AN INVESTIGATION OF THE ANTIBARBITURATE ACTION OF TREBURON

By

J.C. BIJLANI, O.D. GULATI, S.D. GOKHALE AND A.D. JOSEPH

From the Department of Pharmacology, Medical College, Baroda

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The possible antibarbiturate action of treburon was examined against thiopentone sodium, pentobarbitone sodium and phenobarbitone sodium anaesthesia in pigeons and rats. Reduction in the duration of anaesthesia was used as an index of antibarbiturate action. Treburon showed significant dose related antibarbiturate effect against all the barbiturates studied. Treburon did not antagonise paraldehyde anaesthesia nor had it any analeptic effect in unanaesthetised animals.

In a preliminary investigation Joseph *et al.* (1959) reported that treburon antagonises the depressant effect of pentobarbitone in dogs and pigeons. Treburon had no analeptic action in unanaesthetised animals.

In view of the drawbacks of the currently available analeptic agents, further work with treburon seemed worth while. Heparin which is chemically similar to treburon was also studied.

METHODS

The possible antagonistic activity of treburon against the commonly used barbiturates and paraldehyde was tested in pigeons and white rats. Picrotoxin, a known barbiturate antagonist, was used as the reference compound.

White rats of either sex and weighing between 80 to 200 g were obtained from animal colony of the Medical College. White home tamed pigeons were obtained from the local market.

The duration of anaesthesia induced by the barbiturates or paraldehyde was taken as a measure of their depressant action and was used as the index against which the antibarbiturate activity of treburon or picrotoxin was tested. The duration of anaesthesia was taken as the time interval between loss and reappearance of the righting reflex. When the animal could right itself three times in one minute it was considered to have recovered from the effect of anaesthesia.

Doses of depressant drugs which produced anaesthesia in almost 100 per cent of the animals were determined in a preliminary study. The same doses were used subsequently. In each experiment three different doses of treburon were tested against a fixed dose of the agonist (either thiopentone or pentobarbitone, or phenobarbitone or paraldehyde). In a typical experiment animals were divided into six groups of five each and were given the predetermined dose of the agonist. Three groups received three different doses of treburon while the other three received an equal volume of saline and served as control. Unless otherwise indicated the groups were crossed over after 7 to 10 days.

In pigeons drugs were given intravenously through the alar vein, while in rats intraperitoneally. Treburon or heparin or picrotoxin was always given within two mins of loss of righting reflex.

The possible untoward effects of a large dose of treburon (120 mg/kg) were also tested in pigeons and rats. In a few experiments the possible antidepressant action of heparin was also tested.

RESULTS

Pigeons.—Table I summarises the effect of treburon on barbiturate and paraldehyde depression.

Effect of treburon on barbiturate anaesthesia.—A dose of 20 mg/kg of thiopentone sodium anaesthetised the animals for an average of 36 min. Treburon (15 mg/kg, 30 mg/kg and 45 mg/kg) significantly antagonised the depressant effect of thiopentone ($P < 0.01$). Fig. 1 shows that the effect of treburon is related to its dose.

The mean duration af anaesthesia with pentobarbitone sodium (30 mg/kg) ranged from 102 to 109 min. Treburon in the doses used (30 mg/kg, 60 mg/kg and 90 mg/kg) reduced the period of anaesthesia in a statistically significant manner ($P < 0.01$). The effect of treburon was dependant upon its dose (Fig. 1).

With phenobarbitone sodium (100 mg/kg) the mean duration of anaesthesia ranged from 131 to 134 min. Treburon (60 mg/kg, 90 mg/kg, and 120 mg/kg) antagonised the effect of phenobarbitone sodium in a statistically significant manner ($P < 0.05$ with 60 mg/kg and $P < 0.01$ with 90 and 120 mg/kg). The dose response relationship is shown in Fig. 1.

