MODIFICATION BY ENZYME-INDUCING DRUGS OF THE ANTICONVULSANT ACTION OF PHENITOIN

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Summary: The effect of various enzyme-inducing drugs on the anticonvulsant action of phenytoin was investigated. Chlorcyclizine, hydroxyzine, tolbutamide, griseofulvin and chlordiazepoxide antagonised phenytoin. Chlorpromazine did not antagonise phenytoin. The increase in the flexion time/extension time, ratio (F/E ratio) produced by phenytoin was blocked by pretreatment with tolbutamide or chlordiazepoxide but not by griseofulvin.

Key words: enzyme inducers phenytoin anticonvulsant activity antagonism

INTRODUCTION

Phenobarbitone induces enzymes and thus accelerates the metabolism of phenytoin, diconumrol and griseofulvin (4,3,1). Chlordiazepoxide antagonises barbiturates in a similar manner (9). As far as its influence on the actions of phenytoin is concerned, both potentiation and antagonism have been reported (10, 6). Hence experiments were performed to study the influence of various enzyme-inducing agents on the anti-convulsant action of phenytoin.

MATERIALS AND METHODS

Adult male albino rats weighing approximately 200 g were used. Convulsions were produced by Techno Model Convulsimeter (150 mA, 0.2 sec, ear clip electrodes). Only those rats which responded with a positive hind limb extension to this shock were used. All drugs were administered intraperitoneally except griseofulvin which was administered orally. Preliminary experiments were conducted to determine any difference in the duration of anti-convulsant action of phenytoin in rats pretreated with griseofulvin or tolbutamide or chlordiazepoxide or chlorpromazine or hydroxyzine and non-treated rats. The anticonvulsant action defined as the abolition of tonic extension of the hind limbs was tested at various time intervals.

The effect of griseofulvin, tolbutamide and chlordiazepoxide was also studied on the flexor and extensor components of convulsions. The flexor and extensor components of the convulsions were timed and measured correct to 0.1 sec with a stop watch and F/E ratio calculated according to the method of Rauh and Gray (11). Only those rats which had a F/E ratio of approximately 0.3 were selected for the study. The rats were treated with the test substances for 4 days. Thirty six hr after the last dose, phenytoin was administered. Control rats received saline injections and phenytoin only. Shocks were given one hr after phenytoin and F/E ratio was calculated.
RESULTS

The results are summarised in Table I. With a dose of 12.5 mg/kg of phenytoin, the anticonvulsant action persisted for over 17 hr in control rats. In rats treated with griseofulvin or chlordiazepoxide or chlorcyclizine or hydroxyzine or tolbutamide, the anticonvulsant action disappeared much sooner. Chlorpromazine did not diminish the duration of action of phenytoin.

The F/E ratio was consistently raised by a dose of 1 mg/kg of phenytoin. This rise was blocked in rats treated with tolbutamide or chlordiazepoxide. Griseofulvin did not prevent the rise in F/E ratio produced by phenytoin. The data are summarised in Table II.

**Table I:** Modification by various drugs of the anticonvulsant effect of phenytoin (control 100% protection).

The drugs were given once daily for 4 days in the dose indicated against each drug.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>% Protection</th>
<th>at 6 hr</th>
<th>at 17 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>(12)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Griseofulvin 50 mg/kg</td>
<td>(12)</td>
<td>33 P&lt;0.01</td>
<td>33 P&lt;0.01</td>
</tr>
<tr>
<td>Tolbutamide 100 mg/kg</td>
<td>(12)</td>
<td>25 P&lt;0.01</td>
<td>25 P&lt;0.01</td>
</tr>
<tr>
<td>Chloridiazepoxide 100 mg/kg</td>
<td>(12)</td>
<td>25 P&lt;0.01</td>
<td>25 P&lt;0.01</td>
</tr>
<tr>
<td>Chlorcyclizine 30 mg/kg</td>
<td>(12)</td>
<td>25 P&lt;0.01</td>
<td>25 P&lt;0.01</td>
</tr>
<tr>
<td>Chlorpromazine 30 mg/kg</td>
<td>(12)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hydroxyzine 30 mg/kg</td>
<td>(12)</td>
<td>25 P&lt;0.01</td>
<td>25 P&lt;0.01</td>
</tr>
</tbody>
</table>

Figures in parantheses indicate the number of rats.
Phenytoin sodium (12.5 mg/kg ip) was administered 36 hr after the last dose of each drug.

