TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media

INSIDE

Volume 22, No. 5
May 2012

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, reports no financial relationships relevant to this field of study. Peer reviewer Lin Chen, MD, and Executive Editor Gary Evans report no financial relationships relevant to this field of study.

Ivermectin Lotion 0.5% (Sklice™)

This article originally appeared in the March 29, 2012 issue of Pharmacology Update.

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

A NEW TOPICAL PREPARATION FOR THE TREATMENT OF HEAD LICE HAS BEEN approved by the FDA. Ivermectin is a macrocyclic lactone antibiotic that has been used orally both on and off label for head lice since 2001. This new formulation is a topical lotion (oral invermectin is not approved in the United States). It is manufactured by DPT Laboratories and is distributed by Sanofi Pasteur, Inc., as Sklice.

Indications

Ivermectin lotion is indicated for the topical treatment of head lice infestation in patients 6 years of age and older.[1]

Dosage

Ivermectin is applied as a single 10-minute application to the hair and scalp. It is available as a 0.5% lotion.

Potential Advantages

Ivermectin solution is well tolerated and provides another option for the treatment of head lice.

Potential Disadvantages

Approximately 25% of those treated with topical ivermectin were not lice free. It may be less effective than other products (e.g., spinosad or oral ivermectin).

Comments

Ivermectin is believed to cause paralysis and death of mites by selective binding to glutamate-gated chloride channels.[1] Its efficacy was shown in two randomized, vehicle controlled studies in subjects with head lice.[1] The youngest subject from each household was the primary subject for assessment of efficacy. Other members were evaluated for safety. All infected subjects were randomized to ivermectin or vehicle only as a single application. The primary endpoint was percent free of lice 14 days after application. The results from the two studies were 76.1% (54/71) and 71.4% (50/70) for ivermectin compared to 16.2% (12/74) and 18.9% (14/74) for the vehicle. Ivermectin appears to be well tolerated as adverse reactions (conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation) occurred in fewer than 1% of subjects.[1] There are no published comparative studies with other topical agents such as permethrin, benzyl alcohol, malathion, spinosad, or oral ivermectin. For rough comparisons, the cure rate (lice free in 2 weeks) of approximately 74% compared to 44%-68% for permethrin, 76% for benzyl alcohol, 85% for spinosad, 85%-98% for malathion, and 95% for oral ivermectin.[2-5]

Clinical Implications

Head lice is a common infestation in children ages 3-12.[6] Permethrin is commonly used but generally requires two applications. Benzyl alcohol and spinosad need one application with success rates at least as good as topical ivermectin. ■

References

1. Sklice Prescribing Information. Swiftwater, PA: Sanofi Pasteur; February 2012.
2. Stough D, et al. Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). *Pediatrics* 2009;124:e389-e395.
3. Heukelbach J, et al. A highly efficacious pediculicide based on dimeticone: Randomized observer blinded comparative trial. *BMC Infect Dis* 2008;8:115.
4. Benzyl alcohol lotion for head lice. *Med Lett Drugs Ther* 2009;51:57-58.
5. Chosidow O, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med* 2010; 362:896-905.
6. Frankowski BL, et al. Head lice. *Pediatrics* 2010;126: 392-403.

Myocardial Infarction Symptom Presentation

This article originally appeared in the April 2012 issue of Clinical Cardiology Update.

ABSTRACT AND COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

Dr. Boyle reports no financial relationships relevant to this field of study.

Source: Canto JG, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;307: 813-822.

Timely recognition and treatment of myocardial infarction (MI) are crucial if we are to achieve optimal outcomes for our patients. Silent ischemia, or the absence of classical symptoms of ischemia, may delay the diagnosis. In patients presenting with MI, delay in diagnosis and treatment may have disastrous outcomes. Accordingly, Canto and colleagues analyzed data from the National Registry of MI (NRMI) to assess the frequency with which men and women were admitted for MI without chest pain and the effect that presenting without chest pain has on mortality.

