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INSIDE

Financial Disclosure:

Internal Medicine Alert's editor, Stephen Brunton, MD, is a consultant for Abbott, Amylin, Boehringer Ingelheim, Eli Lilly, Endo, Novartis, and Novo Nordisk. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

Another Reason to Get Your Flu Shot

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

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

Synopsis: *There is a surge of coronary deaths following influenza epidemics, which strengthens the importance of flu vaccinations for those at risk for cardiovascular events.*

Source: Mohammad M, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death; results from 8 years of autopsies in 34, 892 subjects. *Eur Heart J.* 2007; epub ahead of print April 17.

THIS STUDY IS A COLLABORATIVE EFFORT OF THE TEXAS HEART Institute and the Influenza Research Institute of St Petersburg, Russia. The authors focused on deaths from St Petersburg, Russia during 1993-2000. Using data from St Petersburg's Influenza Research Center, which defined when epidemics were occurring based on pre-determined thresholds, the investigators reviewed autopsy reports from 34,892 subjects who died as a result of the flu (the autopsy rate in St Petersburg is over 70%!). They compared the average within-epidemic mortality to the average off-epidemic mortality for both respiratory and coronary heart disease deaths. There were 9 flu epidemics during the study period. Each influenza epidemic was associated with an increase in cardiac mortality. During this 8 year period, 11,892 people died of acute MI and 23,000 died of chronic ischemic heart disease. The marked rise in coronary deaths during each flu epidemic generally coincided with a rise in acute respiratory disease deaths. The excess in cardiac deaths persisted for about 10 weeks, with maximum mortality rates for 2 weeks on either side of the peak of acute respiratory deaths. Deaths affected genders equally, but older people disproportionately. The authors were able to model a prediction of future cardiac deaths associated with flu epidemics in St Petersburg.

VOLUME 29 • NUMBER 10 • MAY 29, 2007 • PAGES 73-80

COMMENTARY

This article first got my attention when it was covered by my local newspaper, which noted, "Study links flu, heart attacks." People are interested in anything to do with the flu these days, with dire predictions that the next flu epidemic is not a matter of "if" but "when." In truth, large epidemiologic studies have already linked flu with myocardial infarction (MI) and demonstrated that influenza vaccination can reduce the risk of influenza-associated MI.[1-4] What is new about the current study is the precision of the methods used, including autopsy verification of cause of death. Although the flu shot is indicated for those at risk for cardiac disease,[5] both public perception and medical practice have de-emphasized this indication. In their introduction, the authors point out that about twice as many people die of cardiac causes than pulmonary causes during influenza epidemics. Perhaps the biggest take home message here is that flu shots are not just for those with lung disease, but also for those at risk for cardiovascular disease. ■

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Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

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MANAGING EDITOR: Iris Williamson Young

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail: customerservice@ahcmedia.com

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Subscription Prices

United States

1 year *with* free AMA Category 1 credits: $289

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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

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The Cost of Reducing Bed Side Rail Use

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

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

Synopsis: *Intensive intervention using Advance Practice Nurses reduced the use of side rails on nursing home beds and lowered the rate of bed-related falls and injuries.*

Source: Capezuti E, et al. Consequences of an intervention to reduce restrictive side rail use in nursing homes. *J Am Geriatr Soc.* 2007;55:334-341.

After baseline assessments of bed side rail use in 710 residents of four urban nursing homes during late evening and bedtime hours, consent was obtained for individual evaluation of 80% of the 376 residents who had side rails applied. A master's prepared gerontological Advanced Practice Nurse (APN) conducted individual evaluations and worked with nursing staff and interdisciplinary teams including physicians, social workers and physical therapists, spending 3-6 months at each home. A resident-specific intervention care plan was prepared and presented to the unit staff, including meetings with each facility's nursing director. Educational sessions were provided to each nursing shift at all four institutions and to facility committees, including the quality improvement committee. The APN also participated in each resident's multidisciplinary care conference, and worked with administrative staff to develop purchasing alternatives to side rails.

Post intervention assessments at one month and one year after completion found a 51% reduction in the use of restrictive side rails, accompanied by a statistically significant reduction in the bed-related falls rate from 0.115 to 0.061. Bed-related serious injuries decreased from nine to five after the intervention.

