

# THE INFLUENCE OF SOME DERIVATIVES OF THE PHENOTHIAZINE GROUP ON REFLEXES FROM THE HEART

M. Yu. Ladinskaya

Laboratory of Regional Pharmacology (Director — Member AMN SSSR Professor V. V. Zakusov), Institute of Pharmacology and Chemotherapy (Director — Active Member AMN SSSR V. V. Zakusov), AMN SSSR, Moscow

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A number of investigators have established that certain derivatives of the phenothiazine group possess the ability to dilate coronary blood vessels [1,5]. Moreover, it is known that neuroplegic compounds have found application in cardiac surgery. In connection with this it appeared interesting to investigate the influence of phenothiazine derivatives on reflex reactions arising on constriction of coronary vessels. Two preparations were selected for this investigation, viz. aminazine\* and mepazine\*\*.

## EXPERIMENTAL METHODS

Experiments were performed on cats under urethane anesthesia and on decerebrate cats. The effect of mepazine and aminazine on reflex changes in blood pressure and respiration upon clamping of the descending branch of the left coronary artery was studied. When the vessel was completely compressed for 10 seconds acute ischemia of the corresponding area of the myocardium occurred and was accompanied by reflex changes in blood pressure and respiration. In a series of short-term experiments and one of prolonged experiments the electrocardiographic changes associated with these phenomena were recorded; these changes were characteristic of impaired coronary circulation. The preparations being tested were given intravenously in the short-term experiments and intraperitoneally in the prolonged ones. A more detailed description of the experimental methods has already been published in an earlier communication [4].

## EXPERIMENTAL RESULTS

The experiments showed that compression of the coronary artery is associated with the appearance of reflexes affecting blood pressure and respiration. In the majority of the experiments the reflexes from the heart were depressor in character (95-97%) and only in some cases were these reflexes pressor (3-5%). Reflexes affecting respiration led to increased depth and frequency of respiratory movements.

The investigation showed that aminazine in doses of 0.1-0.5 mg/kg depressed the reflexes from the heart on blood pressure by 50-67% over 7-25 minutes. When the doses are increased to 1-2 mg/kg the vascular reflexes are depressed by 70-80% for 30-40 minutes (Fig. 1, I). The maximum effect following intravenous

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\* Transliteration of Russian — Publisher's note.

\*\* Mepazine (N-methyl-piperidyl-3-methylphenothiazine) corresponds in its chemical structure to pacatal\*\*; it was synthesized at the Chemistry Department of the Institute of Pharmacology and Chemotherapy, AMN SSSR, by S. V. Zhuravlev, A. N. Gritsenko and M. I. Dorokhova. Yu. I. Vikhlyayev has carried out a detailed pharmacologic investigation of mepazine [2].

administration of aminazine occurs after 4-7 minutes. These data were obtained in experiments on anesthetized and decerebrate animals.

In a number of experiments aminazine altered the character of the reflexes, transforming them from depressor into pressor ones.

Injection of aminazine also diminishes the reflexes affecting respiration. The experiments also showed that aminazine diminished slightly the electrocardiogram changes arising upon impairment of coronary circulation. The electrocardiogram changes associated with impaired blood supply to the heart usually consist of the following features: a sharp increase in the T-wave, inversion of the ventricular QRS complex, deviation of the ST interval from the isoelectric line, disturbance of rhythm (Fig. 1, II). Such electrocardiographic changes, arising on compression of the coronary artery, are not abolished but only somewhat diminished by intraperitoneal injection of 1 mg/kg aminazine. The effect lasts for 25-30 minutes.

It must be noted that aminazine possesses, in addition to its depressing effect on reflexes from the heart, marked hypotensive properties. In connection with this it seemed essential to find out the relationship between changes in reflexes from the heart and the level of blood pressure. Artificial lowering of blood pressure was achieved in 2 ways: 1) acute blood-letting and 2) intravenous injection of 1-2 mg/kg papaverine\*.

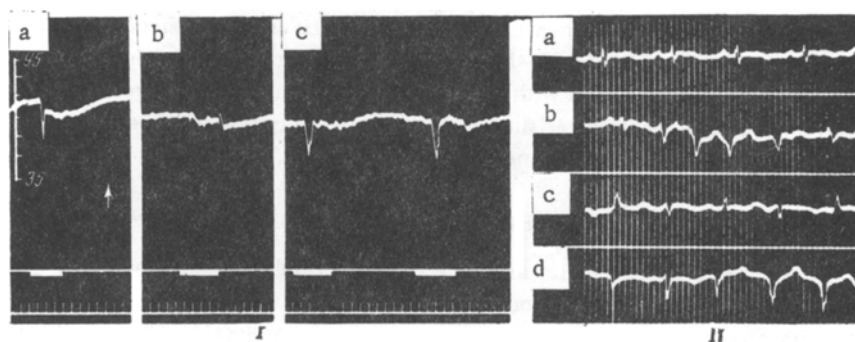


Fig. 1. Effect of aminazine on reflexes from the heart. Cat weighing 2.5 kg. Decerebrate.

