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The Effect of Amantadine on Clomipramine Induced Sexual Dysfunction in Male Rats

Sheshadri Shekar Devaangam, Satyanarayana S, Eswar Kumar K, Vivek B, Velmurugan C, Ashok Kumar

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Abstract

Objective: Several studies have reported that Clomipramine has the ability to suppress male rat sexual behavior. Literature indicates that the activation of brain D_2 receptors causes facilitation of penile erection, and a number of reports have indicated dopamine's involvement in sexual function. Hence this study was undertaken to investigate the effect of Amantadine, a dopamine agonists on the Clomipramine induced sexual dysfunction.

Methods: The study subjects involved a total of 48 males and 48 females, 4 months old Sprague-Dawley albino rats, all housed in a group of six males and females separately in plexi glass cages in an acclimatized colony room (25±0.5^{0}C) maintained on a 12/12 hr light/dark cycle. The male rats were randomly divided into four groups of 12 male rats each. Group I served as controls. Group II, III, and IV were treated with Amantadine (9 mg/kg body weight, *p.o*) 30 min, prior to the treatment with 13.5 mg/kg, 27 mg/Kg and 54 mg/Kg bodyweight *p.o* of Clomipramine respectively for 60 days. The control group received vehicle 1 ml / kg *p.o*. The sexual behavior of the male rats was observed to determine the following parameters: mount latency, intromission latency, ejaculation latency, post ejaculatory pause, and intromission frequency. As well as the sexual behavior; serum testosterone and histopathology of the testes were also investigated in this study.

Results: The results indicate that Amantadine in all aspects failed to antagonize Clomipramine induced sexual dysfunction in male rats. Even the sexual competence of male rats treated with ½ therapeutic dose (TD) of Clomipramine failed to regain their sexual competence in the presence of Amantadine. Testicular damage and decline in testosterone levels continued in the presence of Amantadine.

Conclusion: Overall, the results suggest that Amantadine could not be a safe antidote to antagonize Clomipramine induced sexual dysfunction.

Keywords: Clomipramine; Amantadine; Male rat sexual dysfunction; Testosterone; Testes.

Sheshadri Shekar Devaangam ✉, **Vivek B, Velmurugan C, Ashok Kumar**
Department of Pharmacology, Sri K.V College of Pharmacy, Chickballapur, Karnataka, India.
E-mail: sheshadrishekar@gmail.com

Satyanarayana S, Eswar Kumar K
Department of Pharmacy, College of Pharmaceutical Sciences, Visakhapatanam, Andhra Pradesh, India.

Introduction

The sexual act involves central as well as peripheral mechanisms.[1] Several mediators are involved in the central mechanisms. It is well established that noradrenaline,[2,3] serotonin,[4,5] and dopamine are involved in the central mechanisms.[4,5] Noradrenaline plays an excitatory role, while the role of serotonin is inhibitory.

Clomipramine (Clmp) is a tricyclic antidepressant, which has demonstrated efficacy in depression, obsessive compulsive disorder (OCD) and panic disorder. Clomipramine is the imipramine analogue of chlorpromazine. Due to its action against anxiety disorders and panic attacks, it is the only drug with 2 entries in the essential drugs list of the World Health Organization (WHO). With regards to compulsive disorders, it is now the "gold standard" of therapy against which other drugs are measured.[6-10] However, chronic use of Clomipramine leads to sexual dysfunction in humans[11,12] and neonatal males.[13]

Compared to other tricyclic antidepressants, Clomipramine has much greater effect on dopamine blockade and serotonin reuptake inhibition.[14] These implicate the prolactin release and orgasmic dysfunction mediated through 5-HT_2 receptors.[15,16] Moreover, peripheral antimuscarinic,[17] and alpha adrenergic blockade effects have been implicated in the Clomipramine induced sexual dysfunction.[11,12,18] There are few studies of clinical management of Clomipramine induced sexual dysfunction. Case reports and open trials have suggested that Yohimbine,[19] Bupropion,[20] Cyproheptadine,[21] and Amantadine,[22,23] may be effective in the antidepressant induced sexual dysfunction.