COMMENTARY

While it might seem logical that utilizing side rails for confused nursing home residents would protect them from falling out of bed, geriatric research has consistently shown this to be false. In fact, the use of side rails actually increases the number of falls and even deaths as residents try to climb over them and become entrapped. Over the past 21 years the FDA has collected 691 reports of

side rail entrapment resulting in death or injury, recently issuing guidelines for the manufacture of hospital beds associated with reduced risks of death and injury, and ways to assess existing beds.[1]

Despite the adverse outcomes of using bed side rails, it has proven very difficult to dissuade staff from continuing to use them. Numerous interventions and educational programs have been attempted, only to find later that the rails are still being used.[2]

This article reports a successful intense intervention involving Advanced Practice Nurses in a 3-6 month program, particularly if the institution's management supported the change. A tremendous effort was made to reduce a tiny number of injuries. With continued regulatory focus on this issue, it's likely that a huge amount of resources will have to be devoted to reducing side rail use until safer beds are manufactured. ■

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Omeprazole Before Endoscopy in Patients with Gastrointestinal Bleeding

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

Emeritus Clinical Professor of Medicine, University of Oklahoma College of Medicine, Oklahoma City

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

Synopsis: *High dose PPI infusion prior to endoscopy accelerated resolution of the signs of ulcer bleeding and significantly reduced the need for endoscopic hemostasis therapy.*

Source: James Y Lau, et al. *The New England Journal of Medicine.* 2007;356:1631-1640.

These highly experienced Hong Kong investigators have been major contributors to the literature on GI bleeding and its management. In the present study extending over 17 months, 631 stabilized patients who presented with acute upper GI hemorrhage (hematemesis and/or melena) were randomly assigned to receive either high dose intravenous omeprazole or placebo. This particular study excluded most chronic aspirin recipients due to a parallel study of these patients also underway. Study patients on warfarin received vitamin K or fresh frozen plasma. Heparin was continued in patients with prosthetic heart valves or histories of pulmonary embolism within 6 months. If NSAIDs had been received by patients prior to admission (22-23%), they were discontinued. Patients with hypotension and evidence of acutely continuing bleeding underwent emergency endoscopy and were not included in the study population nor were patients who bled again in the period prior to scheduled endoscopy the day after admission.

Study patients received omeprazole 80 mg as a bolus on admission, followed by continuous infusion of 8 mg per hour until endoscopy the next morning. When scheduled endoscopy was done, study patients with endoscopic evidence of spurting hemorrhage or visible vessels were treated with injected epinephrine using a sclerotherapy needle followed by coaptive thermocoagulation with a 3.2 mm heater probe. Overlying clots were snared away, and underlying vessels were also treated. Duration of omeprazole or placebo infusion was about 15 hours prior to scheduled endoscopy. Ulcers were present in about 60% of patients with a variety of lesions accounting for bleeding in the remainder (including erosions, Mallory-Weiss tears, and some cancers). Of 314 patients who received omeprazole, 60 (19.1%) required endoscopic therapy vs 90 (28.4%) of the 317 patients on placebo (CI 0.51 to 0.90; $p = 0.007$). This was mirrored in the large subgroup of peptic ulcer patients who also had fewer bleeding ulcers seen at endoscopy. There were no differences between groups in requirements for emergency endoscopy or in deaths within 30 days of study entry. There were no medication-related adverse events.

■ COMMENTARY

This excellent study provides strong evidence for the utility of aggressive acid suppression in patients who present with acute upper gastrointestinal hemorrhage. Its limitations (mentioned by the authors) include the lack of chronic aspirin users and the high rate of ulcer disease that continues to be present in Asian countries. There is wide international agreement regarding the value of early endoscopy in patients with UGI hemorrhage, but this study probably can be interpreted to validate the immediate use of intravenous PPIs in patients presenting with upper GI hemorrhage. Such therapy is safe and can be expected to be beneficial in the subgroup of patients with acid-peptic etiologies for GI hemorrhage. Ideally, a similar study should be done in the setting of patient populations expected to have a higher proportion of variceal bleeding (where results might well be different). Although no formal cost analysis was done by these

authors, the results are almost certainly consistent with a cost effective intervention. ■

Special Feature

Plain Old Gonorrhea Increasingly Difficult to Treat

By Carol Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper reports no financial relationship relevant to this field of study.

