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EXPERIMENTAL STUDY

Comparison of the effects of I class antiarrythmics Ethmozine, Ethacizin on spectral characteristics of cardiac rhythm variability in rats

Popova E.P.*

I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Author

Ekaterina A. Popova, Ph.D., assistant professor at the department of pharmacology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia.

Summary

Objective

To investigate the change of spectral characteristics of heart rate variability of outbreed male rats under the influence of Class I antiarrhythmic drugs Ethmozine and Ethacizin.

Materials and methods

Heart rate variability was estimated using the method of spectral analysis assessed with the «Astrocard» equipment (Russia).

Results

We demonstrated that Ethmozine administration decreased the percentage of very low frequency (VLF) and increased the proportion of low (LF) and high (HF) frequency waves by 33% and 37%, respectively. Ethacizin decreased the total spectral power by 81% and consequently led to reduction of all spectral parts' amplitude: VLF, LF, HF oscillations were reduced by 83%, 73% and 87%, respectively. Analysis of spectral structure revealed the decrease of HF oscillations number by 37% and the increase of LF oscillations number by 17%.

Conclusions

Ethmozine increased the role of vegetative nervous system in cardiac rhythm regulation versus humoral factors without changing the interrelation between sympathetic and parasympathetic influences. Ethacizin decreased cardiac rhythm variability in our animal model, when ethmozine did not change heart rhythm variability. Ethacizin increased the influence of sympathetic nervous system on myocardium.

* Corresponding author: Tel. +7 (903) 208-58-35. E-mail: kispo-pharm@mail.ru

Key words
Variability of heart rate, class I ahtiarrhythmics, drug of class I, Ethmozine, Ethacizin.

Introduction

Lately the spectral analysis of cardiac rhythm variability (CRV) allowing estimation of humoral and vegetative factors' impact on chronotropic cardiac function attracts more and more attention of researchers due to its high informativity and relative simplicity [1, 2, 3, 4]. Studies dedicated to effective choice of medication based on such modern techniques like CRV analysis and electrocardiogram (ECG) [4, 5, 6] dispersion marking are of high interest. The use of spectral parameters for the choice of treatment of arterial hypertension, arrhythmias, myocardial infarction (MI), and other cardiovascular diseases (CVD) has been reported [6, 7, 8]. This method is being actively developed nowadays [1].

It is well-known that ischemia, MI, and stable ventricular tachycardia are associated with increased impact of sympathetic nervous system on the heart [9]. At the same time, it has been found that action of several antiarrhythmic agents could be weakened in presence of increased sympathetic influence on heart function. Experimental and clinical evidences demonstrated that antiarrhythmic action of I class antiarrhythmic agents [10, 11, 12] could be reduced or modified after isoproterenol infusion. It is known that CRV analysis may have an important role for the prognosis of CVD. Antiarrhythmic drugs are normally included into combined therapy of ischemia and MI and are used independently for treatment of various arrhythmias.

Antiarrhythmic agents Ethmozine and Ethacizin belong to Class I antiarrhythmics according to the Vaughan-Williams classification and represent ω-aminoacyl-derivatives of phenothiazine. Ethmozine has characteristics of Class IA and IB drugs, it does not influence myocardial contractivity and conductivity, does not decrease blood pressure [13, 14], and has moderate coronary-dilating effects, spasmolytic and M-cholinolytic action. Ethmozine is effective for treatment of extrasystoles, paroxysmal tachycardia, and atrial fibrillation [15]. Ethmozine has kinetic parameters of affinity to sodium channels similar with the Class IC drugs [16]. At the same thime Ethmozine blocks sodium channels in inactive condition like the drugs of IB class [13, 17]. Ethacizin reduces maximal reproducible frequency of atrial and ventricular contractions and is effective in aconitine model of arrhythmia [18]. It also reduces effectively the number of ectopic contractions in experimental model of MI in dogs [19], decreases the dimensions of ischemic area and improves coronary circulation [17, 18]. Electrophysiological studies demonstrated that Ethacizin blocks effectively not only fast entrance of sodium, but also slow entrance of calcium [17, 19]. Ethacizin is being effectively used for treatment of supraventricular and ventricular arrhythmias in clinic.

