

# Ten Dermatology Drug Interactions to Watch

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NEW YORK — There's no doubt that systemic drugs used to treat skin disorders can interact in myriad ways, with results ranging from rashes to death, but some commonly held assumptions about drug interactions are either untrue or controversial.

At a meeting on medical and surgical dermatology sponsored by Mount Sinai School of Medicine, Dr. Mark G. Lebowhl offered his top 10 problematic or misconstrued combinations:

► **Methotrexate and trimethoprim-sulfamethoxazole.** "This is known as Kevorkian therapy for psoriasis," Dr. Lebowhl said. Several deaths are reported every year from this combination, which can cause severe myelosuppression.

Many other interactions can occur with methotrexate. Aspirin and many of the NSAIDs—including salicylate, ibuprofen, and naproxen—can increase methotrexate levels. Moreover, the combination of methotrexate and naproxen also increases naproxen levels. The NSAIDs that do not affect methotrexate levels and are safe to use in combination are flurbiprofen, ketoprofen, and piroxicam. "And the [cyclooxygenase-2] inhibitors were fine until the lawyers got there," he said.

► **Bexarotene and gemfibrozil.** "Bexarotene has been a godsend for patients with mycosis fungoides who are not doing well with PUVA or narrow-band UVB," but the combination of bexarotene with gemfibrozil is dangerous and should never be given, said Dr. Lebowhl, professor and chairman of dermatology at Mount Sinai in New York.

Like other retinoids, bexarotene causes hyperlipidemia. The specific dyslipidemia associated with this agent is hypertriglyceridemia, and gemfibrozil is the best drug for lowering triglycerides. Unfortunately, gemfibrozil raises bexarotene levels, and there have been cases of patients devel-

oping massive hypertriglyceridemia and pancreatitis. Atorvastatin and simvastatin are acceptable alternatives to gemfibrozil.

► **Erythromycin and theophylline.** Erythromycin elevates levels of theophylline, and because the asthma drug has a narrow therapeutic window, toxicity can result. Manifestations of theophylline toxicity include sinus tachycardia, tremor, and gastrointestinal disturbances.

Numerous other interactions have been seen with erythromycin. There have been reports of inappropriate antidiuretic hormone secretion syndrome, which is characterized by hyponatremia and potentially lethal metabolic disturbances, when erythromycin is combined with carbamazepine, Dr. Lebowhl said.

Inhibitors of cytochrome P450 3A, including nitroimidazole antifungals and certain calcium channel blockers and antidepressants, also are hazardous for patients taking erythromycin because they can double plasma erythromycin concentrations.

Erythromycin prolongs cardiac repolarization, and a recent large review found that patients taking erythromycin plus a cytochrome P450 3A inhibitor had three sudden deaths in 194 person-years of follow-up, compared with no deaths in 254 person-years for those patients taking amoxicillin plus a cytochrome P450 3A inhibitor (*N. Engl. J. Med.* 2004;351:1089-96). If a macrolide antibiotic is needed, then azithromycin is a suitable choice, because it does not inactivate the cytochrome enzymes.

► **Azathioprine and allopurinol.** The gout medication allopurinol interferes with the metabolism of azathioprine, increasing plasma levels of 6-mercaptopurine; serious blood dyscrasias can result.

There have been numerous reports of pancytopenia and death when these two agents were given together, Dr. Lebowhl said.

Approximately 11% of the population is partially or completely deficient in the enzyme thiopurine methyltransferase, which is involved in the metabolism of azathioprine. "If you really want to wipe out the

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DR. LEBWOHL

bone marrow, give the combination of azathioprine and allopurinol to a patient who is genetically deficient in this enzyme," he said. An assay for thiopurine methyltransferase should always be obtained before a patient is started on azathioprine.

► **Cyclosporine and many drugs.** Cyclosporine has numerous potential drug interactions, and elevated levels are associated with a host of side effects, Dr. Lebowhl said. Among the more common adverse effects are elevations of BUN and creatinine levels, and ultimately hypertension and renal failure. Drugs such as calcium channel blockers and erythromycin, when used in combination with cyclosporine, can cause elevated cyclosporine levels, but others such as phenobarbital and phenytoin can reduce cyclosporine levels.

Also be cautious in giving cyclosporine to patients on atorvastatin, and monitor the serum creatine phosphokinase levels. The concern is the possible development of rhabdomyolysis, he said.

► **Retinoids and tetracycline.** This combination can result in pseudotumor cerebri, in which patients present with severe headache, vision abnormalities, and nausea and vomiting. Ophthalmologic examination is needed, as papilledema can occur.