The investigators studied more than 1.1 million patients (42% women) presenting with MI, both ST elevation MI (STEMI) and non-ST elevation MI (non-STEMI) from 1994-2006. The in-hospital mortality rate was 14.6% for women and 10.3% for men ($P < 0.001$). The proportion of MI patients who presented without chest pain was an alarming 35%. Women presenting with MI were more likely than men to present without chest pain (42% vs 31%; $P < 0.001$). In addition, advancing age was associated with higher rates of MI without chest pain, but interestingly the gender differences actually became less pronounced with age. Patients presenting without chest pain were more likely to have diabetes, to have delayed presentation, to present with non-STEMI, and to present in Killip class III or IV, whereas those with chest pain were more likely to present with anterior MI and STEMI. Patients without chest pain were less likely to receive aspirin, beta-blockers, antithrombins, antiplatelet agents, or reperfusion therapy. Furthermore, when they did receive the appropriate treatments, those who presented without chest pain experienced significant delays.

After statistical adjustment for clinical characteristics, comorbidities, treatments received, and delays, younger men and

Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Travel Medicine Advisor,*** PO Box 105109, Atlanta, GA 30348.

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 $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

women who suffer MI without chest pain were more than twice as likely to die from their MI than those who had chest pain. However, with advancing age this difference was attenuated, and at age ≥ 75 years men were 32% more likely to die and women were 8% more likely to die than their counterparts with chest pain. The authors conclude that in patients hospitalized with MI, women were more likely than men to present without chest pain and had higher mortality than men within the same age group, but sex differences in clinical presentation without chest pain and in mortality were attenuated with increasing age.

■ COMMENTARY

I am struck by the significant rate of MI without chest pain (35%) in this study. Although this was higher in women (42% vs 31%), the rate of MI without chest pain is still alarmingly high in both sexes and we should have a high index of suspicion for acute MI in patients with atypical presentations. One may intuitively think that non-STEMI were more likely to present without chest pain than STEMI. This is true in the current study, but interestingly more than one-third of all STEMI also presented without chest pain. Delays in treatment were seen in patients without chest pain, and this could lead to serious outcomes in MI patients. This was demonstrated by the higher mortality in those without chest pain in this study. Interestingly, the difference between genders became less apparent with age, but the total proportion of patients presenting with MI without chest pain increased. The reasons for this remain unknown.

The major limitation of this study is that it is a retrospective analysis of registry data. The participating hospitals may not have collected data equally, and the hospitals participating in the NRMI registry may not serve populations that are truly representative of all regions throughout the United States. However, this is an incredibly large study — involving more than a million patients — which strengthens the conclusions made. We should continue to be vigilant for atypical presentations of MI, particularly in women and older patients. Hopefully, increased awareness of painless MI presentation may hasten diagnosis and avoid treatment delays for our patients. ■

The problem with *C difficile* Infection

This article originally appeared in the April 2012 issue of Infectious Disease Alert.

Source: Centers for Disease Control and Prevention. Vital Signs: Preventing *Clostridium difficile* infection. *MMWR* 2012;61(9): 157-162.

THIS REPORT ATTEMPTS TO CATALOGUE THE BALLOONING NUMBER OF cases of *C difficile* infection (CDI) in the United States using available resources, including data collected from the IDSA Emerging Infections Program (which has a catchment area of 111 acute-care hospitals and 310 nursing homes); the 2010 National Health and Safety Network data, which covers 711 acute care hospitals in 28 States; and data derived from 3 CDI prevention programs in 3 different states. A case of CDI was defined a positive test for CD in persons without a positive test within the previous 8 weeks. Enzyme immunoassay for toxin A and/or B was used to diagnose 51% of cases, while nucleic acid amplification test was used in 33% (other tests, not clarified, were used in 12%).

Based on the Emerging Infection Program data, 10,342 cases of CDI occurred in 2010, 44% of which occurred in people < 65 years of age. Based on available data, 94% of these had some kind of health care exposure within the preceding 12 weeks. A total of 75% occurred outside of the hospital (44% were attributed to community-onset and 25% to nursing home onset), while 24% were hospital onset. The authors argue this data may, on the surface, be misleading and that deeper analysis reveals that 21% of hospital-onset cases occurred in nursing home residents and 67% of nursing home cases occurred in patients who had recently been hospitalized.

According to the 2010 NHSN data from acute care hospitals in 28 states, 42,157 laboratory-incidents of CDI were identified, 52% of which were present on admission to hospital (pooled hospital-onset CDI rate = 7.4/10,000 hospital days).

A collection of 71 hospitals in 3 different States participating in CDI prevention programs served as a third source. Using a variety of measures, these programs demonstrated a 20% reduction in CDI rates during a 21-month period of observation (from 9.3 to 7.5 per 10,000 hospital days). The specific measures were not detailed, but involved prompt testing of suspect cases, isolation of suspect and confirmed cases, improved environmental measures, and antibacterial stewardship.

