Combination of Valproate and Paroxetine in Mice Exposed to Picrotoxin

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Abstract

- The frequent coexistence of depression in epileptic patients raises the issue of simultaneous use of antidepressants along with antiepileptic drugs in the management of such cases. However, it is necessary to evaluate the safety of these antiepileptic/antidepressant drug combinations. The present study investigates the effect of the antidepressant paroxetine (a selective serotonin reuptake inhibitor) administered alone or in combination with the anti- epileptic drug sodium valproate on chemoconvulsions induced by picrotoxin (PTX). Seizure score was recorded in vivo, and the levels of thiobarbituric acid-reactive substances and gamma aminobutyric acid (GABA) were measured in the nucleus accumbens of the tested groups of mice. The results show enhancement of seizure severity with significant reduction in GABA levels upon PTX treatment that were reversed by its combination with sodium valproate. On the other hand, paroxetine administered in combination with sodium valproate provided significant protection against PTX-induced convulsions as well as a significant increase in GABA levels in selected brain areas. These results favor their application in management of epilepsy-depression comorbidities.

Background

- Although the mechanisms underlying the epilepsy-depression relationship have not been clearly identified, depression in epileptic cases is multifaceted with many interacting neurobiological and psychosocial determinants. However, the use of antidepressant drugs in epileptics has been a matter of debate for clinicians because of reports that these drugs may have frank convulsant or pro convulsant effects that increase seizure incidence.[12] This might happen due to modulation of pre- and/or postsynaptic receptor function and rate of release of neurotransmitters such as y-amino butyric acid, noradrenaline, dopamine, or serotonin.[13,14] so it is important to recognize and assess possible implications of antiepileptic/antidepressant drug combinations in the management of epileptic cases complicated by depression.

Objectives

- The rationale of the present study is to (l) evaluate the seizure score of the antiepileptic drug sodium valproate with the antidepressant paroxetine in the management of chemically induced seizures in chronically restrained mice, and (2) study the effect of these drug combinations on thiobarbituric acid-reactive substances (TBARS) as a marker of lipid peroxidation and GABA levels in nucleus accumbens in tested mice.

Methods

1. Control group receiving neither antiepileptic nor antidepressant treatment.

2. Sodium valproate-treated group: received sodium valproate dissolved in water (30 mg/kg body weight intraperitoneal) per Siddiqui, A et al [15] .

3. Paroxetine-treated group: was administered paroxetine dissolved in saline (1 mg/kg body weight intraperitoneal). This dose was selected according to David, D et al.[16]

4. Sodium valproate/paroxetine-treated group: given sodium valproate and paroxetine treatment in doses ono mg/kg body weight intraperitoneal and 1 mg/kg body weight intraperitoneal, respectively.

Each mouse of the respective group was placed in a wire mesh restrainer 6 hours daily for 21 days.

Measurement of nucleus accumbens TBARS as a marker of lipid Peroxidation.

Determination of GABA in homogenates of nucleus accumbens isolated from tested mice.

Results

- Table I Effect of different drug treatment regimens on picrotoxin (PTX)-induced convulsions.
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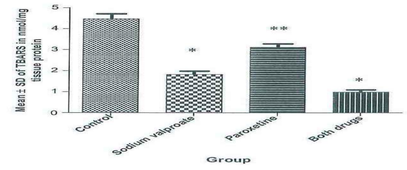
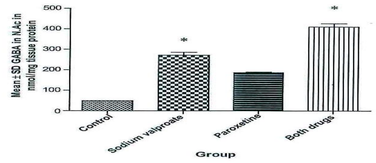
Group	Treatment	Dose (mg/kg)	Onset of convulsions (seconds)	Severity (score range 1–7)		
				25%	Median	75%
1	PTX (sc)	3.5	449.2 ± 26.24	5	5	5
2	Sodium valproate (ip)	50	1408 ± 79.95[a]	1	1[a]	2
3	Paroxetine (ip)	2.5	714.8 ± 22.92[a]	3	4	4
4	Sodium valproate + paroxetine (ip)	50 + 8	1724 ± 52.65[a,b]	1	1[a]	1

Results

Effect of tested drugs on TBARS in nmol/mg tissue protein in nucleus accumbens of mice exposed to chronic restraint model



- Effect of tested drugs on the GABA level in the nucleus accumbens of tested mice



Conclusions

In conclusion, the management of epilepsy is a difficult task when associated with other neuropsychiatric disorders. Therefore, extreme caution should be exercised with respect to selection of the proper antidepressants to treat epilepsydepression comorbidities. The SSRI paroxetine could be recommended in the management of such cases, in combination with sodium valproate, as it may reduce seizure frequency and intensity most likely as a result of decreased brain levels of the oxidative stress marker TBARS with an increase in GABA content of nucleus accumbens of mice exposed to a chemoconvulsive model.