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INSIDE

Risk of Community-Acquired Pneumonia and Use of Gastric Acid-Suppressive Drugs

ABSTRACT & COMMENTARY

Synopsis: *Current use of gastric acid-suppressive therapy was associated with an increased risk of community-acquired pneumonia.*

Source: Laheij RF, et al. Risk of Community-Acquired Pneumonia and Use of Gastric Acid Suppressive Drugs. *JAMA*. 2004;292:1955-1960.

In a survey of 365,000 records of patients followed by general practitioners in Holland for at least 1 year during a 7-year period, 5551 incident cases of pneumonia developed. Users of acid suppression, particularly proton pump inhibitors (PPIs), had a 4.5 fold increased unadjusted risk of pneumonia, compared to untreated controls.

Laheij and colleagues believe that this increased risk can be attributed to the loss of the protective acid milieu of the stomach that normally serves as a barrier to pathogens. Current PPI users were at more risk than patients who had previously discontinued PPI use, and there was no increased risk of pneumonia for those with a distant past history of use of acid-inhibiting drugs. Histamine-2 receptor antagonists (H2RAs) appeared to be associated with a similar unadjusted excess risk of pneumonia to that seen with PPIs. However, the number of patients using various H2RAs and various H2RA doses was too small to allow discrimination of risks beyond those for the entire population of H2RA recipients. Higher PPI doses seemed to produce a further elevation of pneumonia risk vs conventional daily doses. Laheij et al seem quite confident in the reliability of these results from such a large population in a country where follow-up of patients is virtually guaranteed by the national health system.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

This is not the first time that this attribution of pneumonia risk to use of acid suppressing drugs has been made. In an accompanying *JAMA* editorial, the actual described risk is placed at 1 case per 100 patient

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years (about the same as the risk of GI hemorrhage from use of NSAIDs). Nevertheless, the results of this study should not be accepted without reservation. For example, it is likely that much of the use of antisecretory medication is directed toward gastroesophageal reflux disease. GERD itself may represent an important contributor to the pathogenesis of pneumonia (eg, by aspiration). If so, the association of drugs used for treatment might be entirely spurious. Only a prospective study would sort this out, and such a study is quite unlikely to be done. In a marketing flurry based on competition between sucralfate and ranitidine, there was an attempt to demonstrate that ranitidine was associated with nosocomial pneumonia in the hospital. This concept was thoroughly discredited at that time. H2RAs do not produce achlorhydria or even profound hypochlorhydria, and even the much more potent PPIs do not eliminate stomach acid. Although there is a remote possibility that acid suppression may in some cases tilt the balance toward bacterial overgrowth in the stomach, this effect is likely to be counterbalanced by the dramatic decrements in gastric volume that also are associated with antisecretory agents (particularly PPIs). I am sure that we have not heard the last word in this area, but I would urge physicians to realize that the amazing efficacy of currently available H2RAs and PPIs should continue to be made available to all patients with diagnoses that demand acid-suppressive therapy. ■

Dr. Robinson, MD, FACP, FACG, is Medical Director at the Oklahoma Foundation for Digestive Research and Clinical Professor of Medicine at the University of Oklahoma College of Medicine.

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Brenda Mooney.

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Leslie Hamlin,
Associate Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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Risk of *Clostridium difficile* Diarrhea Among Hospital Inpatients Prescribed Proton Pump Inhibitors

ABSTRACT & COMMENTARY

Synopsis: *Although PPIs are considered to be among the safest of drugs, these studies suggest that PPIs increase the risk of development of* C. difficile*-related diarrhea among hospitalized patients.*

Source: Dial S, et al. Risk of *C. difficile* Among Hospital Inpatients Prescribed Proton Pump Inhibitors: Cohort and Case-Control Studies. *CMAJ*. 2004;171:33-38.

DIAL AND COLLEAGUES POINT OUT THAT *Clostridium difficile* is the most common form of nosocomial infectious diarrhea in the Western world, apparently increasing in frequency, severity, and consequential health care costs (more than $1 billion in the United States annually). In general, the pathogenesis of *C. difficile* is closely related to antibiotic-related changes in normal flora followed by overgrowth of the *C. difficile.* Decreased gastric acidity is known to be a risk factor for various infectious diarrheal illnesses, and this may also be true for *C. difficile* colitis.

The first part of Dial et al's studies identified all patients at the Montreal Royal Victoria Hospital who received antibiotics over 9 months. *C. difficile*-related diarrhea developed in 6.8% of the patients, 9.3% of 591 patients who received PPIs, and 4.4% of 596 patients who did not receive these drugs. Since there was apparently more severe concomitant disease in the patient

cohort that received PPIs, a second study was done at a separate teaching hospital where all patients with *C. difficile* and diarrhea were identified and matched by antibiotic class taken and age and inpatient ward with a general group of patients who had received antibiotics. Development of *C. difficile*-related diarrhea was associated with female sex (OR, 2.1; 95% CI 1.2-3.5), prior renal failure (OR, 4.3), previous recent hospitalization (OR, 2.6), and use of PPIs (OR, 2.7; CI 1.4-5.2).

