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Original Research Article

ANGIOTENSIN AT1 RECEPTOR ANTAGONISTS (TELMISARTAN AND VALSARTAN) ENHANCE THE ANTICONVULSANT ACTION OF PHENYTOIN IN THE MOUSE MODEL OF MAXIMAL ELECTROSHOCK SEIZURE TEST

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ABSTRACT

Background: Epilepsy is a common neurological disorder requiring newer targets for its efficient treatment. Recently, brain renin-angiotensin system has gained immense importance because of its involvement in seizure regulation. Hence, the present study was planned to evaluate whether angiotensin receptor blockers (ARBs) possess antiepileptic activity in experimental animals.
Objective: To evaluate the antiepileptic activity of telmisartan and valsartan alone and in combination with phenytoin against seizure induced by maximal electroshock (MES) in albino mice
Materials and Methods: 48 Swiss albino mice of either sex were divided into 8 groups of 6 animals each and were treated with telmisartan and valsartan alone and in combination with phenytoin. MES was induced in mice by electroconvulsiometer (45mA, 0.2 sec). Reduction in duration of tonic hind limb extension (THLE) was considered as the index of antiepileptic effect.
Results: Telmisartan and valsartan dose dependently decrease the duration of THLE as compared to control significantly ($p < 0.05$). Also, combination of sub anticonvulsant dose of phenytoin + telmisartan (8mg/kg) and sub anticonvulsant dose of phenytoin+ valsartan (20 mg/kg) significantly decrease the duration of THLE ($p< 0.01$) as compared to control.
Conclusion: Both telmisartan and valsartan have antiepileptic activity and also potentiated phenytoin, dose of phenytoin can be reduced in epileptic patients with cardiovascular comorbid conditions receiving telmisartan or valsartan.
Keywords: telmisartan, valsartan, phenytoin, renin angiotensin system, maximal electroshock.

INTRODUCTION

Epilepsy is a chronic disorder of brain function characterized by the recurrent and unpredictable occurrence of seizures. Approximately 1% of the world's population has epilepsy. Seizures that occur in people with epilepsy are transitory alterations in behaviour, sensation or consciousness caused by abnormal, synchronized electrical discharge in the brain. Most antiseizure drugs have been identified by tests in rodent models. The maximal electroshock (MES)test, in which an electrical stimulus of sufficient intensity to induce maximal seizures (tonic extension) of the hind limb is applied to animals by means of an electroconvulsiometer, has been used for screening of drugs effective in generalized type of seizures.[1,2]

Angiotensin AT1 receptor antagonists are widely used in clinical practice for treatment of hypertension, congestive heart failure or diabetic nephropathy.[3] It is known that besides the peripheral renin-angiotensin system, all components (precursors and enzymes) of this system are present

in the brain.[4] It has been reported that angiotensin II increases the seizure threshold in pentylenetetrazole induced seizure test in mice which was blocked by losartan suggesting Ang-II peptide might have an anticonvulsant activity mediated through an AT1 receptor. It has also been reported that an up-regulation of AT1 and AT2 receptors in the cortex and hippocampal area of patients with temporal lobe epilepsy with mesial temporal sclerosis supporting renin angiotensin system involvement in the pathology. It was also studied an increased concentration of angiotensin II in the hippocampus of rats in the chronic phase of pilocarpine epilepsy model suggesting the involvement of brain renin angiotensin system in seizure susceptibility.[5]

Taking into consideration, the significant role of renin angiotensin aldosterone system in the brain, we sought to evaluate the influence of ARBs i.e. telmisartan and valsartan on the seizure protective action of phenytoin.

