PHARMACOLOGY

THE EFFECT OF ANALGESICS ON THE CORONARY CIRCULATION

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(Received September 7, 1958. Presented by Active Member AMN SSSR V. V. Zakusov)

Analgesics are widely used in clinical practice in treatment of coronary insufficiency, being required in the eradication of pain accompanying attacks of angina pectoris. The changes caused by analgesics in the blood suppy of the myocardium are, therefore, extremely important.

The literature on the effect of analgesics on the coronary circulation is confined to a few experimental investigations dealing with morphine. Even these few findings were obtained, however, mainly in experiments on the isolated heart, and they are distinctly controversial. Kountz [9], for instance, in experiments on the isolated surviving human heart, observed an increased outflow from the coronary vessels under the influence of morphine. A similar conclusion was reached by Elek and Katz [8] on the basis of experiments on the isolated fibrillating heart. Van Egmond [13] and Wegria [14] showed that morphine causes no essential changes in the coronary blood flow.

According to the findings of a number of authors, phenadon and promedol possess spasmolytic properties. The spasmolytic activity of these drugs in mainly shown, however, in experiments on isolated organs (diminution of the spastic contractions od isolated segments of the gut and dilation of the vessels of the isolated ear of the rabbit, and so on). In the intact animal, promedol and phenadon lead, on the other hand, to an increase in the tone of the smooth muscle of the uterus and gut [3-6]. The question of the spasmolytic properties of these analgesics is thus by no means clear, and in particular their action on the coronary circulation has not been investigated.

The object of the present research was to study the action of analgesics on the coronary circulation. For the investigation we chose the following drugs: thecodin, promedol and phenadon.*

EXPERIMENTAL METHOD

Experiments were conducted on cats anesthetized with urethane and chloralose. The blood supply to the heart was judged by the volume of blood flowing from the coronary sinus in unit time. A detailed description of the method has been given in our previous communication [1]. In order to assess more objectively the influence of the drugs under study on the vessels of the heart, in a series of experiments we recorded the tone of the coronary vessels by means of a perfusion pump, the perfusion volume being constant. The construction and working principle of this apparatus were described by V. M. Khayutin, V. M. Danchakov and V. I. Tsaturov [7]. The advantages of this method are that it permits the state of the vascular tone to be judged independently of the influence of the level of the systemic blood pressure on the vessels of the area being studied. In order to record the tone of the coronary vessels by the autoperfusion method, a special cannula was passed from the subclavian artery, through the arch of the aorta into the orifice of the left common coronary artery, under artificial respiration after thoracotomy. The perfusion pump collects blood from the carotid artery and injects it at a constant perfusion volume into the coronary vessels. The perfusion pressure, recorded by a mercury

* Amidone.

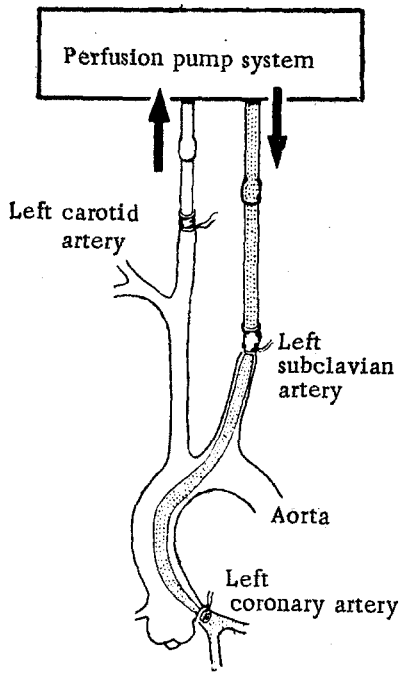

Fig. 1. Scheme of autoperfusion of the left coronary artery of the heart in the cat.

manometer at the outlet of the pump, is determined by the resistance of the vessels of the heart and is an index of their tone. The scheme of the experimental autoperfusion of the coronary vessels by means of the perfusion pump is illustrated in Fig. 1.

The blood pressure was recorded in the femoral or carotid arteries. To prevent the blood from clotting, heparin was injected (1000-1500 units/kg). The test drugs were injected intravenously.

