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Once Again, CDC Predicts Flu Vaccine Delays

By William T. Elliott, MD, FACP

The centers for disease control are warning that this fall's flu vaccine may be delayed again. The delay is not expected to be as severe as last year's vaccine shortage and stems from different problems. Last year, compliance and manufacturing problems resulted in a severe shortage of vaccine. This year, the delay will be caused by less manufacturing capacity as the number of manufacturers has dropped from 4 to 3. Still, the CDC predicts that 64% of the vaccine will be available by the end of October, more than twice the amount available in October last year, with the remaining doses available by November or December.

Antibiotics

Aventis' **telithromycin** (Ketek), the first of a new class of antibiotics, has received an "approvable" letter from the FDA. The drug, which can be taken orally once a day, will be indicated for upper and lower respiratory tract infections including community acquired pneumonia. Telithromycin is the first of a class of antibiotics known as **ketolides**. An approvable status outlines conditions that must be met before the FDA will approve a drug.

Estrogen Replacement Therapy (ERT)

Healthy postmenopausal women have better **blood pressure regulation** while on ERT, suggesting that estrogen plays a role in the ability of the nervous system to control **blood pressure**. In a recent study appearing in *Circulation*, none of the women had hypertension at baseline. In a separate study in the same journal, researchers found that **transdermal estrogen** was better at regulating blood pressure than **oral estrogen**. It is postulated that since transdermal estrogen bypasses enterohepatic circulation, more of the hormone is available systemically (*Circulation.* 2001;103:2903-2908; *Circulation.* 2001;103:2909-2914).

ERT may reduce the risk of **cataracts** according to the Framingham Eye Study. Women who took ERT the longest were the least at risk for developing cataracts. Odds ratios were: never users = 1.0; 1-2 years = 0.8; 3-9 years = 0.7; 10 or more years = 0.4 (*Arch Intern Med*. 2001;161:1448-1454).

Hypothyroid women on **thyroxine** may need to have their dose increased when they are started on ERT. Estrogen leads to an increase in thyroxine-binding globulin and a decrease in serum-free thyroxine. They suggest checking thyroid functions 12

weeks after initiating ERT and adjusting thyroxine doses appropriately (*N Engl J Med*. 2001;344:1743-1785).

Insulin

The search for a **noninjectable insulin** product looks promising. Pfizer and Aventis Pharmaceuticals are partnering on the development of an **inhaled insulin** product. Phase III data presented at the American Diabetes Association's meeting suggests that a single bedtime injection of ultralente with daytime inhaled insulin is at least as effective as **subcutaneous insulin** injections. The drug was evaluated in both type 1 and 2 diabetics. Inhaled insulin-induced insulin antibodies developed higher levels of insulin antibodies, but the clinical significance of this finding is unclear.

Progress on an **oral insulin** product was also presented at the ADA meeting. The insulin molecule is susceptible to degradation in the gut, but by attaching various polymeric oligomers, the molecule can be absorbed. Oral insulin is currently in phase III trials.

Statin Therapy

High **C-reactive protein** (CRP) levels are a predictor of future coronary events and **stroke**. Studies have suggested that statins reduce CRP levels. A new study shows that this effect translates into lower rates of heart disease, even in patients with high CRP levels and low lipids. More than 5700 patients were randomized to treatment with **lovastatin** or placebo. In patients with low lipids, lovastatin reduced CRP levels by 14.8%, and those patients also had a lower incidence of coronary events. An accompanying editorial suggests that measuring CRP levels along with lipid levels may become routine in healthy adults (*N Engl J Med*. 2001;344:1959-1965; *N Engl J Med*. 2001;344:2016-2018).

Lyme Disease

A single 200-mg dose of **doxycycline** given within 72 hours of a tick bite is highly effective at preventing Lyme disease. Researchers from New York randomized 482 patients who had been bitten by *Ixodes scapularis* to doxycycline or placebo. Of those tested, 3.2% of placebo patients developed **erythema migraines** compared to only 0.4% of doxycycline-treated patients. One-third of doxycycline patients noted side effects, primarily nausea and vomiting. The study is to be published in the July 12 edition of *New England Journal of Medicine*, but the findings were released early on the journal's web site because of the importance of the findings.

