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INSIDE

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New Once-a-Day Pill Submitted to FDA

By Melinda G. Young

Melinda G. Young reports no financial relationship relevant to this field of study. This article originally appeared in the August 2006 issue of AIDS Alert.

HIV ANTIRETROVIRAL THERAPY TREATMENT SOON WILL BECOME A WHOLE lot simpler than most antibiotic regimens when the FDA approves the combination pill of efavirenz/emtricitabine/ tenofovir (Truvada/Sustiva).

The combination drug which will be taken in one pill, once daily, was submitted to the FDA in a new drug application by Gilead Sciences of Foster City, CA, and Bristol-Myers Squibb of Princeton, NJ.

"It's the first complete regimen in a single tablet, once a day," says Calvin Cohen, MD, MSc, research director of CRI New England in Boston. Cohen also is the research director for Harvard Vanguard Medical Associates in Boston and is a clinical instructor at the Harvard Medical School in Boston.

Previous combination regimens have combined 3 drugs in a twice-a-day pill or 2 medications in a single tablet, Cohen notes. The new combination puts 2 nucleoside reverse transcriptase inhibitors with one non-nucleoside reverse transcriptase inhibitor.

The combined 3-drug pill has been studied in a large, clinical, randomized study of treatment-naïve patients, Cohen says.

"We have existing data about the benefits and side effects profile of this 3-drug regimen," Cohen says. "That the tablet can be created that puts all of these together and has similar absorption allows us to say it has the characteristics of the regimen when it is given in 3 separate tablets." The 3 tablets have the same absorption as the single tablet, he adds.

So while the new combined single tablet has not been studied as its own entity, once investigators could show that it has the same absorption, the data available about the 3 separate pills given in combination is relevant, Cohen explains.

Efavirenz's safety profile shows that it generally is tolerated by 95% of the people who take the drug, Cohen says. "The 4% to 5% who have to come off Sustiva do so because of side effects, which include disequilibrium because of dizziness or altered dreaming," Cohen says.

"In 95% of the people, it's either well-tolerated from the beginning or they'll have side effects and then it wanes; in some people it does not resolve," Cohen explains. "Somewhere between 25% to 50% will notice something, but in the majority of people it resolves in the first week."

Among others it will resolve after a few weeks but, after continued dosing, about 5% of the people taking efavirenz find it's not for them, Cohen adds.

"Tenofovir and FTC have, in some ways, even more attractive or just as attractive safety profiles. In over 95% of the people who take those 2 drugs, they find

they can tolerate them," Cohen says.

"So the regimen of the 3 drugs roughly is tolerated in more than 90% of the people who start it," Cohen adds.

The 3-drug regimen hasn't been studied fully in a randomized trial versus a protease inhibitor (PI) therapy, Cohen says.

"Those studies are underway now," he says. "What we would be able to conclude is based on other studies done in the past; efavirenz has gone up head-to-head against several PIs and has either come up with superior results or equal efficacy."

But it has never lost in a head-to-head comparison yet, Cohen says. "In fact, it's one of the major reasons why efavirenz is a popular drug in the United States—it's either tied or won, but never lost," Cohen adds.

Adherence studies would suggest that the new once-a-day pill will be more acceptable to patients than regimens requiring 2 or more pills daily, Cohen says.

When patients are asked if a once-a-day pill regimen fits into their schedule, virtually all of them say it does, while only 80% of people asked about a twice-a-day pill will say that it fits into their schedule, Cohen says.

"In every single measure, once-a-day pill had superior adherence with two years of monitoring," Cohen says.

Resistance also is not a major problem for this combination regimen, Cohen says.

"In the long-term studies of regimens very similar to this one, when drugs were given as separate components, only 4% of people developed resistance after a year to any of the drugs," Cohen says. "Part of what we hope is and, in some ways, expect is as we improve the simplicity of going from three pills to one pill a day that people will find the regimen more attractive and less burdensome, and the resistance levels will decrease."