Hence, the present study was conducted to find out whether dopamine agonists such as Amantadine can antagonize the Clomipramine induced sexual dysfunction in male rats. Amantadine acts by increasing dopamine levels centrally, increasing dopamine release, inhibiting amine uptake, or through direct action on dopamine receptors.[24] The doses were selected by extrapolating the human therapeutic dose to rats based on the body surface area.[25]

The Clomipramine doses selected were ½TD, TD, 2TD considering 300 mg as the maximum human therapeutic dose per day and it was found to be 13.5 mg/kg, 27 mg/kg and 54 mg/kg respectively. The influence of Amantadine on Clomipramine induced sexual dysfunction was tested with Amantadine (9 mg/kg) considering 100 mg as the maximum human therapeutic dose.

Methods

A total of 48 male and 48 female Sprague-Dawley albino rats were purchased from central animal house NIMHANS, Bangalore. All animals were housed in a group of six males and females separately in plexi glass cages (62 × 40 × 21) in an acclimatized colony room (25±0.5^{0}C) maintained on a 12/12 hr light/dark cycle. The rats were 4 months old. The males weighed around 300-400 gm each and females weighed 250-350 gm each. They were fed on commercial pellet feed and water was available *ad libitum*. The study was approved by the Institutional Ethical Committee prior to commencement.

The male rats were randomly divided into four groups of 12 male rats each. Group I served as controls. Group II, III, and IV were treated with Amantadine (9 mg/kg body weight, *p.o*) 30 min, prior to the treatment with 13.5 mg/kg, 27 mg/Kg and 54 mg/Kg bodyweight *p.o* of Clomipramine respectively for 60 days. The control group received vehicle 1 ml / kg *p.o*. All the animal studies were carried out after 7 PM in the animal house of Sri K.V College of Pharmacy, Chickballapur.

The sexual behavior of the male rats was studied as explained elsewhere,[26] the copulatory behavior of the male rat was characterized by a series of mounts with or without vaginal intromission from the rear of the female approximately once in every 30 to 120 sec, that eventually culminates in ejaculation. The females responded to each mount with a lordosis response, namely; a dorsoflexion of the spine and deflexion of the tail to one side allowing vaginal access for the male.

Typically, the male achieves vaginal penetration on 50-80% of the mounts. Intromission patterns can be distinguished behaviorally from mounts with penetration by the presence of deep thrust and springing dismount.[27] A mount was defined as the male's pelvis intentionally coming into contact with the female's haunch with accompanying hip movements from the male. An intromission was identified when the male mounted and achieved insertion of the penis into the female as marked by deeper than normal thrust usually followed by abrupt movement away from the female, urgent front leg movements and grooming. Ejaculation was marked by a more profound thrust than that of regular intromission and was followed not by movement away from the female, but by sudden limpness and immobility until the female moves away. After ejaculation and immobility, the male was engaged in the long period of grooming (5-10 min) post ejaculation pause.[26]

An ejaculation occurred after 6-15 intromissions and was followed by a period of 5-10 minutes post ejaculatory interval during which the male is refractory to further copulatory activity. The number of intromissions and latency to ejaculate at first decreases and then subsequently increases with increasing number of ejaculations.[27] The ejaculatory activity of males was confirmed by observing the vaginal smear of the females for the presence of male sex cells. The following parameters were recorded: mount latency (Time taken for the first mount from the introduction of the female into the male cage), intromission latency (Time taken for the first intromission from the introduction of females into the males' cage), ejaculation latency (intervals between the first intromission to the first ejaculation), post ejaculatory pause (Time interval between ejaculations to the next mount/intromission), intromission frequency (Number of intromissions preceding ejaculation) and Mounting frequency (Number of mounts preceding ejaculation).

Using these measures the following parameters were computed: % mounted, % intromitted, % ejaculated, copulatory efficiency (Number intromissions/ number of mounts + number intromission) and inter copulatory interval (Average time interval between intromissions).

