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Continued Occurrence of Accutane®-Exposed Pregnancies

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ABSTRACT

Background: Accutane® a teratogenic prescription drug licensed to treat severe, recalcitrant nodular acne. First-trimester pregnancy exposure can cause major birth defects. The manufacturer began a Pregnancy Prevention Program (PPP) in 1988; however, exposed pregnancies continue to occur. In 1996, the manufacturer began a direct-to-consumer advertising campaign, raising concerns of more exposed pregnancies.

Methods: We examined trends in Accutane use by reproductive-aged women. We also interviewed a series of 14 women in California who had recent Accutane-exposed pregnancies to identify opportunities for prevention.

Results: The estimated number of Accutane prescriptions for reproductive-aged women has more than doubled in the past 10 years; it is the most widely used teratogenic drug in the United States, with approximately 2.5 per 1,000 reproductive-aged women exposed to Accutane in 1999. One-half of the women interviewed reported seeing an advertisement for prescription acne treatment before taking Accutane. Eight of the 14 women used no contraception at the time of the exposed pregnancy; 13 of the 14 women did not use two forms of contraception. Four of the 14 women did not have pregnancy tests before starting Accutane. None reported seeing all PPP components, and four saw only the information on the pill packet. These 14 pregnancies resulted in four live infants who had no apparent birth defects, one live-born infant with multiple defects, four spontaneous abortions, and five induced abortions.

Conclusions: The increase in Accutane use observed among females may be exacerbated by advertising. Physicians and patients must use more caution with teratogenic prescription drugs.

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INTRODUCTION

Accutane®[1] (Roche Laboratories, Nutley, NJ), which is known by the generic name isotretinoin, is a prescription drug licensed by the Food and Drug Administration (FDA). The only approved indication for Accutane is treatment of severe, recalcitrant nodular acne (Physicians' Desk Reference, '99). It is a known human teratogen that can cause multiple major malformations; the embryopathy associated with exposure during the first trimester of pregnancy includes craniofacial, cardiac, thymic, and central nervous system malformations (Lammer et al., '85).

In response to early case reports of infants with Accutane embryopathy (Lammer et al, '85; CDC, '88), an advisory committee to the FDA met in 1988 and recommended a program to help prevent pregnancies exposed to Accutane (Dermatological Drugs Advisory Committee, '88). The manufacturer began a Pregnancy Prevention Program (PPP) in late 1988 that includes educational materials for both prescribers and patients and offers women reimbursement for contraceptive counseling by a physician. The PPP protocol states that women of reproductive potential must either abstain from sexual intercourse or use two methods of effective contraception simultaneously, have a negative pregnancy test before starting Accutane, and wait until the second or third day of their next menstrual period before beginning to take Accutane. The PPP also asks women of childbearing age being treated with Accutane to voluntarily enroll in the Boston University Accutane Survey (BUAS) (Mitchell et al., '95).

Although Accutane is contraindicated in pregnancy, and its package explicitly warns users to avoid pregnancy while taking the product, exposed pregnancies continue to occur (Mitchell et al, '95; Pastuszak et al, '94; Atanakovic and Koren, '99). From initial marketing in 1982 until early 2000, the manufacturer received reports of 1,995 exposed pregnancies including pregnancies among both BUAS enrollees and spontaneous reports (Hoffmann-La Roche, '00). The number of infants born with congenital malformations associated

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with Accutane exposure in utero is not known, but from September 1982 through July 1989, the manufacturer received reports of 71 infants born with congenital malformations following an exposure during pregnancy (Dai et al., '92). Approximately 85 cases of congenital anomalies after exposure to Accutane have been reported to the FDA since 1989. Sixty of these reports have at least one of the features of retinoid embryopathy (A. Vega, FDA Center for Drug Evaluation and Research, personal communication, August 2000).

