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(Research Article)

Evaluation of Anticonvulsant Action of Gabapentin on Aminophylline Induced Convulsions in Rats

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ABSTRACT

GABA, an inhibitory neurotransmitter widely distributed in the CNS, cannot cross blood brain barrier. Gabapentin [GBP], an amino acid, designed as a simple analog related to GABA, is claimed to have anti-epileptic activity and sufficient lipid solubility to penetrate the blood brain barrier. Wistar rats of male sex aged 8-10 weeks weighing about 150–200 g were selected and divided into three groups having ten animals each. Group I (Control-double distilled water), Group II (Standard-Phenytoin) and Group III (Test- Gabapentin). After an interval of 30 minutes all the animals in three groups received Aminophylline 200mg/kg intraperitoneally. The time of onset of convulsions, duration of convulsions and the type of convulsions were noted in the three groups. The mean time taken for the onset of convulsions in control group was 14.5±1.20 min after administration of Aminophylline. Gabapentin significantly (P<0.001) increased the mean time taken for the onset of convulsions after administration of Aminophylline to 470±8.32 min. Gabapentin also significantly (P<0.001) decreased the mean duration of convulsions to 18.5±1.70 min when compared with control group (61.33±1.43) and standard Group (58.16±5.12).

Key Words: Aminophylline induced convulsions, Gabapentin, Anticonvulsant action, CNS, Wistar rats, Chemically induced convulsions.

INTRODUCTION

Methylxanthines, routinely consumed as beverages; are available over the counter as CNS stimulants and produce convulsions at higher doses. Clinical data indicate that intravenous Aminophylline (AMPH) can induce repetitive generalized convulsions in patients undergoing intensive anti-asthmatic therapy and are often resistant to conventional anti-epileptic drugs [1, 2].

GABA, an inhibitory neurotransmitter widely distributed in the CNS, cannot cross blood brain barrier. Gabapentin [GBP], an amino acid, designed as a simple analog related to GABA, is claimed to have anti-epileptic activity and sufficient lipid solubility to penetrate the blood brain barrier [3]. GBP is reported to exhibit protective effect against several animal models of seizure including chemically induced convulsions and is known to display extremely low toxicity [4, 5]. Surprisingly, it does not seem to have any GABA-mimetic action in the CNS but is reported to bind to a specific site in the brain which appears to be an amino acid transport system [6]. The implications of this are unknown and the exact mechanism of action of GBP still needs to be determined [7].

Several studies have shown convulsive potential of AMPH in animals to evaluate protective effects of AEDs and other agents [8, 9]. The present study was aimed at evaluating effectiveness of GBP in inhibiting AMPH-induced convulsions in rats.

MATERIALS AND METHODS

Animals

Wistar rats of male sex aged 8-10 weeks weighing about 150–200g were obtained from the central animal house. The animals were fed pellet diet and water adlibitum and were maintained under standard conditions of temperature, humidity and light (12 hours light/12 hours dark cycle). The experiment complied with the guidelines for animal experimentation of our laboratory and was approved by the Institutional Animal Ethics Committee (IAEC).The guidelines for the investigation of experiments in conscious animals were followed in all tests.

Drugs and Chemicals

The standard solution of Gabapentin (GBP) was prepared by dissolving 300mg of Gabapentin capsules in 1% of Tween 80. The solutions had concentration of 15mg/ml. Aminophylline (AMPH) 10ml ampoules each ml containing 25mg were used. Phenytoin (PHE) 2ml ampoules, (each ml containing 50mg) and double distilled water were used.

Acute Toxicity Studies

Previous studies have shown that median lethal dose of Aminophylline in rats when administered intraperitoneally to be 130mg/kg. Maximum tolerated dose of Gabapentin (GBP) in rats are high (more than 0.9mmol/kg).

