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Study of Antiepileptic Effect of Pentazocine And Combination Of Pentazocine With Phenytoin In Experimentally Induced Convulsions In Albino Rats

Dr .Maddala rajitha[1], J.Balu[2,] A.viswashanthi[3]
[1,2,3](Department Of Pharmacology , Nimra Institute Of Medical Sciences, Vijayawada/ Dr.NTR,UHS, Andhra Pradesh, India)

Abstract:
Aims& objectives: *The present study was designed to compare the anti convulsant effect of pentazocine with standard phenytoin sodium and also combination of different doses of pentazocine with different doses of phenytoin in experimentally induced albino rats.*
Materials& methods: *30 albino rats of either sex weighing 150 to 200 gms were selected and randomly divided in to 5 equal groups with 6 rats in each group, maximal electro shock seizures(MES) were induced in albino rats via trans auricular electrodes (150 mA,0.2 seconds) each rat was pretreated at 30 minutes before MES test with drugs intraperitoneally.*
Statistical Analysis: *Descriptive data that include Mean, Standard Deviation, and standard error value were found for each group and used for analysis. One way ANOVA was used for multiple group comparison. P value of 0.05 or less was considered for statistical significant.*
Resuts: *intraperitoneal administration of pentazocine resulted in reduction of different phases of convulsions during MES method. Different dose combination of pentazocine &phenytoin also reduced the duration of different phases of convulsions*
Conclusion*: the anticonvulsant effect of pentazocine alone is superior to the effect of combination of pentazocine and phenytoin in the seizure models. Pentazocine alone was comparable to that of the standard drug in electrically induced seizures .*
Keywords: *Albinorats, intraperitoneal route , maximal electro shock method, pentazocine, phenytoin*

I. Introduction

The epilepsies are common and frequently devastating disorders[1].The second most common disorder of the central nervous system after stroke[2]. Epileptic seizures often cause transient impairment of consciousness leaving the individual at risk of bodily harm and often interfering employment[3] . Starting from role of bromides on Epilepsy to recent newer anti Epileptics. There is a still need for an ideal anti epileptic agent with properties like broad spectrum of activity, rapid onset of action, least side effects, good oral bioavailability, and low cost. In contrast to opioids activating seizures many studies demonstrated that opioid peptides with pharmacological electivity for mu, delta, Kappa, binding sites are anti convulsants[4-7]. It is interesting to note that mu, delta, kappa, opioids selectively hyperpolarize neurons throughout the CNS[8-10],Therefore it seems possible that opioid peptides may indeed form as endogenous anticonvulsant in the CNS modulating the underlying mechanisms of seizures arrestand refractoriness which are critical to the suppression of convulsions[11-19]. Subcutaneous or intra cerebro ventricular administration of $U_{50,488}$ a highly selective kappa opioid agonist, resulted in a dose and time dependent anticonvulsant action in rats[20].Pentazocine is known to act as a agonist at kappa opioid receptors and a weak antagonist or a partial agonist at mu receptors[21,22] .According to the studies pentazocine increased the anti convulsant effect of phenytoin[23]. By keeping in this view . The present study was undertaken to evaluate the anti convulsant activity of pentazocine and the combination of different doses of pentazocine and phenytoin in experimentally induced seizures in albino rats.

II. Methodology

Albino rats of either sex of average weight (150-200g) which were obtained from National institute of nutrition, Hyderabad, and maintained at the central animal house A.S.R.A.M. Medical College, ELURU used for the study. Institutional animal ethical committee permission was taken for the study. 30 albino rats of either sex weighing 150-200g were selected and randomly divided into 5 equal groups containing 6 in each group.All the test animals were allowed food and water ad libitum 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 intraperitoneal route. Animals were used to induce convulsions by maximal electroshock method. The above test animals were subjected to electroshock of 150mA intensity for

0.2seconds, 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.

2.1 Inclusion Criteria:

o Animals weighing 150-200g.

o Healthy with normal behavior and activity.

2.2 Exclusion Criteria:

o Animals weighing more than 200g and less than 150g.

o Pregnant female and those which have delivered once.

2.3. Groups

Group - I animals (Control group)received 0.5ml/kg body weight distilled water.

Group - II animals (Standard group) Six albino rats received 135mg/kg of phenytoinsodium.

Group - III animals (Test group I ; T1) Six albino rats received pentazocine 30mg/kg

Group - IV animals (Test groupII ; T2) Six albino rats received 15mg/kg of pentazocine andinj phenytoin 10mg/kg.

Group - V animals (Test group- III; T3)six albino rats received 30mg/kg of pentazocine and 20mg /kg of phenytoin.

2.4 The Parameters studied are:

2.4.1.. Duration of convulsions

2.4.2 Hind limb tonic extension-HLE in seconds

2.4.3.duration of recovery in seconds

2.5.Statistical Analysis: Descriptive data that include Mean, Standard Deviation, and standard error value were found for each group and used for analysis. One way ANOVA was used for multiple group comparison. P value of 0.05 or less was considered as significant

III. Results

Table-1

Comparison of duration of convulsions (in seconds) by MES method among 5 groups

- Group I control group given distilled water I.P
- Group II standard group given phenytoin sodium 135mg/kg I.P
- Group III test I given Inj pentazocine 30mg/kg I.P

Group	N(size of sample)	Mean(seconds)	Standard deviation	Standard error
Group-I	6	70.3	3.87	1.61
Group-II	6	21.3	3.93	1.64
Group-III	6	26.5	7.5	3.12
Group IV	6	46.3	6.9	2.88
Group V	6	50	7.07	2.94

- Group IV test 2 given Inj pentazocine 15mg/kg + Inj phenytoin 10mg/kg I.P
- Group V test 3 given Inj Pentazocine 30mg/kg + Inj phenytoin 20mg/kg I.P

