Histopathological Effect of Clomiphene on Seminal Vesicles

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ABSTRACT

Introduction: Clomiphene is a selective estrogen receptor modulator of triphenylethylene group. Mainly used for induction of ovulation in anovulatory infertility. Long term use of the drug has been attributed to serious side effects. The current study is aimed at studying the effect of clomiphene on seminal vesicles of male albino rat.

Material and Methods: The aim of present study was to see the effect of clomiphene citrate on reproductive organs of male rats. In the present study 64 male albino rats weighting on an average 150 gms were used.

Results: Clomiphene treatment induced regressive histological changes in seminal vesicles accompanied by significant decrease in the weight with increasing dose and length of treatment.

Conclusion: The current study is aimed at determining the effects of Clomiphene on seminal vesicles both macroscopically and microscopically.

Keywords: Clomiphene, Seminal Vesicles, Hypothalamus, Infertility, Estrogen, Estradiol

INTRODUCTION

Clomiphene citrate is a synthetic analogue of the non-steroidal estrogen chlorotrianisense, 1-(p-(diethylaminoethoxy)-pheny1)-1, 2 dipheny1-2-chloro-ethylene. Clomiphene citrate is a diastereomeric mixture of two geometric isomers, namely zuclomiphene (cis-clomiphene) and enclomiphene (trans-clomiphene) which are weak estrogen agonist and potent antagonist respectively.[1,2]

Clomiphene citrate, binds to estradiol receptors in various tissues such as the hypothalamus, hypothesis cerebri, ovaries, uterus and cervix due to structural similarity to estradiol. However Clomiphene citrate does not induce the synthesis of new estrabiol receptors, a process essential for the continuous binding of estradiol to the target cells as well as the expression of estrogenic action. Induction of ovulation is due to binding of Clomiphene citrate to the estradiol receptors in the hypothalamus which creates a state of hypoestrogenicity, thereby causing an enhanced Gonadotropin- releasing harmone (GnRH) release followed by an increased secretion of gonadotropins which induces ovulation. Clomiphene citrate is known to stimulate estradiol synthesis in the ovaries which in turn stimulate formation of FSH and LH receptors in the granulose cells of other small follicles which would not develop under normal circumstances and thus lead to development of additional follicles during the clomiphene citrate therapy.

Clomiphene has been used in treatment of male infertility due to oligospermia to stimulate gonadotropin relase and enhance spermatogenesis

Clomiphene is commonly used in the treatment of anovulatory infertility. In in vitro fertilization programmes Clomiphene has also been used in conjunction with human gonadotropins. So the current study is aimed at studying the effect of clomiphene on seminal vesicles of male albino rat.

MATERIAL AND METHODS

The present study was done at Skims Medical College Srinagar Department of Anatomy from 2014-2017.

The present study was aimed to determine the effect of clomiphene citrate on reproductive organs of rats. In the present study the experimental animals used were 64 albino rats weighting on an average 150 gms. The animals were divided in four groups.

GROUP A-(control group)- 16 rats were used in this group. They were fed with routine food and tap water daily.

48 rats were administered clomiphene citrate orally mixed with flour and water as pellets in addition to the routine food and tap water.

The treated rats were classified into following groups according to the dose -

GROUP B- Comprised of 16 rats and were administered 2.5 mg/ 100 gm daily.

GROUP C- Comprised of 16 rats and were administered 3.5 mg/ 100 mg daily.

GROUP D- Comprised of 16 rats and were administered 5 mg/ 100 gm daily.

The animals were kept in four different cages comprising of group A,B,C and D.

Animals in each group were fed routine diet comprising of different vegetables and gram each day. In addition to routine food, animals in group B,C and D were fed with clomiphene citrate mixed with flour as pellets. Drug was administered for twelve weeks regularly.

At intervals of 2, 4, 8 & 12 weeks respectively four rats from each group were killed. The process of block making of tissues was done manually.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the analysis. Descriptive statistics like mean and percentages were used for the

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analysis.

RESULTS

In the present study the experimental animals used were 64 albino rats weighting on an average 150 gms. The animals were divided in four groups.

