PHARMACOLOGY AND TOXICOLOGY

Effect of Nifedipine on Cerebral Saturation Parameters

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The effect of 10 mg nifedipine on cerebral oxygenation was studied in healthy individuals. The duration of investigation was 30 min or 3 h. Nifedipine appreciably increased cerebral oxygenation (by 5.9%, $p<0.01$) against the background of significant increase in heart rate and negligible decrease in systolic arterial pressure. Drowsiness was the most serious side effect of nifedipine (observed in 52.8% examined subjects).

Key Words: *calcium antagonists; nifedipine; drowsiness; cerebral oxymetry; cerebral saturation*

The mechanism underlying the effect of nifedipine is well studied. This drug belongs to dihydropyridine Ca^{2+} antagonists acting as peripheral vasodilators. The target of nifedipine effect is predominantly Ca^{2+} channels of vascular smooth muscle cells. This drug increases the tone of the sympathetic nervous system, thus accelerating heart rate.

Clinical use of dihydropyridine Ca^{2+} antagonists is based on these effects. They are used for the treatment of arterial hypertension [2], effort angina, vasospastic angina pectoris, and in cases when the underlying disease is associated with bradycardia. Today nifedipine is considered as an effective and safe drug.

We studied the effect of nifedipine on the state of cerebral oxygenation (CO).

MATERIALS AND METHODS

Nifedipine test was carried out in 36 individuals (17 men and 19 women) aged 23.80±3.57 years. Initial systolic blood pressure (BP) was 115-125 mm Hg (mean initial systolic BP 118.8±5.7 mm Hg), initial diastolic BP was 75-85 mm Hg (mean initial diastolic BP 79.2±4.8 mm Hg), initial heart rate 62-78 bpm (mean initial heart rate 71.3±5.3 bpm). None of the examined subjects was previously treated by nifedipine.

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Direct computer-aided cerebral oxymetry in the low infrared band was carried in all subjects using a mobile complex consisting of PC (Siemens 286/8MHz/HDD42) and Invos 3100 cerebral oxymeter (Somanetics).

Nifedipine test was carried out as follows. After recording CO values (%rSO_2) at rest for at least 10 min, the patients chewed 1 tablet of nifedipine (10 mg), after which observation was carried out for at least 30 min. Eight patients were observed for 3 h.

Statistical analysis was carried out by the method developed for statistical planning of biomedical experiments [4,5]. Mathematical calculations and statistical data processing were carried out using Excel 7.0 software. In addition to traditional method, an original program in the Excel 97 created for estimation of the main statistical constants (t and p) was used.

RESULTS

The initial CO values in normal subjects were 67.2±1.1%. Changes in CO after nifedipine treatment were similar in all subjects: it progressively increased 4 min after drug intake. The increase became significant by the 7th min (71.8±1.4%, $p<0.01$). Changes in CO between min 10 and min 30 were negligible (Fig. 1). The maximum increase in CO was 5.9% on average.

In 8 individuals the measurements were carried out in an intensive care ward for 3 h (197.2±7.2 min

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TABLE 1. Main Pharmacokinetic Characteristics of Nifedipine Dosage Forms

Parameter	Droplets in flasks, 0.1%	Corinfar dragee, 10 mg	Retard form, tablets (50 mg)
Maximum drug concentration in blood, ng/ml	123.93±33.90	46.88±12.00	33.88±12.60
Mean period of drug presence in blood, h	1.60±0.18	4.57±0.77	16.29±1.60

on average, Fig. 2). All these subjects gave informed consent to the study. No decrease in cerebral saturation was recorded in any of the cases; the parameters remained significantly high. Hence, no trend to recovery of the baseline values was observed.

Nifedipine induced changes in BP: 20 min after intake this parameter decreased to 112.3±4.4/61.2±3.5 mm Hg, but only the diastolic pressure changed significantly; heart rate increased to 91.06±1.32 bpm ($p<0.001$).

Side effects of the drug were observed in virtually all examined subjects. All complained of hot flushes and tachycardia. Objectively pronounced facial hyperemia was observed in all subjects. Eleven subjects noted numbness of the tongue. Headache, giddiness, pulsation and sensation of heaviness in the head were rare (8, 6, 8, and 3 cases, respectively). Drowsiness was observed in at least 19 subjects (52.8%).

Nifedipine can be used in cases when other drugs used for the treatment of cardiovascular diseases (other Ca^{2+} antagonists: verapamil and diltiazem; β-adrenoblockers [1]) are contraindicated.

The main dosage forms of nifedipine are drops, corinfar dragee (10 mg), and corinfar retard (50 mg; Table 1) [3].

Nifedipine concentration in the blood is detected as soon as 10-12 min after intake of corinfar dragee (10 mg). The mean concentrations of nifedipine during the onset and disappearance of the hypotensive effect during treatment by short-acting dosage forms are 35.2±7.4 and 6.5±5.1 ng/ml, respectively.

The rate of nifedipine release into systemic circulation determines the intensity of response. For example, rapid achievement of a certain concentration of the drug in the blood leads to a lesser decrease in diastolic BP in comparison with gradual increase in the drug concentration [6].

The most frequent side effects of nifedipine are hot flushes, skin hyperemia, tachycardia, headache, giddiness. These symptoms are primarily caused by arterial dilatation and reflectory increase of the sympathetic nervous system tone caused by these drugs.

Increase in CO values under the effect of nifedipine results from dilatation of cerebral arterioles. Pronounced facial hyperemia (particularly in patients never receiving nifedipine before) was observed in 100% cases.

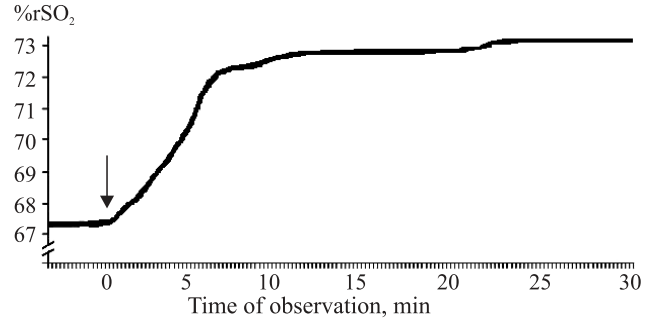

Fig. 1. Time course of cerebral oxygenation under the effect of nifedipine. Arrow shows the moment of drug intake.

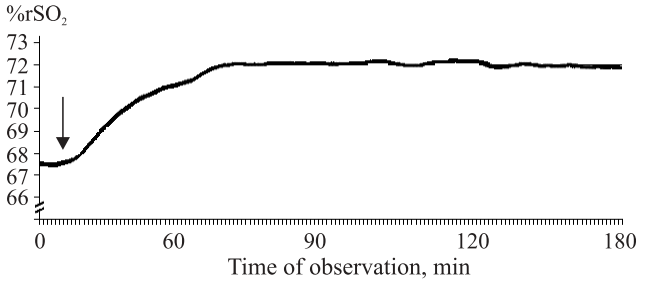

Fig. 2. Time course of cerebral oxygenation during long nifedipine test.

Hence, the effect of nifedipine on the arterial bed is not confined to its effect on heart vessels. It seems that nifedipine dilates large and resistive arteries and promotes rapid opening of collaterals.

Nifedipine rapidly and significantly increased CO values. Cerebral saturation remained elevated for at least 3 h after 10 mg nifedipine. One of side effects of nifedipine is drowsiness, which should be taken into consideration when prescribing the drug to patients working with mechanisms or whose work requires concentrated attention.

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