Half of the animals in each group were sacrificed on 30th day and the remaining on 60th day for blood sample collection and for histopathological examination of the testes. Blood was collected through the cardiac puncture using a 16 no. needle under mild ether anesthesia and allowed to stand for 20 minutes. After centrifugation, serum was separated and stored at -20°C for subsequent hormonal estimation. The testes were also collected and processed in Bouin's fluid,[28] for the histopathological studies. The sections were examined under high power microscope. The evaluation of the cell population was based on the calculation made for each type of developing sperm cells per cross section of ten randomly selected seminiferous tubules. The sertoli cells, spermatogonia, secondary spermatocytes and spermatids were counted under 100× magnification.[29,30]

Results

In terms of the Amantadine and Clomipramine combined influence on sexual behavior of male rats, the number of rats intromitted and ejaculated was reduced, dose dependently and time dependently in the ½TD and TD Clomipramine treated groups. However, in 2TD group, suppression of libido was observed on 60th day. The number of rats intromitting and ejaculating was further reduced when compared to ½TD and TD group. Hence Amantadine failed to antagonize the effect of Clomipramine on sexual behavior. All the latencies for example mount latency, intromission latency and ejaculation latency were increased significantly compared to the controls. The results also conveyed a decrease in the number of intromissions and an increase in the number of mounts, thus leading to a decrease in the copulatory efficiency. Post ejaculation pause was also increased when compared to controls. (Table 1)

With regards to the combined effect of Amantadine and clomipramine on serum testosterone level; the results showed a significant dose dependent decrease in the mean serum testosterone levels in the TD Group and 2TD Group after 30 days treatment. At the end of the 60 days, the mean testosterone levels were further reduced in the TD Group and 2TD Group animals. (Table 2)

Table 1: Effect of chronic oral administration of Amantadine and Clomipramine on sexual behavior parameters of male rats (Data given as mean ±SEM, N=12 for 0-30th day & N= 6 For 30-60thday).

Parameter Studied	Control				AMA + CLMP 13.5 mg/kg			
Days	0	15	30	60	0	15	30	60
% Mounted	100	100	100	100	100	100	100	100
% Intromitted	100	100	100	100	100	100	100	50
% Ejaculated	100	100	100	100	100	75	75	50
Mount latency	5.37±0.84	8.5 ±1.29	8.87± 1.02	7.5± 0.8	4.57±0.32	70±5.3**	69.75 ±5.1**	115± 2.88*
Intromission latency	23.5±4.9	20.65 ±4.8	18.62± 1.4	20.5 ±1.8	177.5±18.7**	190.5±30.5**	237.5 ±13.3**	672.5±376.3*
Ejaculation Latency	360±18.4	375.5 ±9.4	372.5 ±8.8	375±6.45	430±21.95*	945±196.6**	832.5 ±211.6**	1452.5±200.7*
No of intromission	15.625±0.3	15.625±0.3	15.37±0.2	15.5±0.2	17.12±0.44*	24.8±1.77**	23.5±0.5**	13.75±6.8*
No of mounts	2.5±0.32	2.25±0.36	2.62±0.4	3.5±1.08	3.5 ±0.42	4.12±0.4*	3.8±0.47	8.25± 0.7*
Post ejaculation pause	262.5±10.9	290±30.9	225±15.0	270±19.14	335.5 ±32.5*	632.5±248*	667.5±248.0*	1105±401.7*
Copulatory Efficiency	0.85±0.01	0.86±0.2	0.85±0.03	0.82±0.04	0.79±0.16	0.8±0.02	0.86±0.01	0.49±0.22
Inter copulatory Interval	23.13±1.43	24.15±0.5	24.29±0.8	24.2±0.7	21.44±3.4	38.3±7.4	35.58± 8.1	35.3 ± 20. 3

Significant at p values: <0.05, 0.01** compared to control (Mann-Whitney "U" Test)*

Table 1: Effect of chronic oral administration of Amantadine and Clomipramine on sexual behavior parameters of male rats (Data given as mean ±SEM, N=12 for 0-30th day & N= 6 For 30-60thday). *-continued*

