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IATROGENIC MALE INFERTILITY WITH PSYCHOTROPIC DRUGS IN RATS: CASE OF HALOPERIDOL AND CLOMIPRAMINE.

Gynaecology

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ABSTRACT

Objective: To study the effects of haloperidol and clomipramine on fertility in male rats.
Material And Method: This is an analytical experimental study. Three lots of 5 rats were formed: distilled water lot at 0.5 ml/100g; Clomipramine lot at 2 mg/kg/day; haloperidol lot 2.5 mg/kg/day. The diferent product were daily oraly administrated during 45 days. The study variables were: testicular weights, spermogram and hormonal biomarkers (testosterone, FSH, LH).
Results: On the average testicular weight (in grams): control 1.3±0.05; haloperidol 1.2±0.20; clomipramine 1.19±0.009 and on the pH: control 6.8 ±0.12; haloperidol 6.9±0.18; Clomipramine 6.8 ±0.2. There is no significant change in testicular weight and sperm pH compared to controls. Concerning the vitality, number, and morphological abnormalities of sperm cells, there are no significant changes. Vitality in % : control 55.4±3.15, haloperidol 44.9±6.20, Clomipramine 45.2±5.11 and sperm count (x106 / ml): (control 269.6±40.54, haloperidol 145.6±39.77, clomipramine 317.6±98.58). Sperm morphological abnormalities (% of normal morphology): (control 91.2; haloperidol 87.7; Clomipramine 81.8). Clomipramine caused a very significant increase (p=0.0036) in the serum concentration of FSH and LH (in IU/l) (P=0.0001): for control LH 0.46; clomipramine 3.46; for FSH: control 0.87; Clomipramine; however, there is an insignificant increase in testosterone (in ng/ml) with these two psychotropic drugs (control 1.56; haloperidol 2.66; Clomipramine 2.9). However, no significant difference of reproductive hormons were observed with haloperidol group (testosterone 2, 66; FSH 0, 72; LH 0, 26).
Conclusion: Haloperidol and Clomipramine affect male fertility: Clomipramine at the peripheral level and haloperidol at the central level.

KEYWORDS

Male Infertility, Clomipramine, Haloperidol.

INTRODUCTION

Iatrogenic male infertility is still poorly studied in men. Nevertheless, more and more drug side effects on male fertility are reported in pharmacovigilance databases [1]. The drugs and medications involved in male fertility impairment act by affecting the hypothalamic-pituitary-testicular axis, altering erectile function and the ejaculation process, or by decreasing libido [2]. Several molecules are believed to be involved, including tricyclic and neuroleptic antidepressants, particularly clomipramine and haloperidol. Cannabis is thought to cause a decrease in immunity and impaired reproductive function [3]. Animal models have been developed to answer questions about the treatments and causes of certain human diseases in specific theoretical frameworks characterized by certain pathogenic theories related to the biological sciences of the moment[4]. However, although some studies have been conducted, there is insufficient data to correlate claims that clomipramine and haloperidol disrupt reproductive functions.

Thus, we proposed to describe the effects of haloperidol and clomipramine on testicular weight, on spermogram and to determine their action on hormonal biomarkers (testosterone, follicle stimulating hormone**,** luteinizing hormone) in rats.

Materials And Methods

This is an analytical experimental study conducted over a three-month period from July 11 to October 2019 at the Biochemistry and Pharmacology Laboratory of the Faculty of Health Sciences (for the treatment of animals, spermogram and spermocytogram) and at the COGEMO Medical and Surgical Clinic Laboratory (for the determination of pituitary hormones and testosterone).

Experimental design and study variables

The experiments were performed on 6-week-old adult male rats raised at the Faculty of Health Sciences animal facility, averaging 169.09 grams (extremes 121 to 211). They have free access to water and standard food. The animals were acclimatised to the experimental conditions before treatment began for a period of one week

Three groups of rats (with 5 rats each), were prepared and treated daily orally with the different products: the control batch, treated with distilled water at 0.5 ml/100g; the clomipramine batch treated at 2 mg/kg/day; and then the haloperidol batch treated at 0.4 mg/kg/day **[5.6]**.

The doses used with these psychotropic drugs were an adaptation of the human therapeutic doses in relation to the weight in animals [6].
The animals were treated for 45 days. This 45-day treatment period is explained by the fact that, in rodents, sperm production from spermatogonia lasts from 42 to 56 days [7].

