The effect of a combination of sertraline with anticonvulsants on picrotoxin-induced convulsion and lipid peroxidation

Sir,

A rapid increase in our knowledge of the cellular theories of epileptogenesis has resulted in the development of the correlation between oxidative stress and epilepsy. Free radicals are involved in the pathogenesis of various diseases including epilepsy. Chemoconvulsions are followed by the generation of free radicals that cause lipid peroxidation, which may subsequently cause neurodegeneration observed in certain types of human epilepsy. Therefore, a drug that reduces seizure activity should also lower TBARS (Thiobarbituric acid reactive substances) levels. Reduction of TBARS levels compared to those by chemoconvulsants alone would also give an indication of the additional neuroprotective and/or antioxidant properties of the drug.

The coexistence of depression in epileptic patients makes it necessary to treat both the disorders (i.e. epilepsy and depression with antiepileptic and antidepressant drugs respectively) simultaneously. For this reason it has become necessary to evaluate the safety of these drugs upon co-administration.

In the present study we report the effect of picrotoxin (PTX; Sigma Chemicals Co. USA)-induced convulsions on lipid peroxidation (TBARS), and the modulation of TBARS levels by two known anticonvulsant drugs i.e. carbamazepine (CBZ; Novartis India Ltd.) and gabapentin (GBP; Intas Pharmaceuticals, India) when given alone and in combination with antidepressant sertraline (SERT; Unichem Labs Ltd., India). Convulsions were induced by a method similar to that described by Gupta et al. All drugs were dissolved/diluted in distilled water and were given in the volume of 10 ml/kg. Food was withdrawn 3 h before the administration of the drugs. Male albino mice were given 3.5 mg/kg picrotoxin subcutaneously, after suitable latency (4, 2.5 and 6 h after CBZ, GBP and SERT administration respectively) corresponding to the time of peak effect after oral administration of the test drug. Immediately after the administration of PTX, the animal was placed in the observational area. The severity of convulsions was carefully recorded using the scoring system 1-7: hyperlocomotion, piloerection=1; stunning, catatonic posture=2; clonic body tremors=3; prolonged clonic tremors=4; tonic forelimb convulsions followed by clonus=5; repetitive tonic forelimb convulsions followed by clonus=6; tonic extension of both forelimbs and hindlimbs followed by clonus=7. A mean cumulative score was calculated for each treatment group for comparisons and statistical analysis.

TBARS levels were determined in the serum by the method of Yagi. Samples were collected from the tail vein immediately after the observation of seizure pattern.

The project was undertaken with prior approval from the University Animal Ethics Committee. The results are presented as medians with 25 and 75 percentiles for seizure score and mean±SEM for TBARS. Data were analyzed using Kruskal-Wallis one-way ANOVA on ranks, followed by multiple comparison tests for seizure score whereas for TBARS, one-way ANOVA with Dunnett’s test at 95% confidence level was employed. P<0.05 was considered significant.

The results summarized in the table showed that both CBZ and GBP offered significant protection (P<0.05) against PTX-induced convulsions. SERT significantly enhanced (P<0.05) the seizure severity. This is consistent with earlier findings that reported seizure aggravating the effects of selective serotonin reuptake inhibitors (SSRI). Co-treatment of anticonvulsants CBZ and GBP with SERT significantly attenuated the seizure protection by these drugs (P<0.05).

Picrotoxin increased the TBARS level to a significant extent (P<0.01) when compared with normal control (vehicle-treated group). This observation is in line with earlier reports suggesting the implication of oxidative stress in epilepsy. This may be attributed to the fact that enhanced lipid peroxidation can induce seizure activity by direct inactivation of glutamine.

