Comparative Studies on the Effects of Reserpine and it's Derivatives (Bromo and Dibromo) reserpine on the Blood Pressure, Heart Rate and E.EG. of Rabbit

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Abstract

The work deals with the study of the effect of reserpine bromorcscrpinc and dibromoreserpine on the blood pressure, heart rate and EEG of rabbits. For studying their effects on the blood pressure and heart rate these preparations were administered intraperitoneally (IP) in 0.25 and 0.5 mg/kg doses for two consecutive days and the effects were recorded on the third day. In the case of experiments on EEG the compounds were administered I/P in single 5 ing/kg doses and their effects recorded after 8 hours. The evaluation of the data suggests that bromoreserpine and dibromoreserpine are almost as effective as reserpinc as far as their effects on the blood pressure, heart rate and EEG of rabbit are concerned. (JPMA 32:141, 1982).

Introduction

Reserpine produces antihypertensive and tranquilizing action. When used in the treatment of hypertension the effects on CNS can produce undesirable side effects. The discovery of the hypotensive drug syrosingopine which is very much less potent as a CNS depressant, prompted some workers to prepare bromoreser- pine and dibromoreserpine with the aim of producing better hypotensive drugs (Siddiqui et al., 1973). The present work deals with the study of the effects of these derivatives on the blood pressure and LEG of rabbits.

Material and Methods

Animals:
Rabbit's of either sex, weighing 1 .2 to 2 kg supplied by the animal house of the Jinnah Postgraduate Medical Centre, Karachi, were used. The animals were fed lucern and carrots. Water was given ad lihiturn.

Equipment:
A Grass polygraph (model 7B) was used fir taking the records of blood pressure and heart rate. Blood pressure was recorded through a Statham,s transducer. Heart rate was recorded from the E.C.G. tracing obtained through an E.C.G. pulse pre-amplifier (model 7P 6B) on lead I.

Experimental Procedure:

(i) Blood Pressure (lid Heart Rate:
The animal was anaesthetized with peutobarbitone sodium, injected intraperitoneally in 35 mg/kg body weight dose, and tied in supine position to a wooden operation table. The left external jugular vein was cannulated and Connected through a rubber tube to a 5 ml burette containing normal salne. Blood pressure was recorded from the right common car&jtid artery cannulated with polyethylene tube attached to a Statham's transducer. The animal was heparinized (1,000 iu/kg) 10 to 15 minutes before the ligation and cannulation of the common carotid artery. Both the transducer and the polyethylene

tube connecting it to the artery were filled with hyparinized saline (100 iu/ml) before cannulation. For recording the E.C.G. the pin electrodes were pricked in right arm, left arm, right leg and left leg.

(ii)E.E.G.

Conscious rabbits were used for recording the E.F..G. Record was made through two right parietal bipolar leads inserted 6 mm behind the coronol suture. The electrode Needles were stopped 2 mm short of the sagiual suture and also 2 mm apart from each other. The analysis was done by counting the waves (rate per minute) and measuring the amplitude in microvolts,

Preparation tintl - jdministration of Solutions of Reserpine and ifs Dernivatives

Reserpinc (50 mg) was dissolved in 20% ascorbic acid solution by slightly warming it in a water bath. The final volume was made up to 5 ml by the addition of 20% ascorbic acid. The solution thus prepared contained 10 nig of reserpine per ml. For preparing the solutions of bromoreserpine or dibromoreserpine, 25 mg of these compounds were mixed with 25 mg of citric acid to which was added 3 ml of pro-pylene glycol and the linal volume was made up to 5 ml with distilled water. The centents were slightly warmed in a water bath and dissolved by shaking. The solution thus prepared contained 5 nil of bromorescrpine/dibro- moreserpine Per ml.

For studying their effects on blood pressure and heart rate, reserpine, bromoreserpine and dibromoreserpine were injected intraperitoneally in 0.25 and 0.5 mg/kg doses for two days and blood pressure and heart rate were recorded on the 3rd day. Fur experiments on EEG these compounds were administered in single 5 rngf kg I/P (loses and EEG was recorded after 8 hours.