Already, the combination therapy has a 95% success rate without resistance at one year, and the expectation is that as the simpler combination is used, the resistance will remain at a low level past year one, Cohen explains.

"Resistance is a product of erratic drug taking," he says.

Truvada/Sustiva has gained a lot of interest among clinicians both because of its simplicity and its efficacy, Cohen says.

"This doesn't mean it's perfect, but among our choices it is one of the best combinations," Cohen says. "Clinicians are enthusiastic to prescribe a regimen that is more attractive to people with HIV and which also is less burdensome and intrusive."

Treatment-naïve patients also find this one-pill-a-day combination appealing, he notes.

"I already have patients coming in the door asking for the once-a-day pill and whether they can have it yet," Cohen says.

To create the once-a-day combination required Bristol-Myers Squibb and Gilead to form one of the first collaborations of its type in HIV therapy. They formed a joint venture on Dec. 20, 2004, to develop and commercialize the single tablet regimen in the United States.

The proposed new combination pill will contain 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate. ■

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Raw Food Pet Treats: Good for Them, Bad for You?

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationship relevant to this field of study.

This article originally appeared in the August 2006 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Price is Assistant Professor, University of Colorado School of Medicine. Dr. Deresinski serves on the speaker's bureau for Merck, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Dr. Price reports no financial relationship relevant to this field of study.*

ProMED-mailpost, June 29, 2006; www.promedmail.org

EARLIER OUTBREAKS OF HUMAN SALMONELLOSIS related to feeding your pet pig ears or a nice undercooked hamburger patty off the grill have been discussed in this column. This account is the third published report of human salmonellosis associated with pet treats in North America. Investigations have confirmed that raw beef and salmon-containing pet treats were responsible for 9 cases of human salmonellosis in Western Canada and Washington state in 2004-2005. Six of the 9 patients from British Columbia, Washington State, and Alberta, Canada, recalled feeding pet treats to their dogs prior to onset of illness, and another 2 owned dogs. This is likely just the tip of what really occurred, since studies suggest that for every clinically identified case of salmonella infection, 38 unrecognized cases occur in the community.

Stool cultures yielded *S. thompson*, which was indistinguishable by pulse field gel electrophoresis from strains found in dog and salmon pet treats. Samples of salmon and beef pet treats manufactured at the Washington plant, and those collected at the BC plant by Canadian authorities, yielded a variety of organisms, predominately *S. thompson*. Up to 80,000 colony-forming units of salmonella per gram of salmon treats were discovered. Other Salmonella serotypes, including Montevideo, Newport, Give, Meleagridis, Cerros, Muenster, Agona, and Anatum were also found in treats from both the British Columbia and Washington plants. The treats are made from dehydrated, then rehydrated, raw beef and salmon. No irradiation or heat treatment intended to destroy bacteria was employed. No warning labels on the packages advised pet owners to wash their hands after handling. This article serves as a reminder that hand washing is important when handling any kind of raw foods or meats, even if it comes nicely packaged. ■

The Pressure of Air Travel: Headaches on the Plane

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

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Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

This article originally appeared in the July 2006 issue of Neurology Alert. *It was edited by Matthew E. Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Vice Chairman, Professor of Clinical Neurology, Weill Medical College; Chief of Division of Stroke and Critical Care Neurology, NewYork-Presbyterian Hospital, and Dr. Beal is Professor and Chairman, Department of Neurology, Cornell University Medical College. Dr. Drs. Fink and Beal report no financial relationships relevant to this field of study.*

Synopsis: *Barotrauma to the paranasal sinuses may cause sudden and severe headache during airplane travel.*

Source: Berilgen MS, Mungen B. Headache Associated with Airplane Travel: Report of Six Cases. *Cephalalgia.* 2006:26:707-711.

