Teratogens and Teratogenesis: General Principles of Clinical Teratology

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ABSTRACT

Numerous factors hinder our ability to recognize fully human teratogens. Among these are the limitations of animal and epidemiologic studies, the lack of understanding of the mechanisms of action of most teratogens, and the variability in expression of the clinical manifestation. Dose and timing of exposure, interactions with other environmental agents, and host susceptibility influence this variable expressivity. Recent studies suggest the genetic constitution of the mother and the fetus play a central role in the teratogenic response. Techniques currently being developed may help in a near future to identify susceptible individuals and to prevent specific types of drug-induced birth defects.

Introduction

In 1941, Gregg reported the association of cataracts, deafness, and congenital heart disease in the offspring of women exposed to rubella during gestation. Until then, it was generally believed that the placenta isolated and protected the conceptus from the detrimental effects of environmental factors. The thalidomide tragedy further demonstrated the fallacy of this concept. Today, it is a well-recognized fact that exposure to certain environmental agents may represent a hazard to the fetus. However, there is a sharp contrast between the widespread exposure to potentially teratogenic drugs, chemicals, and environmental pollutants prevalent in our society and the small number of disorders known to be caused by these agents. In fact, the teratogenic potential of most of these substances remains largely unknown mainly because of the problems that beleaguer their study in man. Interspecies and intraspecies differences in the susceptibility to the effects of teratogens hinder the extrapolation of data from animal studies to humans. Most epidemiologic studies are fraught with methodologic problems and often lack the sensitivity to identify low degree teratogens. Lack of understanding of the pathogenesis of most teratogens limits the recognition of biologically sound associations and, consequently, our ability to discriminate between true causal relationships and chance occurrences. In addition, the well-recognized variability in phenotypic expression in environmentally-induced patterns of malformation further complicates the recognition of human teratogens.
Clinical Expression

The effect of teratogens on human development follows a limited repertoire of pathogenic mechanisms. This includes excessive or reduced cell death, interference with cell interactions, decreased biosynthesis, abnormal morphogenetic movements, and disruption of tissues. These general pathways are common to different agents. Therefore, it is not surprising that a wide range of teratogens produce similar types of developmental defects, including infertility or embryonic/fetal loss, intrauterine growth deficiency, abnormal central nervous system (CNS) performance, and abnormal morphogenesis. The potential carcinogenic and mutagenic effect of some teratogenic agents should be added to this list, although their mechanisms of action are different. Cancer and mutation induction, as mentioned later on, are stochastic phenomena induced by changes in DNA and, as such, can result from damage to a single cell.

Fifteen to 20 percent of recognized pregnancies terminate spontaneously before the 20th week of gestation, and many of them exhibit developmental abnormalities. Chromosomal aberrations are responsible for most of these abortions, but environmental factors may account for some of them since the human conceptus is most vulnerable to the deleterious effect of teratogenic agents during the first eight weeks of prenatal development. Animal studies at comparable stages have amply demonstrated that death and malformations are most likely to be induced during this period.

While it is well-recognized that teratogens produce growth retardation in addition to resorption and malformations in experimental animals, the effects that most drugs used in pregnancy have on human fetal growth are unknown. However, if one classifies cigarette smoking and alcohol as drugs, teratogens are among the most prevalent causes of intrauterine growth retardation.

Growing attention to the non-structural abnormalities produced by prenatal exposure to known teratogens has led to wider recognition and more precise delineation of the behavioral problems that may be associated with these agents.

Clinical studies have demonstrated that: (1) teratogens rarely produce single anomalies; (2) no single anomaly is specific for any given teratogen; (3) teratogens generally produce specific patterns of malformation; (4) variability of expression is the rule rather than the exception; and (5) not every pregnancy exposed to a teratogenic agent during the critical period and at doses above the threshold will result in an abnormal offspring. This is true even for thalidomide, one of the most powerful teratogens known to man. Paucity of reliable epidemiologic data makes any statement about the risk factors for this drug at best speculative. However, even the highest estimates place the chances of an abnormal offspring following exposure during the critical period below 50 percent.

Factors Contributing to the Variability in Expression

The cause of the variability in phenotypic expression of most teratogens remains largely undefined. However, as noted by Wilson as well as other investigators, data on both animal and human studies suggest that the following factors play major roles in its determination: (1) dose of the agent; (2) timing of exposure; (3) interaction with other environmental factors; and (4) host susceptibility.
Since teratogenesis is a threshold phenomenon, the dose of a teratogen is one of the essential determinants in the prenatal effect of drugs and chemicals. To produce a teratogenic effect, a drug must surpass a specific level.\textsuperscript{4,22} As an example, 50 mg of thalidomide, if given during the critical period, can affect the majority of embryos in a litter, but 0.5 mg will have no effect. Conversely, almost any drug, if administered at a sufficiently high dose, can adversely affect embryonic and/or fetal development. Furthermore, as noted by Brent, teratogenesis is a multicellular phenomenon and both the incidence and the severity of malformations increase with the dose. This is in marked contrast with carcinogenesis or mutagenesis, which are stochastic phenomena.\textsuperscript{4} It should be noted also that the dose determines maternal serum concentration and, hence, the rate of diffusion of most compounds through the placenta. This is specially significant because passive diffusion is the primary mechanism of transfer of drugs through the placenta.\textsuperscript{39}

Major structural defects occur when exposure to a given teratogenic agent takes place during the critical period of development. This period is relatively short, only lasting eight weeks. During the preimplantation period, when the blastocyst lies free within the uterine cavity, exogenous agents may kill the embryo, but there is no evidence that they produce malformations. At this stage, because of the pluripotency of some of its cells, it is possible for the conceptus to overcome minor damage.