Experimental Method

After intraperitoneal injection of AMPH 200mg/kg in rats, the following were observed. The rats showed mild hyperactivity, twitching, incoordination, hyperventilation, initial clonic convulsions followed by generalized tonic-clonic convulsions with hind-limb extension and death.

Wistar rats of male sex weighing between 150-200 g were selected and divided into three groups having ten animals each.

Group I – Control and were given double distilled water (1.5ml) intraperitoneally.

Group II – Standard and were given Phenytoin (135mg/kg) intraperitoneally.

Group III – Test and were Gabapentin (60mg/kg) intraperitoneally.

After an interval of 30 minutes all the animals in three groups received Aminophylline 200mg/kg intraperitoneally. The time of onset of convulsions, duration of convulsions and the type of convulsions were noted in the three groups.

Statistical Analysis

The results were expressed as mean ± SEM. Statistical analysis was carried out by ANOVA followed by dunnet's test. P-values < 0.05 were considered significant.

RESULTS

The results of anticonvulsant action of Gabapentin on Aminophylline induced convulsions in rats are summarized in table 1.

The mean time taken for the onset of convulsions in control group was 14.5±1.20 min after administration of Aminophylline. Gabapentin increased the mean time taken for the onset of convulsions to 470±8.32 min after administration of Aminophylline. Gabapentin also decreased the mean duration of convulsions to 18.5±1.70 min when compared with control group 61.33±1.43 min and standard Group 58.16±5.12 min.

Table 1: Anticonvulsant action of Gabapentin on Aminophylline induced convulsions in rats

Group	Drug	Onset of convulsion in minutes	Duration of convulsions in minutes	Number of animals showing abolition of extensor phase
I –Control	Distill water	14.5±1.20	61.33±1.43	0
II – Standard	Phenytoin (135mg/kg)	13.5±1.36	58.16±5.12	0
III – Test	Gabapentin (60 mg/kg)	470±8.32*	18.5±1.70*	0

*All values are Mean±SEM, n=10, * P<0.001*

DISCUSSION

Aminophylline [AMPH] an ethylenediamine derivative used as intravenous medication in the treatment of severe bronchial asthma can induce life threatening seizures in humans [10, 11]. Aminophylline, a methyl xanthine is known to have strong convulsive potential demonstrated in both animal studies and clinical practice [12, 13]. Previous studies by Czucwar et al showed that AMPH induces repetitive generalized seizures in rats which are refractory to conventional antiepileptic drugs [14].

Studies done by Gupta and Malhotra also showed that AMPH induced repetitive generalized seizures are lethal in rats and mice [15, 16]. The convulsant activity of xanthines is due to their central nervous system stimulating properties which are attributed to their nonselective adenosine antagonistic activity [17, 18, 19, 20], ability to increase intracellular calcium concentration in the neuronal cells [21, 22] and to lower brain adenosine concentration. Phenytoin is an old reputed drug for the treatment of epilepsy. The main mechanism of action is sodium channel blockade in neurons in CNS. Gabapentin, a GABA analog possesses many diverse mechanisms of action, among them, the inhibition of Ca^{++} voltage gated channels through interaction with the α2 δ subunits seems to be the most important [23].

AMPH caused 100% mortality in rats. AMPH causes decreased cerebral blood flow, respiratory alkalosis, systemic hypotension and cardiac tachyarrhythmias. Mortality may also be due to combined effects of direct action on central nervous system and accompanying metabolic and cardiovascular abnormalities.

CONCLUSION

In the present study GBP significantly prolonged the latency to the onset of convulsions while phenytoin did not prolong time taken for the onset of convulsions. GBP significantly reduced the duration of convulsions in rats than phenytoin. However, both phenytoin and GBP did not protect the rats from mortality caused by AMPH.

The results obtained in this study with GBP provide supporting pharmacological evidence of efficacy and possible beneficial effects in AMPH induced convulsions. However, studies with other models of epilepsy in a large number of animals and further studies in human beings would be needed to substantiate the present work.

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