EFFECT OF BICALUTAMIDE; AN ANTIANDROGEN, ON TESTICULAR WEIGHT IN ADULT RATS

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ABSTRACT

Objective: To study the effect of Bicalutamide on testicular weight in adult rats.

Study Design: Laboratory based randomized controlled trial.

Place and Duration of Study: Anatomy Department, Armed Forces Postgraduate Medical Institute (AFPGMI), Rawalpindi, Pakistan in collaboration with National Veterinary Laboratories (NVL), Islamabad, Pakistan from April to May 2008.

Material and Methods: Forty adult male healthy Sprague Dawley rats with no physical deformity weighing 200-300 grams were randomly divided into two groups (A and B), each consisting of 20 animals each. Group A was taken as control group and was administered 5 ml of distilled water orally daily for 24 days while group B (experimental group) was given 5 ml of distilled water daily containing bicalutamide 10 mg/kg/day for 24 days. All the animals were sacrificed on the next day after the last dose. The testes were taken out and weighed. In addition to initial and final weights of the animals, weights of right and left testes were also taken, and their average was taken as a reading for that animal.

Results: Statistically significant difference was found in reduction of testicular weights in the testes of experimental group (1.112 ± 0.018 g) when compared with the control group (1.169 ± 0.011 g).

Conclusion: The results obtained showed that the mean testicular weight of the testes was significantly reduced in the experimental group thus confirming that bicalutamide reduces testicular weights in the Sprague – Dawley rats.

Keywords: Antiandrogen, Bicalutamide, Rats, Testicular weight.

INTRODUCTION

Testes secrete several sex hormones which are collectively called androgens including testosterone (main testicular hormone). Testosterone is synthesized from cholesterol in the leydig cells or is formed directly from acetyl coenzymes and constitutes 20% of total mass of the testis. Hypothalamus secretes gonadotrophin releasing hormones (GnRH), which in turn stimulates the anterior pituitary gland to secrete leutinizing hormone (LH) and follicle stimulating hormone (FSH). Leutinizing hormone is the primary stimulus for secretion of testosterone by the testes and FSH mainly stimulates spermatogenesis. Testosterone is essential for both mitosis and meiosis of germ cells whereas FSH is required for spermatid remodeling[1-5]. Androgens are essential for male development and the maintenance of male secondary sexual characteristics, such as bone mass, muscle mass, body composition and spermatogenesis[6]. Androgens act on their target cells via an interaction with androgen receptors (AR) resulting in direct regulation of gene expression[7].

In adult males, androgen is mainly responsible for maintaining libido, spermatogenesis, muscle mass and strength, bone mineral density and erythropoeisis[8]. The actions of androgen in reproductive tissues, including prostate, seminal vesicle, testis and accessory structures are known as androgenic effects, while the nitrogen-retaining effects of androgen in muscle and bone are known as anabolic effects. Use of antiandrogens can produce reduction in lean muscle mass while causing increase in fat

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mass due to increased insulin resistance as observed in patients of prostate cancer receiving antiandrogens[9-10].

The testes of mature rat lie in the scrotal sac located ventral to the anus. The testes are ovoid in shape, 2 centimeters long and about a little over 1 gram without epididymis. Within the testes are numerous seminiferous tubules where spermatozoa are produced.The length of seminiferous tubule per gram of testis is estimated to be 12.4 ± 0.56 meters[11].

Antiandrogens block the androgen receptors competitively by producing a different conformational change avoiding participation of testosterone in the cellular process. Antiandrogens commonly used in the treatment of prostate cancer in men, may cause impairment of spermatogenesis and thus may cause reduction in testicular weight.

Since a part of original research by the author already published[12] the author has already established the suppression of spermatogenesis by bicalutamide (an antiandrogen) in adult male rats, therefore, present study was carried out to see the effect of antiandrogens on testicular weight in adult rats.

MATERIAL AND METHODS

The study was conducted at the Anatomy Department, Armed Forces Postgraduate Medical Institute (AFPGMI), Rawalpindi in collaboration with National Veterinary Laboratories (NVL), Islamabad from April to May 2008.

Forty adult male Sprague Dawley rats weighing 200-300 grams, were taken. Animals were divided into two study groups. They were kept in separate cages labeled as group A (control) and group B (experimental). The cages were kept at standard temperature of $21^0 \pm 20^0$ C, and the animal room was maintained on 12 hour light/dark cycle. In this study only healthy and active animals with no physical deformity were included. Animals were selected and divided into two groups using non-probability, convenient sampling technique. They were assigned numbers from 1 to 40. Initial body weights (W1) were taken. Group A (control group) was administered 5 ml of distilled water orally daily for 24 days by oral lavage tube. Group B (experimental group) was administered 5 ml of distilled water containing bicalutamide 10 mg/kg/day for 24 days by oral lavage tube. All the animals were sacrificed on the next day after the last dose. The testes were taken out and weighed. Testes were examined by hand lens for colour, consistency and gross appearance. In addition to initial and final weights of the animals, weights of right and left testes were also taken, and their average was taken as a reading for that animal.