Table 1

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Dose (mg/kg) (Route)</th>
<th>Seizure severity (Score range: 1-7)</th>
<th>Serum TBARS n moles/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>25%</td>
</tr>
<tr>
<td>Saline only (No PTX)</td>
<td>10 ml (p.o.)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Saline (PTX)</td>
<td>3.5 (s.c.)</td>
<td>4.300</td>
<td>4.010</td>
</tr>
<tr>
<td>SERT</td>
<td>10 (p.o.)</td>
<td>5.290*</td>
<td>5.010</td>
</tr>
<tr>
<td>CBZ</td>
<td>50 (p.o.)</td>
<td>2.710*</td>
<td>2.320</td>
</tr>
<tr>
<td>CBZ+SERT</td>
<td>50+10 (p.o.)</td>
<td>4.460†</td>
<td>4.320</td>
</tr>
<tr>
<td>GBP</td>
<td>200 (p.o.)</td>
<td>2.905*</td>
<td>2.790</td>
</tr>
<tr>
<td>GBP+SERT</td>
<td>200+10 (p.o.)</td>
<td>4.390†</td>
<td>4.210</td>
</tr>
</tbody>
</table>

n=6. Significant differences between groups at P<0.05. For Seizure score: Data presented as median with 25 and 75 percentiles. [H=29.615; P<0.001] (Kruskal-Wallis one-way analysis of Variance on ranks followed by multiple comparison test). For TBARS: Data presented as mean±SEM. [F(6, 35) = 3.31; P<0.01] (ANOVA followed by Dunnett’s test). * P<0.05 when compared to saline, † P<0.01 when compared No PTX. ‡ P<0.05 when compared between: CBZ Vs CBZ+SERT; GBP Vs GBP+SERT; PTX-picrotoxin; SERT-sertraline; CBZ-carbamazepine; GBP-gabapentin.
Bioavailability of paracetamol and ibuprofen in single and combination dosage in rabbits

Sir,

Paracetamol (PA) is an analgesic and antipyretic drug with no antiinflammatory properties. But Ibuprofen (IB) is an analgesic with antiinflammatory properties. A combination of PA with IB is used for treatment of pain with fever.1 Although the reports on the individual kinetics of either IB or PA2 are available, the effects of the combination on the kinetics of each in experimental animals are largely unknown. In the present study we have investigated the effect of IB on the absorption and distribution kinetics of PA and vice-versa in rabbits, following the method of Glynn and Kendal (1975).

Healthy New Zealand white rabbits of either sex weighing (2.1 ± 0.12) kg were divided into different groups of six each and housed under standard animal room conditions. After overnight fasting, a single dose of 46 mg/kg. b.w. of IB, and 56 mg/kg. b.w. of PA in propylene glycol (Pg) was given orally to each animal of Group I and Group II respectively. Animals of Group III received a single mixture of the above doses of IB + PA each while those of Group IV were given a similar volume of Pg each. All experimental protocols were approved by the departmental animal ethics committee.

Two ml of blood was collected from the ear vein of each animal at 15, 30, 45, 60, 90 and 120 min in centrifuge tubes, allowed to clot and centrifuged. 0.5 ml of supernatant was mixed with 1 ml of trichloro acetic acid (15% w/v), shaken for 2 min and centrifuged at 4000 rpm for 15 minutes. One ml supernatant was taken and diluted to 25 ml with glass distilled water and absorbance of the solutions was recorded at 267 nm for IB (Group I) and 242 nm for PA (Group II). The treated serum solution of Group IV was used as blank.

2 ml of propylene glycol (Pg) was given orally to experimental animals. The mean values (SEM) of the serum concentrations (µg/ml) of the drugs were plotted against time (min), and the pharmacokinetic parameters were calculated5 and are shown in Table 1. The data were analyzed using Student’s ‘ t ’ test and P<0.05 was considered statistically significant.

A combination of IB with PA did not alter the peak times of 45 min of either of the drugs. However, the absorption phase of IB was lowered in the presence of PA (Figure 1).

For PA there was a significant rise of peak concentration (P<0.05) and a fall of absorption phase while the rate of distribution was enhanced in the presence of PA (Figure 1).

The higher peak concentration of PA with a combination dose might be because of less distribution and hence an increase in concentration in the central compartment which led to lower AUC value. The significant increase of Vd and decrease of AUC of both the drugs in combination may lead to sub-therapeutic or ineffective drug concentration.6

References