Parameter Studied	AMA + CLMP 27 mg/kg				AMA + CLMP 54 mg/kg			
Days	0	15	30	60	0	15	30	60
% Mounted	100	100	100	100	100	100	100	0
% Intromitted	100	75	75	50	100	50	41.6	0
% Ejaculated	75	50	25	0	41.6	25	0	0
Mount latency	10.75±0.5**	71.8 ± 4.8**	127.5±12.7**	248.7±52.4*	33.12± 0.98**	115±7.3**	262.5± 20.15**	1800±0*
Intromission latency	637.5± 254.0**	1058.75± 280.23**	1113.7± 259.5**	1165± 366.6*	245±14.01**	1017.5± 295.9**	1220± 283.27**	1800±0*
Ejaculation Latency	817.5± 215.12**	1395± 154.95**	1597.5 ± 133.6**	1800±0*	1382.5 ± 207.35*	1560± 163.5**	1800±0**	1800±0*
No of intromission	16.3±3.9	9±3.4**	8.5 ± 3.4**	5±3*	17.75±3.0	7.75±2.9**	6±2.9**	0*
No of mounts	3.75±0.5	6.3±0.4**	12.5±1.2**	10±1.8*	4.8±0.9	7.6±1.05**	5.8±1.1	0*
Post ejaculation pause	615±258.7*	1137.5± 250.6**	1462.5± 221.15**	1800±0*	1237.5±274.7**	1475±212.7**	1800±0**	1800±0*
Copulatory Efficiency	0.61±0.13	0.35±0.13**	0.61±0.13	0.35±0.13**	0.61±0.13	0.35±0.13**	0.61±0.13	0.35 ± 0.13**
Inter copulatory Interval	18.2±4.8	39.03±17.15	18.2 ± 4.8	39.03± 17.15	18.2 ±4.8	39.03±17.15	18.2±4.8	39.03 ± 17.15

Significant at p values: <0.05, 0.01** compared to control (Mann-Whitney "U" Test)*

Table 2: Influence of Amantadine and Clomipramine on serum testosterone levels in male rats (Data given as mean ± SEM, N=6).

Treatment	Testosterone ng/ml (30 DAYS)	Testosterone ng/ml (60 DAYS)
Control 1ml/kg	6.55 ± 0.66	5.07 ± 0.3
AMA+CLMP 13.5 mg/kg	5.68± 0.6	5.77± 0.45
AMA+CLMP 27 mg/kg	3.8 ± 0.51**	2.97±0.17**
AMA+CLMP 54 mg/kg	1.95 ± 0.14**	1.5 ±0.04**

Significant at p<0.05, 0.01** compared to control (student "t" test)*

Table 3: Amantadine and Clomipramine treatment influence on histology of testes (Data given as mean ± SEM, N=6).

Treatment (days)	Sertoli Cells		Sp gonia		Secondary Spermotocytes		Spermatids	
	30 Days	60 Days	30 Days	60 Days	30 Days	60 Days	30 Days	60 Days
Control 1ml/kg	3.5±0.288	3.5±0.288	8.25±0.4	8.25±0.4	48.75±0.75	48.75±0.75	119.75±2.04	113.8±2.24
AMA+CLMP 13.5 mg/kg	2.75±0.25	3±0.4	7±0.48	6.5±0.28**	49.75±0.9	49.25±2	65.125±1.74 ***	65.12±1.73 ***
AMA+CLMP 27 mg/kg	2.75±0.2	2.25±0.2**	5±0.4**	5±0.7**	35.5±1.56**	29.5±0.86**	48.125±1.30 ***	39.75±1.6 ***
AMA+CLMP 54 mg/kg	1.5±0.2**	1.5 ± 0.2**	4±0.40**	4.5±0.29**	25.75±0.8**	22±0.5**	26.37±1.54 ***	15.87±1.34 ***

Significant at p<0.05, 0.01** compared to control (student "t" test)*

The combined effect of both Amantadine and clomipramine on the histology of the testes at the end of 30 days revealed no significant changes between the control group and ½TD group. Hence, a significant reduction in spermatogonia, spermatids and secondary spermatocytes was observed in the TD group. While in the 2TD group, a reduction in Sertoli cells, spermatogonia, spermatids and secondary spermatocytes was observed. Hence Amantadine had not offered the animals any protection at higher doses of Clomipramine. After 60 days of treatment, the decrease in sperm cell count was also continued with higher doses of Amantadine + Clomipramine. Thus no significant changes were observed between ½TD group and the Clomipramine treated control group. Therefore, Amantadine could not be a safe antidote for the treatment of Clomipramine induced sexual dysfunction. (Table 3, Figs. 1A-G)

