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RESEARCH ARTICLE

Evaluation of Antipsychotic Effect of Levosulpride

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ABSTRACT:
The present study was undertaken to evaluate the antipsychotic activity of formulated levosulpride sustained release formulation was compared with marketed levosulpride sustained release formulation in experimental animal models. Male Wistar rats (180- 220 g) and Albino mice (25-30 g) were used for the study. The antipsychotic effect of the formulated levosulpride sustained release formulation was evaluated on locomotor activity on photoactometer and ketamine induced stereotypic behavior. Different groups of rats were fed orally with a specially prepared diet containing formulated levosulpride sustained release formulation was compared with marketed levosulpride sustained release formulation for 15 consecutive days. Further, the biochemical estimations were done by estimating brain dopamine levels. The formulated levosulpride sustained release formulation significantly decreased the locomotor activity of rats. The formulated levosulpride sustained release formulation significantly decreased ketamine (50 mg/kg, i.p.) induced stereotyped behavior in a dose dependent manner. Formulated levosulpride sustained release formulation significantly decreased the brain dopamine levels. The results suggest that formulated levosulpride sustained release formulation posse's antipsychotic activity.

KEYWORDS: Formulated levosulpride sustained release formulation, ketamine, photoactometer

INTRODUCTION:
The goal in designing sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Levosulpiride, a sulpiride isomer is a selective D_2 receptor antagonist. It is used as antipsychotic, antidepressant, antiemetic agent, prokinetic and antidyspeptic agent. Plasma half life of 4 to 6 hours, time of peak plasma concentration (Tmax) 3 hours, pKa 8.9, bioavailability is 25 to 30% and volume of distribution (Vd) is 0.639 L/kg after an

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oral dose of conventional tablets of levosulpiride. To reduce the frequency of administration and improve patient compliance, the SR formulation of Levosulpiride is desirable. Since Levosulpiride requires frequent dosing to maintain therapeutic drug concentration, it was chosen as an ideal candidate for SR dosage form. Matrix tablets are prepared either wet granulation/ direct compression method. The study is undertaken to design and evaluate the SR tablets of levosulpiride with polymers like Chitosan, Xanthan gum and Guar gum. Chitosan, Xanthan gum and Guar gum is used because of its non-toxic nature, easy compression, swelling properties and accommodation to high level of drug loading. In the present study formulated levosulpride sustained release formulation was compared with marketed levosulpride sustained release formulation.

MATERIAL AND METHOD:

Formulated levosulpride sustained release formulation, marketed levosulpride sustained release formulation, ketamine, photoactometer, spectrofluorimeter.

FORMULATION OF LEVOSULPIRIDE SUSTAINED RELEASE TABLETS:

The levosulpiride sustained release tablets were prepared by wet granulation technique. Levosulpiride was passed through sieve no #40. The release retarding polymers namely chitosan, xanthan gum and guar gum and additive microcrystalline cellulose and magnesium stearate as glidant was passed through sieve #60. Polyvinyl pyrrolidine in isopropyl alcohol was used as granulating agent to get coherent mass. The wet granules were dried at room temperature. The dried granules were passed through sieve no # 14. Mixed with magnesium stearate and compressed into tablets on a 16 station Rotary Cadmach machine.

ANIMALS:

Male Wistar rats (180-220 g) and Albino mice (25-30g) were used for the study[1]. The animals were housed in colony cages and maintained under the standard environmental conditions - temperature 25 ± 2 °C, 12 h light: 12 h dark cycle and 50 ± 5 % relative humidity, with food and water ad libitum. All experiments were carried out during the light period (08.00 -16.00 h). The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and the care of laboratory animals was taken as per the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (Registration number is XIX/PCOL/09).

DRUGS:

Formulated levosulpride sustained release formulation and marketed levosulpride sustained release formulation was suspended in a vehicle consisting of 5% Tween-80 in 0.9% saline. Ketamine was diluted in 0.9% saline. Formulated levosulpride sustained release formulation, marketed levosulpride sustained release formulation and Ketamine (50mg/kg, i.p.) were administered daily for a duration of 15 days to the mice and 8 days to the rats.

Ketamine-Induced Stereotypic Behaviour in Mice:

Animals were divided into six groups and each group consisted of six animals. The control animals received normal diet and treated with Ketamine (50mg/kg, i.p.) for 15 consecutive days. The animals of standard groups received marketed levosulpride sustained release formulation (5mg/kg, i.p.), after 30 min Ketamine was given, (50mg/kg, i.p.) for 15 consecutive days[2]. The animals of test groups received formulated levosulpride sustained release formulation through a specially prepared diet and after 30 min Ketamine was given (50mg/kg, i.p.) for 15 consecutive days. Each mouse was individually placed into plastic cages (37 × 24 × 30 cm^3) divided into quadrants by lines on the floor and allowed to acclimatize for at least 30 min before the testing began. Behavioral tests were performed between 10 a.m. and 4 p.m. The stereotypic behaviour was assessed by counting the number of turning, weaving, head-bobbing and ataxia. Turning was measured by counting turn around every 15 min over 60 min. Weaving and Head-bobbing were measured by counting its neck wave right and left, and go up and down every 15 min over 60 min. Ataxia was assessed by counting the number of falls of each mouse on the floor of the cage every 15 min over 60 min period.