On the 48th day of the experiment, male rats were sacrificed by rapid decapitation [7]. Blood was collected in tubes that did not contain anticoagulants for the determination of pituitary hormones (FSH, LH) and testosterone. Testicles, epididymides and **vas** deferens were collected, removed from the adherent tissue (Figure 1)

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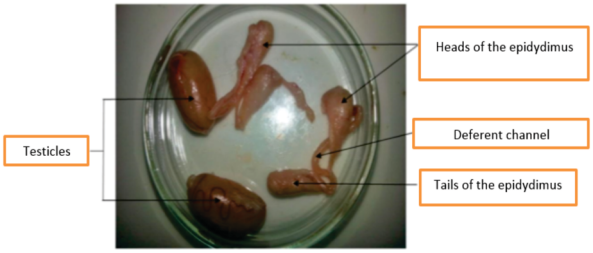

Figure 1: Isolated testes, epididymides and vas deferens in rats

The equipment used was slides, microscope, hemolysis tubes.

Rat semen was obtained by crushing, after incision, its two epididymides in 2 ml of physiological water in order to obtain a fixed volume of suspended semen. Several other dilutions of this same suspension, still in physiological water, were therefore required to determine the rat's sperm parameters (vitality, mobility, sperm count and morphology)

The semen volume used in rats was only an apparent volume or work volume of 2 ml. This volume was obtained by grinding, after incision, the two epididymides first in 1 ml of physiological water, then the same volume of physiological water was added after removing the epididymides so that rat semen suspended in 2 ml of physiological water was obtained.

The pH was measured, not from pure sperm, but directly from the sperm suspension in 2 ml of physiological water. Vitality was assessed according to a particular methodology: preparations of the slide used to count living and dead spermatozoa; staining of spermatozoa, then optical microscopy (objective 40) reading of 200 spermatozoa. On smears the living sperm are stained red by eosin at 2% and the dead were not stained[8].

The determination of pituitary (FSH, LH) and testicular (testosterone) hormones was performed on HUMA READER Single plus ELISA reader, model: 3801 -1754. The results were expressed in ng /ml for testosterone and UI/l for LH and FSH.

The statistical analysis was done on the "Instat plus software". The results have been presented as an average. The Student t-test was used. The significant level has been set at 5%.

RESULTS

In Table I, haloperidol and clomipramine do not significantly alter testicular weight compared to control rats, nor do they affect sperm PH, vitality and morphological abnormalities of spermatozoa. Results show that clomipramine not significantly alter testicular weight, sperm pH, vitality, number, and morphological abnormalities of spermn, when compared to control group.

However, clomipramine, but not haloperidol, caused a very significant increase (p=0.0036) in serum FSH and LH concentration (P=0.0001), whereas there is an insignificant increase in testosterone with these two psychotropic drugs (Table II)

DISCUSSION

In the assessment of male infertility, the weight of the testicles is of great importance because this infertility can be explained by three mechanisms[9]:severe hypo gonadotropic hypogonadism which prevents or interrupts the activation necessary for sperm production (pre-testicular cause), primary testicular diseases affecting the course of spermatogenesis (testicular causes) ,and conditions or lesions preventing the evacuation of spermatozoa from the testicles (post testicular causes). In this study, we investigate the effects of long-time administration of clomipramine and haloperidol in rat. The number of (five in each group) rat used may be considered as the limit in this study. The testicular weights of rats treated with haloperidol and clomipramine were not significantly altered. Infertility would probably be of testicular or post testicular origin. Indeed, for some authors, in the case of normal-sized azoospermia with testicle, it probably acts as an obstacle on the seminal route[10].

The participation of the male species in the fertilization process is reduced to the contribution of gametes, this implies, therefore necessarily the examination of the sperm as a first investigation. In rats treated with both psychotropic drugs, no changes in PH were observed. A normal PH indicates the normality of the seminal vesicles and the prostate. If the PH is acid, it indicates an attack of the seminal vesicles, while a basic PH indicates an alteration of the prostate[11]. The experimental conditions of the collection can be questioned[12]. In the human species, the conditions of sampling are taken into account: masturbation in the laboratory, in a sterile container, semen is collected after 2 to 4 days of sexual abstinence.

