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Study of anticonvulsant activity of quinidine in albino rats using pentylenetetrazole model

K Jagadeesh[1*]
[1]* *Professor and HOD, Department of Pharmacology, ShivamoggaInstitute Of Medical Sciences, Shivamogga, Karnataka,India.*

Address For Corespondance:
Dr K Jagadeesh,
#3683/147,7th cross, BIET college road, Beside Hemavathi Hostel Road,
Anjaneya layout, Davanagere-577004 Karnataka ,India.

Abstract:
Background: *Convulsion is a condition where in the muscles of the body contract and relaxes rapidly and repeatedly resulting in an uncontrolled shaking of the body .It is often a symptom of the epileptic seizure. Gap junctions play an important role in the generation and spread of the epileptic seizures .Quinidine being one of the gap junction blockermay have the potential role in the treatment by inhibiting the development and spread of the seizures.*
Objectives: *To study the anticonvulsant activity of quinidine in albino rats in PTZ model and its comparison with the sodium valproate.*
Material and Methods*: Randomized, prospective, open labeled animal study. 36 rats were randomly divided in to six groups of six each. Individual groups were given normal saline, valproate 54mg/kg, qiunidine 28mg/kg, 35mg/kg, 42 mg/kg. One group did not receive any drug. Seizure was induced by PTZ of 90mg/kg.*
Results*: Quinidine at a lowest dose of 28mg/kg did not have any statistically significant anticonvulsant activity. The other two doses 35mg.kg and 42mg/kg provided the seizure protection by 33.33% and 50% respectively. They also significantly prolonged the latency before onset and alsoreduced the mean duration of seizure.*
Conclusion*: Quinidine at a dose of 35mg/kg and 42mg/kg has a significant anticonvulsant activity when compared to low dose of 28mg/kg.*
Key words: *Quinidine, Albino rats, Pentylenetetrazole, Gap junctions.*

I. Introduction:

The term seizure is derived from the latin word *Sacire,* 'to take possession of' .An epileptic seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. Depending upon the distribution of the discharges, this abnormal brain activity may have various manifestations, ranging from dramatic convulsive activity to experimental phenomenon not readily discernible by an observer. Epileptic seizures can occur even in person who does not have epilepsy as a consequence of head injury, drugs, toxins, eclampsia or febrile convulsions.[1]

The incidence of epilepsy is approximately 0.3 to 0.5% in different populations throughout the world and the prevalence of epilepsy has been estimated at 5 to 10 persons per 1000.[1]

The classification of epilepsy is based on clinical events, abnormal electrophysiology,anatomical site of seizure origin and pathological cause of the problem.Primary generalized epilepsy constitutes 10%of all epilepsies. Onset is almost always in childhood oradolescence. No structural abnormality is present andthere is often a substantial genetic predisposition. Absenceepilepsy, are relatively uncommon,whilst others, like juvenile myoclonic epilepsy, arecommon. Partial epilepsy may arise from any disease of the cerebral cortex, congenital or acquired, and frequently generalize. Partial seizures signify the presence of focal cerebral pathology. Secondary generalized epilepsy may arise from spread of partialseizures due to structural disease, or may be secondaryto drugs or metabolic disorders. Epilepsy presentingin adult life is almost always secondary generalized,even if there is no clear history of a partial seizurebefore the onset of a major attack. The occurrenceof epilepsy in those over the age of 60 is frequently due to cerebrovascular disease and presents specificdiagnostic and management problems[2].

Many drugs are available presently to inhibit of epileptic seizures, but neither effective prophylaxis nor cure is available. The drugs act by either the three ways. Firstly limiting the sustained repetitive firing of the neurons, an effect mediated by the promoting the inactivated state of the voltage gated Na^+ channels. Secondly enhancing the synaptic inhibition of the Gama amino butyric acid and thirdly inhibition of the voltage activated Ca^{2+} channels responsible for the T-type Ca^{2+} currents. Drugs effective in the partial seizures or generalized

tonic clonic seizures act by the first and second mechanism. The drugs active against the absence seizure acts by the third mechanism.[3]

Various in-vivo models employ diverse animal species including both rodents (rats, mice) and non-rodents (cats, dogs, monkeys) and use different chemical, pharmacological and mechanical stimuli to induce seizures.[4]Pentlynetetrazole (PTZ) is one of the most commonly used model for the anticonvulsant screening. PTZ is a tatrazole derivative with consistent convulsive effect in a large number of animal species like mice, rats, cats etc. The mechanism of the convulsant action of the PTZ seems to be related to the inhibition of the inhibitory function of the GABA neurotransmitter. PTZ is used for the screening of the absence seizures.[5]

