDE

Another Myth DeBUNKED

ABSTRACT & COMMENTARY

Synopsis: *Medium-firm mattresses are better for patients with low back pain than are firm mattresses.*

Source: Kovacs FM, et al. *Lancet*. 2003;362:1599-1604.

This report results from a larger study on prevalence and risk factors for low back pain. Participants in this study were patients who had low back pain for at least 3 months. Those with referred pain, systemic disease, cancer, pregnancy, fibromyalgia, multiple beds, and chronic pain medicine or hypnotic ingestion were excluded. Kovacs and colleagues randomized 313 adults who had chronic, nonspecific low back pain to either a medium-firm or firm mattresses. In Europe, mattresses are rated by the European Committee for Standardization (good work if you can get it!) on a 1 to 10 scale. For this study, the firm mattresses were 2.3, and the medium firm ones were 5.6. Mattresses were installed in the participants' homes free of charge; patients and investigators were blinded to the type of mattress each patient received (although patients were fairly accurate in their judgment of the hardness of their new mattresses).

Patients were assessed at baseline and at 90 days. Primary outcomes were self-assessed intensity of pain while in bed and upon rising, as well as degree of disability. Pain was rated on a visual analogue scale, and disability was rated by a Spanish version of the Roland Morris questionnaire.[1] Kovacs et al collected data on a variety of lifestyle and anthropomorphic variables. Overall, 158 patients were assigned firm mattresses, and 155 were assigned to medium-firm mattresses; these groups did not differ from each other. Also, 73% were women, with a medium age of about 44 years. Average duration of pain was 9 or 10 years.

At 90 days, both groups showed improvement in symptoms. Pain intensity while lying in bed improved 70% and 80% for the firm and medium-firm groups, respectively. There was 57% improvement in intensity of pain on rising in both groups, and 30% and 50% improvement in disability in the firm and medium-firm groups, respectively. The improvements in disability and pain on rising were statistically significant for the medium-firm group compared with

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baseline. Seventeen percent and 9% of those with firm and medium-firm mattresses, respectively, had worsening of pain while lying in bed after the new mattresses were installed, but no one requested a mattress change.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

The fact that a study about mattresses and back pain was published in the *Lancet* is a testimony to the prevalence of back pain and the dearth of real science about how to deal with it. Chronic low back pain is extraordinarily common, with an estimated prevalence of 20%, yet there remains no consensus regarding workup or treatment of patients who have it.[2] Kovacs et al note that orthopedic surgeons strongly believe that mattresses play a role in managing low back pain and that a majority of them recommend a firm mattress, apparently on the basis of anecdotes. In the vast majority of cases, no organic cause can be identified, although manual labor is clearly implicated in many patients.[3] Back pain is the second only to headache as a chronic pain condition causing absenteeism and reduced work productivity.[4] Thus, the condition is common and costly, and it is about time that management of patients with back pain be based in science rather than dogma. ■

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Angiotensin II Antagonist as an Alternative to an ACE Inhibitor for Heart Failure after Myocardial Infarction

ABSTRACT & COMMENTARY

Synopsis: *The angiotensin II antagonist valsartan, at 320 mg per day, is as effective as captopril at 150 mg per day in reducing mortality in these high-risk patients. The combination of both drugs adds side effects without benefit.*

Source: Pfeffer MA, et al. *N Engl J Med*. 2003;349:1893-1906.

PREVIOUS RESEARCH FAILED TO SHOW THAT THE angiotensin II antagonist losartan at 50 mg per day was as effective as captopril in reducing mortality in patients with heart failure after myocardial infarction.[1] This raised the question of whether this new class of drugs may be substituted for ACE inhibitors in treating these high-risk patients. Both classes of drugs block the angiotensin pathway and would be expected to confer similar benefits.

This study compared the angiotensin II antagonist valsartan with captopril. Higher doses of the angiotensin II antagonist were used. More than 14,000 patients were randomized after myocardial infarction to receive valsartan at 160 mg twice daily, captopril 50 mg 3 times daily, or both. All patients had left ventricular dysfunction or heart failure. There was no placebo group, but the protective benefit of captopril at this dose over placebo has been demonstrated. The mortality over a median follow-up of 24.7 months was the same for both drugs. There was no increased benefit, but greater drug side effects, from using

the combination. Patients taking valsartan had more hypotension and renal dysfunction, and patients taking captopril had more cough, rash, and taste disturbance.

