

Study of Psychopharmacological Profile of Ondansetron – A selective 5-HT₃ Receptor Antagonist



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ABSTRACT

Since 5-HT₃ antagonists have been shown to influence dopaminergically mediated behaviours originating from nucleus accumbens, so we have investigated the psychopharmacological profile of Ondansetron pertaining to its effects on behaviours dependent on functional status of the nigrostriatal dopaminergic system viz-DA agonist (apomorphine & dexamphetamine) induced SB (stereotyped behaviour) of the oral movement variety & neuroleptic induced catalepsy in rats. Albino rats and mice of either sex, were used for the study. In our study, Ondansetron in mice did not produce motor incoordination, ataxia or muscular hypotonia neither did it inhibit the righting reflex. It did not induce catalepsy at any of the testing time intervals and did not induce stereotyped behavior in rats. Further, pretreatment with Ondansetron did not significantly influence both apomorphine & d-amphetamine induced SB in rats. Ondansetron did not induce cage climbing behaviour in mice. Further pretreatment with Ondansetron did not significantly modify apomorphine - induced cage climbing behaviour in mice. Ondansetron pretreatment did not antagonise haloperidol- induced catalepsy in rats. So, we conclude that Ondansetron does not possess post synaptic striatal D2 DA receptor blocking activity & does not influence striatal D2 dopamine receptor mediated behaviours.

INTRODUCTION -

Ondansetron, a selective 5-HT₃ receptor antagonist, is useful in patients with nausea, vomiting associated with cancer chemotherapy, radiotherapy anaesthesia & surgery. Several lines of evidence have suggested link between serotonergic & dopaminergic systems in the brain. The central serotonergic systems modulate the activity of the central dopaminergic systems. In recent years the effects of selective agonists & antagonists of different types of 5-HT receptors have been studied on dopamine dependent behaviours (1,2,3).

Biochemical studies have demonstrated that 5-HT₃ receptor agonists stimulate DA release in nucleus accumbens (4) while behavioural studies indicate that 5-HT₃ antagonists inhibit dopaminergic neurotransmission in the nucleus accumbens (5,6).

Since 5-HT₃ antagonists have been shown to influence dopaminergically mediated behaviours originating from nucleus accumbens, so we have investigated the psychopharmacological profile of Ondansetron pertaining to its effects on behaviours dependent on functional status of the nigrostriatal dopaminergic system viz-DA agonist (apomorphine & dexamphetamine) induced SB (stereotyped behaviour) of the oral movement variety & neuroleptic induced catalepsy in rats.

AIMS AND OBJECTIVES -

To evaluate psychopharmacological profile of Ondansetron with respect to its effects on behaviours dependent on functional status of the nigrostriatal dopaminergic system

So we have investigated-

- Whether Ondansetron induces catalepsy in rats.
- Effect of Ondansetron pretreatment on apomorphine- induced SB behaviour in rats.
- Effect of Ondansetron pre-treatment on apomorphine- induced cage climbing behaviour in mice.
- Effect of Ondansetron pretreatment on d-amphetamine induced SB in rats.
- Effect of Ondansetron pretreatment on haloperidol -induced catalepsy in rats.

MATERIAL AND METHODS

Animals:

Albino rats and mice of either sex, weighing between 100-180gm and 20-30gm respectively, were used for the study. They were al-

lowed food, water ad libitum up to the time of experimentation. Each animal was used only once. All observations were made between 10 and 17 hours at 27-30°C in a noiseless, diffusely illuminated room. Each group consisted of 10 animals.

Animals were kept under standard laboratory conditions. Procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with the national and international law and policies.

Drugs:

The drugs used were Ondansetron Hydrochloride (Emeset injection, Cipla Ltd.), Haloperidol (Serenace injection, Searle India Ltd.), Apomorphine hydrochloride (Sigma) and Dexamphetamine Sulfate (Koch- light).

d-Amphetamine and Imipramine were dissolved in distilled water while Apomorphine was dissolved in distilled water containing 0.2 mg/ml ascorbic acid. Ondansetron, Haloperidol and Reserpine injection solutions were diluted to required strength with distilled water. All drugs solutions were prepared immediately before use and were injected intra-peritoneally. In rats, the volume of drug injection was 2 ml/kg, while in mice; it was 10 ml/kg. Doses refer to the forms mentioned.

STATISTICS

The results were statistically analyzed by the student's unpaired t-test with differences considered significant at p<0.05.

