Proceeding S.Z.P.G.M.I. Vol: 27(1): pp. 23-26, 2013.

Effect of Finasteride on Hepatocyte Diameter

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ABSTRACT

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5 alpha-reductase, which belongs to one of a new class of drugs that is potentially useful in treating androgenetic alopecia (male pattern baldness), hirsutism and possibly acne. **Objectives:** To evaluate the effects of Finasteride on albino rat hepatocyte diameters. **Materials and Methods:** 52 male albino rats were randomly divided into two equal groups A (which was control) and B (which was experimental). Group B animals were given Finasteride 80 mg/kg body weight between 10-11 am, (provided by FEROZESONS laboratories) dissolved in normal saline, for 30 days through naso-gastric tube. The animals of the control group were given only normal saline through naso-gastric tube for the same period of time. Twenty four hours after the cessation of treatment Livers were collected from the rats of both groups after dissection. 10% Formalin solution was used to fix the liver. 5µm serial sections of liver were cut and stained with haematoxylin/eosin stains for detailed histological study of hepatocytes. **Results:** It was observed that in experimental group the diameter of hepatocytes was increased as compared with control group (p-value <0.001)**. Conclusion:** Finasteride was responsible for mild hepatocellular injury showing increase in the diameter of the hepatocytes.

Key words: Finasteride**,** Androgenetic Alopecia, Albino rat, Liver, hepatocytes.

INTRODUCTION

Finasteride is one of a new class of drugs, 5 alpha-reductase inhibitors that are potentially useful in treating benign prostatic hyperplasia, male-pattern baldness, hirsutism and possibly acne[1]. Finasteride can also be used to mask steroid abuse, and many professional sports have banned Finasteride use for this reason[2]. It was originally prescribed for prostate problems in doses of 5 mg orally. Based on theoretical models, it was expected that the use of Finasteride had also a positive impact on the growing cycle of the hair in men with androgenetic alopecia. Now days this drug is frequently used for the treatment of baldness[3]. Androgenetic alopecia can be defined as a 5 alpha DHT- dependent process with continuous miniaturization of androgen sensitive hair follicles[4]. Within hair follicles, prominent immunostaining of type 2, 5 alpha – reductase was localized in the in the inner layer of outer root sheath (ORS), inner root sheath, the infundibulum of hair follicle and sebaceous ducts[5]. Finasteride inhibits the transformation of testosterone into its active metabolite, dihydrotestosterone, in the target organs, *i.e.* the skin, scalp, liver and prostate. The conversion of testosterone to the active metabolite 5 alpha-dihydrotestosterone (DHT) depends on the presence of steroid Type II 5 alpha-reductase. Finasteride forms stable enzyme complex when it binds to Type II 5 – alpha reductase enzyme and blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone (DHT), resulting in significant decreases in serum and tissue DHT concentrations [6]. Finasteride is metabolized primarily via the cytochrome P4503A4 enzyme sub family in liver. In the pathogenic mechanism of hirsutism and androgenetic alopecia, important role is presumably played by alterations of the mechanisms which transform testosterone into dihydrotestosterone. Furthermore, both in animals and men with alopecia, the drug seems to have led

to an increase in the number and an improvement in the shape of the follicles in the anagen phase, and a simultaneous decrease of dihydrotestosterone at the level of the scalp[7]. Current evidence indicates that oral Finasteride therapy must be continued to sustain initial regrowth and subsequent slowing of hair loss; however, benefit of the drug should be reevaluated periodically. If improvement does not occur within the first year of Finasteride therapy, further treatment with the drug is unlikely to provide benefit [8]. As this drug is extensively metabolized in the liver and its extensive use by the men as self-medication without proper medical advice is increasing day by day and the possible consequences, led to an evaluation of the effects of chronic therapy with this drug.

The present study was designed to observe the effects of Finasteride in a dose of 80 mg/kg body weight for 30 days. Its effect was seen on the gross and histological features of liver in albino rats.

MATERIALS AND METHODS

52 male albino rats of wistar strain, weighing about 250-300 g were used and obtained from Veterinary Research Institute, Lahore. They were kept in cages for 15 days in the animal house for the purpose of acclimatization. A 12 hours light / dark cycle was maintained. The animals were allowed free access to food and water. The determined sample size for each group were 26 animals, which were randomly divided in two groups; A (control) and B (experimental).The dose schedule was as follows:

Group A (control)

This was the control group containing 26 albino rats and they were given 80ml/kg body weight of normal saline through N/G tube between 10-11 am.

Group B (experimental)

26 albino rats of this group were given Finasteride 80 mg/kg body weight between 10-11 am, (provided by FEROZESONS laboratories) dissolved in normal saline.