The objective of this study was to investigate the change of spectral characteristics of heart rate variability of outbreed male rats under the influence of Class I antiarrhythmic drugs Ethmozine and Ethacizin.

Materials and methods

Experiments were performed on wild-type male rats (weight 170–200 g). Animals were kept in cages (10 animals per cage) in vivarium at 12h light/dark cycle, 22–24 °C temperature, 60% humidity, and standard diet.

Animals underwent ECG registration using electrodes fixed on their chest with cuff. The «Poly-Spectrum-Rhythm» equipment (Russia) was used for ECG registration. ECG was registered during 5 minutes. Ethmozine and Ethacizin were administered intraperitoneally in dose 2 mg/kg and 1 mg/kg, respectively, in 0.2 mL volume 30 minutes before ECG registration. Control group animals were injected with 0.2 mL of physiological saline solution. CRV spectral analysis was performed after ECG registration. The above-mentioned equipment is used for measurement of major part of spectral analysis system [20]. We quantified the following parameters [20, 21]:

- RRNN, ms — average duration of RR interval;
- TP, ms^2 — total spectral power of RR interval oscillations;
- VLF, ms^2 — spectral power of RR intervals in very low frequency area;
- LF, ms^2 — spectral power of RR intervals in low frequency area;
- HF, ms^2 — spectral power of RR intervals in high frequency area;
- LFnorm, relative units (r.u.) — spectral power of RR interval in low frequency area expressed in r.u.;
- HFnorm, r.u. — spectral power of RR interval in high frequency area expressed in r.u. (relative values of each spectral component/(TP — VLF component));
- %VLF — % of VLF oscillations in TP;

- %LF — % of LF oscillations in TP;
- %HF — % of HF oscillations in TP.

We studied CRV characteristics in rats of control group (injected with physiological solution) and after Ethmozine or Ethacizin administration. Statistical analysis was done using one-factor dispersion analysis. Newman-Keuls test was used for estimation of differences between groups.

Results and discussion

1. Ethmozine effects on CRV spectral parameters in rats

Ethmozine did not cause significant change of TP (Table 1).

Ethmozine administration decreased VLf spectral power by 22 % and increased Lf spectral power by 64 % (Figure 1).

There was the trend of increased absolute values of HF spectral power. Analysis of spectral structure demonstrated the decrease of VLF proportion and the increase of LF and HF percentage by 33 % and 37 %, respectively. Thus, ethmozine decreased the role of humoral factors and increased the role of vegetative factors without changing TP characterizing CRV. The interplay between sympathetic and parasympathetic influences did not change significantly. Ethmozine administration did not result in significant change of the heart rate (HR).

2. Ethacizin effects on CRV spectral parameters in rats

Ethacizin decreased TP by 81 % and consequently reduced the power of VLF, LF, and HF spectral components by 83 %, 73 %, and 87 %, respectively (Figure 1). Spectral structure analysis demonstrated the decrease of HF percentage by 39 % and the increase of LF percentage by 17 %. Similar changes were registered with analysis of normalized spectral powers. Characteristics expressed in r.u. demonstrated the

Table 1. **Change of statistical parameters and spectral characteristics of CRV in rats after Ethmozine (2 mg/kg, intraperitoneally) and Ethacizin (1 mg/kg, intraperitoneally) (n=10).**

