Compliance Plan Set for Teratogenic Acne Drug

BY TIMOTHY F. KIRN
Sacramento Bureau

In a move that caught many in the medical community by surprise, the Food and Drug Administration last month announced a comprehensive—and mandatory—risk management program for the teratogenic acne drug isotretinoin that demands complete compliance by year's end.

The program, called iPLEDGE, will require registration and ongoing compliance by all physicians and patients by Dec. 31, 2005. The iPLEDGE initiative replaces Roche's voluntary SMART program for Accutane and similar programs for the four generic versions of isotretinoin.

The FDA informed physicians in November 2004 that SMART would be replaced. "This is a system that has long been coming, and some would say is long overdue," said Sandra Kweder, M.D., deputy director of the FDA's Office of New Drugs.

The program's implementation will be incremental, starting with the Oct. 31, 2005, deadline for registration of wholesalers and pharmacies to obtain isotretinoin from a manufacturer. Prescribing physicians and their patients will then have two more months to be registered and in full compliance. Under the program, wholesalers of Accutane or the four currently approved generic equivalents will distribute isotretinoin only to pharmacies that have registered with the safety program and continue to demonstrate ongoing compliance.

Those pharmacies will dispense prescriptions only when the prescribing physician has registered the individual patient being treated and certified that the patient has been informed of the teratogenicity risks and has had two negative pregnancy tests (a screening test and a confirmatory test) performed by a laboratory or in the physician's office. Patient registration will be done over the Internet or by phone.

Patients must also register themselves and sign a consent form agreeing to use two forms of birth control while on the drug. Patients will be required to have repeat pregnancy testing every month while they are on the drug and another 1 month after they stop. Prescriptions will need to be filled within 7 days of pregnancy testing.

The package insert and the patient informed consent form have been updated and now contain a new warning that there have been suicides reported in patients taking isotretinoin. Both inform patients about what signs to watch for and tell them to contact their health care provider if they recognize any of those signs.

The new program replaces the old, required program for Accutane known as SMART (System to Manage Accutane Related Teratogenicity) and the other similar programs for the generic products. Under SMART, physicians who wanted to prescribe Accutane needed to complete an education program to obtain the yellow stickers that needed to be attached to the paper prescriptions for pharmacies to fill the prescriptions. When attaching a sticker, the physician was also required to register the patient and to certify that the patient had undergone pregnancy testing and that the results were negative.

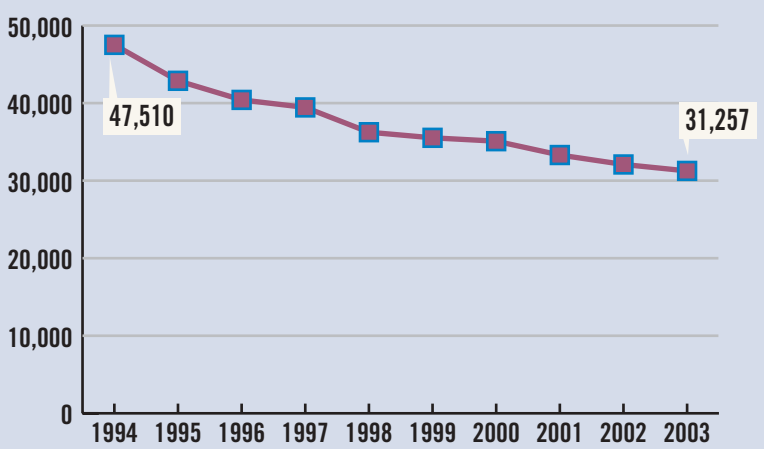
FDA determined that the SMART program needed to be replaced with a more stringent program because data from the first 2 years of the program, which went into effect in 2002, showed that it had not significantly reduced the rate of pregnancies occurring in patients on isotretinoin, which was its aim. Some also claimed that not all physicians were being fully compliant with the pregnancy testing requirement of the program.

Moreover, too few patients were signing up with the voluntary patient registry that was a part of the program.

