Birth Defect Risk Leads To Paxil Label Change

BY SHARON WORCESTER
Southeast Bureau

New data linking paroxetine use during the first trimester of pregnancy with increased risk of major congenital malformations has prompted changes to the drug's label.

Preliminary results of a retrospective epidemiologic study sponsored by GlaxoSmithKline Inc., the drug's maker, show paroxetine (marketed as Paxil), was associated with more congenital malformations (adjusted odds ratio 2.20) and more cardiovascular malformations (adjusted odds ratio 2.08) than other antidepressants in almost 3,600 pregnant women.

The prevalence of congenital malformations in the study was 4%, compared with about 3% in the general population.

The prevalence of cardiovascular malformations was 2%, compared with about 1% in the general population, according to a "Dear Healthcare Professional" letter issued by the company and the Food and Drug Administration.

Ventricular septal defects were the most common cardiovascular malformation in the study.

The GSK findings, along with those from two other recently published abstracts, warrant the voluntary label change, according to the company.

In one of the abstracts, Pia Wogelius, Ph.D., of the epidemiology department at Aarhus University Hospital, Denmark, and colleagues reported a link between SSRIs and major congenital malformations, including cardiac malformations. The risk of malformation was increased among women who had prescriptions for SSRIs filled in the 30 days before conception through the end of the first trimester, compared with those who had no SSRI prescriptions filled during the same period. These data did not specifically look at Paxil use.

The other abstract described a preliminary analysis of data obtained from the National Birth Defects Prevention Study suggesting an association between SSRI use between 1 month before and 3 months after conception and a significantly increased risk of omphalocele. The risk was greatest among paroxetine users, Sura Alwan, a Ph.D. student at the University of British Columbia, Vancouver, reported at the annual meeting of the Teratology Society.

'Health care providers are advised to carefully weigh the potential risks and benefits of using paroxetine therapy in women during pregnancy.'

SSRI use in that study also was linked with an increased risk of tetralogy of Fallot, she told FAMILY PRACTICE NEWS.

The Paxil labeling changes will be in the pregnancy subsection of the "precautions" section of the labels for Paxil and Paxil CR. The new language cites the GSK data but also notes that these data conflict with those from previous studies, including those from the Swedish Medical Birth Registry, which showed no increased risk of major malformations in infants born to 708 women exposed to SSRIs—including paroxetine—during pregnancy.

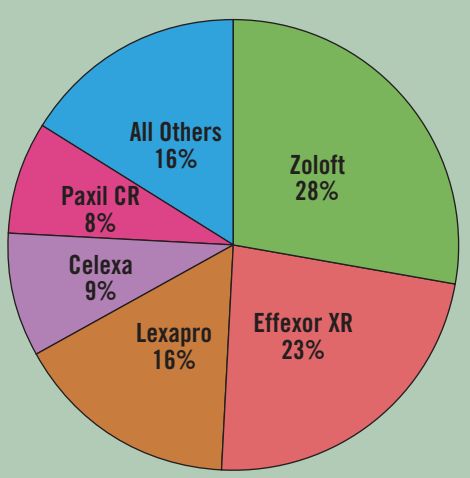
The conflicting data make it difficult to establish a causal relationship between SSRI use and major congenital malformations. Due to the lack of adequate and well-controlled studies, Paxil maintains its Pregnancy Category C status, according to GSK.

"As with all Pregnancy Category C drugs, health care providers are advised to carefully weigh the potential risks and benefits of using paroxetine therapy in women during pregnancy," the company said in the letter.

Results of the GSK study are posted at the company's Clinical Trial Register at http://ctr.gsk.co.uk/welcome.asp. ■

DATA WATCH

Zoloft Was the Leading SSRI/SNRI in 2004



Note: Based on share of total wholesale purchases for selective serotonin reuptake inhibitor/selective norepinephrine reuptake inhibitor market.
Source: IMS Health

RICHARD FRANKI, RESEARCH/DESIGN

DRUGS, PREGNANCY, AND LACTATION

Reviewing the Safety of SSRIs

Over the past few years, several published studies have addressed the reproductive safety of the selective serotonin reuptake inhibitors. Recent studies have focused on the risk for neonatal discontinuation syndrome or symptoms of perinatal jitteriness associated with use of SSRIs during the latter portions of pregnancy.

