

## EFFECT OF IN UTERO OR NEONATAL EXPOSURE OF FLUTAMIDE ON THE REPRODUCTIVE DEVELOPMENT IN MALE RATS

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Flutamide is an anti-androgenic drug used in treatment of prostate cancer. In this study, we compared the effect of in utero or neonatal exposure of flutamide on the reproductive development in male rats. On gestation days 10- 19, pregnant Sprague-Dawley (SD) female rats were injected sc with flutamide 0, 1, 12.5 or 25mg/kg/day. Neonatal male rats were injected sc on days 5-14 after birth with flutamide 0, 20, 100 or 500µg/animal. Corn oil was treated to control group. The reproductive organ weights, expression of steroid hormone receptors, serum level of testosterone and testis descent were examined. In utero exposure of flutamide (12.5, 25mg/kg/day) caused hypospadias, cryptorchidism, agenesis of prostate and Cowper's glands, retained nipples and decreased anogenital distance. Flutamide (12.5, 25mg/kg/day) also produced gonocyte degeneration in fetal testes. Flutamide (25mg/kg/day) significantly decreased the weight of testes, epididymis, seminal vesicles and *levator ani plus bulbocavernous* compared to those of the control. In addition, the serum level of testosterone was slightly increased. In testes androgen receptor (AR) and estrogen receptor (ER) protein expressions were increased but SF-1 protein expression was unaffected. Flutamide given to neonatal male rats for 10 days delayed testes descent and induced a significant decrease of the weights of ventral prostate, seminal vesicles and Cowper's glands only at highest dose of flutamide (500µg/animal), whereas the weight of the testes and epididymis were not changed. Neonatal exposure of flutamide significantly decreased the AR expression in testes dose-dependently, but ER and SF-1 protein expression were not affected. Our data suggest that flutamide, an anti-androgenic compound, induces imperfect male sexual organ development and in uterus exposure is more affective than neonatal exposure.

Key words: Flutamide, Male reproductive tract, Steroid hormone receptor, Testes