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Effect of Largactil on Physiology of Reproduction in Adult Male Rat

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Abstract

Largactil is a dopamine antagonist, serotonin and nor epinephrine reuptake inhibitor. Considering the importance of this drug in treating some nervous diseases, its side effects seem to be important on the endocrine axis. In this research the effect of Largactil was studied on the concentrations of testosterone, FSH and LH level and spermatogenesis. The experiment was done on 40 male Wistar rats strain that were divided to 5 groups of 8. The control group received nothing. The sham group was given distilled water as a solvent. The experimental groups were injected 50, 100 and 150 mg/kg of the drug orally for 21- days. The blood samples were taken at 22nd day and the concentrations of testosterone; FSH and LH were measured by RIA method. In addition, at the 22nd day, the testes were separated and histological changes were examined among experimental groups. The results were evaluated by using ANOVA and Duncan's test. The results showed that, 150 mg/kg of Largactil reduced serum testosterone level while it increased FSH and LH levels (P<0.05). Histological investigations of the testes showed a decline on spermatogenesis chain in dose of 150 mg/kg of the drug. According to our findings, Largactil decreases the concentration of testosterone level and the number of spermatogenic cells and increases FSH and LH levels at high doses. Also, it may weaken the function of reproductive activity.

Keywords: Largactil, reproduction, gonadotropin, spermatogenesis, rat.

Introduction

There is no clear mechanism for depression. Most researchers believe that some brain neurotransmitters decrease include dopamine, serotonin and nor epinephrine induce depression, thus we can say psychotropic agents are the elevators of these neurotransmitters[1]. Largactil is a dopamine antagonist drug and inhibits the reuptake of serotonin and noradrenalin form the synaptic cleft; this psychotropic agent has antidepressant and anxiolytic properties[2].

According to studies Largactil is effective in the treatment of major depression, long term anxiety disorder, insomnia, chronic pain and itching skin disease. Side effects of this drug on sexual function in men are including impotence, ejaculation difficulties and also there are some reports about galactorrhea and breast enlargement in both sexes[3].

Taking 3 and 6 (mg) of Largactil is efficient for treatment of adults which suffer from primary insomnia[4].

This drug according to its blood-brain barrier (BBB) permeability and because of antagonistic properties of H_1 receptor, is useful as on antihistamine for allergic patients[5], and is useful for management of mucositis pain in patients with cancer[6]. Largactil significantly decreases itching and erythema by blocking both H_1 and H_2 receptors[7]. Anorexia nervosa patients showed significantly higher of histamine H_1 receptor binding potential of Largactil in the amygdala and hippocampus[8]. According to findings in schizophrenia central histaminergic system increases, so Largactil can recoil function of this system as a H_1 receptor antagonist[9]. Antidepressant medications routinely prescribed to counter the manifestations of depression, are themselves associated with a range of adverse effects on sexual function such as erectile dysfunction, inhibited ejaculation and impotence[10,11].

According to new studies Imipramine, another drug of this family, has been shown to have a potent inhibitory effect on sperm motility (in vitro)[12].

Due to the fact that anti-depressant medication is now being blamed for causing male infertility and sperm DNA degeneration[13-16] and on the other hand because of depression increase among societies and prevalent usage of anti-depressant drugs like Largactil we tried to investigate the side effects of Largactil on pituitary-gonad and testis tissues.

We hope the results of our investigation be profitable to contemplate limiting policy when taking or prescribing this drug.

Material and Methods

In this research we selected 50 male Wistar rats with the body weight of 180-220 grams, and divided in 5 groups of 8: Each group maintained in a polycarbonate cage with the same unlimited food and water. The cages located in a room with 20-25 ˚c temperature and 12 hours light and dark situation. The 5 groups include control, sham and three experimental groups.

The rats of experimental groups 1, 2 and 3 received 50,100 and 150 milligrams Largactil per kilograms live weight per day (mg/kg/day) in oral way respectively, the other group's left untreated (control) or received an equivalent amount of distilled water as solvent during the experimental period of 21 days. 24 hours after the last treatment, all the rats anesthetized by ether and then blood samples took from heart by syringe directly and kept in a distinct tube with no anticoagulation agent. In the next step the samples centrifuged with the rate of 3000rotation/min. and finally the blood serums decreased from clots in order to serum LH, FSH and testosterone determination via RIA method. For histological studies of testis tissue the testes were cut off, weighted and kept in formalin for 17-18 hours and then microscopic slides were prepared and stained by Hematoxylin – Eosin.