COMMENT BY JOSEPH E. SCHERGER, MD, MPH

This study clarifies a role for angiotensin II antagonists as an alternative to an ACE inhibitor for treating patients with heart failure after myocardial infarction. As the editorial by Mann and Deswal in this same issue states, dosage is important.[2] The angiotensin II antagonist valsartan, taken at 320 mg per day, may be substituted for a full dose ACE inhibitor. ACE inhibitors remain a first choice due to their lower cost and less serious side effects. However, some patients simply cannot tolerate an ACE inhibitor, usually due to a protracted cough or allergic reaction. In this day of multiple drug use for cardiac disease, it is good to know that using both drugs in combination does not confer added benefit. ■

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Dr. Scherger is Clinical Professor, University of California, San Diego.

Is Everyone at Risk for Venous Thrombosis on Long-Distance Air Flights?

ABSTRACTS & COMMENTARY

Synopsis: *Although there is an increased risk for venous thromboembolic events after long-haul airplane flights, the relative risk is in the lower range of the established transient risk factors and the highest risk applies only to individuals with pre-existing permanent risk factors (ie, age older than 45 years and/or abnormally elevated body mass index).*

Sources: Schwarz T, et al. *Arch Intern Med*. 2003;163:2759-2764; Perez-Rodriguez E, et al. *Arch Intern Med*. 2003;163:2766-2770.

During the past decade, at least 200 cases of air-travel related venous thrombosis have been reported in the literature[1] and almost certainly, thousands more cases have occurred but have not been reported. In fact, the term "economy class syndrome" was coined in 1977 to suggest that the restricted seat space in economy sections of aircraft was a major contributor to this syndrome.[2] Other physiological mechanisms such as decreased air pressure and release of nitric oxide in airplane cabins associated with dehydration (due to the consumption of alcohol and caffeine) along with venous stasis were also considered to be contributory factors to this potentially very serious travel problem. The World Health Organization declared that a link probably existed between air travel and deep venous thrombosis (DVT), that it mainly affects passengers with additional risk factors, but that scientific data were insufficient and that further studies were warranted.[3]

Two interesting articles published in the December 2003 issue of the *Archives of Internal Medicine* address the problems of isolated calf muscle venous thrombosis (ICMVT) with and without complicating pulmonary emboli. Schwarz and associates reported the results of their study of 964 flight passengers who intended to take a long-haul flight and compared them with 1213 nontraveling control subjects. Ultrasonographic studies were performed 1 week before the outgoing flight, and a second examination was performed within 48 hours after the return flight. Examinations were performed in the same way in the control group. ICMVT was found in 20 passengers and 10 controls, whereas 7 passengers and 2 control subjects presented with DVT. Symptomatic pulmonary embolism occurred in only one passenger with DVT. All of the subjects had normal findings on baseline ultrasonography. The second article by Perez-Rodriguez and colleagues was a retrospective review of pulmonary thromboembolism (PTE) occurring among international travelers at the Madrid-Barajas airport for a 6-year period of time. They concluded that air travel is a risk factor for PTE and that the incidence increases with the duration of the air travel, but because the incidence is quite low, social alarm is not justified.

COMMENT BY HAROLD L. KARPMAN, MD

Air flights longer than 8 hours in duration double the risk of ICMVT; however, in the well-controlled study performed by Schwarz et al, all the passengers with ICMVT or DVT had at least one risk factor (ie, older than 45 years of age or elevated body mass index, which, incidentally, was present in 21 of the 27 passengers with venous thrombotic events).[4] The results in this study also suggested that the incidence of ICMVT may be used as a surrogate marker of DVT associated with air travel. Schwarz et al had also previously demonstrated that short-term low-molecular-weight heparin in patients with ICMVT prevents thrombus progression.[4]

There were at least 3 limitations to this study: 1) The results may not apply to the general population; 2) The

baseline characteristics of passengers and controls did not match in each category; and 3) For ethical reasons, it was recommended to all passengers that they not consume alcoholic beverages and that they perform stretching exercises during their flights. These 3 limitations may be significant and may have had important effects upon the final results; however, this is the first controlled study evaluating DVT after long-haul flights and the conclusions of Schwarz et al are important. They concluded that their results supported the World Health Organization statement that, although there exists an increased risk for venous thromboembolic events after long-haul flights, the relative risk is in the lower range of the established transient risk factors and that the highest risk applies only to individuals with pre-existing permanent risk factors. In addition, although stretching exercises and adequate hydration for all passengers is clearly recommended, prophylactic anticoagulant therapy and/or compression stockings should not be recommended at this time, but that their use should be carefully investigated in future, well-designed, randomized studies in large, at-risk groups. ■

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CT Virtual Colonoscopy for Colorectal Neoplasia

ABSTRACT & COMMENTARY

Synopsis: *Unlike previous studies that demonstrated superiority of optical colonoscopy, this trial found that the 2 procedures were similar for detection of clinically significant lesions.*

Source: Pickhardt P, et al. *N Engl J Med*. 2003;349(23): 2191-2200.

