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Oseltamivir (Tamiflu) Resistance in Seasonal Influenza A (H1N1) Viruses

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

Sansum-Santa Barbara Medical Foundation Clinic, Santa Barbara, CA.

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

Synopsis: *Preliminary data indicate that the prevalence of influenza A (H1N1) virus strains resistant to the antiviral medication oseltamivir is high. Therefore, interim guidelines issued by the CDC are to use zanamivir or a combination of oseltamivir and rimantidine if influenza A (H1N1) infection is suspected.*

Source: CDC. Health Advisory. CDC Issues Interim Recommendations for the Use of Influenza Antivirals in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008-2009 Season. http://www.cdc.gov/flu/professionals/antivirals/index.htm. Accessed 12/22/08.

INFLUENZA ACTIVITY HAS BEEN RELATIVELY LOW THUS FAR IN THE 2008-2009 season in the United States. However, of the influenza viruses isolated and tested to date there is significant resistance among the influenza A (H1N1) viruses to the antiviral oseltamivir. As of mid-December 2008, 50 influenza A (H1N1) viruses from 12 states were tested. Ninety-eight percent were resistant to oseltamivir, but all were susceptible to zanamivir, amantadine, and rimantidine. Influenza A (H3N2) and B viruses remain susceptible to oseltamivir.

In light of this information, on December 19, 2008, the CDC issued interim guidelines for antiviral treatment or prophylaxis in suspected cases of influenza. The use of influenza tests that can distinguish influenza A from influenza B is encouraged. If a patient has a positive test for influenza A and treatment is indicated, the use of zanamivir should be considered. Alternatively, the combination of oseltamivir plus rimantidine could be used. If the patient has a positive test for influenza B, oseltamivir or zanamivir (no preference) may be given. The same recommendations hold for persons who are candidates for chemoprophylaxis as well. Ideally, local or state surveillance data should be used to determine which types (A or B) and subtypes (H1N1 or H3N2) are currently circulating in a given area, but this information may not be available at the time clinical decisions need to be made.

Based on preliminary information, it does not appear that oseltamivir-resistant influenza A (H1N1) viruses cause more severe symptoms compared to oseltamivir-sensitive influenza A (H1N1) viruses. In addition, since oseltamivir-resistant influenza A (H1N1) viruses are antigenically similar to

the (H1N1) virus included in the 2008-2009 influenza vaccine (A/Brisbane/59/2007), ongoing influenza vaccination remains an effective strategy to prevent influenza.

COMMENTARY

In the United States, four antiviral medications are approved for treatment and prophylaxis of influenza. The adamantanes (amantadine, rimantidine) have activity only against influenza A viruses, whereas the neuraminidase inhibitors (oseltamivir, zanamivir) have activity against both influenza A and influenza B viruses. In January 2006, when widespread resistance developed to the adamantanes among influenza A (H3N2) viruses, oseltamivir and zanamivir became the recommended influenza antiviral medications for the United States. Now we are seeing the recommendations shift again, in light of the oseltamivir-resistant influenza A (H1N1) viruses circulating this year.

This development is not unique to the United States. The World Health Organization collects data from multiple laboratories participating in the Global Influenza Surveillance Network (GISN), the European Influenza Surveillance Scheme (EISS), and the European Surveillance Network for Vigilance against Viral Resistance (VirGil). In January 2008, Norway reported an increased number of influenza A (H1N1) viruses with resistance to oseltamivir. By June 2008, data from the European region of WHO indicated that 25% of the influenza A (H1N1) viruses tested were resistant to oseltamivir. Finland, France, Luxemburg, the Netherlands, Norway, the Russian federation, and Ukraine all reported a prevalence of 25% or greater, with Norway having the highest prevalence (67%).[1]

The trend of rising oseltamivir resistance does not appear to be correlated with oseltamivir use or abuse since the use of oseltamivir generally is quite uncommon in European countries. Moreover, it does not appear that persons with resistant viruses were in contact with or linked to one another. Therefore, the reason for the emergence of these resistant viruses is unknown. However, zanamivir and oseltamivir differ in certain specific aspects of their chemical structures, which explains the lack of emergence of zanamivir resistance.[2] Zanamivir, available only as an inhaled formulation, is indicated for influenza treatment of patients 7 years or older but should not be used in patients with chronic underlying airway disease.