Finally the data were statistically analyzed using the SPSS software. The means of sham and experimental groups were compared with the control group using the ANOVA and Duncan's multiple range tests. $p \leq 0.05$ was considered as a significant difference.

Results and Discussion

Largactil treatment caused a significant decrease in testosterone concentrations at the end of the day 21, in the experimental group with the maximum dosage of the drug (experimental group 3) in contrast to control group (figure-1); but serum LH and FSH levels showed significant increase in the same group (figure-2,3).

Histological studies of testis tissue demonstrated significant decrease in the number of primary spermatocyte, spermatogonia and spermatid in experimental group3 but the number of sertoli and leydig cells didn't change significantly compared to the control group(figures 4,5,6,7,8,9).

Sperm density declined significantly in the experimental group 3 (figures 5, 7).

There wasn't a significant change in body and testes weights compared to the control group.

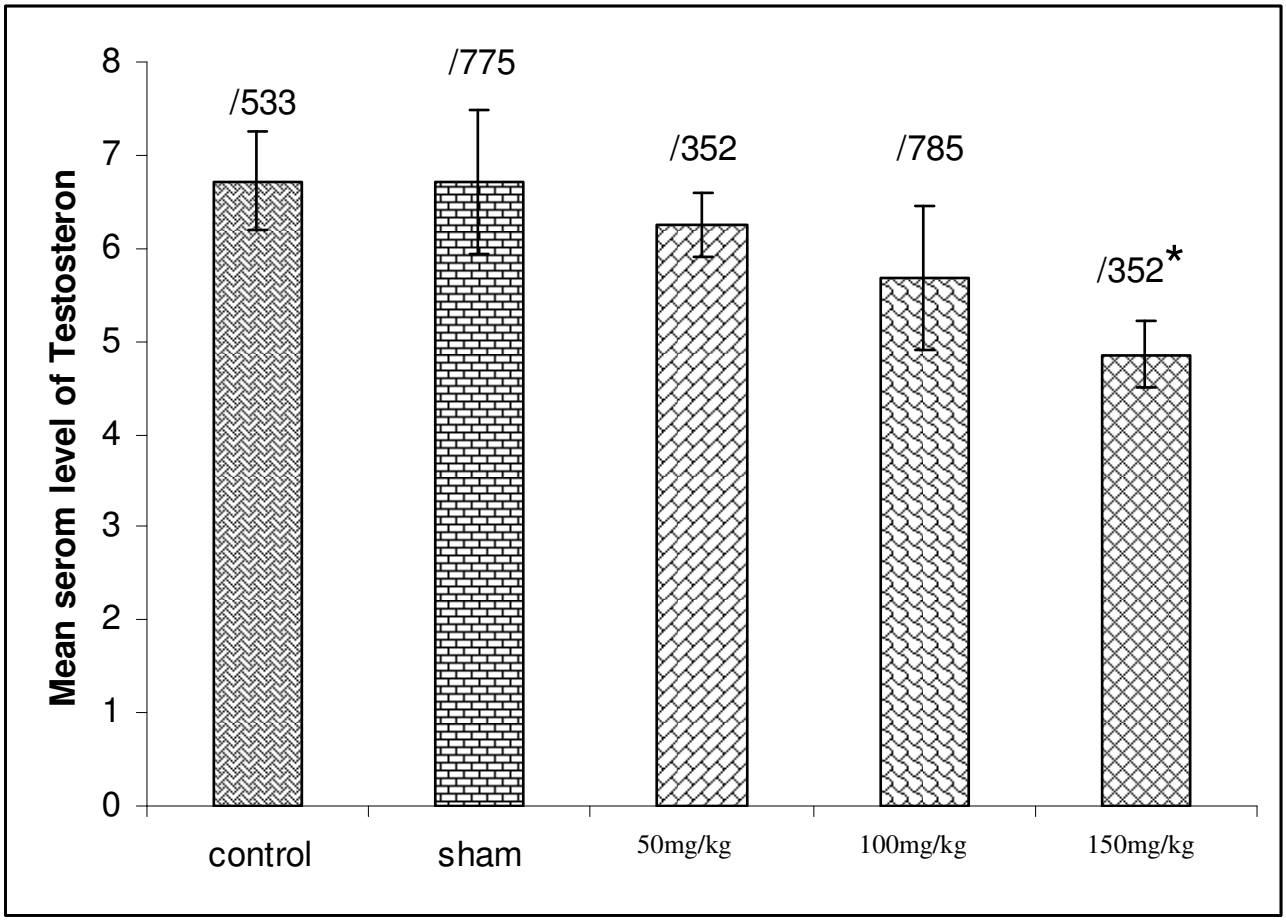

Figure-1
Changing of mean serum level of testosterone in experimental groups in contrast to the control group at the end of experimental period. Indicates significant difference between control and experimental groups ($p \leq 0.05$)

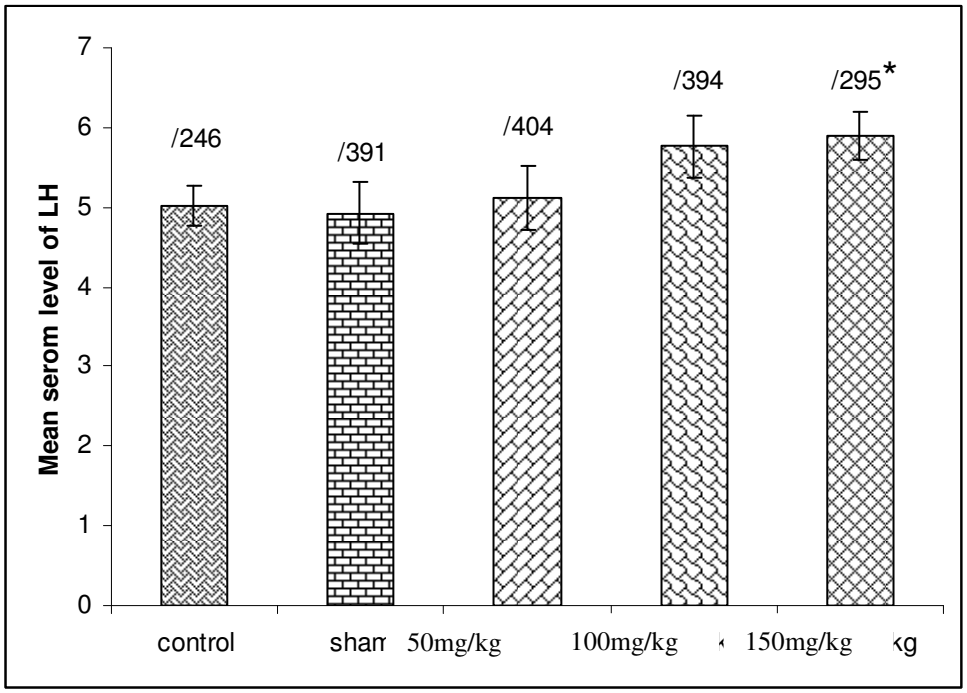

Figure-2
Changing of mean serum level of LH in experimental groups in contrast to the control group at the end of experimental period Indicates significant difference between control and experimental groups ($p \leq 0.05$)