THIS MULTICENTER STUDY COMPARED RESULTS OF initial virtual colonoscopy with a 3-dimensional computerized tomographic (CT) approach with subsequent standard video colonoscopy. In this study, 1233 patients were evaluable (others had incomplete colonoscopy or CT failure or poor preparation). Pneumocolon for CT colonoscopy was patient controlled. For polyps 8 mm or larger, virtual colonoscopy was more than 92% accurate with > 99% accuracy for larger polyps (and quite acceptable levels of specificity). All centers had comparable results for virtual colonoscopy. Optical colonoscopy was actually a bit less sensitive than radiography. Two malignant polyps were found with virtual colonoscopy, one having been initially missed on optical colon examination. Time in x-ray was 14.1 minutes vs 31.5 minutes in the endoscopy suite (mean total time including recovery was 95.9 minutes). Overall, 54.3% of patients rated virtual colonoscopy as more uncomfortable, but more patients still related an overall preference for virtual colonoscopy. Pickhardt and colleagues recommend virtual colonoscopy for screening of low-risk or average-risk individuals and suggest that finding a polyp of 8 mm or larger on this exam should mandate immediate optical colonoscopy and polypectomy. In this study, 86.5% of the patients screened would not have required optical colonoscopy if the 8 mm level of polyp size had been selected.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Virtual colonoscopy has finally arrived as a viable option for colon screening. As an accompanying *New England Journal of Medicine* editorial points out, colon screening has been recommended for all average-risk adults beginning at age 50, a formidable medical undertaking with a high cost. Could virtual colonoscopy replace a significant fraction of currently recommended optical colonoscopies? The answer is unclear, but there are a number of potential disadvantages to the radiographic approach. First, unlike optical colonoscopy that is potentially simultaneously diagnostic and therapeutic, virtual colonoscopy provides no therapeutic benefit. Patients who need a follow-up standard colonoscopy with polypectomy almost certainly will require a second aggressive colon-cleansing regimen since immediate endoscopy for positive findings will seldom be available. Although the ultimate commercial cost for virtual colonoscopy is uncertain, it is likely to be quite high. Overall expense of a protocol that includes both modalities may be unacceptably high. Most medical insurance currently doesn't cover virtual colonoscopy. Admittedly, as a gastroenterologist, I am biased toward optical colonoscopy. As a patient, I am quite sure that I would opt for endoscopic examination of my colon. However, if the availability of virtual colonoscopy led to increased numbers of patients willing to undergo colon screening, I and most other gastroenterologists would have to welcome this new procedure to the overall diagnostic armamentarium. ■

Best Office Test for Quadriceps Weakness

ABSTRACT & COMMENTARY

Synopsis: *In L3 and L4 radiculopathies, unilateral quadriceps weakness was best detected by a single leg sit-to-stand test. Patients of similar age with radicular pain caused by L5 or S1 radiculopathies could perform this test.*

Source: Rainville J, et al. *Spine.* 2003;28:2466-2471.

THIRTY-THREE CONSECUTIVE PATIENTS WITH L3 OR L4 radiculopathy were compared to 19 controls of comparable age to determine the best method for detecting quadriceps weakness in the office setting. Controls had either L5 or S1 radiculopathy to allow for the effect that pain might have in preventing full effort. Radiculopathy was in all instances documented by magnetic resonance or computerized tomographic scan, demonstrating compression of the appropriate nerve root. Patients were excluded if they had bilateral radiculopathy, peripheral neuromuscular disease, physical signs suggesting nonorganic amplification of symptoms, hip or knee arthritis, cancer, or psychiatric disorders. Four testing methods were studied: 1) The single leg sit-to-stand test, with the seated patient asked to extend one leg, hold that foot above the floor, and rise to the standing position with the other leg. The examiner could hold the patient's hands for balance; 2) The step-up test, with the patient stepping up onto a standard 7-inch step-stool, again holding the examiner's hands for balance; 3) The knee-flexed manual muscle test, with the patient supine, the hip flexed to 90°, the knee maximally flexed, and the patient attempting to extend the knee against the examiners resistance; and 4) The knee-extended manual muscle test, as in the knee-flexed manual muscle test but with the knee extended and the examiner trying to overcome knee extension. Reliability of findings was enhanced by a second examiner separately performing the identical examination. Statistical analysis was performed using frequency and means calculations, with kappa values calculated to determine inter-rater reliability.

