РАЗДЕЛ II. ФАРМАЦЕВТИКА**Lepyavka S.V., Safronenko A.V., Demidov I.A., Antonenko G.V.****Comparative analysis of the effectiveness of the use of benzodiazepines of various durations of action during premedication of patients with arterial hypertension and amiodarone-associated thyrotoxicosis***Rostov State Medical University Ministry of Health of Russia
(Russia, Rostov-on-Don)**doi:10.18411/spc-15-11-2018-07**idsp: 000001:spc-15-11-2018-07***Annotation**

In work on 51 patients, it was proved that in patients with arterial hypertension with cardiac arrhythmias and amiodarone-associated thyrotoxicosis, use of long-acting benzodiazepine diazepam in prolonged mode (three days before surgery) in combination with magnesium sulfate compared with short-acting benzodiazepine midazolam provides after premedication and immediately after surgery a more stable hemodynamic situation with limited blood pressure and heart rate variability.

Key words: premedication, thyrotoxicosis, amiodarone, benzodiazepines.

Introduction

Amiodarone is currently an effective and widely used drug for the treatment and prevention of life-threatening ventricular cardiac rhythm and other forms of cardiac arrhythmias [1]. However, like any pharmacological drug, it can cause unwanted effects from various organs. One of the most common side effects is a violation of the functional state of the thyroid gland, due to the pharmacological characteristics of the drug - a high content of iodine in its molecule [2]. The frequency of use of amiodarone in cardiology practice in the appointment of antiarrhythmic drugs reaches 24,1% [3]. The frequency of thyroid dysfunction when taking amiodarone ranges from 15% to 20% [4,5].

Due to the antiadrenergic activity of amiodarone and its blocking effect on the conversion of thyroxine to triiodothyronine, the classic symptoms of thyrotoxicosis - goiter, sweating, hand tremor, weight loss - can be expressed slightly or completely absent. The clinical picture is usually dominated by cardiovascular and mental disorders: deterioration of arrhythmias, angina pectoris in patients with coronary artery disease, dilated cardiomyopathy syndrome, manifested by a decrease in the pumping function of the heart and the appearance of heart failure [6], thyrotoxic encephalopathy (nervous excitability, emotional lability (nervous excitability, emotional instability, sleep disturbance) [1,7].

In such a complex clinical situation, the cardiac effects of an excess of thyroid hormones, the variability of systemic hemodynamics, and the lability of the patient's psyche, which manifest themselves in the postoperative period, are of serious danger [8]. One of the ways to eliminate the risk of unpredictable cardiovascular and mental reactions immediately after surgery in such a category of patients is a competent pharmacological organization of premedication [9].

The aim of the work was to reduce the risk of unstable hemodynamic reactions in patients with arterial hypertension and cardiac arrhythmias against the background of amiodarone-inducible thyroid dysfunction during the postoperative period due to pharmacological optimization of premedication.

Material and research methods

The study was conducted on 51 patients with arterial hypertension and type I amiodarone-associated thyrotoxicosis. All patients underwent neurosurgical operations in connection with the brain lesions, post-traumatic defects of the skull, degenerative-dystrophic diseases of the spine. Patients were monitored at the Department of Anesthesiology and Resuscitation №2 of the Rostov Regional Clinical Hospital, Department of Anesthesiology and Resuscitation №1, Therapeutic Department №2 of the Rostov State Medical University of the Ministry of Health of Russia.

Criteria for the inclusion of patients in the study were: hypertension; arrhythmias - ventricular and supraventricular arrhythmias, paroxysmal supraventricular tachycardias, refractory to antiarrhythmic drugs, except for amiodarone; taking amiodarone to treat arrhythmias; amiodarone-associated thyrotoxicosis type I; preparation for surgery. The exclusion criteria were dilated cardiomyopathy, chronic heart failure, amiodarone-associated thyrotoxicosis type II.

51 patients with arterial hypertension with type I amiodarone-associated thyrotoxicosis were divided into groups depending on the premedication scheme and the use of long-acting or short-acting benzodiazepines. Group 1 (n=30) - at the stage of preoperative preparation, patients received prolonged premedication (within three days before the operation) with long-acting benzodiazepines (diazepam) and magnesium preparations. Group 2 (n=21) - short-acting benzodiazepines (midazolam) were used in premedication.

