Dev. Reprod. Vol 5, No 2, 2002(Suppl). pp 51

An Effects on Teratogenicity by Exposure with Cyclophosphamide during Early Organogenic Period

Seung Jun Kwack,, Gyu Seek Rhee, Soon Sun Kim, Kyung Hee Sohn, Soo Young Chae, Chul Hoon Park, Yo Woo Choi and Kui Lea Park

Division of Reproductive & Developmental Toxicology, National Institute of Toxicological Research, Korea Food and Drug Administration, Seoul, Korea.

INTRODUCTION

Cyclophosphamide, a commonly used anti-cancer and immunosuppressive agent, is a well known teratogenic compound in animals. The effects on male fertility and female pregnancy have been largely studied in animals treated with cyclophosphamide. However, the relationship between the effects of maternal cyclophosphamide treatment on specific day of organogenesis and the pregnancy outcome is unknown. Therefore, we investigated the relationship in pregnant female Sprague-Dawley(SD) rats administrated intravenously with cyclophosphamide during early organogenic periods(10, 11, or 12 days of gestation).

MATERIALS and METHODS

Adult SD male rats and virgin female rats were obtained from the KFDA Laboratory Animal Resources under SPF-conditions. After 1 week acclimatization, males were mated overnight with untreated females(mating ratio, 2:1, ♀:♂). After mating, vaginas of the untreated females were flushed with saline to assess the present of spermatozoa and the day when sperm were found in the vagina was designated Day 0 of gestation. Each experimental group was assigned to 5 animals. Pregnant female SD rats administrated intravenously with cyclophosphamide(5, 10, 20, and 40 mg/kg), which was dissolved in sterile saline solution, at 10, 11, or 12 days of gestation. Pregnant dams were caesarean sectioned at gestational day 20 and investigated the pregnant index of mother and the viability, weight, sex, and type of malformations of fetus.

RESULTS and DISCUSSION

Cyclophosphamide dose-dependently decreased the relative and absolute weight of liver and spleen, but increased the relative weight of right and left kidneys in dams. The number of live fetus was not observed at 10 days of gestation in doses of cyclophosphamide 20 and 40 mg/kg and at 11 days in doses of 40 mg/kg. Among the external malformations of fetus, the excencephaly was prominent by treatment with cyclophosphamide. Although the rate and intensity of malformations induced by cyclophosphamide were highest at day 12 and lowest at day 10 of gestation, the teratogenic potency of cyclophosphamide was significantly increased in dose- dependent manner. These results suggest that the exposure by cyclophosphamide at specific gestational period plays an important role in teratogenicity. And the fetal toxicity is very potent during early stage in period of organogenesis by exposure with cyclophosphamide.