TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media LLC

INSIDE

Volume 18, No. 1
January 2008

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, receives funds from Johnson & Johnson.

New Recommendations for the Prevention of Hepatitis A

ABSTRACT & COMMENTARY

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Dr. Deresinski reports no financial relationship relevant to this field of study. This article originally appeared in the December 2007 issue of Infectious Disease Alert. *It was peer reviewed by Connie Price, MD, Assistant Professor, University of Colorado School of Medicine. Dr. Price reports no financial relationship relevant to this field of study.*

Synopsis: *Low rates of hepatitis A in both groups indicate that hepatitis A vaccine and immune globulin provided good protection after exposure.*

Sources: Victor JC, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *N Engl J Med*. 2007;357:1685-1694; CDC. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). 2007;56: 1080-1084. Available at http://cdc.gov/mmwr/preview/mmwrhtml/mm5641a3.htm/.

Previously, the recommendation in the United States for post-exposure prophylaxis of hepatitis A virus (HAV) infection has consisted of the administration of a single dose of immune serum globulin (ISG). While some other countries recommended the use of HAV vaccine for this purpose, the evidence to support this stance had been judged to be inadequate. New data, however, have now led to a change in recommendations in the United States.

Victor and colleagues randomized household and day-care center contacts of individuals with acute hepatitis A virus (HAV) infection who were 2 to 40 years of age to receive, within 14 days after exposure, either a single dose of HAV vaccine or of immune serum globulin. Of the 1414 subjects who were susceptible to HAV infection, 1090 were included in the final analysis of this study performed in Kazakhstan. The mean age of the subjects was 12 years and the mean interval from exposure to prophylaxis receipt was 18 days.

Laboratory-confirmed symptomatic HAV infection occurred in 25 (4.4%) of the vaccine recipients and in 17 (3.3%) of those given ISG (relative risk, 1.35; 95% CI, 0.70 to 2.67), thus meeting pre-set criteria for non-inferiority of vaccine prophylaxis. It is noted by Victor et al, however, that at all study points examined, infection rates for vaccine recipients were higher than those observed in those given ISG. Nonetheless, "the risk of infection in the vaccine group was never more than 1.5% greater than that in the immune globulin group." These

results have led to a change in the APIC and CDC recommendations for post-exposure prophylaxis of HAV infection, as well as for prophylaxis in the international traveler, as discussed below.

COMMENTARY

The results of this randomized trial fill in a data gap, which has allowed the CDC, upon the advice of APIC, to provide updated recommendations. It must be stressed, however, that the changes only strictly apply to the age cohort included in the study, those 2- to 40-years-old. There is no comparably reliable data that might apply to younger or older individuals, or to individuals who are immunocompromised. As a consequence, the recommendations state that "decisions to use vaccine or ISG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age and chronic liver disease." It must also be recognized that, although vaccination efficacy was not inferior to that of ISG, according to preset criteria, the overall data did suggest that ISG "performed modestly better than vaccine." Nonetheless, the drawbacks to ISG use, including the temporary nature of the protection provided, the pain associated with injecting the large volume often required, limitations in product supply, and the concerns of some about safety, make the vaccine an attractive alternative.

The bottom line is that the updated recommendations state that "Persons who recently have been exposed to HAV and who have not previously received hepatitis A vaccine should be administered a single dose of single-antigen vaccine or ISG (90.02 mL/kg) as soon as possible." Note the stress on the "single-antigen vaccine" — this is a consequence of a lack of data regarding the efficacy of the HAV-HBV combined vaccine, which contains a smaller amount of HAV antigen. For those 12 months to 40 years of age, "single-antigen hepatitis A vaccine, at the age-appropriate dose, is preferred to IG." For those > 49 years of age, IG is preferred. IG should be used for children < 12 months of age, immunocompromised persons, persons with known chronic liver disease, and in those in whom the vaccine is contraindicated. The efficacy of either vaccine or ISG, when administered more than 2 weeks after exposure, remains unknown.