MATERIALS AND METHODS

Study design: Experimental animal -based study.
Sample size: n=6 for 8 groups, Total N= 48
Groupings:
C: Control
T_1: Telmisartan 5mg/kg
T_2: Telmisartan 8mg/kg
V_1: Valsartan 10mg/kg
V_2: Valsartan 20mg/kg
P: Phenytoin 10mg/kg
P+T2: Phenytoin 10mg/kg+ Telmisartan 8mg/kg
P+V_2: Phenytoin 10mg/kg + Valsartan 20mg/kg

Experimental animals

Swiss albino mice of either sex weighing 20-30 g were procured from animal house of JNIMS, Imphal for experimental purpose. They were housed in departmental polypropylene cages under standard laboratory diet and water ad libitum and acclimatized for 10 days. 12 hours dark-light cycle was maintained. The animals were fasted for 8 hours prior to the experiment and care was taken to avoid coprophagy. Each mouse was used only once. The animals were grouped in 8 groups with 6 animals in each group. The experiment was approved by the Institutional Animal Ethics Committee, RIMS.

Drugs

Angiotensin AT1 receptor antagonists, telmisartan (Abbott, India) and valsartan (Novartis, India) and antiepileptic drug phenytoin (Abbott, India) were used. All drugs were suspended in 1% solution of Tween 80 (Sigma, USA) in distilled water and were injected once intraperitonally (i.p) in a volume of 5ml/kg body weight.

Experimental model

Anticonvulsant activity was tested using MES model. The animals were pretested with an electrical current of 45mA for 0.2sec via trans auricular electrodes using an INCO electro convulsiometer. Only those showing tonic hindlimb extension (THLE) were taken for the study. A recovery period of 3-4 days was given before repeating the experiment. The drugs and the control were given intraperitoneally 1 hour before the electroshock in the same manner as done in the pretesting. Later, a sub anticonvulsant dose of phenytoin was determined and its combination with the most effective dose of telmisartan and valsartan was seen in the same model.

Statistical Analysis

The values were expressed as mean ± SEM. The statistical analysis was carried out by SPSS software. One way analysis of variance (ANOVA) followed by post hoc Dunnett's t- test were applied. P values <0.05 were considered significant.

RESULTS

The results of the test are tabulated below in Table 1.

The duration of THLE in mice treated with vehicle was 16.67 ±1.11secs. The duration of THLE in the groups treated with telmisartan 5mg/kg and 8mg/kg were 14.17± 0.40 secs and 10.40 ± 0.75 secs respectively. The reduction in the duration of THLE in the group treated with telmisartan 8mg/kg was found to be significant (p= 0.02) compared to control. The duration of THLE in the groups treated with valsartan 10mg/kg and 20mg/kg were 14.50±0.56 secs and 10.83±0.60 secs respectively. The decrease in the duration of THLE treated with valsartan 20mg/kg was found to be statistically significant ($p<0.05$) as compared to control.

Phenytoin at 20 mg/kg abolished the THLE stage completely. The duration of THLE at sub anticonvulsant dose of phenytoin (10mg/kg) was 8.33±0.88 secs and was found to be significant as compared to control (p= 0.013).

The duration of THLE when sub anticonvulsant dose of phenytoin 10mg/kg was combined with the most effective dose of telmisartan 8mg/kg and valsartan 20mg/kg were 7.33± 0.88 secs and 8.50 ± 0.65secs respectively. These decreased in the duration of THLE were found to be statistically significant as compared to control group($p<0.01$).

Table 1: Effect of telmisartan and valsartan on MES induced seizures in mice, alone and in combination with phenytoin

Groups	Duration of THLE (mean ± SEM) in secs
Control, C	16.67 ± 1.11
Telmisartan,5mg/kg T1	14.17 ± 0.40
Telmisartan, 8mg/kg T2	10.40 ± 0.75*
Valsartan, 10 mg/kg V1	14.50 ± 0.56

Valsartan, 20mg/kg V2	10.83 ± 0.60*
Phenytoin,10 mg/kg P	8.33 ± 0.88*
P+T2	7.33 ± 0.88**
P+ V2	8.50 ± 0.65**
ONE WAY F ANOVA d.f P	18.71 7,31 < 0.001

p <0.05 compared to control, **p <0.01 as compared to control

DISCUSSION

The effect of ARBs viz. telmisartan and valsartan on the antiepileptic activity of the standard antiepileptic drug phenytoin was assessed by using maximal electroshock seizure test in albino mice.

