Research In Pharmaceutical Biotechnology Vol. 3(10), pp. 131-134, December 2011
Available online at http://www.academicjournals.org/rpb
DOI: 10.5897/RPB11.011
ISSN 2141-2324 ©2011 Academic Journals

Full Length Research Paper

Ketamine hydrochloride induces anxiety behaviour activities in adult male mice

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Accepted 22 November, 2011

The trafficking and abuse of Ketamine are a concern to law enforcement and drug treatment providers because of the drug's increasing availability and its use in facilitating sexual assaults globally. The aim of this study is to investigate some of the effects of administration of ketamine intramuscularly (IM) on bebaviour in mice. The presumably 16 healthy male mice were used for this study; the animals were randomly divided in to two (2) groups, A and B, of eight (8) animals each. Group A were given 8 mg/ kg of the Ketamine (IM) and B were serve as control for 7 days. The exploratory and non – exploratory behaviours of the animals were assessed for 5 minutes using the elevated plus maze (EPM). The results suggested possible anxiolytic and schizophrenic symptoms after the administration.

Key words: Ketamine, behaviour, schizophrenic symptoms, intramuscular, elevated plus maze.

INTRODUCTION

Ketamine hydrochloride, a Schedule III drug under the Controlled Substances Act, is a dissociative anaesthetic that has a combination of stimulant, depressant, hallucinogenic, and analgesic properties. Ketamine produces dissociative anesthesia, which is characterized by catatonia, amnesia, and analgesia, with or without actual loss of consciousness (Katzung, 2004). The drug is an arylcyclohexylamine chemically related to phencyclidine (PCP), a drug frequently abused because of its psychoactive properties. The mechanism of action of ketamine may involve blockade of the membrane effects of the excitatory neurotransmitter glutamic acid at the N-metheyl-D-aspartate (NMDA) receptor (Katzung, 2004; Trevor et al., 2002). Legally used as a preoperative veterinary anesthetic, ketamine is abused for these properties and used to facilitate sexual assault. Common street names for ketamine are K, special K, ket, kit kat, vitamin K, purple, special la coke, cat valium, super acid, super C, lady K, super K, ketaject, and cat tranquilizers.

Distribution of liquid and powdered ketamine typically occurs among friends and acquaintances, most often at raves, nightclubs, and at private parties. Distribution of liquid and powdered ketamine typically occurs among friends and acquaintances, most often at raves, nightclubs, and at private parties; street sales of ketamine are rare (IB, 2004). Behrens (2009) reported that abusing ketamine, which inhibits the NMDA receptor, can result in symptoms indistinguishable from schizophrenia in the mouse prelimbic cortex. Ketamine produces its cardiovascular stimulation by excitation of the central sympathetic nervous system and possibly by inhibition of the uptake of norepinephrine at sympathetic nerve terminals. Increases in plasma epinephrine and norepinephrine levels occur as early as 2 min after intravenous ketamine and return to baseline levels 15 min later (Katzung, 2004; Trevor et al., 2002). The elevated plus maze test is used to asses anxiety in experimental animals; the basic measure is the animal's preference for dark, enclosed places over bright, exposed places. These findings and reports suggest the need for further experimental and clinical studies of the role of ketamine intake on the body systems, most especially the brain/ behaviour in particular. The aim of this study is to investigate some effects of ketamine on the explorative activities of mice using elevated plus maze (EPM).

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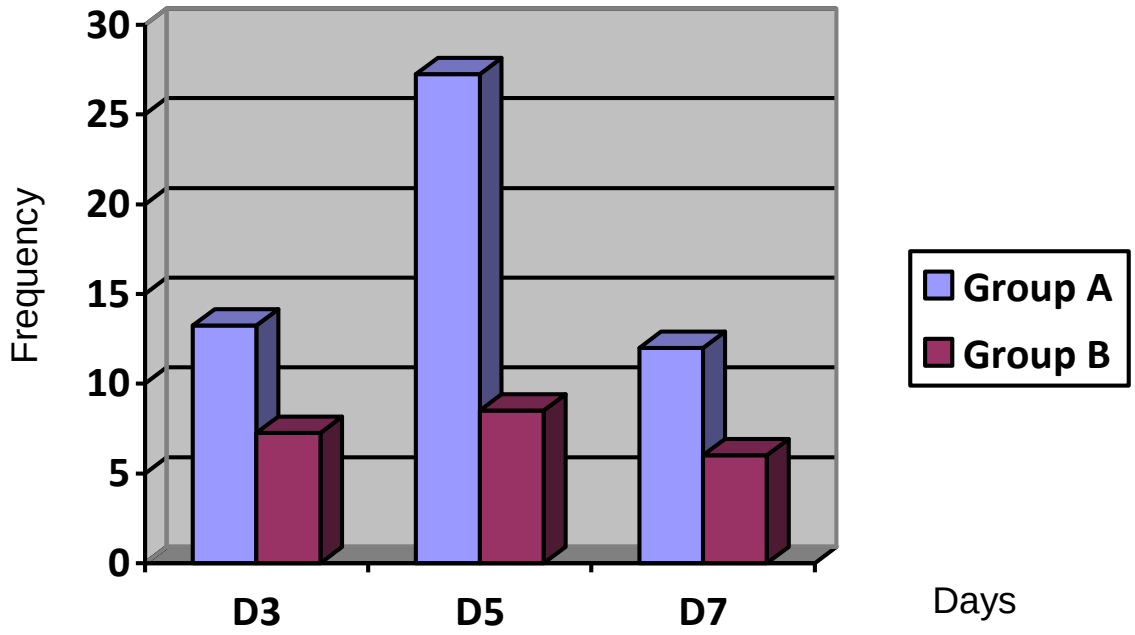

