ADVERSE EFFECTS OF A CLINICALLY RELEVANT DOSE OF HYDROXYUREA USED FOR THE TREATMENT OF SICKLE CELL DISEASE ON MALE FERTILITY ENDPOINTS

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Abstract: This study was designed to evaluate the effect of a clinically relevant dose of hydroxyurea (HU) on testis and epididymal function of sickle cell patients using a transgenic sickle cell mouse strain (Tg58xTg98) hereafter referred to as transgenic sickle cell mouse (TSCM). Adult male TSC mice were randomly assigned to a treatment or a control group (N = 12/group). Treatment consisted of 25 mg/kg body weight of HU administered by oral gavage, seven days a week for a maximum of eight weeks. Control TSC mice received the vehicle for HU (saline) as described for the treatment group. Six treated and control animals were anesthetized on day 28 or 56 post initiation of study, with isoflurane followed by a mid-ventral laparotomy to permit blood collection from the inferior vena cava. Sera were extracted from blood samples by centrifugation at 1000 x g for 10 minutes prior to being stored at –20°C until used for quantification of circulatory testosterone concentrations. Subsequently, testes and epididymides were recovered and weighed, cauda epididymides were excised, and stored spermatozoa were recovered for the assessment of sperm density and motility in Whitten’s medium (Whitten and Biggers, 1968; J Reprod Fertil 17:399). The right testis of each HU-treated and control TSCM sacrificed on day 56 of the study, were fixed and submitted for histopathology. Hydroxyurea exhibited toxicity to the testis of treated mice as exemplified by decreased mean testis weight (P<0.05; treatment x time interaction) during the two time periods studied compared with controls. Furthermore, this therapeutic agent also decreased serum testosterone concentrations, epididymal weights as well as sperm density, (day 56: 4.0 ± 2.3 x 10⁶) compared with controls (13.0 ± 2.9 x 10⁶; P<0.05). Progressive sperm motility was also adversely affected by HU on the second month of treatment (2.50 ± 0.50%; P<0.05). Four out of five of the treated animals had moderate degenerative seminiferous tubules with only Sertoli cells and cell debris remaining in most of the tubules compared with controls which, did not show any signs of degenerative seminiferous tubules. These data demonstrate that HU perturbs testosterone synthesis and release, the process of spermatogenesis and epididymal maturation, probably due to inhibition of macromolecules such as DNA, RNA and proteins required for functional sperm production.

Keywords: Hydroxyurea, testosterone, testis toxicity, epididymis, sperm motility, sperm density

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