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Evaluation of the effect of cinnamaldehyde per se and its interaction with ondansetron on haloperidol induced catalepsy in albino mice

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Abstract

Background: The aim of this study is to evaluate the per se effect of cinnamaldehyde which is obtained from bark oil of cinnamon tree and its interaction with ondansetron on catalepsy in Swiss albino mice.
Methods: Haloperidol induced catalepsy model was used. A group of 36 healthy mice of either sex weighing 20-30 grams were divided at random into six groups (n=6). Cinnamaldehyde with 98 percent purity was obtained. Catalepsy was induced by haloperidol (1mg/kg, i.p). Control group received tween-20 20% (10ml/kg, p.o), standard groups were administered ondansetron (0.5mg/kg and 1mg/kg, p.o), test groups received cinnamaldehyde in strength of 100mg/kg, and 200mg/kg and combination group of ondansetron plus cinnamaldehyde (0.5mg/kg + 100mg/kg) per oral, respectively.
Results: In this acute study, from 60 min onwards after haloperidol administration, ondansetron at both doses (0.5 mg/kg and 1 mg/kg), showed significantly lower cataleptic scores as compared to all groups. Cinnamaldehyde at both strengths did not show any significant effect as compare to control at any point of time (P>0.05). Combination of ondansetron 0.5 mg/kg with cinnamaldehyde 100mg/kg, showed significant increase in cataleptic score as compared to ondansetron 0.5 and 1mg/kg alone (P>0.05). Which suggest that cinnamaldehyde abolishes the protective effect of ondansetron in haloperidol induced catalepsy.

Keywords: Obliterate, catalepsy, ondansetron, cinnamaldehyde

Introduction

Schizophrenia is a type of functional psychosis in which severe personality changes and thought disorders occur [1]. Schizophrenics are usually introvert split personalities who show

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retreat from reality with no coherence between their thought, speech and action [2]. Primary pathology of schizophrenia is dopaminergic over-activity in limbic area. Neuroleptics are used to reduce its symptoms but these drugs produce anti-psychotic and extrapyramidal symptoms both at the same dose, which is due to excessive blockade of D2 receptors in nigrostriatal pathway and mesolimbic system simultaneously. That becomes the major drawback. Extrapyramidal symptoms are characterized by acute dyskinesia, dystonia, akinesia and akathisia. The effects such as akinesia, rigidity and tremors are called Parkinson's like syndrome, because in Parkinson's disease the major clinical symptoms include difficulty to move and change posture (akinesia and rigidity) and tremors [3]. Therefore, phenothiazines (chlorpromazine or haloperidol) are commonly used to produce Parkinson's like extrapyramidal symptoms in laboratory animals and to study antiparkinson drugs. The central serotonergic system modulates nigrostriatal dopaminergic transmission. 5-HT3 antagonists are reported to diminish neuroleptic-induced catalepsy [4]. Hence ondansetron, a 5-HT3 antagonist was used as standard drug in this study to compare the ant cataleptic effect of the test compound, cinnamaldehyde.

Cinnamon is a spice obtained from the evergreen tree of the lauraceae family primarily located in Asia and Australia and is utilised as herbal medicine [5, 6, 7]. Its bark oil primarily contains cinnamaldehyde and eugenol and minor amounts of cinnamyl acetate (5%), caryophyllene (3.3%) and linalool (2.4%) [8, 9]. The chemical composition of cinnamon varies considerably depending on the location and method of distillation. However cinnamaldehyde and eugenol are constant components. Special taste and smell of cinnamon is due to cinnamaldehyde which is also present in the oil from leaves and roots of cinnamomum along with bark [10].

Considering numerous pharmacological activities of cinnamon oil including antimicrobial [11], antifungal [12], antioxidant [13], antidiabetic [14], anti-inflammatory [15], antitermitic [16], nematicidal [17], mosquito larvicidal [18], insecticidal [19], antimycotic [20], anticancer agent [21], antipyretic [20], anti-peptic ulcer [22] and anti-allergic [23]. etc. We choose to explore pharmacological activities of the active principle of cinnamon i.e. cinnamaldehyde and its interaction with ondansetron on catalepsy in Swiss albino mice.