I) Change in reflexes affecting blood pressure under the influence of aminazine: a) background; b) 10 minutes after intravenous injection of 2 mg/kg aminazine; c) 31 and 34 minutes after injection of aminazine. Records (from above down): blood pressure, stimulus mark, time marker (5 seconds).  
II) Changes in the electrocardiogram on clamping the descending branch of the left coronary artery: a) normal cat electrocardiogram; b) electrocardiogram with the coronary artery clamped; c) electrocardiogram 10 minutes after intravenous injection of aminazine 1 mg/kg; d) electrocardiogram 30 minutes after injection of aminazine.

It was established on the basis of these experiments that as the blood pressure decreased, the reflexes from the heart showed some diminution. When the blood pressure is lowered by 10 mm Hg the reflexes from the heart decrease by 10-20% (the variability of the changes is connected with the initial absolute magnitude of the reflex). Following injection of aminazine under conditions of lowered blood pressure to a similar level, the vascular reflexes diminish by 50-60%. These data permit the conclusion that aminazine possesses a marked ability to inhibit reflexes from the heart.

\* Control experiments showed that papaverine did not depress the reflexes from the heart.

The experiments also showed that aminazine inhibited the reflex changes in blood pressure and respiration for considerable periods of time. This raised the question whether the magnitude and character of the reflexes did not alter on compression of the coronary artery for prolonged periods of time (3-4 hours) without the administration of any pharmacologic substances. It was demonstrated that such was not the case.

Mepazine, in doses of 1-2 mg/kg, diminishes the reflexes from the heart by 35-50% over 20-30 minutes (Fig. 2, I). These data were obtained on anesthetized animals and animals decerebrated at the collicular level.

It must be emphasized that mepazine, which exerts a markedly weaker effect on the reflexes from the heart than aminazine, is substantially more effective than the latter in normalizing the electrocardiographic changes associated with impaired nutrition of the heart muscle. Thus, intraperitoneal and intravenous injections of 2-5 mg/kg mepazine abolish completely the electrocardiographic changes for 1-2 hours (Fig. 2, II). Normalization of the electrocardiogram under the influence of mepazine consists of the following: diminution of the T-wave, disappearance of inverted QRS complexes, increase in voltage of the waves, restoration of regular rhythm. These data showed that mepazine improves cardiac blood supply under conditions of myocardial ischemia produced by clamping the coronary artery.

Since many of these experiments were performed on anesthetized animals it seemed interesting to discover the effect of narcotic substances on the effect of neuroplegic compounds relative to reflexes from the heart. There are references in the literature [3] indicating that narcotic substances (urethane, medinal) exert a weak effect on reflexes from internal organs. A special series of experiments was therefore performed on animals immobilized by means of the curare-like preparation ditilin\*. It was found that aminazine given to

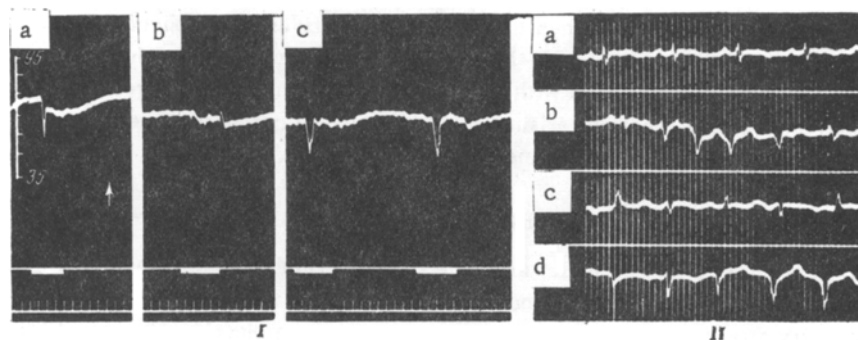


Fig. 2. Effect of mepazine on reflexes from the heart. Cat weighing 4 kg. Urethane anesthesia.

I) changes in blood pressure reflexes under the influence of mepazine: a) background; b) 4 and 5 minutes after intravenous injection of 1 mg/kg mepazine; c) 25 minutes after injection of mepazine. II) Electrocardiogram changes upon clamping of the descending branch of the left coronary artery: a) normal cat electrocardiogram; b) electrocardiogram upon compression of the coronary artery; c) electrocardiogram 15 minutes after intravenous injection of 1 mg/kg mepazine; d) electrocardiogram 1 hour after injection of mepazine.

ditilin-immobilized cats in the dose of 1 mg/kg diminished reflexes from the heart by 55-60% for 25-30 minutes. Mepazine under analogous conditions (2 mg/kg) inhibited reflex changes in blood pressure by 30-40% for 15-25 minutes.

\* Ditilin was given intravenously in divided doses (150-200 mg in 20 ml solution) throughout the experiment,

The experiments thus showed that aminazine and mepazine inhibited reflexes from the heart to a somewhat lesser extent in unanesthetized animals. Evidently, the effect of the neuroplegic substances under investigation is enhanced to some extent in the presence of anesthesia. However, no substantial differences could be obtained under different experimental conditions.