Source: MMWR. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. 2007; 56:332-336.

QUINOLONE-RESISTANT NEISSERIA GONORRHEA (QRNG) continues to spread with alarming frequency across the United States. Quinolones were first recommended for the treatment of GC by the CDC in 1986. The first quinolone-resistant isolates were reported in Asia and Hawaii in 1991, and sporadic cases occurred in the United States between 1991-1999. However, since 2000, there has been a steady increase in QRNG cases, first in Hawaii, then in California and other Western states, then in men who have sex with men (MSM) throughout major cities in the United States, and now it is appearing with increasing frequency in heterosexual men. In 2003, the CDC revised the treatment recommendations, such that areas experiencing > 5% QRNG no longer use quinolones for first-line treatment of GC.

Surveillance for GC resistance in the United States began in 1986 through a CDC-sponsored program called GISP. Data is presently collected from urethral swabs from 6,000 males annually presenting to 26 to 30 STD clinics throughout the United States. The GISP program provides increasingly important resistance data on STDs in an era with declining use of cultures. Quinolone resistance is defined as an MIC > 1 microgram/mL to ciprofloxacin; intermediate resistance is defined as an MIC 0.125-0.500 microgram/mL.

Since 2001, the prevalence of QRNG in MSM has increased from 1.6% to 29% in 2005; preliminary data for 2006 suggests the current rate is much higher (38%). Resistance in heterosexual men has occurred more slowly, beginning with 0.6% in 2001 and increasing to 3.8% in 2005; preliminary 2006 data suggest the current rate is closer to 6.7%. Certain cities, like Philadelphia and Miami are experiencing even greater rates of resistance, especially in gay men. ■

The CDC now recommends a single dose of intramuscular ceftriaxone 125 mg for uncomplicated urogenital and anorectal GC. Alternate regimens would include a single dose of cefoxitin 2 grams with probenecid, ceftizoxime 500 mg, cefotaxime 500 mg, or cefiximine oral suspension 400 mg. For persons with severe penicillin or cephalosporin allergies, intramuscular spectinomycin 2 grams can be given (but would presently require being ordered through the public health department, resulting in a delay in treatment). A single oral dose of azithromycin 2 grams is another good option for patients with uncomplicated GC with severe PCN allergy. However, the routine use of azithromycin is not recommended because of concerns regarding the rapid emergence of resistance.

A single dose of intramuscular ceftriaxone 125 mg is also recommended for pharyngeal GC; the alternate regimens above may not be adequate for pharyngeal infection. In addition, quinolones are no longer recommended for treatment of conditions such as PID that may be caused by GC. ■

A test of cure 2-weeks post-treatment was previously required for persons receiving quinolone therapy. Since quinolones are no longer recommended, a test of cure is not necessary for treatment of uncomplicated GC. However, a culture and susceptibility studies should be obtained in any person with persistent symptoms. Keep in mind that the SF PHD identified 3 cases of combined quinolone and cephalosporin resistance in 2003. As of 2004, the IDSA has listed GC as one of the target organisms in their "Bad Bugs, No Drugs" campaign. ■

Is the Tingling on My Scalp Helping my Headaches? Occipital Nerve Stimulation for Cluster Headaches

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor of Clinical Neurology, Weill Medical College

Dr. Jamieson reports no financial relationship relevant to this field of study.

Synopsis: *Occipital nerve stimulation appears to decrease the cluster pain and attack frequency in most, but not all, patients with chronic drug-resistant cluster headaches.*

Source: Burns B, et al. *Lancet Neurology*. 2007;6:314-321.