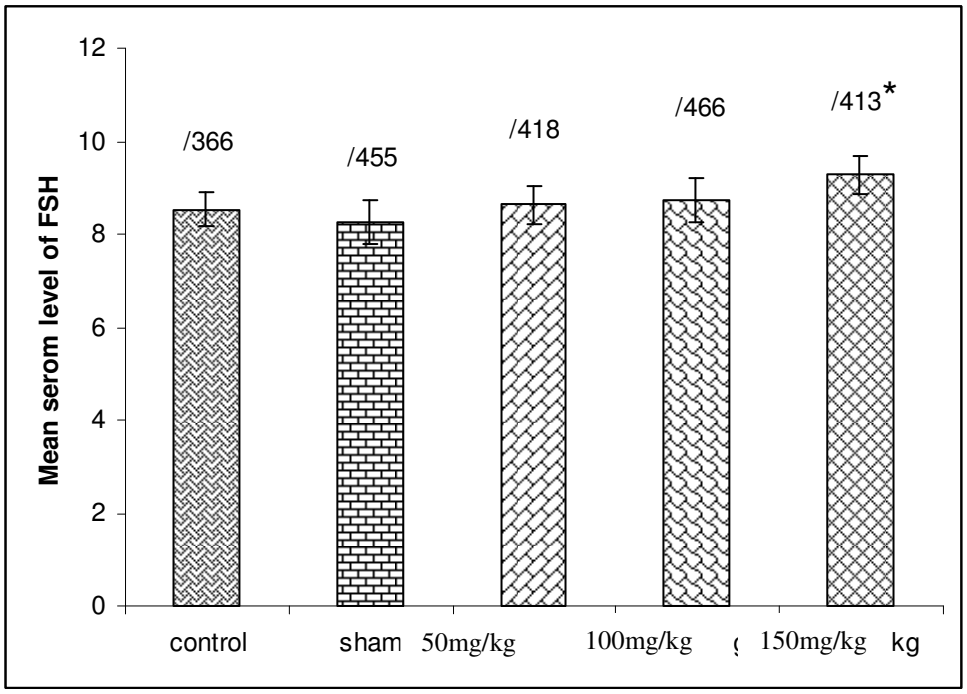

Figure-3
Changing of mean serum level of FSH in experimental groups in contrast to the control group at the end of experimental period Indicates significant difference between control and experimental groups ($p \leq 0.05$)

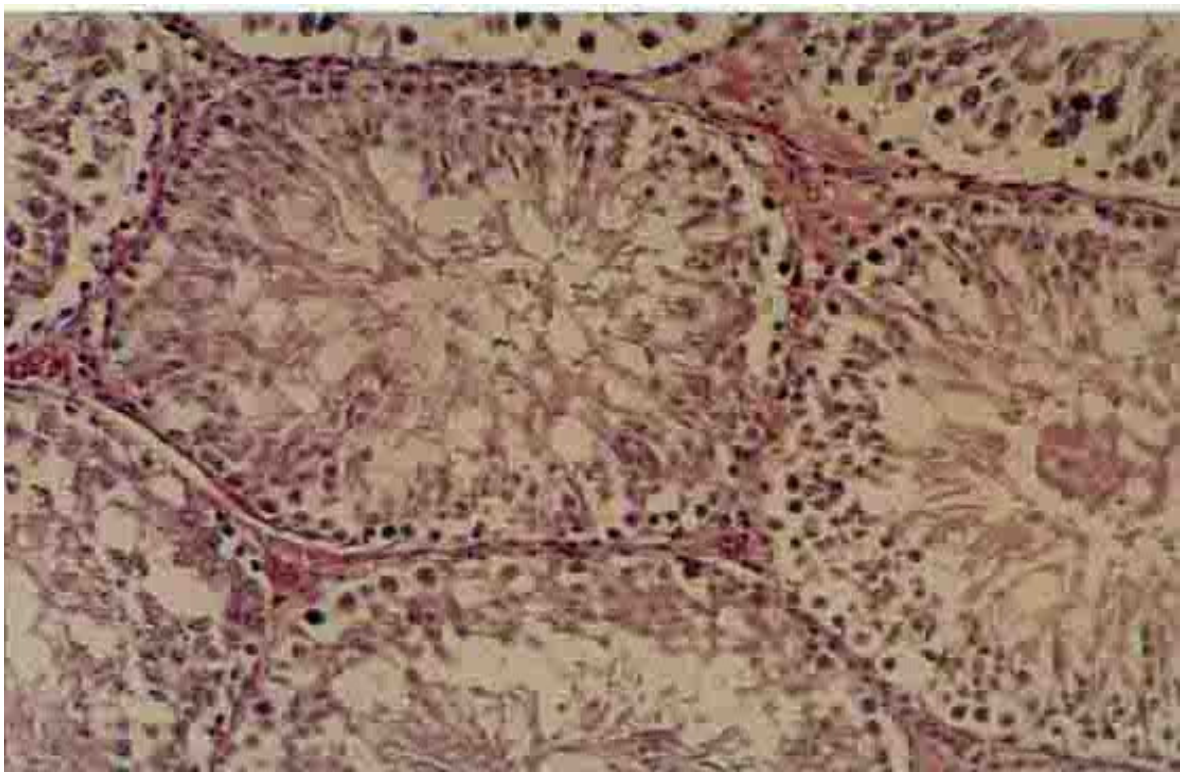

Figure-4
Testis tissue in control group (H and E staining; x40)