The standard recommendation for travelers to countries with high or intermediate HAV endemicity has been the administration of the vaccine. However, it was also recommended that individuals traveling to an area of high endemicity less than 4 weeks after the initial vaccine dose also be considered for receipt of ISG. The updated recommendations now state that hepatitis A single-antigen vaccine alone can be recommended for travelers < 40 years of age at any time prior to departure. For optimal protection, older adults, immunocompromised individuals, and those with chronic medical conditions, including chronic liver disease, should also receive ISG (0.02 mL/kg) at a separate injection site. For those < 12 months of age, or those who refuse vaccine or are allergic to it, a single dose of ISG will provide protection for up to 3 months. If travel is to last > 2 months, the dose of ISG should be 0.06 mL/kg, and dosing should be repeated if travel time exceeds 5 months. ■

Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodicals postage rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to Travel Medicine Advisor, PO Box 740059, Atlanta, GA 30374-9815.

Subscription Information: Customer Service: (800) 688-2421 or fax (800) 284-3291. Hours of operation: 8:30am-6pm Monday-Thursday; 8:30am-4:30pm Friday ET. Email: customerservice@ahcmedia.com Website: www.ahcmedia.com. Subscription rates: USA, one year (12 issues) $449. Add $12.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions. For pricing information, call Tria Kreutzer at (404) 262-5482.

HPV Infection in Men

ABSTRACT & COMMENTARY

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This article originally appeared in the December 2007 Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD.*

Synopsis: *Genital HPV infection is common, and is often found at multiple sites in young heterosexual men. Risk factors for HPV infection in men include number of female sex partners (FSP), condom use, and smoking. Multiple anatomic sites should be sampled in heterosexual men to optimize detection of HPV.*

Sources: Partridge JM, et al. Genital human papillomavirus infection in men: Incidence and risk factors in a cohort of university students. *J Infect Dis*. 2007;196:1128-1136; Nielson CM, et al. Risk factors for anogenital human papillomavirus infection in men. *J Infect Dis.* 2007;196:1137-1145; Giuliano AR, et al. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: The HPV detection in men study. *J Infect Dis.* 2007;196:1146-1152.

THESE THREE STUDIES PUBLISHED BACK TO BACK IN the *Journal of Infectious Diseases* serve to better characterize HPV infection in heterosexual men. The first study from the group in Seattle followed a cohort of 240 heterosexually-active male university students from 2003 until 2006 and obtained genital samples at 4-month intervals for HPV-DNA analysis by PCR while the students maintained a web-based log of their sexual activity. By 24 months, the cumulative incidence of new infection with HPV was 62.4%. Report of a new sex partner in the preceding 8 months approximately doubled the relative risk of acquiring infection. A history of smoking increased the risk of acquiring infection with HPV by a factor of 1.6.

The second study conducted under CDC auspices recruited 463 men 18-40 years old from Tucson and Tampa and also used HPV detection by PCR and completion of a self-administered questionnaire at one time point only. Prevalence in this slightly older population of HPV infection of any type was 65.4%, 29.2% for oncogenic types, and 36.3% for non-oncogenic types. Lifetime and recent number of Femme Sex Partners (FSPs), condom use, and smoking were modifiable risk factors associated with HPV infection.

The third paper was a more in-depth analysis of technical factors associated with detection of HPV DNA derived from the dataset of the CDC study described above. Bottom line results from this study demonstrated that, at minimum, the penile shaft and glans penis/coronal sulcus should be sampled in heterosexual men, and that for optimal detection, scrotal, perianal and anal samples should be obtained as well.

COMMENTARY

Beginning in the 1970s, the association between oncogenic types of HPV infection and cervical cancer became well established. By the 1990s, increasingly sensitive molecular diagnostic techniques were available for the detection and typing of HPV in clinical samples. Appropriately, these techniques were generally initially applied in the clinical setting in young women. While genital malignancy can be associated with HPV infection in heterosexual men, HPV infection in men is mainly of importance to the extent that men provide a reservoir of infection and their sexual behavior affects women's risk of cervical cancer. Previously available information regarding penile HPV infection has been limited by the fact that it was derived from 3 sources: 1) studies of male partners of women with cervical cancer; 2) small cross-sectional studies of select populations such as men being treated for STDs or military recruits; or 3) small prospective studies.

The 3 studies described above greatly expand our knowledge of the true prevalence of HPV infection in men and our understanding of risk factors for acquisition. The high rates of HPV infection in men should be considered when developing strategies for the prevention of HPV infection in female adolescents and young women.