Statistical Analysis

Data was entered in a database using SPSS (Statistical Package for Social Sciences) windows version 13. Descriptive statistics were used to describe the data. The statistical significance of the difference of various quantitative changes between the experimental and control groups was evaluated by student t test. The difference was regarded statistically significant if the *p* value was equal to or less than 0.05. *p* value was found by means of t distribution table. In case of mean body weights, the comparison was done within the group by applying paired sample t test, and between the groups by independent sample t test.

RESULTS

Besides the weights of animals at the beginning and at the end of the experiment, absolute weight of testes and gross examinations were also carried out. All the animals survived and remained active during the duration of experimental period.

The mean initial and final body weights of the animals in the control group were 246.75 g ± 3.28 and 264.253 g ± 2.93 respectively (table 1) while in experimental group, the mean initial body weight was 249.15 g ± 2.26 and the mean final body weight was 271.95 g ± 1.83. Analysis of the mean initial and final body weights of the animals of both groups revealed significant

increase in final body weights in both groups with a *p* value of < 0.001.

The mean absolute testicular weight in the control group was 1.169 g ± 0.011 while the mean absolute weight of testes in experimental group was found to be 1.112 g ± 0.018 (table 3). The mean absolute weight of the testes in the experimental group was significantly lower than the control group with the *p* value of < 0.012 (table 2)

Table-1: Mean body weights (g) of animals of control and experimental groups

Groups	Initial	Final	Statistical significance of difference (*p* – value)
Control (A)	246.75 ± 3.28	264.25 ± 2.93	< 0.001
Experimental (B)	249.15 ± 2.26	271.95 ± 1.83	< 0.001

Statistical significant difference between group A & group B:
Initial body weights $p < 0.55$
Final body weights $p < 0.03$

Table-2: Mean absolute weights (g) of testes in the control and experimental groups

Groups	Absolute weight of testes (g)	Statistical significance of difference (*p* – value)
Control (A)	1.169 ± 0.011	0.012
Experimental (B)	1.112 ± 0.018	

Testes were pink, firm in consistency and ovoid in shape. Morphologically, there was no difference between the control and experimental groups.

DISCUSSION

In the present study, no change was found in the colour, consistency and appearance of testes in both groups, however, the difference was noted in the mean body weight of the animals as well as the weight of the testes.

The mean body weights of the animals in both control and experimental groups were increased, suggesting that bicalutamide had no effect on mean body weights. On the other hand the mean absolute weight of the testes itself in the experimental group was significantly lower than the control group. This finding suggests, that bicalutamide although had not reduced the overall weight of the animal, but, it had significantly reduced the absolute weight of the testes. This effect of reduction in testicular weight probably resulted because of reduction in spermatogenesis due to its selective antiandrogenic effect on organ weight. This finding is in contrast to an earlier study conducted by Chandolia et al[13] who found no effect of bicalutamide on testicular weight in adult rats. In their study, however, reduction in testicular weight was seen in GnRH antagonist (Gonadotrphin releasing hormone antagonist)

Figure-1: Photograph of the testis of the rat being weighed on an electronic weighing scale.

implying effect of blockage of hypothalamo – hypophyseal – gonadal axis.

In another study conducted by Leonelli[14], on effect of flutamide (another antiandrogen) in male rats, significant reduction in testicular weight was noted. In that study, the male rats were exposed perinatally to flutamide which damaged the organizational processes of sexual differentiations resulting in reduced organ weight. On the other hand in a study conducted by Macleod et al[15], male rats exposed to flutamide in utero were found to have no effect on testicular weight when measured in early puberty suggesting that androgen action postnatally is important in achieving the normal testicular weight.

Similarly in a study conducted by Marchetti and Labrie[16], the effect of daily treatment with flutamide on testicular function in adult male rats found no effect on testicular weight. Since the experiment was conducted for shorter duration of 10 days and that too with a smaller dose, it resulted in inconsistent result.

Our finding of reduced testicular weights after administration of bicalutamide is consistent with another study by Tinwell et al[17], where they measured testicular weights in rats treated with flutamide for 10 days. They found significant reduction in testicular weight for majority of treated animals. Similarly, reduction of testicular weight and associated histological changes were noted after administration of antiandrogen in an androgen stimulated testes of rats in a study conducted by Wason et al[18].

CONCLUSION

In the current study, although bicalutamide had no effect on the overall body weights of animals, but it certainly reduced the mean testicular weights in the adult Sprague – Dawley rats.

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