FDA News

The FDA status of **levothyroxine** (Synthroid) is in limbo despite a 40-year safety record. Prior to 1962, drugs were not required to file a New Drug Application (NDA). Synthroid was released in 1958, and therefore never submitted a NDA. The FDA recently notified Abbott Labs that the company needed to file documentation showing the safety and efficacy of Synthroid. Abbott requested a waiver, but the FDA denied their request. In the meantime, 2 advocacy groups, the National Organization of Women and the Grey Panthers are demanding that the drug be withdrawn from the market because it hasn't demonstrated safety and efficacy. The American Association of Clinical Endocrinologists has countered in rather strongly worded fashion suggesting that removing the drug would be "extremely misguided and unwarranted." ■

Diclofenac Gel for the Treatment of Actinic Keratosis

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

Diclofenac gel for the treatment of actinic keratosis (AK) is reaching the market several months after it received FDA approval. The gel combines the anti-inflamatory diclofenac with hyaluronate sodium for the topical treatment of these common skin lesions. SkyePharma has licensed the marketing rights for the United States, Canada, and Mexico to Bioglan Pharma. Diclofenac gel will be marketed under the trade name Solaraze.

Indications

Diclofenac gel is indicated for the topical treatment of AK.

Dosage

Diclofenac gel is applied to lesion areas twice daily. The amount should be enough to cover each lesion adequately. The recommended duration of therapy is from 60 to 90 days. One-half gram of gel will cover about 25 cm^2 of lesion. Diclofenac gel is supplied in tubes of 25 g and 50 g at a strength of 30 mg/g (3% w/w). Patients should avoid exposure to sunlight or sunlamps.

Potential Advantages

Diclofenac gel provides an alternative to other topical treatments such as masoprocol and 5-fluorouracil and

may be better tolerated in terms of local adverse events.

Potential Disadvantages

Common side effects compared to vehicle are contact dermatitis (19% vs 4%), rash (35% vs 20%), and dry skin (27% vs 12%). About 18% of patients discontinue treatment due to side effects compared to 4% for the vehicle.[1] Optimal therapeutic effect may not be evident for up to 30 days. Due to some systemic absorption, albeit low, diclofenac gel should be used with caution in patients with active gastrointestinal ulcers, or bleeding, or severe renal or hepatic impairment. Also, concomitant administration of NSAIDs should be minimized.[1]

Comments

Diclofenac is a cyclooxygenase inhibitor used widely in the oral from for the treatment of pain and inflammation. It is also used as a topical ophthalmic drop for post cataract surgery and prior to corneal refractive surgery. In the topical formulation, diclofenac is formulated with hyaluronate sodium. Hyaluronate has been reported to enhance drug delivery to pathogical sites.[2] The mechanism of action of diclofenac in AK is not known, but it has been proposed that the inhibition of antiangiogensis may be a mechanism of action.[2] In clinical trials reported by the manufacturer, diclofenac gel had a success rate of 18-47% compared to 10-20% for the vehicle.[1] Success was defined as complete clearance of AK lesions 30 days after a treatment regimen. Statistical differences were demonstrated for lesions on the forehead and face but not on the scalp, arm/forearm, and the back of the hand, although numerical advantage was reported for these body locations.

Diclofenac may be better tolerated but currently there are no comparative studies with 5-fluorouracil or masoprocol. Cost is currently not available.

Clinical Implications

AK is a common premalignant inflammatory skin lesion involving areas of the body exposed to the sun. The prevalence of the disease is believed to be about 25% in the Western Hemisphere and more prevalent in individuals with fair complexion and older than the age of 50 years.[3,4] Left untreated, AK may progress to squamous cell carcinoma. Treatment ranges from topical application of 5-fluorouracil or masoprocol to excisional surgery, Mohs surgery, cyrosurgery, or radiotherapy, but each has its limitations. Diclofenac gel offers another, perhaps better-tolerated option for treatment of these common skin lesions. ■

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Imatinib (Gleevec) for CML Treatment

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

Imatinib (gleevec) was recently approved for the treatment of chronic myeloid leukemia (CML). The drug is considered a major breakthrough in oncologic therapy and its approval was heralded with much fanfare, which included a cover story in Time magazine. The drug is revolutionary because it targets the molecular understructure of cancer cells, leaving healthy cells alone. Because of this and intense public pressure, the drug was approved by the FDA less than 3 months following application.