In group 1, premedication was carried out with diazepam (three days before surgery at night per os 5-10 mg and 1 hour before anesthesia a 0,5% solution at a dose of 0,15 mg/kg intramuscularly. Additionally, magnesium sulfate 25% solution of 5 ml was injected.

In group 2, premedication was performed with midazolam 0,5% solution in a dose of 0,07-0,1 mg / kg intramuscularly 40-60 minutes before anesthesia.

In patients of the two groups, the risk of ASA did not exceed 3 points and was 2-3 points.

The age of patients in groups 1 and 2 ranged from 41 to 77 years, averaging $57,9 \pm 4,1$ years in group 1, $61,5 \pm 3,7$ years in group 2. In the 1st group of men there were 21 (70%) and women 9 (30%). In the 2nd group of male patients there were 14 (67%) and women - 7 (33%).

The monitoring of systolic blood pressure (DBP), diastolic blood pressure (DBP), an ECG at the postoperative stage made it possible to evaluate the effectiveness of various methods of sedation to reduce the risk of dangerous cardiovascular reactions.

Clinical methods were used in the work: an objective status assessment according to the classification of the American Society of Anesthetists (ASA), the level of sedation according to the Richmond scale of agitation and sedation (RAAS) and the Ramsay scale. The depth of sedation was monitored using BIS monitoring (A – 2000XP, Aspect Medical Systems, USA).

Blood pressure monitoring was carried out using the BPlab device (Petr Telegin, Nizhny Novgorod), and ECG monitoring was performed on the Valenta three-channel heart monitor (NPO Neo, St. Petersburg). To characterize the heart rate variability, the dynamics of mean square deviation (SDNN, Standart Deviation of all NN intervals) of the RR-intervals on the ECG were analyzed.

Statistical analysis of the results was performed using Statistica 10 (StatSoft, USA) using the module of descriptive statistics, frequency analysis, assessment of the reliability of differences in averages.

Results.

After premedication in group 1 in 22 (73%) and in group 2 in 15 (71%) patients, the level of sedation on the RAAS scale was 0 and –1 point. Patients noted slackness, maintained contact with the medical staff, noted a decrease in the “internal tremor” and anxiety, assessed their condition as “light”. In 8 (27%) patients in group 1 and 6 (29%) patients in group 2, the level of sedation on the RAAS scale was -2 and –3 points. Deepening sedation to level V and VI on the Ramsay scale, or -4 and -5 on the RAAS scale, was not observed in any patient after premedication.

Benzodiazepines are often used in premedication, because they quickly eliminate anxiety, intracranial pressure is reduced, have an anticonvulsant effect, reduce the need of brain neurons for oxygen provision, which together is important when performing neurosurgical operations. In addition, the price-quality ratio of benzodiazepines is cost-effective: with a low price of drugs, the power of sedation in patients is high. Magnesium preparations enhance the stress-protective effect of anxiolytics, as they regulate the transfer of excitation in the nervous system [10]. In the work of Fisher V.V. et al. [11] it was proved that magnesium preparations, as an addition to standard premedication, have a favorable effect on the functional state of the endothelium, regulate the intracellular content of magnesium and calcium ions, which allows them to be classified as means of protection against operational stress. With arterial hypertension, cardiac arrhythmias, amiodarone-associated thyrotoxicosis, the variability of integrative indicators of systemic hemodynamics is high, which ensures the instability and unpredictability of cardiovascular reactions. Thus, in patients of groups 1 and 2, the initial heart rate variability was low, as evidenced by the low values of the standard deviation of the duration of the cardiac cycle (SDNN) (Table 1). Low values of SDNN in patients of group 1 ($31,2 \pm 5,7$ ms) and group 2 ($33,5 \pm 4,9$ ms) indicated a high activity of sympathetic influence on the cardiac conduction system. High initial values of the heart rate (HR) in patients of groups 1 and 2 were also the result of changes in the regulation of heart activity (Table 1).