Influenza, be it avian influenza or seasonal influenza, continues to challenge the medical community worldwide. Influenza occurs in the tropics as well as colder climates, affects all age groups, and is highly contagious, placing all of us at risk, including global travelers. The 2008 southern hemisphere flu season just finished and was relatively mild, perhaps reflecting a more appropriate "match" with the vaccine viruses. Vaccination should be encouraged for both travelers and non-travelers throughout the 2009 influenza season since the oseltamivir-resistant viruses appear antigenically similar to the influenza A (H1N1) virus included in both the northern and southern hemisphere vaccines.

As this is an evolving issue, clinicians should check weekly for the updated reports and influenza information at http://www.cdc.gov/flu. ■

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Acute Mountain Sickness in Children

ABSTRACT & COMMENTARY

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

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

Synopsis: *More than one-third of children traveling to relatively high altitudes experience symptoms of acute mountain sickness, but symptoms are relatively mild and usually self-limited.*

Source: Bloch J, Duplain H, Rimoldi SF, et al. Prevalence and time course of acute mountain sickness in older children and adolescents after rapid ascent to 3450 meters. *Pediatrics* 2009;123:1-5.

Faced with limited data about acute mountain sickness in children traveling rapidly to high altitude, Swiss researchers studied symptoms in 48 children (ages 10-17, mean age 13) who traveled 2 ½ hours from low altitude (568 meters) to 3450 meters (approximately 11,200 feet). During the subsequent two days, 38% developed symptoms of mountain sickness; most of these became symptomatic during the first few hours at altitude. Symptoms were relatively mild and decreased over the days of the study; five of the subjects took acetaminophen for headache, but no further treatment was required. The authors concluded that pharmacologic prophylaxis may not be needed.

COMMENTARY

Acute mountain sickness presents as headache, fatigue, abdominal discomfort, dizziness, and/or sleep difficulties in individuals who have ascended to high altitude. Several factors affect the risk of developing acute mountain sickness.

Previous experience suggests that children and adults are equally affected, but that adults older than 50 years are less likely to become symptomatic.[1] Even among pre-verbal children, 22% had acute mountain sickness during their first few hours at an American ski resort at 3488 meters elevation, while 20% of their adult companions developed symptoms.[2] Nonetheless, a recent study showed that 92% of children and only 25% of their parents developed acute mountain sickness after ascending within 24 hours from sea level to 3500 meters in Chile.[3]

The rate and extent of ascent affect the risk of symptoms, but it is difficult to predict an individual traveler's risk. Bloch and colleagues identified 38% of their pediatric subjects as being symptomatic following ascent from 568 meters to 3450 meters during 2 ½ hours on a train. This is more than the 22% of preverbal children who became symptomatic during a 1 ½ hour drive and brief gondola ride from 1703 meters to 3488 meters,[2] but less than the 84% of adults who were symptomatic following a one-hour flight from 1300 meters to 3740 meters in the Himalayas.[4] It is not always possible to compare results from different studies under different conditions to predict accurately the risk of acute mountain sickness for a specific traveler.

Not all childhood fussiness during vacations is due to high altitude exposure. Several years ago, symptoms suggestive of acute mountain sickness developed in 28% of children at 2835 meters and 21% of children vacationing at sea level.[5] Traveling children might benefit from child-friendly scheduling, age-appropriate activity planning, and symptomatic care whether they are at high altitude or not.

Acetazolamide often is used to prevent altitude sickness in travelers, but this product is not approved for this indication by the U.S. Food and Drug Administration for use in children younger than 12 years of age. Bloch and colleagues suggest that preventive medication might not be needed in children since the symptoms were mild in their 48 subjects and diminished over two days. Alternatively, one might argue that acetazolamide is relatively safe when used for brief periods and that avoiding a day of ill feelings is of great enough benefit to accept the small cost and risk of treatment. (Similarly, antibiotics routinely are used in travelers who develop diarrhea even though antibiotics are relatively safe, and travelers' diarrhea is usually mild and self-limited.) Rather than discourage the use of acetazolamide in children and adolescents, one might suggest that the use of the product be individualized based on personal risk-benefit considerations. Travelers with a previous history of acute mountain sickness are at greater risk of recurrent symptoms and likely would warrant preventive treatment. Pediatric travelers ascending rapidly, becoming active immediately on arrival, and performing critically

important tasks might also be provided appropriately with pharmacologic prophylaxis.

