Perinatal Toxicology: Problems and Hazards

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**Abstract.** The toxicology of the perinatal period, comprising the last week of gestation and the first week of independent life, is seldom considered in the testing of drugs, but it is a unique period in the life of the individual, and there are good reasons why it should receive more attention.

**Key words:** Perinatal – Drug toxicity – Diazepam – Bupivacaine – Placenta – Drug disposition

Perinatal toxicology is very rarely considered when potential human medicines are considered, yet drugs are often given to women in labour, and may affect the foetus and neonate in the perinatal period. The perinatal period, for this purpose, may be taken as comprising the last week of gestation and the first week of independent life, although in clinical work it usually includes the last trimester of pregnancy as well. It is an important period in relation to drug toxicity for a number of reasons.

The foetus goes through very extensive changes in the transfer from the uterus to an independent existence. These changes are more dramatic and more extensive than any the individual will ever subsequently encounter. Drugs may interfere with these unique changes. Secondly, the placenta provides for the very rapid transfer of xenobiotics from the maternal to the foetal circulations. Drugs given to the mother are usually given for her well-being and comfort, and the foetus is being exposed to drugs which were intended for another person. Thirdly, the neonate is immature in a number of ways, and in particular in the handling of drugs. The liver enzyme systems are poorly developed. The excretory capacity of the kidney is limited. The ratio of surface area to body weight is high, as is the body water content. The plasma protein levels are low. Drugs remain in the tissues of the neonate for a long time in comparison with the older infant. Fourthly, the period is one in which there is rapid development of tissues and rapid cell multiplication. Such cells are more susceptible to toxic effects. Finally, this is a period of very rapid myelination. Nerve fibres, not yet
myelinated, are susceptible to toxic effects; furthermore, if myelination is delayed, nerve function will be impaired.

There is a very rapid transfer of xenobiotics from the maternal to the foetal circulations. In this Department, for instance, it was found that diazepam given intravenously to the mother reached detectable levels in the cord blood after as short an interval as 30 s. As the interval between injection and sampling increased, the concentration in the cord blood also increased, up to 12 min (the duration of the study). The level of drug in the vein was always higher than that in the artery, indicating a progressive transfer of drug from the maternal to the foetal circulation (McAllister 1980). More polar compounds are also quickly transferred (Arwood et al. 1979).

There is a very substantial variation between neonates in their ability to handle drugs, and the premature infant is particularly handicapped in this matter. Concurrent disease states, if present, may be made worse by drugs persisting in the foetal tissues.

The toxic effects that the neonate may suffer from drugs may be divided into four categories. First, there are those toxic effects which are extensions of the known pharmacological or toxicological effects of the drug. Thus, pethidine given to the mother will cause respiratory depression in the neonate. Maternal epidural anaesthesia with bupivacaine will cause irritability and excess crying even as late 6 weeks after birth. Since it can hardly be suggested that the drug persists in the neonatal tissues for such a period, one is forced to conclude that the early stimulation of the central nervous system produced by the drug causes a long lasting adverse effect on the functioning of that system (Rosenblatt et al. 1981).

Secondly we may consider unforeseen toxic effects. One example is the increased level of free bilirubin found in the plasma of infants whose mothers had had intravenous diazepam. This effect was attributed, not to the drug, but to the use of sodium benzoate as a preservative in the solvent. Thirdly, some effects are at present hypothetical. There is evidence that the perinatal liver can form epoxides (Jerina et al. 1970). These may be mutagenic, and the life expectancy of the neonate being maximal, there is the possibility of later carcinogenesis. Finally, there is every likelihood that drugs will be found toxic to infants in the perinatal period in ways that cannot at present be foreseen.

Can these effects on perinatal health be serious, and can they be long lasting? In the compromised neonate, for example, who suffers from hyaline disease of the lungs, the respiratory depression produced by the administration of pethidine to the mother may mean the difference between life and death. But even in the otherwise healthy neonate, we have noted the prolonged effect of maternal bupivacaine; follow-up may show that these effects are long lasting. In animal studies, Cortese et al. (1981) have shown that doses of methylmercury, below the no-effect level as conventionally determined, cause prolonged changes in conditioned avoidance behaviour.

With regard to the toxicological testing of drugs, it may be asked whether any additions should be made to the present procedures. One of the main targets of drug toxicity in the perinatal period is the developing nervous system of the infant. The encephalisation of man is so great by comparison with other species