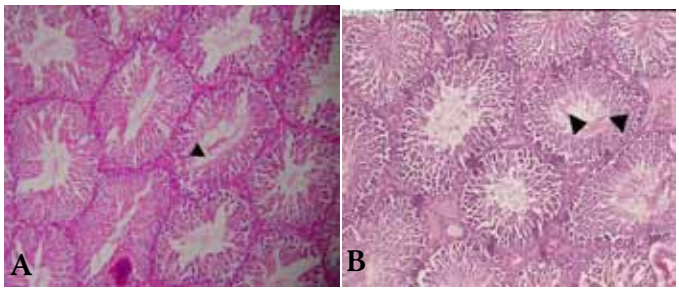

Figure 1: (A) Lumen filled with spermatozoa (arrows) (Control 400× normal); (B) Damaged epithelium & Lumen filled with spermatozoa (arrows) (Ama + 13.5mg Clmp 30 days treatment (400×)

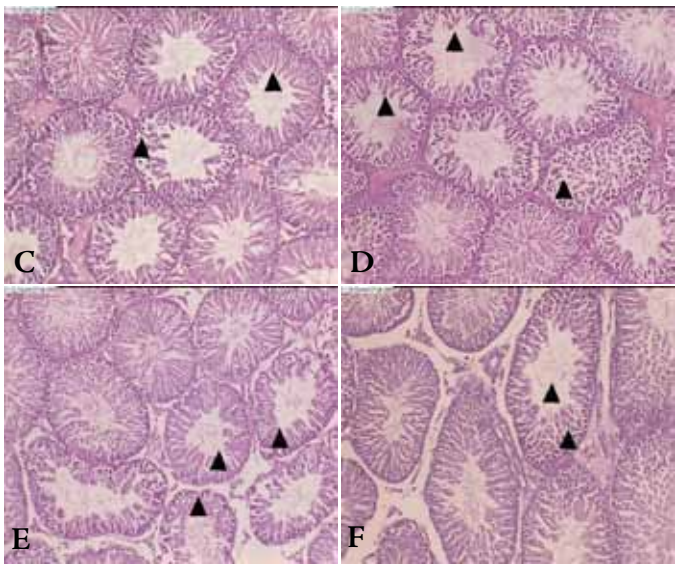

Figure 1: (C) congested seminiferous tubules & Lumen with decreased spermatozoa (arrows), (Ama + 13.5 mg /kg Clmp 60 days treatment 400×); (D) Lumen with decreased spermatogenesis & fragmented nuclei (arrows) (Ama + 27mg Clmp 30 days treatment 400×). ; (E) Loss of basement membrane & Disturbed architecture of seminiferous Tubule (arrows) (Ama + 27 mg/kg Clmp 60 days treatment 400×); (F) Empty lumen & Scattered Seminiferous (arrows) (Ama + 54 mg/kg Clmp 30 days treatment 400×).

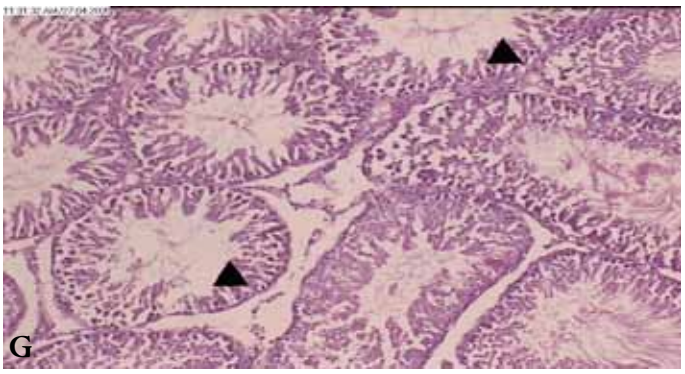

Figure 1: (G) Empty lumen (arrows) (Ama + 54 mg / kg Clmp 60 days treatment 400×).

