Communications

Safety of Drug Therapy for Nausea and Vomiting of Pregnancy

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Nausea and vomiting of pregnancy are common complaints during the first trimester. Ironically, studies suggest that this may be a favorable occurrence resulting in fewer perinatal deaths than in patients with no symptoms of nausea and vomiting.[1,2] Drugs used in the treatment of nausea and vomiting of pregnancy have received a great deal of attention in the literature. Although teratogenicity testing in humans is impossible, observational studies, both retrospective and prospective, with large numbers of subjects have been reported. As most congenital anomalies result from multiple causes, ie, interactions between genetic and environmental influences, it is possible that susceptibility to teratogenic effects of specific drugs may vary among different populations.

Reports of Teratogenicity Caused by Bendectin®

Bendectin was first marketed in 1956 containing dicyclomine, an antispasmodic; doxylamine, an antihistamine; and pyridoxine (Vitamin B_6). The drug was reformulated in November 1976, in the United States, to eliminate dicyclomine because of lack of evidence for effectiveness. Scattered reports of congenital deformities associated with Bendectin given during pregnancy have received criticism for lack of documentation of direct cause and effect. In Canada in 1969, Patterson[3] reported a 34-week premature baby with limb deformities whose mother had taken Bendectin in the first month of pregnancy. In 1977, Patterson[4] reported another baby with similar deformities whose mother had taken Bendectin and claimed that sufficient evidence existed based on these and other similar reports to suggest that Bendectin was possibly not safe during pregnancy. In response, the Canadian Medical Association[5] released a report which documented that in some 130 cases of birth defects reported worldwide in children born to women who had taken Bendectin, no specific pattern of abnormality was found. After citing numerous studies which showed no evidence incriminating Bendectin and considering that over 20 million pregnant women worldwide have had Bendectin prescribed, the Association concluded that "Although none are entirely safe, drugs that control nausea and vomiting are indicated when simple, nonpharmacotherapeutic measures are ineffective."[5]

In England in 1978, a report by Donnai and Harris[6] and subsequent letters[7-9] brought attention to an association between the use of Debendox (trade name for three-ingredient Bendectin in England), and congenital malformations. Subsequently, there were several reports[10,11] of similar congenital abnormalities in infants whose mothers did not take Bendectin and some criticism[12] of poor documentation of cause and effect considering the extensive use of Debendox in England without extensive reports of ill effects. In the United States, the Food and Drug Administration has on record over 90 cases reported by physicians in which a pregnant woman has taken Bendectin and given birth to a child with abnormalities.[13] No direct link has thus far been established between

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the drug and these birth defects. An October 1979 statement issued by the Food and Drug Administration[13] concluded that "The current physician labeling for the drug reflects Food and Drug Administration's evaluation that there is no adequate evidence linking Bendectin with an increased risk of birth defects."[13]

Antinauseants During Pregnancy

In a large prospective study, Milkovich and Van Den Berg[14] found that of 628 children whose mothers had taken Bendectin during gestation, the incidence of congenital anomalies was no higher than among 4,353 children whose mothers had no drug prescribed for nausea and vomiting of pregnancy. They also studied the effects of prochlorperazine, meclizine, and cyclizine in a large number of patients and concluded that these drugs are not teratogenic when taken in recommended doses. In an earlier study by Yerushalmy and Milkovich,[2] of 4,277 gravidas, 330 were prescribed meclizine or cyclizine and 473 were prescribed ten other antinauseants including Bendectin. No evidence was found that meclizine, cyclizine, or Bendectin increased the risk of birth defects.

The prospective study of Smithells and Chinn[15] and a retrospective study by Nelson and Forfar[16] found no evidence that meclizine or cyclizine were teratogenic in man. A large prospective study by Shapiro et al[17] found no indication that doxylamine or dicyclomine were harmful to the fetus in over 1,000 women exposed during the first four lunar months of pregnancy. Smithells and Sheppard[18] recently traced 2,298 patients whose mothers had been given prescriptions for Bendectin during pregnancy and found no evidence to suggest teratogenicity with Bendectin (three ingredients). Results of evaluations conducted by the Food and Drug Administration indicate that Bendectin is not teratogenic. The label on meclizine and cyclizine containers states, "Warning—Not for use by women who are pregnant or who may possibly become pregnant, unless directed by a physician, since this drug may have the potentiality of injuring the unborn child."[19] This statement resulted from teratogenicity in laboratory rats when the drug was given in very high doses. In July 1979, the Food and Drug Administration's tentative final order on anti-emetic drugs for over-the-counter use authorized removal of the restriction of the use of meclizine and cyclizine in pregnant females because current data do not support teratogenicity of meclizine or cyclizine in humans.[19]

Conclusions

There is no good evidence to indicate that Bendectin, meclizine, or cyclizine are associated with an increase in congenital abnormalities. A small reservation may be held because it is often impossible to distinguish between coincidence and a low level of cause and effect relation.

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