Figure 1. Showing head dipping (HD) of exploratory activity in mice.

MATERIALS AND METHODS

Animal care

All experimental investigations were done in compliance with human animal care standard outlined in the "Guide to the care and use of Animals in research and teaching", as approved by the Institute of Laboratory Animal Resource, National Research Council, DHHS, and Pub. No NIH 86 to 23. The animal right committee of the University of Ilorin, Nigeria gave the permission to carry out this work. The study was carried out using presumably healthy adult male mice with average body weight of 25.06 g. The animals were kept under standard and good laboratory conditions (12 hours light and 12 hours darkness, temperature, humidity and ventilation). They were given standard rat diet, purchased from Bethel Feeds, Ilorin, Nigeria.

Experimental design

Total of 16 adult male mice were used for this study. The animals were randomly divided in to two (2) groups, A and B of eight (8) animals each. Group A were given 8 mg/kg body weight of Ketamine (IM), produced by LABORATE Pharmaceutical, India, and B serve as control group for 7 experimental days.

Neurobehavioural observations

The neurobehavioural analysis was done at 0800 h of the day using elevated plus maze to study the locomotion, exploration, and motor coordination in both the treated and control animals (Brown, 2010; Iheanyi et al., 2010; Adeniyi et al., 2010). The results are shown in Figures 1 and 2.

Procedure

Both the treated and control animals were placed in the center of the apparatus to explore for 5 min. Measurements compared included total time spent in the closed arms (CAD) as well as, entries into the open and closed arms (T) and head dipping (HD) (Brown, 2010; Iheanyi et al., 2010; UCLA, 2011; Adeniyi et al., 2010).

Statistical analysis

The data were expressed as means ± Standard Error of Mean (SEM), and were statistically evaluated with SPSS software version 14.0 software. Data collected were analyzed using the student's t – test.

RESULTS

Gross observations

There were no significant changes in the skin colour and fur arrangement; the colour of their eyes was normal compared to the control groups.

The animal weight changes

The treated group lost shed weight drastically, especially between the 2nd and 4th days of treatment, when compared with the control group (Figure 3).

Animal behaviour

After administration of ketamine, the mice loss their gat within 1 to 2 min and become weak and sleep for about 5

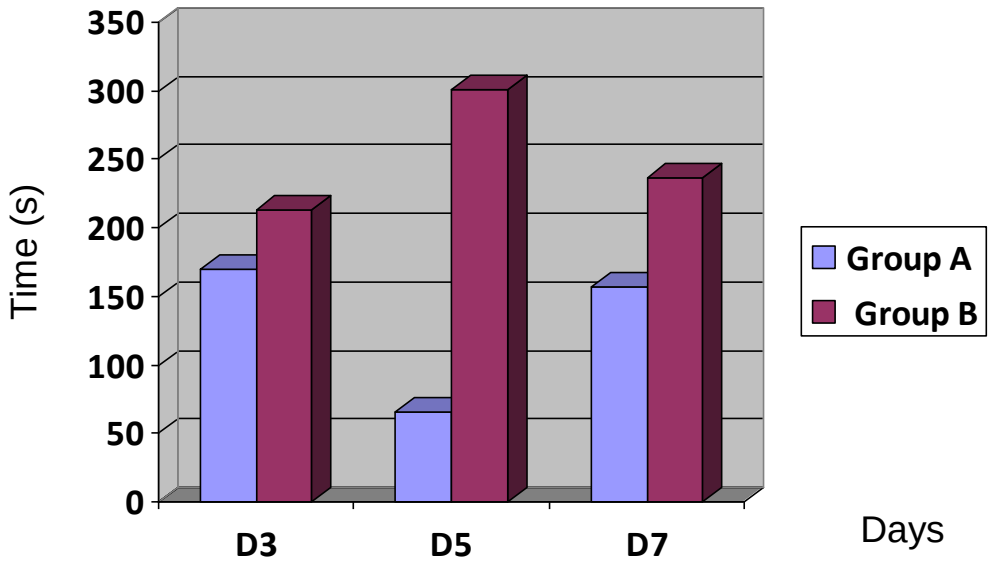

Figure 2. Showing closed arm duration (CAD) of exploratory activity in mice (in s).

