Study on the anticonvulsant activity of Pentazocine in albino rats

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ABSTRACT

Pentazocine, which is known to act as an agonist at kappa opioid receptors and a weak antagonist or a partial agonist at mu receptors has shown significant anticonvulsant activity in MES test and abolition of this anticonvulsant activity by high dose but not by low dose of Naloxone. The present study was designed to compare the anticonvulsant effect of Pentazocine with standard Sodium Valproate in albino rats. An attempt was also made to determine the possible opioid receptor mechanism involved. 30 albino rats of either sex weighing 150-200 gms were selected and randomly divided into 5 equal groups. Maximal Electroshock (MES) seizures were induced in albino rats via trans auricular electrodes (120mA, 0.2 seconds). Each rat was pretreated at 30 minute before MES test with the drugs intraperitoneally. The different groups were group 1 receiving Propylene glycol (0.5ml/kg), Group 2 receiving Sodium Valproate (300mg/kg), group 3 receiving Pentazocine (30mg/kg), group 4 receiving Pentazocine (30mg/kg) and Naloxone (0.1mg/kg), group 5 receiving Pentazocine (30mg/kg) and Naloxone (1mg/kg). Data was statistically analysed by Mann Whitney test and ANOVA. Intraperitoneal administration of Pentazocine resulted in reduction of different phases of convulsions during the MES method. The anticonvulsant effect of Pentazocine was antagonized by the high dose Naloxone (1mg/kg) but not by low dose (0.1mg/kg) of intraperitoneal Naloxone. The results suggest that Pentazocine has anticonvulsant activity which is mediated by kappa receptors. Naloxone in high dose is known to block kappa receptors, thereby blocking the anticonvulsant effect of pentazocine.

Key words: Pentazocine, Naloxone, kappa opioid receptors, maximal electro shock seizure.

INTRODUCTION

Epilepsy is one of the most common neurological disorders. Worldwide, the prevalence is estimated to be 0.5 – 1%, and there is a life time incidence of 1 – 3%. It has important medical, social and psychological consequences. Despite the introduction of several new therapeutic

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options in the 1990s, a significant fraction of the patients with epilepsy continue to live with uncontrolled seizure. [1] There is still a need for an ideal antiepileptic agent with properties like broad spectrum activity, rapid onset of action, least side effects, good oral bioavailability and low cost. [2] Although most people with epilepsy become seizure free with appropriate therapy, 30-40% of patients will continue to have seizures despite the use of antiepileptic drugs either alone or in combination. [3]

The potential importance of endogenous opioids in modulating and regulating aspects of brain electrical activity has been described recently. [4] Subcutaneous or intracerebroventricular administration of U50, 488, a highly selective kappa opioid agonist, resulted in a dose and time dependent anticonvulsant action in rats.[5] Pentazocine is known to act as an agonist at kappa opioid receptors and a weak antagonist or a partial agonist at mu receptors. [6] This has shown significant anticonvulsant activity in maximal electroshock test. This anticonvulsant property was not antagonized by naloxone indicating that the anticonvulsant action was mediated by non-mu receptors, as naloxone is selective mu receptor antagonist. [7, 8]

In the light of the development cited above an attempt has been made in this work to compare the anticonvulsant effect of pentazocine with standard sodium valproate in albino rats.

EXPERIMENTAL SECTION

The study was undertaken at the department of pharmacology, J.J.M.Medical College, Davangere after obtaining the approval from Institutional Ethics Committee. Albino rats, of wistar strain, weighing between 150-200gm of either sex were used for the study. The animals were fed with standard laboratory food and water. Animals were randomly divided into 5 equal groups containing 6 in each group

Group 1: Control group C1, Rats receiving 0.5ml/100gm of Propylene Glycol
Group 2: Standard group S1, Rats receiving 300mg/kg of Sodium Valproate in propylene glycol
Group 3: Test group T1, Rats receiving 30mg/kg of Pentazocine dissolved in distilled water
Group 4: Test group T2, Rats receiving 30mg/kg of Pentazocine dissolved in distilled water and also with 0.1mg/kg of Naloxone twenty minutes after receiving Pentazocine
Group 5: Test group T3, Rats receiving 30mg/kg of Pentazocine dissolved in distilled water and also 1mg/kg of Naloxone intraperitoneally twenty minutes after receiving Pentazocine.

All the test animals were allowed food and water adlibitum both being withdrawn just prior to experimentation. All the test animals were subjected to further experiment of this study after 24hrs (to avoid any possible "Kindling" effect). All the preparations were administered intraperitoneally. All animal Handling and animal care was done as per the guidelines set by Indian National Science Academy, New Delhi, India.