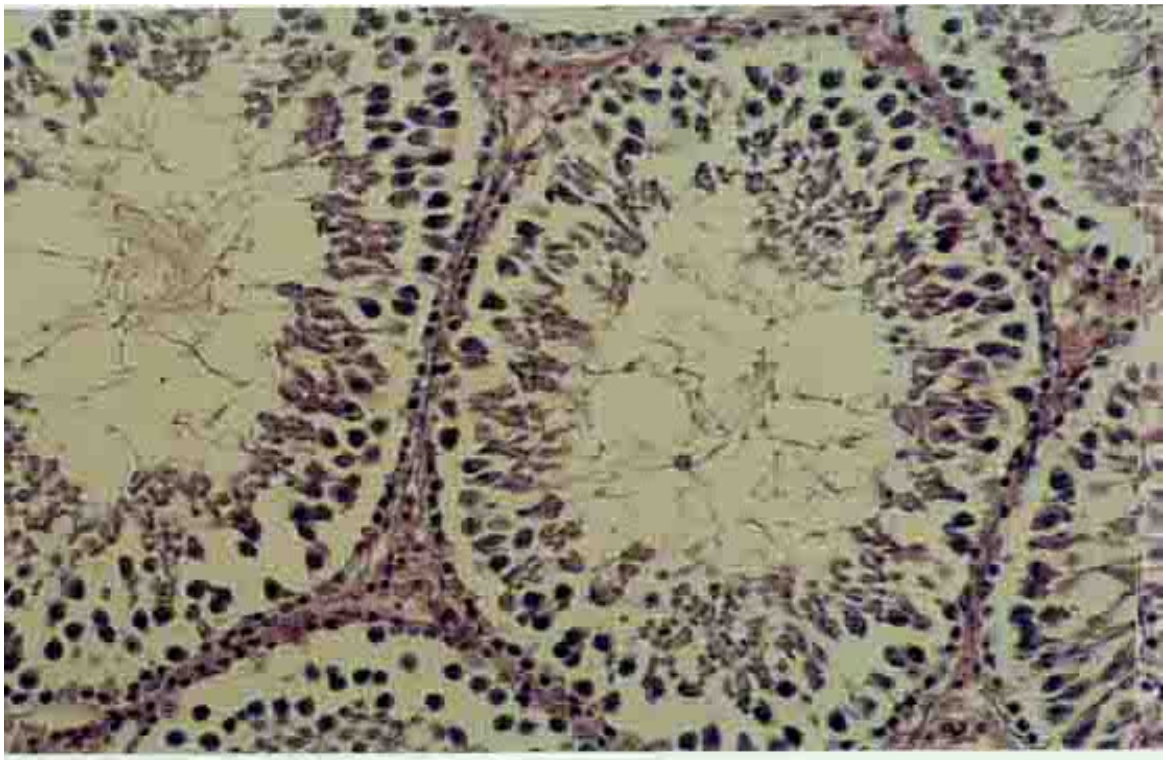

Figure-5
Testis tissue in experimental group 3 (H and E staining; x40)