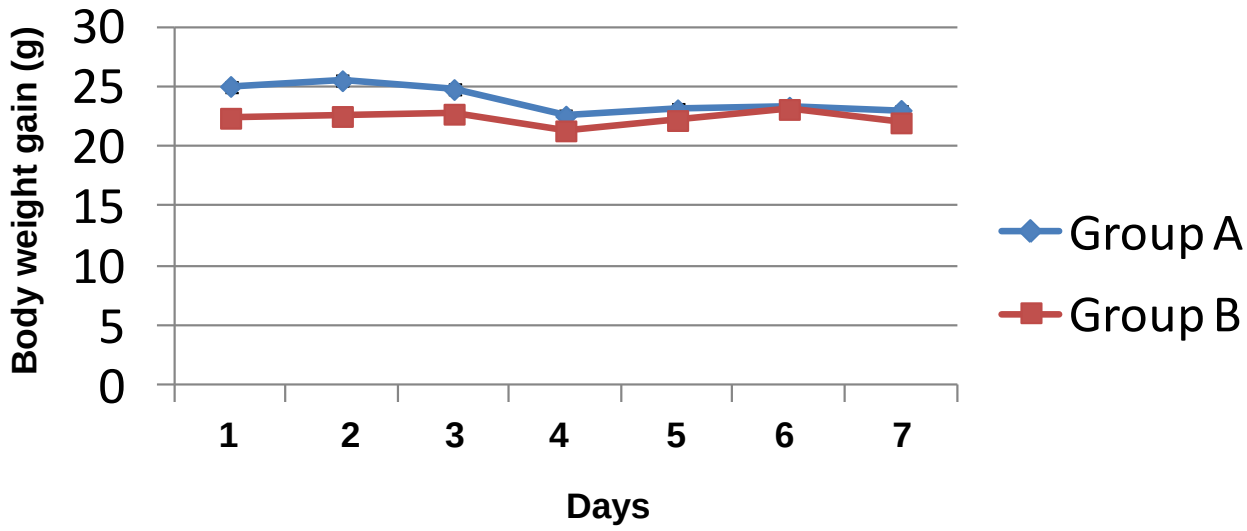

Figure 3. showing the average body weight changes (g) during experimental period.

minutes thereafter woke up. Rate of Head deeding (HD), Closed arm duration (CAD) and Transition (T) were significantly ($p < 0.05$) different between treated and the control group (Figures 1 to 2).

DISCUSSION

The intramuscular administration of 8 mg/kg body weight of Ketamine for 7 days resulted in reduction of closed arm duration (CAD) in mice that is, increase in activities of mice in the open arm of the maze; however there was a statistical increase ($p < 0.05$) in head dipping (HD) of the mice. Ketamine and other drugs that block NMDA receptor channel have potent antiepileptic activity in animal models, though these drugs have yet to be tested clinically (Katzung, 2004; Trevor et al., 2002). Considerable evidence exists such that the release of glutamate during neuronal injury can, by activating the NMDA receptor, cause further cell injury and death (Katzung, 2004). Thus, a particularly exciting finding is that blocking the NMDA receptor can attenuate the neuronal damage caused by anoxia in treated animals. The mechanism of action of ketamine may involve blockade of the membrane effects of the excitatory neurotransmitter glutamic acid at the NMDA (N-methyl-

Daspartate) receptor subtype (Katzung, 2004). Ketamine is a highly lipophilic drug and is rapidly distributed into highly vascular organs, including the brain, and subsequently redistributed to less well perfused tissues with concurrent hepatic metabolism and both urinary and biliary excretion. Ketamine is the only intravenous anesthetic that possesses analgesic properties and produces cardiovascular stimulation. These characteristics may account for the anxiety behaviours, elevated HD and lowered CAD (Adeniyi et al., 2010) in mice treated with ketamine during 7 days of this study. Since Rodents, such as rats and mice, are most active in the dark (Benstaali et al., 2001; Kopp, 2001), they are expected to spend more time in the closed arm of the maze during the 5 min of their exposure (Schellinck et al., 2010) however, the opposite is the case in the treated animals; spending more time exploring open arm is an indication of hyperactivity/anxiety in these animals injected with Ketamine. The behavior of mice in the EPM represents anxiety-related behavior in humans has reported by Schellinck et al. (2010).

Conclusion

The intramuscular administration of 8 mg/kg body weight of Ketamine for 7 days resulted in reduction of closed arm duration (CAD) in mice that is, increase in activities of mice in the open arm of the maze; however there was a statistical increase ($p < 0.05$) in head dipping (HD) of the mice. The results suggested possible anxiolytic and schizophrenic symptoms after the drug administration.

From all the changes observed from comparism between the treated and control group, we thereby concluded that the administration of ketamine resulted in alterations in locomotory activities in treated animals.

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