The authors acknowledge problems with this data, including the definition of CDI — while some cases are defined based on laboratory test results alone, the NHSN data requires concurrent symptoms with 3 or more loose stools per day. Test assays with varying sensitivity also differ between facilities, yielding potentially different results (hospitals using the newer nucleic acid testing may get unfairly dinged for enhanced case detection). In addition, adherence to the case definition of hospital-onset if > 72 post-admission obviously biases the results towards implicating hospitals as the "source" for infection — since the inherent time delay in the recognition of symptoms, ordering the test, and submitting a sample all serve to push forward the time of diagnosis — at least based on a lab report and not symptom-onset.

While the effort to enhance reporting of CDI is laudable (CDI is not even listed as a "reportable" pathogen in our country) does anyone truly believe the problem begins with hospitals or that hospitals are to blame? The plan for Medicare and Medicaid Services Inpatient Prospective Payment System Quality Reporting Program to tie reimbursement to CDI hospital rates is preposterous — and only serves to take much needed dollars away from hospital efforts to prevent this infection.

These punitive efforts are missing the point: Every patient should feel comfortable their life is not in danger when receiving appropriate and necessary antibiotics — which is presently not the case. I recently saw a patient nearly die from CDI following receipt of a single dose of peri-operative cefazolin for a routine hip procedure. What we really need is a focus on how people acquire this organism, limiting exposure in long-term care facilities (where isolation and environmental hygiene is often lacking), eliminating CD from food sources, methods to quickly identify patients at risk before they receive antibacterials, and improving methods to prevent infection in patients at risk. ■

ID drug shortages threaten patient safety

Source: Griffith MM, et al. The impact of anti-infective drug shortages on hospitals in the United States: Trends and causes. *CID* 2012: 54: 684-691

RECENT EFFORTS TO TREAT A PATIENT IN HOSPITAL WITH ACUTE pneumocystis pneumonia (PCP) were hampered by a lack of available injectable trimethoprim-sulfamethoxazole. The hospital pharmacy staff begged a few doses from the county and from the veteran's hospital in Palo Alto, but eventually I was forced to switch this patient to oral atovaquone, a second-line agent. At least the patient got through the more critical period of treatment, and gradually improved. Unfortunately, this scenario is becoming all too familiar to infectious disease specialists. Hardly a month goes by where I am not faced with a difficult therapeutic decision precipitated by a drug shortage of some kind. Coupled with the rise in antibacterial resistance, drug shortages can have a significant impact on medical care.

This salient article examines the clinical dilemmas created by the increasing frequency of critical drug shortages, and summarizes the current anti-infective drug shortages in the United States. Were you aware there is an entity called the Center for Drug Evaluation and Research (CDER) Drug Shortage Program of the FDA, which tracks the availability (or non-availability) of pharmaceuticals and anti-infectives in use? The CDER defines a drug shortage as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand…"

Such shortages often lead to clinical dilemmas, result in delays in initiation of treatment (while staff attempt to clarify availability of drug and hunt for a supply); often require an alternate and possibly less effective therapy, with the potential for worse outcome.

As of February 2011, a total of 193 agents were officially listed on the CDER's drug shortage list, 13% of which were anti-infectives. Some of these agents have been on the CDER list for months or years. In 2008, 5 anti-infective agents were listed on the CDER drug shortage list, one of which had not been resolved as of February 2011. Shortages of 6 of 11 agents listed in 2009 and 12 of 17 listed in 2011 had not been resolved and remain in short supply or are unavailable.

The government's role is mostly passive in this process, and can provide only oversight and monitoring, although they are charged with monitoring good manufacturing practice (GMP), and can help to precipitate a drug shortage by halting production of a drug or vaccine if a company fails to meet GMP standards. Drug shortages occur for a variety of reasons, including the lack of raw materials; a company can shut down manufacturing because of problems in a facility, or the FDA can interrupt production (as has been the case with Influenza vaccine and PCN G). For example, manufacturing issues hampered the production of injectable acyclovir, the only agent recommended for the treatment of HSV and VZV encephalitis. The shortage of PCN G in 2007, which is manufactured by a single company, created a serious problem for physicians attempting to treat neurosyphilis (inferior agents such as tetracycline and ceftriaxone had to be used). Manufacturing issues hampered production of injectable TMP-SMZ in May 2010, a problem that has still not been fully resolved; creating difficult decisions when attempting to treat PCP and infections due to Stenotrophomas maltophilia.

