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By Louis Kuritzky, MD

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Air Travel and DVT Risk: Is Hypobaric Hypoxia the Culprit?

Source: Toff WD, et al. *JAMA*. 2006;295:2251-2261. Erratum in: *JAMA*. 2006;296:46.

That air travel is associated with increased risk of deep venous thrombosis (DVT) is well established. Recent data have suggested that very long flights (> 5 hours) are disproportionately associated with risk. We (*Internal Medicine Alert*, May 29, 2006) previously reviewed data that compared subjects sitting and watching movies for similar time periods as matched subjects taking a plane flight, and noted that there is something about air travel that activates coagulation factors differently than simply sitting in a chair.

Pressurization in airplane cabins produces a mean arterial oxygen saturation of about 93% in healthy persons (mean), but lower levels in older individuals and persons with cardiopulmonary disorders. Such relative hypoxemia has been shown in vitro to induce procoagulant activity as well as inhibit fibrinolysis; in vivo studies amongst healthy volunteers corroborate this.

Toff et al studied healthy volunteers (n = 73) in a single-blind fashion by comparing hemostatic markers after an 8-hour period of seated exposure in a hypobaric chamber. Persons with known thrombophilic disorders were excluded. Analyses included measurement of platelet aggregability, coagulation activation, fibrinolysis, platelet activation, and endothelial activation.

There was no demonstrable difference in measured markers of mean prothrombotic activity in these healthy volunteers. At least in healthy individuals, hypobaric hypoxemia does not appear to affect DVT risk in a meaningful fashion. ■

GERD: Size Matters

Source: Jacobson et al. *N Engl J Med*. 2006;354:2340-2348.

Obesity is a recognized risk factor for gastroesophageal reflux disease (GERD). In addition to the clinical observation that obese individuals suffer GERD more often, trial data have corroborated that BMI and GERD have a linear association. However, studies of the relationship between BMI and GERD have generally been restricted to overweight or obese individuals, rather than including all subjects. Hence, whether weight gain in non-overweight individuals increases their risk for GERD has not been previously reported.

Subjects for this report (n = 10,545) included participants in the Nurses Health Study. In response to a questionnaire about frequency and severity of GERD symptoms, there was a direct relationship between increasing weight and frequent GERD symptoms. When compared to women with a BMI of 20-22.4, there was a direct relationship between BMI and GERD: the relative odds ratio for frequent symptoms was 33% less for persons with a BMI < 20, 38% more for BMI 22.5-24.9, and there was a greater than 100% increase for persons with BMI 25.0-27.4 (all of these BMI measurements are below the threshold for overweight/obese). Weight change (an increase in weight, that is) was also associated with increased risk for GERD, even when persons simply increased their weight from one normal weight category to another.

Increased body weight, even in non-obese individuals, is associated with GERD. Weight reduction has been shown to improve these symptoms. ■

Does aTNFa for RA Increase Infections and Malignancies?

Source: Bongartz T, et al. *JAMA*. 2006;295:2275-2285. Erratum in: *JAMA*. 2006;295:2482.

Anti-TNF antibody (aTNFa) therapy offers significant benefit to sufferers of rheumatoid arthritis (RA). TNF is involved in critical functions related both to infectious disease and tumor suppression. For instance, CD8 lymphoctye tumor killing is mediated by TNF. Hence, the risk that either infectious or malignant diseases might be more prevalent in persons who have been treated with aTNFa is plausible. Individual trials using aTNFa have not demonstrated a 'signal' of greater risk for infections or cancer, but because both are somewhat uncommon, they might be easily missed.

Bongartz et al pooled data from aTNFa trials which lasted at least 12 weeks, providing data on 3,493 patients. Serious infections were defined as those which required antimicrobial treatment and/or hospitalization. Ultimately, this pooled data set indicated that the odds ratio for malignancy was increased greater than 3-fold, and risk for serious infection was doubled. For malignancies, there was a dose-dependent effect: higher aTNFa doses produced increased risk. In their closing commentary, the authors suggest that because of the difficul-

ty in identifying rare events during clinical trials submitted for FDA drug registration, planning meta-analysis ahead of time to include future ongoing trials might recognize signals of serious disease earlier. ■

Postexposure Treatment with Doxycycline and Tick-Borne Relapsing Fever

Source: Hasin T, et al. *N Engl J Med*. 2006;355:148-155.

