Psychotropic Drugs in Pregnancy and Lactation

A psychotropic drug may be prescribed for a woman of childbearing age for the treatment of various neuroses and psychoses. If she is pregnant or lactating, the drug may pass via placental transport to her fetus, or via breast milk to her infant. Concern has been expressed as to the possibility of toxic effects. The literature on the effects of several psychotropic drugs provides a basis for recommendations on the use of these drugs in pregnant and lactating mothers.

In the first trimester of pregnancy, a drug that is teratogenic for humans may produce an easily recognizable malformation, e.g., phocomelia from thalidomide. In addition, animal experiments suggest that exposure to various drugs late in fetal development may cause physiologic, biochemical, or microscopic morphologic deviations. Behavioral abnormalities in laboratory animals have been attributed to late intrauterine or neonatal drug exposure ("behavioral teratogens").1 The documentation of neurochemical alterations in these functionally impaired animals has fostered additional concerns about the safety of various medications in the human.

INTRAUTERINE EXPOSURE

Of those psychotropic agents investigated, only lithium appears to be one that requires extra circumspection prior to its use by a pregnant woman. Ten years ago,2 teratogenic effects were demonstrated in animals, including mammals, following lithium administration. At first, collaborative studies designed to detect a lithium effect in humans failed to establish any increased risk.3 However, subsequent reports have described an unusual distribution of a rare cardiovascular abnormality (Epstein's anomaly)4,5 following fetal exposure to this agent. The contribution of concomitant multiple drug use in these patients cannot be assessed.

Neonates with congenital goiter and nephrogenic diabetes insipidus6 have had serum lithium levels of approximately 1 mEq/liter. A blood level greater than 1 meq/liter in neonates has also been associated with transient toxic disturbances including hypothermia, cyanosis, bradycardia, shallow respirations, diminished suck, hypotonia, and ECG T-wave alterations.

The possibility of teratogenic effects from other psychotropic drugs remains less convincing. There have been conflicting reports of an increased incidence of oral-facial malformations7 following early fetal exposure to diazepam. Increased frequencies of cesarean section, fetal heart rate abnormality, depressed Apgar score, altered tone, and reluctance to feed have been attributed to exposure to diazepam8-11 and abnormalities of motor and arousal processes12 have been demonstrated in rodents exposed to diazepam during the final "trimester."

The effect of chlordiazepoxide (Librium) taken during pregnancy has been evaluated in three major studies with a total patient population of more than 40,000 live births. In one of these studies it was suggested that chlordiazepoxide may be hazardous to the fetus exposed to the drug during the first 42 days of pregnancy, there being a 4½-fold increase of severe abnormalities in live births.13 Subsequent studies have failed to confirm such a high risk.14,15

Tricyclic antidepressants have been shown to increase the risk of teratogenicity in the human. However, rodents exposed in utero to imipramine have shown morphologic and behavioral abnormalities.16,17

There have been contradictory reports on human embryonic development following exposure to the antipsychotic drugs, especially the phenothiazines. In a study of 315 pregnant women who had received various types of phenothiazines, 11 gave birth to malformed infants.18 However, a larger study of
1,209 drug users failed to demonstrate an increased risk. In marked contrast, rats exposed during fetal life to either chlorpromazine or haloperidol had structural malformations, evidence of impaired maze learning performance, alteration in spontaneous motor activity, changes in operant responses, and susceptibility to induction of seizures. Chlorpromazine has altered brain neurotransmitter levels in animals and haloperidol has caused enduring changes in dopaminergic receptor sites.

**BREAST MILK EXPOSURE**

Complex pharmacokinetic factors regulate the excretion of drugs into human breast milk. To substantiate an increased hazard to the nursing of a mother receiving psychotropic medications, both a significant neonatal drug exposure and an increased adverse effect must be documented. The sensitivity of methods used to detect and quantitate drugs in milk has increased with concurrent advances in technology. Unfortunately, there have been no controlled studies in humans in which potential behavioral changes in association with measurements of drug levels in breast milk were studied. Rather, there are numerous case reports of acute toxic reactions. The accumulation of data from animal models on behavioral teratogenic effects raises questions that require further evaluation in human studies.

Information is sparse on the excretion of lithium into human breast milk and its effects on the nursing infant. Analysis of reports has suggested a complex developmental regulation between levels of this agent in maternal plasma/breast milk and breast milk/infant serum. In one study, lithium concentrations in breast milk were approximately one half those of maternal serum, whereas levels in milk were almost equal to those in the infants’ serum. Infants with serum lithium concentrations of about 0.6 mEq/liter manifest cyanosis, lethargy, decreased tone, and poor feeding.

Diazepam and its active metabolite, N-desmethyl-diazepam, were present both in breast milk and nursing infants’ blood, but more extensive studies will be required to clarify the degrees of accumulation. Further documentation is required to establish the excretion of benzodiazepines, including chlordiazepoxide and clorazepate, into breast milk. Although the metabolites of diazepam have been measured in breast-fed infants, only one nursing whose mother was receiving diazepam (30 mg/day) was lethargic and losing weight, with an EEG pattern characteristic of excessive sedative medication.