High altitude pulmonary edema is much less common but much more severe than simple acute mountain sickness. Risk factors for high altitude pulmonary edema in children include pre-existing viral upper respiratory infection[6] and trisomy 21.[7] It is likely that lower oxygen saturations are involved in triggering symptomatic altitude illness in these and other susceptible individuals. Even normal children have low oxygen saturations at high altitude; an oxygen saturation of 90% should be considered normal at 2500 meters elevation, and 85% is normal at 3200 meters elevation.[8] (New data suggest that the oxygen saturation in adult mountaineers breathing ambient air at 8400 meters just after initiating a descent from the summit of Mount Everest is about 54%.[9])

Children living long term at high altitude also face health risks, but several of these risks seem to be moderated by population-specific genetic factors.[10] What else is new for high altitude travelers? Travelers journeying between Golmud, China and Lhasa, Tibet now can enjoy the comforts of oxygen-supplemented train cars during their 14-hour voyage.[11] ■

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Meeting Update: Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) 2008

By Lin H. Chen, MD

Dr. Chen is Assistant Clinical Professor, Harvard Medical School Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA.

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

At the 57th Annual Meeting of the American Society of Tropical Medicine and Hygiene in New Orleans, Louisiana, held from December 7-11, 2008, the Centers for Disease Control and Prevention presented malaria and travel vaccine updates. Dr. Paul Arguin from the Domestic Malaria Unit presented "Malaria Update: Surveillance, Prevention, Treatment." In 2007, 1505 cases of malaria were reported to the National Malaria Surveillance System, including 1 death. The most common species identified was *Plasmodium falciparum* (43.4%), followed by *P. vivax* (20.3%). The species in 30% of cases was unknown. Among the patients for whom information was available, 47% were U.S. civilians, 17% were foreign civilians, 2% were military, and 34% were of unknown status. Heading the list of countries where infection occurred were Nigeria (20.3%), India (13.1%), Ghana (10.4%), Tanzania (4.2%), Liberia (4%), and Uganda (3.3%). Among the foreign residents, 19.7% were from India.

Among the U.S. residents, the main countries that were associated with malaria acquisition were Nigeria (24.7%), Ghana (11.6%), India (11.2%), Uganda (4.0%), Honduras (3.6%), and Haiti (3.8%). Estimated relative risk showed West and Central Africa and Oceania to be the regions of highest risk, whereas Central and South Central Asia were the regions of lowest risk. The most common reasons for travel were, once again, visiting friends and relatives (VFR) at about 50%, followed by tourism for about 10% of travelers.

Of interest, one U.S. traveler from New York was documented with *P. knowlesi* acquired in 2008 in Palawan in the Philippines, with species identification confirmed by PCR at the CDC. *P. knowlesi* is a simian malaria species that naturally infects macaques in Southeast Asia. It became recognized as a human pathogen in a number of reports.[1-5] On microscopy, it resembles human species. *P. knowlesi* has a 24-hour replication cycle and can cause severe and fatal infections. Large numbers of human cases were reported initially from Malaysian Borneo. Subsequently, human cases were reported from Peninsular Malaysia, Singapore, and the Philippines. One case previously was reported in a Finnish traveler.[6]

Treatment updates highlighted the artemisinins. Artemether-lumefantrine gained recommendation for approval by the FDA advisory panel on December 3, 2008. In addition to atovaquone-proguanil, artemether-lumefantrine may become the second drug approved for treatment of malaria for travelers going to areas where reliable supplies of the drug may not be available. A second artemisinin drug, artesunate, has become available through WRAIR via the CDC malaria hotline in the past 2 years. Criteria for the release of artesunate are: the patient has malaria; parenteral treatment is required; artesunate is preferred (quinidine not available, has failed, the patient is intolerant, or the drug is contraindicated). Thus far, 37 patients have been treated in the United States through this protocol. Mean age was 35 years, 60% were male; 90% *P. falciparum* malaria, 7% *P. vivax* malaria; 84% had exposure in Africa, 10% in Asia, 6% in the Americas. Measures of delays in treatment showed the time from request of drug to shipping was 2.7 hours, and the time to arrival was 2.9 hours. Time from request to treatment was approximately 7.2 hours.