PATIENTS WHO SUFFER FROM CLUSTER HEADACHES report that the pain is so brutal that they are willing

to consider any therapy that promises even slight relief from the agony of unilateral periorbital knife-like pain. Options for successful treatment of cluster headaches are limited. Preventative medication to decrease the frequency and severity of the pain is often only minimally effective. The medications used to treat the acute pain may be used excessively or may not be appropriate for cluster patients with vascular risk factors. Surgical procedures that target the trigeminal nerve or cranial parasympathetic outflow tracts have been attempted with variable results and with risk of significant complications. Deep brain stimulation of the hypothalamus, an area of activation in cluster headaches, has been shown to be effective but the potential surgical complications make this treatment inappropriate for all but the most intractable of patients. While some cluster headaches remit for months to years, the patient with chronic cluster headaches, without intervening headache-free periods, is particularly disabled by the unremitting excruciating pain. The patient with chronic cluster headaches may either have had episodic cluster periods with periods of relief or may have always had unrelenting headaches. The patient with chronic cluster headaches is often amenable to any treatment that offers promise of partial pain relief.

These 2 papers, one from Belgium (Magis et al) and one from the United Kingdom (Burns et al) examined the benefit of occipital nerve stimulation in patients with chronic medication-unresponsive cluster headache. Suboccipital injection of steroids or local anesthetics have been of occasional benefit in cluster patients but the effect is transient and repeated injections often lose efficacy. Occipital nerve stimulation has been used in intractable migraine patients and its efficacy in these 2 groups of drug-resistant cluster headache patients was evaluated, even though its mechanism of action is not clear. Peripheral neurostimulation has been beneficial in patients with pain disorders such as neuropathic pain, with possible extrapolation to patients with primary headache disorder. Multiple pain pathways, including cervical, somatic trigeminal, and dural trigeminal vascular afferents, which converge on second-order neurons in the brain stem and on third-order cortical neurons, may be impacted by stimulation of the occipital nerve. The perceived clinical benefit of occipital nerve injection and the appreciation of any relief of pain in patients with cluster headaches served as the impetus for the evaluation of occipital nerve stimulation.

The patient population of the 2 papers was very similar, with 8 patients (one woman and 7 men) of average age in the mid-forties, in each study. All patients had suffered from cluster headaches for years (minimum 7 years) to decades with headache that persisted despite aggressive medical therapy. The stimulation technique differed, as the British patients had bilateral occipital nerve stimulators inserted, whereas the Belgian patients had the stimulator surgically implanted only on the side of the headache. The stimulation parameters were adjusted to obtain paresthesias in the innervation territory of the greater occipital nerve.

The assessment of response differed between the 2 papers but was subjective in both. The patients monitored by Magis et al used headache diaries before and after treatment to assess clinical response. Burns et al used a less quantitative assessment in which the patients were asked to give an overall impression of their response and their use of triptan medications before and after the treatment. They were also asked if they would recommend the treatment to a fellow cluster sufferer. No blinding of treatment was possible since paresthesias indicated that stimulation was occurring. However, frequent technical problems with battery life and electrode migration led to interruption of the stimulation with increase in cluster-attack frequency and severity. The stimulation was also intermittently discontinued in order to monitor response. These interruptions were not blinded as the patients knew when the stimulation was no longer operating because the paresthesias disappeared.

The outcomes reported by both sets of investigators were encouraging. Both studies found that most patients had decreased cluster attack pain and frequency that persisted over months. Magis et al reported that 2 patients were pain free after follow-up of 16 and 22 months. Three patients had 90% reduction in attack frequency and 2 patients had improvement of around 40%. Length of follow-up was variable but was greater than 3 months for all the patients. One patient who had no benefit at 4 months with intolerable paresthesias discontinued treatment. Seven out of 8 patients were able to decrease medication use. These patients all had unilateral stimulation on the side of the headaches.

Burns et al followed their 8 patients for a range of 6-27 months of bilateral stimulation. Two patients had marked improvement and would recommend treatment. Three patients had only moderate improvement but would still recommend treatment. One patient had only mild improvement and would not recommend treatment. The benefit accrued over weeks but appeared relatively durable.

Both groups of patients had frequent technical malfunctions requiring surgical replacement of batteries and electrodes. However, unlike other surgical treatments, specifically deep brain stimulation of the hypothalamus, there were no serious complications of treatment.

Patients were selected based on the refractoriness of the headaches, and the pre-implantation response to occipital nerve block did not seem to predict the outcome of successful occipital nerve stimulation.