THIS SUMMER, MOST HEADACHES CAUSED BY AIRPLANE travel will be due to long security lines and delayed take-offs. But once the plane is in the air, more than just cramped seats and lack of food may cause headaches. Berilgen and colleagues describe 6 men in their 30s and 40s who suffer from intermittent but recurrent, severe, short lasting, unilateral, periocular headaches thought to be related to sinus barotrauma, caused by changes in cabin pressure. The most severe pain lasted from 15-20 minutes. Five of the men described the headaches as occurring during landing, especially at seaside airports. Only one man had an occasional headache of the same description while a plane was gaining altitude. Most of the men did not have any accompanying symptoms, and only half had any other headache type. None suffered from cluster-like headaches. Three of the men had a long smoking history. No abnormalities were found on a thorough evaluation of the men, including brain and sinus imaging, performed soon after a headache.

■ COMMENTARY

Subclinical congestion and inflammation in the ethmoid sinus and middle turbinate mucosa, with a vacuum effect triggering ethmoid nerve branches of the trigeminal nerve and nociceptors on the anterior ethmoid artery, is a possible explanation for the attacks. The name barotrauma-related headache was suggested to identify the mechanism of these brief but severe, travel-related headaches. Prevention of these headaches may be possible with the use of a potent nasal and sinus decongestant (oxymetazoline) prior to boarding the airplane and just before the approach to landing. ■

Hemophilia Carriers and Bleeding Risk in Anemic Older Adults

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

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Dr. Artz reports no financial relationship to this field of study.

This article originally appeared in the August 2006 issue of Clinical Oncology Alert. *It was edited by William Ershler, MD, and peer reviewed by V.R. Veerapalli, MD. Dr. Ershler work for INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC, and Dr. Veerapalli Staff Clinician, INOVA Fairfax Cancer Center Falls Church, VA. Dr. Ershler serves on the speaker's bureau for Wyeth and does research for Ortho Biotech, and Dr. Veerapalli reports no financial relationship relevant to this field of study.*

Synopsis: *Future research is needed to confirm the bleeding risk, identify factor levels predisposing to bleeding, and determine optimal prophylaxis/intervention strategies.*

Source: Plug I, et al. Bleeding in Carriers of Hemophilia. *Blood*. 2006:108:52-56.

HEMOPHILIAS REFER TO BLEEDING DISORDERS FROM deficiencies of factor VIII (hemophilia A) or factor IX (hemophilia B). Common bleeding sites include joints, muscles, and the GI tract, although clinical severity varies depending in large part to factor levels. As an X-linked recessive disorder, men are mostly affected and women are heterozygous carriers. The factor levels in female carriers average about 50% of normal although wide variation occurs attributable to random X-chromosome inactivation and potentially other factors as well. In general, carriers have not been considered at increased bleeding risk unless levels were below 40%. Minimal data have actually examined the association of carriers and factor levels with bleeding risk and severity.

In this observational study, all women who were tested for being carriers of hemophilia A or B in the Netherlands were contacted. Factor levels were documented from medical charts. Among the 766 questionnaires on bleeding history, 546 were returned (80%). The final analysis entailed 274 carriers and 245 non-carriers. The mean age was similar at 39 and 40 years, respectively, although more carriers had factor levels ascertained. The median factor levels were 0.60 IU/mL for carriers and 1.02 IU/mL for non-carriers. Carriers showed an increased risk of small wound (RR = 2.2) and joint bleeds (RR = 1.9), but no increased risk of epistaxis, bruising, or gum bleeding. Bleeding for greater than 3 hours after a medical intervention was increased in carriers, as was the need to receive a medical intervention (intervention not specified). A trend existed for increased bleeding risk for clotting factor levels between 0.60 to 0.41 IU/mL and more severe bleeding for levels 0.40 IU/mL and below.

COMMENTARY

Plug and colleagues conclude that female hemophilia carriers have an increased risk of bleeding, and that levels below 0.60 IU/mL serve as a marker for increased risk. The data are provocative and challenge traditional assumptions that bleeding risk may only be increased at levels of < 40% (40 IU/mL). Limited data have explored at what factor level, particularly for hemophilia carriers, does the risk of bleeding increase.

