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

K. SAMU IYER AND T. A. RAJALAKSHMY

Department of Pharmacology, Medical College, Calicut-8

Summary: The effect of various enzyme-inducing drugs on the anticonvulsant action of phenytoin was investigated. Chlorcyclizine, hydroxyzine, tolbutamide, griseofulvin and chloridiazepoxide antagonised phenytoin. Chlorpromaxine 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 chloridiazepoxide but not by griseofulvin.

Key words: enzyme inducers phenytoin anticonvulsant activity antagonism

INTRODUCTION

Phenobarbitone induces enzymes and thus accelerates the metabolism of phenytoin, dicoumarol 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 Convulsiometer (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 chlorcyclizine or chloridiazepoxide 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 phenytion 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 chl

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.

Drugs		*% Protection*	
		at 6 hr	at 17 hr
Control	(12)	100	100
Griseofulvin 50 *mg/kg*	(12)	33 $P<0.01$	33 $P<0.01$
Tolbutamide 100 *mg/kg* ip	(12)	25 $P<0.01$	25 $P<0.01$
Chlordiorepoxide 100 *mg/kg* ip	(12)	25 $P<0.01$	25 $P<0.01$
Chlorcyclizine 30 *mg/kg* ip	(12)	25 $P<0.01$	25 $P<0.01$
Chlorpromaxine 30 *mg/kg* ip	(12)	100	100
Hydroxyzine 30 *mg/kg* ip	(12)	25 $P<0.01$	25 $P<0.01$

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.

ridiazepoxide 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 chloridiazepoxide. Griseofulvin did not prevent the rise in F/E ratio produced by phenytoin. The data are summarised in Table II.

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

* Drug One dose daily for 4 days		*F/E ratio ± SE*	*Probability*
Control	(12)	.480 ± .070	
Griseofulvin 50 *mg/kg* orally	(12)	.520 ± .052	$P>0.1$
Chloridiazepoxide 100 *mg/kg* ip	(12)	.333 ± .004	$P<0.02$
Tolbutamide 100 *mg/kg* ip	(12)	.288 ± .034	$P<0.02$

Figures in parentheses indicate the number of observations.

* Phenytoin was administered 36 hr after the last dose of each drug.

DISCUSSION

Increase 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.

Chloryclizine and hydroxyzine antagonised the anti-convulsant action of phenytoin. This is in agreement with earlier literature reports. (4,5).

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 domonstrable 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 chlordiazepoxide 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 grandmal 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.

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