METHODS

Catalepsy testing in Rats:

For observation and measurement of catalepsy the animals were placed in individual perspex cages (30x 20x 20cm), 30 min before the drug treatment to allow adaptation of new environment. Rats were tested for catalepsy according to the method of Costall and Naylor (6). The animals were tested for catalepsy by placing both front limbs of the animal over an 8 cm high wooden block and measuring the time that the animal maintained this posture. Animals maintaining the imposed posture for 10 sec or more were said to be cataleptic. Animals were tested for catalepsy 0.5, 1.0, 2.0, 3.0 and 4.0 hours after Ondansetron and haloperidol treatment.

Ondansetron was tested in the doses of 1.25, 2.5 and 5 mg/Kg i.p. in rats while haloperidol was tested in the dose of 1 mg/kg i.p.

Ondansetron on Stereotyped Behavior (SB) Induced by Apomorphine and D-Amphetamine in Rats:

For observation of SB, the rats were placed in individual cages made of wire netting, measuring 30x 20x 20cm, 30min before drug treatment to allow adaptation to the new environment.

The intensity of SB was assessed over a 30 sec observation period at 10 min intervals through its duration, using the scoring system of Costall and Naylor (6) where periodic sniffing = score 1, continuous sniffing = 2, periodic biting, gnawing or licking = 3 and continuous biting, gnawing and licking = 4. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group.

Ondansetron and haloperidol were injected 30 min before apomorphine or d-amphetamine treatment. Control groups received 2 ml/kg body weight of distilled water i.p. 30 min before receiving apomorphine or d-amphetamine.

Ondansetron was tested in the doses of 1.25, 2.5 and 5mg/kg i.p. while haloperidol was tested in the dose of 0.5 mg/kg i.p.

Ondansetron On Haloperidol-induced catalepsy In Rats:

For Observation and measurement of catalepsy the rats were placed in individual Perspex cages (30x20x20cm) 30 min before the drug treatment to allow adaption to the new environment. Catalepsy was evaluated by placing both front limbs of the animal over an 8 cm high wooden block and measuring the time for which the animal maintained the imposed posture. Scoring modified from that of Costall and Naylor (6), was as follows: maintaining the cataleptic posture 0- 10 sec. (0), 11-30 sec. (!); 31-60 sec (2) ; 61-120 sec (3); 121 sec and more (4). Animals were tested for catalepsy 1 and 2 hours after haloperidol treatment. Catalepsy score of each animal in the group at the respective testing time interval was taken to compute the mean value of the group.

Ondansetron was injected 30 min before haloperidol while the control groups received distilled water (2 ml/kg i.p.) 30 min before receiving haloperidol.

Ondansetron was tested in the doses of 1.25, 2.5 and 5 mg/kg i.p. while haloperidol was tested in doses of 0.5 and 1 mg/kg i.p.

Ondansetron On Apomorphine-Induced Cage Climbing Behavior In Mice:

Effect of pretreatment with Ondansetron or haloperidol on apomorphine-induced cage climbing behavior was studied by the method of Costall et al. (6). Mice exhibited climbing behavior following i.p. apomorphine (0.5 to 1 mg/kg). To quantify this behavior, animals were placed in individual cages made of wire netting, measuring 20 cm x 25 cm and 15 cm high. Thirty minutes were allowed for the animals to acclimatize themselves to the new environment. Mice were individually tested for climbing behavior, taking the percentage of time spent climbing during the 30 min after the first climb as as measure of climbing (the climbing index).

Further the maximum time (in min) spent in a single climb throughout the duration of the apomorphine effect was also determined.

Ondansetron and haloperidol were injected 30 min before apomorphine while the control groups received distilled water (10 ml/kg i.p.) 30 min before receiving apomorphine.

Ondansetron was tested in the doses of 0.625, 1.25 and 2.5 mg/kg I.p. while haloperidol was tested in the dose of 0.5 mg/kg i.p.

OBSERVATION AND RESULTS

GENERAL OBSERVATIONS:

Ondansetron in the doses of 1.25, 2.5 and 5 mg/kg i.p. in rats and 0.625, 1.25 and 2.5 mg/kg i.p. in mice did not produce motor

in-coordination, ataxia or muscular hypotonia, neither did it inhibit the righting reflex. As doses beyond 5 mg/kg i.p. in rats and 2.5 mg/kg i.p. in mice had produced ataxia, motor incoordination, muscular hypotonia and mortality; for subsequent studies Ondansetron was therefore used in doses of 1.25, 2.5 and 5 mg/kg i.p. in rats and 0.625, 1.25 and 2.5 mg/kg i.p. in mice.