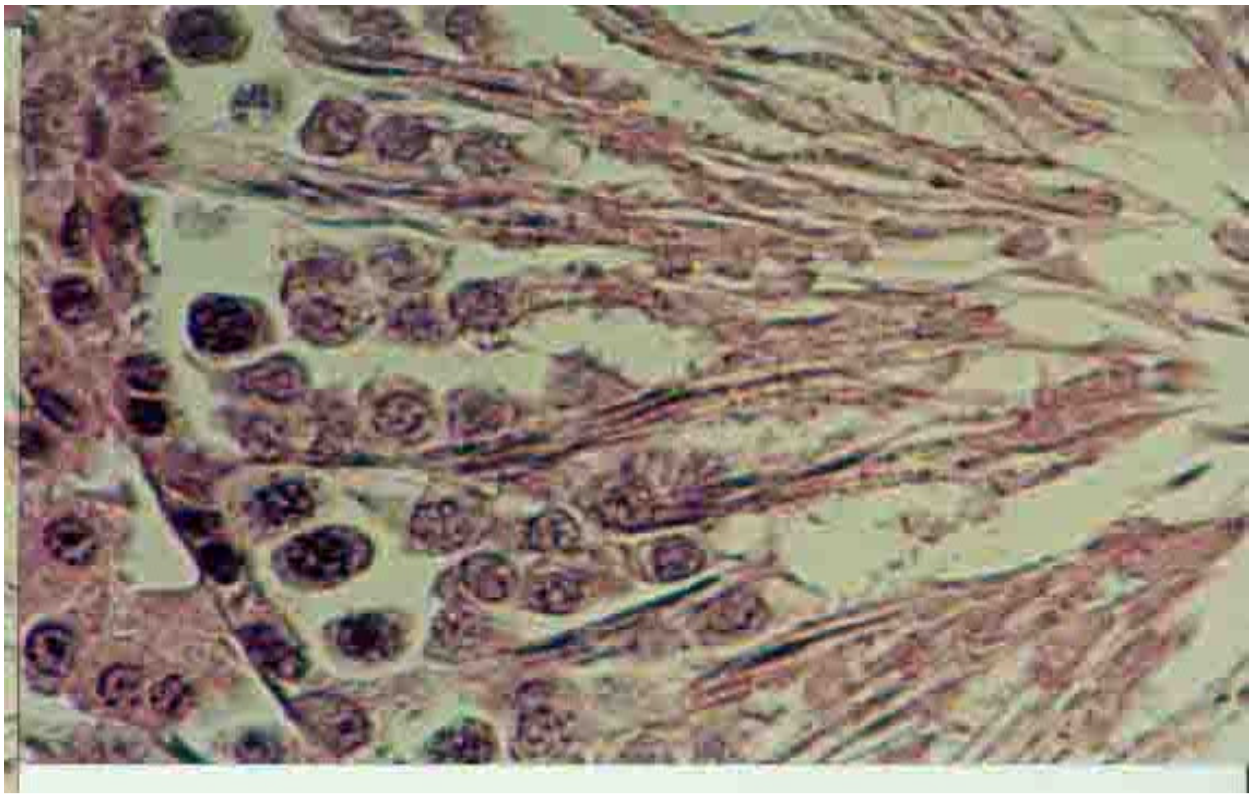

Figure-6
A seminiferous tubule of testis tissue in control group (H and E staining; X 100)

