

The Pregnancy Registry Program at Glaxo Wellcome Company

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Registries can be used to provide an early warning system for potential teratogenic effects associated with the use of specific medications during pregnancy. Glaxo Wellcome has developed 5 international registries: (1) the Acyclovir Pregnancy Registry, (2) the Antiretroviral Pregnancy Registry, (3) the Lamotrigine Pregnancy Registry, (4) the Sumatriptan Pregnancy Registry, and (5) the Bupropion Pregnancy Registry. The purpose of these registries is to gain more information about the potential teratogenicity of these drugs during pregnancy. Two potential limitations of such registry data are recognized: (1) the utility of the data collected depends on the size of the sample; and (2) the registered patients may not be representative of all patients using the medication. However, these types of registry reports can be a valuable and cost-effective way to collect data regarding the use of medications during pregnancy when conventional methods (eg, cohort studies) are not appropriate or feasible. (*J Allergy Clin Immunol* 1999;103:S362-3.)

Glaxo Wellcome currently has 5 ongoing pregnancy registries, all of which are international: the Acyclovir Pregnancy Registry, the Antiretroviral Pregnancy Registry, the Lamotrigine Pregnancy Registry, the Sumatriptan Pregnancy Registry, and the Bupropion Pregnancy Registry. The registries are a joint effort of Glaxo Wellcome and the advisory committees from each registry. For Glaxo Wellcome, the Centers for Disease Control and Prevention (CDC) was an integral part of the original formation of the registries. The objective of these registries is to provide an early warning of any potential teratogenicity associated with prenatal exposures to any one of these drugs to reduce the uncertainty associated with administration of these drugs during pregnancy. The drugs involved are classified by the Food and Drug Administration as pregnancy category B or C.

The *Acyclovir Pregnancy Registry* was established over 10 years ago. Since then, it has monitored over 1000 pregnancies. Among the 682 births that followed first-trimester exposure, 18 birth defects have been observed, a frequency that does not differ from that of the general population.

The *Antiretroviral Pregnancy Registry* was established in 1989 for zidovudine. Subsequently, Hoffman LaRoche requested that Burroughs Wellcome (Glaxo Wellcome since 1995) include ddC (zalcitabine) in the registry. At that time ddC was under evaluation in clinical trials. Bristol-Myers Squibb Company has also joined the registry

Abbreviation used

CDC: Centers for Disease Control and Prevention

with ddI (didanosine) and d4T (stavudine). Glaxo Wellcome has added 3TC (lamivudine), and Hoffman LaRoche Inc has added saquinavir. Although zidovudine is the only antiretroviral agent licensed for use during pregnancy, the registry includes case reports of women exposed to any combination of these antiretroviral agents during pregnancy.

The *Lamotrigine Registry*, established recently, is monitoring the use of this anti-epileptic drug. The registry also includes women who became pregnant during clinical trials with lamotrigine in the United States and elsewhere.

The *Sumatriptan Pregnancy Registry* monitors birth outcomes after maternal use of this treatment for migraine, and the *Bupropion Pregnancy Registry* monitors birth outcomes after maternal use of this drug.

There are several reasons that registries exist for these drugs and not for drugs used in the treatment of other diseases affecting women of childbearing age. These drugs are often used on a long-term basis, and therefore unintentional exposure during the first trimester of pregnancy is likely to occur. There may be adverse medical consequences to the woman if she stops taking the drugs. There is also little or no information available on the effects of these drugs on the human fetus. Additionally, the chronic medical conditions for which these drugs are indicated may themselves be suspected of causing adverse birth outcomes.

An important goal of the registries is to increase sample sizes. Glaxo Wellcome is challenged to increase awareness of the registries (to increase recruitment) without appearing to promote use of these drugs in pregnancy. An effective way to increase participation in the registries is to use simple reporting methods. Health care professionals have said that they would be more willing to enroll pregnant women if the case report forms were simple and brief. However, a fine balance needs to be maintained between the goals of the advisory committee for each registry, which urges the collection of more data, and the needs of the practitioners, who provide enrollees and request simple registration procedures.

To encourage participation by practitioners, the phone number and purpose for the registries are now in the package inserts for the products, resulting in dramatic increases in the number of calls made to the registries

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0091-6749/99 \$8.00 + 0 1/0/95687

from patients, as well as from health care professionals. Procedures for patient registration, collection of follow-up data, and data analysis are described as follows.