INDUCTION OF CATALEPSY IN RATS:

Ondansetron in the doses of 1.25, 2.5 and 5 mg/kg i.p. in rats did not induce catalepsy at any of the testing time intervals.

Haloperidol (1 mg/kg i.p.) induced catalepsy in 100% of the rats at all the testing time intervals.

EFFECT OF ONDANSETRON PRETREATMENT ON APOMORPHINE-INDUCED SB IN RATS:

The results are given in table 1. Ondansetron (1.25, 2.5 and 5 mg/kg i.p.) did not induce SB in rats. Apomorphine (0.5, 1 and 2 mg/kg i.p.) induced dose-dependent SB in rats (Table 1).

Pretreatment with Ondansetron (1.25, 2.5 and 5 mg/kg i.p.) did not significantly influence apomorphine induced SB. However, pretreatment with 0.5 mg/kg i.p. haloperidol abolished the SB induced by 0.5, 1 and 2mg/kg i.p. apomorphine (Table 1).

Study	Treatment dose mg/kg	Intensity score Mean \pm S.E.M.
I	APO 0.5	1.2 \pm 0.13
	OND 1.25 + APO 0.5	1.3 \pm 0.15
	OND 2.5 + APO 0.5	1.0 \pm 0.00
	OND 5 + APO 0.5	1.1 \pm 0.10
	HAL 0.5 + APO 0.5	0.0
II	APO 1	2.1 \pm 0.10
	OND 1.25 + APO 1	2.2 \pm 0.13
	OND 2.5 + APO 1	2.1 \pm 0.10
	OND 5 + APO 1	2.0 \pm 0.00
	HAL 0.5 + APO 1	0.0
III	APO 2	3.3 \pm 0.15
	OND 1.25 + APO 2	3.2 \pm 0.13
	OND 2.5 + APO 2	3.4 \pm 0.16
	OND 5 + APO 2	3.1 \pm 0.10
	HAL 0.5 + APO2	0.0

Table 1 showing effect of Ondansetron (OND) and haloperidol (HAL) pretreatment on apomorphine (APO) – induced SB in rats.

P>0.05

Number of animals n = 10

EFFECT OF ONDANSETRON PRETREATMENT ON D- AMPHETAMINE -INDUCED SB IN RATS:

The results are given in table 2. Ondansetron (1.25, 2.5 and 5 mg/kg i.p.) did not induce SB in rats d-amphetamine (5 and 10 mg/kg ip) induced dose-dependent SB in rats.(table 2)

Pretreatment with Ondansetron (1.25, 2.5 and 5 mg/kg i.p.) did not significantly modify d-amphetamine induced SB (Table 2).

However pretreatment with 0.5 mg/kg i.p. haloperidol abolished the SB induced by 5 and 10 mg/kg i.p. d-amphetamine (Table 2)

Study	Treatment Dose mg/kg	Intensity Score Mean \pm S.E.M.
I	DAM 5	1.4 \pm 0.16
	OND 1.25 + DAM5	1.3 \pm 0.15
	OND 2.5 + DAM 5	1.1 \pm 0.10
	OND 5 + DAM 5	1.4 \pm 0.16
	HAL 0.5 + DAM5	0.0
II	DAM 10	2.9 \pm 0.10
	OND 1.25 + DAM10	2.7 \pm 0.15
	OND 2.5 + DAM 10	2.8 \pm 0.13
	OND 5 + DAM 10	3.0 \pm 0.00
	HAL 0.5 + DAM 10	0.0

Table 2 showing effect of Ondansetron (OND) and haloperidol (HAL) pretreatment on d- amphetamine (DAM) – induced SB in rats.

P>0.05

Number of animals n = 10

EFFECT OF ONDANSETRON PRETREATMENT ON HALOPERIDOL -INDUCED CATALEPSY IN RATS:

The results are given in table 3. Ondansetron at 1.25, 2.5 and 5 mg/kg i.p. did not induce catalepsy in rats. Haloperidol (0.5 and 1 mg/kg i.p.) induced dose dependent degree of catalepsy in rats at both 1 and 2 hour testing time intervals (Table 3).

Pretreatment with 1.25, 2.5 and 5 mg/kg i.p. Ondansetron did not significantly modified cataleptic effect of haloperidol (0.5 and 1 mg/kg i.p.) at both 1 and 2 hour testing time intervals. (Table 3).