Indications

Imatinib is indicated for the treatment of patients with CML in blast crisis, accelerated phase, or in chronic phase after failure with interferon therapy.[1]

Dosage

The recommended dose of imatinib is 400 mg daily for patients in chronic phase CML and 600 mg daily for patients with accelerated phase or blast crisis. The dose may be increased if there is disease progression, inadequate hematologic response after 3 months of therapy, or the loss of a previously achieved response. For patients with chronic phase CML, the dose may be increased from 400 mg daily to 600 mg daily if tolerated (ie, absence of severe adverse hematologic or nonhematologic reactions). For patients with accelerated phase or blast crisis the dose may be increased from 600 mg to 800 mg (400 mg twice daily).[1] The drug should be taken with a meal and with a large glass of water to reduce gastrointestinal irritation. The drug should be continued as long as it remains effective.

The dose should be adjusted or withheld if severe nonhematologic adverse reactions (hepatotoxicity or fluid retention) or severe hematologic adverse reactions (neutropenia or thrombocytopenia) occur. Complete blood counts should be performed weekly for the first month and biweekly for the second month of therapy, and every

2-3 months thereafter.[1]

Imatinib is supplied as 100 mg capsules.

Potential Advantages

Imatinib appears to have significant advantages over current therapies for CML such as interferon alpha. Imatinib appears to have a better and more rapid response, fewer adverse effects, and can be given orally.[2,4] It also appears to be effective in patients who have failed interferon therapy.[3]

Potential Disadvantages

The most frequent side effects are nausea (55-68%), vomiting (28-54%), fluid retention (52-58%), diarrhea (33-49%), and muscle cramps (25-46%). Severe fluid retention (eg, pleural effusion, pericardial effusion, pulmonary edema, ascites) has been reported in 1-2% of patients and increases with higher imatinib dose and age older than 65 years. Severe superficial edema has been reported in 1-3% of patients. Cytopenias are more frequent with patients with accelerated CML or blast crisis than with chronic phase CML. The frequencies of cytopenias range from 16-30% for grade 3 and 8-46% for grade 4. The frequency of anemia was 4-40% and less than 1-10%, respectively. Severe elevation of transaminases or bilirubin can also occur and the patients should be monitored at baseline and monthly or as clinically indicated.[1] Due to the expedited FDA approval and limited follow-up time, toxicities as a result of long-term use are not known.[1]

Imatinib is metabolized primarily by cytochrome P450 3A4, and as such, pharmacokinetics of the drug can be affected by substances which inhibit, induce, or are substrates of this isoenzyme. Imatinib is also a inhibitor of CYP3A4 and CYP2D6.[1]

Comments

Imatinib is an inhibitor of BCR-ABL tyrosine kinase. This deregulated kinase is produced by the BCR-ABL fusion gene and appears to have a pathogenic role in CML. BCR-ABL oncoprotein, found on the Philadelphia chromosomes, is a result of the reciprocal translocation of 2 normal genes, BCR and ABL. Tyrosine kinase activity is apparently required for the oncogenic activity.[5] Imatinib has produced significant responses in patients with CML. A total of 1027 patients were studied in the clinical trials: 532 with chronic phase CML and prior interferon treatment, 235 with accelerated phase disease, and 260 with myeloid blast crisis.[1] Response was most impressive in chronic phase interferon patients with 88% showing a hematologic response, 88% complete response, and 49% showing a major cytogenetic response and 30% showing a complete response. Responses in accelerated phase and myeloid blast crisis were 63%, 28%, 21%, and 14% and 26%, 4%, 13.5%, and 5%, respectively.[1] The median time to hematologic response was 1 month. Hematologic response was defined as a 50% reduction in white cell count from baseline maintained for 2 weeks. Complete response was defined as a reduction in white-cell count to less than 10,000 mm^3 and platelet counts to less than 450,000 mm^3 maintained for at least 4 weeks.[3] Cytogenetic response was defined as 35% or less of cells in the metaphase that were positive for the Philadelphia chromosome in the bone marrow.[3] Complete response is 0%. Increased survival or improved disease-related symptoms have not been demonstrated in a controlled trial.

The drug is extremely expensive. Monthly cost is about $2400 and annual cost is about $30,000. Novartis will provide the drug free to uninsured patients with an annual income of under $43,000 and a sliding scale for those from households with an annual income of $43,000-$100,000.[6]

Clinical Implications

CML is a clonal disorder characterized by leukocytosis and the presence of immature white blood cells in the peripheral blood and hypercellular marrow with myeloid hyperplasia in the bone marrow. It is estimated that there are about 25,000 people in the United States with the disease. CML generally progresses through a chronic phase, accelerated phase, and blast crisis (acute leukemia), with median survival about 6 years. Current therapies—all with limitations—include allogeneic bone marrow transplantation, chemotherapy (eg, hydroxyurea), and interferon-alfa with or without cytarabine. Imatinib provides a breakthrough treatment for CML compared to interferon. Although the drug is directed at the abnormal "target" in CML, it is not a cure, is not completely effective, and does have side effects. Also, the long-term effects are not known due to inadequate follow-up of study patients. Whether imatinib is only specific to CML or can be effective in other types of cancers (eg, gastrointestinal stromal tumor) is yet to be determined. ■

