44 Principles of teratology of drugs and radiation

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Teratology is the study of birth defects. In this chapter, the potential of drugs and radiation to produce birth defects in humans will be explored. Wilson (1) has estimated that of all human malformations, less than 1% are due to radiations and 4% to 6% are due to drugs and environmental chemicals.

Whether an agent produces a teratogenic effect is dependent on the timing of the insult. The teratologic literature is usually reported in post-conception weeks. Clinical dating is always 2 weeks greater than post-conception dating as it is based on the patient's last menstrual period or ultrasound measurements, which are reported in menstrual weeks. To avoid confusion, all timing of teratogenic exposure will be discussed in menstrual weeks. The conceptus is relatively resistant in the first 2 weeks of its existence (menstrual weeks 3 and 4) when either no effect or loss of the pregnancy is the major outcome of exposure to teratogenic agents. During this time period, the embryo has sufficient reparative powers, if not destroyed, to recover and few malformations occur. The most likely times for chemical teratogenesis are menstrual weeks 5 to 12 inclusive, which corresponds to the time of major organ differentiation. For radiation injury, the most likely times for exposure are menstrual weeks 10 to 17 inclusive (2), which correspond to the time of maximum neuronal cell proliferation and migration to the cerebral cortex. No gross malformations due to radiation have been seen in humans without the child exhibiting growth retardation, microcephaly, or gross eye malformations. After the time of gestation of maximal sensitivity, the effects of teratogens in general are to produce growth retardation (3–6). After 27 menstrual weeks, based on atomic bomb survivors, there is no proven risk of central nervous system effects, specifically severe mental retardation from the radiation (7,8).

The criteria for a human teratogen are listed in Table 1 (9). In addition to these criteria, the existence of a dose–response relationship supports the contention that an agent is a teratogen. Thus, for a teratogen with increasing dose of the exposure, there should be an increase in the number or severity of defects produced. Also it should produce similar defects in experimental animal systems.

DRUGS AS TERATOGENS

Drugs that fulfill the criteria for a human teratogen may produce their effect directly, indirectly, or through a toxic intermediate. Direct-acting teratogens cause damage in their native form and require only access to the conceptus to do harm. An example of direct-acting teratogens are cytotoxic antineoplastic agents, which cause direct cell damage leading to cell death, which may result in malformation or pregnancy loss.

Indirect-acting teratogens act by perturbing maternal homeostasis to produce damage. Narcotic analgesics are not

themselves teratogens; however, they can act as indirect teratogens when taken in sufficient doses to produce maternal hypoxia from respiratory depression. Hypoxia then acts directly to produce malformations by causing cell death in the developing conceptus. Therefore, by acting to compromise maternal respiration, narcotics may act as indirect teratogens.

Unlike the first two methods by which a drug can act as a teratogen, those drugs whose teratogenic potential is expressed through a toxic intermediate are not as readily predicted by animal experiments. This is because there are many pathways by which drugs may be metabolized and these may vary between species or even between individuals of the same species. The developing field of pharmacogenetics is expanding our knowledge of these differences. However, because of this variation, the toxic intermediate may not be produced in all individuals or species. A teratogen acting through a toxic intermediate may be a human teratogen and not one in animal species usually tested, or vice versa. An example of a human teratogen that would fit into this class is thalidomide, which is not a teratogen in the guinea pig.

In addition to the difficulty in extrapolating from animal experiments to man, there are other difficulties with fulfilling the criterion of Table 1. The drug in question might prevent the loss of an already malformed fetus. The condition for which the drug is used might produce the malformation. The fetal malformation might cause maternal symptoms for which the drug is taken. Finally, the drug may be commonly used in combination with other drugs that produce the malformation or only a combination of agents, not the individual agents by themselves, might produce the malformation.

Because of these difficulties and the sometimes poor quality of data, differences exist between experts on the teratogenic potential of many agents in humans. An additional reason for conflict in expert opinion on human teratogens is the reason for which the assessment was made. If one wishes to counsel a pregnant woman already exposed to an agent as to its teratogenic potential, then it is appropriate to ignore the potential therapeutic benefit of the agent and use only the information on birth defects available on it (10). If, on the other hand, one wishes to prescribe a medication for a condition during pregnancy, it is appropriate to use an assessment that balances the therapeutic benefit to the teratogenic risk. The FDA pregnancy categories (11) are an attempt at such an assessment (Table 2).

It has been reported that one in five women use FDA class C, D, or X drugs at least once during pregnancy (12). As the FDA classification system is extensively used, it is important to recognize its limitations. It is not a teratogenic risk classification. It is a fetal risk classification, which includes both teratogenic risk and the risk of fetal harm by the drug later in pregnancy. It also does not include information on the point in

Table 1 Criteria for Recognizing a Human Teratogenic Agent (9)

- 1. An abrupt increase in the frequency for a particular defect or group of defects
- 2. Coincidence of this increase with a known environmental change, such as widespread use of a new drug or sudden exposure to a chemical or a source of radiation
- 3. Known exposure to the environmental change early in pregnancies yielding the characteristically defective infants
- 4. Absence of other factors common to all yielding infants with the characteristic defect or defects

Table 2 FDA Pregnancy Categories for Drugs (11)

- Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester; there is no evidence of a risk in later trimesters, and the possibility of fetal harm appears remote
- Category B: Either animal reproductive studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal reproductive studies have shown an adverse effect, other than a decrease in fertility, which was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters
- Category C: Either studies in animals have revealed adverse effects on the fetus, teratogenic or embryocidal or other, and there are no controlled studies in women, or studies in women or studies in women and animals are not available. Drugs of this class should be given only if the potential benefit justifies the potential risk to the fetus
- Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk as when the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective
- Category X: Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant

pregnancy when the risk occurs or if there is a dose threshold above which the harm occurs.