TABLE I

Effect of treburon on the duration of anaesthesia induced by barbiturates and paraldehyde in pigeons

Depressant agent mg/kg i. v.	Treburon mg/kg. i. v.	No. of animals	Mean duration of anaesthesia in min and S. D.	Probability
Thiopentone sod				
20	Control	10	36.0 ± 2.5	
,,	15	10	13.3 ± 2.6	< 0.01
,,	Control	10	36.0 ± 2.9	
,,	30	10	6.2 ± 1.2	< 0.01
,,	Control	10	36.0 ± 2.4	
,,	45	10	4.0 ± 1.0	< 0.01
Pentobarbitone sod				
30	Control	9	109.0 ± 4.6	
,,	30	9	73.0 ± 5.3	< 0.01
,,	Control	9	104.0 ± 10	
,,	60	10	38.0 ± 4.8	< 0.01
,,	Control	10	102.0 ± 6.1	
,,	90	10	9.3 ± 1.0	< 0.01
Phenobarbitone sod				
100	Control	10	131.0 ± 5.9	
,,	60	10	124.0 ± 6.0	< 0.05
,,	Control	10	134.0 ± 7.8	
,,	90	10	107.0 ± 3.9	< 0.01
,,	Control	10	132.0 ± 5.0	
,,	120	10	93.0 ± 3.0	< 0.01
[1] Paraldehyde				
100	Control	5	41.0 ± 3.1	
,,	30	5	39.0 ± 3.4	> 0.05
,,	Control	5	41.0 ± 3 5	
,,	60	5	40.0 ± 0.8	> 0.05
,,	Control	5	44.0 ± 7.3	
,,	90	5	37.0 ± 3.0	> 0.05
[1] Phenobarbitone sod				
100	Control	5	132.5 ± 6.8	
,,	Picrotoxin 0.05 mg/kg	5	28.9 ± 5.4	< 0.01

[1] No cross over tests were done

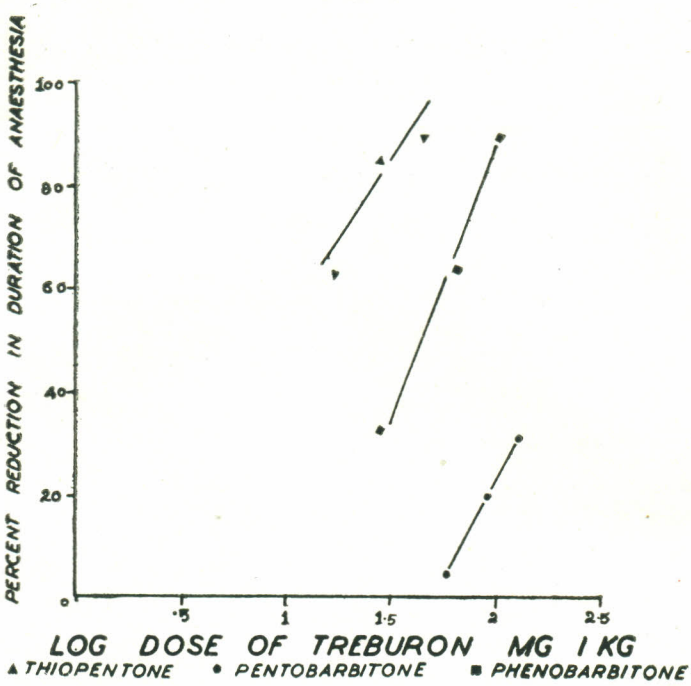

Fig. 1. Effect of treburon on barbiturate anaesthesia in pigeons.

Effect of treburon on paraldehyde anaesthesia.—Paraldehyde (100 mg/kg) produced anaesthesia of a mean duration of 41 to 44 min. Treburon (30 mg/kg, 60 mg/kg and 90 mg/kg) however, did not significantly reduce the duration of anaesthesia.

Effect of heparin on barbiturate anaesthesia.—Heparin (10 mg/kg) did not significantly reduce the duration of anaesthesia induced with pentobarbitone sodium (30 mg/kg), phenobarbitone sodium (100 mg/kg) and thiopentone sodium (20 mg/kg).

