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Original Research Article

Accentuation of general anaesthetic activity of ketamine by glutamate NMDA (N-methyl D-aspartate) receptor antagonist

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ABSTRACT

Background: The aim of the present study was to evaluate the potentiation of general anaesthetic activity of ketamine by NMDA receptor antagonist 'amantadine' in wistar albino rats.
Methods: The wistar albino rats of either sex were divided into three groups of five animals in each group. Group I received ketamine 80mg/kg, group II received ketamine 40mg/kg along with amantadine 40mg/kg and group III received ketamine 80mg/kg along with amantadine 40mg/kg to evaluate the potentiation of general anaesthetic effect of ketamine. The sleep latency time and the total sleeping time were measured in all the three groups.
Results: The sleep latency time of group III is significantly decreased ($p < 0.035$) and as equal to that of group II when compared to group I. The sleeping time of group III is significantly increased ($p < 0.001$) when compared to group I.
Conclusions: Amantadine - the NMDA receptor antagonist potentiates the general anaesthetic activity of ketamine.

Keywords: Amantadine, General anaesthetic effect, Ketamine, NMDA receptor antagonist

INTRODUCTION

General anaesthetics are drugs that produce a behavioural state referred as general anesthesia. General anesthesia is defined as a global but reversible depression of central nervous system (CNS) function resulting in the loss of response to and perception of all external stimuli. The components of anaesthetic state include amnesia, immobility in response to noxious stimuli, attenuation of autonomic responses to noxious stimuli, analgesia and unconsciousness.[1,2]

NMDA receptors are calcium gated channel receptors. Endogenous agonists of NMDA receptor are glutamic acid, aspartic acid and glycine. Activation of this receptor causes opening of calcium channels and depolarization of neurons. The NMDA-receptors are involved in sensory input at the spinal, thalamic, limbic and cortical levels.[3,4]

Ketamine has been used therapeutically in both human and veterinary medicine for more than 50 years. Ketamine is an arylcyclohexylamine, a congener of phencyclidine. It is an intravenous general anaesthetic agent which induces

dissociative anaesthesia in which patient have profound analgesia, unresponsiveness to commands, and amnesia, but may keep their eyes open, move their limbs involuntarily and breath spontaneously.[1] It binds to PCP-binding site (Phencyclidine binding site) of NMDA receptor and blocks the receptor non-competitively.[1,2] Ketamine is misused commonly as an addictive agent. Studies are under way to evaluate its uses in treatment-resistant depression, treatment of addiction. It is used as an analgesic agent in hospital emergency care practice. It is also evaluated experimentally as a model for schizophrenia.[5,6]

Amantadine is a tricyclic amines. As an antiviral agent it inhibits the replication of Influenza A viruses at low concentration and other enveloped viruses at high concentration. As an antiparkinsonian drug it alters the dopamine release in striatum, and also blocks NMDA-glutamate receptor noncompetitively. It is used as the initial therapy of mild parkinsonism, and also as an adjuvant to levodopa.

In high concentration it produces neurotropic effects like delirium, hallucination. It may also exacerbate pre-existing psychiatric symptoms.[1,2,7] Amantadine (AMA) is currently evaluated for its effect in depressed patients infected with Borna disease virus.[8,9] and to improve fatigue, distractibility, rigidity, bradykinesia, arousal level, initiation, purposeful movement, attention and concentration, sequencing skills and processing time in children.

Amantadine is also evaluated for its psychotropic effect to control the symptoms of irritability and hyperactivity in autistic disorder. It is also evaluated for its effect in children with enuresis in reducing wetting frequency. Amantadine also showed effectiveness in resistant depression, obsessive compulsive disorder in adults. It can also be used in traumatic brain injury indicated neuroprotective effect in controlling agitation and aggression.[10]

The primary objective of the study is to evaluate the potentiation of general anaesthetic activity of ketamine by NMDA receptor antagonist amantadine. The secondary objective of the study is to evaluate the potentiation of general anaesthetic activity of low dose ketamine by amantadine

METHODS

Animals

Total of 15 wistar Albino rats of either sex weighing 150-200g were used in this study. Animals were housed at a temperature of 28±2°C, relative humidity of 55-65% and Dark:Light cycle of 12:12h. Animals were allowed for free access to food, water and ad libitum. The experiments were started after getting the Institutional Animal Ethical Committee (IAEC) approval (IAEC-3/Pharmacology/05/16). Pregnant animals, animals with infection, disease, injuries, and deformities were excluded from the study. All the animals were divided into 3 groups of 5 animals each.