Results

Blood Pressure:

The control values (13 animals) for systoflc, diastolic and mean blood pressure were 109.7± 1.7,87.3±2.1, 94.7±2.0 mmHg respectively. After the administration of 0.25 and 0.5 mg/kg (loses of reserpine these values came down to 96.0±4.6, 72.8±5.8, 80.8±5.1 mmHg and 82.0±3.2, 62.3±4.6, 68.2±4.0 mmHg (Table 1).

Table I

The effect of 0.25 and 0.5 mg/kg Reserpine on the Blood Pressure and Heart Rate of Anaesthetized Rabbits.

	Control	*RESERPINE*	
		0.25	0.5
1. Blood Pressure			
(i) Systolic	109.7±1.7 (13)	96.0±4.6 (5)	82.0± 3.2 (6)
(ii) Diastolic	87.3±2.1 (13)	72.8±5.8 (5)	62.3± 4.6 (6)
(iii) Mean	94.7±2.0 (13)	80.8±5.1 (5)	68.2±4.0 (6)
2. Heart Rate	291.2±8.1 (13)	225.6±8.8 (5)	207.0±10.6 (6)

Figures in parentheses indicate the number of observations. The values represent mean±standard error. Comparison of the values obtained in reserpine treated animals with that of the control group indicates that the differences are statistically significant ($P < .05$).

After the injection 0f bromoreserpine these values were 98.8±3.3,77.2±3.3,84.4± 3.3 mrnHg and 89.7±4.6, 68.0±4.1 75.7± 4.5mml-lg (Table II).

Table II

The Effect of 0.25 and 0.5 mg/kg Bromoreserpine on the Blood Pressure and Heart Rate of Anaesthetized Rabbits.

	Control	*BROMORESERPINE*	
		0.25	0.5
1. Blood Pressure (mmHg)			
(i) Systolic	109.7±1.7 (13)	98.8±3.3 (5)	89.7±4.6 (7)
(ii) Diastolic	87.3±2.1 (13)	77.2±3.3 (5)	68.0±4.1 (7)
(iii) Mean	94.7±2.0 (13)	84.4±3.3 (5)	75.7±4.5 (7)
2. Heart Rate	291.2±8.1 (13)	234.0±5.0 (5)	233.0±7.8 (6)

Figures in parentheses indicate the number of observations. The values represent mean ± standard error. Comparison of the values obtained in bromoreserpine treated animals with the control values indicates that the differences are statistically significant ($P < .05$).

In the dibromoreserpine treated animals the values were 92.3±4.8, 74.3±3.4, 80.4±1.9 mmlTg, and 88.6±4.3, 70.6±3.9 and 76.6±4.0 mmHg (TaHe III). Evaluation of the data shows that all these compounds produced statistically significant fall in the systolic, diastolic and mean blood pres sure. The differences between the effects ef reserpine, bromoreserpine and dibrorroresc rpinc were, however, statistically not significant.

Heart Rate

In the control group (13 animals) the mean value for the heart rate was 291 .2±8. 1 per minute. After the administration of 0.25 and 0.5 mg/kg rcserpine the rate decreased to 225.6±8.8 and 207.0±10.6 per minute (Table I). After the injection of bromoreserpine the values were 234.0±5.0 and 233.0±7.8 per minute (Table II). in the dibromoreserpine treated animals the rate came down to 216.9± 9.7 and 221.1±15.1 per minute (Table III).

Table III

The Effect of 0.25 and 0.5 mg/kg Dibromoreserpine on the Blood Pressure and Heart Rate of Anaesthetized Rabbits.

	Control	*Di-Bromoreserpine*	
		0.25	0.5
1. Blood Pressure (mmHg)			
(i) Systolic	109.7±1.7 (3)	92.3±4.8 (7)	88.6± 4.3 (7)
(ii) Diastolic	87.3±2.1 (13)	74.3±3.4 (7)	70.6±3.9 (7)
(iii) Mean	94.7±2.9 (13)	80.4±1.9 (7)	76.6± 4.0 (7)
2. Heart Rate	291.2±8.1 (13)	216.9±9.7 (7)	221.1±15.1 (7)

Figures in parentheses indicate the number of observations. The values represent mean±standard error. Comparison of the values obtained in dibromoreserpine treated animals with the control values indicates that the differences are statistically significant ($P < .05$).

