Original Research Article

Potentiation of anticonvulsant effect of phenytoin by celecoxib against maximum electroshock induced convulsions in albino rats

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ABSTRACT

Background: Epilepsy, a chronic neurological disorder affects more than 1% of world population. Despite the availability of a number of antiepileptics, refractoriness to them exists in approximately one third of cases worldwide. Induction of cycloxygenase and increased levels of proinflammatory mediators are seen in epilepsy. P-glycoprotein upregulation due to phenytoin was found to contribute to its pumping out of cell, leading to refractoriness to phenytoin therapy. Also, cycloxygenase-2 inhibitors were found to prevent P-glycoprotein upregulation. Since cycloxygenase-2 inhibition decreases levels of proinflammatory cytokines responsible for neuroinflammation, this study aims to evaluate anticonvulsant effect of celecoxib and also to investigate whether it potentiates the anticonvulsant effect of phenytoin.
Methods: Maximum electroshock seizures (MES) were induced in Albino rats using electroconvulsiometer to evaluate tonic convulsions, identified by tonic hind limb extension (THLE) in rats. A delay in onset of THLE and a reduction in duration of THLE were taken as deciding parameters to ascertain anticonvulsive activity. Rats randomly divided into groups, received pretreatment with celecoxib at 3 doses (10, 20, 40 mg/kg), phenytoin (6.25 mg/kg), phenytoin (12.5 mg/kg) and combination of phenytoin (6.25 mg/kg) with celecoxib (ED50, i.e. 20 mg/kg), before inducing MES seizures and findings compared to control group.
Results: Celecoxib (20 and 40 mg/kg) showed significant anticonvulsant effect by MES test. Also, its combination with phenytoin caused significant decrease in the duration of THLE when compared to phenytoin alone at the same dose.
Conclusions: The results of this study indicate that celecoxib potentiates the anticonvulsant effect of phenytoin.

Keywords: Celecoxib, Phenytoin, Maximum electroshock test, Prostaglandin E2, P-glycoprotein

INTRODUCTION

Epilepsy is a chronic neurological disease, which affects more than 1% of the human population.[1] It is characterized by a long-lasting tendency to develop epileptic seizures. Epileptic seizures are a consequence of electrical disturbance in the brain, characterized by an imbalance between excitation and inhibition.[2] There has been considerable progress in the pharmacotherapy of epilepsy over the last few decades, including the introduction of new antiepileptic drugs such as gabapentine, lamotrigine and topiramate. In spite of the currently available therapeutic arsenal of old and new antiepileptic drugs, more than 30% of patients keep on developing seizures that are refractory to the currently available antiepileptics. According to international league against epilepsy, resistant epilepsy is the epilepsy which occurs when a person has not become seizure free with two anti-epileptic

drugs.[3-6] Moreover, current drug therapy of epilepsy is complicated by adverse drug reactions, teratogenic effects and long term toxicities. Among the currently available antiepileptics, none can completely cure the patient nor prevent future episodes of convulsions, which thereby substantiate the necessity to develop newer and more effective anti-epileptic drugs.

The presence of prostaglandins in the mammalian brain is well-documented and prostaglandins are either directly or indirectly involved with neuronal activity.[6] It has been known since long time that levels of cyclooxygenase (COX) and prostaglandins (PGs) are found to elevated in brain during or after induction of seizures in animal models, it was hypothesized that COX-inhibitors reduces seizures by inhibiting the synthesis of prostaglandins.[7,8] Based on previous studies, phenytoin is known to upregulate P-glycoprotein (Pgp) levels in the rat brain capillaries, leading to pumping out of phenytoin from the brain. This upregulation of PG appears to be responsible for development of resistance to the antiepileptic, phenytoin.[9-11] Celecoxib on the contrary, prevented this Pgp upregulation in rat brain capillaries.[12,13] This action of celecoxib on Pgp expression is the underlying mechanism for suggesting the potentiation of anticonvulsant effect of phenytoin by celecoxib.[14]

Thus, the present study is undertaken to investigate the anticonvulsant activity of celecoxib and also to determine whether it potentiates the anticonvulsant effect of phenytoin in rat models of maximal electroshock seizure (MES) induced tonic convulsions.