Dissection and fixation of liver

Twenty four hours after the cessation of treatment, the animal of all the groups were killed by euthanasia using pentabarbitol intraperitoneally with dose of 200mg/kg. The body weight of each animal was recorded before dissection. The liver was identified and cut after ligating the vessels. The liver was weighed and observed for any gross abnormality and was preserved in 10% formalin for histological evaluation. All four lobes of liver were placed into individual cassettes and processed in automatic tissue processor then embedded in paraffin. The central portions of the blocks were sectioned at 5 micron intervals with rotary microtome. The sections were mounted on glass slides, deparaffinized, hydrated and stained with haematoxylin & eosin. Diameter of hepatocytes was measured using 40x lens of light microscope using linear and squared ocular graticule. Ten hepatocytes having well defined boundaries and similar sizes were selected on each slide. Maximum diameters in two directions were taken. Diameters of control group A were taken as reference. The diameter of the hepatocytes of experimental groups was compared with the control group.

Statistical analysis

Diameter of hepatocytes was described by Mean±S.D and was analyzed by T-test using statistical package of Social Sciences (SPSS) version 16.

RESULTS

The mean diameter of hepatocytes was measured to be 17.5 µm (±2.0SD) in experimental group B and 12.1 µm (±0.50SD) in control group A. In this comparison it was observed that in experimental group the diameter of hepatocytes was increased as compared with control group and this difference was statistically significant (p-value <0.001, Table.1, Fig.1)

DISCUSSION

Finasteride, is a specific inhibitor of steroid Type II 5 alpha-reductase, an intracellular enzyme present in high concentrations in the prostate,

Table 1: Effect of Finasteride compared for diameter of hepatocytes (µm) in the liver of experimental group B with control group A

	Groups		T-test
	Experimental	Control	
Mean diameter of hepatocytes (µm)	17.5	12.1	T = 13.27
Standard Deviation	± 2.0	±0.5	P < 0.001
Minimum	15.4	11.4	
Maximum	25.1	12.8	

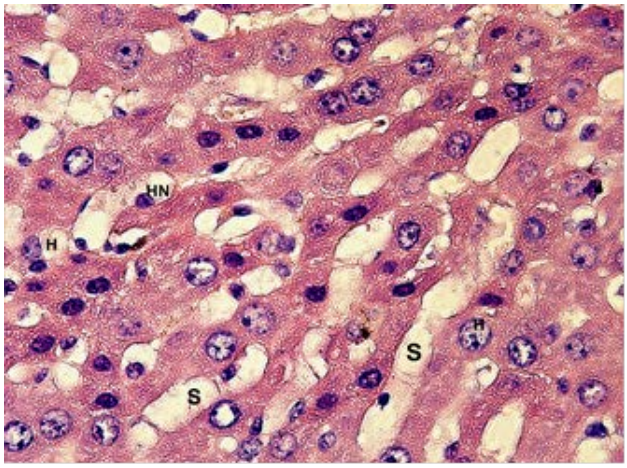

Fig. 1: Photomicrograph of rat liver of experimental group B showing hepatocytes (H) H&E 40X

seminal vesicles, epididymis, liver, and is detectable in the inner root sheath of hair follicles and epidermal keratinocytes [9].The conversion of testosterone to the active metabolite 5 alpha-dihydrotestosterone (DHT) depends on the presence of Type II 5 – alpha reductase. This drug is extensively metabolized in the liver in rat hepatic microsomes by hydroxylation at the t-butyl group (omega-OH Finasteride), followed by further oxidation to the corresponding acid (omega-oic acid Finasteride), with omega-aldehyde Finasteride as an intermediate. In a study, specific human cytochrome P450 (CYP) isozyme(s) involved in the in vitro metabolism of [14C] Finasteride using CYP isozyme-selective inhibitors and microsomes containing specific recombinant human CYP isozyme (expressed in human AHH-1 TK+/-cells) was identefied[10]. We hypothesized that the Finasteride in a dose of 80 mg/kg body weight for 30 days will affect the diameter of liver hepatocytes. In our study the diameter of the hepatocytes of the experimental group B was significantly increased as compared with the control group A (p-value<0.001).It may be due to the fact that toxic metabolites of Finasteride reacts with glutathione inside mitochondria and produces a localized depletion of glutathione that would result in oxidation stress. As oxygen tension within the cell decreases, there is loss of oxidative phosphorylation and decrease generation of ATP. The depletion of ATP results in failure of the sodium pump with influx of sodium and water, and cell swelling[11].

CONCLUSION

The present study was performed on the albino rats and revealed that Finasteride was responsible for destroying the normal architect of the liver and increase in the diameter of the hepatocytes, although these effects were observed at very high doses relative to the dose recommended for humans use. However it is suggested that frequent and unnecessary use of this drug should be avoided.

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