EXPERIMENTAL RESULTS

The experiments showed that morphine possesses the property of increasing the volume flow of the coronary circulation. In doses of only 1-2 mg/kg it led to an increase in the outflow of blood from the coronary sinus by 20-30% by comparison with its original level. Concurrently with an increase in the rate of blood flow, a fall of 25-30 mm Hg in the blood pressure was observed. When larger doses of morphine were given (3-4 mg/kg), the outflow of blood from the coronary sinus increased by 50-60% over the initial level (Fig. 2, a). The effect lasted from 10 to 15 minutes, depending on the dose of the drug.

The experiments in which the coronary vessels were perfused showed that after injection of morphine a marked fall in the perfusion pressure was observed, giving evidence of a decrease in the resistance of the vessels of the heart to the blood flow (see Fig. 2, b). The increase in the blood supply of the heart under the influence of morphine was evidently connected with its direct effect on the tone of the heart vessels. The experiments with morphine thus showed that the drug had a positive action on the coronary circulation, lowering the tone of the coronary vessels.

We obtained quite different results in the experiments with promedol. In the majority of experiments, promedol in doses of 1-2 mg/kg caused a decrease in the volume rate of the coronary blood flow by 15-20% by comparison with the original level. In only a few experiments when promedol was given in these doses were no essential changes observed in the magnitude of the outflow of blood from the coronary sinus. As the result of an increase in the dose of promedol to 3 mg/kg, the decrease in the rate of the coronary blood flow reached 40-45% (Fig. 3, a). In response to injection of promedol, as a rule a fall in the blood presure of 15-25 mm Hg was observed. It might have been assumed that the fall in the rate of blood flow was not, in this case, an index of constriction of the coronary vessels, but merely pointed to the fact that when the level of the blood pressure was lowered, a smaller volume of blood passed through the vessels of the heart in unit time. However, experiments in which the tone of the vessels of the heart was recorded showed that under the influence of promedol the resistance of the coronary vessels was, as a rule, increased (see Fig. 3, b).

We obtained analogous results in experiments with phenadon, which, in doses of 1-2 mg/kg, led in the majority of cases to a decrease in the volume rate of the coronary blood flow by 25-60% by comparison with the initial level. The duration of its action in these conditions was 15-25 minutes. In some experiments, however, after injection of phenadon no changes were observed in the magnitude of the outflow of blood from the coronary sinus. The results of the experiments on the study of the tone of the vessels of the heart under the influence of phenadon were in agreement with the findings obtained when the outflow of blood from the coronary sinus was recorded. When the coronary vessels were perfused during the action of phenadon, in roughly half the experiments the tone of the vessels was increased, whereas in the remaining cases no essential changes in the tone of these vessels could be found.

Thecodin in doses of 1-2 mg/kg caused no perceptible changes in the volume rate of the coronary blood flow. In some experiments a fall in the outflow of blood from the coronary sinus, insignificant (by 15-20%) by comparison with the initial level, was observed and this, as shown by special experiments, was evidently not connected with the influence of thecodin on the tone of the coronary vessels.