An example of the problems of the system can be seen by looking at vitamin A. Vitamin A is an essential fat-soluble nutrient and a known human teratogen. Its U.S. recommended daily allowance (RDA) for pregnancy is 8000 IU/day. Yet when taken in supplements during pregnancy of more than 10,000 IU/day, it is teratogenic (13). According to the FDA classification system, it should be category D or X. Vitamin A in large doses or severe deficiency is harmful to the fetus and this information is not conveyed by the FDA’s simple classification system. Recognizing this problem, Braggs, Freeman, and Yaffe (14) in their compendium have modified the FDA risk classes. In the case of vitamin A, they classify it as “A*” with the “*” footnote indicating category X if used in doses above the U.S. RDA.

There are several excellent compendiums of data on teratogenic risk (14–16) to which the reader is referred for details on specific agents. The most common human teratogens used today are listed in Table 3. These agents should be avoided in women who are pregnant or potentially pregnant. The most common agents that have teratogenic potential but whose therapeutic benefit outweighs their risk are listed in Table 4. When assessing maternal drug therapy in pregnancy, the first consideration is whether the drug is necessary for maternal survival or well-being. Once it is established that this is the case, the most effective agent with the least toxicity and the lowest teratogenic potential should be used in the appropriate dose. Vital therapy should not be withheld from a pregnant woman because of teratogenic risk.

RADIATION AS A TERATOGEN

Unlike drugs, radiation always acts directly on the conceptus to produce birth defects or pregnancy loss. For this reason, it is easier to extrapolate from animal experiments to the human condition for radiation defects. Ionizing radiation produces gross congenital malformations, intrauterine growth retardation, and embryonic death. All of radiation’s effects have a dose–response relationship and a threshold of exposure below which there is no difference between irradiated and non-irradiated populations. Only ionizing radiation has a clearly established teratogenic potential. Ionizing radiation dosage is reported in either Rads (rad) or Grays (Gy). One rad equals 0.01 Gy. To avoid confusion, all doses will be reported in rads.

Growth retardation and central nervous system effects including microcephaly, mental retardation, and eye malformations are the most prominent manifestations of intrauterine radiation exposure in humans. Severe mental retardation has not been observed in patients who received less than 50 rads in utero, and there has been no report of radiation-induced limb or other gross anomalies in humans where growth retardation or central nervous system anomalies were not also present (17). Mental retardation has never been seen with radiation exposure prior to 10 menstrual weeks of gestation in humans (2), in spite of the fact that major organ differentiation occurs from 5 to 12 menstrual weeks of gestation. Radiation exposure prior to 10 menstrual weeks results in a high rate of loss and therefore a wide range of malformations are not seen (2,17) although theoretically possible (18).

The gestational ages of 10 to 17 menstrual weeks represent the time when the maximum number of infants with mental retardation and central nervous system or eye defects are produced (2). At 18 menstrual weeks, or greater, few cases of mental retardation are seen (2); however, growth retardation continues to be produced. In humans, although malformations are not seen at doses of less than 50 rads, some disturbances of growth can occur with as little as 25 rads (17). However, at exposures in the range of 20 to 5000 mrad, which is the range of most diagnostic radiology studies, there is an extremely low risk of malformations when compared with the spontaneous rate for humans (17). The association of prenatal radiation exposure and childhood leukemia or other cancers remains to be determined (3–6). However, an increased incidence, 1.5 to 2.4 over the background rate, as a result of in utero exposure to radiation at the dosage ranging from

Table 3 Common Agents That Are Teratogens

Anabolic steroids
 Androgens
 Anticancer agents
 Diethylstilbestrol
 Etretinate
 Isotretinoin
 Oral hypoglycemics
 Vitamin A in large doses
 Vitamin D in large doses

Table 4 Agents That Have Teratogenic Potential But Are Used in Pregnancy Because the Benefit of Their Use Outweighs the Risk of Teratogenesis

Phenytoin
 Antimalarials
 Propylthiouracil
 Aminoglycosides
 Antituberculins

1 to 4 rads, has been reported (19,20). Since X-ray studies with 5 rads or less exposure to the conceptus carry a very low risk, and if medically indicated, it should be performed with the patient's informed consent (18); fetal dosages for some commonly used radiologic procedures are available through the American College of Obstetricians and Gynecologists Committee Opinion number 299 (7).

Special mention should be made of radioiodine during pregnancy. Iodine-131, if given in millicurie doses, can damage or ablate the developing fetal thyroid resulting in either congenital hypothyroidism or hypothyroidism of late onset (17). This can occur after the onset of the iodine-concentrating ability of the fetal thyroid at around menstrual weeks 10 to 12 of gestation (7). Radioiodine is therefore contraindicated in pregnancy.

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