They were used to induce convulsions by minimal electroshock method. The above test animals were subjected to electroshock of 150mA intensity for 0.2 seconds, through auricular electrodes, (covered in cotton wool and saline moistened). A majority of rats showed tonic flexion and extension of fore and hind limbs, clonus, stupor followed by post ictal depression and recovery. Only those rats showing the convulsive responses were used for experiment. These results in seizures and various phases of seizures were noted and duration was recorded. The Parameter mainly studied was hind limb tonic extension

Statistical Analysis: Descriptive data that include Mean, Standard Deviation, and range value were found for each group and used for analysis. Mann Whitney test was used for comparison

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between two groups. One way ANOVA was used for multiple group comparison. P value of 0.05 or less was considered for statistical significance.

RESULTS

Highly significant (P<0.05) reduction of hind limb tonic extension was seen in group 3 that received Pentazocine 30mg/kg body weight when compared to control group. There was no significant differnce of hind limb tonic extension between group 2 that received Pentazocine 30mg/kg body weight & group 3 that received 300mg/kg of Sodium Valproate. [Table 1, Graph 1]

The results of group 4 that received Pentazocine 30mg/kg BW and low dose Naloxone 0.1mg/kg BW, in MES method when compared to group 3 that received only Pentazocine 30mg/kg BW, mean duration of hind limb tonic extension was increased, but statistically not significant. [Table 1, Graph 2]

Table 1: Statistical analysis showing comparison of hind limb extension in MES

Groups	Hind limb extension (Mean ± S.D)	Groups compared	Mean difference	P value
Group 1 Control C1	12.3 ± 1.2	1 and 2	12.2	_
Group 2 Standard S1	-	1 and 3	9.0	0.005**
Group 3 Test group T1	3.3 ± 3.9	2 and 3	3.3	_
Group 4 Test group T2	3.8 ± 4.3	3 and 4	0.5	0.93,NS
Group 5 Test group T3	11.8 ± 0.7	3 and 5	8.5	0.004*

NS: Not Significant   *: Significant (<0.05)   **: Very Significant (<0.005)

Results of group 5 that received Pentazocine 30mg/kg BW and high dose Naloxone 1mg/kg BW, in MES method when compared to group 3 that received only Pentazocine 30mg/kg BW, highly significant (P<0.05) increase in hind limb tonic extension was seen. [Table 1, Graph 2]