REGISTRATION PROCEDURES

Registration can be initiated by the patient or a health care professional. For patient-initiated registration, a woman who realizes she became pregnant while taking the drug calls the registry. The patient is asked for the name of her physician (or other health care professional). Information is then sent to the health care professional, who can then share the information with the patient. Alternatively, the health care professional can call to register a patient. At enrollment, baseline data related to demographic information are collected (by phone, fax, or mailed case report form), including concomitant medication use, pregnancy history, timing, dose, and duration of exposure. Minimal information to facilitate follow-up at time of delivery is obtained. For acyclovir, the indication for treatment is reported. No patient names or other identifying information are maintained in the database. The health care professional may request that the patient's initials and medical record number be recorded to facilitate record review after delivery; however, this information is dropped from the database at completion of follow-up. Company employees must not advise patients, and they may not collect information from patients. If a woman requests more information at the time of the telephone call, she is referred to the American Social Health Association, Teratogen Information Services, or other resources.

FOLLOW-UP PROCEDURES

At the time of enrollment into a registry, the estimated date of delivery is obtained and entered into the computer. A few weeks before the estimated delivery date, a follow-up form is sent to the provider for these "prospective cases." The follow-up form includes questions on prenatal exposures to the drug of interest and to other agents, possible maternal infections, and other conditions that may be related to an adverse birth outcome. Birth defects are classified according to published criteria from CDC. Follow-up is aggressive but not long-term; that is, it does not continue past the first year. Long-term follow-up would necessitate obtaining informed consent from the mother, as well as transfer of follow-up responsibilities from the obstetrician to the pediatrician, a procedure that is considered to be impractical. The rate of patients lost to follow-up is 20% to 25%, which is typical for this type of voluntary registry.

If a birth defect is reported, a description of the case is sent immediately to the registry contact at the Birth Defects and Developmental Disabilities Branch of CDC for review. When a case is "closed," a letter is sent to the health care professional to thank him or her for contributing to the registry and to encourage future participation in reporting data to the registries. The registries also accept retrospective cases, for which reports on birth

outcome and exposure are received simultaneously. Although retrospective cases are included in the tables produced from the data, they are not used for calculating rates of birth defects.

DATA ANALYSIS

At the time of data analysis, exposures are stratified by trimester. From the prospective reports, the total rate of birth defects is estimated and compared with the rate of birth defects expected within the general population (between 3% and 7% of live births). Birth defect reports are assessed for evidence of patterns or uniqueness. Retrospective reports are considered along with prospective ones. Semiannually, all health care professionals who have registered patients receive a copy of the registry data report.

The advisory committees for the registries include representatives from the Sexually Transmitted Diseases Division and the Birth Defects and Developmental Disabilities Division of CDC. Academic medical practitioners, nonacademic practitioners, and epidemiologists also participate. The Antiretroviral Pregnancy Registry Advisory Committee includes representatives from the sponsoring companies, the CDC Division of HIV/AIDs, AIDS program, National Institute of Child Health and Development, and the AIDS Clinical Trials Group. The Lamotrigine Registry includes representatives from CDC, neurologists, and other experts on epilepsy.

The advisory committees for each registry meet twice yearly to review data, study methods, data collection instruments, and data collection procedures. Methods for promoting awareness of the registry are also discussed. Committee members review all of the closed cases and summarize the data in a semiannual report, which includes a consensus statement about the conclusions they have drawn from the data.

The registries receive referrals from multiple sources including CDC, physicians, patients, investigators for clinical trials, genetic counselors, teratogen information centers, the American Social Health Association, and company sales representatives.

CONCLUSIONS

The utility of registry data depends on the sample size, which in turn depends on continued collaboration with health care professionals. The registry approach has limitations and potential biases, primarily because women reported to the registry are a selected group and may not be representative of all women taking the drug. This selection bias is another reason for continuing to stress recruitment in a number of geographic areas and beyond the locations of physicians' practices. Inclusion of voluntary agencies and hotlines would facilitate patient recruitment. Nevertheless, when conventional methods, such as cohort studies, are not appropriate or feasible for studying rare exposures and rare outcomes, use of registry data is valuable and cost-effective.