Rhythms in Drug-Induced Teratogenesis

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Introduction

Despite the lessons to be learned from the thalidomide disaster some 20 years ago, recent studies indicate that pregnant women are still consuming therapeutic agents in alarming quantities. Moreover the developmental risks imposed by the maternal use of substances of abuse are, perhaps more than many other risk factors, preventable. The etiology of human malformations includes both (1) genetic factors and (2) drugs and environmental agents (for established teratogens see Brendel et al. 1985).

The influence a teratogenic drug has on the conceptus depends mainly on: (1) physical properties and metabolic patterns of the compounds. The situation is especially complex in the prenatal stage since maternal and fetal pharmacokinetic factors contribute to fetotoxic actions. Thus developmental toxicity involves the following parameters: maternal pharmacokinetics (including the rates of absorption, distribution, metabolic conversion and elimination), placental transfer, distribution within the embryonic or fetal organism, prenatal drug metabolism in the fetus, final concentration at the target cell within the fetal compartment. Thus agents may by direct or indirect mechanisms influence fetal development. (2) Developmental stage. Stage sensitivity indicates that susceptibility to teratogenesis varies during gestation. The most critical period in the development or growth of a particular tissue or organ is during the time of most rapid cell division. During the period of organogenesis (from day 18 through about day 60 of gestation in the human conceptus which corresponds to gestational days 7–13 in mice, e.g.) mammalian embryonic tissue is an especially sensitive target for attack by teratogenic insults. (3) Dose of compound. Dose-response relationships refer to the phenomenon that, as the exposure or dosage increases, frequency and severity of the teratogenic effect increase, as well. Also threshold effects are known. (4) Background genotype. (5) Physiological and pathological status of the mother.

Chronobiological Aspects in Teratology

Circadian influences on many biological systems have been well documented. Included among the phenomena which exhibit circadian rhythms in susceptibility are responses to drugs in adult organisms (Reinberg and Smolensky 1983). These rhythmic variations in drug response have been predominantly attributed to variations in pharmacokinetics relative to treatment scheduling.

There are only a few interesting and significant observations regarding the circadian phase influence of drug exposure on subsequent dysgenesis of the fetus. This has been reported for cortisone (Isaacs 1959), dexamethasone (Sauerbier 1986a), hydroxyurea (Clayton et al. 1975), 5-fluorouracil (Sauerbier 1986b), cyclophosphamide (Schmidt 1978; Sauerbier 1981, 1983), cytosine arabinoside (Endo et al. 1987) and ethanol (Sauerbier 1987, 1988).

While performing these teratological studies it will be worthwhile limiting the mating regimen of the animals to a few hours during a 24-h span to give an approximation of the embryonic age. Otherwise the variation in response may result from different developmental stages. This is of particular importance for animals with a short gestational period such as mice, e.g. Thus it can be clearly shown that the circadian phase of drug administration has a bearing on teratogenicity. Also the success rate of breeding is significantly dependent on the circadian stage, being greatest in the morning in mice (Sauerbier 1982).

In the following a short survey is given of those experimental studies that apply to the circadian phase dependent in utero exposure of potential teratogens with emphasis ethanol chronotoxicity.
Glucocorticoids

Glucocorticoids such as cortisone and dexamethasone are known to produce left palates in rodents at the time of palatal shelf closure (e.g., days 11–15 of gestation for mice). Significantly more cleft palates have been observed during the dark phase, particularly near the onset of the light phase as compared to the other circadian stages (Isaacson 1959; Sauerbier 1986a). In general the frequency distribution of cleft palates is negatively correlated to the circadian fluctuations in serum corticosteroid levels (Sauerbier 1986a), which in turn may be mediated by changes in the hypothalamic-pituitary-adrenal system as having a regulatory influence. Probably circadian-based hormonal effects that modify functional activity through membrane-receptor concentrations may influence teratogenesis (Sauerbier 1989).

Anticancer Drugs

Hydroxyurea

Clayton et al. (1975) have examined the teratogenic effects of 750 mg/kg hydroxyurea in rat fetuses following maternal treatment on day 12 of gestation. The incidence of deformities (most common malformations, digital and limb defects) is greatest during the light phase with the maximal amplitude at the dark to light transition. The temporal pattern of teratogenesis has been found to be correlated with motor activity, mitotic rates and DNA synthesis.

5-Fluorouracil

Circadian variability of fetal tissues to 5-fluorouracil toxicity has been observed in mice (Sauerbier 1986b, 1989). One hundred percent of the embryos were malformed (mainly digital defects and kinky tail) by the 1400 hours injection of 30 mg/kg on day 11 of gestation whereas 78.2% are so affected when the drug is given at 0100 hours (fetal loss, 32.2% vs. 16.7%).

Cyclophosphamide

Cyclophosphamide is widely used as a cancer chemotherapeutic agent and as an immunosuppressant. Its use is associated, however, with certain undesirable or toxic effects including fetal malformations. The developmental toxicity of cyclophosphamide has been studied in a variety of mammalian species (Chernoff et al. 1989), which is manifested as lethality, weight reduction and/or a spectrum of external malformations including digital defects, encephalocele, cleft palate, open eyelid, abnormal vertebral