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ON THE DECREASE OF MYOCARDIAL OXYGEN CONSUMPTION INDUCED BY CHLORACYZINE

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1 The effects of chloracyzine (2-chloro-10-(3-diethylaminopropionyl)-phenothiazine hydrochloride; antianginal drug) on myocardial oxygen consumption were studied in open-chest cats and cat isolated hearts using oximetry and polarography respectively.

2 It was found that chloracyzine produced a decrease in myocardial oxygen consumption accompanied by a reduction in coronary blood flow preceded by transient coronary dilatation. Chloracyzine produced an insignificant increase in arterial pressure; heart rate increased slightly in the open-chest experiments but not in the isolated heart.

3 It is suggested that reduced oxygen uptake after chloracyzine is realized through improved efficiency in the use of oxygen.

Introduction

The use of β-adrenoceptor blocking agents for the treatment of angina pectoris emphasizes the importance of reduction of cardiac oxygen expenditure in relief of this disease. Decrease of compensatory sympathetic drive after propranolol and hence of heart work, often results in heart failure in patients who are on the border-line of it. Reduction of the myocardial demand for oxygen, without reducing heart activity was found in our studies of 2-chloro-10-(3-diethylaminopropionyl)-phenothiazine hydrochloride (chloracyzine), synthesized and investigated at the Moscow Institute of Pharmacology (Vikhljaev & Kaverina, 1959; Zhuravlev, Gritsenko & Ermakova, 1968). It was shown to have spasmolytic properties and prevent or relieve spasms of the coronary vessels, on which grounds it was proposed as an antianginal drug. Besides its effect on the coronary vessels, it exhibits an atropine-like activity, some ability to increase arterial pressor responses to catecholamines, and a moderate antihistaminic effect. It has been marketed in the USSR for many years, and used for the treatment of angina pectoris.

In the course of a systematic survey of the effect of different antianginal drugs on myocardial oxygen consumption, chloracyzine was found to have particularly interesting properties in this respect. This paper is concerned with its effect on the oxygen balance of the heart.

Methods

Open-chest cat

The experiments were performed on cats weighing 3–4 kg, anaesthetized with pentobarbitone (40 mg/kg, i.v.) and respired with a pump. The heart was exposed through a left thoracotomy, heparin (1,500 iu/kg) being used as anticoagulant. Arterial pressure was recorded from the carotid artery with a mercury manometer. Outflow from the coronary sinus was collected with a plastic cannula inserted into the sinus orifice via the right auricle. The cannula was held in a fixed position by a suture that was passed around the coronary sinus and tied. This arrangement excluded contamination of sinus blood with mixed venous blood. The position of the cannula was checked post mortem. The coronary venous outflow was recorded continuously with a Gaddum flowmeter. The blood was returned to the femoral vein by a pump. Coronary oxygen saturation was recorded continuously by directing the coronary outflow through a cuvette connected to a transmission-type oximeter. The arterial haemoglobin oxygen saturation was determined by taking arterial samples in the course of the experiment. The haemoglobin oxygen saturation of the blood samples was measured with a haemoreflector and haemoglobin content was determined by a photometer. Myocardial oxygen consumption was calculated by multiplying the coronary venous flow by the arterio-venous difference in haemoglobin oxygen saturation and oxygen capacity of the blood (haemoglobin content in mg/100 ml blood $\times$ 1.34). The effect of chloracyzine (2 or 5 mg/kg, i.v.) was compared with that of two other coronary antispasmodics, aminophylline (3 or 7 mg/kg, i.v.) and prenylamine (1 or 2 mg/kg, i.v.).

Isolated heart

Under light ether anaesthesia the heart was quickly

removed, suspended in a Langendorff apparatus and perfused via the aortic root with oxygenated Krebs solution (kept at 37°C) at a constant pressure of 80 cm water. The coronary perfusate of the beating heart was collected and measured with a Gaddum recorder. Oxygen content in the coronary outflow and inflow were recorded polarographically in the following manner. Krebs solution was continuously directed to a cell which held two electrodes. One of them was a platinum wire 0.2 mm in diameter, insulated by a glass covering throughout its length except for a distance of 1 mm at the tip. It formed the cathode for determination of oxygen content. The reference electrode was a Ag–AgCl plate (5 × 5 mm). A polarizing source, adjusted to 0.6 V, and a recording device were connected between the reference electrode and the cathode. The oxygen electrode was calibrated by Krebs solution with known oxygen content (for details see Kisin & Buyanov, 1963). Chloracyzine (0.2 or 0.5 mg) was injected into the aortic root through a catheter. Student's *t*-test was used for statistical analysis of results.

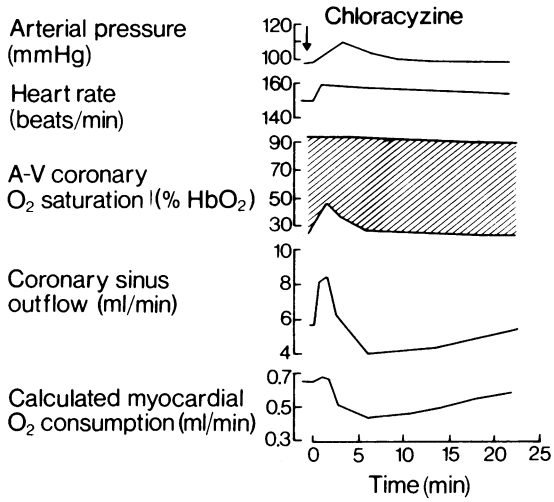

Figure 1 Effect of chloracyzine (5 mg/kg, i.v.) on myocardial oxygen consumption in open-chest cat.