COMMENTARY

Patients with drug-resistant chronic cluster headaches have an existence dominated by unpredictable, unrelenting pain, and are desperate for any treatment that offers a modicum of relief. The patients in these studies were taking large quantities of medications with minimal benefit and were willing to undergo multiple surgical procedures to obtain benefit. The results are encouraging, even if the pathophysiological mechanism to explain it is elusive. The technique appears to be safe with only frustrating technical glitches. The lack of blinding was, probably, only of minimal consequence given the refractoriness of the pain. The similar result with either unilateral or bilateral stimulation is curious and needs further study. The results with unilateral stimulation are encouraging enough to indicate that the treatment should be unilateral, at least initially, in the appropriate patient with unilateral symptoms. These 2 papers give hope to a group of patients who are despondent and frustrated. For the appropriate patient who understands the uncertainty of the individual response, occipital nerve stimulation can offer hope of an existence with decreased pain. ■

Pharmacology Update

Sitagliptin and Metformin Tablets (Janumet)

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

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

THE FDA HAS APPROVED A NEW COMBINATION product for the treatment of type 2 diabetes mellitus. Sitagliptin, the recently approved dipeptidyl peptidase-4 (DPP-4) inhibitor is combined with metformin in two different dose configurations. Sitagliptin/metformin is marketed by Merck & Co., Inc as Janumet.

Indications

Sitagliptin/metformin is indicated as an adjunct to diet and exercise for the treatment of type 2 diabetics in patients who are not adequately controlled on either drug alone or who are already being treated with both drugs.[1]

Dosage

The starting dose of sitagliptin/metformin should be individualized based on the patient's current regimen. The dose may be titrated upward but should not exceed 100 mg of sitagliptin or 2000 mg of metformin daily. The tablets should be taken twice daily with meals.[1]

Sitagliptin/metformin is available as 50 mg sitagliptin/500 mg metformin and 50 mg sitagliptin/1000 mg metformin.

Potential Advantages

Sitagliptin/metformin provides a product with two different mechanism of action. The addition of sitagliptin to patients inadequately controlled on metformin alone improves glycemic control with a reduction of HbA1c of 0.65%,[1,2] and may improve compliance.

Potential Disadvantages

The most common adverse events are gastrointestinal related associated with metformin (eg, nausea, vomiting, diarrhea). The combination has little flexibility in individualizing the dose. The effect of long-term inhibition of DPP-4 is not known as DPP-4 plays an important role in the regulation of differentiation and growth of T lymphocytes and inactivation of bioactive peptides (eg, neuropeptides, circulating peptide hormones, growth hormone-releasing hormone).[3,4]

Comments

Sitagliptin/metformin is a new combination product with two distinct mechanisms of action. Sitagliptin is a DPP-4 inhibitor prolonging the action of incretin hormones. This results in glucose dependent insulin release, inhibition of glucagon release, delayed gastric emptying, and increases satiety.[5] Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity.

The fixed combination has not been studied in any clinical trial. The approval was based on a 24-week study (n = 701) with sitagliptin (100 mg daily) added to metformin (1500 mg daily or higher) in patients inadequately controlled on metformin alone.[1,2] This addition resulted in a placebo-adjusted reduction of HbA1c of 0.65%. The mean baseline HbA1c was 8%. Adjusted reductions in fasting plasma glucose and 2-hour postprandial glucose were 25 mg/dL (baseline 170) and 51

mg/dL (baseline 275).

Hypoglycemia and weight gain are not associated with these two drugs. The daily wholesale cost is about $5, similar to the sitagliptin alone.

Clinical Implications

Sitagliptin/metformin is the newest combination product to be approved for the treatment of type 2 diabetes. There are currently many combinations available including sulfonylurea metformin combinations, glitazone/metformin and glitazone/sulfonylurea combinations. The combinations may be more convenient for those who are already taking the two drugs separately. ■

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CME Questions

26. Ms Angie Plasty, a 54-year-old woman with dyslipidemia and a family history of early myocardial infarction, asks you if she should have a flu shot. She has no lung disease or chronic medical illnesses. You advise her that she:

a. does not need a flu shot, since she has no lung disease or chronic medical conditions, and is younger than 65.
b. does not need a flu shot, since flu is a risk factor for cardiovascular death in men only.
c. does need a flu shot, as she is at increased risk for cardiovascular disease, and influenza can increase the risk of cardiovascular mortality.
d. does need a flu shot, since you recommend it for all your patients, regardless of age or health status.