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Do PPIs directly cause what we have considered to be antibiotic colitis, which has been associated with *Clostridium difficile*? There was 1 case identified in these patient populations who in fact did develop *C. difficile*-related diarrhea without any prior antibiotic administration. However, this scenario is clearly not common. On the other hand, it is certainly possible that *C. difficile*, like other intestinal pathogens, may be sensitive to inhibition by an acidic milieu. If so, potent gastric inhibition could facilitate successful GI colonization by exogenous *C. difficile*. Ten percent of patients who received antibiotics in the cohort segment of the study were receiving H2-receptor antagonists (vs 50% on PPIs). H2-receptor antagonist therapy did not increase risk for the development of *C. difficile*-related diarrhea. Since a great many hospitalized patients receive PPIs with little or no therapeutic justification, hospitals should consider the advisability of attempting to educate physicians to administer these agents only when clearly indicated. Additional studies should be done, including direct assessment of pH on viability of oral *C. difficile* inocula. ■

The Re-emergence of Wild Poliovirus in Africa

ABSTRACT & COMMENTARY

Synopsis: *Travel Medicine providers must be aware of the need for continued surveillance of their patients for an adequate polio immunization status given the developments in Africa.*

Sources: CDC. Wild Poliovirus Importations—West and Central Africa, January 2003-March 2004. *MMWR.* 2004; 53(20):433-435.

WORLD HEALTH ORGANIZATION POLIO EXPERTS WARN of largest epidemic in recent years, as polio hits Darfur. (WHO Press Release 22 June 2004. Available at http://www.who.int/mediacentre/releases/2004/pr45/en.)

Wild poliovirus (WPV) was imported into 8 countries that were previously felt to be polio-free in west Africa (Benin, Burkina Faso, Cote d'Ivoire, Ghana, Togo) and Central Africa (Cameroon, Central African Republic, Chad) from January 2003 to March 2004. The polio-free period before these recent importations ranged from 28 to 55 months. The MMWR summarized 63 cases, which were all shown to be poliovirus type 1 and linked to strains that circulate in endemic regions of Nigeria and Niger. Nigeria and Niger reported 497 cases of polio type 1 or type 3 during the same period. Two of the 8 index patients in the 8 countries had recent travel to a polio-endemic country, and the other 6 lived near centers where foreign trade with polio-endemic countries occurred. In spite of the supplementary immunization activities (SIAs) organized in all 8 countries, 4 continued to have WPV transmission after at least 2 rounds of immunizations.

In addition, the WHO press release reported re-infection with polio in Sudan, which had been polio-free for 3 years. The report warns of a spreading epidemic of polio through west and central Africa. Apparently, the number of children paralyzed in west and central Africa in 2004 is 5 times those which occurred in the same period in 2003.

COMMENT BY LIN H. CHEN, MD

Poliomyelitis is caused by 3 serotypes of poliovirus, which are enteroviruses transmitted via the fecal-oral route. Acute poliovirus infection can be asymptomatic or present as acute poliomyelitis, which is a nonspecific febrile illness followed by aseptic meningitis and/or paralysis.[1] Paralysis can be classified as spinal, bulbar, or spino-bulbar disease. Post-polio syndrome, characterized by muscle pain and weakness or paralysis, may develop decades later in up to 40% of persons who had paralytic poliomyelitis in childhood.[1] Infection with 1 serotype of poliovirus does not confer immunity to the other serotypes. An inactivated polio vaccine (IPV, Salk vaccine) became available in the United States during 1955, and was widely used until oral polio vaccine (OPV, Sabin vaccine) became available in the 1960s. The introduction of the polio vaccine rapidly reduced the incidence of poliomyelitis.

In 1988, the World Health Assembly established the goal of global polio eradication by 2000. Although the deadline has been postponed until 2005, much progress has been made. Three of the 6 WHO regions (Americas, Europe, and western Pacific) have been certified polio free, and only 6 countries were considered polio endemic in 2003: Afghanistan, Egypt, India, Niger, Nigeria, and

Table

Wild Polio Cases (Data from references 2, 3, 8)

Country	2002	2003	2004 *
African Region			
Benin	0	2	3
Botswana	0	0	5
Burkina Faso	1	11	2
Cameroon	0	2	0
Central African Republic	0	1	0
Chad	0	25	4
Cote d'Ivoire	0	1	3
Ghana	0	8	0
Niger	3	40	12
Nigeria	202	355	133
Sudan	0	0	1 (June 2004)
Togo	0	1	0
Zambia	2	0	0
Eastern Mediterranean Region			
Afghanistan	10	8	2
Egypt	7	1	0
Lebanon	0	1	0
Pakistan	90	103	12
Somalia	3	0	0
South-East Asian Region			
India	1603	225	8
Worldwide	1921	784	185

*January-April, unless otherwise specified

Pakistan.[2] On the one hand, transmission has become limited within the Eastern Mediterranean Region and South-East Asian Region (*see Table*).[2] On the other hand, the situation has deteriorated in Africa, where an additional 10 countries have reported polio cases in 2003 to 2004, including the 8 countries in west and central Africa noted in the CDC report, as well as Sudan and Botswana.[2]

Laboratory surveillance has demonstrated importation of viruses from Nigeria/Niger into most of the other African countries. Furthermore, genomic sequencing demonstrated the poliovirus in Lebanon in 2003 originated in India; the poliovirus found in Zambia during 2002 was imported from Angola.[3]