Occasionally, the demand for certain anti-infectives may outstrip production (as has occurred with Polymixin B, isoniazid, and mupirocin nasal ointment). Changes in clinical guidelines may also create an increased demand for certain agents, which existing production can not meet. Shortages of vaccines have also posed problems, including vaccines for Influenza, varicella, herpes zoster, yellow fever, and Hepatitis B.

In addition, a company can choose to halt or stop production of any agent for any reason, and they are not legally required to provide an explanation, nor are they required to provide status updates regarding any particular drug. Some drugs just disappear from the market, presumably as a marketing decision. Companies are required to provide 6 months notice to the FDA before ending production of a "medically necessary" drug. If they are the only manufacturer, the definition of medically necessary may be open for debate. For example, when Wyeth began marketing tigecycline in 2005, their other product, parenteral minocycline, was dropped from the market. It turns out that IV minocycline may prove to be one of the most useful agents against some strains of multidrug resistant *Acinetobacter baumannii*.

A panel of experts from several national associations has proposed changes to the FDAs current role, and a current U.S. Senate bill seeks to amend the law regarding manufacturer notification before halting production of any agent that could potentially lead to a shortage, as well as other recommendations made by a U.S House of Representatives Bill (Preserving Access to Life-Saving Medications Act). Those with opinions regarding this subject should contact their U.S. congressman or senator. ■

Correction: The correct answer to CME question 3 on p. 24 in the April 2012 *TMA* was inadvertently edited out. The correct answer is: E. none of the above.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Does Aspirin Prevent Cancer?

In this issue: Aspirin and cancer prevention; rivaroxaban for pulmonary embolism; new rhinosinusitis practice guidelines; and FDA actions.

Is recommending aspirin next?

Should aspirin be recommended to prevent cancer? Many lines of evidence have suggested that regular low-dose aspirin reduces the risk of colorectal cancer. Can the inexpensive wonder drug reduce the risk of other cancers as well? Researchers in England led by Dr. Peter Rothwell recently published three meta-analyses that looked at aspirin use and long-term cancer incidence and metastasis, as well as the short-term effect on cancer incidence and mortality, and the effect of aspirin on cancer metastasis. More than 200 studies were included in the meta-analyses, which were initially done to assess aspirin's benefit on vascular disease. The three new studies used a combination of case-control, cohort, and randomized clinical trials.

In the long-term study, the 20-year risk of cancer death and metastases was evaluated whereas the short-term study looked at a 3-5 year time frame. The trial for prevention of metastatic disease included five large, randomized trials of daily aspirin vs control in patients who had new solid cancer diagnosed during the trial. In the long-term study, the odds ratio for colon cancer incidence was 0.62 in favor of aspirin, and the odds ratio was 0.58 for death from colon cancer in favor of aspirin. There were similar reductions in the rates of esophageal, gastric, biliary, and breast cancer. The rate of distant metastases was also reduced. The other two studies also showed reduced rates of cancer and reduced rates of metastatic disease.

In the short-term study, cancer rates were 24% lower with aspirin use at 3 years. Curiously, aspirin did not reduce the risk of vascular events but there was no increased risk of major bleeding, including intracranial hemorrhage.

In the meta-analysis of five trials looking at the rate of metastatic disease, a 36% reduction in cancer metastasis was noted, including a 46% reduction in metastatic adenocarcinoma (all three studies published online in *Lancet* and *Lancet Oncology* March 21, 2012.) An accompanying editorial points out that these studies show that aspirin at any dose reduces nonvascular deaths by 12% and cancer death by 15% with benefits seen within 3 years for higher doses (> 300 mg/day) and at 5 years for lower doses (< 300 mg/day). The major critique of the studies comes from the United States where the Women's Health Initiative Study and the Physicians' Health Study both failed to show benefit from aspirin on cancer mortality. Both of these studies used low-dose aspirin every other day, a dose that may be too low to show biological effect on cancer. Another critique suggests that aspirin may lead to earlier diagnosis of colorectal cancer since it may cause earlier gastrointestinal bleeding, explaining the lower mortality rate. Despite these concerns, the editorialists suggest that this "impressive collection of data moves us another step closer to broadening recommendations for aspirin use. Moreover, future evidence-based guidelines for aspirin prophylaxis can no longer consider the use

