Ten Dermatology Drug Interactions to Watch

BY NANCY WALSH
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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 controverted.

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

► Methotrexate and trimethoprim-sulfamethoxazole. This is known as Kevorkian therapy for psoriasis,” Dr. Lebwohl said. Several deaths are reported every year from this combination, which can cause severe myelosuppression. Major problems 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 is 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. Lebwohl, professor and chairman of dermato-logy at Mount Sinai in New York.

Like other retinoids, bexarotene causes hyperlipidemia. The specific dyslipidemia associated with this agent is hypertriglyceri-demia, and gemfibrozil is the best drug for lowering triglycerides. Unfortunately, gemfibrozil raises bexarotene levels, and there have been cases of patients developing 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 nar-row therapeutic window, toxicity can re-sult. Manifestations of theophylline tox-in include sinus tachycardia, tremor, and gastrointesti-nal disturbances.

Numerous other interactions have been seen with ery-thromycin. There have been reports of inappropriate antidiuretic hor-mone secretion syndrome, which is characterized by hyponatremia and po-lydipsia. When used in combination with theophylline, when erythromycin is combined with carbamazepine, Dr. Lebwohl said.

Inhibitors of cytochrome P450 3A, including ritonavir, amiodarone, and certain calcium channel blockers and an-tidepressants, also are hazardous for pa-tients taking erythromycin because they can double plasma erythromycin concentrations.

Erythromycin prolongs cardiac recap-tORIZATION, and a recent large review found that patients taking erythromycin plus a cyclosporine P450 3A inhibitor had three sudden deaths in 194 person-years of follow-up, compared with no deaths in 234 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, be-cause it does not inactivate the cytochrome enzymes.

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

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 Approximately 11% of the population is partially or completely deficient in the en-zyme thiopurine methyltransferase, which is involved in the metabolism of azathioprine. “If you really want to wipe out the bone marrow, give the combination of azathioprine and allopurinol to a pa-tient who is genetically deficient in this enzyme,” he said. An assay for thiopurine methyl-transferase should always be obtained before a patient is started on azathioprine.

Combining methotrexate and trimethoprim-sulfamethoxazole is known as Kevorkian therapy for psoriasis,” Dr. Lebwohl said. Among the most common ad-verse effects are elevations of BUN and creatinine levels, and ultimately hyper-tension and renal failure. Drugs such as calcium channel blockers and ery-thromycin, when used in combination with cyclosporine, can cause elevated cy-closporine levels, but others such as phe-nobarbital and phenytoin can reduce cy-closporine 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 com-bination can result in pseudotumor cere-bri, in which patients present with severe headache, vision abnormalities, and nau-sea and vomiting. Ophthalmologic ex-amination is needed, as papilledema can occur.

► Ampicillin and allopurinol. In virtual-ly every survey, the frequency of morbidity and drug reaction on first-time expo-sure 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 combination to avoid, he said.

► Epinephrine and β-blockers. “This is an old story,” Dr. Lebwohl said. There have been many reports of malignant hypoten-sion among patients on β-blockers who are given epinephrine, but these have in-cluded 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 continues to be controversial for years, Dr. Lebwohl 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 con-traceptives alone, so the difference is not statistically significant. Nonetheless, there have been numerous reports of preg-nancies, 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 in- correct. “I don’t think a month goes by in my practice where a male or a post-menopausal female comes in saying they can’t take acitretin because they would have to give up all alcohol,” Dr. Lebwohl said.

The risk with this combination is that, in the presence of alcohol, acitretin is con-verted 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
Mid-Atlantic Bureau

A significant annual increase in invasive melanoma, es-pecially 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 recommend-ed, mean that physicians should stress these prevention measures in Hispanic neighborhoods (Cancer 2006; doi 10.1002/cncr.21654).

“We recommend that efforts are undertaken imme-diately to give 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 in-formation on sun avoidance, as well as instructions in 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 2000.

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 non-significantly 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 nonsignifi-cantly 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 prog-nosis 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 pre-vention counseling among patients with dark skin, many of whom believe their skin color offers some nat-ural 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, 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 pat-terns of utility of sunscreen in the Hispanic population to offer good advice for Hispanic individuals, but again, as with all individuals, it is important to avoid intense in-termittent sun exposure and sunburns,” she said.

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