Effect of picrotoxin on phenobarbitone anaesthesia.—Picrotoxin (0.05 mg/kg) anatagonised the depressant effect of phenobarbitone sodium (100 mg/kg). It reduced the mean duration of loss of righting reflex from 132.5 to 28.9 min. ($P < 0.01$).

Rats.—The effect of treburon on the duration of anaesthesia produced by the three barbiturates and paraldehyde are summarised in Table II.

TABLE II

Effect of treburon on duration of anaesthesia of barbiturates and paraldehyde in rats

Depressant agent mg/kg i. p.	Treburon mg/kg i. p.	No. of animals	Mean duration of anaesthesia in min and S.D.	Probability
Thiopentone sod				
30	Control	10	26.3 ± 3.5	
,,	25	10	15.6 ± 2.1	< 0.01
,,	Control	10	25.5 ± 4.6	
,,	50	10	9.9 ± 2.3	< 0.01
,,	Control	10	25.8 ± 3.0	
,,	75	10	5.4 ± 1.5	< 0.01
Pentobarbitone sod				
30	Control	10	134.3 ± 2.7	
,,	25	10	114.8 ± 4.1	< 0.01
,,	Control	10	131.5 ± 4.3	
,,	50	10	102.8 ± 3.9	< 0.01
,,	Control	10	134.1 ± 5.3	
,,	75	10	83.0 ± 2.1	< 0.01
Phenobarbitone sod				
100	Control	10	172.0 ± 5.1	
,,	75	10	123.7 ± 4.2	< 0.05
,,	Control	10	171.0 ± 7.1	
,,	100	10	99.2 ± 7.3	< 0.01
,,	Control	10	171.3 ± 6.3	
,,	125	10	77.1 ± 4.0	< 0.01
[1] Paraldehyde				
30	Control	5	50.2 ± 6.6	
,,	50	5	47.8 ± 5.8	> 0.50
[1] Phenobarbitone sod				
100	Control	5	168.0 ± 9.4	
,,	Pictrotoxin 0.05 mg/kg	5	98.8 ± 4.4	< 0.01

[1] No cross over tests were done

Effect of treburon on barbiturate anaesthesia.—With thiopentone sodium (30 mg/kg) the mean duration of anaesthesia varied from 25.5 to 26.3 min. Treburon in the doses used (25 mg/kg, 50 mg/kg and 75 mg/kg) reduced the duration anaesthesia in a statistically significant manner ($P < 0.01$). The effect of treburon was related to its dose (Fig. 2).

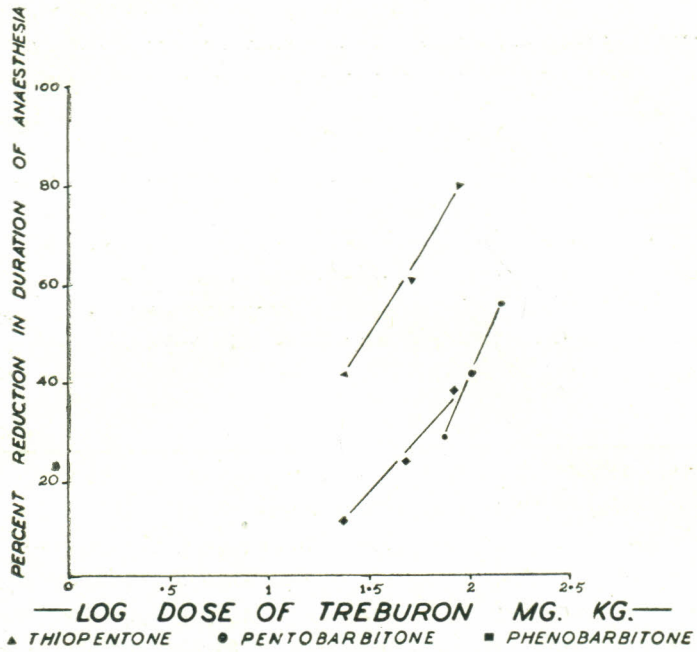

Fig. 2. Effect of treburon on barbiturate anaesthesia in rats.