Seizures are adequately controlled with the presently available antiepileptic drugs in nearly 70% patients with epilepsy; however not effective for the remaining 20-30% patients with the intractableseizures. These patients not responding to the classical anti epileptic therapy end up suffering from the refractory epilepsy, an entity that is associated with the considerable medical, social and psychiatric morbidity.[6]

Cell to cell transmission in the central nervous system takes place by either the chemical or an electrical synapse. The electrical synapses are formed by gap junctions(GJs), in places where the membranes of the presynaptic and the post synaptic neurons comes close together. These GJs are formed by the proteins known as conexins (CXs), which acts as a low resistance bridges through which the ions can pass through easily .[7]One of the reasons postulated for the incomplete efficacy of the currently available anti-epileptic drugs is because none of them block the transmission through the GJs.[8]

Quinidine is a dextro-isomer of the antimalarial quinine obtained from the bark of the cinchona tree. It's most commonly used as an anti-arrhythmic drug.[9]Quinidine has been found to block the conduction through the gap junctions in the mammalian cells. By virtue of this property, quinidine has the potential to suppress the convulsions.[10]

Hence the present study was undertaken to evaluate the anticonvulsant activity of the quinidine in albino rats using the PTZ model and also to compare it with the valproate.

II. Material and Methods:

The present study was a randomized, prospective open labeled animal study.36 AlbinoSprougeDawleyrats of either sex with average weight of 150-200gms aged between 6 - 8 weeks not used previously for any other studies were involved into the study.

An acclimatization period of one week in the animal laboratory at the room temperature was allowed for the rats before the experiments were started.

On the day of the experiment animals were brought form the animal house. All the animals were checked to rule out any infection, injury or any other illness.

Drugs used in the study were i) Quinidine 28, 35, 42 mg/kg ii) Pentylenetetrazole 90mg/kg

iii)Valproate 54mg/kg

The animals were randomly divided into six groups of six each. It consisted of two control groups. One standardgroup and three test groups.

Control 1(C1): Normal saline
Control 2(C2): No drug
Standard 3(S3): Valproate 54mg/kg
Test1(T1): Quinidine 28mg/kg
Test 2(T2): Quinidine 35mg/kg
Test 3(T3): Quinidine 42mg/kg

Animals were injected the control, standard and the test drugs,intraperitoneally under aseptic precautions as per the study group.Thirty minutes later PTZ wasadministered S.C into the scruff of the neck under aseptic precautions.Later animals were observed for 30 minutes for the occurrence of the seizure and timing was maintained using the digital clock.The occurrence of the clonic seizure more than five seconds was taken as positive seizure response and abolition of the clonic seizure was considered as protection against the PTZ seizures.

The following parameters were studied

a. Occurrence of the seizure
b. Time of onset of the seizure activity(seizure latency) in seconds
c. Duration of clonic phase of seizure in seconds

At the end of the thirty minutes the animals were inspected for any injury or residual damage.

All quantitative data were presented as mean and standard error of mean (SEM).For comparison between the groups one way ANOVA was used with post hoc Turkey's test.The p value <0.05 was considered as significant.

III. Results:

Table 1: Comparison of seizure % and mean seizure latency

Group	Seizure%	Seizure latency in Seconds (Mean± SEM)	P Value
C1	100	129.00±52.66	-
C2	100	127.67±522.12	>0.05
S	33.33	839.67±342.79	<0.001
T1	100	264.17±107.85	>0.05
T2	66.67	633.17±258.49	<0.001
T3	50	711.17±290.33	<0.001

Table 2: Comparison of mean seizure latency after administration of 3 doses of quinidine

Sl.No	Group	Seizure latency in seconds (Mean± SEM)	Group	Seizure latency in seconds (Mean± SEM)	p value
1	T1	264.17±107.85	T2	633.17±258.49	<0.001
2	T1	264.17±107.85	T3	711.17±290.33	<0.001
3	T2	633.17±258.49	T3	711.17±290.33	>0.05

Table 3: Comparison of mean seizure latency of three doses of quinidine with valproate