Physicians can access the iPLEDGE program on the Internet by going to www.ipledgeprogram.com or by calling 866-495-0654. ■

DATA WATCH

Hospital Discharges for Ectopic Pregnancy on the Decline



Note: Based on weighted national estimates from Healthcare Cost and Utilization Project's Nationwide Inpatient Sample.
Source: Agency for Healthcare Research and Quality

Kevin Foley, Research

Drugs, Pregnancy, and Lactation

Hair Testing, Prenatal Drug Exposure

A recently published study on recreational drug use during pregnancy and the possible link to fetal gastroschisis highlights an increasingly important area of research: hair testing as a biomarker for pregnancy exposure to recreational drugs or drugs of abuse. Our laboratory is one of several sites in North America with expertise in measuring these substances in hair, an area many obstetricians may not be aware of.

Forensic scientists have known for some time that drugs taken by an individual are grown into the hair, and do not go away. The first use of this technology was to detect long-term exposure to heavy metals. Over the last 15-20 years, more drugs of abuse have been determined to grow into adult hair, including cocaine, heroin, marijuana, LSD, amphetamine, and methamphetamine. In 1988, we determined that the same is true for the baby. Because the hair present at birth grows during the last 3 months of gestation, an analysis of a baby's hair can provide information on possible drug exposure during that time. We have now shown this is true for almost every drug of abuse, as well as nicotine.

BY GIDEON KOREN, M.D.

With babies, the same substances can also be measured in meconium, and exposure can be traced to as early as 14 weeks' gestation, when meconium begins to form. Hair and meconium testing have become quite routine in certain settings in North America, with the predominant use among child protection agencies or children's aid societies. This testing is also used for research and clinical purposes and by neonatologists, pediatricians, and other health care professionals who have a medical reason to test, often in the context of diagnosing issues in the child, and when maternal consent is provided. For such studies to be conducted, the guardian's consent is needed; sensitive attitudes and high ethical standards need to be practiced.

It's possible to use meconium analysis to test for excessive maternal alcohol intake by measuring fatty acid ethyl esters, conjugates of alcohol with fatty acids, which stay in the meconium of the baby. Recent work from investigators in Berlin determined that fatty acid ethyl esters can also be measured in the hair of the parents. Animal studies indicate they can be measured in a baby's hair, which is being investigated in human studies that are underway.

Analyzing hair samples provides an opportunity to look, not just at one sample of urine or blood that represents the last day or so of exposure but, rather, long-term exposure. At our laboratory, we use hair testing to determine when exposure occurred, which eliminates the uncertainties when this information is obtained from the individual.

Last year we published a review (Clin. Biochemistry 2004;37:429-38) that discussed hair and meconium testing to confirm the prenatal use of alcohol and tobacco. It is important for clinicians to recognize that positive neonatal or meconium tests for drugs of abuse are strong evidence for maternal addiction, as these drugs have been used long after the mother knew she had conceived.

In a study conducted at the Motherisk laboratory published in 2003 (Arch. Dis. Child. Fetal Neonatal Ed. 2003;88:F98-F100), we found that meconium was somewhat more sensitive than hair samples of newborns for detecting cocaine and cannabis, and found a significant correlation between hair and meconium levels of cocaine, cannabis, and opiates. We concluded that both methods were useful biologic markers of illicit drug exposure in utero and also useful in suspicious cases where the neonatal urine test is negative.

In the recent gastroschisis study, investigators used maternal hair analysis from samples taken between 14 and 33 weeks' gestation in 22 pregnant women with a fetus diagnosed with the disorder and in 25 pregnant women with a normal fetus (BJOG 2005;112:1022-5).

In 10 of the 22 cases of babies with gastroschisis, there was evidence on enzyme-linked immunosorbent assay (ELISA) that the mother had taken a recreational drug in the periconceptional period and in the first trimester. But when they checked these results against those obtained from gas chromatography with mass spectrometry (GCMS), which is most specific, four cases (three of cocaine use and one of methamphetamine use) were confirmed.

While the study is small and therefore cannot establish an association, it marks the first time that "objective measurements of maternal intake of recreational drug compounds at these critical periods of development for the fetus have been carried out," as the researchers noted. Clearly, hair testing can be a very powerful tool in these studies and in individual cases to help determine whether a woman is using drugs. ■

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