The current situation reflects a trend associated with routine vaccination coverage in the endemic countries. In Niger and Nigeria, the extent of coverage with 3 doses of oral poliovirus vaccine was estimated to be 25% in 2002, whereas the vaccine coverage was 48% in Afghanistan, 63% in Pakistan, 70% in India, and 97% in Egypt.[2] In India, polio vaccine coverage in 2002 was low in the states where polio commonly circulated, Bihar and Uttar Pradesh (21% and 41%, respectively).[4]

The 144 indigenous cases of polio reported in the United States since 1979 were due to vaccine-strain virus of the live oral poliovirus vaccine (OPV); only 6 additional cases were imported (1979-1993).[5] A more immunogenic vaccine, the enhanced-potency IPV was initially licensed in the United States in 1987.[6] In 1997, the Advisory Committee on Immunization Practices recommended sequential IPV-OPV for routine childhood immunization.[6] In 1999, the recommendation changed to an all-IPV schedule in order to eliminate the potential risks of vaccine-associated paralytic polio (VAPP).[1,5]

The risk of acquiring polio during travel is low. In the 1990s, polio was estimated to occur at an incidence of 1 symptomatic case and 20-1000 asymptomatic cases per 1,000,000 non-immune travelers visiting developing countries for 1 month.[7] By comparison, 3000-6000 per 1,000,000 travelers may contract hepatitis A, 800-2400 travelers may contract hepatitis B, 30 travelers may contract typhoid, and 3 may contract cholera.[7]

The estimated risk of polio in travelers should be lower at preset, given the global reduction of polio in the past decade. However, travelers visiting any polio-epidemic or polio-endemic areas should be current with their polio immunization: Children should have had their routine polio immunizations (at 2, 4, and 6-18 months, followed by a booster at 4 to 6 years of age), and adults should receive a polio booster (given at age 18 or older) before their trip.[1] The progress in polio elimination in the Eastern Mediterranean Region and South-East Asian Region continues to reduce the risk of exposure to polio for travelers visiting these areas. Nonetheless, long-term carriage of polioviruses has been documented in immunodeficient individuals, and questions remain as to whether these rare carriers of poliovirus can reintroduce poliovirus circulation into the population. In summary, given the recent spread of polio in the African region, travelers visiting the area should continue to ascertain that their polio immunizations are up to date, or receive a booster dose of inactivated polio vaccine (IPV). ■

Dr. Chen, MD, is Assistant Clinical Professor and Harvard Medical School Director.

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Rabies Infections in Organ Donor and Transplant Recipients

ABSTRACT & COMMENTARY

Synopsis: *The Centers for Disease Control (CDC) has confirmed the diagnosis of rabies in 4 recipients of transplanted organs and their common donor. All 4 transplant recipients presented with rapidly progressive encephalitis within 21 to 27 days after receiving their transplant and all subsequently died.*

Source: Investigation of Rabies Infections in Organ Donor and Transplant Recipients- Alabama, Arkansas, Oklahoma, and Texas, 2004. *MMWR. Dispatch* 2004;53:586-589. Update: investigation of rabies infections in Organ Donor and Transplant Recipients-Alabama, Arkansas, Oklahoma, and Texas, 2004 53 (Dispatch).

On June 30, 2004, the CDC confirmed the diagnosis of rabies in 3 transplant recipients, all of whom died with a diagnosis of encephalitis of unknown etiology. The common organ donor was an Arkansas resident who presented in Texas with severe mental status changes and low grade fever. A diagnosis of subarachnoid hemorrhage was suggested following neurologic imaging. The hemorrhage expanded resulting in cerebral herniation and death. The patient's family agreed to donation of his organs, and there appeared to be no contraindication to donation based on standard screening and testing. On May 4, the liver and kidneys were transplanted into 3 recipients at a transplant center in Texas.

The patient who received the donor liver was a man who, 5 days after uncomplicated transplant surgery, was discharged to home. However, 21 days after transplant, he was readmitted to the hospital with tremors, lethargy and anorexia, but without a fever. His neurologic status worsened rapidly; a lumbar puncture showed a lymphocytic pleocytosis and mildly elevated protein. Magnetic resonance imaging (MRI) of the brain initially showed increased signal in the cerebrospinal fluid and a second MRI 6 days after admission showed progression to diffuse encephalitis. His neurologic status continued to worsen and he subsequently died.

The first kidney recipient was a woman who presented 25 days after transplant with right-sided flank pain and underwent an appendectomy. Two days post-operative, she began having diffuse muscle twitching and mental status changes. Initial computed tomography (CT) and MRI studies were normal, yet she continued to deteriorate with seizures, hypotension, and respiratory failure. Repeat CT imaging, 14 days after admission, indicated severe cerebral edema, and she subsequently died.

The last organ recipient, who received the second kidney, presented 27 days after transplant with a change in mental status and myoclonic jerks. He was also afebrile. An initial MRI was normal. The lumbar puncture had a lymphocytic pleocytosis and mildly elevated protein. A second MRI 10 days after admission showed diffuse edema. He continued to deteriorate neurologically, and subsequently died.