The accumulation of various antipsychotic drugs in breast milk has been extensively evaluated in animal models: perphenazine rapidly became concentrated in the milk of lactating ewes, whereas haloperidol levels never exceeded serum concentrations; chlorpromazine and prochlorperazine were present in breast milk of lactating dogs following receipt of large dosages of these drugs. In lactating mothers, utilizing specific detection techniques, chlorpromazine was found in all milk samples when the maternal serum levels of chlorpromazine were between 16 and 52 ng/ml. There was no consistent relationship recognized between maternal plasma level and breast milk concentration. One infant with drowsiness and lethargy had been exposed to a chlorpromazine level of 92 ng/ml in breast milk.

Conflicting statements are found in studies of the passage of tricyclic antidepressants, especially imipramine, from human plasma to breast milk. Sovner and Orslak and Eschenhof and Rieder detected imipramine and its metabolite in breast milk, but amitriptyline could not be identified following acute ingestion. Failure to detect a drug after acute ingestion does not, however, exclude its potential excretion following chronic medication ingestion.

In animal experiments, nurslings exposed to neuroleptic drugs administered to their mothers have shown behavioral and neurochemical changes that persist even after cessation of drug exposure. For example, progressive motor dysfunction occurred in 2-week-old rabbits receiving breast milk containing haloperidol. Correlative biochemical studies in these animals showed increased concentrations of homovanillic acid, a dopamine neurotransmitter metabolite. Motor dysfunction does not appear in a similarly treated rodent population, suggesting species specificity. However, neurochemical assessment in these “unaffected” rat pups demonstrated alterations of dopaminergic receptor binding sites.

In studies with the neuroleptic agents, penfluridol and pimozide, exposure during the first seven days after delivery resulted in diminution of active avoiding responses, impaired habituation, and alterations in spontaneous locomotion. The significance of these animal experimental results for the human subject has yet to be established.

**SUMMARY**

Accurate prediction of fetal/neonatal risks following maternal psychotropic drug consumption by the human will require much additional study. Based upon our present understanding of fetal exposure to psychotropic drugs, there would appear to be an increased risk for spontaneous malformations in the case of lithium. There have been inconsistent reports of structural abnormalities following
exposure to phenothiazines and benzodiazepines. In animal models that demonstrate structural changes due to neuroleptic exposure, in general, extremely large dosages of medication had been given. Thus, their correlative value is limited.

Behavioral alterations in animals following drug exposure during pregnancy tend to support increased concerns about the safety of psychotropic drugs for the fetus but cannot be used alone in making a final decision. Behavioral studies evaluating drugs in breast milk have been restricted to experimental animals; hence, the associated risks from this form of drug dosing in man remain unknown. At present, neither gross anatomic nor motor side effects have been apparent in the infant. The question of the development of subtle behavioral changes as a long-term consequence will remain undetermined until careful assessments have been completed.

RECOMMENDATIONS

The Committee on Drugs continues to support the established principle that no medication should be prescribed for a pregnant or lactating woman unless it is necessary for her health or that of her child. If medication is utilized, the most effective drug with the fewest side effects should be selected. When practical and consistent with the essentiality of controlling her symptoms, a woman should be withdrawn from psychotropic medication prior to conception. Based upon currently available information, when continued drug therapy is necessary, a patient receiving lithium should be changed if possible, to a less hazardous medication prior to conception. However, except for lithium, the existing evidence provides no basis for changing other psychotropic medications in a pregnant woman.

The literature reports that most psychotropic drugs administered to a lactating woman can be found in her breast milk. The concentration tends to be low and therefore, there is little likelihood of an effect on the infant. Thus, there appears to be no concrete evidence at the present time with which to recommend that a woman requiring psychotropic medication avoid breast-feeding. However, it must be emphasized that if a mother chooses to breastfeed while receiving medications, the infant should be observed for signs of drug effects. Subtle but long-term effects on the developing nervous system of even low doses of these drugs may be present, but currently undetected.

The Committee acknowledges the need for prospective studies of drug utilization during pregnancy and lactation. There is also a need to develop additional methodology for behavioral testing in drug evaluations.

REFERENCES

INTEGRAL INVOLVEMENT OF SEVERELY HANDICAPPED STUDENTS WITHIN REGULAR PUBLIC SCHOOLS

The authors contend that least restrictive environment involves more than merely placing severely handicapped students in regular schools. In addition to regular school placement, systematic efforts to promote positive interactions between severely handicapped students and their nonhandicapped peers must be made. An array of formal and informal methods for promoting integration, directed toward both school staff and students, are provided to assist teachers of the severely handicapped in systematically integrating their students into the regular school milieu.

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Pediatrics 1982;69;241

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