Parameters	Control group	Ethmozine	Ethacizin
Statistical parameters			
1. RRmin, ms	118.3±1.75	118.5±4.7	117.7±3.84
p*		>0.05	>0.05
2. RRmax, ms	156.8±9.3	162.3±11.7	149.9±12.9
p*		>0.05	>0.05
3. RRNN, ms	133.8±5.8	131.8±4.4	130.4±4.87
p*		>0.05	>0.05
4. CV, %	4.3±1.8	5.3±1.33	3.9±1.05
p*		>0.05	>0.05
Spectral characteristics			
5. TP, ms2	277±15.5	277.4±79.3	53.19±10.9*
p*		>0.05	0.0001
6. VLF, ms2	205.5±16.3	160.9±53*	35.1±8.07*
p*		0.02	0.0001
7. LF, ms2	59.8±9.25	97.9±35.7*	16.4±4.3*
p*		0.004	0.0001
8. HF, ms2	12.5±4.25	18.7±8.6	1.6±0.56*
p*		>0.05	0.0001
9. LF norm, r.u.	82.8±1.8	83.9±4.8	89.9±4.9*
p*		>0.05	0.0001
10. HF norm,r.u.	17.2±1.8	16.1±4.8	9.8±4.37*
P*		>0.05	0.0001
11. LF/HF	4.96±0.7	5.6±1.7	10.6±3.8*
p*		>0.05	0.0001
12. %VLF	68.1±5.1	57.9±7.9*	65.9±5.9
p*		0.003	>0.05
13. %LF	26.4±4.1	35.1±7.3*	30.98±5.7
p*		0.004	>0.05
14. %HF	5.12±1.27	7±2.1*	3.1±0.98*
p*		0.026	0.0001

RRmin, ms — minimal duration of RR interval;
RRmax, ms — maximal duration of RR interval;
RRNN, ms –average duration of RR interval;
* significance of differences between Ethmozine and Ethacizin groups and control group.

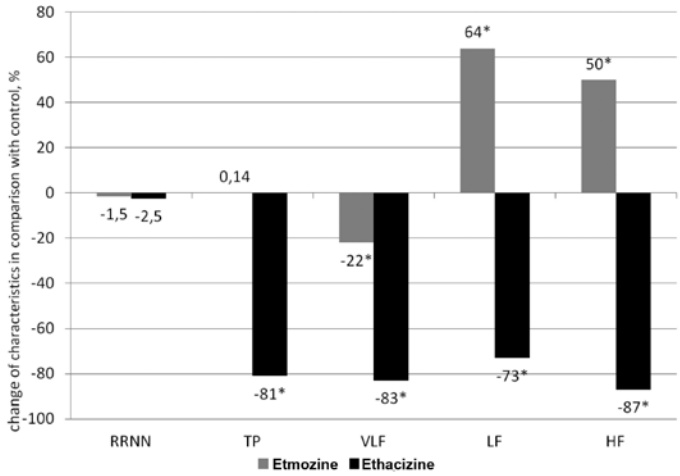

Figure 1. Ethmozine (2 mg/kg, intraperitoneally) and ethacizin (1 mg/kg, intraperitoneally) effects on CRV spectral characteristics in rats (n=10).
* — p<0.05

change of LF and HF spectral powers and did not consider changes of VLF component thus reflecting the interplay between sympathetic and parasympathetic vegetative nervous system. Ethacizin increased Lf spectral power by 8.6 % and decreased Hf spectral power by 43 %. Ethacizin caused evident decrease of CRV, increased sympathetic influence on myocardium and decreased the role of vagus nerve on cardiac rhythm regulation. Ethacizin did not change HR.

Ethacizin significantly reduced CRV in rats, whereas Ethmozine had no effect on this parameter. Significant decrease of CRV after Ethacizin administration comparing with Ethmozine is probably related to its ability to block calcium channels. There are evidences of strong negative modulation of CRV by calcium channel blockers [6]. It is worth to point out that Ethacizin decreases vagus nerve effects on animal heart and incrases sympathetic activity. Ethacizin does not change the influence of humoral factors on cardiac rhythm. Ethmozine increases the role of vegetative nervous system on chronotropic cardiac function if the role of humoral factors is lowered. At the same time the interrelation between sympathetic and parasympathetic influences remains unchanged.

Conclusion

Ethacizin decreases CRV in rats, whereas Ethmozine does not change this parameter.

Ethacizin administration leads to increased sympathetic activity of myocardium in experimental animals without significant change of humoral factors role in cardiac rhythm regulation.

Ethmozine administration decreased the influence of humoral regulation of cardiac rhythm. The role of vegetative nervous system increases, but the interrelation between sympathetic and parasympathetic effects remains unchanged.

Conflict of interest: None declared

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