Table 1

The results of daily monitoring of blood pressure and ECG in patients of clinical groups before and after sedation with different tactics

Indicators	Group	Before premedication, M $\pm$ m	After premedication, M $\pm$ m	After operations, M $\pm$ m
SBP 24, mm Hg	1 (n=30)	140,2 $\pm$ 1,7	131,1 $\pm$ 2,3*	127,4 $\pm$ 2,5*
	2 (n=21)	142,2 $\pm$ 2,5	137,9 $\pm$ 2,1	135,4 $\pm$ 2,1*
	p ₁₋₂	>0,05	<0,05	<0,05
DBP 24, mm Hg	1 (n=30)	87,1 $\pm$ 2,3	78,1 $\pm$ 1,9*	76,2 $\pm$ 1,5*
	2 (n=21)	89,2 $\pm$ 1,9	86,7 $\pm$ 1,8	83,9 $\pm$ 1,7*
	p ₁₋₂	>0,05	<0,05	<0,05
HR 24, in minutes	1 (n=30)	82,4 $\pm$ 1,5	71,1 $\pm$ 1,6*	74,6 $\pm$ 1,8*
	2 (n=21)	81,9 $\pm$ 1,3	78,2 $\pm$ 2,2	77,7 $\pm$ 1,9
	p ₁₋₂	>0,05	<0,05	>0,05
SDNN, ms	1 (n=30)	31,2 $\pm$ 5,7	65,4 $\pm$ 6,2*	52,3 $\pm$ 4,2*
	2 (n=21)	33,5 $\pm$ 4,9	44,2 $\pm$ 5,8*	39,6 $\pm$ 6,1
	p ₁₋₂	>0,05	<0,05	<0,05

Note: * - significant differences compared with baseline values at $p < 0.05$

High initial rates of intravital, short-term and medium-term BP variability in patients of the two groups also indicated a high tone of sympathetic influences and instability of the hemodynamic situation. As a result, the anesthesiologist is faced with the difficulty of ensuring the safety of anesthesia for patients in this category due to the existence of a risk of both hypertensive and hypotensive unwanted vascular reactions. Reasonable sedation tactics can help avoid adverse effects on the patient's body when performing operations, as well as in the postoperative period.

Immediately after sedation in group 1, there was a statistically significant decrease in mean daily SBP, DBP, averaged HR values per day, as well as an increase in the variability of RR intervals (Table 1) compared with baseline data. In group 2, after sedation, only a significant increase in SDNN was observed. In the same observation period in patients of group 1, there was a sharp restriction of intravital variability of the SBP, short-term and medium-term variability of the SBP and DBP. In patients of group 2, after premedication, only the short-term variability of SBP and DBP was effectively reduced according to the results of the SMAP.

After surgery, in patients of group 1, compared with baseline values, there was not only an effective reduction in SBP, DBP, HR, but also intravital, short-term and medium-term BP variability. In group 2, compared with baseline values, only BP, DBP and their short-term variability decreased, while HR, SDNN, intravital and medium-term BP variability did not significantly change. The more pronounced and favorable dynamics of the studied parameters in group 1 led to the formation of statistically significant differences between SBP and DBP, SDNN, intravital variability of SBP, short-term BP variability in the use of long-acting benzodiazepines in the prolonged mode in combination with magnesium preparations compared to the single use of benzodiazepine depressants. No undesirable hypotensive reactions after sedation, during and after surgery were observed in one patient.

Thus, in a difficult clinical situation in patients with arterial hypertension with disturbed heart rhythm and type I amiodarone-associated thyrotoxicosis, use of long-acting benzodiazepine diazepam in a prolonged mode (three days before the operation) in combination with magnesium sulfate compared with short-acting benzodiazepine midazolam provides, after premedication and immediately after surgery, a more stable hemodynamic situation with limited variability of blood pressure and cardiac rhythm.

Conclusion

Patients with arterial hypertension and cardiac arrhythmias and amiodarone-associated thyrotoxicosis I type use long-acting benzodiazepines diazepam prolonged mode in combination with magnesium sulfate compared to benzodiazepine short-acting midazolam provides more effective reduction in blood pressure variability, increased variability of the duration of the cardiac cycle, which provides more stable and predictable hemodynamic reactions.

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