Table-2 Comparison of duration of THLE by MES method (in seconds) among 5 groups

Group	N(size of sample)	Mean(seconds)	Standard deviation	Standard error
Group-I	6	11.75	2.07	0.8
Group-II	6	0	0	0
Group-III	6	0	0	0
Group IV	6	3.3	1.09	0.45
Group V	6	3.4	0.54	0.22

- Group I control group given distilled water I.P
- Group II standard group given phenytoin sodium 135mg/kg I.P
- Group III test I given Inj pentazocine 30mg/kg I.P
- Group IV test 2 given Inj pentazocine 15mg/kg + Inj phenytoin 10mg/kg I.P
- Group V test 3 given Inj Pentazocine 30mg/kg + Inj phenytoin 20mg/kg I.P

Table-3 Comparison of duration of Recovery phase by MES method among 5 groups

Group	N(size of sample)	Mean (seconds)	Standard deviation	Standard error
Group-I	6	50.6	3.2	1.35
Group-II	6	13	2.36	0.98
Group-III	6	24.3	5.74	2.39
Group IV	6	45.8	10.8	4.52
Group V	6	35.1	5.91	2.46

- Group I control group given distilled water I.P
- Group II standard group given phenytoin sodium 135mg/kg I.P
- Group III test I given Inj pentazocine 30mg/kg I.P
- Group IV test 2 given Inj pentazocine 15mg/kg + Inj phenytoin 10mg/kg I.P
- Group V test 3 given Inj Pentazocine 30mg/kg + Inj phenytoin 20mg/kg I.P

IV. Discussion

Pentazocine is weak competitive antagonist at the mu receptor and agonist at the kappa receptor in higher doses weak sigma agonist.Therefore according to the studies mentioned above the probable anticonvulsant action of pentazocine is due to kappa and sigma receptors[24-29] .

At the molecular level the mu, delta kappa receptors largely couple through pertusis toxin sensitive G protein. Upon receptor activation G protein coupling results in a large number of intracellular events including[30,31]

a) Inhibition of adenylcyclase leading to decrease in C_{Amp} with consequent decrease in cell excitability.
b) Activation of potassium channels and subsequent increase in potassium conductance to produce hyperpolarization of neurons and a decrease in their excitability.
c) Inhibition of calcium conductance by suppressing voltage gated N type of calcium channels.

Several studies reported that the sigma receptor modulate the neuronal firing and the neurotransmitter release.Nuwayhid and werling recently demonstrated that sigma receptor agonists regulate the NMDA induced dopamine release from rat striated slices via protein kinase c.Debonnel and colleagues demonstrated that sigma ligands modulate glutamatergic and seratonergic neurons.Several studies demonstrated both type1 and type2 sigma receptors regulate calcium efflux from the endoplasmic reticulum. In this present study Pentazocine alone and combination of pentazocine with phenytoin evaluated for anticonvulsant activity by maximal electroshock method induced seizures The test drugs are compared with both the control (distilled water) and the standard (phenytoin sodium). Analysis of the results of group - III that received 30mg/kg body weight of pentazocine when compared to control group, the mean duration of various parameters were reduced like duration of convulsions (table-1), hind limb extension(table-2), duration of recovery from postictal depression(table-3) was found significant. And when compared with the standard phenytoin sodium, the mean duration of various parameters like duration of convulsions (p value- 0.18), tonic hind limb extension found to be non significant . The recovery phase (p value – 0.0029) little bit significant . This implies that pentazocine in a dose of 30mg/kg body weight have significant anticonvulsant activity. Therefore the result of the present study demonstrated that Pentazocine elicited and effective protection against MES seizures in Albino rats .

Analysis of the results of group - IV that received combination of inj pentazocine 15mg/kg body weight and phenytoin sodium 10mg/kg when compared to control group the various parameters of like duration of convulsions(table1), total hind limb extension(table2) , duration of post ictal depression recovery(table3), is significant. when compared with standard phenytoin sodium mean duration of various parameters like duration of convulsions, total hind limb extension, recovery phase are significant. When compared with group - V mean duration of various parameters found to be non significant. Analysis of the results of group - V that received combination of inj pentazocine 30mg/kg body weight and phenytoin 20mg/kg when compared to control group the mean duration of various parameters like duration of convulsions, total hind limb extension , duration of post ictal depression recovery is significant. when compared with standard phenytoin sodium mean duration of various parameters like duration of convulsions, total hind limb extension, recovery phase are significant. When compared with group - IV mean duration of various parameters found to be non significant .As expected Phenytoin provided complete protection against MES while Pentazocine when co administered with sub anticonvulsant dose of Phenytoin and even combination of anti convulsant doses combination of both drugs was not provided significant protection . This observation not agrees with an earlier report, that in a study by Hans Hassofrey it was suggested that prior administration of morphine like analgesics like Fentanyl, Pentazocine increased the Anti Electroshock effect of Phenytoin and Phenobarbitol.

The reason for the contrary results of the study from the previous studies may not be properly known. It may be due to species variation or any other Pharmacokinetic, Pharmacodynamic mechanisms may be involved which need to be evaluated by further studies

V. Conclusion

The present study demonstrated that Pentazocine elicited an effective protection against MES seizures in Albino rats This implies that pentazocine in a dose of 30mg/kg body weight have significant anticonvulsant activity. Pentazocine when co administered with sub anticonvulsant dose of Phenytoin and even combination of anti convulsant doses of both drugs was not provided significant protection.Therefore pentazocine not increasing the anticonvulsant effect of phenytoin but decreasing . Further studies are needed to know the interactions between both drugs.

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