Prevention of seizures induced by maximal electroshock in the laboratory animals is the most commonly used preliminary screening test for characterizing potential antiepileptic drugs.[6] The MES induced seizure test represents grand mal type of epilepsy. The efficacy to reduce the duration of tonic hind limb extensor phase in the MES has been shown to correlate with the ability to prevent generalized tonic clonic seizure in man.[7]

MES induced tonic seizures can be prevented either by drugs that inhibit voltage dependent Na+ channels, such as phenytoin and valproate or drugs that block glutamatergic excitation mediated by the NMDA receptor. MES induced model causes activation of Ca2+ and Na+ channels and drugs inhibiting this influx can prevent MES induced tonic hind limb extension. The tonic extensor phase is selectively abolished by the drugs effective in generalized tonic clonic seizure.[8]

The result obtained is in accordance with the established evidence that phenytoin is effective primarily against MES induced seizures.[7] According to Sweetman SC et al,[9] the daily maintenance dose of phenytoin in human is 200-500 mg and on extrapolation of the dose to albino mice according to body surface area (Ghosh MN, 2008), [10] it came roughly 26 mg/kg body weight. But for convenience, 20 mg/kg of phenytoin was taken for the study and it was found to completely abolish THLE phase in MES model. So, a sub-anticonvulsant dose of 10mg/kg phenytoin was taken to assess the effect of its combination with telmisartan and valsartan

The result of the present study also suggests that ARBs viz. telmisartan and valsartan alone possess antiepileptic activity against MES induced seizure in mice. An early study reported that AT1 receptor antagonist, telmisartan and olmesartan in a dose dependent manner showed increase in antiepileptic activity in MES induced seizures in mice.[11] In addition, Pereira MG et al. reported a significant decrease in seizure severities when epileptic animals were treated with AT1 receptor blocker which supports the present study.[12]

At present, anticonvulsant mechanism (s) of angiotensin AT1 receptor antagonists is not precisely known. Possible mechanism of anticonvulsant action of angiotensin receptor antagonist could be due to blockade of the brain renin angiotensin system by these drugs. The functional inhibition of the renin angiotensin system in the brain by losartan may significantly impair the triggering and maintenance of seizure. It is possible that they may act by modulation of GABAergic and glutamatergic neurotransmission.[11]

Knowing that telmisartan and valsartan are able to cross the blood brain barrier,[13,14] and the blockade of angiotensin II action may indirectly interfere in the modulation of excitatory and inhibitory components of CNS, this can be proposed as a possible mechanism of action by which the angiotensin receptor blockers impaired the epileptic seizures described in this study.

The present study also indicates that the protective action of antiepileptic drug phenytoin against MES induced seizures in mice is potentiated by co-administration of angiotensin receptor blockers viz. telmisartan and valsartan. K. Lukawski et al have reported that angiotensin receptor blockers losartan and telmisartan alone did not influence the threshold for electro convulsion test. However, both potentiated the anticonvulsive activity of valproate.[15]

The concept of rationale polytherapy developed within recent years is based on the assumption that combining some antiepileptic drugs may result in supra-additive (synergistic) efficacy and infra-additive (antagonists) toxicity resulting in an enhanced efficacy/toxicity profile.[16] Though the exact mechanism of antiepileptic activity of ARBs cannot be ascertained from the present investigation it may be speculated that they potentiate the antiepileptic activity of phenytoin possibly by modulating the inhibitory and excitatory neurotransmitters, blockage of the voltage dependent ion channels like Na+ and Ca2+ and thereby exerting synergistic effect with low dose of phenytoin which inhibits sodium influx.

CONCLUSION

The results of the present study suggest that drugs which targets the brain renin angiotensin system deserve further investigation as possible antiepileptic agents. The combination of sub anticonvulsant dose of phenytoin with either telmisartan or valsartan elicited a similar antiepileptic efficacy to the standard antiepileptic drug phenytoin but did not show superior activity than phenytoin in the maximal electroshock seizure test. It also suggests that ARBs may be beneficial in the treatment of epileptic patients with co morbid

cardiovascular diseases. But further studies on experimental animals and human beings are necessary to support the present work.

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Declarations

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Conflict of interest: None declared

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