Roche Laboratories began direct-to-consumer print advertisements for prescription acne medication in 1996, added television and radio ads in 1997, and expanded the campaign to the entire United States in 1998 (Eileen Leach, Roche Laboratories, personal communication, June '98). The Roche advertisements do not mention any specific medication brand names, but Accutane is the only prescription acne medication marketed by Roche. The advertisements also do not provide any warning on the teratogenicity of Accutane. Direct-to-consumer advertisements are likely to increase demand (Hollon, '99), raising concerns that an increased number of exposed pregnancies will occur.

We estimated the recent use of Accutane by women of reproductive age in the United States. We also interviewed a case series of women who had recent Accutane-exposed pregnancies. The objective of the study was to increase awareness of the continued occurrence of Accutane-exposed pregnancies 11 years after inception of the PPP, and to learn more about why these exposed pregnancies happen. A brief report of this investigation was published in the Morbidity and Mortality Weekly Report (CDC, '00).

METHODS

We estimated the use of Accutane by women aged 15–44 years using data from IMS HEALTH National Prescription Audit Plus™ (NPA Plus™) and the National Disease and Therapeutic Index™ (NDTI™). NPA Plus data come primarily from a panel of 20,000 stores selected randomly from the IMS HEALTH pharmacy database of more than 34,000 reporting stores, which account for more than one-half of all retail pharmacies in the continental United States. NDTI provides a compilation of statistical and demographic information about the patterns and treatments of disease encountered in office-based practices in the continental United States. We obtained the total number of prescriptions for Accutane by year from NPA Plus. From NDTI, we derived the proportion of female users as well as the percentage of female users who were 15–44 years of age, by year. By combining these two sources, we estimated the total number of reproductive-aged women exposed to Accutane by year. We used U.S. Census Bureau population estimates for 1999 to calculate the prevalence of Accutane exposure among reproductive-aged women.

During March 1999, we interviewed a series of 14 women who had recent Accutane-exposed pregnancies. Eligible women were those residing in California who had a pregnancy exposed to Accutane with date of last menstrual period (LMP) after January 1, 1997. Women were referred to our study by the BUAS and the California Teratogen Information Service and Clinical Research Center (CTIS); therefore women either must have voluntarily enrolled in the BUAS or called the CTIS for information about their exposure to be eligible for inclusion. California was selected as the study site because of its large population and the willingness of the CTIS to provide referrals.

The BUAS and CTIS contacted women by telephone who met the eligibility criteria, briefly explained our study, and asked if they were willing to be contacted by a Centers for Disease Control and Prevention (CDC) investigator. Women enrolled in the BUAS who gave oral consent also had to return a signed written consent form before being contacted by the CDC. Women who had contacted CTIS gave oral consent to be contacted by the CDC. The CDC protocol for this investigation was approved by the CDC Institutional Review Board (IRB) and the Committee for the Protection of Human Subjects of the State of California Health and Human Services Agency.

The interview instrument included questions on the indication for and use of Accutane, contraceptive history, pregnancy history, procedures used in the initial prescription of Accutane, and exposure to advertisements for prescription acne medication. All interviews were private with only the investigator and the subject present. The women were interviewed in their own homes whenever that was acceptable to them. If they preferred, a telephone interview was offered as an option. Nine women were interviewed in person and five women were interviewed by telephone.

Respondents were asked to sign a medical record release for themselves; they were also asked to sign a medical record release for their child if the outcome of the exposed pregnancy was a live birth. Information from the medical records was used to validate the date of LMP, dates and results of pregnancy tests, pregnancy outcome, and any defects diagnosed in the fetus/infant. The medical record was used as the gold standard if a discrepancy existed between the medical record and the self-reported responses obtained during the interview.

RESULTS

The estimated annual number of Accutane prescriptions has more than doubled from fewer than 750,000 prescriptions in 1989 to more than 1,800,000 prescriptions in 1999, with the proportion of prescriptions written for women remaining relatively stable at about 50%. Reproductive-aged women (15–44 years old) have accounted consistently for approximately 90% of prescriptions for women. The trend in total prescriptions for reproductive-aged women (Fig. 1) is similar to the trend for all Accutane prescriptions. The total number of prescriptions to reproductive-aged women has in-