EFFECT OF CALCIUM ANTAGONISTS ON BLOOD DEOXYGENATION

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In connection with the widespread use of calcium antagonists in the pharmacotherapy of ischemic heart disease, the investigation of their effects on the oxygen balance of the myocardium, which largely depends on fluctuations in the level of affinity of hemoglobin for oxygen [2, 5], is of great importance. Under physiological conditions oxygen is released from 30-35% of the oxyhemoglobin, indicating the existence of a significant reserve for possible additional supply of oxygen to the ischemic myocardium. A decrease in the affinity of hemoglobin for oxygen, according to the P_{50} test, by 2.0-4.2 mm Hg corresponds to an increase of 20-30% in the oxygen supply to the tissues [9, 10]. There is no information as yet in the literature on the effect of verapamil, and sensit on the affinity of hemoglobin for oxygen and on other parameters of the kinetics of blood deoxygenation [5, 7].

The effect of verapamil, nifedipine, and sensit on blood deoxygenation was studied, as being of possible interest for the future clinical study of the problem of the differential use of these calcium antagonists and allowing for this feature of their pharmacologic activity.

EXPERIMENTAL METHOD

The effect of the drugs on blood deoxygenation was studied by the method of polarographic coulometry [8], in our own modification [3, 6] and determination of the deoxygenation index (DIB) and the deoxygenation constant of the blood (DC). DIB was measured in conventional units as the change in electrolysis current at the time of semisaturation of the sample with oxygen. DC was obtained as the tangent of the angle of slope of the straight line reflecting the change in electrolysis current of the cell as a function of oxygen saturation of the sample, at the point corresponding to 50% deoxygenation. To standardize the measurements of DIB in each blood sample taken from a rat, the deoxygenation effect of 2,3-diphosphoglycerate (2,3-DPG), a natural modulator of the affinity of hemoglobin for oxygen, was first studied. Only those blood samples which gave a specific effect to injection of 2,3-DPG were used in the work. The calcium antagonists chosen for study were tested in concentrations of 10^{-8}-10^{-4} M, allowing for their possible concentration in the tissues of the body when the compounds were injected within the conventionally therapeutic dose range. Each group of experiments included 10 determinations of the test parameters of blood deoxygenation. The significance of differences between the experimental data and control was determined by Student's test.

EXPERIMENTAL RESULTS

The experimental results show that verapamil and nifedipine, in the concentrations tested, significantly lowered DIB compared with the control, evidence of the slowing of blood deoxygenation in response to the action of these drugs on erythrocytes (Table 1).

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TABLE 1. Effect of Verapamil, Nifedipine, and Sensit on Some Parameters of Blood Deoxygenation

Preparation	Blood deoxygenation of parameter	
	DIB	DC
Control	2,88±0,45	3,4±0,60
2,3-DPG, $5.9 \cdot 10^{-4}$ M	11,62±2,84*	10,8±1,2*
Verapamil, $4.3 \cdot 10^{-4}$ M	1,25±0,02*	3,3±0,40
Verapamil, $4.3 \cdot 10^{-5}$ M	1,17±0,03*	2,7±0,16
Nifedipine, $2.9 \cdot 10^{-7}$ M	1,05±0,03*	2,1±0,07*
Nifedipine, $2.9 \cdot 10^{-8}$ M	1,19±0,05*	2,4±0,19
Control	1,66±0,07	2,8±0,03
Sensit, $7.9 \cdot 10^{-7}$ M	2,96±0,11*	1,9±0,06*
Sensit, $7.9 \cdot 10^{-8}$ M	1,88±0,07*	1,8±0,08*

Legend. Asterisk indicates results differing statistically significantly from control.

Nifedipine in a concentration of $2.9 \cdot 10^{-7}$, besides reducing DIB, also reduced DC, evidence of a fall in the rate of blood deoxygenation and an increase in the affinity of hemoglobin for oxygen.

Sensit, in the concentrations studied, unlike verapamil and nifedipine, caused a small but significant rise of DIB with a clear tendency for the effect to increase with an increase in concentration of the drug. The deoxygenation rate (DC) fell at the same time, on the part of the deoxygenation curve corresponding to 50% blood desaturation (Table 1).

The results thus do not enable the specific features of the action of the calcium antagonists to be linked with their common effect on calcium metabolism or on their structure. Verapamil and sensit, which can be regarded as derivatives of the phenylalkylamine series, differ significantly in their effect on blood deoxygenation. On the other hand, verapamil and nifedipine, which belong to different groups of chemical compounds, possess a similar action on blood deoxygenation. The study of the effect of calcium antagonists on erythrocyte membrane permeability is of definite interest to the establishment of their mechanism of action on blood deoxygenation, for it has been shown that even under physiological conditions the rate of diffusion of 50% of the oxygen of oxyhemoglobin is quite high, namely 0.6 sec, and this figure is subject to considerable fluctuations [1, 4].

The characteristics of the action of calcium antagonists mentioned above must be taken into account when they are used in clinical cardiology, for inhibition of blood deoxygenation by preparations such as verapamil and nifedipine may aggravate oxygen deficiency. The fact that sensit has a stimulating effect on blood deoxygenation may make it a drug of preference for the treatment of arrhythmias associated with ischemic heart disease.

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