The evaluation of the data revealed that all these compounds s produced a statistically significant decrease in heart rate. The differences between the effects of reserpinc, bromoresperpine and dibromoreserpine were, however, statistically not significant (Table IV).

Table V

The Effect of 5 mg/kg Reserpine and its Derivatives on the E.E.G. of Rabbits.

	Frequency (cycles/minute)		*Amplitude (micro volts)*
	Minimum	*Maximum*	
Control	39.30±2.4	50.2±1.7	20.0±1.4
Reserpine	41.2 ±2.3 (6) P>1.0	49.8±1.6 (6) P>1.0	31.2±1.8 (6) P<.01
Control	43.5 ±1.7	48.8±1.6	19.8±1.6
Bromoreserpine	41.8 ±1.3 (6) P>1.0	50.7±2.1 (6) P>1.0	32.7±3.7 (6) P<.05
Control	39.1 ±1.8	47.3±1.5	24.4±1.9
Dibromoreserpine	38.6 ±1.4 (9) P>1.0	46.6±1.6 (9) P>1.0	33.0±3.1 (9) P<.05

Each value represents mean±standard error. Figures in parentheses indicate the number of animals.

The effects of 5 mg/kg doses of reserpine, bromoreserpine and dibromoreserpine are shown in Table V.

Table IV

Comparison of the Effects of 0.25 and 0.5 mg/kg doses of Bromoreserpine and Dibromoreserpine with Reserpine on the Blood Pressure and Heart Rate of Anaesthetized Rabbits.

	Mean Blood Pressure (mmHg)		*Heart Rate*	
	A	B	A	B
Reserpine	80.8±5.1 (5)	68.2±4.0 (6)	225.6±8.8 (5)	207.0±10.6 (6)
Bromoreserpine	84.4±3.3 (5)	75.7±4.5 (7)	234.0±5.0 (5)	233.0± 7.8 (6)
P/values	1.0	1.0	1	.05
Reserpine	80.8±5.1 (5)	68.2±4.0 (6)	225.6±8.8 (5)	207.0±10.6 (6)
Dibromoreserpine	80.4±1.9 (7)	76.6±4.0 (7)	216.9±9.7 (7)	221.1±15.1 (7)
P/values	1.0	1.0	1.0	1.0

Figures in parentheses indicate the number of observations. The values represent mean±standard error.

A:-0.25 mg/kg. B:-0.5 mg/kg

These effects were also almost similar.

Discussion

The hypotcusive effect of resperine is well established in man (Wilkins, 1954) and in several laboratory animals i.e. cat (Moyer, 1954), clog (Trapold et al., 1954), rabbit (Moyer et al., 1954) and monkey (Schneider and Earl, 1954). The Hypotensive effect is primarily due to a decrease in the peripheral resistence, produced by prevention of' uptake of Noradrenaline and its subsequent depletion at sympathetic nerve endings (Iversen, 1973; Smith, 1973). Reserpinc induced brady-cardia has also been reported in human beings and experimental animals (Pulmeer et al., 1954). The bradvcardia is Considered to be due to an increase in the parasympathetic activity produced due to central vagal stimulation and inhibition of physiologically antagonistic sympathetic activity (Nickerson, 1970). The observations reported in this paper arc, therefore, in accordance with those reported earlier.
Experiments on bromoreserpine and dibr-omoreserpine indicate that these compounds are almost as effective as reserpine as far as their effects on the blood pressure and heart rate of anaesthetized rabbits arc concerned.
The action of reserpinc on EEG is due to its sedative effect, as the pattern of waves resembles that seen

in normal sleep (Jarvik, 1970). Comparative study in the present work indicates that reserpinc, bromoreserpine and dibromoreserpinc produced almost similar effects on EEG.
On the basis of the above mentioned observations, it is concluded that bromoreserpine and dibromoreserpine are neither more çotent than reserpine in their effects on blood pressure nor are they milder in their central effects, as far as studies on the cardiovascular system and EEG øf rabbits are concerned.

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