Drug was administered to Groups B, C and D and Group A comprised the control group. Based on duration of treatment, Groups were subdivided into subgroups. Testis, Epididymis, Seminal vesicles and Prostate of male albino rats were studied both macroscopically and microscopically.

Seminal Vesicles

Macrosopic: On gross examination, a slight to moderate decrease in weight of seminal vesicles was noticed from 2nd to 12th weeks of experiment (table-1)

Microscopic: The structure of seminal vesicles was most affected due to the treatment compared to testis and epididymis. Changes were observed in seminal vesicles even when there was no change in testis and epididymis. When alternations were present in the testis and epididymis, however, changes were also observed in seminal vesicles.

Group B; Lowest dose of clomiphene, 2.5 mg/100/ day was administered in rats of this group. After eight weeks (B3) of treatment in this group microscopic changes appeared in the seminal vesicles (Figure-1).

Group C; In this group rats were administered the intermediate dose of clomiphene, 3.5 mg/ 100/day. Microscopic changes were present in the majority of treated animals at four week interval (C2) and in all of those treated for 8th weeks (C3) to 12th week (C4) (Figure-2).

Group D; In this group rats were administered the highest dose of clomiphene, 5 mg/ 100/day. Microscopic changes were present in most of the treated rats.

DISCUSSION

In present study 64 male albino rats were divided into four groups. Animals in Group A served as control and were fed with normal laboratory food with plain water. Animals in Groups B,C and D were administered clomiphene in addition to normal food. The animals were scarified in each group at intervals of 2,4,8 and 12 weeks respectively. The aim was to observe the macroscopic and microscopic changes, on Testis, epididymis, seminal vesicles and prostate. Haematoxylin and Eosin were used for staining for microscopic study.

Weight of animal

Average weight of animals in group A,B,C and D was 150, 145, 148 and 140 gms respectively at beginning of experimentation and at the completion of 12 weeks was 350, 183, 172 and 170 gms respectively. This indicated

Group	Subgroups	Time weeks	Seminal vesicles MGS/ 100gn B.W
A	A1	2	5
	A2	4	6
	A3	8	6
	A4	12	9
B	B1	2	4
	B2	4	2
	B3	8	2
	B4	12	1
C	C1	2	5
	C2	4	2
	C3	8	1
	C4	12	1
D	D1	2	2
	D2	4	2
	D3	8	1
	D4	12	1

Table-1: Showing average weight (in mgs) of seminal vesicles

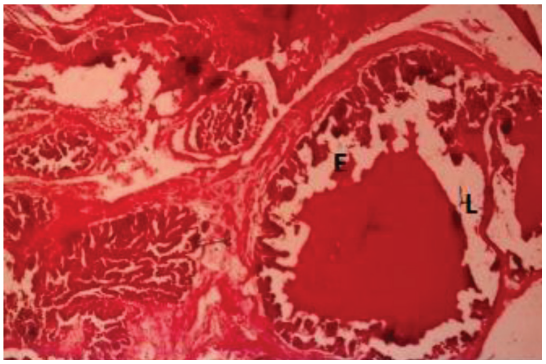

Figure-1: Microphotograph of seminal vesicle of normal rat showing highly folded columnar epithelium (E). Dense secretory material is present in the lumen (L) between the folds Magnification × 40

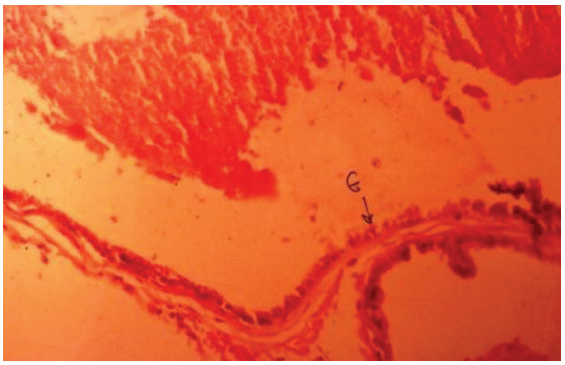

Figure-2: A Microphotograph of seminal vesicle of rat in group C4 showing shorter epithelium (E) than in normal, being reduced to low columnar shape or cuboidal shape. Magnification × 400

