Drugs During Pregnancy
An Issue of Risk Classification and Information to Prescribers

Rune Sannerstedt,1 Per Lundborg,1 Bengt R. Danielsson,1 Ingemar Kihlström,1 Gunnar Alván,1 Britta Prame2 and Eva Ridley2

1 Members of the teratology review panel of LINFO (Drug Information Ltd), Stockholm, Sweden
2 LINFO (Drug Information Ltd), Stockholm, Sweden

Summary

The Swedish system for the classification of fetal risk of drugs was the first of its kind and was implemented in 1978. Drugs for use in pregnant women are classified in 4 general categories – A to D. The US Food and Drug Administration (FDA) introduced a system in 1979 also using the letters A to D, together with an X category. However, the definitions differ considerably between the FDA system and the Swedish system, resulting in a very different allocation of drugs to the respective categories.

In the Swedish system, category A includes drugs that have been extensively used and/or for which there are reliable clinical data indicating no evidence of disturbance of the reproductive process. Category B includes drugs for which data from pregnant women are insufficient for making any solid estimation of human teratogenic risk, and classification is therefore based on animal data, with allocation to 3 subgroups. For products in category C, the pharmacological action of the drug may have undesirable effects on the human fetus or newborn infant. Finally, category D contains drugs for which human data indicate an increased incidence of malformations. The categorisation statement is always followed by a short explanatory text. In contrast to the FDA system, the Swedish system has been well accepted, as judged by an interview study including 934 physicians and pharmacists. We believe that much of the American dissatisfaction may be a consequence of shortcomings in the category definitions of the FDA system. The FDA system requires an unrealistically high quality of data, e.g. the availability of controlled studies in pregnant women that fail to demonstrate a risk to the fetus are needed for a drug to be assigned to category A. Consequently, the majority of drugs on the US market are allocated to category C, interpreted as 'risk cannot be ruled out'. The distribution of drugs into the various categories is thus very different between the Swedish and FDA systems.

We think that the issue of this debate reflects a fundamental problem related to public health information: how should a large, compounded, changing and difficult to evaluate databank be organised before it is made available to professionals and secondarily to lay people?
Among all the possible causes of birth defects, drugs have been the subject of increasing awareness since the thalidomide disaster in the early 1960s. Most pharmacotherapeutic agents, when used properly in therapeutic doses, have not shown any developmental toxic potential. A limited number of drugs, e.g. the anticonvulsants phenytoin and valproic acid (sodium valproate), have been associated with a significantly increased risk of malformations. Very few medicinal products, such as the retinoids, have been associated with a high risk of malformations. Confounding factors, like heredity, smoking, alcohol (ethanol) consumption and working conditions, have to be taken into account in exposed pregnancies before a causal relationship can be established.

Evaluating whether a new drug is a significant human teratogen is in many ways more difficult than assessing other forms of toxicity. It is not possible to use laboratory tests as indicators for a graded response of adverse effects, as can be done for potentially nephro- or hepatotoxic drugs. No or very few data on pregnancy outcomes are generated in clinical trials, since women of child-bearing potential not taking contraception are usually excluded. After approval, there is no systematic post-marketing surveillance of exposed pregnancies, and this results in an over-representation of recorded adverse outcomes while little information is available on the number of pregnancies with normal outcomes. Furthermore, in contrast to other types of organ toxicity, a teratogenic drug usually only causes malformations during a restricted period (weeks) in early pregnancy. It is also important to assess the risk to the fetus and neonate of adverse effects other than malformations. These could be effects on the developing central nervous system, which may not be observed until early childhood (e.g. as retarded development or learning difficulties).

In view of these difficulties, in the early phase of the life cycle of a drug, evaluation of teratogenicity and other developmental toxic effects has to be based on results from animal reproduction studies. Results from animal studies cannot, of course, be uncritically extrapolated to humans. When assessing findings (or absence of findings) in animal studies several factors have to be taken into consideration:

- What is known about metabolism and pharmacokinetics in the species studied?
- Is the administration route relevant?
- At which plasma concentrations are adverse effects/no effects observed?
- How do these plasma concentrations relate to human therapeutic concentrations?
- Are the observed adverse effects a class effect for all pharmacological substances of this type?
- What is the mechanism behind observed adverse effects (e.g. maternal toxicity, evidence of direct embryo/fetotoxicity, death of offspring secondary to impaired maternal care)?
- Is the mechanism of relevance to humans?

These issues illustrate the great difficulties – and the different types of knowledge needed in clinical disciplines, epidemiology, pharmacology, toxicology, pharmacokinetics and experimental teratology – when evaluating the potential of a specific drug to cause developmental toxic effects. It is almost impossible for the prescribing physician or the patient to self-assess the risk for developmental toxicity on the basis of available human and animal data. Nevertheless, it is appropriate for society and the pharmaceutical industry to try to define any such risk to the fetus and child which are related to the use of drugs.

In Sweden, a classification system based on clinical and animal data was implemented in 1978, with the aim of providing clinically useful information to prescribing doctors and other professionals responsible for pharmacotherapy.1,2 Accordingly, since 1978 the Swedish catalogue of approved drugs (FASS) has contained information on possible risks associated with the use of individual drugs during pregnancy and lactation. The classification is subject to continuous follow-up and re-evaluation by a teratology review panel, made up of people from the abovementioned disciplines.

In this article the Swedish system is presented, together with some indications that it is achieving