References

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Cognitive Function in Postmenopausal Women Treated with Raloxifene

Source: *Yaffe K, et al. N Engl J Med. 2001;344:1207-1213.*

Cognitive function was studied in 7705 postmenopausal women with osteoporosis who were enrolled in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. The primary outcomes were bone mineral density and vertebral fractures. Postmenopausal women who met criteria for osteoporosis (14,674 were excluded) were enrolled via 180 sites in 25 countries and randomized to receive either raloxifene 60 mg or 120 mg or placebo for 3 years. There were roughly 2500 women in each arm. Cognitive testing was done using the Short Blessed Test for orientation, concentration, and memory; the Trails Making Test for visuospatial scanning, sequential processing, motor speed, executive function, and attention; and the Word List Memory and Recall tests for memory if the subject spoke English, French, or Spanish (4424 women).

The mean age of the women at enrollment was 66 years old. There were no significant differences among the 3 treatment groups on any of the cognitive tests at baseline or after 3 years. More women in the raloxifene groups than in the placebo group reported new or worsened hot flashes, but there was no correlation between presence or absence of hot flashes and cognitive performance.

Comment by Sarah L. Berga, MD

The main conclusion of this study is that short-term raloxifene exposure does not cause cognitive decline in relatively young postmenopausal women with osteoporosis. This study does not tell us whether long-term raloxifene use would increase, decrease, or not alter the risk of dementia. Less than 5% of the enrollees developed dementia while participating in the trial. The low incidence likely reflects the relatively young age of the women. This study also does not tell us about mood, sleep, libido, and other central nervous system outputs that comprise quality of life. We learn nothing about how raloxifene use might compare to estrogen use. While the study might, at first blush, be interpreted as providing reassurance about the null cognitive effects of raloxifene use, I would caution against such optimism. Further, to determine the effect of any intervention on risk of dementia, one would have to start women on the agent in question before age 70 and follow them at least 10 years. The best study design would be to randomize women to an estrogen, a selective estrogen receptor modulator (SERM), and a placebo within 1-2 years of menopause and then to compare the effects of "never" use to "always" use 30-40 years later. This is not a study likely to be done, so we will have to try to discern risks and benefits based on other investigative strategies. There are those who argue that a hiatus in exposure to an estrogen for several years sets in motion a neurodegenerative process that late in life exposure to estrogen cannot undo. Expecting to undo dementia once it is clinically apparent seems analogous to expecting late in life exposure to "undo" established kyphosis from osteoporosis. Because of the inherent plasticity of the brain, by the time dementia is evident, more than 30% of the neurons are dead. It seems ridiculous to expect estrogen or SERM use to resurrect dead neurons as much as it seems unrealistic to expect estrogen to restore vertebral bodies to their original shape once compressed. Like many age-related infirmities, the best treatment for dementia is prevention.

Is there reason to suspect that raloxifene may be less beneficial for CNS than estrogen? I believe that there is. To make a complicated story short, the brain bits that subserve memory and other cognitive functions have estrogen receptors. They express both ERα and ERβ, but it appears that ERα occupation is critical to maintaining key neurotransmitter systems and for protecting the brain from both oxidative and anoxic injury. Thus, while raloxifene may have some estrogenic action in the brain, it is unlikely to match the panoply of physiological actions that the cognate ligand, estradiol, confers by fully occupying ER (α, β, and membrane).[1]

We are forced to make educated guesses based on the available information. My educated guess based on the extant animal and primate literature is that the most neuroprotection ligand will be an estrogen, not a SERM that is an ERα antagonist. Phytoestrogens apparently occupy ERβ and not ERα, so while they do not antagonize ERα-mediated activities, they also are unlikely to provide full neuroprotection based on what we understand today. Our job is to help our patients "pick their poison" based on their risk factors, underlying conditions, and personal preferences. It is a difficult task even when the patient is well and with few complaints. Stay tuned for an evolving story. ■

Dr. Berga is Professor and Director, Division of Reproductive Endocrinology and Infertility, University of Pittsburgh, Pittsburgh, Pa.