Estimates of risk of first-trimester exposure to SSRIs derive from data accumulated over the last 15 years, which support the absence of major congenital malformations associated with first-trimester exposure.

BY LEE COHEN, M.D.

Data on the teratogenicity of SSRIs come from relatively small cohort studies and larger, international teratovigilance programs, and they have cumulatively supported the reproductive safety of fluoxetine (Prozac) and certain other SSRIs. These include a Scandinavian-based registry study of 375 women exposed to citalopram (Celexa) in the first trimester, which failed to indict SSRI as a teratogen.

A recent metaanalysis conducted by researchers at the Motherisk Program in Toronto supported the absence of teratogenicity associated with first-trimester exposure to several SSRIs.

Another recent report from the Swedish Medical Birth Registry failed to identify higher rates of congenital malformations associated with prenatal exposure to a number of SSRIs, including fluoxetine, citalopram, paroxetine (Paxil), and sertraline (Zoloft).

But at the Teratology Society's annual meeting in June, investigators from the University of British Columbia, Vancouver, reported an increased risk of omphalocele and craniosynostosis associated with first-trimester exposure to SSRIs. Using data from the National Birth Defects Prevention study, they compared data on 5,357 infants with selected major birth defects with 3,366 normal controls and interviewed mothers about exposures during pregnancy and other possible risk factors. Children with chromosomal anomalies or known syndromes were excluded.They found an association between exposure to any SSRI during the first trimester and omphalocele (odds ratio of 3).

Paroxetine accounted for 36% of all SSRI exposures and was associated with an odds ratio of 6.3 for omphalocele. Use of any SSRI during the first trimester was also associated with having an infant with craniosynostosis (odds ratio of 1.8). No association was noted between SSRI use and the other classes of major malformations studied.

This preliminary unpublished report is also described in a letter to physicians from GlaxoSmithKline, which markets paroxetine as Paxil. The letter includes additional data from an uncontrolled study of SSRI use during pregnancy, which noted a twofold increased risk in overall congenital malformations and cardiovascular malformations (most were ventricular septal defects) in offspring exposed to paroxetine, compared with other SSRIs. These data were derived from an HMO claims database.

Clinicians may be confused about SSRIs with the volley of new reports that suggest potential teratogenic risk associated with this class of compounds. Indeed, previous reports fail to describe such an association. Many of the more recent findings derive from either retrospective data sets taken from HMO claims data or from case-control studies, which also have certain methodologic limitations, compared with prospective cohort studies.

These recent findings of increased risk with prenatal SSRI exposure are inconsistent with earlier published findings. Nevertheless, large case-control studies can uncover an association not previously identified because of the inadequate statistical power of previous cohort studies, which were not large enough to detect an infrequent anomaly.

Even if we assume the associations from the new case-control study are true and that they are indeed causal, an odds ratio of 6.4 is associated with an absolute risk for omphalocele of only 0.18%. Absolute risk is of greater clinical value than relative risk and should be taken into account before patients are arbitrarily counseled to discontinue antidepressants during pregnancy.

The new findings are not necessarily a cause for alarm. Patients who are planning to conceive and are at significant risk for depressive relapse associated with antidepressant discontinuation may benefit from a switch to an antidepressant for which there are the greatest amount of data supporting reproductive safety. These antidepressants include the SSRIs fluoxetine, citalopram, escitalopram (Lexapro), as well as the older tricyclics.

However, for women who present when pregnant and still taking SSRIs, including paroxetine, discontinuation of the medication should not be arbitrarily pursued. Abrupt discontinuation of antidepressants can threaten maternal affective well-being.

DR. COHEN directs the perinatal psychiatry program at Massachusetts General Hospital, Boston, which offers information about pregnancy and women's mental health at www.womensmentalhealth.org. He is a consultant to manufacturers of several antidepressant drugs, including SSRIs.