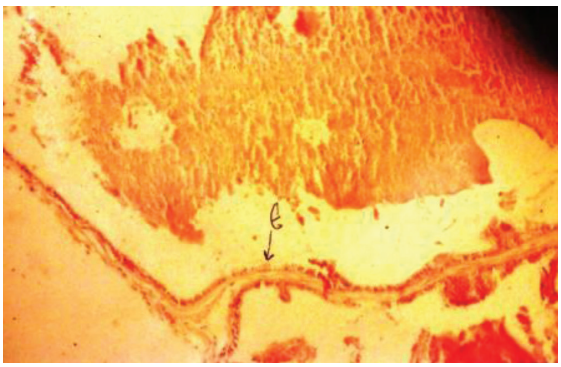

Figure-3: A Microphotograph of seminal vesicle of rat in group D3 showing shorter epithelium (E) than in normal, being reduced to low columnar shape or cuboidal shape. Magnification × 200

progressive decrease in rate of weight gain of animals, possibly due to degenerative changes in reproductive organs. Holtkamp, Greslin, Root & Lerner (1960)[1] observed that rats receiving the highest dose of 7mg/100mgs/day gained 33 gms in weight while control animals gained 65 mgs. This indicated dose related progressive decrease in rate of body weight gain.

Similar effects were also observed by Charles. J. Flickinger (1977).[2] They found that rats receiving the highest dose of 5 mgs/ 100gms/ day for 12 weeks gained 20 gms in weight while control animals gained 100 mgs. This indicated that with increase in dose and duration of drug intake there was progressive decease in rate of body weight gain.

Seminal Vesicles

Effect of clomiphene were studied in present study on the seminal vesicles of rats both macroscopically and microscopically.

A decrease in weight of seminal vesicles in clomiphene treated rats was observed during present study. From 2nd week there was mild decrease in weight followed by severe decrease by 8th to 12th weeks. Histological changes were present in the majority of treated animals at the 8 week interval and in all of those treated for 12 weeks. Microscopically, the epithelia of the seminal vesicles were greatly reduced in height from their normal tall columnar, cuboidal or even squamous shape. This effect was particularly pronounced in those rats receiving 5mg/100g/ days for 12 weeks. Thus with increasing dose and length of treatment there was a general trend to reduction in the height of the cells and to increased cytological alterations

Holtkamp, Greslin, Root & Lerner [1960][1] demonstrated that in immature male rats clomiphene in doses from 1mg/100g/ day and greated yielded lower relative weights of seminal vesicles. Degree of lowering was dose dependent. In mature male rats, clomiphene treated rats had lower seminal vesicle weights after 20 days of treated with 1mg/100g/days. These organs were about ¾ of control weight. No difference was observed at 10 days.

Similar finding were observed by Nelson.W.O, D.J.Patanelli [1962][3] They observed weight of seminal vesicles were decreased at all doses above 0.25mg/kg and were at hypophysectomy levels at doses of 205mg/kg and higher

Charles. J.Flickinger [1977][2] observed that the weight of seminal vesicles were less than those of control rats decreased with increasing dose and length of treatment. Microscopically, the normally tall columnar epithelia were reduced to a low columnar or cuboidal shape.

Singh Sk [1983][4] observed that clomiphene treatment in musk shrew induced regressive histological changes in seminal vesicles accompanied by significant decrease in the weight.

The treatment also caused significant decrease in the level of fructose in the seminal vesicles.

In the present study the changes in the epithelium of the seminal vesicle consisted of large decline in cell size. The change probably result from decreased androgen stimulation of these target tissues. In support of this contention is the fact that these alterations in clomiphene treated rats closely resemble those observed after castration or estrogen treatment [Price and Williams - Ashman,1961][5], [Brandes,1966, 1974][6] as well as administration of cyproterone acetate [Loving and Flickinger, 1976][7] or treatment with various progestogens [Patanelli and Nelson (1959)[8], Setty and Kar (1967)[9], Terner and Mclaughlin (1973)[10], Flickinger (1977b)[11]].

CONCLUSION

The epithelium was much shorter than in normal, being reduced to a low columnar shape or cuboidal shape or was completely atrophied. The lumen lacked visible accumulations of secretory product. Clomiphene treatment induced regressive histological changes in the seminal vesicles.

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