THE EFFECT OF ANALGESICS ON THE REFLEX REACTIONS OF THE CORONARY VESSELS

N. V. Kaverina

Laboratory of Specific Pharmacology (Head – V. V. Zakusov, Active Member of the AMN SSSR) of the AMN SSSR Institute of Pharmacology and Chemotherapy, Moscow
(Presented by V. V. Zakusov, Active Member of the AMN SSSR)
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One of the most important tasks of research on problems of the therapy of coronary insufficiency is to find pharmacological substances which can be used to influence the reflex reactions which bring about constriction of the cardiac vessels. These reactions are known to play a significant role in the development of angina pectoris attacks. In this connection, the mechanism of the effect of analgesic substances, which have been clinically observed to stop angina pectoris attacks, on the coronary circulation is an interesting question.

Our earlier investigations [2] showed that of the analgesic substances, morphine, thecodine [hydroxy-codeine hydrochloride], promedole [4-phenyl-4-propoxy-1,2,5-trimethyl-piperidine hydrochloride] and phenadone [Methadon], morphine alone has the property of dilating the cardiac vessels; the other analgesics, on the contrary, somewhat increase the tonus of the coronary vessels. One can therefore assume that the clinical efficacy of these agents is not due to their direct effect on the cardiac vessels.

The purpose of this investigation was to study the effect of analgesic substances on the reflex reactions of the coronary vessels in response to stimulation of the carotid sinus receptors and the afferent nerves.

There have been a series of investigations concerned with the question of how analgesic substances affect autonomic reflexes, but the results of these investigations are extremely inconsistent.

For example, Vercauteren [8], who investigated the effect of morphine on the reflex changes of the blood pressure in response to stimulation of the carotid sinus receptors, concluded that morphine, even in small doses, can inhibit these reflexes. According to Z. N. Ivanova's observations [1], promedole inhibits the cardiovascular and respiratory reactions elicited by stimulation of the lower respiratory tract. M. Yu. Ladinskaya [5] also observed analgesics to induce inhibition of the blood pressure reflexes which develop with pressure on a coronary artery.

Other researchers who studied the effect of analgesics on vascular reflexes, however, have concluded the exact opposite. For example, Vandenlinden [7] observed intensification of the blood pressure reflexes in response to stimulation of the carotid sinus receptors to occur under the influence of morphine. R. P. Kruglikova-L'vova [4] concluded that morphine and promedole increase the reflexes on the blood pressure induced by stimulation of the bladder interoceptors. G. V. Kovalev [3] reached a similar conclusion after studying the effect of analgesics on vascular reactions induced by stimulation of interoceptors.

From the brief review of the literary data given above, it is evident that the research which has been carried out on the effect of analgesic substances on autonomic reflexes is not systematic in nature and has obtained only contradictory results. No specific investigation has been made of the effect of these agents on the reflex reactions of the coronary vessels. This is, however, a question of great clinical, as well as theoretical, importance.

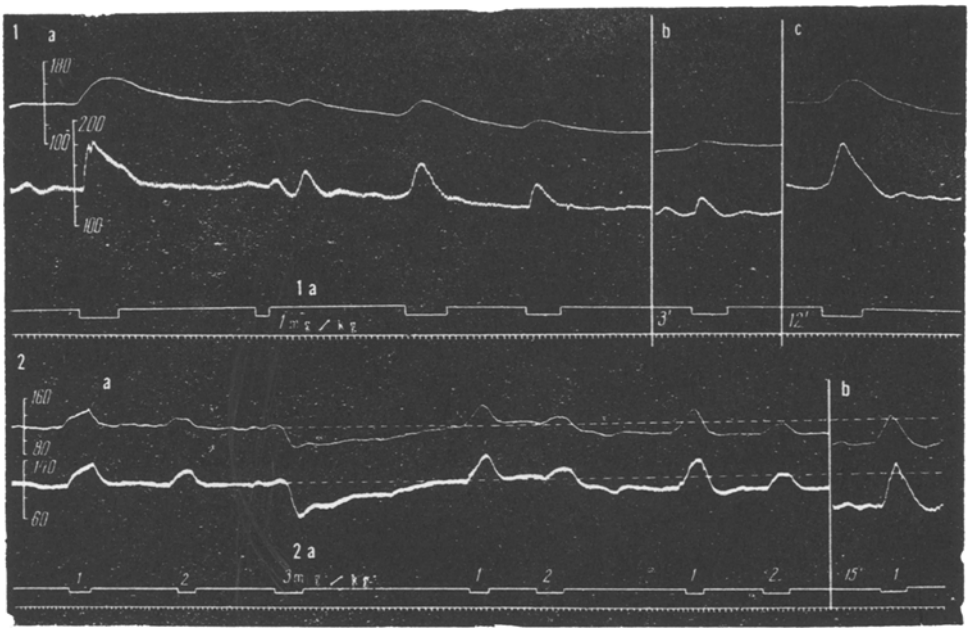

Fig. 1. Effect of morphine (1 mg/kg) on the reflex reactions of the coronary vessels: a) inhibition of reflexes from the tibial nerve affecting the coronary vessels and blood pressure caused by morphine in a dose of 1 mg/kg; b) increase in reflexes from the tibial nerve (1) and the carotid sinus (2) affecting the coronary vessels caused by morphine in a dose of 3 mg/kg. Curves show (from top to bottom): resistogram; blood pressure; stimulation of reflexogenic zones and administration of morphine; time (in 5-sec marks). Key: 1a) Morphine; 2a) morphine.