The diagnosis of rabies was confirmed in all 3 cases at the CDC by immunohistochemical testing, and by the detection of rabies virus antigen in fixed brain tissue by direct fluorescent antibody tests. Pathology of the brain tissues of all 3 patients showed encephalitis with viral inclusions suggestive of Negri bodies. In addition, rabies virus antibodies were demonstrated in the blood from 2 of the 3 recipients, as well as the donor. Detecting anti-rabies antibodies in the donor suggests that he was the likely source of rabies transmission to the transplant recipients. Additional investigation and testing of the donor specimens is ongoing.

However, it has now been determined by Dr. Frank Wilson at the Arkansas Department of Health, that the donor had reported being bitten by a bat. In addition, a fourth case of rabies appears to be related to this outbreak in that an additional liver transplant recipient died

of rabies encephalitis. In this fourth case, the source was not his liver donor, but appears to have been a stored segment of iliac artery recovered from the donor who had been determined to have had rabies. It had been stored at the facility for potential use in future liver transplants.

COMMENT BY MARY-LOUISE SCULLY, MD

Rabies is an acute, fatal encephalitis caused by neurotropic viruses in the genus *Lyssavirus*, family Rhabdoviridae. Bites of rabid mammals cause the majority of rabies cases.[1] It is very rare for nonbite exposures, such as scratches, contamination of open wounds, or direct mucous membrane contact with rabies infected material to cause rabies. Human-to-human transmission of rabies is extremely rare, but documented cases have been reported in 8 recipients of transplanted corneas in 5 countries.[2] However, this is the first documented occurrence of rabies transmission among solid organ transplants. It is likely that infections occurred via infected neuronal tissue in the transplant organs, since rabies is not spread hematogenously.

This report has generated a wave of appropriate questions and concerns regarding rabies post-exposure prophylaxis (PEP) in both domestic and healthcare contacts of rabies infected patients, as well as hospital personnel who may have had contact with the rabies infected organs. In the domestic setting, rabies can be transmitted when infectious material, such as saliva, enters a wound, a break in the skin, or mucous membranes, (eg, eyes, nose, or mouth). Therefore, domestic exposures to rabies patients that includes bites, sexual activity, exchanging kisses on the mouth, sharing, eating, or drinking utensils, or cigarettes, warrant rabies PEP.

There are no documented cases of rabies transmission to health care workers caring for patients with rabies.[3] Adherence to Standard Precautions for contact with blood or body fluids (eg, gloves, gown, mask goggles, or face shield, as indicated for the type of patient contact) prevents rabies transmission.[4] However, rabies PEP is recommended for health care workers who have been exposed to saliva, nerve tissue, or cerebral spinal fluid of a rabies patient. In addition, rabies PEP is recommended to health care workers after percutaneous injuries (needlesticks or scalpel cuts) because potentially infectious nerve material could be contained in the bore of the needle following tissue penetration in a rabies patient. Therefore, the recommendation is related to the possibility of exposure to infected nerve tissue not just blood exposure. Exposure to feces and urine are not considered a risk for rabies transmission.

Despite over 20,000 transplants being performed every year, no human rabies cases associated with solid organ transplants have previously been reported. Donor eligibility is determined through donor physical examination, laboratory data for organ dysfunction, and testing for selected bloodborne viral pathogens and syphilis. In addition, a series of questions are posed to the family and contacts of the donor. Presently, no testing for rabies is performed. In this case, the donor's death was attributed to a noninfectious cause since imaging studies showed a subarachnoid hemorrhage and subsequent cerebral herniation. Clearly, the challenge ahead is striking a balance between the need for donor testing to minimize the risk of such infectious disease transmissions without adversely affecting the access and availability of organs for transplantation. Currently, the CDC is working with federal and organ procurement agencies to review donor screening practices. More information regarding rabies in transplant organ recipients, and the indications for rabies PEP in health care and domestic contacts is available from the CDC at www.cdc.gov/ncidod/dvrd/rabies. ■

Dr. Scully, MD, works at the Sansum-Santa Barbara Medical Foundation Clinic in Santa Barbara, CA.

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Dying of Malaria in the United States

ABSTRACT & COMMENTARY

Synopsis: *Nearly 1 in every 100 US travelers with malaria reported to the National Malaria Surveillance System died of the infection. The majority of deaths were preventable.*

Source: Newman RD, et al. Malaria-Related Deaths Among U.S. Travelers, 1963-2001. *Ann Intern Med.* 2004;141: 547-555.

All 165 cases of malaria-related deaths in the United States reported to the National Malaria Surveillance System from 1963 to 2001 were reviewed. Two-

Table

Summary of key findings of review of malaria deaths among U.S. travelers, 1963-2001, and recommended action items to reduce mortality

1. Many patients who died did not take any malaria chemoprophylaxis. Educate health care providers about available resources for up-to-date prophylaxis recommendations:
   Health Information for International Travel (the "Yellow Book")
   (www.cdc.gov/travel/yb/index.htm)
   CDC Travelers' Health Website (www.cdc.gov/travel)
   Educate travelers about the need for malaria chemoprophylaxis; especially important for those visiting friends and relatives.

