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THE STUDY OF EFFICACY OF NIMODIPINE IN POTENTIATION OF THE ANAESTHETIC EFFECT OF KETAMINE IN GUINEA PIGS

Tamilarasi.S[1], Abdul Rahman A[2], Parameswari R[3]

ABSTRACT

Objectives : To investigate whether nimodipine potentiates the anaesthetic effect of ketamine, in guinea pigs.

Materials and Methods : 18 adult male guinea pigs of weight 400-600 grams were utilized. They were randomly divided into three groups of 6 each. First group received only Injection. Nimodipine 10 mg/kg intraperitoneally. Second group received only Inj.Ketamine 50 mg/kg i.p. Third group received Inj.Nimodipine 10 mg/kg, 30 minutes before Inj.Ketamine 50mg/kg i.p. After administration of the drug, animals are watched for its righting reflex. Induction time is the time duration from administration of the drug till the animal loses its righting reflex is noted. The duration of anesthesia(time duration from the animal loses its righting reflex till it regains the same) were noted in each group. The observations are analyzed with suitable statistical tool.

Results : Ketamine has got anesthetic effect and when nimodipine is administered along with ketamine, it has significantly potentiated the anaesthetic effect of ketamine ($P<0.05$) compared to ketamine alone. Nimodipine has got no anaesthetic effect.

Conclusion : This study suggests that nimodipine, potentiates the anaesthetic effect of ketamine, hence nimodipine, could be a potential adjunct to ketamine, achieving a therapeutic effect at a lower concentrations of ketamine, hence limiting their dose related toxicities, which needs to be explored further.

Key Words : Ketamine, Nimodipine, Anesthetic effect, Induction Time, Righting reflex.

INTRODUCTION

Nimodipine, a dihydropyridine type of Ca^{2+} channel blocker [1], has been used in clinical conditions associated with vasospasm of the cerebral vasculature, which occurs after subarachnoid hemorrhage (SAH). It has been proved that nimodipine has improved the neurological outcome and prevented the neuronal damage caused by free radicals released during ischemia due to vasospasm. Apart from nimodipine, nitrendipine has also got a role in the management of SAH.

Many theories have been postulated, regarding how the intravenous and inhalational agents produce general anesthesia [2]. Of which lipid membrane bilayer theory and ion channel theory were the widely accepted one [3]. The role of Ca^{2+} in general anesthesia is often a controversial one. It was earlier proposed that general anesthesia was due to surge in the cytoplasmic free Ca^{2+}. But later on it has been postulated by Bleak man et al [4], that halothane, and enflurane did not alter the basal Ca^{2+} levels in cultured rat hippocampal neurons and eventually these anaesthetic agents inhibit the elevation of Ca^{2+} by high K + stimulation. Many Ca^{2+} channel blockers like nitrendipine, has been attributed to alteration of nitrous oxide anesthesia, tolerance. In a study conducted by Singh J [5] et al, Nimodipine was found to potentiate the anesthetic effect of ethanol and phenobarbitone. Keeping this background, this study tries to bring out the role of a Ca^{2+} channel blocker (nimodipine) in general anesthesia and to check whether a Ca^{2+} channel blocker could potentiate the anesthetic effect of ketamine [6], an intravenous anesthetic agent in guinea pigs.

MATERIAL AND METHODS

Animals: 18 adult male guinea pig weighing 400-600 grams were obtained from the central animal house Madurai Medical College, Madurai. The animals were

[1]Associate Professor, Institute of Pharmacology, Madurai Medical College, Madurai.
[2]Pharmacology Postgraduate, Institute Of Pharmacology, Madurai Medical College, Madurai.
[3]Director & Professor, Institute Of Pharmacology, Madurai Medical College, Madurai.

housed in standard cages and acclimatized for 15 days. Guinea pigs were maintained in standard diet and water ad libitum. Approval for the study was obtained from the Institutional Ethical committee, Madurai Medical College, Madurai. Animals were kept in overnight fasting before the day of experiment.

Drugs and Chemicals : Nimodipine tablet was utilized (USV limited, Solan, HP, Batch No 28007590). Polyethylene glycol (Glaxo chemicals, Bombay), and glycerin (PRS Pharmaceuticals, B.No MG-218) were also used in this study. A 0.1% solution of nimodipine (1ml = 1mg) was prepared using the solvents of the following composition: 969 grams of polyethylene glycol, 60 grams of glycerin and 100 g of sterile distilled water. Ketamine Injection (Ciron drugs, Thane, Batch No A 02078) was also utilized.

Drug Administration : The drugs used in this study were administered intraperitoneally, using 23-25 gauze needles [7]

Procedure : 18 Guinea pigs were randomly divided into three groups of 6 animals each and named as Group I, II, and III. Group I received only Inj.Nimodipine 10 mg/kg i.p. Group II received only Inj.Ketamine 50mg/kg i.p. Group III received Inj. Nimodipine 10 mg/kg i.p, 30 minutes before Inj.Ketamine. Immediately after administration of the drug, animals were watched for their righting reflex every 15 seconds. Righting reflex is the ability of the animal to maintain its posture, when it is disturbed. After administration of the drug, the following time parameters were noted.