METHODS

The experiments were conducted on cats anesthetized with arethan and chloralose. The method of resistography was used to determine the effect of pharmacological substances on the reflex reactions of the heart. This method, proposed by V. M. Khayutin [6], is based on the principle of artificial stabilization of the blood flow in the vessels and uses a special pump to perfuse the vessels with the animals' own blood. A detailed description of this method and a diagram showing the experimetal plan can be found in an earlier article of ours [2].

A catheter was introduced into the mouth of the left coronary or circumflex artery; blood from the carotid artery entered this catheter in a volume which was constant per unit of time. Under these conditions, the pressure recorded at the pump outlet reflects change in vascular resistance, rising with constriction and falling with dilatation of the vessels. The advantage of this method is that it makes it possible to estimate changes in the tonus of the cardiac vessels independently of the changes in systemic arterial pressure which occur in the organism. In connection with the study of the reflex reactions of the coronary vessels, this is of particular value, because the reflex changes in the blood pressure developing in response to stimulation of the afferent system can mask the true condition of the tonus of these vessels when the estimations are based on measurement of the blood flow in the vessels of the heart.

The blood pressure was recorded in the femoral artery with a mercury manometer. Heparin (800-1000 units/kg intravenously) was used to prevent blood coagulation.

Reflexes on the cardiac vessels were induced by stimulating the carotid sinus receptors (pressure on the carotid artery) and the afferent fibers of the tibial and medial nerves. This stimulation was effected by square-wave pulses with a frequency of 50-60 hertz and a voltage of 5-15 volts.

RESULTS

The experiments conducted demonstrated that analgestics, in relatively small doses, can inhibit the reflexes of the cardiac vessels. For example, morphine in doses of 1-2 mg/kg decreased the reflexes an average of

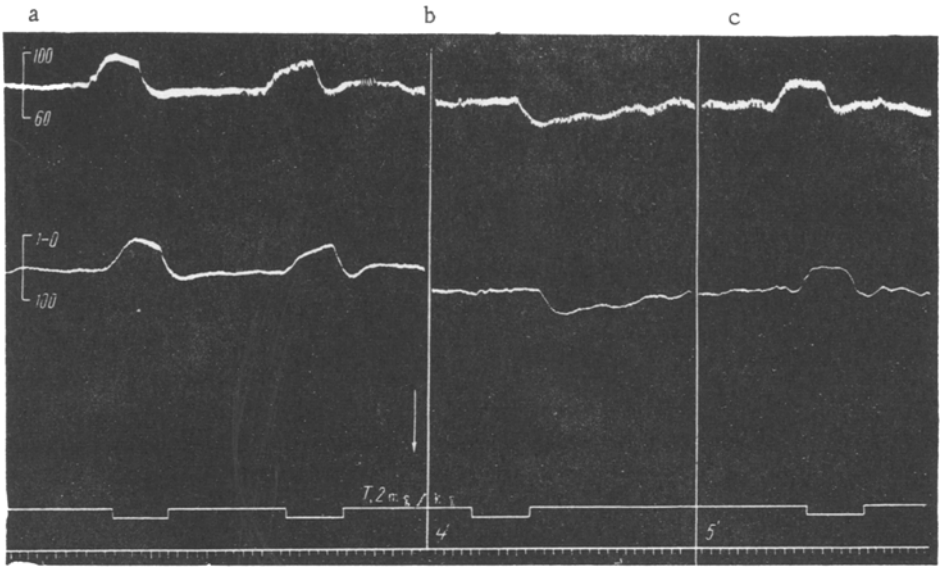

Fig. 2. Effect of thecodine on the reflex changes in the resistance of the coronary vessels and in the blood pressure provoked by stimulation of the carotid sinus. Symbols the same as in Fig. 1.

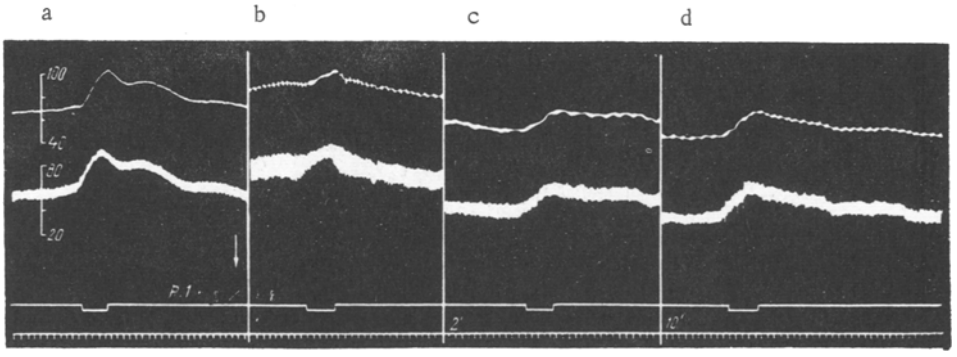

Fig. 3. Effect of phenadone on the reflex changes in the resistance of the coronary vessels and in the blood pressure provoked by stimulation of the medial nerve. Symbols the same as in Fig. 1.