Sperm mobility in treated rats is not significantly altered compared to that of control rats. Indeed, many acquired lesions are responsible for male infertility. It is possible that infertility may occur as a result of trauma and/or ischemia during sperm cord twisting, surgery[13]. In men, normal spermatogenesis is performed in a testicular temperature 3 to 4°C lower than the body temperature. The 1°C increase causes a decrease in sperm count of about 14%[14]. Since rats are raised in a pen, this can promote oligospermia. Indeed, sedentary lifestyle induces a decrease in sperm count, volume, and concentration[14]. Some authors report that the use of drugs and certain medications affects male fertility and presents a risk of oligospermia[15]. For others, the effect of drugs on male fertility may be explained in general by a direct gonadototoxic effect, alteration of the hypothalamic-pituitary-testicular axis, impairment of erectile function and ejaculation process, or decreased libido[16,17]. Indeed, tricyclic antidepressants such as clomipramine are agents that can cause sexual, erectile, ejaculatory dysfunction. Often effect is reversible upon discontinuation of treatment[18]. Necrospermia observed in rats therefore does not seem to be related to drugs. In the literature, it can be found in humans in cases of inflammation of the genital tract[19].

In the assessment of male infertility, endocrine exploration has a prominent place [9,20,21], so we performed the serum FSH, LH and testosterone assays in rats. The FSH level was significantly high in rats, which is similar to the existence of secretory azoospermia. Indeed, the FSH assay makes it possible to differentiate between excretory and secretory azoospermies [20]. If FSH is normal, the diagnosis of pre-testicular infertility can be ruled out in the profile of excretory azoospermia by obstacle on the genital tract if the FSH level is increased, as is the case in our rats, so a clomipramine-related secretory azoospermia of peripheral origin that caused a significantly high level in rats can be suspected [22]. On the other hand, if the FSH level is collapsed, it would be a secretory azoospermia of central origin (hypo gonadotropic hypogonadism), in which case LH and testosterone will also be collapsed [20]. However, in this work, concerning Clomipramine, LH is also quite high, and testosterone is moderately high. The synthesis of testosterone is dependent on LH/FSH which act on Sertoli cells [9]. In humans, emotional state can affect spermatogenesis by influencing the neurotransmitters of the hypothalamic-pituitary-gonadal axis, depression in humans can have an impact on testosterone levels; depression was associated with decreased interest and pleasure [23]. Isn't there an emotion in rats related to their pre-mortem aggression?

Tricyclic or imipraminic antidepressants inhibit the recapture of catecholamines in the central nervous system, may be responsible for hyperprolactinemia and therefore reversible spermatogenesis abnormalities [24]. Haloperidol in rats caused the collapse of FSH and LH, giving the appearance of a preliminary step towards hypo gonadotropic hypogonadism. We did not measure prolactin levels in Rats. For some authors [25], the use of free testosterone assays to define hypogonadism should be strongly discouraged as it leads to a constant underestimation of circulating testosterone and therefore to misdiagnosis. Diagnosis therefore seems difficult in partial forms where serum testosterone can be between 2 and 2.5 ng/ml [25]. This is the case with our study.

CONCLUSION

Clomipramine and haloperidol have effects on male fertility in rats, but act at different levels. While clomipramine acts at the peripheral level (peripheral secretory azoospermia), haloperidol acts at the central level (hypo gonadotropic hypogonadism). However, these results deserve to be further developed before being extrapolated to humans.

Table I: Effects Of Haloperidol And Clomipramine On Morphological Variables Of The Rat.

	Control	Haloperidol	Clomipramine
Average testicular weight (grams)	6.8± 0.12	1.2±0.20	1.19±0.09
Spermogram			
PH	6.8±0.12	6.90±0.18	6.8 ± 0.2
Vitality (%)	55.4±3.15	44.9±6.20	45.2±5.11
Sperm count (x^{106}/ 2ml)	269.6±40.54	145.6±39.77	317.6±98.58
Spermocytogram (%)			
Normal morphology	91.2	87.7	81.8
Abnormal morphology	0.014	0.055	0.098

Table II: Effects of Haloperidol and Clomipramine on testosterone, FSH and serum LH in rats.

	Witnesses	Haloperidol	Clomipramine
Testosterone (ng/ml)	1,56± 0,15	2,66 ± 2,42	2,9 ±1,58
Follicle stimulating hormone (FSH) (IU/L)	0,87±0,15	0,72±39,94	1,38 ±0,48
Luteinizing Hormone (LH) (IU/L)	0,46±0,47	0,26±0,19	3,46±0,84

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