Important bias may exist in observational studies. Because carriers and non-carriers were ascertained from living in a household with a known case, the impact of environment should have been similar. Plug et al believe that awareness of carrier status does not necessarily impact report of bleeding tendency,[1] but one can not exclude this. The important finding that carriers have an increased risk of bleeding after trauma and medical interventions related to factor levels, may be biased from health care providers knowledge of carrier status and/or factor levels. Physicians may be more likely to monitor and/or treat bleeding symptoms in a known carrier, particularly if factor levels were low. Another limitation is that factor levels analyzed were the lowest level available in the chart. If factors levels were lower at the time of bleeding, the risk of bleeding from low factors levels would be underestimated.

Plug et al's work does challenge traditional assumptions, and raises awareness of the potential for bleeding in carriers of hemophilia, even at factor levels below between 40 and 60% of normal. The data have enough limitations to definitive recommendations. Prospective data on bleeding risk and severity related to factor levels are needed. Many questions remain unanswered and require more research. Should we routinely check levels in known or suspected carriers before surgery? Should prophylaxis for high-risk surgery be considered when levels are < 0.60 IU/mL? If so, what therapy should be used? ■

Reference

1. Mauser Bunschoten EP, et al. Bleeding Symptoms in Carriers of Hemophilia A and B. *Thromb Haemost*. 1988;59:349-352.

CME Objectives

The objectives of *Travel Medicine Advisor* are:

• 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 of 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.

Raloxifene's Role for Estrogen- and Age-Related Problems

What is the role of raloxifene for the treatment of osteoporosis and breast cancer prevention? Raloxifene is a selective estrogen-receptor modulator similar to tamoxifen. There has been considerable interest in the drug in the role of treatment for osteoporosis and, perhaps, breast cancer prevention, especially in light of the Women's Health Initiative findings on conjugated estrogen/progesterone. A new study does little to clarify the issue, however, suggesting, like previous studies, that raloxifene has benefits, but also significant risks associated with its use.

As part of the Raloxifene Use for The Heart (RUTH) trial, more than 10,000 postmenopausal women with CHD or multiple risk factors for CHD were randomized to raloxifene 60 mg daily or placebo and followed for a median of 5.6 years. The 2 primary outcomes were coronary events and the rate of breast cancer. Raloxifene had no effect on the risk of primary coronary events (533 vs 553 events; HR, 0.95; 95% CI, 0.84 -1.07) but was associated with a reduced risk of invasive breast cancer (40 vs 70 events; HR, 0.56; 95% CI, 0.38-0.83). However, the all-cause death rate was the same in both groups, and raloxifene use was associated with an increased rate of fatal stroke (59 vs 39 events; HR, 1.49; 95% CI, 1.00-2.24) and venous thromboembolism (103 vs 71 events; HR 1.44: 95% CI, 1.06-1.95). The drug was associated with a reduced risk of clinical vertebral fractures (64 vs. 97 events: HR, 0.65; 95% CI, 0.47-0.89) (*N Engl J Med*. 2006;355:125-137). In an accompanying editorial, Marcia L. Stefanik, PhD, from the Stanford University Medical School reviews risk benefit profiles of raloxifene for women.

Reviewing data from the RUTH trial, as well as other studies, the author suggests that a key issue in contemplating raloxifene use is balancing the benefits of reduction in the risk of breast cancer and vertebral fractures with the increase risk of venous thromboembolism and fatal stroke. She suggests that raloxifene should be contemplated in women with an increased risk of breast cancer, but asks" What level of breast cancer risk would justify the use of raloxifene for prevention of breast cancer for a given person . . ." and suggest that the answer to that question is currently unknown. She also states that, "For now, there's no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns." (*N Engl J Med*. 2006;355:190-192).

The Truth About Multivitamins

More than half of the adult population in the United States takes multivitamins on a regular basis, yet little is known about the benefits or lack of benefits of vitamins. The National Institutes of Health has published a "State-of-the-Science Conference Statement" on multivitamin/mineral

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supplements and chronic disease prevention as an early release article on the *Annals of Internal Medicine* web site on August 1. The statement deals with the current patterns of vitamin use, nutrient intake of vitamin users and nonusers, the efficacy of single vitamins and minerals, the efficacy of multivitamins, the safety of multivitamins, and where future research is needed. Regarding single vitamins and minerals, the results have been disappointing.