The single leg sit-to-stand test was the most sensitive, with positivity in 61% (20/33). None of the controls failed this test. Knee-flexed and knee-extended manual muscle testing was positive in 42% and 9% of patients, respectively, with 1 control having weakness on the former. Step-up onto stool testing was positive in 27% of patients (9/33) but in no controls. Single-leg sit-to-stand quadriceps testing should be incorporated into the neurologic exam of suspected L3 or L4 radiculopathy where standard muscle tests fail to demonstrate quadriceps weakness. Suspected femoral neuropathy would be another scenario where this would be useful. Knee-extended manual muscle testing of the quadriceps is a waste of time.

COMMENT BY MICHAEL RUBIN, MD

How might sensory deficits be quantified in radiculopathy? Forty-eight patients with lumbosacral radiculopathy, secondary to magnetic resonance-documented L5 or S1 unilateral disc herniation, were examined using current perception threshold (CPT) evaluation to study A-beta, A-delta, and C fiber function.[1] Using a neurometer device, 3 electric current frequencies, 2000, 250, and 5 Hz, were administered to the L5 and S1 dermatome on the dorsal side of the first and fifth metatarsal, respectively. A visual analog scale was used to score pain intensity. Eleven healthy volunteers served as controls, and both legs were studied in all subjects.

Among radiculopathy patients, CPT values were significantly higher, at all frequencies, in the affected leg compared to the contralateral leg. Compared to controls, values were higher at 2000 and 250 Hz but not at 5 Hz. No significant CPT difference was found between the left and right legs in controls for any frequency. CPT testing may be useful to quantify small-fiber sensory nerve dysfunction in patients with radiculopathy. ■

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Dr. Rubin is Professor of Clinical Neurology, New York Presbyterian Hospital-Cornell Campus, New York, NY.

Pharmacology Update

Estradiol Topical Emulsion (Estrasorb)

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

A TOPICAL ESTRADIOL EMULSION HAS BEEN APPROVED for treating symptoms of menopause. Currently available estrogen products include pills, patches, and vaginal rings. The new estrogen emulsion provides another option for estrogen therapy. Novavax Inc markets this topical formulation as Estrasorb.

Indications

Estradiol emulsion is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.[1]

Dosage

The content of a pouch is applied to the clean, dry skin of each leg each morning. The emulsion should be applied to the thigh and calf. Each 1.74 g pouch contains 4.35 mg of estradiol hemihydrate. Two pouches are designed to deliver 0.05 mg of estradiol daily.[1]

Estrasorb is supplied in boxes of 56 pouches.

Potential Advantages

Estradiol emulsion offers a new option for estrogen therapy that some women may find more acceptable. The emulsion appears to be well tolerated.

Potential Disadvantages

Estradiol emulsion does not relieve local vaginal symptoms or vulvar atrophy. There is potential for estradiol transfer to males who have physical contact with female application sites. A 25% increase in serum estradiol concentration was observed in adult males upon contact at 2 and 8 hours after application for a 2-day period.[1]

The application of sunscreen 10 minutes before estrogen emulsion increases the exposure of estradiol by about 35% and by 15% if applied 25 minutes after estradiol emulsion.[1]

Comments

Estradiol emulsion is formulated with soybean oil, water, polysorbate 80, and ethanol. Its efficacy was demonstrated in a 12-week, randomized, placebo-controlled trial involving 200 postmenopausal women. There was a 66% reduction in the number of hot flushes at 4 weeks and 85% reduction at 12 weeks compared to 45% and 53% for those treated with placebo. Severity scores of hot flushes at 12 weeks were reduced by 61% with the estradiol emulsion compared to 23% for placebo.[1] The emulsion is generally well tolerated. Pruritus was reported in 4% of patients and appeared to be the only formulation-specific side effects. There are currently no published trials comparing the estradiol emulsion with other formulations of estradiol. The cost of the emulsion was not available at the time of this review.