Reference

1. Neele SJM, et al. *J Clin Endocrinol Metab*. 2001;86: 1422-1424.

Herbal Medications—Not Harmless Anymore

Sources: *Piscitelli SC, et al. 8th Conference on Retroviruses and Opportunistic Infections (CROI), Chicago, Ill, Feb. 4-8, 2001. Abstract #743; Southwell H, et al. 8th CROI, Chicago, Ill, Feb 4-8, 2001. Abstract #497.*

In the first of these abstracts, 10 hiv-negative volunteers underwent pharmacokinetic studies to determine the potential interaction between garlic and saquinavir. In this study, the volunteers were given 1200 mg of saquinavir 3 times daily with meals for 3 days, and baseline levels were drawn on the morning of day 4. Garlic capsules of known allicin content were given twice daily with meals for days 5-25. Saquinavir was again added for days 22-24. At day 25, the AUC, Cmin, and Cmax levels of saquinavir were measured and determined to be approximately 50% of baseline levels. It was also noted that even after a 3-week washout, the 3-day saquinavir levels remained approximately 60-70% of baseline. Piscitelli and associates stated that garlic supplements may produce a prolonged induction of saquinavir metabolism.

In the second abstract, 324 patient interviews were conducted at the University of Cleveland from April to July 2000. The summary of these interviews showed that 267 (82%) confirmed using some type of alternative medication. In fact, more than 567 different forms of alternative therapies were catalogued during these interviews. Most patients (59%) stated they had informed their physician about their alternative therapy use, but it was found to be documented in the chart only 13% of the time. Patients were more likely to inform their physicians about their use of anabolic steroids or protein supplements than teas or alternative therapies.

Comment by Thomas G. Schleis, MS, RPh

In recent years, the sales of complementary and alternative medicines (CAMs) have skyrocketed. Once limited to health food stores, CAMs can now be found on the shelves of most pharmacies and grocery stores. The increase in sales of these products can be attributed to many different factors. The desire to achieve a healthier lifestyle, dissatisfaction with traditional medications and their side effects, and the desire for a potential cure when one does not exist in traditional medicine are just some of the reasons for this phenomenon. While some data support the clinical efficacy of some CAMs, much of their use is the result of anecdotal information.

For a number of years, the industry surrounding the sales and marketing of CAMs was under little regulation, in part because the products appeared to be safe. Unfortunately, while these preparations may individually be safe in many cases, a number of serious drug interactions have surfaced over the last 3-5 years as CAMs have become more commonly used. HIV medications and warfarin are pharmaceuticals that have exhibited potentially serious drug interactions with many of the herbal preparations (*see Table 1*). Unfortunately, patients with HIV or cancer are often individuals who are looking for alternative therapies to supplement their traditional therapy—especially when the long-term prognosis is not good.

In Piscitelli et al's abstract, the interaction between garlic and saquinavir was studied. Garlic capsules are commonly taken by the lay public to slow the process of

Table 1

Drug Interactions of Herbal Preparations with HIV Medications, Antifungals, and Warfarin

Drug	*Herbal Preparation*	*Interaction*	*Reference*
Garlic	Saquinavir*	Dec saquinivir levels	1. Piscitelli SC, et al.
	Warfarin and other drugs with antiplatelet activity	Inc effect of warfarin	Theorized
Ginkgo biloba	Warfarin and other drugs with antiplatelet activity	Inc effect of warfarin	Theorized with warfarin, documented with aspirin (2)
Ginseng	Warfarin	Inc effect of warfarin	3. Janetzky K, Morreale AP.
Milk Thistle	Saquinavir*	Dec saquinavir levels	4. Study ongoing at this time.
St. John's wort	Indinavir*	Dec indinavir levels	5. Piscitelli SC, et al.
	Warfarin	Dec effect of warfarin	6. Yue QY, et al.
	Azole antifungals	Dec antifungal activity	Theorized

*Could potentially interact with all antiretroviral protease inhibitors such as amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir as well as non-nucleoside reverse transcriptase inhibitors such as delavirdine, efavirenz, and nevirapine.