**Table II:** The effect of various drugs on the flexion/extension time (F/E ratio) determined following the administration of phenytoin sodium (1 mg/kg ip).

<table>
<thead>
<tr>
<th>* Drug</th>
<th>One dose daily for 4 days</th>
<th>F/E ratio ± SE</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>(12)</td>
<td>.48±.070</td>
<td>P&gt;0.1</td>
</tr>
<tr>
<td>Griseofulvin 50 mg/kg orally</td>
<td>(12)</td>
<td>.52±.052</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>Chloridiazepoxide 100 mg/kg</td>
<td>(12)</td>
<td>.33±.004</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>Tolbutamide 100 mg/kg</td>
<td>(12)</td>
<td>.28±.034</td>
<td>P&lt;0.02</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the number of observations.
* Phenytoin was administered 36 hr after the last dose of each drug.
mg/kg of phenytoin, the anticonvulsant action of phenytoin (control 100% protection) was treated with griseofulvin or chlorpromazine (which antagonised the anti-convulsant action of phenytoin). This rise in F/E ratio as an index of anticonvulsant action has been employed by a number of workers (11, 17). Phenytoin decreases the extension time and increases the flexion time and increases the \( F/E \) ratio (12). Our unpublished study also confirms that dose related increases in \( F/E \) ratio occurs consistently after the administration of phenytoin.

Chlorpromazine is reported to be an enzyme-inducing drug (15,2). Chlorpromazine has also been reported to potentiate phenytoin (10). Hence a study of its prolonged administration on the action of phenytoin appeared indicated. However, in the present study, chlorpromazine did not antagonise phenytoin.

Griseofulvin antagonised the anticonvulsant action of phenytoin. However, as measured by the rise in the \( F/E \) ratio at 1 hr it was not possible to demonstrate an antagonism. Equivocal results have been obtained on its antagonistic activity towards tolbutamide (7). It is possible that the enzyme induction may not be sufficiently strong for antagonism to be demonstrable in 1 hr. It is also possible that griseofulvin is only a selective enzyme inducer. As far as its antagonism to warfarin is concerned, it was possible to demonstrate the antagonism in 3 out of 10 patients only; in the other 7 patients enzyme induction did not take place (14).

Tolbutamide has been reported to be an enzyme inducing agent. Thus it protects against the toxicity of organophosphorous compounds (13) and reduces the concentration of concurrently administered warfarin to trace amounts (16). The antagonism of phenytoin is probably mediated by an induction of enzymes.

Jori et al. (9) reported that after 4 days of chloridiazepoxide administration, rats become resistant to the hypnotic action of pentobarbitone. We have been able to demonstrate its antagonism towards the anticonvulsant action of phenytoin. Chloridiazepoxide precipitates grand mal seizures in patients under adequate control with phenytoin (6). Phenytoin was administered 36 hr after the last dose of chloridiazepoxide. Chloridiazepoxide is a drug of addiction and definite withdrawal symptoms with convulsions have been reported (8). With an increased excitability present during the withdrawal period, the dose of phenytoin employed may be insufficient to increase the \( F/E \) ratio or to produce anticonvulsant activity.

REFERENCES

SHORT COMMUNICATION

EFFECTS OF PHENIRAMINE MALEATE ON PROTEOLYTIC ENZYMES

Summary: The effects of pheniramine maleate and tolbutamide on the metabolism of parathion were investigated. It was found that the activity of some proteolytic enzymes was slightly inhibited by pheniramine maleate. The inhibition was more pronounced in adult mice than in young rats.

Key words: histamine acid phosphate, proteolytic enzymes, parathion, pheniramine maleate, tolbutamide.

Proteolytic enzymes played an important role in the metabolism of parathion. Kesava Rao et al. (16) had reported that the activity of some proteolytic enzymes in the brain of sheep was inhibited by pheniramine maleate. In the present study, the effect of pheniramine maleate on the activity of proteolytic enzymes in mice and rats was investigated.

Sheep were killed by decapitation and then beaked jacketed with 10% (w/v) using 0.5 ml distilled water for 10 min. The activity of proteolytic enzymes was estimated using a Beckman spectrophotometer.

The protease activity was assayed by the method of Van Slyke (14). The protease activity was expressed as the amount of substrate converted to product per unit time.