27. Which of the following outcomes results when side rails in nursing home beds are used for confused residents?

a. reduced falls out of bed
b. more restful sleep patterns
c. entrapment and injuries
d. less sedative medication use
e. none of the above

28. Based on results of this study, omeprazole (or presumably other IV PPI therapy) should be administered to patients with GI hemorrhage thought to be due to:

a. all causes
b. angiodysplasia and diverticular disease of the colon
c. acid-peptic disorders (eg, gastric and duodenal ulcers)
d. hemorrhage due to esophageal varices
e. GI bleeding due to upper GI malignancies

Answers: 26 (c); 27 (c); 28 (c)

CORRECTION

In the April 15 issue, dosages in the Clinical Brief "Under the Macrolide-Resistant Streptococci Induction" were reversed.

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*
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.

MI: Try to have it Monday Thru Friday

Hospital legends about the relative availability (or unavailability) of services/personnel on weekends vs weekdays often lead to jocularity about the wisdom of choosing one's day to be admitted to the hospital carefully! Yet, whether such issues as calendar timing (being admitted on the weekend vs weekday) really make a difference is largely unknown.

Using a database comprised of more than 59,000 patients admitted to New Jersey hospitals for an acute MI between 1999-2002, an appraisal of the relationship between day of admission and outcomes was performed.

The relative risk of 30-day mortality was 8% greater for persons admitted on a weekend than during the week (12.9% vs 12.0%). Similarly, utilization of services such as cardiac catheterization within 48 hours was remarkably lower if admitted on a weekend (odds ratio for catheterization by day 2 = 0.51). The authors reflect that "our study suggests that a hospital workweek of Monday through Friday is not optimal for the care of patients with acute MI." ■

Kostis WJ, et al. N Engl J Med. 2007;356:1099-1109

Can MRI Provide Better Clarity About Contralateral Breast Cancer?

Amongst the population of women who are diagnosed with and treated for breast cancer (BCA), an additional cancer is detected in the contralateral breast in as many as 10% of cases (identified by clinical examination, mammography, or both). Mammography has generally been considered the "gold standard" in this regard.

MRI is more sensitive than mammography for detection of primary BCA. The American College of Radiology Imaging Network conducted a trial of women diagnosed with BCA who had already been examined with negative mammography of the contralateral breast (n = 969). MRI diagnosed thirty of these women (3.1%) to have biopsy-confirmed BCA that had been missed by both mammography and clinical examination. More than half of the occult cancers were invasive, and (fortunately), all were node-negative at the time of discovery.

Although current costs of MRI do not favor its utilization for routine screening, in the higher-risk group of women with known BCA, it has superior performance in diagnosing disease in the contralateral breast than mammography. ■

Lehman CD, et al. N Engl J Med. 2007;356:1295-1303.

Dapsone Gel 5% for Acne

Dapsone (DAP) is a sulfone that possesses both antimicrobial and anti-inflammatory activity, but its use systemically is limited by substantial toxicity, including methemoglobinemia and hemoloysis. In the recent past, consideration of DAP as a topical agent was limited by the poor solubility of DAP in traditional vehicles. Recently, a gel formulation with adequate DAP delivery has been developed.

DAP 5% gel was studied in persons greater than age 12 with acne (n = 3,010). Two identical placebo-controlled, double-blind trials were performed using DAP 5% twice daily vs placebo gel.

DAP produced statistically significant and clinically relevant improvements in acne at the 12 week endpoint of the study; a divergence between placebo and DAP was visible beginning as early as two weeks into the study. Subjects with G-6-PD deficiency (who are particularly sensitive to hemolysis) were proactively included in the trial and monitored for hemoloysis.

DAP was well tolerated with no evidence of serious adverse effects. The overall adverse effect profile was not statistically different from placebo.

In an era of increasing Propionibacterium acnes (the primary causative bacterium for acne) resistance to many of the antibacterial agents commonly used for acne treatment, DAP may offer a new therapeutic alternative. ■

Draelos ZD, et al. J Am Acad Dermatol. 2007;56:439-447.

In Future Issues: **Ureteral Stents Not Effective, Increase Symptoms**