Induction Time : It is the time duration from the administration of the drug till the animal loses its righting reflex. Once the animal is anaesthetized, it's been watched for the breathing pattern, and if necessary supplemental oxygen was provided.

Duration of anaesthesia : It is the time duration from the animal loses its righting reflex till its regains the same.

The induction time and the duration of anaesthesia in each group were recorded. Group I served as control, which had received only Inj.Nimodipine (10 mg/kg i.p) alone.

Statistical Analysis : The results of nimodipine pretreated group (Group III) and ketamine alone group (Group II) were analyzed statistically using unpaired Students 't'test. Since nimodipine has got no anesthetic effect (Group I) it was not included in the statistical analysis.

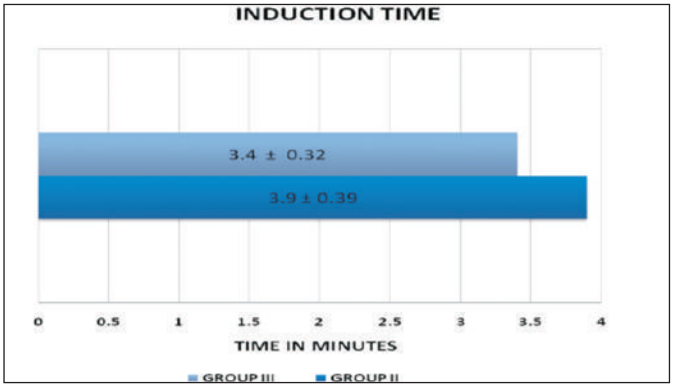
RESULTS

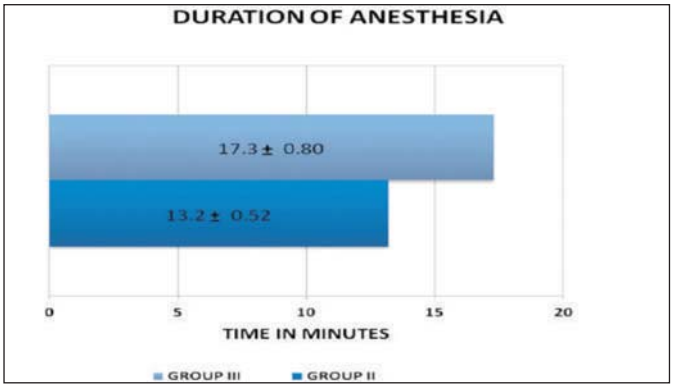
Nimodipine alone has got no anesthetic effect. Ketamine has got significant anesthetic effect. Nimodipine pretreatment significantly (P = 0.04) potentiated the anesthetic effect of ketamine In guinea pigs (Table 1). The Induction time was decreased and the duration of anesthesia was prolonged.

Table 1. : Showing Induction time in minutes & Duration of Anesthesia in mins.

GROUP	Induction time (Mins) Mean ± S.D	Duration of Anesthesia (Mins) Mean ± S.D
GROUP II Ketamine alone	**3.9 ± 0.39**	**13.2 ± 0.52**
GROUP III Nimodipine + Ketamine	**3.4 ± 0.32 #**	**17.3 ± 0.80 ***

P value =.04 * P value = .001
Group II- Ketamine alone & Group III- NM pretreated





DISCUSSION

The anesthetic effect of ketamine was primarily due to blockade of excitatory neurotransmitter Glutamate at NMDA receptors (α1 subunit) [8]. It has also been reported that ketamine inhibits the voltage gated Ca^{2+} channels [9]. Cardozo et al [10] demonstrated the presence of L and other type of Ca^{2+} channels play an important role in the mechanism of general anesthesia. Unlike other anesthetic agents whose primary site of action is reticular activating system, Ketamine acts upon cortex and sub cortical area thus producing ' dissociative anesthesia' [11]. It has been reported that the stimulation of NMDA receptors, activates voltage operated Ca^{2+} channels[12] and nimodipine [1] [13] has been shown to decrease Ca^{2+} dependent release of glutamate and hence decreasing the availability of the excitatory neurotransmitter glutamate in nerve cells. Thus nimodipine may synergistically act with NMDA receptor blockers. Singh et al [5] reports that nimodipine could potentiate the anesthetic effect of ketamine and Pentobarbitone even though the mechanism of action is different for both the drugs. Even though ketamine has got good analgesic property, the main drawback is the excessive sympathetic stimulation in therapeutic doses by inhibition of reuptake of catecholamines [14] which may lead to oxidative stress due to lipid peroxidation. Oxidative stress, along with catecholamines leads to intracellular surge of Ca^{2+} which could disrupt the neuronal cell wall integrity. Nimodipine produces allosteric modification of L type Ca^{2+} channels and prevents the entry of Ca^{2+} into the cell and thus help preventing neuronal injury. Thus Nimodipine could be a potential adjunct to Ketamine, achieving a therapeutic Effect (desired plane of anaesthesia) at a lower Concentration of ketamine, hence limiting ketamine's dose related toxicity.

CONCLUSION

To conclude Nimodipine potentiates the anesthetic effect of ketamine which needs to be further evaluated in human experiments.

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