TABLE 3

Study	Treatment Dose mg/kg	catalepsy Score Mean ± S.E.M. at 1 hr & 2 hr.	
I	HAL 0.5	1.2 ± 0.13	1.0 ± 0.0
	OND 1.25 + HAL 0.5	1.3 ± 0.15	1.1 ± 0.1
	OND 2.5 + HAL 0.5	1.5 ± 0.16	1.3 ± 0.15
	OND 5 + HAL 0.5	1.4 ± 0.16	1.2 ± 0.13
II	HAL 1	2.5 ± 0.16	2.3 ± 0.15
	OND 1.25 + HAL 1	2.6 ± 0.16	2.4 ± 0.16
	OND 2.5 + HAL 1	2.8 ± 0.13	2.6 ± 0.16
	OND 5 + HAL 1	2.7 ± 0.15	2.5 ± 0.16

Table 3 showing effect of Ondansetron (OND) pretreatment on haloperidol (HAL) induced catalepsy in rats.

P>0.05

Number of animals n = 10

EFFECT OF ONDANSETRON PRETREATMENT ON APOMORPHINE -INDUCED CAGE CLIMBING BEHAVIOR IN MICE:

The results are given in table 4. Ondansetron at 0.625, 1.25 and 2.5 mg/kg i.p. did not induce cage climbing behavior in mice. Further, pretreatment with Ondansetron (0.625, 1.25 and 2.5 mg/kg i.p.) did not significantly influence apomorphine induced cage climbing behaviour. However, pretreatment with 0.5 mg/kg i.p. haloperidol completely abolished the climbing behavior induced by 0.5, 0.75 and 1 mg/kg i.p. doses of apomorphine (Table 4).

TABLE 4

Study	Treatment Dose mg/kg	climbing index% max time (min) mean ± S.E.M. mean ± .S.E.M	
I	APO 0.5	22.7 ± 3.2	2.4 ± 0.9
	OND 0.625 + APO 0.5	22.1 ± 3.4	2.2 ± 0.6
	OND 1.25 + APO 0.5	21.9 ± 3.5	2.5 ± 0.7
	OND 2.5 + APO 0.5	22.6 ± 3.3	2.6 ± 1.1
	HAL 0.5 + APO 0.5	00.00	00.00
II	APO 0.75	48.2 ± 3.6	7.2 ± 0.8
	OND 0.625 + APO 0.75	47.9 ± 3.2	6.9 ± 0.5
	OND 1.25 + APO 0.75	48.6 ± 3.7	7.1 ± 0.7
	OND 2.5 + APO 0.75	48.1 ± 3.3	6.8 ± 0.6
	HAL 0.5 + APO 0.75	00.00	00.00
III	APO 1	74.8 ± 3.4	10.7 ± 0.8
	OND 0.625 + APO 1	74.5 ± 3.2	10.4 ± 0.5
	OND 1.25 + APO 1	73.9 ± 3.6	10.6 ± 0.7
	OND 2.5 + APO 1	72.7 ± 2.9	11.1 ± 0.9
	HAL 0.5 + APO 1	00.00	00.00

Table 4 showing effect of Ondansetron (OND) and haloperidol (HAL) pretreatment on apomorphine induced cage climbing behavior in mice.

P>0.05

Number of animals n = 10

SUMMARY & CONCLUSIONS

In the present study the psychopharmacological profile of Ondansetron pertaining to its effects on behaviours dependent on the functional status of the nigrostriatal dopaminergic system was investigated in rats & mice.

The results & conclusions derived thereof are summarised as follows-

1. Ondansetron in the doses of 1.25,2.5,& 5 mg/kg i.p in rats & 0.625,1.25, & 2.5 mg/kg i.p in mice did not produce motor incoordination, ataxia or muscular hypotonia neither did it inhibit the righting reflex.
2. Ondansetron in the doses of 1.25, 2.5, & 5 mg/kg in rats did not induce catalepsy at any of the testing time intervals.
3. Ondansetron 1.25, 2.5 & 5 mg/kg i.p did not induce stereotyped behavior in rats. Further, pretreatment with Ondansetron (1.25, 2.5, & 5 mg/kg) did not significantly influence both apomorphine & d-amphetamine induced SB in rats.
4. Ondansetron (0.625,1.25 & 2.5 mg/kg) did not induce cage climbing behaviour in mice.Further pretreatment with Ondansetron (0.625,1.25,2.5 mg/kg) did not significantly modify apomorphine - induced cage climbing behaviour in mice.
5. Ondansetron (1.25,2.5 & 5 mg/kg) pretreatment did not antagonise haloperidol- induced catalepsy in rats.

Taken together our results we conclude that Ondansetron does not possess post synaptic striatal D2 DA receptor blocking activity & does not influence striatal D2 dopamine receptor mediated behaviours.

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