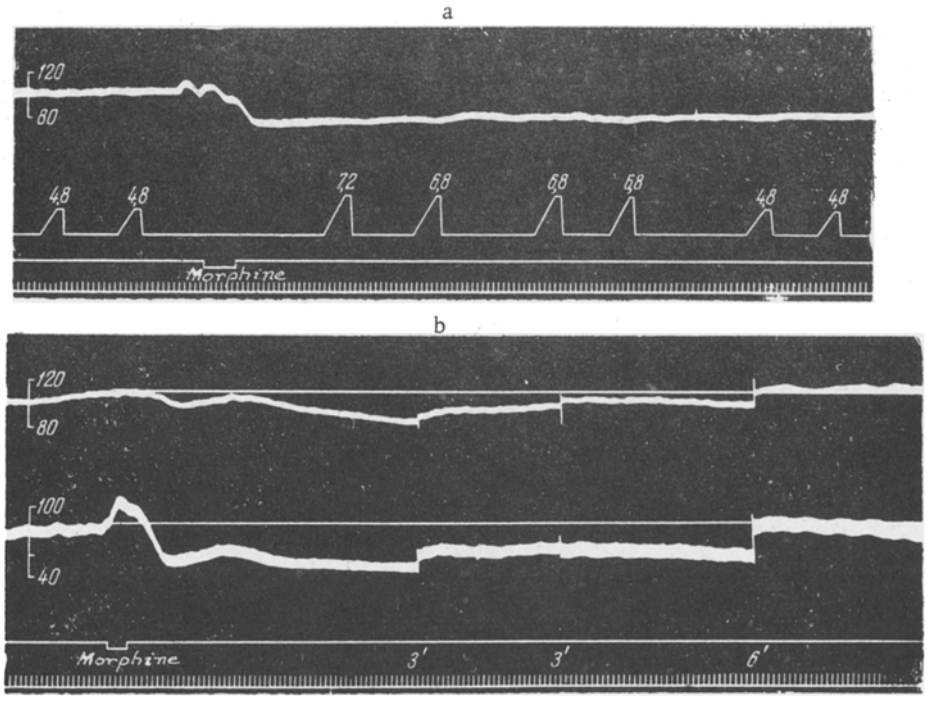

Fig. 2. The effect of morphine on the volume rate of outflow of blood from the coronary sinus (a) and on the tone of the coronary vessels (b). Significance of the curves (from above down): a) blood pressure, outflow of blood from the coronary sinus in ml/minute (height of the column — blood flow in 15 seconds, figures above the columns — minute volume of blood flow), marker of injection of morphine (3 mg/kg), time marker (5 seconds); b) perfusion pressure, reflecting the resistance of the vessels of the heart and its initial level, blood pressure and its initial level, marker of injection of morphine (2 mg/kg), time marker (5 seconds).

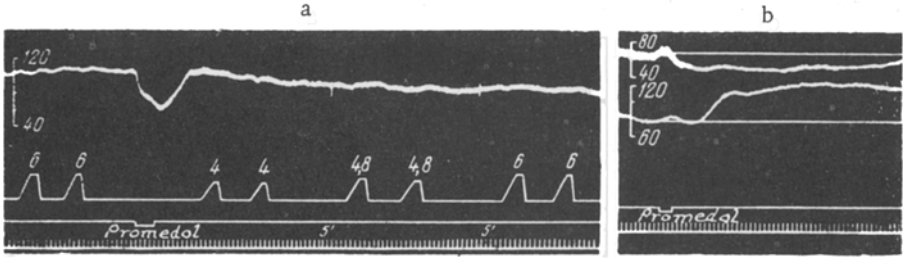

Fig. 3. The effect of promedol on the volume rate of outflow of blood from the coronary sinus (a) and on the tone of the coronary vessels (b). Significance of the curves as in Fig. 2, a and b respectively. The dose of promedol injected in (a) was 3 mg/kg, and in (b) 2 mg/kg.

The experiments thus showed that, of the analgesic drugs tested, only morphine possessed the power of augmenting the blood supply to the heart. Promedol and phenadon led in the majority of cases to a decrease in the volume rate of the coronary blood flow and to an increase in the tone of the coronary vessels. Thecodin caused no essential changes in the state of the coronary circulation.

Our findings do not, it seems, support certain clinical observations, according to which analgesics (for example, promedol) are effective in the treatment of angina pectoris [2 and others].

According to M. Yu. Ladinskaya's observations, however, analgesics lead to normalization of the

electrocardiographic changes caused by closure of the lumen of one of the coronary arteries. A temporary restriction of the blood flow in one of the coronary arteries may, we know, cause the appearance of reflex expressed by the development of spasm of the other vessels of the heart [10-12]. Taking these findings into consideration, it may be considered that the effectiveness of the majority of analgesics in angina pectoris is due not only to the suppression of the pain syndrome but also to suppression of these reflex reactions just described, and has nothing to do with the direct action of these drugs on the vessels of the heart.

Our findings, which indicate the possible aggravation of the blood supply of the myocardium by the use of promedol and phenadon, must be taken into consideration in clinical practice.

SUMMARY

The author studied the effect of analgesics (morphine, thecodin, phenadon and promedol) on the blood output from the coronary sinus and the tone of the coronary blood vessels in cats. Of the analgesics mentioned only morphine increases the cardiac blood supply . In the majority of cases the introduction of promedol and phenadon leads to a decrease of the volume velocity of the coronary blood flow, increasing the tone of coronary vessels. Thecodin exerts no material effect on the coronary circulation.

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* Original Russian pagination. See C.B. Translation.