2. Many patients who died did not completely adhere to recommended chemoprophylaxis regimens.
   Advise travelers about the importance of complete adherence to prescribed malaria chemoprophylaxis regimens.

3. Many patients who died did not seek prompt medical care once symptoms began.
   Clinicians providing pretravel advice need to stress importance of seeking medical care for illnesses in the 3 months after return.
   All travelers should develop a plan for illness (abroad or after return to the United States).

4. Diagnostic delays common among fatal cases.
   Take basic travel history when relevant.
   Order malaria blood films for suspected malaria.
   Read blood films immediately; qualified laboratory personnel should be on call.
   Repeat negative blood slides from suspected malaria cases (a total of 3 blood film examinations in 24 hours).

5. Delays in initiating antimalarial treatment contributed to many fatalities. Promptly initiate appropriate antimalarial treatment. If diagnosis of malaria is suspected and cannot be confirmed, or if diagnosis of malaria is confirmed but species cannot be determined, immediately initiate antimalarial treatment that is effective against *Plasmodium falciparum*.
   Educate health care providers about resources on up-to-date treatment recommendations:
   CDC Malaria Website (www.cdc.gov/malaria)
   CDC Malaria Hotline (24-hour advice line for clinicians (770-488-77788)
   Intravenous quinidine should be available on hospital formularies.
   If quinidine is not available, obtain it from a local source (othr pharmacy or regional distributor).
   If no local source available, contact Eli Lily and Company, the current U.S. manufacturer or quinidine gluconate (800-821-0538, Monday to Friday, 7:30 a.m. to 6 p.m., or 317-276-2000 after hours) to arrange for rapid shipment of the drug.

thirds occurred in US travelers, and 92.7% of deaths were due to *Plasmodium falciparum* infection. From 1985 to 2001, the case fatality rate was 1.3% for *P. falciparum*, 0.06% for *P. vivax*, 0.3% for *P. malariae*, and 0.3% for *P. ovale*. Most cases were acquired in Africa, with Kenya, Nigeria, and Liberia accounting for 40.6% of fatal cases. The median duration of stay was 22 days, ranging from < 1 day to 23 years.

Of the 123 who died from 1985 to 2001, only 34 individuals were known to have taken chemoprophylaxis and, of these, only 20 (58.8%) took an appropriate agent and 6 (30%) of these were non-adherent. As a consequence, only 7 of 123 (5.7%) were known to take appropriate chemoprophylaxis and to adhere to their regimen!

The median interval from return to symptom onset was 5 days. Of the 90 patients for whom data was available, only one-third received a diagnosis of malaria on the day of their initial contact with medical care, so that the median time to diagnosis was 4 days (range, 1 to 17 days). Of the 109 who received medical attention before dying, 6 had a delay in initiation of antimalarial therapy of 12 to 24 hours and 18 (16.5%) never received any. Of 90 recipients of antimalarials for whom data was available, 9 (10%) were given inappropriate therapy.

Of the 195 (85.4%) deaths considered preventable, the patient's own decisions, such as non-adherence to prophylaxis and delay in seeking care, contributed to the outcome. In two-thirds, however, medical errors, both pre- and post-travel, may have contributed to the fatal outcome.

COMMENT BY STAN DERESINSKI, MD, FACP

Several months ago, I saw a young woman recently returned from visiting family in India. She had had a febrile illness for 11 days. She had been to an urgent care center twice and, on one occasion, went to a local hospital emergency department at 3 AM with a temperature of 39.9°. She had not taken malaria prophylaxis in India and was concerned about malaria, a concern which she told me she reported to health care workers during these contacts. Despite all this, no malaria smear was obtained and no diagnosis made! She, fortunately, turned out to be infected with *P. vivax* (as well as having dengue!), for if it had been *P. falciparum*, she likely would have been added to the national database of malaria fatalities.

Although, as indicated by the above analysis, patients may contribute to their adverse outcomes, many of the errors listed by health care workers in this report are inexcusable. A key element is to always maintain a level of suspicion, asking about travel in all febrile patients (and to listen to the patient when they think they may have malaria). Malaria smears should be performed and examined immediately. If negative, smears should be repeated twice over the next

24 hours (*see Table*). Therapy should be initiated immediately. In cases in which plasmodia are detected and *P. falciparum* cannot be excluded in a patient traveling from an area with chloroquine resistance (ie, most malarious regions of the world), treatment should be initiated with drugs active against chloroquine resistant *P. falciparum*. For patients who require parenteral therapy for *P. falciparum* infection, the unavailability of quinine sulfate suitable for intravenous administration, together with the removal of quinidine from many hospital formularies, led to unacceptable delays in initiation of therapy in some of the cases reviewed in this report. Until (and if) artemesinin derivatives become available in the United States, hospital pharmacies should maintain a small supply of quinidine for such emergency use—*P. falciparum* infections in non-immune hosts can be fatal within hours of presentation if untreated.

Nearly 1 in 100 US travelers with malaria diagnosed and reported to the National Malaria Surveillance System died—not a good record. ■

Pharmacology Update

Abacavir Sulfate and Lamivudine Tablets (Epzicom)

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

THE FDA HAS APPROVED A COMBINATION OF 2 ANTIretrovirals, abacavir and lamivudine, for the treatment of HIV-1 infections. Each tablet contains 600 mg of abacavir and 300 mg of lamivudine for once daily administration. The combination is marketed by GlaxoSmithKline as Epzicom.