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) 262-5404. E-mail: neill.kimball@ahcmedia.com.

of aspirin for the prevention of vascular disease in isolation from cancer prevention." (*Lancet* published online March 21, 2012). ■

Rivaroxaban for pulmonary embolism

Rivaroxaban, Janssen's oral factor Xa inhibitor, may be an effective alternative to heparin/warfarin for treatment of symptomatic pulmonary embolism, according to a new study. The drug is currently approved for the prevention of stroke in patients with nonvalvular atrial fibrillation and for deep vein thrombosis (DVT) prophylaxis following hip replacement. It has also been shown to be an effective treatment for DVT, although it is not approved for this indication. The new study was a randomized, open-label, event-driven, noninferiority trial comparing rivaroxaban to standard therapy with enoxaparin followed by adjusted-dose vitamin K antagonist for 3, 6, or 12 months for the treatment of pulmonary embolism. The primary outcome was symptomatic recurrent venous thromboembolism with a secondary safety outcome of clinically relevant nonmajor bleeding. In more than 4800 patients who were randomized, rivaroxaban was noninferior to standard therapy with 50 events in the rivaroxaban group (2.1%) vs 44 events in the standard therapy group (1.8%) (hazard ratio [HR], 1.12; confidence interval [CI] 0.75 to 1.68, noninferiority margin 2.0; $P = 0.003$). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard therapy group, while major bleeding occurred in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard therapy group (HR 0.49; 95% CI, 0.31 to 0.79; $P = 0.003$). The authors conclude that a fixed-dose regimen of rivaroxaban was noninferior to standard therapy with enoxaparin and warfarin for the initial and long-term treatment of pulmonary embolism, and potentially showed an improved benefit-risk profile (*N Engl J Med* published online March 26, 2012). The doses of rivaroxaban used in the study were 15 mg twice a day for 3 weeks followed by 20 mg once daily for the duration. Rivaroxaban offers the advantage of oral therapy compared to enoxaparin and the lack of need for blood test monitoring compared to warfarin. ■

New practice guideline for rhinosinusitis

The Infectious Diseases Society of America has published its first Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. The guideline points out the difficulty in distinguishing bacterial vs viral sinus infections. The following are suggestive of bacterial infection: persistent symptoms of sinusitis lasting more than 10 days without evidence of improvement; onset of severe symptoms or signs with high fever, purulent discharge, or facial pain lasting at least 3-4 consecutive days; or onset with worsening symptoms or signs characterized by new onset of fever, headache, or increased nasal discharge following a viral URI. The guideline recommends empiric antibiotic therapy with amoxicillin-clavulanate rather than amoxicillin alone in both children and adults. Children should be treated for 10-14 days while adults should be treated for 5-7 days. The guideline further recommends beta-lactam agents for treatment of sinusitis rather than respiratory floroquinolones, macrolides, trimethoprim-sulfamethoxazole, or second- or third-generation oral cephalosporins due to emerging resistance patterns. Doxycycline may be used as an alternative. (*Clin Inf Dis* 2012;54:e72-e112. DOI: 10.1093/cid/cis370). ■

FDA actions

The FDA has approved the first new erythropoiesis-stimulating agent in more than 10 years. Peginesatide is approved to treat anemia associated with end-stage renal disease in patients on dialysis. The approval was based on two randomized, active-controlled, open-label trials which showed that the drug was as effective as epoetin in maintaining hemoglobin levels. The drug is not approved for chronic kidney disease patients who are not on dialysis or for cancer-related anemia. Peginesatide is marketed by Affymax Inc. as Omontys.

The FDA has approved the first generic ibandronate (Boniva), the popular once-monthly bisphosphonate to treat or prevent osteoporosis in postmenopausal women. Three companies have received approval to manufacture the drug including Apotex Inc., Orchid Healthcare, and Mylan Pharmaceuticals. The generic as well as the brand is dispensed with a medication guide regarding the possible risk of esophagitis, hypocalcemia, bone or muscle pain, osteonecrosis of the jaw, and atypical femoral fractures.

The FDA has also recently approved generic escitalopram (Lexapro), a selective serotonin reuptake inhibitor (SSRI) to treat adults with depression and generalized anxiety disorder. Teva Pharmaceuticals will be the first to market the generic in 5-, 10-, and 20-mg strengths. Like other SSRIs, escitalopram carries a box warning regarding increased risk of suicidal thinking and behavior in children, adolescents, and young adults. ■