Clinical Implications

Findings from the Women's Health Initiative indicated that oral estrogen increases the risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep-vein thrombosis.[2] The FDA recommends that estrogen be considered for treating moderate-to-severe vasomotor symptoms and moderate-to-severe symptoms of vulvar and vaginal atrophy. The use should be at the lowest dose and for the shortest duration possible.[3] Estradiol emulsion is not indicated for genitourinary symptoms. It thus becomes an alternative to oral tablets or the transdermal patch. Tablets are subject to first-pass metabolism, and the patch has been associated with local reactions. Oral estrogen, but not transdermal estrogen, has been associated with increased levels of C-reactive protein, an independent predictor of cardiovascular events.[4-6] The clinical relevance of this difference is, however, not clear as increased C-reactive protein may be related to metabolic hepatic activation or expression rather than a systemic pro-inflammatory effect, as no increase in other markers of inflammation was detected.[4-7] ■

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CME Questions

1. **Virtual colonoscopy provides all of the following except:**
   a. accurate delineation of colon polyps of 8 mm or larger size.
   b. adequate patient acceptance and comfort.
   c. the opportunity to diagnose and eradicate lesions in a single procedure.
   d. much less time consuming than standard optical colonoscopy.
   e. comparable results across a number of separate centers.

2. **Which of the following is true about chronic low back pain?**
   a. In most cases, a precise organic etiology can be identified.
   b. The condition is mostly a nuisance, with little impact on overall health and productivity.
   c. Well-validated treatment algorithms exist.
   d. A medium firm mattress reduces it better than does a firm mattress.
   e. Most patients transiently get worse when they get a new mattress.

Answers: 1 (c); 2 (d)

By Louis Kuritzky, MD

Combined Levothyroxine Plus Liothyronine Compared to Levothyroxine Alone in Primary Hypothyroidism

Prior to sophisticated development of drug therapy, thyroid hormone was administered as a derivative of animal thyroid glands, with varying amounts of T3 and T4. Currently, although solitary levothyroxine (T4) is the preparation provided to more than 90% of patients with hypothyroidism (hTHY), there has been some enthusiasm for use of combination products (T3 and T4) or T3 alone. However, it remains controversial whether T3 provides additional benefit over simply using T4 and anticipating adequate T3 derivation from that. A 1999 study had suggested that dual treatment enhanced cognitive function.

Clyde and colleagues randomized 46 stable hTHY patients to T4 alone vs T4 + T3. T3 was provided in a dose of 7.5 mg b.i.d. to replace 50 mg of T4 (ie, if a patient had been previously well controlled on 150 mg/d T4, they were switched to 100 mg T4 + 7.5 mg T3 b.i.d).

Both regimens provided appropriate suppression of TSH and adequate levels of T4 and T3, indicative of accurate therapeutic replacement. As might be anticipated, T3 supplementation resulted in higher serum T3, accompanied by compensatory reduced T4, although neither measurement exceeded boundaries of normal. No discernible benefit for symptoms, cognitive performance, or mood was demonstrated for dual treatment. The accompanying editorial reflects upon 2 additional recently published trials with similar results. Though the idea of combination thyroid replacement is appealing for patients who report hypothyroid symptoms despite laboratory documentation of adequate replacement, these recent data questions the viability of such an approach, which also entails greater complexity and expense. ■

Clyde PW, et al. JAMA. 2003;290: 2952-2958.

Specific Site Involvement in Fixed Drug Eruption

Fixed drug eruption (FDE) is the recurrent presentation of cutaneous drug allergy manifest at the same local site. In the United States, the glans penis is one of the most common sites of FDE, often precipitated by tetracycline or trimethoprim-sulfamethoxazole (TMP-SMX).

This study provides details on 105 FDE patients seen in the Istanbul Medical Faculty Department of Dermatology Clinic 1996-2000. To confirm the FDE diagnosis and precipitating agent, oral provocation testing was performed.

TMP-SMX and naproxen were the most common causes of FDE (63.8% and 23.8%, respectively). Less common causes were oxicams such as piroxicam [Feldene] (4.8%), acetaminophen (0.95%), and dimenhydrinate (0.95%).

The most commonly involved sites for FDE were the genital mucosa (50.5%), trunk (38.1%), lips (37.1%), and hands (32.4%). Drug-specific differences were noted, in that TMP-SMX most often produced genital FDE, whereas NSAIDs most commonly affected the lips. Site-specific associations between drugs and FDE may help clinicians confirm diagnostic hypotheses. ■

Ozkaya-Bayazit E. J Am Acad Derm. 2003;49:1003-1007.

