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Sperm Toxicity Evaluation after Cyclophosphamide Treatment in Rabbits

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Sperm toxicity test is an essential endpoint in fertility and early embryonic development study among preclinical tests of newly developed drugs. Generally, the rat has been used as an animal model to evaluate effects of chemicals on male reproductive system in human risk assessment. However, other species are needed if rats cannot be used in sperm analysis because of chemical properties. In this study, we carried out sperm toxicity test using rabbits. Cyclophosphamide monohydrate (CPM) was selected as reference sperm toxicant. In the single dose toxicity study, fifteen healthy and sexually mature New Zealand White male rabbits weighing 3.9-4.9 kg, aged 8-10 months, were assigned to the vehicle control, 60 and 120 mg/kg groups. The vehicle control group received only 5 % DMSO in saline. All animals died in the 120 mg/kg group and one death and a decrease in body weight were observed in the 60 mg/kg group. These were considered to be treatment-related. No treatment-related clinical signs were examined in the 60 mg/kg group. There were no treatment-related changes in sperm concentration, motility and morphological abnormality of ejaculated semen in the 60 mg/kg group. In the 4- day repeated dose toxicity study, 10 healthy and sexually mature male rabbits weighing 3.3-4.6 kg, aged 7 months were selected. CPM was given subcutaneously at dose levels of 0 and 30 mg/kg/day for 4 days. The vehicle controls received only physiological saline. Semen analysis was conducted at 0, 32, 46, 61, 74 and 81 days after final treatment. One animal died in the 30 mg/kg group. Opacity of eyeball, no stool, emaciation and a decrease in locomotor activity were observed in 1 animal of the 30 mg/kg group. A decrease in body weight was seen from days 11-81 after treatment in the 30 mg/kg group. Sperm concentration and motility were decreased on day 61 after treatment in the 30 mg/kg group, while the incidence of morphological sperm abnormalities compared well between the groups. It was concluded that CPM can induce sperm toxicity in the later phase only after one spermatogenic cycle in rabbits.

Keyword: sperm toxicity, cyclophosphamide monohydrate, rabbits