Sl.No	Group	Seizure latency in seconds (Mean± SEM)	Group	Seizure latency in seconds (Mean± SEM)	p value
1	S	839.67±342.79	T1	264.17±107.85	<0.001
2	S	839.67±342.79	T2	633.17±258.49	>0.05
3	S	839.67±342.79	T3	711.17±290.33	0.05

Table 4: Comparison of mean seizure duration in the study

Sl.No	Group	Seizure duration In seconds (Mean±SEM)	p value
1	C1	38.33±15.65	-
2	C2	43.17±17.62	>0.05
3	S	8.67±3.54	<0.001
4	T1	37.32±15.24	>0.05
5	T2	13.83±5.65	<0.001
6	T3	10.67±4.35	<0.001

Table 5: Comparison of the mean seizure duration after administration of 3 doses of quinidine

Sl.No	Group	Seizure duration In seconds (Mean±SEM)	Group	Seizure duration In seconds (Mean±SEM)	p value
1	T1	37.32±15.24	T2	13.83±5.65	<0.001
2	T1	37.32±15.24	T3	10.67±4.35	<0.001
3	T2	13.83±5.65	T3	10.67±4.35	>0.05

Table 6: Comparison of mean seizure duration of three doses of quinidine with the valproate

Sl.No	Group	Seizure duration In seconds (Mean±SEM)	Group	Seizure duration In seconds (Mean±SEM)	p value
1	S	8.67±3.54	T1	37.32±15.24	<0.001
2	S	8.67±3.54	T2	13.83±5.65	>0.05
3	S	8.67±3.54	T3	10.67±4.35	>0.05

IV. Discussion:

Seizures were seen in all the groups. In both the normal saline group and the no drug group seizures were seen in all the animals. In the valproate group seizures were seen in the 4 rats offering a seizure protection of 33.33%. In the quinidine group of 28mg/kg all the rats experienced seizure, 35mg/kg group 4 rats experienced seizure offering a protection of 33.33%. Similarly in the 42mg/kg group seizure was seen in 3 rats providing 50% of protection.

There was no significant ($p>0.05$) difference between the mean duration of latency before the seizure onset between the normal saline group (129±52.66 sec) and the no drug group (12767±52.12 sec). Valproate prolonged the onset of seizure in a statistically significant ($p<0.001$) manner (839.67±342.79 sec).There was no significant (>0.05) effect on the latency of onset of seizures at 28 mg/kg quinidine (264.17±107.85

sec).However the other two doses of the quinidine prolonged the latency of onset of seizure in in a significant ($p<0.005$) manner.35mg/kg by 633.17±258.49) and 42 mg/kg by 711.17±290.33 sec.

When three dose of quinidine were compared among themselves, there was statistically significant ($p<0.001$) difference between mean values of the 28 mg/kg group (264.17±107.85 sec) and other two groups i.e. 35mg/kg by 633.17±258.49 sec and 42 mg/kg by 711.17±290.33 sec.There was no statistical significance in the difference in the mean values of 35 mg/kg and 42 mg/k group.

When the latency of seizure seen with valproate was compared with that of three doses of the quinidine, there was statistically significant difference seen with 28mg/kg quinidine group. No statistically significant difference was seen with the other two groups i.e. 35 mg/kg and 42 mg/kg.

There was no statistically significant difference between the mean duration of clonic phase of the seizure between the normal saline group (38.33±15.65 sec) and no drug group (43.17±17.62 sec)

Valproate reduced the duration (8.67±3.54 sec) of seizuresignificantly. Among the three doses of quinidine, there was no statistically significant difference in the 28mg/kg (37.32±15.24) but there was statistically significant difference seen between the other groups i.e. 35 mg/kg group 13.83±5.65 and 42mg/kg 10.67±4.35.

When the three doses of quinidine was compared among them self, there was significant difference ($p<0.001$) between 28 mg/kg group and the other two groups.But the difference in the mean values in the other two groups was not significant ($p>0.05$).

When the mean duration of seizure seen with the valproate was compared with the three quinidine group. Significant difference was seen with the quinidine 28 mg/kg group. Thedifference seen with the other two groups were not statistically significant.

V. Conclusion:

Quinidine has in vivo anticonvulsant activity in the PTZ induced seizures and its anticonvulsant activity is comparable with the valproate. Further studies are required to evaluate the efficacy of quinidine in other seizures. Clinical trials to be conducted in humanbeings to evaluate its anticonvulsant activity.

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