Anticoagulation Therapy for Stroke Prevention in Patients with Atrial Fibrillation

There is little challenge to the credibility of anticoagulation for stroke prevention in atrial fibrillation (SPAF) as demonstrated in numerous large clinical trials. Nonetheless, clinicians may not apply the same sanguine approbation when considering the options in "real life" settings, perhaps wondering whether clinical trial results reflect a more pristine patient population and whether the risk benefit-ratio will be similar in their particular local setting.

The cohort study reported by Go and colleagues assessed nonvalvular atrial fibrillation patients (n = 11,526) from an integrated health care system in Northern California, which might more accurately represent nonacademic practice milieu. The effect of warfarin treatment was very salutary (compared to no antithrombotic therapy), providing a 64% reduction in odds of thromboembolism. Similarly, warfarin treatment was associated with reduced all-cause mortality (31%). Although the risk of intracranial hemorrhage in persons on warfarin was increased (hazard ratio = 1.97), the absolute number of events was very small (0.46 per 100 person-years) and far out-weighed by the other beneficial effects, including stroke reductions of 61%.

Clinicians should be heartened that application of literature-proven interventions may yield similar positive effect in traditional ambulatory settings. ■

Go AS, et al. JAMA. 2003;290: 2685-2692.

"Painful" Heart Block

By Ken Grauer, MD

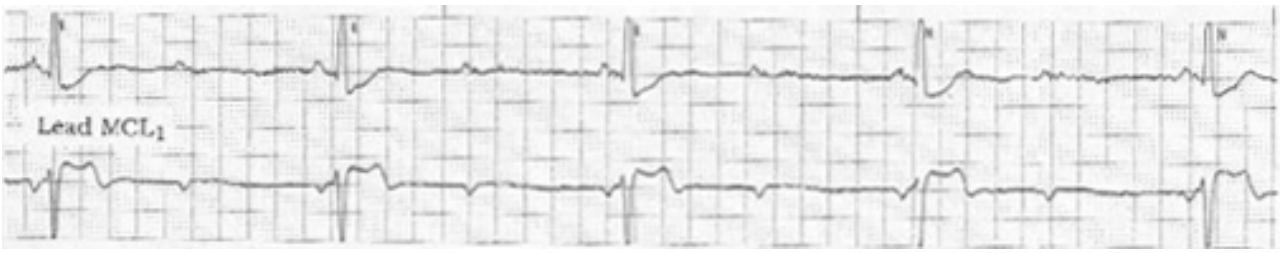

Figure. Simultaneously recorded lead II and lead MCL_1 rhythm strip obtained from a middle-aged man with vomiting and severe pain.

Clinical Scenario: The simultaneously recorded lead II and lead MCL_1 rhythm strip shown in the Figure was obtained from a middle-aged man in severe pain from a musculoskeletal disorder. He was not having chest pain, and had no known history of cardiovascular disease. He had an episode of vomiting shortly before this tracing was recorded. Is there evidence of "heart block?" If so, what type? What might you specifically look for on additional telemetry tracings to confirm your diagnosis of the arrhythmia?

Interpretation/Answer: The ventricular rhythm is slow and fairly regular at a rate just under 30 beats/minute. The QRS complex is narrow. P waves are present in both monitoring leads. These P waves are fairly consistent in morphology and upright in lead II. This suggests a sinus mechanism for the underlying rhythm, albeit at a slow and somewhat variable atrial rate. There appear to be two P waves for each QRS complex. However, attention to the PR interval just preceding each QRS complex reveals a constant and normal PR interval duration. This suggests that at least every other P wave is being conducted to the ventricles. The rhythm is therefore 2° AV block with 2:1 AV conduction.

Several points are deserving of mention. First, slight variation in the atrial rate is commonly seen in patients with 2° AV block. This phenomenon is known as a ventriculophasic sinus arrhythmia, which may be related to slight variation in sinus node perfusion caused by the AV block.

