

## BETA BLOCKADE AND ANTICONVULSANT ACTIVITY OF PROPRANOLOL

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**Summary:** Racemic and dextro forms of propranolol were equipotent in their anticonvulsant activity in normal rats by the MES test. In an attempt to determine any difference in the anticonvulsant activity of the two forms a variety of adrenergic agents were used, viz. phenoxybenzamine, reserpine, alphamethyl dopa and acetazolamide. There was no difference between the two forms, in the absence or presence of several adrenergic drugs employed. However, racemic but not dextro propranolol reduced MET, in normal as well as in nialamide primed rats.

**Key words:** d-and dl - Propranolol                          reserpine                          alphamethyl-dopa  
phenoxybenzamine                          acetazolamide                          anticonvulsants  
nialamide

### INTRODUCTION

A number of anticonvulsant drugs exhibit antifibrillatory properties and it has been suggested that a common mechanism like membrane stabilization operates in both these situations. Phenytoin and carbamazepine, widely used anticonvulsants, were found to possess antifibrillatory properties (3,13). Similarly several antifibrillatory agents were screened for anticonvulsant properties with variable results (9, 16). Propranolol possesses antifibrillatory activity (5) and also anticonvulsant activity (12). The antifibrillatory activity of propranolol tested against digitalis-induced arrhythmia did not show any marked predilection for dextro or levo forms of propranolol. But in adrenergically-induced fibrillation eg : arrhythmia induced by adrenaline in a cyclopropane sensitized myocardium the levo form was several times more potent (4) thus underscoring the contribution of beta-blockade in the antifibrillatory activity of propranolol. It is possible that a similar difference between the two forms of propranolol exists for anticonvulsant activity.

Employing the racemic and the dextro forms of propranolol an attempt was made to investigate the contribution of beta blockade in the production of anticonvulsant activity of propranolol. Administration of phenoxybenzamine (alpha-receptor blocker), alphamethyl dopa (precursor of alpha-methyl noradrenaline) or reserpine (catecholamine depleter) either antagonize the anticonvulsive effects of anticonvulsants or facilitate convulsions (1, 11). Accordingly the interactions of these drugs with racemic and dextro propranolol were also investigated.

The anticonvulsant ED50 of acetazolamide (carbonic anhydrase inhibitor) is modified by a number of substances which have adrenergic and adrenergic blocking properties (8). Thus the ability of two isomers of propranolol to modify the anti-convulsant effect of acetazolamide was also investigated.

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## MATERIALS AND METHODS

Male albino rats weighing between 180-200 g were used for the experiments. Electroshocks were given with a Techno model (Model, C.) convulsiometer. Maximal electroshock seizures were produced with 150 m.A. current for 0.2 sec through ear clip electrodes and the duration of tonic extension phase was noted. MET tests were done according to the method of Swinyard *et al.* (15) as quoted by Bapat *et al.* (1).

The two isomers of propranolol (2 mg/kg and 4 mg/kg) were given 30 min prior to shock. Phenoxybenzamine (15 mg/kg) was given 1½ hr prior to shock. Alphamethyl-dopa (400 mg/kg) was dissolved in 0.1-N HCl and given 24 hr prior to shock. Reserpine (Serpasil, 8 mg/kg) was given 5 hr prior to shock. Acetazolamide was prepared by dissolving it in 0.1-N NaOH and given in a dose of 3 mg/kg 1½ hr before shock. Nialamide was given 4 hr prior to shock. All drugs were made upto appropriate volume in normal saline and injected intraperitoneally.

## RESULTS

Both the racemic and dextro propranolol were equally effective in reducing the extension time by the MES test (Table I). Substances which modify the adrenergic tone, like alpha-methyl-dopa reserpine or phenoxybenzamine did not bring out any difference between the racemic and the dextro propranolol. The anti-convulsant activity of acetazolamide was not differentially altered by the two forms of propranolol (Table I).

TABLE I: Modification of the effect of dextro and racemic propranolol on the extension time of tonic-extension seizure in rat subjected to MES and pretreated with various drugs.