Results

Open-chest cat

Chloracyzine induced a decrease in myocardial oxygen consumption (Figure 1). The decrease in oxygen uptake was 15% for a dose of 2 mg/kg and 26% for 5 mg/kg (Table 1). Coronary blood flow increased for 2–4 min and then was reduced in accordance with the level of myocardial oxygen consumption. Coronary sinus oxygen saturation was greatly increased during coronary dilatation. When coronary blood flow was reduced there were no significant changes in oxygen saturation. Despite the

Table 1 Effects of chloracyzine in the open-chest cat at the time of maximum decrease in myocardial O_2 consumption

	Chloracyzine 2 mg/kg, i.v. (9)		*Chloracyzine 5 mg/kg, i.v. (10)*	
	Control	*5 min after injection*	*Control*	*7 min after injection*
Myocardial O_2 consumption (ml/min)	0.90 ± 0.04	0.76 ± 0.05†	0.86 ± 0.05	0.64 ± 0.03‡
Arterial O_2 saturation (%HbO_2)	94 ± 4	95 ± 3 NS	96 ± 3	96 ± 3 NS
Coronary sinus O_2 saturation (%HbO_2)	27 ± 2	29 ± 2 NS	28 ± 2	31 ± 3 NS
Coronary sinus outflow (ml/min)	8.2 ± 0.4	7.0 ± 0.4†	7.8 ± 0.4	6.2 ± 0.5†
Mean arterial pressure (mmHg)	95 ± 6	97 ± 7 NS	90 ± 7	95 ± 8 NS
Heart rate (beats/min)	161 ± 8	169 ± 9 NS	165 ± 7	180 ± 8*

Values are mean ± s.e. mean. Number of experiments in parentheses.
* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

decrease in oxygen uptake after chloracyzine, the heart rate increased and mean arterial pressure was not reduced, in fact, it increased in many instances.

Aminophylline caused a pronounced and almost equal increase in myocardial oxygen consumption and coronary blood flow. Marked coronary dilatation induced by prenylamine was accompanied by an insignificant increase in oxygen uptake.

Isolated heart

Chloracyzine again reduced myocardial oxygen consumption. The decrease was 16% and 30% for doses of 0.2 mg and 0.5 mg respectively (Table 2). Coronary flow was also reduced (after an initial increase for the first 1–2 min) but to a smaller degree than myocardial oxygen consumption which resulted in a significant increase in coronary outflow oxygen content.

Discussion

In the open-chest preparation, the decrease in myocardial oxygen consumption after chloracyzine was chiefly due to reduction in coronary blood flow, while the reduced A–V O_2 difference played a role only in the initial stage. By contrast, the latter was the main factor for reduction in oxygen uptake in the isolated heart. A possible explanation for this difference is impairment, in the latter case, of the mechanism coordinating the coronary blood flow and myocardial oxygen consumption.

Chloracyzine was able to produce a small increase in mean arterial pressure; heart rate increased slightly in the open-chest experiments but not in the isolated heart. These effects can be attributed to the atropine-like action of chloracyzine and to its ability to augment the pressor action of catecholamines. Markova (1963) reported a tendency to increase cardiac output. All these findings indicate that despite the decrease in oxygen consumption, heart activity is at least not reduced. Chloracyzine thus increases the heart efficiency.

It was found previously that chloracyzine increases the coefficient of oxidative phosphorylation in homogenates of the myocardium of rats treated with this drug (Kisin, 1973). Ability of other phenothiazine derivatives to increase the efficiency of oxidative phosphorylation was also reported. Zubovskaya (1960) showed that mepazine and promazine when added to the homogenates of myocardium of the rabbit caused a rise in the P : O coefficient. Improvement in the process of formation of energy-rich phosphates is a possible explanation for the increase in heart efficiency after chloracyzine.

The decrease in myocardial oxygen consumption induced by chloracyzine as well as its spasmolytic properties may be responsible for the positive effect of this drug in angina pectoris (Kisin, 1973). It seems likely that the drug decreases myocardial oxygen uptake through improved efficiency in the use of oxygen. This approach may be of interest as in such a case a reduced oxygen uptake is not associated with reduced heart activity which is often undesirable.

I wish to thank Dr V. V. Buyanov for help in carrying out the experiments.

Table 2 Effects of chloracyzine in the isolated heart at the time of maximum decrease in myocardial O_2 consumption

	Chloracyzine 0.2 mg (7)		*Chloracyzine 0.5 mg (8)*	
	Control	*3 min after administration*	*Control*	*5 min after administration*
Myocardial O_2 consumption (μg/min)	202 ± 15	164 ± 11†	211 ± 14	148 ± 15‡
Coronary inflow O_2-content (μg/ml)	20 ± 2	20 ± 2	20 ± 2	20 ± 2
Coronary outflow O_2-content (μg/ml)	3.2 ± 0.2	4.9<0.4‡	3.5 ± 0.3	7.2 ± 0.7‡
Coronary outflow (ml/min)	12.1 ± 0.8	11.2 ± 0.7 NS	13.0 ± 0.6	11.5 ± 0.8*
Heart rate (beats/min)	120 ± 10	116 ± 11 NS	128 ± 9	122 ± 12 NS

Values are mean ± s.e. mean. Number of experiments in parentheses.
* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

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