METHODS

Seizures were induced in Albino rats by maximum electroshock method using electro-convulsiometer. The anticonvulsant effect of celecoxib in 3 graded doses and also of celecoxib (ED_{50}, calculated to be 20 mg/kg) in combination with phenytoin (subanticonvulsant dose, calculated to be 6.25 mg/kg) was assessed on this model. The anticonvulsant effects of the above 4 groups were compared with that of phenytoin (anticonvulsant dose i.e. 12.5 mg/kg).[15,16] The current study was given approval by the institutional animal ethics committee.

Male and female Wister Albino rats which weighed from 100 gm to 200 gm were utilized for this study. Rats in the animal house were kept in polypropylene cages at controlled temperature set between 20 to 24°C and the relative humidity set between 50 to 60% with standard 12 hour light-dark cycle beginning at 6.00 a.m. Standard pellet diet and water were provided to the rats as and when required. The chemicals and drugs used for the test method were celecoxib (Zydus Cadilla Pharmaceuticals), phenytoin (Zydus Neurosciences) and polyethylene glycol (SD Fine chem. Limited). Individual doses of the drugs to be administered were calculated for each rat according to their body weight and the drug was delivered to the rat through intra-peritoneal (IP) route. Also, the ED_{50} of

celecoxib and the subanticonvulsant dose of phenytoin was determined in the pilot study.[17]

MES method

MES method of evaluating anti-seizure activity of a drug against generalized tonic-clonic seizures (grandmal seizures). Screening of rats was done one day prior to the test by subjecting to maximal electroshock using an electroconvulsiometer with an alternating current of 150 mA intensity for 0.2 seconds using trans-auricular electrodes. 42 rats which were screened positive for MES seizures, identified by the development of characteristic tonic-clonic seizures were selected and then randomly allocated to 7 groups with 6 rats in each group (Table 1). Rats were kept in separate polypropylene cages for conditioning them to the laboratory environment for 3 days and to avoid any possible kindling effect. The night before the experiment, food was withheld but water was allowed freely. On the day of the MES test, the drug solutions to be injected were freshly prepared in the morning and administered to the rats via IP route. After 40 minutes of drug administration, rats were subjected to an electrical stimulus (alternating current of 150 mA intensity for 0.2 sec through trans-auricular electrodes, originating from the electro-convulsiometer) to induce maximal seizures of its hind limbs, with tonic extension as the endpoint of the test.[17] Experimental procedure was performed at nearly the same time each day. The 2 main parameters observed were onset of tonic hind limb extension (THLE) and duration of THLE (Table 1).

Delay in the onset of THLE and reduction in the duration of THLE by the drug were taken as the primary deciding parameters for determining the drug's anti-seizure effect.[17]

Alleviation in the above 2 parameters by celecoxib in 3 doubling doses (10, 20 and 40 mg/kg) and also by combination of celecoxib (ED_{50} i.e. 20 mg/kg) in combination with phenytoin (sub-anticonvulsant dose i.e. 6.25 mg/kg) were compared with that of control (normal saline, 2.5 ml/rat) and phenytoin (anticonvulsant dose i.e. 12.5 mg/kg).[15,16]

Statistical analysis

Results were conveyed as mean±standard error of mean. One-way analysis of variance (ANOVA) was used for the statistical analysis of data, followed by post-hoc analysis done by least significant difference (LSD) test for multiple comparisons. A probability value of $p < 0.05$ was considered as significant.

RESULTS

Pretreatment with 2 doses of celecoxib (20 and 40 mg/kg, administered IP 40 minutes before MES) significantly delayed the onset of THLE (5.52±0.2 and 6.43±0.26 seconds respectively) in comparison to normal saline pretreatment (3.45±0.28 sec). The standard drug phenytoin

sodium in doses of 6.25 mg/kg and 12.5 mg/kg (administered IP 40 minutes before MES) also delayed the onset of THLE (6.56±0.27 and 7.26±0.26 seconds respectively) in comparison to normal saline (3.45±0.2 seconds) (Table 1).

Pretreatment with 2 doses of celecoxib (20 and 40 mg/kg, IP 40 minutes before MES) significantly decreased the duration of THLE (8.97±0.30 and 5.10±0.18 seconds respectively) in comparison to normal saline pretreatment (12.90±0.16 seconds). The standard drug phenytoin in doses of 6.25 mg/kg and 12.5 mg/kg IP also decreased the duration of THLE (4.72±0.17, 2.32±0.20 seconds

respectively) in comparison to normal saline pretreatment (12.90±0.16 seconds) (Table 1).