Indications

Abacavir/lamivudine is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infections.

Dosage

The recommended dose is one tablet daily. It may be taken without regard to meals.[1]

Abacavir/lamivudine is supplied at bottles of 30 tablets. Each containing 600 mg of abacavir and 300 mg of lamivudine.

Potential Advantages

The combination permits a once-daily dose of these 2 nucleoside reverse transcriptase inhibitors (NRTI) as one tablet thus reducing tablet burden and potentially improving compliance. The alternative would be 2 × 150 mg lamivudine and 2 × 300 mg of abacavir.

Potential Disadvantages

Missed doses of a once-daily regimen potentially has greater therapeutic consequence that with a multiple dose regimen. Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir. In clinical trials, hypersensitivity was reported in about 8% of subjects with a median onset of 9 days.[1]

Comments

The combination of abacavir and lamivudine improves convenience and significantly reduces tablet burden when this 2-NRTI combination is used. The efficacy as a once daily regimen was assessed in a randomized, double-blind study in 770 HIV-infected, treatment naïve patients.[1] Patients received either abacavir 600 mg daily or 300 mg twice daily with lamivudine 300 mg daily or efavirenz 600 mg twice daily. Through 48 weeks, no differences were detected between these regimens in terms of viral load or discontinuation due to adverse events or other reasons. Bioequivalence was established between abacavir/lamivudine as a single tablet and components administered individually.[1] A regimen of abacavir, lamivudine, and efavirenz has been reported to be more effective than abacavir, lamivudine, and zidovudine.[2] Similarly the combination of abacavir, lamivudine, and efavirenz was superior to that of abacavir, lamivudine, and tenofovir.[3] The cost for abacavir/lamivudine is same as the sum of the components taken individually.

Clinical Implications

The preferred combination regimens for treatment naïve patients recommended by the Panel of Clinical Practices for Treatment of HIV-1 Infected Adults and Adolescents are efavirenz plus (zidovudine or tenofovir or stavudine) plus lamivudine.[3] An alternative is efavirenz plus (either didanosine or abacavir) plus lamivudine. For two-NRTIs as part of a combination regimen, the Panel recommends lamivudine plus zidovudine or stavudine as combinations of choice. Abacavir and lamivudine may be used as alternatives. Epzicom offer a more convenient and lower tablet burden than the individual components when this combination is used. ■

Dr. Elliott, MD, FACP, is Chair of the Formulatory Committee at Northern California Kaiser Permanente and Assistant Clinical Professor of Medicine at the University of California, San Francisco. Dr. Chan, PharmD, PhD, is Pharmacy Quality and Outcomes Manager for Kaiser Permanente, Oakland, CA.

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Pharmacology Update

Tinidazole tablets (Tindamax™)

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

THE FDA HAS APPROVED A 5-NITROIMIDAZOLE FOR the treatment of trichomoniasis, giardiasis, and amebiasis. Tinidazole, a second-generation nitroimidazole antiprotozoal agent, is marketed as Tindamax™ by Presutti Laboratories.

Indications

Tinidazole is indicated for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in both females and males. It is also indicated for the treatment of giardiasis and amebiasis (intestinal and amoebic liver abscess) caused by *E. histolytica*. It is not indicated for the treatment of asymptomatic cyst passage.[1]

Dosage

For the treatment of trichomoniasis, the recommended dose is a single 2 g dose taken with food. The sexual partner should be treated with the same dose at the same time.

For giardiasis, the adult dose is a single 2 g dose taken with food. In pediatric patients (older than 3 years of age), the dose is a single 50 mg/kg dose (up to 2 g).

For intestinal amebiasis, the adult dose is 2 g daily for 3 days with food, and for pediatric patients, 50 mg/kg/d (up to 2 g) for 3 days. For amoebic liver abscess, the recommended dose is 50 mg/kg/d with food (up to 2 g) for 3-5 days.

Alcoholic beverages should be avoided while on tinidazole, and for 3 days thereafter.

Tinidazole is available as 250 mg and 500 mg tablets. The tablets can be ground to a fine powder and made into a suspension with artificial cherry syrup for pediatric use.[1]

Potential Advantages

Tinidazole has good in vitro activity against both metronidazole and metronidazole-resistant *T. vaginalis* and shown effectiveness against metronidazole-refractory vaginal trichomoniasis.[2,3] The elimination half-life of tinidazole is 12-14 hours, about twice that of metronidazole (6-7 hours), and may be better tolerated.[4]

Potential Disadvantages

As with metronidazole, tinidazole is contraindicated during the first trimester of pregnancy. Convulsive seizures and peripheral neuropathy has also been reported with these drugs. Approximately 38% of *T. vaginalis* isolates showed cross-resistance to metronidazole. Drugs that may interact with metronidazole may also interact with tinidazole (eg, alcohol, lithium, phenytoin, fosphenytoin, cyclosporine, tacrolimus fluorouracil, rifampin, phenobarbital, cholestyramine). Similar to metronidazole, tinidazole may produce transient leucopenia and neutropenia although no persistent hematological abnormalities have been observed in clinical trials. Total and differential leukocyte counts are recommended if retreatment is needed.[1] Common side effects include metallic/bitter taste, dyspepsia, weakness/fatigue/malaise, and vomiting.[1]