Prevention emphasized individual risk assessment based on destination country (transmission intensity, focal areas with transmission even when, within a country, the overall risk is low), type of traveler (especially VFRs), accommodations, etc. Major upcoming changes are: new country-specific guidance table that is separate from yellow fever; malaria risk categories updated to include five groups (limited malaria, *P. vivax*-predominant, chloroquine-sensitive, chloroquine-resistant, and mefloquine-resistant areas); and inclusion of primaquine as a first-line drug. The updated recommendations emphasize personal protective measures for areas considered as having limited malaria. For areas with mainly *P. vivax*, use primaquine as the first-line preventive agent.

Nina Marano, DVM, MPH, Dipl ACVPM, from the Division of Quarantine and Global Migration, presented "Travelers' Vaccine Update from the CDC." She reviewed the prevention of rabies, Japanese encephalitis, yellow fever (YF), and gave a preview of the 2010 Yellow Book.

The CDC initiated a country-specific rabies risk assessment based on rabies endemicity in the country, availability of biological agents, and travelers' expected risk of exposure. Rabies risk assessment is used to guide pre-exposure prophylaxis recommendations for travelers. Special risk among children is noted, and mapping of the risk areas by category of risk is planned. Emphasis is placed on dog avoidance and prevention of bites and scratches. A short supply of rabies vaccines in the United States occurred in 2008 due to renovation of a manufacturing plant, and restrictions on rabies vaccines applied to pre-exposure prophylaxis that affected travel clinics in particular. Since October 2008, the supply for post-exposure vaccines has stabilized.

As many travel medicine practitioners know, the only FDA-approved Japanese encephalitis vaccine is JE-Vax, whose manufacture was discontinued around 2005, and allocations took place in 2008. The restriction limits 9 doses of the vaccine per month to previous customers only. A new, inactivated, cell-culture derived JE vaccine has been undergoing FDA review and likely will receive approval very soon. For travelers at risk (spending 1 month in endemic areas or short-term travel with itineraries that may pose increased risk, such as significant rural exposure or outdoor activities), provide advice regarding insect bite precautions and refer to providers or clinics that previously have ordered JE-Vax from Sanofi-Pasteur.

A recent publication updates yellow fever vaccine risks (Lindsey, et al. Adverse event reports following yellow fever vaccination. *Vaccine* 2008;26:6077-82). The revised estimates are based on 660 adverse events reported to VAERS from 2000 to 2006. The denominator is obtained from the number of doses purchased for civilians, or 200,000 doses per year. A survey of 3400 U.S. providers in 2006 obtained the age and sex of vaccine recipients. Ninety-five percent of the AEs were associated with primary vaccines, and 61% were women. Median time to occurrence was 1 day, with a range 0-50 days. There were 72 serious adverse events (SAE), including 12 neurotropic disease (YF-AND), 6 viscerotropic disease (YF-AVD), and 4 deaths. SAE rates are calculated. (*See Table.*) A new ACIP work group for YF vaccine plans to update the recommendations.

A World Health Organization YF risk mapping work group is planning to update the risk map and harmonize CDC and WHO recommendations. The work group will

Table. Yellow Fever Severe Adverse Event (SAE) Rates* and Age Groups

Type of SAE[a]	All Ages	Age 40-49 years	Age 50-59 years	Age 60-69 years	Age >70 years
All SAE[a]	4.7	4.5	2.7	6.3	12.6
YF-AND[b]	0.8	0.9	0.4	1.6	2.3
YF-AVD[c]	0.4	0	0	1.0	2.3

*Rate = per 100,000 doses
[a] Severe adverse event
[b] Yellow fever vaccine-associated neurotropic disease
[c] Yellow fever vaccine-associated viscerotropic disease

Data from: Lindsey, et al. Adverse event reports following yellow fever vaccination. *Vaccine* 2008;26:6077-6082.

focus on countries that are non-holoendemic, and define areas within countries as endemic, transitional, or low risk. YF vaccine will be recommended for travel to areas that are endemic or transitional. The decision to vaccinate for travel to areas that are low risk will be based on itinerary, extent of exposure, and risk factors. Updated YF vaccine recommendations include: risk areas are updated for Brazil, Paraguay, and Argentina; vaccine is not needed for travel to Tobago; and vaccine is needed only for certain areas of Chad, Mali, Mauritania, Niger, and Sudan.

