# Peculiarities of Cardiotropic Effect of Aconitine

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In experiments on anesthetized cats, aconitine produced direct arrhythmogenic and cardiotoxic effects on the myocardium combined with indirect cardiotropic effects mediated via activation of extracardial nerves. Aconitine demonstrated pronounced cholinolytic properties and blocked vagal arrhythmogenic effect.

**Key Words:** *aconotine; cardiotropic effect; arrhythmogenic effect; antiarrhythmic effect*

Among the methods recommended by Pharmacological Committee of the Russian Federation to model cardiac arrhythmia [2,4], the most efficient is intravenous injection of aconitine in a dose of 20-40 μg/kg [1-4,10]. Aconitine potentiates activation of fast sodium channels [5] and promotes self-excitation of contractile cardiomyocytes [2]. However, cardiac rhythm disturbances are induced by aconitine even in small doses (2-4 μg/kg), when it is injected suboccipitally into the cerebrospinal fluid, which attests to the presence of a neurotropic component in the mechanisms of aconitine-induced arrhythmia [6]. We hypothesized that aconitine can modulate vagus-induced atrial fibrillation (AF) [8,9] also recommended by Pharmacological Committee as the model for testing new antiarrhythmic preparations [4]. Our aim was to study the effect of aconitine on cardiac function against the background stimulation of the vagus nerve (VN).

## MATERIALS AND METHODS

Experiments were carried out on 11 artificially ventilated temperature-controlled (37°C) cats (body weight 2.5-3.5 kg) anesthetized with chloralose and nembutal (75+15 mg/kg). Vagal AF was induced by paired transvenous stimulation of the right atrium (5 msec, 4-fold threshold, 25 Hz) against the background of persistent stimulation of the cervical portion of VN (2 msec, 6-fold threshold, 40 Hz) [8,9] performed with an ESU-2 stimulator (Kursk). Intracardial ECG was recorded with a cardiointervalometer [7] coupled with an N338-2 recorder (Krasnodar); visual control was performed with an IM-789 8-channel indicator (Ukraine). Aconitine was injected intravenously in fractions of 5 μg/kg every 10 min. In series I ($n$=6), β-adrenoceptors were not blocked, while in series II ($n$=5) β-adrenoceptors were preliminary blocked with intravenous propranolol (1 mg/kg). *P-P* and *P-Q* intervals on the ECG, effective atrial refractory period, AF duration, and vagus-induced chronotropic effect (CE) were determined at the beginning of the experiments and between aconitine injections. The degree of CE was assessed by prolongation of *P-P* interval during stimulation of VN by train of 3 pulses (2 msec, 6-fold threshold, 40 Hz) applied synchronously with *P*-wave. The data were statistically analyzed using the method of direct and indirect differences.

## RESULTS

Initial values of *P-P* and *P-Q* intervals, effective refractory period, vagal CE, and AF duration were 356±8, 76±4, 140±6, 290±24 msec, and 127±5 sec, respectively. In all experiments the first injection of aconitine (5 μg/kg) considerably decreased ECG amplitude, vagal CE, and AF duration (Table 1), but provoked no spontaneous disturbances of the cardiac rhythm, which attests to activation of sympathetic and parasympathetic structures by aconitine and its marked cholinolytic activity blocking the arrhythmogenic effect of VN.

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**TABLE 1**. Cardiotropic and Neurotropic Effects of Aconitine (*M±m*)

| Parameter, % of initial value | Experimental series | Aconitine dose, μg/kg | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 5 | 10 | 15 | 20 | 25 |
| *P-P* | I | 100 | 101.6±2.1 | 98.8±1.9 | 98.8±2.2 | 100.6±4.7 | 111.1±14.3 |
| | II | 129.6±4.9 | 141.3±8.0* | 147.8±8.1* | 151.4±8.3* | 152.4±11.2* | — |
| *P-Q* | I | 100 | 99.5±0.5 | 99.6±1.9 | 96.4±3.6 | 101.1±1.7 | 102.5±2.5 |
| | II | 100 | 104.0±3.6 | 103.0±4.3 | 107.9±6.3 | 99.4±4.5 | — |
| Effective refractory period | I | 100 | 101.9±3.4 | 106±6 | 103.4±7.7 | 96.2±9.8 | 101.0±14.5 |
| | II | 118.0±5.6 | 122.9±9.5 | 127.8±10.0 | 135.7±7.6* | 131.7±16.5 | — |
| Vagal CE | I | 100 | 61.0±10.4* | 35.2±5.6* | 23.9±3.0* | 16.0±4.4* | 9.4±3.3* |
| | II | 75.2±6.7 | 57.1±8.0* | 46.5±13.4* | 48.2±14.8* | 34.5±24.7* | — |
| AF duration | I | 100 | 21.1±10.9* | 15.6±7.7* | 14.0±6.6* | 16.6±9.3* | 12.2±10.8* |
| | II | 55.6±5.9 | 24.2±13.0* | 15.9±12.4* | 0±0* | 0±0* | — |

**Note.** *$p<0.05$ compared to the control (without aconitine).

Increasing of the total dose of aconitine to 10 μg/kg induced short-term episodes of spontaneous atrial and/or ventricular arrhythmia in 2 cats in series I and in 2 cats in series II. Therefore, aconitine in this dose exerts a direct arrhythmogenic effect independent on β-adrenoceptor activity. When applied in a dose of 15 μg/kg, aconitine provoked diverse cardiac rhythm disturbances occurring against the background of decreased ECG amplitude. In series I, intravenous propranolol (1 mg/kg) injected 25-30 min after the first dose of aconitine caused immediate death of 2 cats. Other 4 cats died without propranolol when the dose of aconitine was increased to 28±1 μg/kg. In series II, the mean lethal dose of aconitine was 23±1 μg/kg ($p<0.05$). Significant decrease of aconitine lethal dose under conditions of propranolol β-adrenoceptor blockade attests to a potentiating effect of sympathetic nerves on aconitine-treated myocardium. The blockade of β-adrenoceptors not only promoted death, but essentially changed the course of the experiment (Table 1). For example, in series I aconitine decreased AF duration without affecting the *P-P* interval. In series II, the decrease in AF duration was more pronounced, while *P-P* interval increased with increasing the dose of aconitine.

Short-term AF in series I at high doses of aconitine and its earlier elimination under conditions of β-adrenoceptor blockade attest to the involvement of sympathetic nerves in induction of fibrillation with 2-pulse atrial stimulation.

Despite considerable disturbance of cardiac activity induced by aconitine, it did not affect the duration of *P-Q* interval.

Thus, the toxic and arrhythmogenic effects of aconitine result from direct myocardial and indirect neural activities of this agent, which should be taken into consideration when assessing cardiotropic, neurotropic, and antiarrhythmic potencies of drugs tested using the model of aconitine-induced arrhythmia.

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