While not addressed in these studies, the state of knowledge regarding the natural history of anorectal HPV infection in gay/bisexual men is very limited as well. Despite the increasing acceptance of periodic performance of anorectal Pap smears in this population (especially in the San Francisco Bay Area), the utility and cost effectiveness of this practice remains unestablished, and will remain so until larger and more in-depth studies of HPV infection anorectal cancer are made in gay men as well. ■

Cognitive Decline After CABG: A Note for Travel

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford is on the speaker's bureau for Pfizer.

This article originally appeared in the December 2007 issue of Clinical Cardiology Alert. *It was peer reviewed by Rakesh Mishra, MD, FACC. Dr. Mishra is with the Berkeley Cardiovascular Medical Group, Berkeley, CA. He reports no financial relationships relevant to this field of study.*

Source: Djaiani G, et al. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. *Circulation*. 2007;116:1888-1895.

COGNITIVE DECLINE AFTER SURGERY REQUIRING cardio-pulmonary bypass (CPB) may be due to cellular debris picked up by the cardiotomy suction device. Cell savers, which clean and process shed blood prior to retransfusion, are used extensively during non-cardiac surgery, but have not been systematically studied in cardiac surgery. Thus, Djaiani and colleagues from Toronto, Canada, hypothesized that using a cell saver instead of the cardiotomy sucker would reduce cognitive decline after CABG. A cohort of 226 patients > age 60 years scheduled for CABG were randomized to cell saver or control with cardiotomy suction. Exclusion criteria included redo surgery, other cardiac surgery required, emergency surgery, symptomatic cerebrovascular disease, or atrial fibrillation. A preoperative transesophageal echo was done to exclude a cardiac source of emboli. Transcutaneous Doppler-detected emboli were assessed during aortic clamping in a subgroup of patients. Neuropsychological testing was performed one week before surgery and 6 weeks after.

Results: Baseline data were not different in the 2 groups. Cognitive dysfunction occurred in 6% of the cell saver group and 15% of the control patients (P = .038). Cognitive improvement occurred in 19% vs 17% of patients (P = NS). There was no difference in aortic atheroma. Doppler embolic counts, which could be done in about one third of patients, was 90 in the cell saver group and 133 in the control (P = NS). Retransfusion blood volume was a median of 800 mL in the control group and 401 mL in the cell saver group. Djaiani et al concluded that processing shed blood with a cell saver before retransfusion resulted in a clinically significant reduction in cognitive dysfunction post-CABG.

COMMENTARY

A cardiotomy suction device that returns blood from the pericardium and thorax to the patient's circulation is an integral part of CPB that reduces blood loss and blood transfusion requirements. However, this blood has been shown to contain high levels of lipid microparticles and cellular debris, which can cause microembolization of the brain. These microemboli are likely an important cause of cognitive decline after cardiopulmonary bypass. Previous studies have documented significant cognitive declines in 7% to 14% of patients undergoing cardiopulmonary bypass, about half of which are frank strokes, probably due to large emboli from cellular debris. The other half are more subtle declines detectable by neuropsychological testing and are probably due to microemboli from lipids. Cell savers, which are used extensively in other types of vascular surgery, separate red blood cells from plasma and debris by washing and differential centrifugation. In this study, their use decreased cognitive decline by 60% and eliminated stroke. Interestingly, Transcranial Doppler emboli counts were not different, suggesting that these come mainly from aortic manipulation, which would not be affected by the cell saver. Thus, the cell saver's effect on reducing cognitive decline is probably due to removing lipid microparticles and smaller cellular debris. Also, the cell saver removes inflammatory mediators in the plasma, which may decrease the inflammation reaction to microemboli.

The cell saver increases hemoglobin during the first 24 hours after surgery, but also increases INR by removing clotting factors and reducing platelets. Blood loss and transfusion requirements were the same in both groups in this study, but 2 times more fresh frozen plasma was administered to the cell saver group.

This study suggests that efforts to reduce aortic manipulation (large emboli prevented) and decrease lipid microembolization from the cardiotomy suction devices will have a major benefit on cognitive function after cardiopulmonary bypass. Whether the cell saver system will become the preferred technique for the latter will require more study, since it may have adverse effects on homeostasis. ■

ISTM Course 2008

The International Society of Travel Medicine is pleased to sponsor Travel Medicine Review and Update, to be held March 14-16, 2008, in Dallas/Fort Worth, Texas. This course is co-sponsored by Mount Auburn Hospital, a teaching hospital of Harvard Medical School. For further information, please go to www.istm.org. ■

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.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5413. E-mail: iris.young@ahcmedia.com.

drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■