Health Information for International Travel, the CDC Yellow Book, 2010 will be available in May 2009. The editorial team includes Amanda Whatley, Gary Brunette, Phyllis Kozarsky, Alan Magill, and David Shlim. It will be in a larger size, with bulleted presentation and new tables to be easy to use in clinical settings. New items include pre-travel consultation, perspectives, and health considerations for newly arrived immigrants and refugees. A new chapter will highlight selected destinations and itineraries. Finally, new sections will focus on medical tourism, mental health, drug interactions, respiratory infections, as well as special groups (air crews, long-term travelers, and expatriates), and additional diseases. The changes promise to enrich an already valuable resource for travel medicine practitioners. ■

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Travel Practices of Solid Organ Transplant Recipients

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD

Dr. Mileno is Director, Travel Medicine, The Miriam Hospital, Associate Professor of Medicine, Brown University, Providence, RI.

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

Synopsis: *New data have identified subgroups of solid organ transplant recipients who are at increased risk for illness during travel. Both men and those persons traveling for the purpose of visiting friends and relatives should be targeted for pre-travel care within this subgroup.*

Source: Uslan DZ, Patel R, Virk A. International travel and exposure risks in solid-organ transplant recipients. *Transplantation* 2008;86:407-412.

The risks for illness acquired during travel are greater in immunocompromised travelers. Solid organ transplantation poses increased potential for acquisition of new fungal infections, given impaired cell-mediated immunity caused by immunosuppressive drug regimens. Impaired immunity also may lead to increased morbidity from bacterial infections common to travelers such as *Salmonella* sp, *Listeria monocytogenes*, *Mycobacteria,* and *Legionella* sp.

The currently reviewed survey of travel patterns has assessed more than 1100 patients who had undergone solid organ transplantation at Mayo Clinic using a self-administered anonymous questionnaire. Most traveled to low-risk regions and had low rates of travel-associated illness. However, 18% of the group who traveled to high-infection risk destinations such as Asia, Central or South America, Africa, or the Middle East developed illness requiring medical attention during travel. One traveler developed allograft rejection.

Men, in general, and persons who were born outside of the United States and Canada were more likely to travel to high-infection risk destinations. Those traveling for the purpose of visiting friends and relatives are reported to be more likely to contract infections due to longer stays and higher risk-taking behavior.

Of note, preventive measures were inconsistent, with fewer than 50% of these immunocompromised travelers to high-risk destinations reporting use of DEET. Of 1134 respondents, 303 reported travel outside of the United States and Canada after transplantation. Ninety-six percent of these travelers reported that they did not seek pre-travel advice prior to travel. Travel-related illness requiring medical attention occurred at a rate comparable to that of non-immunocompromised persons (8%), except for 49 persons who traveled to high-infection risk destinations. Of this group, 18% experienced severe illness.

COMMENTARY

Travel within the first few months after transplantation is likely to represent the greatest risk period for infectious complications; however, the risk of infection diminishes six months after transplantation. Late-onset infections can include community-acquired pathogens, invasive or endemic fungal infections, or zoonotic infections. The authors acknowledge the limitations of basing broad conclusions on a survey with a 44% response rate and a confined study population. Still, the rate of illness in SOTR traveling to high-risk destinations is compelling, and it underscores the need for pre-travel preparation and access to high-quality medical care during travel for solid organ transplant recipients as well as other immunocompromised travelers. ■

Thousands of Years Later — a New Kind of Leprosy

By Carol A. Kemper, MD, FACP

Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center. Editor Stan Deresinski, MD, FACP, is Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center. Peer reviewer Connie Price, MD, is Assistant Professor, University of Colorado School of Medicine.

Dr. Kemper and Dr. Price report no financial relationships relevant to this field of study. Dr. Deresinski serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck.

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DIFFUSE LEPROMATOUS LEPROSY (DLL) IS AN ESPECIALLY virulent form of multibacillary disease, occasionally seen in patients from Central and South America and Southeast Asia. Lucio's phenomena is a highly anergic and more severe form of DLL, resulting in extensive skin and subcutaneous involvement, with an abundance of organisms infiltrating tissues. Dermal infarcts occur, occasionally resulting in extensive necrosis, with histopathologic evidence of obliterative vasculitis of dermal and subcutaneous vessels. These extensive skin lesions increase the risk for superinfection and sepsis.