Taking into account the long duration and complexity of surgical operations on intrathoracic organs, it is extremely important to be able to diminish maximally reflexes from the heart by means of pharmacologic agents, at the same time maintaining for as long as possible normal blood supply to the heart muscle.

It has already been indicated that mepazine abolishes completely disturbances of blood supply to the myocardium with preservation of reflexes from the heart which are a little diminished. At the same time, it is well known that many neuroplegic compounds are able to potentiate the action of analgesics.

It was shown earlier that analgesics (phenadon\*, promedol\*, morphine and tecodin\*) inhibited reflex changes of blood pressure and respiration associated with compression of the coronary artery [4]; the most active substances as regards reflexes from the heart were phenadon and promedol.

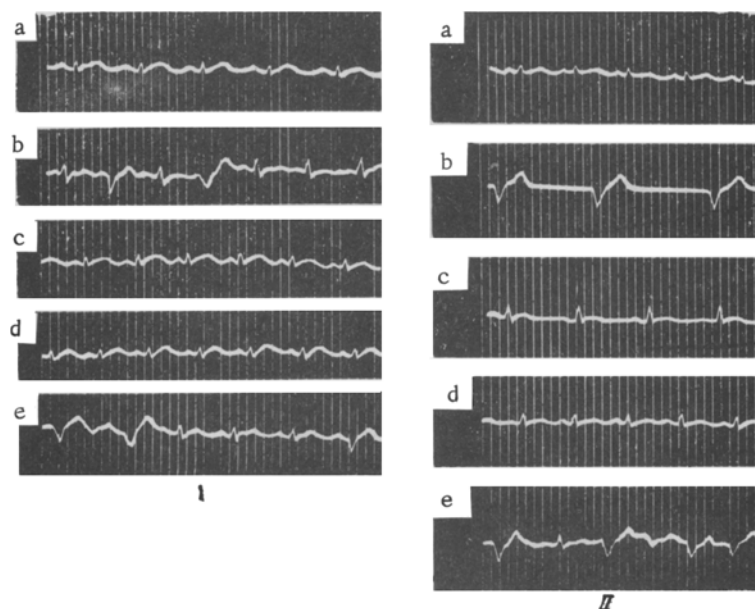


Fig. 3. Changes in the electrocardiogram upon compression of the descending branch of the left coronary artery. Cat weighing 4.4 kg (long-term experiment).

I, a) Electrocardiogram of cat prior to experiment; b) electrocardiogram with compression of coronary artery; c) electrocardiogram 30 minutes after intraperitoneal injection of 5 mg/kg mepazine and 0.25 mg/kg phenadon; d) electrocardiogram 24 hours after injection of mepazine and phenadon; e) electrocardiogram 50 hours after injection of mepazine and phenadon. II, a) normal cat electrocardiogram; b) electrocardiogram with compression of coronary artery; c) electrocardiogram 30 minutes after intraperitoneal injections of 5 mg/kg mepazine and 1 mg/kg promedol; d) electrocardiogram 3 hours after injection of mepazine and promedol; e) electrocardiogram 4 hours after injection of mepazine and promedol.

As has been mentioned above, mepazine has more marked capacity for improving myocardial blood supply than aminazine. Observations mentioned above formed the basis for a special series of experiments on the combined action of analgesics and mepazine. The experiments were carried out according to the following scheme. Under long-term conditions, the unanesthetized animal was given 0.25 mg/kg phenadon intraperitoneally and 20 minutes later 5 mg/kg mepazine by the same route. In a number of experiments the two preparations were given simultaneously. It was found that mepazine and phenadon, when used in combination in the doses indicated, abolished completely the electrocardiographic changes arising upon compression of the coronary artery. The effect produced by these preparations lasted 48-50 hours (Fig. 3, I). The combined action of mepazine and promedol was investigated in a similar manner. The dose of promedol used was 1 mg/kg, of mepazine 5 mg/kg. These two substances used in combination smooth out the electrocardiographic changes over a period of 4 hours (Fig. 3, II). These data indicate that the combined administration of analgesics and mepazine prolongs the action of the preparations to a considerable extent (5-20 fold).

The present investigations permit the conclusion that mepazine and aminazine promote diminution of reflex changes of blood pressure and respiration arising upon occlusion of the coronary arteries. The data obtained also demonstrate that aminazine exerts a stronger effect on reflexes from the heart than mepazine. However, mepazine abolishes completely the electrocardiographic changes associated with impairment of cardiac blood supply. Aminazine lacks this property almost entirely.

The present experiments suggest that the combined use of mepazine and analgesic substances may prove useful in clinical work.

#### SUMMARY

Short-term experiments were performed on anesthetized and decerebrate cats. A comparative study was carried out on the effect of aminazine and mepazine on the reflex reactions when cardiac blood supply was impaired.

It was established that mepazine and aminazine depressed the reflexes from the heart and decreased the electrocardiographic changes. The effect of aminazine on the reflexes from the heart is more pronounced than that of mepazine.

The latter completely eliminates the changes in the electrocardiogram connected with disturbance of coronary circulation. In the case of aminazine this property is almost absent. In combined administration of mepazine and analgesic substances (phenadon, promedol) the effect of these preparations is considerably prolonged.

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