Comments

Tinidazole is a second generation 5-nitroimidazole similar to metronidazole. It has been established as an effective drug against trichomoniasis, giardiasis, and amebiasis. The cure rate for trichomoniasis for a single 2-g dose ranged from 80% to 100%.[1,5-8] The cure rate for tinidazole ranged from 80% to 100% for giardiasis, 86% to 93% for intestinal amebiasis, and 81% to 100% for amoebic liver abscess.[1,9,10] In general, tinidazole was equal to, or more effective than, metronidazole. In addition, these agents share similar side effects although some studies suggest that tinidazole is better tolerated.[4,8] The average wholesale cost for a 2-g dose of tinidazole is $18.24 which is significantly more expensive than generic metronidazole.

Clinical Implications

Trichomoniasis is a common sexually transmitted disease. It is estimated that there are about 7.4 million cases annually. Current treatment is metronidazole as a single 2 g dose. For patients that are not responsive, options have included an increase in the dose of metronidazole or multiple doses of the drug (eg, 500 mg twice daily × 7 days or 2 g for 3-5 days).[11] Tinidazole provides an effective alternative for patient intolerant of or not responsive to metronidazole. Tinidazole is also a convenient single dose alternative to metronidazole and furazolidone for giardiasis. ■

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CME Questions

1. Which of the following is correct?

a. Most malaria deaths in the United States are due to *P. vivax*.
b. Patients with suspected *P. falciparum* malaria must be given intravenous quinine sulfate.
c. Malaria smears should only be examined in reference laboratories for initial examination in order to avoid the unnecessary administration of antimalarial therapy.
d. Quinidine is effective in the treatment of *P. falciparum* infection.

2. One of the following statements regarding poliomyelitis is *false*?

a. Poliovirus infection can present with acute paralysis as well as asymptomatic infection.
b. Patients with paralytic polio may develop a post-polio syndrome decades later.
c. Acute poliomyelitis has been eliminated from the WHO Region of the Americas, the European Region, and the Western Pacific Region.
d. Adults traveling to polio-epidemic and polio-endemic countries should be immunized with a booster of polio vaccine, if none has been given in adulthood.
e. Polio has been eradicated from all areas of the world.

3. Which of the following statements regarding rabies is incorrect?

a. Domestic exposures to rabies patients that warrant rabies PEP include bites, sexual activity, exchanging kisses on the mouth, direct mucous membrane contact with saliva, sharing, eatin, or drinking utensils, or cigarettes.
b. Exposure urine or feces is not considered a risk for rabies transmission.
c. Rabies virus is also transmitted hematogenously.
d. Rabies PEP is recommended for healthcare workers who have been exposed to saliva, nerve tissue, cerebral spinal fluid, and percutaneous injuries from rabies patients.
e. Rabies transmission to transplant patients mostly likely occurred via neuronal tissue contained in the transplanted organs.

Answers: 1. (d); 2 (e); 3. (c)

In Future Issues:

Congenital HHV6 and HHV7 Infections

UPDATES

By Carol A. Kemper, MD, FACP

Amazing Teen Survives Rabies

ProMED-mail post November 25, 2004; www.promedmail.org

A 14-YEAR-OLD WISCONSIN GIRL has remarkably survived acute encephalitic rabies! Although the full details have not disclosed by her physicians (who plan to publish this remarkable case), she did not receive vaccine at presentation, but was instead put into a drug-induced coma and treated with various antiviral agents. It is not clear which of these interventions was important to her survival. The few survivors of rabies that have been described, of whom there are less than a handful, all received post-exposure prophylaxis or at least vaccine.

Her story, which was initially reported in the *New York Times* on the same day, is fairly typical for ~50% of the cases or rabies reported in the United States during the past 25 years. She was bitten by a bat, although she did not appreciate the fact; the bite was small and painless and she thought she had simply been scratched. She did not seek medical assistance. About 6 weeks later, she developed altered mental status, slurred speech, and other symptoms of rabies, and was admitted to hospital. Unfortunately the bat was not retrieved, and no virus was recovered from the teen, as it may have been helpful to examine this particular virus for virulence and attenuation factors. ■

India, Genetics, and HIV

Jayaraman K. *Nat Med*. 2004,10:1148.

RESEARCHERS HAVE UNCOVERED numerous genetic factors that may be directly contributing to the growing problem of HIV in India. According to this editorial, Dr. Narinder Mehra, an immunologist with the All India Institute of Medical Science in New Dehli, has shown that many Asian Indians carry various genetic factors which predispose them to HIV infection, and more rapid progression of HIV, onc3e infected. First among these is a paucity of the variant CCR5 chemokine receptor gene (CCR5-Δ32), which is present in < 1% of Indians, rendering them more susceptible to progressive HIV. Epidemiological studies have found that ~20% of those of northern European descent are heterozygous for this mutation and ~1% are homozygous. While CCR5-Δ32 heterozygotes are probably not protected from HIV infection, it does afford modest protection against disease progression. The frequency of this allele is exceedingly low in African and Asian populations.

