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EFFECT OF DIPHENHYDRAMINE AND CHLOROPYRAMINE ON THE REPRODUCTIVE PERFORMANCE OF MALE RATS

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ABSTRACT

The effect of diphenhydramine HCL(10mg/Kg) and chloropyramine HCL (7 mg/Kg) On the reroductive performance was studied in adult male rats.After 30 days or oral adminstration, these drugs did not cause significant changes in the quality of the epdidymal spermatoze and serum testosterone cencentration.Treatment for a period of 60 days, diphenhydramine HCL produced significantly reduction in cell concentration, percentage of the progressive motility of spermatozoa and serum testosterne concentration. The increase in the percentage of the dead and morphologically abnormal sperms was not significant.Chloropyramine HCL for a period of 60 days caused significant reduction in the percentage of the progressive motility of the spermatozoa and serum testosterone consentration,whereas other measured parameters were not significantly altered.It is concluded that prolonged adminstration(60 days) of disphenhydramine HCL and chloropyramine HCL affect adversely the reproductive performance of adult male rates, although disphenhydramine was the most effective in this respect.

INTRODUCTION

Histamine (H_1) - receptor antagonists are

widely used for symptomatic treatment in hypersensitivity and other conditions where release of endogenous histamine occurs.In therapeutic doses,all H_1 antigonists elicit adverse reactions . ALthough these are rarely serious anf often disappear with continued therapy,They are sometimes so troublesome that the drug must be eithdrawn(Goodman et al.,1985;Tripathi,1985 ; Robinson, 1987).
In labratory animals , Sadusk and Palminsano (1965)demonstrated that cyclizine, chlorcyclizine and meclizine have teratogenic effects, and their use in pregnant women is contraindicated .

The effect of some antihistamine on male reproductive system and fertility has not been extensively investigated.Therefore the present study was designed to examine the effect of short and long term adminstration of the commonly used antihistamines (diphenhydramine HCL and chloropyramine HCL) on the reproductive performance of male rats.

MATERIALS AND METHODS

Animals

Sixty male albino rats, 3-4 months old, 400 - 500 gm body weight , were used . They were kept in polypropylene cages (2 rats each) under controlled conditions of temperature (24-26 C) and lighting (14 hrs light/10 hrs dark). Food (standard rat diet) and water were supplied ad Lib.

Drugs:

The used antihistamines were diphenhydramine HCL (Allermine,The State Company for Drug Industries,Samarra,Iraq) and choropyramine HCL (Synopen,Ciba-Geigy Limited,Basle,Switzerland)

Each drug was suspended in distilled water prior to its administration.

Experimental groups:

The animal were divided randomaly into 3 groups (20 rats each).The first group received distilled water and served as control. The second and third groups received therapeutic doses of diphenhydramine HCL (10 mg/Kg) and chloropyramine HCL (7 mg/Kg),respectively.All doses were administered daily for periods of 30 and 60 days.The animals were observed for general behavioral activity throughout the experiments.

After 30 and 60 days of treatment, 10 animals of each group were killed by decapitation

Blood samples were collected by cadiac puncture.Serum was seperated and stored at -20 C for testosterone assay.Epididymides were dissected out, sectioned and immediatly the content of the tail of each epididymis was squeezed gently in a clean watch glass,diluted 10 times with isotonic solution of sodium citrate at 37 C. The progressive motility of the spermatozoa was then estimated. The percentage of dead and morphologically abnormalaperms were counted using eosin-nigrosin stained smears. Sperms count was done using hemocytometric technique.

Hormone assay:

SB - TESTO radioimmunoassay kits (CIS,France) were used for direct determination of testosterone in serum samples.

Statistical analysis:

The student's t-test was used to determine the level of significance between experimental and control values (Steel and Torrie,1960).

RESULTS

Before treatment, the control and experimental rats showed normal behavior and vigorous activity. After treatment with antihistamines for 30 and 60 days, the rats became dull and less active as compared to the control, and

this effect was very marked in diphenhydramine -treated rats. Treatment of male rats with diphenhydramine and chloropyramine for 30 days did not cause significant (P>0.05) changes in the evaluated epididymal sperm characters, sperm cell concentration,progressive motility of spermatozoa and percentages of dead and morphologically abnormal spermatozoa. Serum testosterone concentrations were not significantly (P>0.05) affected by diphenhydramine and chloropyramine,although a decrease was observed in chloropyramine-treated rats (Table 1).

Treatment with diphenhydramine HCL, for a period of 60 days , resulted in significant (P<0.05) reduction in sperm cell concentration , percentage of progressive mptility of the spermatozoa and serum testosterone concentration (Table 2). The increase in the percentages of dead and morphologically abnormal sperms was not significant (P>0.05). The percentage of the progressive motility of spermatozoa and serum testosterone concentration were reduced significantly (P<0.05) in animals treated with chloropyramine HCL for 60 days (Table 2), whereas sperm cell concentration,dead and morphologically abnormal sperms did not change significantly (P>0.05).

DISCUSSION

It is well known that diphenhydramine HCL has astrong antimuscarinic and sedative effects which results in dullness, drowsiness,blurring of the vision and other symptoms of central nervous system (CNS) depression and atropine-like effects, whereas chloropyramine HCL has a moderate antimuscrinic and sedative effects (Goodman et al.,1985; Tripathi,1985). This may explain the decrease in general behavioral activity of the treated rats, especially those treated with diphenhydramine HCL.

Table 1. Effect of 30 days oral administration of diphenhydramine HCL and chloropyramine HCL on epididymal sperm characters and serum testosterone concentrations in male rats.

