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Long-Term Effects of Contramal on Reproductive Physiology of Female Albino Mice

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Abstract:

The study aims to explain the dose-dependent possible deleterious effects of administration of Contramal, the known analgesic on the reproductive physiology of female albino mice. Contramal at a dose of 0.05mg/kg administered intramuscularly daily once for 60 days. Alterations in hormonal parameters like estrogen, progesterone, follicular stimulating hormone and Luteinizing hormone were investigated. Decrease in body and tissue weight were also recorded.

The present study investigates the dose-dependent deleterious effects of Contramal (Tramadol), a commonly prescribed analgesic, on the reproductive physiology of female albino mice. Experimental animals were intramuscularly administered Contramal at 0.05 mg/kg once daily for 60 days, while controls received saline. The study assessed alterations in body and organ weights along with hormonal parameters including estrogen, progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Results indicated significant reductions in body weight, ovary and uterus weights, as well as considerable alterations in the hormonal profile of treated mice. Long-term administration of Contramal markedly decreased steroidogenic activity, suggesting potential anti-steroidal effects. The findings highlight that chronic exposure to Contramal can adversely affect female reproductive health by disrupting the hypothalamic-pituitary-gonadal axis and altering biochemical as well as morphological parameters

***Key words**: Contramal Analgesic, Hormonal parameters, anti-steroidal effects.*

Introduction

Contramal, known generically as tramadol, is considered as a typical opioid drug and have some special pharmacological characters. It is one of the most commonly prescribed analgesic drugs to treat moderate to severe pain. Many investigators have reported that these drugs inhibit gonadotrophin secretions and causes sterility in female, where as in males, they reduced the level of plasma testosterone and affect the secretary functions of accessory sex organs resulting the condition similar to castration. Clout D.H (1971), Sreenivasan and Vijayan (1996) have demonstrated that opiates and opioids exert an inhibitory action on the intramuscular metabolism. According to Karla (1984), opioid, adrenergic systems and steroids are known to affects the regulation of luteinizing hormone in rats.Daniell (2008) stated that opioid treatment force to impaired endocrine function and deregulated sex steroid balance in women. Long-term opioid use exposes women to unique risks, including endocrionopathy reducing fertility reported by Beth (2012). According to Evans et.al (1993), the opioid drugs being CNS influencing drugs inhibit the release of FSH and LH from pituitary by acting through hypothalamus, blocking the neural stimulation to the gonadotropins releasing hormone resulting into the alterations in biochemical parameters of reproductive physiology including morphological changes. Therefore, the present study was undertaken to find out the effect of administration of contramal (im) on reproductive physiology of female albino mice.

Materials And Methods

The study was carried on female albino mice weighing about 35±2 g. They kept under standard laboratory condition with proper diet and water *ad libitum.*

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The mice were divided in to two groups i.e. Group I : Control :Injected (im) with 0.2ml saline water as vehicle daily one time up to 60 days. Group II : Experimental : administered (im) with 0.05 mg/kg dose of Contramal daily once up to 60 days. Only healthy mice were used for experimental purpose. After 30 and 60 days of treatment control and experimental Female mice were weighed. For the biochemical analysis the blood sample was collected from both the groups i.e. control and experimental. The blood was collected from the retro-orbital veins and collected in glass vial. The samples were then centrifuge at 2500 rpm for 15 minute to collect the serum for biochemical analysis. Serum Estrogen, progesterone, FSH and LH was estimated by using kits purchased from Roche Diagnostics, Germany.

Results And Discussion

Table:1 Body weight and organ/tissue weight of Female Albino mice administered with Contramal for 60 days

S.N	Body weight and organ/tissue weight	Days of Treatment		
		Control/Expt.	30 Days	60 Days
1	Body Weight(g)	Control	35.04±1.09	38.18±1.10
		Experimental	27.00±1.50	24.08±0.90
2	Ovary (mg)	Control	18.03±6.10	22.61±3.30
		Experimental	15.09±4.14	11.43±2.70
3	Uterus (mg)	Control	118.45±6.10	125.44±5.58
		Experimental	99.15±6.10	79.14±5.04

Results are means ± of SE of six replicates.
Figures in parenthesis indicate percentage change over control.

Table:2 Concentration of serum FSH, LH, Estrogen and Progesterone of Female Albino mice administered with Contramal for 60 days

S.N	Biochemical Parameter	Days of Treatment		
		Control/Expt.	30 Days	60 Days
1	Estradiol(pg/ml)	Control	86.04±0.09	90.00±0.10
		Experimental	84.14±0.11	76.10±0.05
2	Progesterone(ng/ml)	Control	14.02±0.04	16.00±0.10
		Experimental	12.08±0.02	11.24±0.11
3	FSH (IU/L)	Control	03.08±0.06	03.44±0.12
		Experimental	02.88±0.13	02.14±0.08
4	LH (IU/L)	Control	02.74±0.13	03.08±0.10
		Experimental	02.98±0.07	02.04±0.15

Results are means ± of SE of six replicates.
Figures in parenthesis indicate percentage change over control.

No mortality was observed during the experimental period. The administration of Contramal had significant effects on body and organ weight of treated female rats. The mice administered with vehicle (Group I) showed steady gain in body weight up to 60 days, whereas the mice treated with Contramal showed decrease in body weight (Table-1) due the anti-steroidal activity of drug with their anti-anabolic action. A similar observation was reported in morphine and nicotine treated albino rats by Chinoy and Seethalakshmi (1978). According to findings of Chinoy and Seethlakshmi(1978), decrease in organ weight and low protein content indicates the retarded gonadal growth as FSH is essential for protein synthesis in gonads The long term administration of Contramal showed significant changes in the values of FSH and LH due to the lowered steroidogenesis, which is dependent on availability of pituitary gonadotropins hormones stated by Hopwood et.al.(1998). This observations is supported by Kasson and Hsuch(1985) and Meyer and Curr (1987) on the similar studies with nicotine. Paulis and Abbas (2015) supported the same observation when studied on the chronic administration of contramal in female albino mice diminished both pituitary hormones i.e FSH and LH due to the opioid nature of drug which decreases the release of GnRH or interfere with signalling pathways that lead to the release of luteinizing hormone and follicle-stimulating hormone through pituitary gland decrease the release of FSH and LH by the pituitary gland. Colameco and Coren (2009), and Seyfried and Hester(2012).The level of Estrogen exhibit more significant changes in the ovary and uterus after 60 days of treatment due to disrupting the hypothalamic-pituitary-gonadal (HPG) axis,

which regulates the production of these hormones supports the present findings and Similar findings was recorded by Daniel(2008) that the opioids may also have direct effects on the ovaries, potentially interfering with their ability to produce estrogen and progesterone. In the present study the lowered values of estrogen and progesterone in contramal treated mice attributed with findings of Paulis and Abbas(2015).They reported that the administration of Tramadol Decrease Gonadal Hormones I.E Estrogen And Progesterone In Female Rats.

Conclusion

Long-term administration of Contramal had adverse effects on body and tissue weight. It also exert the on the biochemical parameters like FSH, LH, Estrogen and Progesterone and overall reproductive physiology of albino mice. Thus, the study suggests that the repeated use of drug may pose anti-steroidal effects.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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