- Group I: animals received 0.5 ml of normal saline orally + ketamine 80mg/kg i.p.[11]
- Group II: animals received amantadine 40mg/kg orally + ketamine 40mg/kg i.p
- Group III: animals received amantadine 40mg/kg orally + ketamine 80mg/kg i.p.

All the experiments were conducted in dim light and quiet place to avoid external stimuli. Animals were handled minimally with care to minimize the stress and suffering.

Drugs

Ketamine (Neon), amantadine (Cipla) and normal saline were used in the study. Ketamine was given intraperitoneally (i.p.) to induce general anesthesia. Test drug amantadine was given orally. Normal saline was given orally to the control group and also used to dissolve Amantadine. The drug solutions were prepared freshly before the experiment.

Assessment of potentiation of general anaesthetic activity of ketamine

The method employed in this study was described by Vogel. All the test drugs were given orally after 12hr fasting. After 1hr of administration of test drugs, ketamine (40mg/kg or 80mg/kg, i.p.) was given to induce sleep. The onset time of sleep (loss of righting reflex) was noted for all the animals.

After induction of sleep, rats were placed in its back on the warmed pad (37^0C). When the sleep gets over, rats will come to its normal posture (recovery of righting reflex) and the time was noted. The time interval between the intraperitoneal injection of ketamine and start of sleep was recorded as latency time (min).

The interval between loss of righting reflex and recovery of righting reflex was measured as sleeping time (min).[12]

Statistical analysis

The data was analysed by one-way ANOVA followed by post hoc test and $p < 0.05$ was considered as significant. Results were presented as Mean±SEM.

RESULTS

Table 1 and Figure 1 shows the latency period. The latency period of group I (ketamine 80mg/kg) is 3.60±0.2min. Group II which received low dose ketamine (40mg/kg i.p.) and amantadine (40mg/kg orally) showed the latency period of 3.40±0.2min.

Group III (ketamine 80mg/kg i.p. along with amantadine 40mg/kg orally) showed the latency period of 2.0±0.3 (p <0.035) which is significantly less than that of group I.

Table 1: The latency time and sleeping time.

Groups	Latency time (min)	Sleeping time (min)
Group I	3.60±0.2	80.6±2.8
Group II	3.40±0.2	31.2±1.9***
Group III	2.0±0.3*	102.2±2.7***

*p<0.05, **p<0.01, ***p<0.001; Results were expressed as Mean±SEM

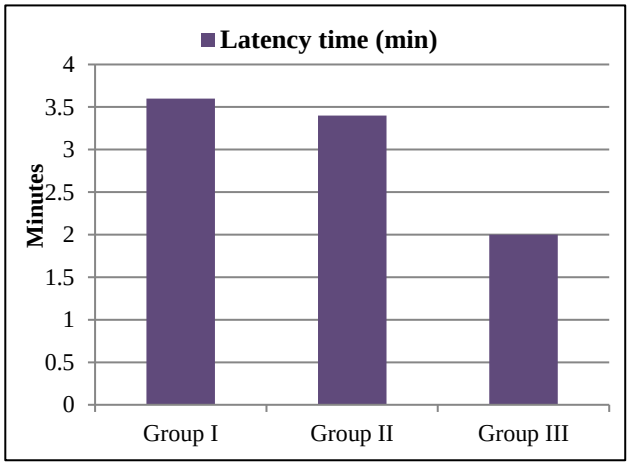

Figure 1: The latency time of sleep after ketamine injection.

Table 1 and Figure 2 shows the sleeping time. The sleeping time of ketamine 80mg/kg i.p. (group I) is 80.6±2.8min. Low dose ketamine 40mg/kg along with amantadine 40mg/kg showed sleeping time of 31.2±1.9min which is significantly lower than that of group I. Ketamine 80mg/kg i.p. along with amantadine 40mg/kg showed the sleeping time of 102.2±2.7 (p<0.001) which is significantly higher than that of group I and group II. No mortality was recorded during the study. Respiration and heart rate were regular during the experiment.

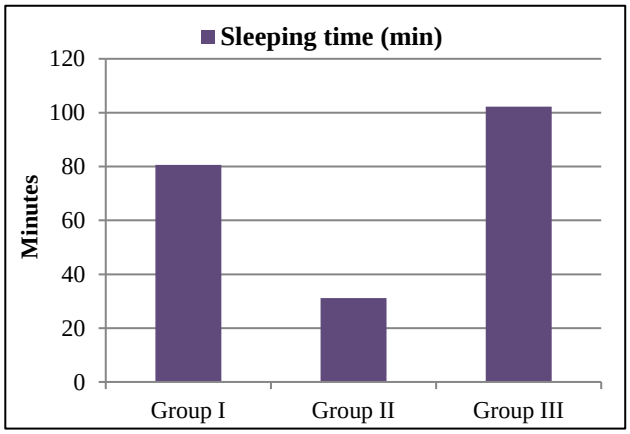

Figure 2: The sleeping time after ketamine injection.