The mean duration of loss of righting reflex with pentobarbitone sodium (30 mg/kg) ranged from 131.5 to 134.1 min. Treburon in the doses used (25 mg/kg, 50 mg/kg and 75 mg/kg) shortened the period of loss of righting reflex in a statistically significant manner ($P < 0.01$). The effect of treburon was related to its dose (Fig 2.)

The mean duration of anaesthesia with phenobarbitone sodium (100 mg/kg) ranged from 171.7 to 172.0 min. Treburon (75 mg/kg, 100 mg/kg and 120 mg/kg) reduced the period of loss of righting reflex in a statistically significant manner ($P < 0.05$ in the case of the lowest dose and $P < 0.01$ in case of the higher two doses). The effect of treburon was dependent upon its dose (Fig. 2).

Effect of treburon on paraldehyde anaesthesia.—Paraldehyde (30 mg/kg) produced anaesthesia of a mean duration of 50.2 min. Treburon (50 mg/kg) did not reduce the period of loss of righting reflex significantly ($P > 0.5$).

Effect of picrotoxin on phenobarbitone sodium anaesthesia.—Picrotoxin (0.05 mg/kg) reduced the mean duration of loss of righting reflex with phenobarbitone sodium from 168.0 min to 98.8 min ($P < 0.01$).

Treburon (100 mg/kg) did not produce any overt manifestation of stimulation in conscious rats and pigeons. In the doses used no other manifestations of acute toxicity were noticed in either the pigeons or the rats.

DISCUSSION

The present study has shown that treburon reduces significantly the duration of anaesthesia produced (in pigeons and rats) by three commonly used barbiturates, thiopentone, pentobarbitone and phenobarbitone. The antibarbiturate effect of treburon is related to its dose. The antibarbiturate action of treburon was seen at its best against thiopentone anaesthesia; phenobarbitone anaesthesia was the least affected while pentobarbitone anaesthesia occupied an intermediate position.

Barbiturate antagonists in common use can be divided into two groups on the basis of the mechanism of their antibarbiturate action. These two groups are the pharmacological antagonists which compete with barbiturates for a common site in the central nervous system and physiological antagonists which have opposite effects mediated through actions at different sites. The first groups of agents is exemplified by megimide (Hahn, *et al.*, 1956), and the second group by leptazole, nikethamide and picrotoxin. Lack of effectiveness against paraldehyde anaesthesia and absence of any central nervous system stimulant action in normal animals indicates that treburon may have a specific antibarbiturate effect probably mediated through competition for a common site in the central nervous system. However it would be necessary to test treburon against more non-barbiturate central nervous depressant before making any definite conclusions as to its site and mode of action.

On the basis of results of the present study it would not be possible to suggest the use of treburon in cases of acute barbiturate poisoning. All the commonly used analeptic agents have to be given repeatedly in cases of acute barbiturate poisoning. The effect of repeated doses of treburon in animals treated with barbiturates has not been examined in the present study. Moreover, repititious use of treburon is not without danger (Hirschboeck *et al.*, 1954; Wright, 1952). The interesting feature of the present study is that treburon has no convulsive action in single doses of 100 mg/kg in conscious pigeons or rats. In view of the hazards of the currently available analeptic agents an examination of the possible antibarbituratic activity of analogues of treburon would be worthwhile.

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REFERENCES

Hahn, F., Oberdorf, A. and Schunk, R. (1956). *Disch. med. Wschr.*, **81**, 1580.

Hirschboeck, J. S., Madison, F. W. and Pisciotta, A.V. (1954). *Amer. J. Med. Sci.*, **227**, 279.

Joseph, A.D., Jindal, M.N. and Patel, M.A. (1959). *Lancet*, **i**, 815.

Wright, I.S. (1952). *Cardiologia*, **21**, 709.