LOCOMOTOR ACTIVITY:

The locomotor activity of rats was measured using Photoactometer[3] (INCO, Ambala, India).

BIOCHEMICAL ESTIMATION:

The animals were sacrificed by cervical dislocation, whole brain was rapidly frozen at -5°C and brain dopamine levels was spectrofluorimetrically estimated by the methods of Ansell and Beeson10 as modified by Cox and Perhach[4].

STATISTICAL ANALYSIS:

Results are expressed as Mean ± S.E.M (n = 6). The statistical analysis[5] of data was done using one-way analysis of variance (ANOVA), followed by Dunnett's *t* test[6]. Probability level less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION:

Ketamine-Induced Stereotypic Behaviour in Mice:

Ketamine (50mg/kg, i.p.) produced stereotypic behaviour in mice. Formulated levosulpride sustained release formulation(5mg/kg, i.p.) through a specially prepared diet for 15 successive days remarkably

($p<0.01$) decreased this stereotypic behavior of mice produced by ketamine.

Animals treated with marketed levosulpride sustained release formulation (5mg/kg, i.p.) reversed stereotypic behaviour induced by ketamine. The effect of Formulated levosulpride sustained release formulation was found to be comparable to that of marketed levosulpride sustained release formulation.

TURNING BEHAVIOR OF MICE:

Turning behavior was measured by counting the turnaround behavior of each mouse every 15 min over 60 min periods. Formulated levosulpride sustained release formulation 15 successive days showed significant ($p<0.05$) decrease in turning behavior of mice induced by ketamine.

Animals treated with marketed levosulpride sustained release formulation (5mg/kg, i.p.) decreased the turning behaviour(Table 1).

WEAVING BEHAVIOR OF MICE

Weaving pattern was measured by counting its paw movements standing on hind legs every 15 min over 60 min period. Formulated levosulpride sustained release formulation remarkably ($p<0.01$) decreased weaving pattern of mice produced by ketamine Animals treated with marketed levosulpride sustained release formulation decreased the weaving behaviour (Table 2).

HEAD-BOBBING BEHAVIOR OF MICE

Head-bobbing pattern was measured by counting its neck movements towards right and left and up and down every 15 min over 60 min period. Administration of Formulated levosulpride sustained release formulation for 15 successive days remarkably reduced head-bobbing pattern of mice produced by ketamine. Animals treated with marketed levosulpride sustained release formulation reduced head-bobbing pattern of mice (Table 3).

ATAXIA BEHAVIOR OF MICE

Ataxia was assessed by counting the number of falls of each mouse on the floor of the cage every 15 min over 60 min period. Administration of Formulated levosulpride sustained release formulation reduced falling behaviour of mice at 15 and 30 mins. Administration of marketed levosulpride sustained release formulation remarkably ($p<0.01$) decreased falling behaviour of mice. There was no falling attempt at 60 min (Table 4).

LOCOMOTOR ACTIVITY

Administration of Formulated levosulpride sustained release formulation, through a specially prepared diet for 15 successive days markedly ($p<0.05$) decreased locomotor activity in rats measured using photoactometer. The effect of Formulated levosulpride sustained release formulation was found to be comparable to that of marketed levosulpride sustained release formulation.

BRAIN DOPAMINE LEVEL

Administration of Formulated levosulpride sustained release formulation for 15 consecutive days showed markedly significant ($p<0.05$) effect on brain dopamine level. However, administration of Formulated levosulpride sustained release formulation and marketed levosulpride sustained release formulation for 15 consecutive days showed remarkably significant ($p<0.01$) decrease in brain dopamine level in rats compared to control group.

Ketamine Induced stereotypy is a commonly employed interceptive behavioural model to evaluate antipsychotic potential of any drug. Marketed levosulpride sustained release formulation (antipsychotics agent) was used in the present study as standard antipsychotic agents. Administration of Formulated levosulpride sustained release formulation in a specially prepared diet for 15 successive days showed significantly inhibition of stereotypic behavior in mice as reflected by reduced turning, weaving, head-bobbing and ataxia. Administration of Formulated levosulpride sustained release formulation for 15 successive days resulted in significantly decrease in locomotor activity which showed the CNS depressant activity of Formulated levosulpride sustained release formulation. Administration of Formulated levosulpride sustained release formulation for 15 successive days resulted in significantly decrease in dopamine levels in brain of rats in the present study. A central role for D2 receptor occupancy in antipsychotic action is now well established, buttressed by neuroimaging studies using positron emission tomography and single photon emission computed tomography. However, the importance of dopamine receptors in the treatment of psychosis does not by itself constitute proof of the involvement of dopamine in psychosis. Administration of Formulated levosulpride sustained release formulation may increase the number of dormant receptors, hence resulting in decrease in dopamine turnover in extracellular spaces in the brain.

CONCLUSION:

The present investigation concludes that the Formulated levosulpride sustained release formulation inhibit dopaminergic neurotransmission and possibly blocks dopamine D2 receptor.

Thus, Formulated levosulpride sustained release formulation possesses antidopaminergic activity. The

results suggest that the Formulated levosulpride sustained release formulation may have potential clinical application in the management of psychiatric disorders.

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