These authors from MD Anderson report on two such cases occurring in 2002 and 2007 at their facility, the first of which was so severe as to prompt transfer to the burn unit. The second occurred in an older Latino from Mexico, who presented with extensive skin lesions on his lower extremities. Within days, he became septic and died. Autopsy confirmed the presence of DLL, with diffuse AFB infiltrating blood vessels.

Having done gene sequencing on other organisms, the authors turned their hand to the organisms responsible for these two cases. Sequences of the 16S ribosomal subunit and five other genes were examined and compared to other mycobacterial cases, including *M. leprae*. The 16S ribosomal sequences were only 97.9% homologous with *M. leprae* — a huge difference, considering that gene sequences in other cases of leprosy are essentially identical. The five other genes reportedly showed important differences as well. The strain identified from

these two individuals constitutes a new strain of leprosy — called *M. lepromatosis*.

Analysis of tissue from two other similar cases of DLL occurring in Singapore yielded this same organism. All four patients died of their disease. While its distribution worldwide has not yet been determined, the discovery of this new mycobacterial organism may explain some of the variation seen in cases of leprosy. ■

CME Questions

1. Oseltamivir resistance in seasonal influenza is:
   a. equal to the development of zanamivir resistance.
   b. related to overuse and abuse of oseltamivir.
   c. being detected in influenza A (H1N1) viruses.
   d. being detected in influenza A (H3N2) and influenza B viruses.
   e. found only in the United States.

2. Acute mountain sickness:
   a. occurs in most children visiting U.S. ski resorts.
   b. is potentially preventable with the use of acetazolamide.
   c. causes permanent health problems.
   d. is less common than high altitude pulmonary edema.

3. Regarding malaria cases reported in the United States, which of the following statements is true?
   a. Cases most commonly occurred in foreign visitors.
   b. Cases rarely were identified to be *P. vivax*.
   c. Cases most frequently occurred in VFR travelers.
   d. The most commonly identified species was *P. knowlesi*.
   e. Cases were most common after travel to Southeast Asia.

4. Which statement is true about travelers who have previously undergone solid organ transplantation?
   a. Eight percent will require medical attention overall.
   b. Eighteen percent will require medical attention if they travel to a high-risk destination.
   c. Men, in general, are more likely to become ill during travel following solid organ transplantation.
   d. Persons visiting friends and relatives are more likely to contract infections than are other travelers.
   e. All of the above are true.

Answers: 1. c; 2. b; 3. c; 4. e

CME Objectives

• To present the latest data regarding the diagnosis and treatment of various travel-related diseases;

• To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas fo the world; and

• To alert the readers to recent disease outbreaks and epidemics. ■

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*.

How Best to Control Hypertension?

In this issue: Drug combinations for hypertension; tenecteplase for out-of-hospital cardiac arrest; CAM most commonly used for back, neck, and arthritis pain; FDA Actions.

Combination therapy for hypertension

What's the best drug combination with an ACE inhibitor for treatment of hypertension in patients at risk for cardiovascular disease? Current guidelines recommend a diuretic, as witnessed by the number of ACE inhibitor/diuretic combination products that are currently marketed. However, a new study suggests that the calcium channel antagonist may be a better selection than a diuretic. Researchers from several medical schools in the United States and Sweden randomized 11,506 patients with hypertension who were at high risk for cardiovascular events to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary endpoint was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. The average patient was 68 years old at entry and the group included patients with a history of ischemic heart disease, peripheral vascular disease, stroke, LVH, and diabetes. The study was terminated early after 3 years when it was found that the benazepril/amlodipine group had a significantly lower risk of the primary endpoint: 9.6% vs 11.8% (hazard ratio 0.80; 95% confidence interval, 0.72-0.92; $P = 0.002$). This represents a 2.2% absolute risk reduction and a 19.6% relative risk reduction in the benazepril/amlodipine group vs benazepril/hydrochlorothiazide. The authors conclude that the combination of benazepril/amlodipine is superior to benazepril/hydrochlorothiazide in reducing cardiovascular events in patients with hypertension who are at risk (Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. *N Engl J Med* 2008;359:2417-2428). An accompanying editorial from the chair of the seventh report of the Joint National Committee on hypertension suggests it is time to re-examine the recommendation of initial therapy with a thiazide-type diuretic. He also states, however, that regardless of the drugs chosen for treatment of hypertension, the most important factor is reducing blood pressure to goal levels (Chobanian AV. Does it matter how hypertension is controlled? *N Engl J Med* 2008;359:2485-2488).