50-70% of the original values. Their complete inhibition was even observed in a few cases. The effect of the morphine was not lasting. The reflexes usually returned to the original level 12-15 minutes after the administration of the preparation (Fig. 1a). Increasing the morphine dose to 2.5-3 mg/kg did not enhance the effect. In a series of experiments in which morphine was administered in doses in 3-4 mg/kg, moreover, the reflexes of the coronary vessels increased 5-10% of the original level. The reflexes remained increased for some time ($1\frac{1}{2}$-2 hours). In most cases, we were unable to observe the restoration of the reflexes to the original level due to the conditions of the method employed (Fig. 1b).

Thecodine had a similar effect on the reflex reactions of the coronary vessels. It should be noted, however, that thecodine's effect on these reflexes was more pronounced than that of morphine. Even in doses of 0.3-0.5 mg/kg, thecodine inhibited the reflexes 30-40% of the original level. When the dose was increased to 1-2 mg/kg, the resulting inhibition of the reflexes usually amounted to 60-80% (Fig. 2). Thecodine did not cause lasting inhibition of the reflexes; the original reflexes were usually restored after 12-15 minutes. Administered in large doses (3-3.5 mg/kg), thecodine, like morphine, caused the reflexes of the cardiac vessels to increase. In may experiments, this increase was very pronounced – as much as 80-90% of the original values.

Promedole also showed an ability to inhibit the reflexes of the cardiac vessels. In doses of 0.3-0.5 mg/kg, it caused the reflexes to decrease 75-85% of their original level. The inhibitory effect of promedole on the reflex

reactions of the coronary vessels was most clearly expressed when the drug was administered in small doses. When the promedole dose was increased to 2-3 mg/kg, the reflexes either did not change or, sometimes, increased slightly (4-5% of the original).

Phenadone, like the other analgesic substances, caused inhibition of the reflex reactions of the coronary vessels. When administered in doses of 0.5-1 mg/kg, it inhibited the reflexes by 30-60% of the original (Fig. 3). Under our experimental conditions, it was inconvenient to use phenadone in larger doses, because, in doses such as 2-3 mg/kg, phenadone induces disturbances of cardiac activity and acute blood pressure fall.

All the experimental analgesic substances, therefore, in relatively small doses, cause inhibition of the reflex reactions of the coronary vessels. These doses of the analgesics, however, roughly correspond to the therapeutic. The use of these substances in larger doses, however, caused the reflex reactions of the cardiac vessels to increase in a majority of cases. The different effects caused by the different doses of the analgesic substances are, it would seem, one explanation for the contradictory conclusions reached by the various researchers concerned with this question.

It should also be noted that the degree of change induced by the analgesics in the reflexes of the coronary vessels was identical regardless of which reflexogenic zone was stimulated to produce them.

The changes in the blood pressure reflexes, which were recorded at the same time as those of the cardiac vessels, were parallel to the changes in the reflexes affecting the coronary vessels.

Earlier investigations [2] allowed us to establish that morphine alone of the experimental analgesic substances (morphine, thecodine, promedole and phenadone) can increase the blood supply of the heart. Promedole and phenadone, in a majority of cases, increased the tonus of the coronary vessels, thus reducing the volumetric rate of the coronary blood flow. Thecodine caused no significant changes in the condition of the coronary circulation.

On the basis of these data, it would seem that the efficacy of most analgesic substances in angina pectoris is not due to their direct effect on the vessels of the heart. As the data of the present investigation have shown, however, analgesic agents can inhibit the reflex reactions causing constriction of the cardiac vessels when administered in doses corresponding to the therapeutic.

These data allow the hypothesis that the efficiency of analgesic substances in angina pectoris is due not only to their elimination of the pain syndrome, but also to their ability to inhibit the reflex reactions which cause constriction of the coronary vessels and therefore promote the development of coronary circulatory disturbances.

When using these analgesic substances clinically, one should also keep in mind the fact that these substances, in larger doses, can promote the deterioration of myocardial blood supply conditions by raising the tonus of the coronary vessels or intensifying their reflex reactions.

The only exception to this rule is morphine, which, in a majority of cases, improves the myocardial blood supply.

SUMMARY

The author studied the effect of analgetic substances (morphine, thecodine, promedol, and phenadon) on the reflex reactions of coronary vessels, provoked by stimulating the carotid sinus receptors and afferent nerves. The analgetic substances given in therapeutic doses are capable of depressing the mentioned reflexes.

Conversely, in a number of cases large doses of the analgetic increased the reflex reactions of coronary vessels.

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