DISCUSSION

Ketamine is a short-acting anaesthetic drug without serious undesirable side effects, such as respiratory or cardiovascular depression.[13] Amantadine as mentioned above is a NMDA antagonist with antiviral and dopamine releasing action.[5] The latency time of low dose ketamine (40mg/kg b.w.) and amantadine combination is as equal to that of ketamine 80mg/kg. Amantadine 40mg/kg b.w. significantly decreased the latency time and significantly increased the duration of sleeping time of ketamine 80mg/kg.

Abdelmawgoud A et al, conducted a prospective, randomized, double-blinded placebo-controlled study in female patients who were planned for abdominoplasty surgery. In the study preoperative oral amantadine was compared with placebo. Amantadine 200mg was given on the evening before surgery and 200mg, 60min prior to surgery.

The dose of anaesthetic agents propofol, isoflurane was titrated with the guidance of Bispectral index (BIS) to measure the depth of anesthesia during induction and maintenance of anesthesia and also measured the total dose of fentanyl needed to maintain adequate analgesia.

Author concluded that preoperative oral amantadine 200mg on the evening of surgery and 200mg, 60min before surgery reduced the induction time, induction dose of propofol, intraoperative anaesthetic and analgesic requirements compared to placebo in female patients during abdominoplasty surgery.[14]

Another study conducted by Daniel LC, who demonstrated the NMDA antagonists like MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclo-hepten-5,10-imine], phencyclidine (PCP) and ketamine increases the potency of general anaesthetics.

In this study the potency of general anaesthetics from different chemical classes was tested after pre-treatment with subanaesthetic doses of non-competitive N-methyl-D-aspartate (NMDA) antagonists in mice. Changes in general anaesthetic potency were assessed in the study by determination of alteration in the duration of loss of righting reflex for pentobarbital and changes in the minimum alveolar concentration (MAC) for the volatile anaesthetics like halothane and diethyl ether. Author concluded that the non-competitive NMDA antagonists like MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclo-hepten-5,10-imine], phencyclidine (PCP) and ketamine, increases the potency of general anaesthetics and the action may be due to the block of central NMDA receptors to the production of anesthesia by a variety of agents.[15]

Budhiraja S et al, demonstrated the prolongation of ketamine induced anesthesia by melatonin.[16]

Imre G et al, demonstrated the various effects of subanesthetic doses of ketamine. Author found out that the dose range of 4-16mg/kg ketamine induced hyperlocomotion in a dose dependent manner and this was not influenced by the dark/light cycle.[17]

Snijdelaar DG et al, used Amantadine before and after surgery to prevent post-operative central sensitization, acute opioid tolerance and opioid-induced hyperalgesia in a randomized, double blind, placebo-controlled study in 24 patients who underwent radical prostatectomy. Author found out that the cumulative morphine consumption was significantly lowered by amantadine and also number of patients reporting bladder spasm was significantly lowered.

Author concluded that perioperative Amantadine reduced the mechanical sensitivity around the wound, incidence of bladder spasm and the requirement of postoperative morphine.[18]

Dehar NA et al, studied the potentiation of thiopentone sodium induced hypnosis by Berberis aristata in rodents. Author used three different doses (5mg/kg, 10mg/kg, 20mg/kg) of pure Berberine extract of Berberis aristata root and concluded that the Berberine chloride produced significant dose dependant decrease in total motility, locomotor activity, motor incoordination (change in gait) and loss of righting reflex.[19]

In present study authors only monitored the latency time and the sleeping time. Respiratory rate, cardiac activity, locomotor activity and brain activity during the anesthesia were not monitored. The adverse effects and the effects on recovery were not evaluated in present study.

The potentiation of general anaesthetic activity of ketamine by amantadine may be due to its NMDA receptor antagonistic activity at the cortex and the subcortical area of brain where ketamine acts.[5]

CONCLUSION

Authors concluded that amantadine in the dose of 40mg/kg potentiates the anaesthetic duration of ketamine. It also decreases the latency period of anesthesia.

This shows that amantadine may be used as a preanesthetic medication in animals to increase the duration of ketamine induced general anesthesia. Further studies are needed to find out the adverse effects, effects on recovery and the effects on various systems.

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