There was no significant difference in the delay in the onset of THLE between the 7th group i.e. celecoxib 20 mg/kg and phenytoin sodium 6.25 mg/kg (6.98±0.12 seconds) when compared with 5th group i.e. phenytoin 6.25 mg/kg alone (6.57±0.27 seconds) (Table 1). However, there was a significant difference in the reduction of duration of THLE between the 7th group i.e. celecoxib 20 mg/kg and phenytoin sodium 6.25 mg/kg (3.82±0.16 seconds) when compared with 5th group i.e. phenytoin 6.25 mg/kg alone (4.72±0.17 seconds) (Table 1).

Table 1: Effect of drugs on maximum electroshock induced seizures in Albino rats.

Group	Drug (dose mg/kg)	Time in various phases of convulsions (seconds)		Recovered/death
		Onset of THLE	**Duration of THLE**	
1	Normal saline (2.5 ml/rat)	3.45±0.29	12.90±0.16	Recovered
2	Celecoxib (10)	3.87±0.20	11.44±0.26	Recovered
3	Celecoxib (20)	5.52±0.26*	8.97±0.30*	Recovered
4	Celecoxib (40)	6.43±0.26*	5.10±0.18*	Recovered
5	Phenytoin (6.25)	6.57±0.27*	4.72±0.17 *	Recovered
6	Phenytoin (12.5)	7.62±0.26*	2.32±0.20*	Recovered
7	Celecoxib (20) + phenytoin (6.25)	6.98±0.12*	3.82±0.16*	Recovered

Values are expressed as mean±SD of mean of 6 rats. One way ANOVA followed by LSD test for post-hoc analysis (*$p<0.05$ is taken as significant value).

DISCUSSION

Celecoxib (20 mg/kg), celecoxib (40 mg/kg), phenytoin (6.25 mg/kg), phenytoin (12.5 mg/kg) and celecoxib (20 mg/kg) and phenytoin (6.25 mg/kg) pre-treatment significantly ($p<0.05$) delayed the onset of THLE and also reduced the duration of THLE when compared to normal saline (NS) pre-treatment, indicating that the drug in the above 5 groups in their respective doses have anticonvulsant effect in rats. Also, phenytoin (12.5 mg/kg) IP pretreatment showed a significantly greater ($p<0.05$) delay in onset of THLE and greater reduction in the duration of THLE when compared to celecoxib (40 mg/kg) IP pretreatment, suggesting that phenytoin (anticonvulsant dose) is a more potent anticonvulsant when compared to celecoxib (at its maximum tolerated dose i.e. 40 mg/kg) in MES model in rats. The above findings indicate that COX-2 inhibition has anticonvulant effect, as observed in the MES induced seizures in Albino rats.

The addition of celecoxib (20 mg/kg) to phenytoin (6.25 mg/kg) did not show any significant difference in the delaying of onset of THLE when compared to phenytoin alone at 6.25 mg/kg. However, the addition of celecoxib (20 mg/kg) to phenytoin (6.25 mg/kg) significantly decreased the duration of THLE when compared to phenytoin alone at 6.25 mg/kg, indicating the potentiation of anticonvulsant effect of phenytoin by celecoxib in Albino rats.

Shafiq et al reported similar findings with celecoxib on MES induced convulsions.[16] Another study which

demonstrated anticonvulsant effect of celecoxib was done by Jung et al, who proved that oral celecoxib reduced the duration of seizures in pilocarpine induced rat models.[18] A recent study by Citraro et al showed that selective COX-2 inhibitor etoricoxib possesses protective activity against generation of absence seizures in WAG/Rij rats.[19] Another study down by Dir et al against picrotoxin-induced seizures also showed that rofecoxib prolonged the time of onset of seizures and also reduced the duration of seizures.[20] It was reported in an earlier study that non selective COX inhibitors like aspirin, paracetamol and diclofenac sodium also antagonized the MES and pentylenetetrazole induced convulsions in mice.[21]

The present study also showed that celecoxib potentiates the anticonvulsant effect of phenytoin, which is similar to findings from two studies done by Dhir et al who reported potentiation effect of another selective COX-2 inhibitor, rofecoxib on different anti-epileptics i.e. tiagabine and topiramate respectively on pentylenetetrazol-induced convulsions in mice.[22,23] Kaminski et al reported that non-selective COX inhibitors like ibuprofen and piroxicam potentiated the anticonvulsive effect of phenytoin against MES induced seizures in mice.[24]