During the embryonic period, each organ system undergoes a critical stage of differentiation, which occurs at a precise moment. It is at these specific times that the developing embryo is most vulnerable to the effect of environmental agents and that specific malformations can be produced. The critical period ends by the 56th day of gestation, when most differentiation has been completed. This is followed by the fetal period, during which the most important events are accrual of body mass, reduction of the umbilical hernia, closure of the palate, differentiation of the genitalia, and histogenesis of the CNS, which is completed in post-natal life. Therefore, exposure to teratogens during the fetal period does not produce a pattern of malformation with multiple organ involvement. Instead, it may result in varying degrees of intraterine growth retardation and defects of the areas undergoing completion of their morphogenetic processes, including abnormalities in the histogenesis of the central nervous system.\textsuperscript{40}

The concurrent administration of two or more drugs or chemicals may influence the effects of a teratogen.\textsuperscript{21,33,39,43} The interactions between the chemicals can be either homergic—when the chemicals produce the same overt effects—or hetergic—when one of the chemicals produces an effect and the other causes synergism or antagonism.\textsuperscript{33} Recent studies suggest that perhaps the most important factors in the response to teratogens are the genetic constitutions of the mother and the fetus. It is a well established fact that the unequal sensitivity of different species and strains to the teratogenic effects of a given environmental agent depends largely on their genetic constitution.\textsuperscript{8,31,32} As noted by Kalter, this interspecies and intraspecies variability may be manifested in a number of ways: (1) an environmental agent may have a teratogenic effect in some species and be innocuous in others; (2) it may cause the same type of abnormalities in different species, but with varying incidence and severity from one species to another; and (3) it may cause dissimilar defects in different species.\textsuperscript{17}

While the source of this variability is
believed to be genetic, its basic mechanisms are not yet fully understood. Fraser suggested that the different rate of cleft palate induced by cortisone in the Ajax (100 percent) and the C57BL mice (18 percent) can be explained by the multifactorial/threshold model. He based this assertion on the correlation between timing of palate closure in untreated embryos and the frequency of cleft palate in embryos exposed to cortisone or 6-aminonicotineamide.  

On the other hand, Goldman et al attribute the differences in the incidence of cortisone-induced cleft palate in inbred mouse strains to the number of steroid receptors present in each strain. Others have suggested that the interspecies and intraspecies differences in response to a teratogen may be due to genetically determined differences in metabolic rates and pathways. For example, Chlorcyclizine, an antihistaminic drug, is teratogenic in rats but not in humans. The drug is metabolized to norchlorcyclizine in both species, but the steady state level of the metabolite is approximately three times higher in the rat than in man, which may account for the disparity of response. Differences in metabolic pathways and resultant metabolites may be responsible for the dissimilar defects caused by imipramine in experimental animals of different species.

Teratogenicity results from the formation of an epoxide metabolite and its subsequent covalent binding to fetal rat macromolecules. They inhibited the activity of the hydratase controlling the rate of transhydrodiol formation from phenytoin and showed that the amount of covalent binding of this arene oxide correlated with the severity of malformations. These, as well as other studies, suggest that the rates of formation and detoxification of these reactive metabolites are under genetic control. Shum et al studied the teratogenic effect of benzo[a]pyrene (BP) to test this hypothesis. They used inbred mouse strains with high and low cytochrome P450 inducibility, which is under the control of a single gene, the Ah locus, and showed that differences at this Ah locus correlated with teratogenesis. In mothers with low P450 inducibility, fetuses heterozygous at the Ah locus had more resorptions, deaths, growth deficiency, malformations, and reactive BP metabolites than fetuses from the same uterus homozygous for high inducibility. When the mother had high cytochrome P450 inducibility and activity, there was no difference between fetuses with high or low cytochrome P450 inducibility. This demonstrates, first, that the fetuses producing the largest amounts of BP reactive metabolites, because of their genetic constitution, were the most severely affected and, second, that the mother's genotype can determine ultimate fetal outcome.

In humans, the capacity of the liver to metabolize drugs may be less limited than in other species. In vitro studies have demonstrated the presence of a microsomal drug-oxidizing enzyme system in human fetal liver early in gestation, and recent works suggest that hydratase dehydrogenase may be found in liver peroxisomes. Buehler and Delimont observed decreased epoxide hydratase levels in children with stigmata of Dilantin teratogenesis and suggested that the enzyme deficiency follows an autosomal recessive pattern of inheritance. Using an in vitro assay, Strickler et al demonstrated an increase
in arene oxide metabolites in children with phenytoin-induced malformations.37 These studies have opened a new chapter in our understanding of the basic mechanisms of teratogenesis. Refinement of these techniques may allow, in a near future, the identification of susceptible individuals and thus help to prevent the occurrence of some drug-induced birth defects.

References