► **Ampicillin and allopurinol.** In virtually every survey, the frequency of morbil-

iform drug reaction on first-time exposure to ampicillin and amoxicillin is 5%. One report found that the rate increased to 22.5% when ampicillin was given with allopurinol, however, so that's another combination to avoid, he said.

► **Epinephrine and  $\beta$ -blockers.** This is an old story, Dr. Lebowhl said. There have been many reports of malignant hypertension among patients on  $\beta$ -blockers who are given epinephrine, but these have involved massive quantities of epinephrine. "We're not talking about a punch biopsy here," he said.

For most dermatologic procedures—with the notable exception of large-quantity liposuction—malignant hypertension is not an issue because so little epinephrine is used.

► **Antibiotics and oral contraceptives.** Whether antibiotics interfere with oral contraceptives has been controversial for years, Dr. Lebowhl said.

In one study, women taking antibiotics and birth control pills had a contraceptive failure rate of 1.6%. The failure rate, however, is 1% in women on oral contraceptives alone, so the difference is not statistically significant. Nonetheless, there have been numerous reports of pregnancies, particularly in women on low-dose estrogen pills, so "be cautious and warn them about the potential interaction," he said.

► **Acitretin and ethanol.** The belief that postmenopausal women and men must avoid alcohol while taking acitretin is incorrect. "I don't think a month goes by in my practice where a male or a postmenopausal female comes in saying they can't take acitretin because they would have to give up all alcohol," Dr. Lebowhl said.

The risk with this combination is that, in the presence in alcohol, acitretin is converted to etretinate, which has a much longer period of teratogenicity. The real risk is only in women with childbearing potential. ■



## Melanoma 'Epidemic' in Hispanics Warrants Preventive Action

BY MICHELE G. SULLIVAN  
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A significant annual increase in invasive melanoma, especially in the occurrence of tumors more than 1.5 mm thick in California Hispanics points to a "developing epidemic" of the cancer in that population, Dr. Myles Cockburn and associates have reported.

The results of their epidemiologic study, combined with studies suggesting that Hispanics don't practice skin self-exam or use sunscreen as often as recommended, mean that physicians should stress these prevention measures in Hispanic neighborhoods (*Cancer* 2006; doi 10.1002/cncr.21654).

"We recommend that efforts are undertaken immediately to target both primary and secondary prevention messages to Hispanic communities," said Dr. Cockburn of the University of Southern California, Los Angeles, and his coinvestigators. "This effort should include information on sun avoidance, as well as information on self-screening and recommendations on regular skin checks by a qualified professional."

The researchers used data from the California Cancer

Registry to estimate the annual changes in invasive melanoma among Hispanics and non-Hispanic whites from 1988 to 2001.

During the study period, the incidence of the disease rose about 4% per year for white males, 3% per year for white females, 2% per year for Hispanic males, and nonsignificantly for Hispanic females.

However, the researchers said, the overall 2% annual increase for Hispanic males included an annual increase of 7% for the period of 1996-2001.

Even though the annual increase in melanoma was less in Hispanics than in whites, Hispanics had a far greater incidence of thick lesions at presentation. Tumors thicker than 1.5 mm at diagnosis accounted for 24% of lesions in white men but 35% of lesions in Hispanic men.

In addition, 54% of invasive melanomas among white males were thin (less than 0.75 mm), but only 44% of the lesions were thin in Hispanic men. The incidence of thin tumors diagnosed among whites increased by 5% per year during the study period but increased only nonsignificantly among Hispanics. The incidence of thick tumors among white men increased at 12% per year, compared with a 15% annual increase among Hispanic men.

The increase in thick tumors at diagnosis is troubling because thicker lesions have a substantially poorer prognosis than do thin lesions, the authors wrote.

"These trends have important ramifications for melanoma prevention, because primary and secondary melanoma prevention efforts are focused on non-Hispanic populations," they said.

The study points up the importance of primary prevention counseling among patients with dark skin, many of whom believe their skin color offers some natural protection from the sun's effects, said Marianne Berwick, Ph.D., an epidemiologist with the University of New Mexico, Albuquerque.

"It is obviously important for Hispanic individuals, just as for all individuals, to look for new or changing spots on their skin—all over their skin, not only on places that are highly sun exposed—because melanoma can occur at any place on the body," she said in an interview.

"We still don't know enough about sun exposure patterns or the utility of sunscreens in preventing melanoma to offer good advice for Hispanic individuals, but again, as with all individuals, it is important to avoid intense intermittent sun exposure and sunburns," she said. ■