Graph 2 : Bar diagram showing mean values of tonic hind limb extension in MES method
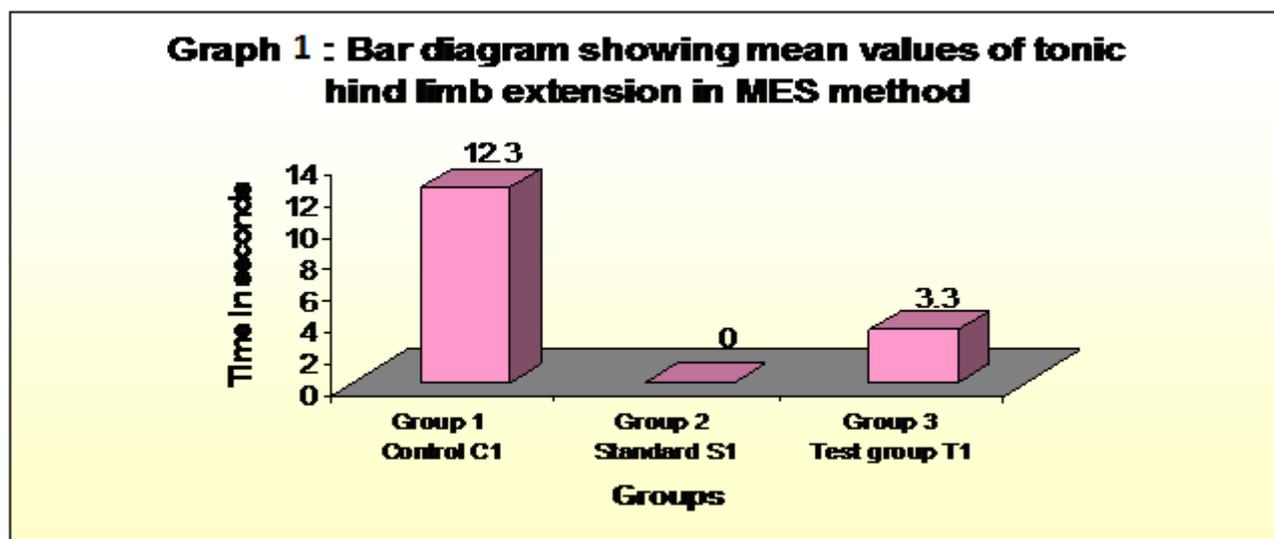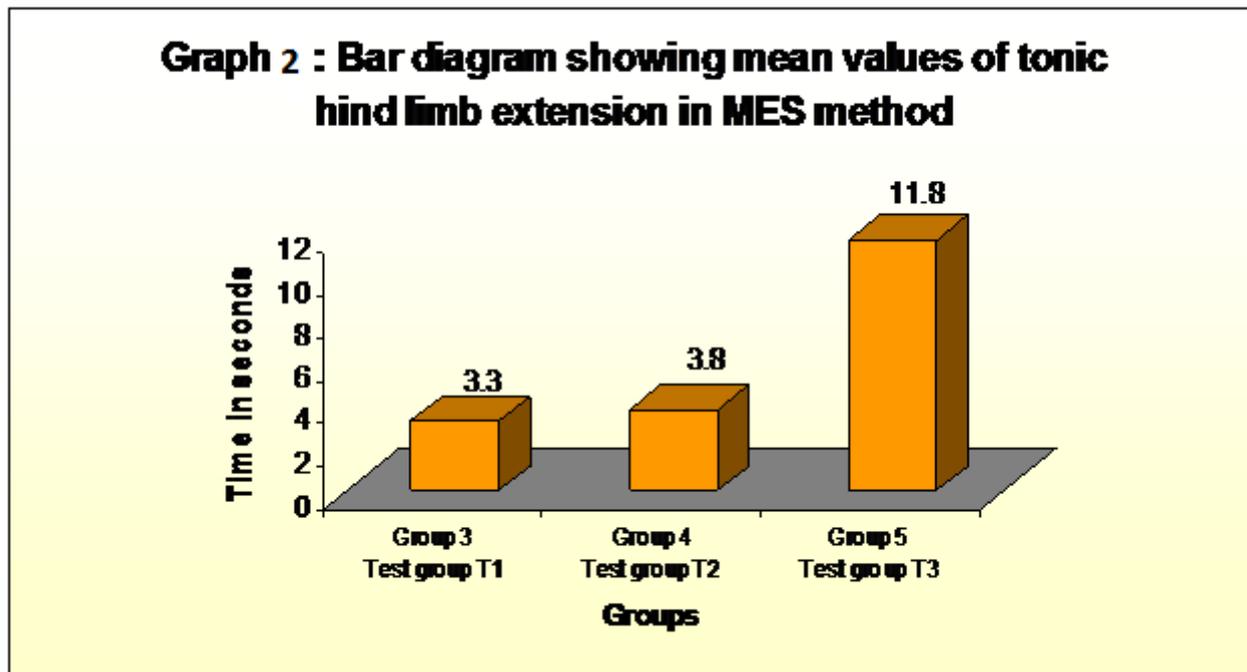
DISCUSSION AND CONCLUSION

The results of the present study demonstrate that Pentazocine elicited an effective protection against MES seizures in albino rats. This anticonvulsant effect was very much significant when compared to control. Pentazocine which is known to act as agonist at kappa opioid receptors and a weak antagonist or a partial agonist at mu receptors, [6] has shown significant anticonvulsant activity in MES test. Naloxone in high dose (1mg/kg) but not in low dose (0.1mg/kg) completely antagonized the anticonvulsant effect of Pentazocine. Naloxone at low dose blocks mu receptors and at high dose blocks kappa receptors. This suggests the mechanism of action for Pentazocine has an anticonvulsant involving a kappa opioid receptors system.

This observation was similar to the study done by Anshu Moncha et al in mice. [7] The results of present study partly confirms the results of Bermann and Adler who also showed a potent anti – MES effect of Pentazocine but failed to observe an antagonism with a high dose (10mg/kg) of Naloxone. The failure of Naloxone to block the anticonvulsant effect of Pentazocine is due to long pre treatment schedule of 30 minutes used for Naloxone, which as such is a short acting antagonist in rodents. [9] But another study made by Khanna et al showed dose dependent anticonvulsant effect of Pentazocine against maximal electroshock seizure in mice and this was antagonized by both doses of Naloxone (1& 10mg/kg).[8]

Collectively, these observations indicate that the stimulation of kappa receptors in the brain results in MES seizure protection. In view of these observations, Dynorphin A (1-13), which is an endogenous ligand for kappa receptors.[60] had shown to attenuate MES seizure in rats. [11] Observations of the present study and from the other studies indicate that kappa opioid system plays an important role in MES seizure protection.

At the end of the study it can be concluded that Pentazocine, kappa opioid receptor agonist and a weak antagonist or partial agonist at mu receptors, has shown significant anticonvulsant action in

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MES test. Naloxone (pure opioid receptor antagonist) in high dose (1mg/kg) antagonized the anticonvulsant effect of Pentazocine.

In view of the promising results with Pentazocine, the screening and evaluation of highly selective kappa drugs may prove beneficial to the development of novel therapeutic approaches to epilepsy.

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