From the above MES test findings, it can be deduced that COX-2 levels are increased in seizures, since its inhibition was found to be beneficial in alleviating seizures. It is well known fact that COX-2 is rapidly induced following a proinflammatory event with a subsequent release of mediators of inflammation, prostaglandins. The levels of pro-inflammatory mediators like prostaglandin E2 (PGE2),

interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) increased in epilepsy as was demonstrated in several studies done in animals.[25] In neuroinflammation, activated microglia was shown to release IL-1β which led to the induction of COX-2 and synthesis of PGE2 in astrocytes of mice brain.[26] TNF-α caused induction of COX-2 and synthesis of PGE2 leading to an increased vascular permeability and cellular alterations in capillary endothelial cells of bovine brain.[27] Production of PGE2, was found to be increased along with COX-2 induction following rodent models of epilepsy in studies done previously.[28,29]

PGE2 binds to 4 types of G protein-coupled receptors (GPCRs), which are EP1, EP2, EP3, and EP4. Activation of EP1 and EP2 types results in an increased calcium ion influx leading to enhanced release of glutamate presynaptically. These 2 types of GPCRs also play an important part in neuroinflammation.[30,31] Blocking of EP2 receptor using 3-aryl-acrylamide derivatives led to attenuation of status epilepticus induced neuro-inflammation and neuronal injury in rats.[32]

COX-2 inhibitors inhibited the synthesis of pro-inflammatory cytokines, PGE2 and IL-1β in the brain hippocampus of rats, thereby reducing neuroinflammation. It is thus proposed that the anticonvulsive effect of COX-2 inhibitors is because of a reduction in the production of PGE2 levels. This reduced PGE2 further causes a decreased activation of EP receptors which lowers calcium ion influx and lowers the release of the glutamate, an excitatory neurotransmitter, thus preventing the seizures.[33] Both IL-1β and TNF-α expression was also decreased by indomethacin, a non-selective COX inhibitor in pilocarpine induced status epilepticus in rat hippocampus, thus indicating a regulatory action of COX-2 on the above proinflammatory cytokines.[34] Kunz and Oliw proved that rofecoxib prevented neuroinflammation in the rat hippocampus in kainate induced epilepsy.[35] Oliveira et al demonstrated the anticonvulsant effect of celecoxib, which was reversed by intracerebroventricular administration of PGE2 and reported that PGE2 induces neuroinflammation and has epileptogenic properties.[36] Polascheck et al reported that parecoxib (another COX-2 inhibitor) pretreatment for 18 days, followed by pilocarpine-induced status epilepticus prevented the subsequent increase in PGE2 and reduced seizure severity in the rat hippocampus and piriform cortex.[37] Thus, neuroprotection was offered by COX-2 inhibitors in rat models of epilepsy.

P-glycoprotein (Pgp) upregulation pumps out drugs from the brain, which seems to the underlying mechanism for the development of resistance to phenytoin.[38] Multiple attempts to selectively inhibit Pgp pump to improve pharmacotherapy in epilepsy have been attempted in the past.[39,40] It was found that phenytoin pretreatment for 21 days upregulated Pgp in capillary endothelial vessels in rats.[10] In a recent study, the upregulation of Pgp by phenytoin was demonstrated using a radiopharmaceutical containing carbon C-11 N-desmethyl-lopermaide and visualised under positron emission tomography (PET).[11]

Celecoxib was found to prevent Pgp upregulation in rat brain capillaries in pilocarpine induced status epilepticus model.[13] COX-2 inhibitors like NS-398 and SC-58236 stimulated delivery of phenytoin in brain of epileptic rats having down-regulated Pgp.[14] The levels of phenytoin in the brain was significantly increased by COX-2 inhibition in rats with recurrent seizures by suppressing Pgp expression in chronic epileptic rats, suggesting that COX-2 inhibitors increases phenytoin delivery to the target sites in the brain, thereby explaining its potentiating effect.[14]

CONCLUSION

Celecoxib potentiated the anticonvulsant effect of phenytoin in rats. Further studies are required to establish the therapeutic role of using COX-2 inhibitors as effective potentiating agents when used in combination with existing antiepileptic drugs, which could be beneficial in refractory epilepsy. However, the limitation to the long term use of a COX-2 inhibitor is its increased cardiovascular risk, for which newer COX-2 inhibitors are required to be developed with favourable risk-benefit ratio. Discovering newer drugs which target pro-inflammatory cytokines involved in brain inflammation could also prove to be a promising therapeutic strategy in refractory epilepsy.

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