The second key point relates to classification of the various types of AV blocks. The mildest form is 1° AV block, in which each sinus impulse is conducted to the ventricles, albeit with some delay (manifested by prolongation of the PR interval to beyond 0.20 second). Complete (ie, 3°) AV block occurs when no sinus impulses are conducted to the ventricles. Since some P waves in the Figure are being conducted while others are not, the rhythm in the Figure must represent some type of 2° AV block. The most common of the three forms of 2° AV block (by far!) is Mobitz type I (ie, AV Wenckebach), which is characterized by progressive lengthening of the PR interval in consecutively conducted beats until an impulse is blocked. Because the defect with Mobitz I tends to occur at a higher level in the conduction system (usually at the AV node), the QRS complex will usually be narrow, the disorder is more likely to reverse with Atropine (which acts primarily on the AV node), and long-term prognosis is generally good. In contrast, Mobitz II 2° AV block is characterized by the presence of consecutively conducted beats with a constant PR interval before sudden non-conduction of one or more sinus impulses. The QRS complex will usually be wide with Mobitz II, reflecting its generally lower (usually ventricular) site of origin. Because of a very high risk of abrupt progression to complete AV block or ventricular standstill, cardiac pacing is recommended for most patients with Mobitz II 2° AV block, whereas pacing will usually not be needed for Mobitz I patients who are hemodynamically stable.

It is important to appreciate that a third type of 2° AV block also exists, in which the presence of 2:1 AV conduction makes distinction between the Mobitz I and Mobitz II forms much more difficult (because consecutively conducted impulses do not occur, one *cannot* tell if the PR interval is "lengthening" prior to the dropped beats). This is the situation shown in the Figure. Despite persistent 2:1 AV conduction, several factors still favor the less severe (Mobitz I) conduction abnormality in this case. The patient in question has no known history of heart disease. Marked vagal stimulation (from pain or other stimuli) can of itself temporarily depress AV nodal conduction enough (even in normal subjects) to produce varying degrees of AV block, especially Mobitz I. Statistically, Mobitz I is much more common than Mobitz II, especially in patients without underlying heart disease. And finally, the fact that the QRS complex is narrow makes it much more likely that the conduction disturbance is Mobitz I. Attention to other rhythm strips recorded on this patient could confirm our clinical suspicion if clear evidence of Wenckebach conduction was found, since it would be rare indeed for a patient to switch back and forth between Mobitz I and Mobitz II forms of 2° AV block. Adequate treatment of the patient's pain in this case resulted in swift resolution of the conduction disturbance. ■

PHARMACOLOGY WATCH

Vioxx Might Control Postoperative Knee Pain

Oral rofecoxib (Vioxx) may have a role in controlling postoperative pain patients undergoing knee surgery. Researchers in Chicago enrolled 70 patients who were undergoing total knee arthroplasty and randomized them to rofecoxib 50 mg the day prior to surgery, 1-2 hours prior to surgery, and for 5 days postoperatively, then 25 mg daily for another 8 days; or matching placebo at the same times. The main outcome was postsurgical analgesic consumption and pain scores, as well as nausea and vomiting, joint range of motion, sleep disturbance, and patient satisfaction with analgesia and hematologic anticoagulation parameters. Rofecoxib resulted in significantly reduced use of epidural analgesia and in-hospital opioid consumption ($P < .05$). Pain scores were also lower in the rofecoxib group while in the hospital ($P < .001$) as well as 1 week after discharge ($P = .03$). Rofecoxib also resulted in less postoperative nausea, a decrease in sleep disturbance, as well as increased knee flexion at 1 month—including a shorter time in physical therapy to achieve effective joint range of motion. The drug had no effect on warfarin usage or INR levels postoperatively. Interestingly, Buvanendran and colleagues did not include changes in renal function or evidence of GI intolerance in the study analysis. They did conclude however that rofecoxib is effective at reducing postoperative pain and opioid consumption after major orthopedic surgery (*JAMA*. 2003;290:2411-2418).

Echinacea Has No Value for URIs

Just in time for winter, another study showed that *Echinacea* has no value for reducing the duration or severity of upper respiratory tract infections (URIs). The herbal remedy is commonly used worldwide for this indication. In this study of children in the Pacific Northwest, 707 URIs occurred in 407 children over 2 years. Three hundred thirty-seven URIs were randomized to treatment with *Echinacea* while 370 were assigned to placebo. *Echinacea* was begun at the onset of symptoms and continued throughout the infection for maximum of 10 days. Data analysis showed there was no difference in the duration of URIs with *Echinacea* or placebo ($P = .89$), and there was no difference in the overall estimate of severity of URI symptoms ($P = .69$). There was also no statistically significant difference between the 2 groups for peak severity of symptoms, number of days of peak symptoms, number of days of fever, or parental global assessment of severity of URI. Rash occurred during 7.1% of URIs treated with *Echinacea* and 2.7% of those tree with placebo ($P = .008$). The study concludes that *Echinacea* was not effective in treating URI symptoms in patients 2 to 11 years old but was associated with an increase in skin rash (*JAMA*. 2003;290:2824-2830).