Method

Experimental animals

Swiss albino mice of either sex weighing between 25-35gm, were procured from the central animal house, M.G.M. Medical College, Indore and acclimatized for a period of 7 days at room temperature (25±2 °C) and 50±15% relative humidity. They were housed in standard cages and maintained on standard laboratory diet and water ab libitum. The study was carried out in the Department of Pharmacology, M.G.M. Medical College, Indore (M.P.) and India. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC).

Drugs and groups

Cinnamaldehyde having 98% purity was obtained from the Science centre, Indore (M.P.). Ondansetron 0.5 and 1mg/kg and cinnamaldehyde 100 and 200 mg/kg were prepared in 20% of tween-20 (vehicle) and administered per oral with the help of oral gavage. Haloperidol 1mg/kg was dissolved in distilled water and given intraperitoneally. 4,12 Group I received tween-20 20% (10ml/kg), Group II and Group III received ondensetron in the strengths of (0.5 mg/kg) and (1mg/kg) respectively. Group IV and Group V were administered cinnamaldehyde in the strengths of (100mg/kg) and (200mg/kg) respectively and Group VI was given combination of cinnamaldehyde and ondensetron (100mg/kg + 0.5mg/kg).

ISSN 2515-8260 Volume 09, Issue 02, 2022

Experimental design

Catalepsy was induced by haloperidol (1mg/kg, i.p) and assessed at 30 min interval until at the end of 240 min. Catalepsy was assessed in terms of the time for which the mouse maintained an imposed position with both front limbs extended and resting on a 4 cm high wooden bar. The end point of catalepsy was considered to occur when both front paws were removed from the bar or if the animal moved its head in exploratory manner. A cut off time of 1100 seconds was applied. [24]

Scoring method

If the animal maintained the imposed posture for at least 20 seconds, it was considered to be cataleptic and given one point. For every additional 20 second, that the cataleptic posture was maintained, one extra point was given [25]. Ondansetron, cinnamaldehyde and their combination were administered only once, one hour prior to the haloperidol administration.

Statistical analysis

Results were analyzed by SPSS Version 21. For each group, mean ± SEM was calculated, and the data was analyzed by one way ANOVA followed by multiple Tukey's post hoc comparison test for both acute and chronic study. $P < 0.05$ was considered to be significant.

Results

In haloperidol induced catalepsy administration of ondansetron at both doses (0.5 mg/kg and 1 mg/kg), showed significantly lower cataleptic scores as compared to all groups at 30min, 60min, 90 min and 120min ($P<0.05$) , while at 240 min only ondansetron 1 mg/kg maintained lesser cataleptic score ($P<0.05$). Cinnamaldehyde 100 mg/kg and 200 mg/kg did not showed any significant effect as compare to control at any point of time. ($P>0.05$) Combination of ondansetron 0.5 mg/kg with cinnamaldehyde 100mg/kg, showed significant increase in cataleptic score as compared to ondensetron 0.5 and 1mg/kg alone ($P>0.05$). Which suggest that cinnamaldehyde abolishes the protective effect of ondansetron in haloperidol induced catalepsy. (Table 1)

Table 1: Effect of cinnamaldehyde *per se* and its interaction with ondansetron on haloperidol induced catalepsy

Treatment	Dose mg/kg orally	Score after haloperidol (20sec=1point)				
		30min	60min	90min	120min	240min
Control Tween-20 (20%)	10 ml/kg	28.00±1.667	33.17±2.334	42.67±3.938	41.50±1.176	44.50±1.38
Ondansetron	0.5	11.00±0.85 *	16.83±0.70 *	25.83±0.94 *	32.17±1.19 *	42.33±4.32 #
Ondansetron	1	10.67±0.66 *	15.33±0.76 *	21.50±1.05 *	26.83±1.10 *	32.17±2.13 *
cinnamaldehyde	100	30.00±1.06† #	36.00±2.28† #	44.00±2.53† #	43.00±1.00† #	48.33±3.26 † #
cinnamaldehyde	200	31.50±1.87† #	32.00±2.28† #	41.33±2.95† #	40.83±1.77† #	46.00±3.89 #
Ondansetron + cinnamaldehyde	0.5 + 100	29.67±1.30† #	33.33±1.43† #	39.17±0.79† #	42.00±1.29† #	48.50±3.08 † #
One-way ANOVA	F	100.78	21.99	24.88	39.98	21.05
	P	<0.001	<0.001	<0.001	<0.001	<0.001

One way ANOVA followed by multiple Tukey's comparison test, Values are mean ± SEM. DF = 5, 30, *P<0.05, compared to control, † P<0.005, compared to ondansetron 0.5mg/kg group, #P<0.005, compared to ondansetron 1 mg/kg group.