Borrelia persica IS THE CAUSATIVE agent of tick-borne relapsing fever (TBRF). The Borrelia name will be familiar to clinicians because of Lyme disease, caused by *Borellia burgdorferi*. The tick bite of *Ornithodoros tholozani*, which may be encountered in environs such as caves, may easily be missed by victims. Incubation of TBRF is 2-18 days. Post-exposure prophylaxis with short-term antibiotic treatment has been shown to be effective for Lyme disease, but no similar data exist from controlled trials to confirm efficacy of treatment for TBRF.

Military training in Israel includes camouflage and survival exercises that take place in an area where TBRF is endemic. Subjects who had participated in this activity (n = 93) were meticulously examined by a physician for signs of tick bite immediately after their potential exposure. In a randomized blinded fashion, subjects received doxycycline daily for 5 days (200 mg day 1, then 100 mg subsequent doses), vs placebo. To ensure consistent drug administration, subjects had direct supervision for each dose.

Ten cases of TBRF occurred in the placebo group, as confirmed by blood smear, and none of the person in the treatment group. As has been seen in other populations, this dosing regimen of doxycycline was well tolerated, with no significant adverse effects.

In this trial, doxycycline was found to be 100% effective when administered within 5 days of exposure to *Borellia persica*. ■

Secondary Prevention of Stroke: Persistence Pays Off

Source: Shaya FT, et al. *Am Jour Managed Care*. 2006;12:313-319.

THE BENEFITS OF PHARMACOTHERAPY for secondary prevention of stroke (SPS) are well established. For instance, warfarin reduces stroke in atrial fibrillation by as much as 60%; aspirin or clopidogrel provide meaningful reduction in recurrent stroke also. Of course, data about successful SPS comes primarily from controlled clinical trials. Ultimately, clinicians and the public alike would like to have insight into the effectiveness of interventions for SPS in the public sector, as well as which factors maximize effectiveness of tools shown to be efficacious in clinical trials.

Shaya et al studied a group selected from the Maryland Medicaid population (n ≥ 400,000), all of whom must enroll in 1 of 8 managed care organizations in that state. Study subjects (n = 925) had been prescribed aspirin, warfarin, or clopidogrel post-stroke. The authors sought to examine the relationship between persistence—consistent renewal of study medication in a timely fashion—and risk of subsequent stroke. The Cox proportional hazards model used in this report is appropriate because it adjusts for factors such as age, race, sex, site of residence, and concomitant medications such as antihypertensive and lipid lowering drugs.

Persistence was associated with a 57% greater likelihood of avoiding a recurrent stroke. As many as 20% of subjects had not been persistent with clopidogrel, aspirin, or warfarin. Clinicians must continue to be vigilant for factors that impair patients' opportunity to persist with medications effectively. ■

That Darned Cold Sore: What a Difference a Day Makes!

Source: Spruance SL, et al. *J Am Acad Dermatol*. 2006;55:47-53.

IT MIGHT COME AS A SURPRISE THAT despite numerous methods for treatment of genital herpes, herpes zoster, and mucocutaneous herpes infections in persons with HIV, the antiherpetic antivirals (acyclovir, famciclovir, penciclovir) do *not* have an FDA-approved indication for herpes labialis (HRL), commonly known as the 'cold sore.' Given that the antivirals have shown great success in treatment of recurrences of herpes at other tissue sites, it seems reasonable to suspect that prompt treatment of HRL might be beneficial.

This randomized trial compared famciclovir 1500 mg/d given on *one day only*, either as 1500 mg single dose, or 750 mg bid, vs placebo. Subjects (n = 711) who had a history of recurrent HRL were instructed to take famciclovir at the earliest prodromal sign, prior to the appearance of skin lesions. They were also to return for clinician evaluation for the next 4 consecutive days.

The primary end point of the study was time to full healing of herpetic lesions. In the placebo group, the mean number of days to healing was 6.2 days. Both single-day famciclovir treatment groups showed greater than 30% reduction in the number of days to heal, with approximately equal efficacy for split-dose or single-dose therapy. ■

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Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: robert.kimball@thomson.com
World Wide Web: www.ahcpub.com
Address Correspondence to: American Health Consultants 3525 Piedmont Road, Building Six, Suite 400 Atlanta, GA 30305.

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