Valsartan, Captopril Have Similar Benefits

Valsartan and captopril have similar benefits in patients with myocardial infarction complicated

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by left ventricular systolic dysfunction, heart failure, or both, according to a new study. Previous studies have shown that ACE inhibitors reduce mortality and cardiovascular morbidity in this group, but it was unclear if angiotensin receptor blockers (ARBs) conveyed the same benefit. In this international study, nearly 15,000 patients with myocardial infarction were randomized to valsartan, captopril, or a combination of valsartan and captopril. The primary end point was death from any cause. The median follow-up was just more than 2 years. During that time, the death rate in all 3 groups was remarkably similar (979 of 4909 deaths valsartan, 958 of 4909 deaths captopril, 941 of 4885 deaths combination [hazard ratio valsartan vs captopril 1.0; 97.5% CI, 0.9-1.11; $P = 0.98$], [hazard ratio valsartan and captopril vs captopril, 0.98; 97.5% CI, 0.89-1.09; $P = 0.73$]). The valsartan plus captopril group had the most drug-related adverse events, while in the monotherapy groups valsartan was associated with more hypotension and renal dysfunction, while cough, rash, and taste disturbance were more common with captopril. Pfeffer and associates conclude that valsartan is as effective as captopril in patients with myocardial infarction who are at high risk for cardiovascular events, but combining valsartan with captopril did not offer an advantage (*N Engl J Med*. 2003;349:1893-1906).

In-patients Likely to Continue Lipid Use

In-patients who are started on lipid-lowering therapy following coronary intervention are 3 times more likely to continue on the drugs compared to patients who are started on the same therapy as outpatients. Using data from the EPILOG trial in which patients underwent percutaneous coronary intervention for stable or recently unstable coronary artery disease, 175 patients were discharged from the hospital on lipid-lowering therapy and 1951 were discharged on no lipid-lowering therapy, with the intent to start them on treatment as outpatients. After 6 months of follow-up, 77% of patients who were started in the hospital were still taking lipid-lowering therapy compared with only 25% of those who were discharged without lipid-lowering therapy ($P < .001$). Aronow and colleagues suggest that initiation of lipid-lowering therapy in the hospital is effective strategy to enhance subsequent use of the drugs in these high-risk patients (*Arch Intern Med*. 2003;163:2576-2582).

More on Metformin/Lactic Acidosis

When it comes to the relationship between metformin and lactic acidosis, the emperor may have no cloths. The drug, which has been used to treat type 2 diabetes for more than 40 years, has always carried with it the stigma that it may cause lactic acidosis in at-risk patients. Metformin hydrochloride is a biguanide that is similar in structure to phenformin hydrochloride, which was withdrawn from the market because of a documented risk of lactic acidosis. Metformin increases glucose oxidation without substantially affecting fasting lactate production and peripheral tissues unlike phenformin, and the true rate of metformin-associated lactic acidosis has never been demonstrated. Recently, researchers from Stanford performed a thorough review of the literature on this topic and performed a meta-analysis on 194 studies involving nearly 37,000 patient years in the metformin group and 30,000 patient years in the nonmetformin group. No cases of fatal or nonfatal lactic acidosis were found in either group. Their conclusion is that there is no evidence that metformin therapy is associated with an increased risk of lactic acidosis or with increased lactate levels compared with other antihyperglycemic treatments (*Arch Intern Med*. 2003;163:2594-2602). The study is important because metformin is an effective treatment for type 2 diabetes, and has some unique properties including stabilizing weight gain or even facilitating weight loss. The drug has also recently become multisource (generic) and is affordable for diabetic patients who must pay for their medications.

FDA Notes

The FDA has approved tadalafil (Cialis), Eli Lilly and Icos Corp's entry into the lucrative phosphodiesterase inhibitor market. With the success of sildenafil (Viagra), and newcomer vardenafil (Levitra) already generating huge profits, Cialis is being touted as a longer acting, less expensive alternative for the treatment of erectile dysfunction. The drug, which exerts its effect over 36 hours, has already been dubbed "the weekend drug" in Europe, where it as been available for some time.

Bristol-Myers has received approval to market the first chewable oral contraceptive for women. The product is a new formulation of Ovcon 35 (norethindrone and ethinyl estradiol), which is spearmint flavored and can be chewed or swallowed whole. If chewed than swallowed, the woman should drink a full 8 oz of liquid immediately afterward to make sure the entire dose reaches the stomach. ■