Discussion

In this study, the hormonal and peripheral testicular parameters indicate that Amantadine, a dopamine agonist did not change the Clomipramine induced sexual dysfunction in male rats. Pharmacological evidence demonstrated that the elevation of cerebral levels of 5-HT affects the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH), for inhibiting the liberation of gonadotrophin releasing hormone (GnRH) in the hypothalamus, with subsequent effects on the process of spermatogenesis and steroidogenesis in adult rats.[31,32] Serotonin is present in the testis and accessories glands, besides many organic tissues. In these glands, monoaminoxidase, the enzyme that metabolizes 5-HT is also detected.[33-36] In rats, the testicular 5-HT can originate from the nerve endings in the capsule, the mast cells and the Leydig cells.[34,35,37] In the testis, the 5-HT can reduce the steroidogenesis and spermatogenesis by decreasing the intra-testicular flow due to arterial constriction or by inhibiting the fundamental enzymes for steroidogenesis.[38,39] On the other hand, a number of reports indicate that dopamine is involved in sexual function.[40,41]

Earlier reports have also indicated that Clomipramine causes a decline in testicular cell development in male rats treated with ½TD, TD and 2TD of clomipramine.[42] Hence Amantadine, a dopamine agonist was used to determine its usefulness on the ability to antagonize the Clomipramine induced sexual dysfunction. The study revealed that Amantadine did not antagonize Clomipramine induced sexual dysfunction and hence is not useful to treat Clomipramine induced sexual damage in male rats. As per the reports,[43-45] Amantadine did not possess dopamine agonistic action in rats. The same reason may be responsible for the absence of efficacy against Clomipramine induced sexual dysfunction.

In the sexual behavior study, the number of rats mounted, intromitted and ejaculated was decreased, dose dependently and time dependently. Prolongation of intromission latency, ejaculation latency and post ejaculation pause were also continued with Amantadine treatment. Copulatory efficiency also decreased gradually, dose dependently and time dependently indicating that erection failure was continued. Overall, Amantadine failed to improve sexual behavior of male rats treated with different doses of clomipramine in the sexual behavior study. The Amantadine + Clomipramine 27 mg/kg reduced the level of serum testosterone, dose dependently and time dependently. This indicates that Amantadine also failed to alter the Clomipramine induced decline in testosterone levels. (Table 2)

All the parameters measuring spermatogonia, spermatids and secondary spermatocytes were significantly decreased dose dependently, mostly due to decreased levels of FSH, LH and testosterone, which are essential for the completion of the spermatogenesis process. Overall, it appears that Amantadine did not offer any protection against Clomipramine induced sexual dysfunction. The testes are the gonads in males and contain three different types of cells namely: Leydig cells (responsible for the production of testosterone); spermatogonia (responsible for spermatogenesis, i.e., sperm cells) and Sertoli cells (responsible for the secretion of androgen binding protein, inhibin, sulfated glycoprotein-2 and transferrin).[46] FSH is responsible for the development and differentiation of spermatogonia through different stages namely spermatogonia, preleptotene, leptotene, early pachytene, late pachytene, and secondary spermatocytes after the attainment of puberty.[47] FSH acts predominantly to support spermatogonial (SG) number, to prevent the premature degeneration of SGs and spermatocytes (SCs). The principal effect of testosterone is to facilitate the progression of SCs in further stages of spermatogenesis, perhaps by maintaining their attachment to Sertoli cells.[46] In other words, FSH is responsible for sperm maturation, while LH is responsible for steroidogenesis.[48]

Brown and Redfern in1976 reported that the anti-parkinsonian effect of Amantadine was not mediated through dopamine. Furthermore, Mercur et al. (1991) concluded that Amantadine failed to elevate the dopamine levels in the rat substantia nigra, zona compacta neurons. While Kornhuber and Weller (1993) confirmed that the anti-parkinsonian effect of Amantadine was due to its action against N-methyl-D-aspartate (NMDA) type of glutamate receptor. Hence the above findings indicate that anti-parkinsonian effect of Amantadine may not be mediated with elevation of dopamine, as our results also substantiate the above findings. The results also indicated that Amantadine did not influence dopamine mechanism and it was not effective in improving the condition of Clomipramine induced sexual dysfunction in rats.

Conclusion

The present study revealed that Amantadine, a dopamine agonist failed to antagonize the Clomipramine induced sexual dysfunction in male rats. The fall in testosterone, sexual behavior and sperm cell count were continued even in the presence of Amantadine. The results also indicate that Amantadine unable to antagonize the ½TD Clomipramine induced sexual dysfunction in male rats. Moreover, Amantadine could not be considered a safe antidote to treat Clomipramine induced sexual dysfunction in male rats.

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