Original Articles

SOME PHARMACOLOGICAL ACTIONS OF NITROHARMIDINE NITRATE

S. Khan, A. Qayum and S.M. Yusuf

Abstract

Nitroharmidine nitrate produced hypertension and bradycardia in anaesthetized rats, antagonized the effects of d-tubocurarine on the indirectly stimulated tibialis anterior muscle of cat, and induced contractions in the isolated guineapig ileum, an effect which was antagonized by atropine.

Introduction

Nitroharmidine nitrate has been prepared from the alkaloid harmidine which was isolated by Siddiqui (1962) from the plant Peganum harmala. Preliminary screening tests revealed that this material produced a stimulant effect on the indirectly stimulated tibialis anterior muscles of rat and rabbit (Yusuf et al., 1975). The present work deals with further studies on its pharmacological actions.

Material and Methods

Solutions of nitroharmidine nitrate were prepared in distilled water. Experiments were performed on rat blood pressure and heart rate, cat sciatic nerve and tibialis anterior muscle preparation, and guinea-pig ileum. The details of the experimental procedures are as follows:-

Blood Pressure and Heart Rate

Male albino rats (weighing 300-400 G) were anaesthetized with sodium pentobarbitone (30 mg/kg I.P.) and the carotid blood pressure was recorded on a Grass polygraph (model 7B). The heart rate was calculated from the ECG tracings. Trachea was cut open cannulated to prevent respiratory obstruction. Experiment was started 15-20 minutes after the operative procedure. Solutions of nitroharmidine nitrate were injected through a cannula fixed in the external jugular vein.

Muscle Nerve Preparation

Experiments were performed on cats (weighing 2-3 kg) anaesthetized with sodium pentobarbitone (30 mg/kg I.P.) and the sciatic nerve tibialis anterior muscle preparation was made according to the method described by Edery (1959). The nerve was stimulated at the rate of 5 per minute with square wave stimuli of 0.3 millisecond duration. Voltage applied was between 3-6 volts. Drugs were injected through the femoral vein. Respiration was maintained with the help of artificial respiration when ever required. Contractile responses of the muscle were recorded on Grass polygraph.

Isolated Guinea-Pig Ileum

Guinea-pigs of either sex (weighing 500-600 G) were used. On the day of experiment the animal was killed by a blow on the head and a 2 cm long piece was removed from the terminal portion of the ileum after opening the abdomen. This was fixed in an isolated organ bath of 5 ml capacity containing oxygenated Tyrode solution at 37°C. Each tissue was allowed to rest for half an hour before starting the experiment. Contractions were recorded on a revolving smoked drum.

Results

Blood Pressure and Heart Rate

When used in 1 and 2 mg/kg doses nitroharmidine nitrate produced a rise in blood pressure accompanied with a decrease in the heart rate (Table I). The hypertensive response which started 10±2.5 seconds after the injection, was preceded by a mild hypotension in some of the experiments.

Table I: The Effect of Nitroharmidine Nitrate on the Mean Blood Pressure and Heart Rate of Anaesthetized Rat.

NITROHARMIDINE ug/kg	*BLOOD PRESSURE (mm Hg)*				*HEART RATE (beats/minute)*			
	Control	*Test*	*% increase*	*P*	*Control*	*Test*	*% decrease*	*P*
1 (6)	89.3 ± 3.6	110.2 ± 3.5	23.6 ± 2.3	<.01	317.7 ± 9.7	265.7 ± 12.4	16.5 ± 1.6	<.01
2 (6)	93.3 ± 2.9	126.8 ± 3.0	36.1 ± 2.1	<.01	333.7 ± 11.3	247.0 ± 13.0	25.8 ± 3.5	<.01

Figures in parentheses indicate the number of animals.

Departments of Pharmacology and Therapeutics, Jinnah Post graduate Medical Centre, Karachi and Bolan Medical College, Quetta, PCSIR Laboratories, Peshawar.

Muscular Contractions

In 200, 400 and 800 ug/kg doses nitroharmidine nitrate produced an increase in the height of the contractile responses of the indirectly stimulated tibialis anterior muscle. The mean values of the percentage increase in the height of the contractile responses are shown in Table II. Nitroharmidine nitrate antagonized the effects of d-tubocurarine on this preparation.

Table II: The Effect of Nitroharmidine Nitrate on the Amplitude of Contractions of the Indirectly Stimulated Tibialis Anterior Muscle Preparation of Anaesthetized Cat.

Nitroharmidine ug/kg	*Amplitude of contractions (mm)*		*% increase*	*P*
	Control	*Test*		
200 (6)	14.0 ± 0.3	16.5 ± 0.7	17.8 ± 4.0	<.02
400 (6)	13.3 ± 0.4	21.7 ± 0.8	63.2 ± 7.7	<.01
800 (6)	13.8 ± 0.6	24.0 ± 1.2	73.4 ± 4.1	<.01

Figures in parentheses indicate the number of animals.

GuineaPig Ileum

Nitroharmidine nitrate contracted the isolated guinea-pig ileum when used in concentrations of 20, 40, 80 and 160 ug/ml. These contractile responses were antagonized by atropine sulphate.

Discussion

These studies revealed that nitroharmidine nitrate produced bradycardia in rats and contracted the isolated guinea-pig ileum, an effect which was blocked by atropine. It was also observed that it increased the amplitude of contractile responses of the indirectly stimulated tibialis anterior muscle of the cat and antagonized the effect of d-tubocurarine on this preparation. These effects indicate that the alkaloid possesses parasympathomimetic properties. The hypertension produced in rats is, on the other hand, an apparently paradoxical effect. However, as it has been shown that the parasympathomimetic drug Physostigmine produces hypertension in rats (Gokhale et al., 1963; Varagic, 1955; Varagic and Vojvodic, 1962), the hypertensive action of nitroharmidine nitrate can be well correlated with the above mentioned parasympathomimetic properties. Our observations, therefore, indicate that as far as some of its pharmacological actions are concerned, nitroharmidine nitrate behaves like the parasympathomimetic drug physostigmine.

References

Edery, H. (1959) Effects of diacetyl monotime on neuromuscular transmission. Br. J. Pharmacol., 14:317.

Gokhale, S.D., Gulati, O.D. and Joshi, N.Y. (1963) Effect of some blocking drugs on the pressor response to Physostigmine in the rat. Br. J. Pharmacol., 21:273.

Siddiqui, S. (1962) Reinvestigation of the alkaloidal constituents of peganum harmala J. Pakistan Sci. Ind. Res., 5:207.

Varagic, V. (1955) The action of eserine on the blood pressure of the rat. Br. J. Pharmacol., 10:349.

Varagic, V. and Vojvodic, N. (1962) Effect of guanidine, hemicholinium and mebutamate on the hypertensive responses to eserine and catecholamines. Br. J. Pharmacol., 19:451.

Yusuf, S.M., Qayum, A., Qureshi, K.A. and Khan, S. (1975) Nitroharmidine nitrate on neuromuscular transmission: A preliminary report. JPMA., 25:33.