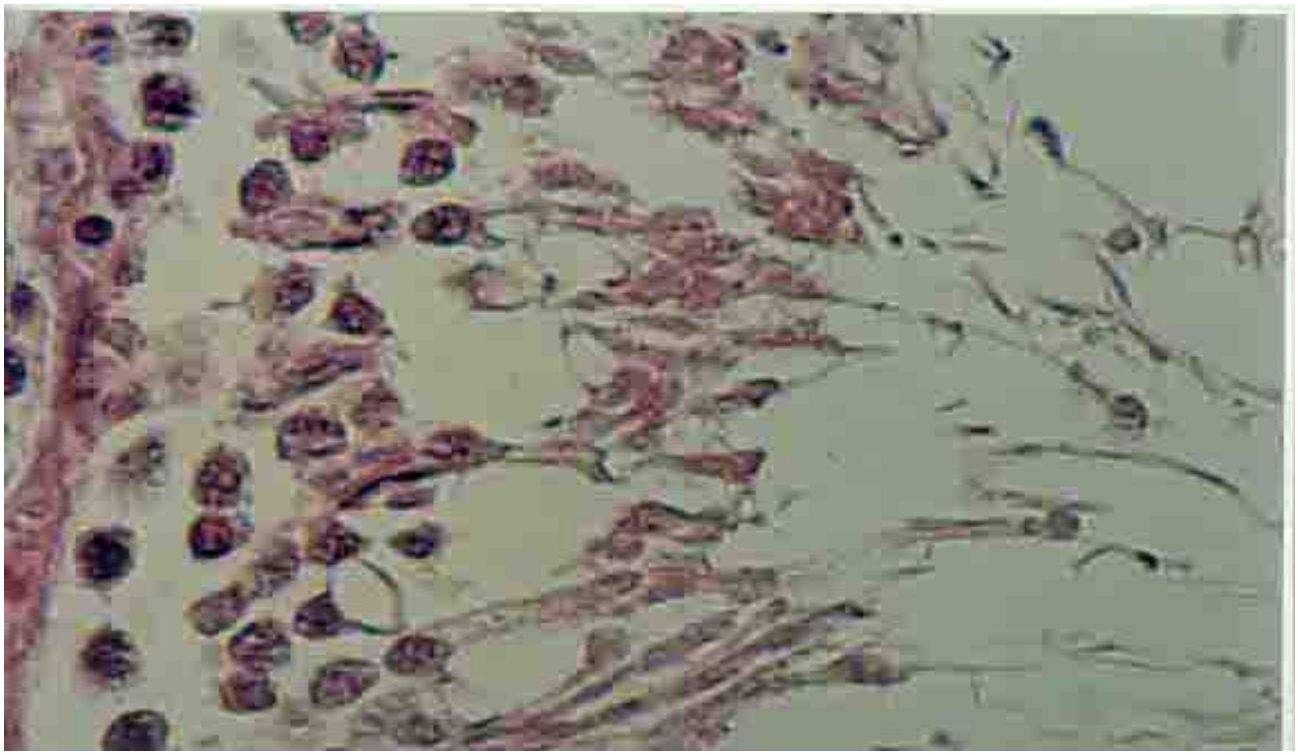

Figure-7
A seminiferous tubule of testis tissue in experimental group 3 (H and E staining; X100)

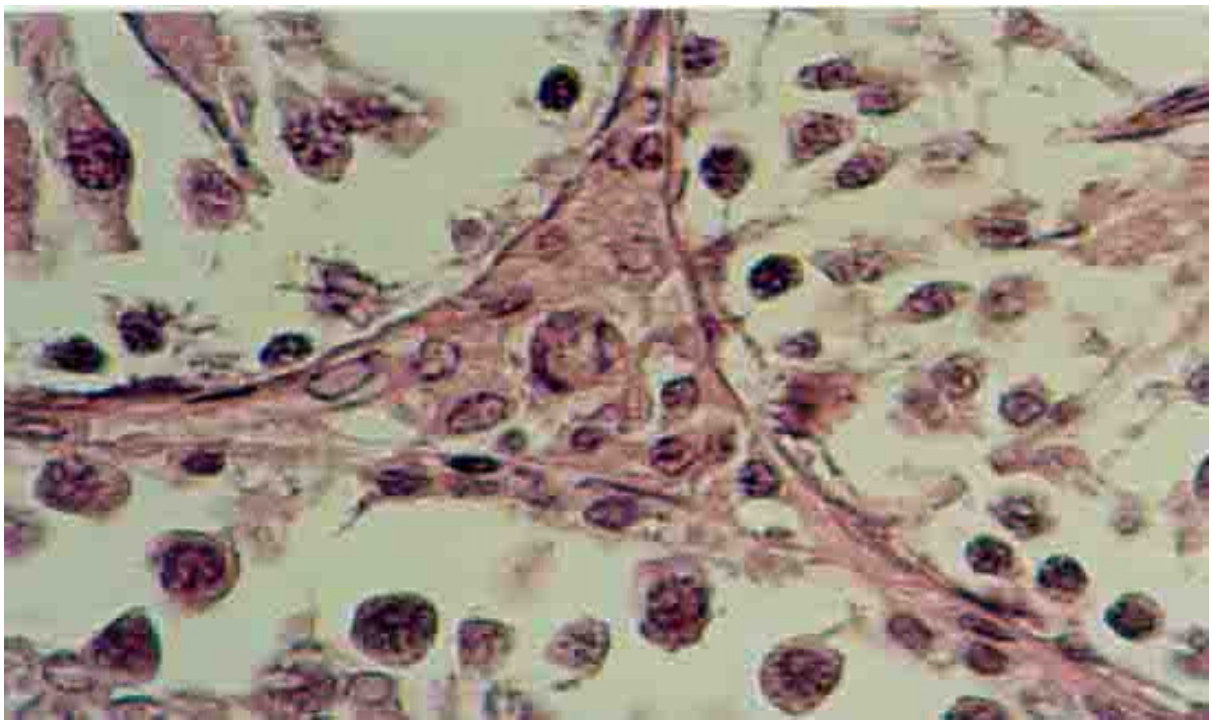

Figure-8
Leydig cells in control group (H and E staining; x100)