A survival benefit with tenecteplase?

Thrombolytic therapy during out-of-hospital cardiac arrest does not improve outcomes according to a new study. There has been considerable interest in thrombolytic therapy during cardiopulmonary resuscitation since it has been shown that 70% of these arrests are due to acute myocardial infarction or pulmonary embolism. European researchers randomized 1050 patients with witnessed out-of-hospital cardiac arrest to tenecteplase or placebo during cardiopulmonary

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

resuscitation. The primary endpoint was 30-day survival and the secondary endpoints were hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, and neurologic outcomes. The trial was discontinued early when it was found that there was no survival benefit with tenecteplase. Thirty-day survival was 14.7% with tenecteplase and 17% with placebo. Secondary outcomes similarly showed no benefit from tenecteplase. The authors conclude that when tenecteplase was used during advanced life support for out-of-hospital cardiac arrest there was no improvement in outcomes in comparison to placebo (Bottiger BW, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med* 2008;359:2651-2662).

CDC report on CAM use

There is a 40% chance that your patients are using complementary and alternative remedies according to new report from the Centers for Disease Control & Prevention. Not including vitamins and minerals, the use of a complementary and alternatives medicine (CAM) in adults and children has increased in the last 5 years. Treatments include non-vitamin, non-mineral natural products (fish oil, flaxseed oil, echinacea), chiropractic or osteopathic manipulation, deep breathing exercises, massage, and meditation. Children are also using alternative treatments, especially if their parents use them. Despite lack of evidence of efficacy, echinacea is the most common remedy used by children. In adults, use of CAM treatments for URIs is actually down, perhaps indicating better patient education. Back pain, neck pain, and arthritis pain are the most common reasons why people turn to CAM, according to this recent survey. These results point out the need to query patients about the use of complementary and alternative medicines.

FDA Actions

The FDA is requiring a boxed warning on sodium phosphate bowel-cleansing products because of the risk of acute phosphate nephropathy associated with use of these products. Sodium phosphate cleansing products are most commonly used as bowel preparation for procedures such as colonoscopy. According to the warning, the products Visicol® and OsmoPrep® should be used with caution in people older than age 55; those suffering from dehydration, kidney disease, colitis, or delayed bowel emptying; and people taking other medications that may affect kidney function. These products should also not be used in conjunction with other oral laxatives containing sodium phosphate, and over-the-counter products, such as Fleet® Phospho-Soda®, should also be used with caution if given in a high dose to the patient population at risk.

The FDA is requiring a warning on all anti-epileptic drugs regarding the risk of suicidal thoughts and behavior. The warning is based on review of nearly 200 studies that showed that patients on anti-epileptic drugs were at almost twice the risk of suicidal behavior or thoughts compared to patients on placebo. Along with the warning, the agency is also requiring a Medication Guide for patients as part of its Risk Evaluation and Mitigation Strategy. Over 20 drugs will be required to change their labeling including the commonly used agents phenytoin, carbamazepine, divalproex, gabapentin, lamotrigine, primidone, and topiramate.

The FDA is considering a ban on the long-acting beta agonists salmeterol (Serevent®) and formoterol (Foradil®) for the treatment of asthma. An expert committee comprised of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee voted unanimously to withdraw the indication for the treatment of asthma for the two drugs based on evidence from meta-analyses showing increased risk of death associated with use of long-acting beta agonist when not paired with a steroid inhaler. The committee did not vote to ban Advair® or Symbicort®, inhalers that combine a long-acting beta agonist with a steroid. If the FDA follows the subcommittee's recommendations, the drugs would no longer be indicated for treatment of asthma but would remain on the market to treat chronic obstructive pulmonary disorders. The FDA has not indicated when it will act on the subcommittee's recommendations.

The FDA has approved fenofibric acid (Trilipix™) for use with a statin for the treatment of dyslipidemia. This is the first fibrate approved for use with statins. The approval is based on a large trial in which the drug was used in combination with rosuvastatin (Crestor®), atorvastatin (Lipitor®), and simvastatin (Zocor®). There have been safety concerns about using fibrates and statins together, particularly gemfibrozil, but the newer generation fibrates appear safer. Abbott, the manufacturer of Trilipix, is collaborating with AstraZeneca to develop a fenofibric acid/rosuvastatin fixed combination product within the next year. ■