Treatment	NO.of rats	Sperm cell concentration (10^6/ml)	percentage of			Serum Testosterone concentration (ng/ml)
			Progressive motility of spermatozoa	dead sperms	mophologically abnormal	
Control	10	789.0 ± 64.591	75.5 ± 2.034	11.508 ± 1.079	3.451 ± 0.171	1.632 ± 0.289
Diphenhydramine HCL (10 mg/Kg)	10	798.5 ± 58.793	73.0 ± 1.855	11.930 ± 1.044	4.147 ± 1.697	1.726 ± 0.299
Chloropyramine HCL (7 mg/Kg)	10	714.5 ± 53.977	72.5 ± 2.608	11.786 ± 1.039	4.391 ± 0.416	1.124 ± 0.249

Values are means + S E M

Means were not significantly different (P > 0.05)

Table 2. Effect of 60 days oral administration of diphenhydramine HCL and chloropyramine HCL on epididymal sperm characters and testosterone concentrations in male rats.

Treatment	NO.of rats	Sperm cell concentration (10^6/ml)	percentage of Progressive motility of spermatozoa	percentage of dead sperms	percentage of mophologically abnormal	Serum Testosterone concentration (ng/ml)
Control	10	855.0 ± 52.426	77.5 ± 1.536	11.292 ± 0.769	3.697 ± 0.336	2.535 ± 0.487
Diphenhydramine HCL (10 mg/Kg)	10	645.5* ± 53.032	67.5* ± 3.184	12.871 ± 0.861	4.816 ± 0.564	1.222 ± 0.303
Chloropyramine HCL (7 mg/Kg)	10	741.5 ± 44.163	69.0* ± 3.316	12.440 ± 0.562	4.342 ± 0.330	1.289* ± 0.246

Values are means + S E M

*Significant at P<0.05 (treated versus control)

The reduction in quality of epididymal spermatozoa and serum testosterone concentrations associated with the decreased general behavioral activity may be due to the effect of the drug that reduces CNS activity which has recognized role of integrating both internal and external stimuei affecting reproductive function(Yen,1986).CNS depression and atropine -like effects of antihistamine might have resulted in less resposive rats to light and/or diminished food intake, since the light is one of the external stimuli which has an important influence on the neuroendocrine system and the nutritional deficiences advesely affecting the reproductive organs (Hafez,1970).

The results of the present study seem to agree with those of Hassan et al. (1983) who found that prolonged administ ration (60 days) of antazoline, dextrochlopheniramine maleate and mecloprodine in therapeutic doses interfere with spermatogenesis and sperm maturation in rats, whereas diphenylpyraline and promethazine HCL,in therapeutic doses,had no hazardous effects on reproductive organs and fertility capacity of male rats. These findings suggest that H_1 antagonists may act differently depending upon their respective chemical class. The decrease in serum testosterone concentration is in agreement with that reported by Hassan et al. (1983). These auhors found that some antihistamines lowered serum testosterone concentration in male rats when administered for a period of 60 days. The decrease in the quality of epididymal sperms in the present investigation could be attributed to the decrease in serum testosterone concentration, since testosterone is one of the important hormones for stimulation and regulation of spermatogenesis and for normal function of the epididymis, which is resposible for maturation of spermatozoa (Prasad et al ., 1973; Heras et al., 1988). Some workers (Amelar et al., 1980; Brokaw, 1986) considered that sperm

motility is one of the most important parameters in evaluating the fertility potential of asemen specimen. Furthermore, the type of movement also influences fertility capacity (Blandan and Rumery, 1964).

It is concluded that short term treatment (30 days0 with diphenhydramine HCL and chloropyramine HCL had no significant adverse effects on the epididymal sperms quality and serum testosterone cocentration,although the depressant effect was prominent in diphenhydramine-treated rats. Long term treatment (60 days) produced significant changes in epididymal sperms quality and serum testosterone concentration, although diphenhydramine HCL induced more deleterious effects than chloropyramine HCL on the reproductive performance of male rats.

تأثير الداي فينهايدرامين والكلوروبيرامين على الكفاءة التناسلية لذكور الجرذان

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الخلاصة

عوملت مجموعة من ذكور الجرذان البالغة بمادة داي فينهايدرامين هايدروكلورايد (١٠ ملغم/كغم) ومجموعة اخرى بمادة كلوروبيرامين هايدروكلورايد (٧ ملغم/كغم) يوميا عن طريق الفم. بعد ٣٠ يوما من بدء المعاملة لم تظهر كلا المادتين أي تأثير معنوي على صفات النطف المأخوذة من ذيل البربخ ومستوى التيستوستيرون في مصل الدم. ولكن بعد ٦٠ يوما من بدء المعاملة اظهرت النتائج وجود انخفاض معنوي في عدد النطف والنسبة المئوية لحركة النطف ومستوى التيستوستيرون في مصل الدم. وكانت الزيادة في نسب النطف الميتة والمشوهة غير معنوية في الجرذان المعاملة بمادة داي فينهايدرامين هايدروكلورايد اما تلك المعاملة بمادة كلوروبيرامين هايدروكلورايد لمدة ٦٠ يوما فقد أظهرت انخفاضا معنويا في النسبة المئوية لحركة النطف ومستوى التيستوستيرون في مصل الدم. وقد استنتج من هذه الدراسة أن معاملة ذكور الجرذان البالغة لفترة طويلة (٦٠ يوما) بمادة داي فينهايدرامين هايدركلورايد أو كلوروبيرامين هايدروكلورايد يؤدي الى انخفاض كفاءتها التناسلية. وان التأثير السلبي للمادة الاولى بهذا الجانب يكون أكبر مما هو عليه في المادة الثانية.

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