Several other interesting differences were identified in Asian Indians: they have a high level of polymorphism in the major histocompatibility complex (MHC) region (which, among other things, appears to possibly modulate their response to Mycobacterium tuberculosis infection), as well as genes which appear to encode for a unique repertoire of peptides to block autoreactive antigens. Such differences will be important to identify if worldwide peptide-based vaccines for HIV are to be developed. Complicating these findings, many Indians are infected with HIV subclade C, and may not be candidates for vaccines targeting subclade B (the predominate subtype present in the United States). ■

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Illicit Botox Products

ProMED-mail post December 3 and December 8, 2004; www.promedmail.org

BOTOX, WHEN INJECTED DIRECTly into a muscle in small amounts (~15-50 IU of botulinum exotoxin A, depending on the size of the muscle), is extremely but transiently effective at diminishing wrinkles. The increasing use of Botox in cosmetic salons by non-medical personnel—and the potential for misuse of illicit products—puts individuals at risk for facial paralysis, deformity, and even death. Experts caution that a precise understanding of anatomy is necessary to achieve optimal

results, and that only 2000 IU—a dilution away from dosages used above—can be a lethal dose.

Sadly, 4 individuals, including a physician, a chiropractor, and their female companions did not get this message. After their purported self injection with an illicit botox-like product, all 4 were acutely hospitalized over the Thanksgiving weekend with suspected botulism, and are now on ventilatory support. Three of them had evidence of botulinum type A toxin in their blood streams.

True Botox (Allergen Inc. Irvine, CA) is FDA-approved for use as an anti-wrinkle treatment, is subject to rigorous manufacturing standards, and provides a fairly uniform and dependable dose of exotoxin. Although tests are still inconclusive, authorities found evidence at the scene to suggest that a product called botulinum neurotoxin type A may have been used, which is an illegal product sold by an Arizona distributor called Toxin Research International. Apparently, this product is far less costly than Botox (which sells for $1250 per vial, enough for about 5-10 people), and may even contain live *C. botulinum*. Illicit botox products are being actively marketed on the web, especially in South America and Asia, and now even in the United States. ■

Sharing Your MRSA With Your Pet

Van Duijke ren E, et al. *Emerg Infect Dis*. 2004;10.

DURING INVESTIGATION OF AN outbreak of MRSA in a local nursing home in the Netherlands, which involved 48 residents and 15 nurses, Van Duijkeren and colleagues identified a 31-year old nurse with recurrent colonization with MRSA, despite repeated attempts at decolonization with both topical and oral agents. She did have psoriasis, with numerous skin lesions (which obviously makes it more difficult to clear her), which appeared to initially clear with topical mupirocin to her nares. However, within weeks she developed recurrent infection with multiple positive cultures of nares, throat, perineum, and skin lesions. She received aggressive treatment with topical applications of triamcinolone and tetracycline to treat the skin lesions, plus a combination of orally administered doxycycline and rifampin. Again, she appeared to have cleared with multiple negative cultures. But within weeks, she was again culture-positive.

Further investigation showed that her husband and grandmother (who cared for their child) were culture-negative, but nares specimens from her 1-year-old child (who also had psoriasis) and her pet dog were both positive. All 3 isolates were similar by PFGE. Clearance of the whole family was successfully accomplished, once the dog received a course of doxycycline and rifampin (Van Duijkeren et al thought that topical muperocin to the dog's nostrils was too impractical).

Shared MRSA between humans and their pet dogs has been previously reported—even a horse was suspected of being involved in an outbreak of MRSA infection in a veterinary hospital. This is the first report of successful clearance of MRSA from an entire family once their pet dog was also effectively treated. ■

Could Sepsis Respond to Nicotine?

Mattay MA, et al. *Nat Med*. 2004;10:1161-1162; Wang H, et al. *Nat Med*. 2004;10:1216-1221.

THIS FASCINATING ARTICLE suggests that nicotinic acetylcholinergic receptors play an important part in the immune system response to sepsis—raising the intriguing notion that nicotine could reduce mortality in sepsis by down-modulating the inflammatory response. It turns out that one of the predominant negative-inhibitory pathways of the inflammatory system are nicotinic acetylcholine receptors (7nAChR) located on tissue macrophages, which modulate the efferent vagus nerve (this is termed the cholinergic anti-inflammatory pathway). Down modulation of this pathway leads to decreased NF-χB activation, decreased production of inflammatory cytokines and tumor necrosis factor, and ultimately, prevents shock. This important immunomodulatory effect was nicely demonstrated by Wang and colleagues, who administered nicotine to mice lethally challenged with intraperitoneal bacteria. Mortality in the mice was reduced from 84% to 51%, even when the nicotine was administered after the mice became ill. Treated mice had evidence of decreased activation ex vivo of a transcriptional factor for NF-χB production and reduced levels of high mobility group box 1 protein (HMGB-1) in serum. HMGB-1 is an important molecule in the cascading inflammatory response and activation of plasminogen activator inhibitor-1. These scientists theorize that either nicotine or other inhibitor of the nicotine 7nAChR receptor may reduce mortality from sepsis. ■

PHARMACOLOGY WATCH

Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

GEMINI Trial

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

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. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ahcpub.com.

.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.