Ten Dermatology Drug Interactions to Watch

BY NANCY WALSH
New York Bureau

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.

- Many antidepressants 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 [cytochrome P450] inhibitors were fine until the lawyers got there,” he said.

- Bexarotene and gemfibrozil. “Bexarotene can be used 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 dermatology at Mount Sinai in New York.

- Like other retinoids, bexarotene causes hypertriglyceridemia. 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 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 narrow therapeutic window, toxicity can result. Manifestations of theophylline toxicity include seizures, 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 polyuria. Leukemoid reactions, which occur when erythromycin is combined with carbamazepine, Dr. Lebwohl said.

- Inhibitors of cytochrome P450 3A, including ritonavir and saquinavir, and certain calcium channel blockers and antipodiretics, 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 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, like other retinoids, bexarotene causes hypertriglyceridemia. 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 developing massive hypertriglyceridemia and pancreatitis. Atorvastatin and simvastatin are acceptable alternatives to gemfibrozil.

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

- Combing methotrexate and trimethoprim-sulfamethoxazole “is known as Kevorkian therapy for psoriasis.”

DR. LEBWOHL

In addition, 54% of invasive melanomas among white men increased at 12% per year, compared with 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 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 among Latinos 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.

Melanoma ‘Epidemic’ in Hispanics Warrants Preventive Action

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

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 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 disseminate 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 instruction 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.

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There have been many reports of malignant hypertriglyceridemia (often called “hypertriglyceridemia”) since the 1980s, but the explosive increase among white men was unexpected. The increase in thick tumors at diagnosis is troubling because thicker lesions have a substantially poorer prognosis than do thin lesions, the authors wrote.

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