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Discussion

Cinnamon has been documented to have numerous pharmacological activities. Either the different extracts or the active principle of Cinnamon *i.e.* Cinnamaldehyde, have shown various activities. Till date its pharmacological activities like antimicrobial, anti-cancer activity have been proven but it has not been properly explored and results on various models of analgesia, antidepressant activity, extra pyramidal effects, anti-anxiety effects and sleeping time etc. have been inconclusive. Hence we conducted our experiments using the active principle-Cinnamaldehyde, which was obtained from Science Centre, Indore having 98% purity.

We studied the effect of Cinnamaldehyde per se as well as its interaction with the established standard drugs using animal model haloperidol induced catalepsy with ondansetron. Further we evaluated the effect of cinnamaldehyde on haloperidol induced catalepsy**.** The study was done on albino mice and haloperidol was given i.p. to induce catatonia. Typical neuroleptic agents such as chlorpromazine, haloperidol and reserpine induce a cataleptic state in rodents which is widely used as a model to test the extrapyramidal side effects of antipsychotic agents. Effects of cinnamaldehyde per se and its combination with ondansetron were compared with groups of ondansetron alone. (Table 1)

Ondansetron at both doses (0.5 mg/kg and 1 mg/kg) showed significantly lower cataleptic scores as compared to all groups. The effect of ondensetron 1 mg/kg was maintained till 240 min after haloperidol while the effect of ondensetron at 0.5 mg/kg stated vanishing 120 min onwards. In our study cinnamaldehyde at different doses neither showed EPS producing potential nor showed any protective effect on haloperidol induced catalepsy score at any point of time ($p > 0.05$). When cinnamaldehyde 100 mg/kg was combined with sub therapeutic dose of ondansetron *i.e.* 0.5mg/kg, the protective effect of ondansetron was abolished and the cataleptic score was equivalent to control group ($p > 0.05$).

Neuroleptic-induced catalepsy has been linked to blockade of postsynaptic striatal dopamine D1 and D2 receptors [26]. Several other neurotransmitters like acetylcholine, serotonin, angiotensin, adenosine or opioids have also been linked to the catalepsy induced by neuroleptic agents. [27] As per the previous experiments it was observed that cinnamaldehyde has some potentiating effect on different drugs probably through change in pharmacokinetics, but in this experiment we found that cinnamaldehyde is obliterating the action of ondansetron. Ondansetron is a $5HT_3$ antagonist [25] and cinnamaldehyde is inhibiting the protective effect of ondansetron, this may suggest that cinnamaldehyde may be having $5HT_3$ agonistic activity.

Various studies so far discussed indicated that cinnamaldehyde *per se* does not have any significant CNS activity, but it has potentiating effect on drugs like diclofenac sodium, diazepam. The potentiating effect of cinnamaldehyde might be due to change in pharmacokinetics like increasing the absorption, displacing from the plasma protein binding site or by decreasing metabolism and excretion of the concerned drug. But at the same time cinnamaldehyde in majority of experiments blocked the action of certain drugs like pentazocin, escitalopram, ondansetron, which suggest that cinnamaldehyde might be having direct action on receptors like $5HT_3$, opioid. In case of haloperidol induced catalepsy model cinnamaldehyde blocks the action of ondansetron which points towards agonistic action on 5 HT_3 receptors.

Conclusion

An approach of using combination of cinnamaldehyde with standard drugs might improve and prolong the desired actions of the drugs at low doses. Concurrent administration of cinnamaldehyde should be avoided with drugs like ondansetron because of its potential of

lowering their therapeutic effects. Pharmacokinetic studies are also required to further explore and to characterise exact extent and mechanisms of such interactions.

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