Beta-carotene was found to cause an increase in lung cancer incidence and deaths in smokers and male asbestos workers and no benefit in preventing other types of cancers. Other cancer preventative studies have shown no benefit from beta-carotene and, some have even suggested, increase rate of stroke and CVD in women smokers. Vitamin A has not been the subject of individual trials but, when paired with beta-carotene or zinc, there is no impact on the incidence of cancer.

Four trials have looked at vitamin E, and the results have been mixed. The largest was the Women's Health Study, which suggested a decrease rate of cardiovascular deaths with vitamin E but no decrease in the incidence of CVD events. Vitamin B_6 was looked at, and 2 small studies showed no benefit regarding cognitive decline in elderly men and women. Folic acid with or without vitamin B_{12} has been shown to decrease the rate of neural tube defects in women of childbearing age, but was not shown to prevent cognitive decline in older adults. Selenium was found to decrease the rate of liver cancer in Chinese patients who were at risk, and there may be some benefit in reducing the rate of lung, prostate, and colorectal cancer. Calcium has been shown to increase bone mineral density in post menopausal women, and calcium coupled with vitamin D has been shown to decrease the risk for hip and non-vertebral fractures. Calcium and vitamin D may increase risk of kidney stones, and has not been shown to reduce the risk of colorectal cancer.

The use of multivitamins and mineral supplementation (MVM) has been studied in 5 randomized, controlled trials. Although the study methodology was quite variable, there is a suggestion that MVM may decrease risk of cancer. No studies have shown any benefit as far as cardiovascular disease, and the benefit for cataract prevention is mixed. Progression of macular degeneration may be slowed by certain multivitamins, and may represent the single most important benefit from multivitamins. The conference statement also stated that the FDA should be given more oversight over the vitamin industry, and that more rigorous randomized controlled studies should be done of individual vitamins, minerals, and MVM, including safety of these products, as well as the interactions with nutrients and medications (www.annals.org 1 August 2006, to be published in print 5 September 2006).

Statins and Hepatitis C

Statins may be effective therapy for hepatitis C infections, and may even be used in combination with interferon to inhibit replication of the hepatitis C virus, according to new study. Japanese researchers recently evaluated the effect of various statins with or without interferon on hepatitis C replication. The synthetic statin fluvastatin was the strongest inhibitor of HCV replication, while atorvastatin and simvastatin were less effective. Lovastatin's effect was relatively weak, while pravastatin displayed no anti-HCV activity. The authors suggest that statins, especially fluvastatin, could be "potentially useful as new anti-HCV reagents" in combination with interferon (*Hepatology*. 2006;44:117-125).

Preventing Hot Flashes

Gabapentin may be as effective as estrogen in preventing hot flashes in postmenopausal women, based upon a recent study. In a randomized, double-blind, placebo-controlled trial on 60 postmenopausal women randomized to conjugated estrogen 0.625 mg daily, gabapentin titrated to 2400 mg daily, or placebo for 12 weeks. The primary outcome, the hot flash composite score, was no different between estrogen or gabapentin (72% improvement vs 71%), with placebo reducing symptoms by 54%. No differences were seen in severity of hot flashes or depression symptoms, although side effects were slightly higher in the gabapentin group (*Obstet Gynecol*. 2006;108:41-48). The authors acknowledge that this is a small study with a significant placebo effect. However, in light of the Women's Health Initiative findings, non-estrogen alternatives for heart flashes are welcome.

FDA News

The FDA is opening the door to allow Duramed's Plan B emergency contraceptive to be available over-the-counter to women 18 and older. Previously the FDA had tabled the OTC application indefinitely, but new FDA leadership is more receptive. The drug is currently available only by prescription. ■