Table 2
Alternative Medicine References

Reference	Source
http://www.naturaldatabase.com	Worldwide web
Journal of Alternative and Complementary Medicine	Mary Ann Liebert, Inc. 2 Madison Avenue Larchmont, NY 10538 914-834-3100 www.liebertpub.com
The Review of Natural Products	Facts and Comparisons 111 West Port Plaza Suite 300 St. Louis, MO 63146 800-223-0554
Clinical Pharmacology	Gold Standard Multimedia 320 West Kennedy Blvd. Suite 400 Tampa, FL 33606 (813) 258-4747 www.gsm.com

atherosclerosis and to control hypertension. Garlic administration has been shown to reduce blood sugar levels, cholesterol, triglycerides and LDL, increase HDL, reduce platelet adhesiveness, and increase fibrinolytic activity. It is also touted as a means to ward off coughs and colds although scientific confirmation of this is lacking. The interaction between garlic and saquinavir was significant in healthy individuals, although what the effect in HIV-infected patients would be cannot be directly extrapolated since HIV-infected patients exhibit AUC and Cmax levels about twice those in healthy, non-HIV-infected individuals. It would have also been interesting to have sampled some patients who did not receive garlic at all, to see if their baseline levels were identical to their levels when challenged several weeks later. It would also have been helpful to compare the amount of allicin in capsules vs. that contained in prepared foods to determine the relative risk of garlic obtained in the diet. Nonetheless, an interaction of the magnitude seen in this study is cause for alarm.

Complicating the effective monitoring of drug interactions between CAMs and pharmaceuticals is that many patients do not consider CAMs to be "drugs," or do not divulge the use of these preparations to their physician or health care professional for fear of ridicule. Even if patients do divulge this information, it is seldom documented in the patient's medical record, as evidenced in the second abstract. This may be the result of health care professionals not seeing the value of recording all medications that a patient is taking. I would argue that it is necessary to document all of the medications that a patient is taking, be it of pharmaceutical or natural origin. All health care professionals need to become more familiar with herbal preparations, their potential side effects, and drug interactions. Fortunately, there are a number of resources available that are updated on a regular basis to keep abreast of the current literature. (*See Table 2.*) It would be worthwhile for every medical practice to have at least one of these references available. ■

Dr. Schleis is Director of Pharmacy Services, Infections Limited, Tacoma, Wash.

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Therapeutics & Drug Brief

Magic Mushrooms and Mefloquine

Source: *ISTM Physicians (TRAVEL-MED@YorkU.CA); March 19-20, 2001.*

Physicians on the international travel Medicine (ISTM) chat line reviewed a case of an 18-year-old student traveling in Southeast Asia and India as part of a class "project" who developed an acute reaction following an ingestion of raw "magic mushrooms" in Thailand. He presented several days later to a physician in Calcutta complaining of nausea, sweats, palpitations, and intermittent attacks of confusion, anxiety, and, according to friends, possible paranoia. He was also experiencing bad dreams.

He was also receiving mefloquine for malaria prophylaxis.

He consumed the mushrooms—also known as LSG/ecstasy mushrooms—and some possible marijuana, along with several friends, none of whom had a similar reaction. Such mushrooms have been popular with certain travelers looking for a "natural" (someone said the word—organic?) high since the 1960s and are apparently available at clubs and resorts in Southeast Asia.

Whether this young man's symptoms were secondary to the mushrooms, the mefloquine, or both is uncertain. However, retrospective data suggest that up to 11.3% of travelers, none with previously identified psychiatric problems, report some kind of neuropsychiatric symptoms while receiving mefloquine, including sleep disturbances, vivid dreams, and fatigue in about one-half to frank depression in 0.5% (see Kemper CA. *Infectious Disease Alert* 2000;19:112). About 1.2% report prolonged symptoms lasting longer than 2 months.

Critics of these data argue that good prospective data identifying a significant risk of neuropsychiatric problems in persons receiving mefloquine is lacking. Mefloquine remains an important prophylactic antimalarial agent for many travelers. Since a major complaint of some patients appears to be a perception of a lack of adequate warning regarding potential side effects, travel medicine clinics may find a simple handout outlining potential problems helpful. It seems reasonable to add that patients should probably not take psychoactive substances with their mefloquine. ■

The Therapeutics & Drug Brief was written by Carol A. Kemper, MD, Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center, Santa Clara, Calif.

CME questions

Testing form inserted in this issue

14. If left untreated, AK may progress to squamous cell carcinoma.
a. True
b. False

15. Which of the following is true regarding the use of alternative medications?
a. When they occur, drug interactions with alternative medications are of little consequence.
b. St. John's wort increases the blood levels of indinavir.
c. All patients should be questioned regarding their use of alternative medications and such information documented in the patient medical record.
d. All of the above

16. Which one of the following steroids binds to both ERα and ERβ in the central nervous system and initiates physiological postreceptor responses?
a. Tamoxifen
b. Tibolone
c. Raloxifene
d. Ethinyl estradiol
e. Estradiol

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