<i>Drugs</i>	<i>Number of animals</i>	<i>Extension time in sec. <math>\pm</math> SEM</i>	<i>'P' value</i>
Control	30	3.84 $\pm$ 0.08	..
d-propranolol	20	2.96 $\pm$ 0.08	<0.01
d-l-propranolol	20	2.74 $\pm$ 0.09	<0.01
Phenoxybenzamine	20	3.79 $\pm$ 0.09	>0.5
Phenoxybenzamine+d-propranolol	20	3.00 $\pm$ 0.06	<0.01
Phenoxybenzamine+d-l-propranolol	20	2.9 $\pm$ 0.05	<0.01
Reserpine	15	5.1 $\pm$ 0.32	<0.01
Reserpine+d-propranolol	15	2.5 $\pm$ 0.08	<0.01
Reserpine+d-l-propranolol	15	2.33 $\pm$ 0.08	<0.01
Alpha-methyl-dopa	15	4.46 $\pm$ 0.01	<0.1
Alpha-methyl-dopa+d-propranolol	15	2.94 $\pm$ 0.08	<0.01
Alpha-methyl-dopa+d-l-propranolol	15	3.04 $\pm$ 0.09	<0.01
Acetazolamide	15	2.9 $\pm$ 0.05	<0.01
Acetazolamide+d-propranolol	15	2.82 $\pm$ 0.05	<0.01
Acetazolamide+d-l-propranolol	15	2.76 $\pm$ 0.06	<0.01

There was no statistically significant difference between the values for d and d-l propranolol.

However, d-propranolol did not lower the MET either in normal rats or in rats in which the MET was elevated by the prior administration of nialamide (MAO inhibitor) but racemic propranolol lowered MET in both these situations (Table II).

TABLE II: Effect of racemic and dextro propranolol on MET in rats primed with nialamide.

Drugs	Number of animals	Extension time in sec. $\pm$ SEM	'P' value
Control	30	16 $\pm$ 0.002	..
Nialamide	15	24.7 $\pm$ 0.09	< .01
d-propranolol	15	16.1 $\pm$ 0.22	> .05
d-l-propranolol	15	13.1 $\pm$ 0.12	< .01
Nialamide + d-propranolol	15	23.3 $\pm$ 1.5	< .01
Nialamide + d-l-propranolol	15	16 $\pm$ 1.4	> .05

## DISCUSSION

The anticonvulsant activity of a drug can be measured by the reduction in extension time which probably reflects the ability of the drug to prevent the seizure spread (7). Both forms of propranolol reduced extension time and thus prevented seizure spread. There was no difference in potency between these two forms in normal rats.

When the adrenergic tone was diminished by the administration of reserpine or alphamethyl-dopa, there was no difference between the two forms. Adrenergic influences are prominent in the anti-convulsant activity of acetazolamide. Dichlorisoprenaline enhances the anticonvulsant activity of acetazolamide and other drugs altering adrenertic tone also modify the ED<sub>50</sub> of acetazolamide (8). However, we did not find any difference between racemic and d-propranolol in modifying the anticonvulsant action of acetazolamide.

The present experiments suggest that adrenergic receptor blockade does not play any part in the anticonvulsant activity of propranolol. The convulsant facilitating activity of reserpine may not be due to depletion of catecholamines (7,10). To a large extent it is related to the increase in excitability of central nervous system with no unique relation with catechol amines (6). The anticonvulsant activity of phenytoin has been analysed and found that it is not related to the presence of catecholamines and yet it is antagonized by reserpine. Hence it is doubtful whether the use of reserpine can lead to any firm conclusion (10).

Phenoxybenzamine antagonizes the anticonvulsant activity of a number of anticonvulsants e.g.: phenytoin and chlordiazepoxide (11). The anticonvulsant activity of racemic propranolol is also antagonized by phenoxybenzamine (12). Since the anticonvulsant activity of phenytoin is not dependent on catecholamines (10) it is unlikely that the antagonism by phenoxybenzamine is related to the alpha-blocking property of phenoxybenzamine (11). Even though there was no difference between racemic and d-propranolol in the presence of phenoxybenzamine conclusions on the nature of receptors cannot be drawn since phenoxybenzamine appears to be a non-specific antagonist of anticonvulsants (12). It is quite possible that some other property

of propranolol is responsible for the anticonvulsant activity for example, local anaesthetic activity. The correlation between local anaesthetic activity and anticonvulsant activity has been stressed by other workers also (2).

Racemic propranolol lowered MET in normal and MAO inhibitor primed rats. D-propranolol did not lower such MET. Hence, this lowering of MET can be taken as an effect peculiar to racemic propranolol or as an effect of beta-adrenergic receptor blockade. This raises the question of role of catecholamines in the convulsive threshold. Previous reports are conflicting and diverse actions on the convulsive threshold are reported (14). Certain workers claim to have produced protection from shock after administration of adrenaline probably due to elevation of MET by adrenaline (17). In that case, it can be reasonably argued that normally present adrenaline performs the tonic function of keeping the MET raised. Racemic propranolol but not d-propranolol antagonizes this property and hence brings the MET down. The concerned receptors may therefore be of beta type.

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