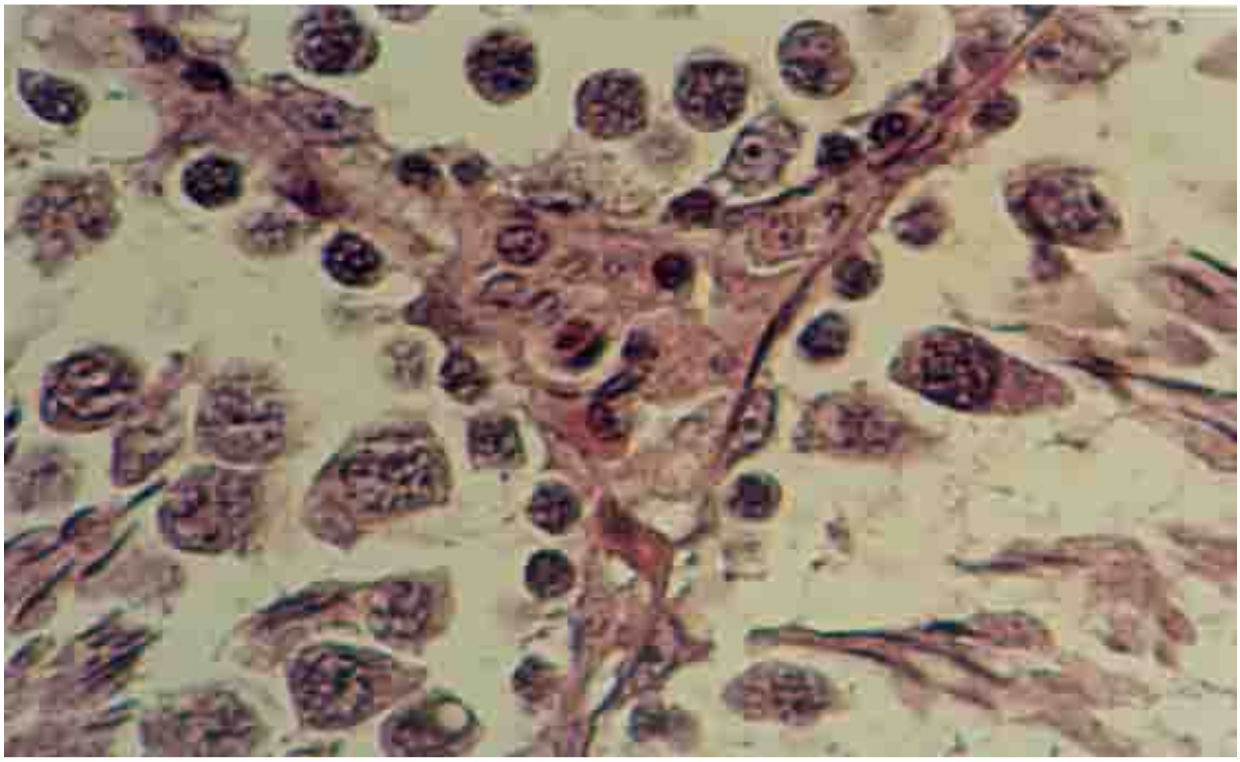

Figure-9
Leydig cells in experimental group 3 (H and E staining; x100)

According to results mean serum level of testosterone decreased significantly in experimental group 3: Largactil inhibits the reuptake of serotonin and lead to increase this neurotransmitter level, serotonin increase inhibits the intermediary enzymes in testis steroidogenesis pathway and cause testosterone decline[17]. Largactil increase melatonin[18], this hormone decrease STAR protein generation and because of that, cholesterol to pregnenolone conversion must be inhibit. The antidepressant Largactil suppress histamine-induce ACTH release[19], so both ACTH and cAMP decrease, lead to adrenal cortex activity decline to steroidogenesis and because of that the most important excitatory stage by ACTH for regulatory secretion of adrenal cortex (protein kinase A enzyme activation to convert cholesterol to pregnenolone), must be decrease. Testosterone decrease, could induce negative feedback in HPG axis and cause hypothalamic GnRH elevation and then pituitary FSH, LH increase consequently[20-23]. This is just the possible result for FSH and LH increase after the testosterone decrease in experimental group 3 at the end of 28th day in our investigation. Testis histological studies showed sperm density decline in seminiferous tubules; testosterone has direct effects on spermatogenesis[24-27]: so testosterone reduce could be the important reason for decrease the number of spermatogonia , primary spermatocyte, spermatid and sperm density decline, consequently.

Conclusion

We suggest that, high doses of Largactil antidepressant drug, because a decrease in serum testosterone concentration and spermatogenesis; so we strongly recommend, Largactil prescription in patients which have some disorders in generation of sex hormones, should be restricted. Synchronic prescription of Largactil and steroidogensis activator drugs could be an effective solution to decrease the side effects.

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