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Anti-arrhythmic effects of sophoridine and oxysophoridine

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KEY WORDS sophoridine; oxysophoridine; arrhythmia; myocardial contraction; heart atrium; myocardial ischemia; ventricular fibrillation

ABSTRACT

AIM: To compare the effects of oxysophoridine (Oxy) and sophoridine (Sop) on experimental arrhythmias and myocardial physiologic properties. **METHODS**: Arrhythmias were induced by drugs and myocardial ischemia. Physiologic properties were determined on isolated heart atria. **RESULTS**: Oxy 500 mg·kg^{-1} (1/6 LD_{50}) decreased the incidence of ventricular arrhythmias induced by aconitine ($P < 0.01$), increased the threshold dose of ouabain-induced ventricular premature (VP, $P < 0.05$), ventricular tachycardia (VT, $P < 0.05$), ventricular fibrillation (VF, $P < 0.01$), and cardiac arrest. ($P < 0.01$). After iv Oxy 500 mg·kg^{-1} into the rats with ligation of left anterior descending coronary artery, the total numbers of ectopic beats were decreased ($P < 0.05$), the incidence of VF was lowered, and the duration of VT was shortened ($P < 0.01$). Oxy 250 mg·kg^{-1} (1/13 LD_{50}) iv shortened the duration of arrhythmias induced by $BaCl_2$ ($P < 0.01$) and delayed the onset of arrhythmias induced by chloroform-epinephrine ($P < 0.05$). Oxy produced dose-dependent positive inotropic effects in the isolated left atria of guinea pigs, increased the concentration of epinephrine to elicit automaticity in left atria, decreased slightly the excitability, and prolonged the functional refractory period. Sop produced the similar effects on arrhythmias as Oxy. **CONCLUSION**: Oxy produced the similar anti-arrhythmic effects as Sop did at the equivalent effective dose.

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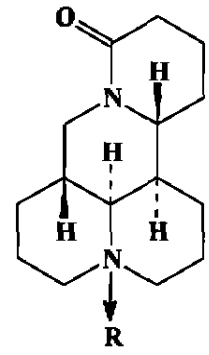
INTRODUCTION

Oxysophoridine (Oxy) and sophoridine (Sop) are alkaloids isolated from *Sophra alope* L. Sop produced anti-arrhythmic effects[1-3], and the mechanism is similar to that of amiodarone[4]. Up to now, we have not found any report of Oxy on arrhythmias. This paper was to study the effects of Oxy and Sop on experimental arrhythmias and the physiologic properties in isolated heart atrium.



R = H Sophoridine
R = O Oxysophoridine

MATERIALS AND METHODS

Chemicals and reagents Oxy and Sop were extracted from *Sophora slope* L by Ningxia Pharmaceutical Institute. Oxy (white powder, M_r 264, mp 162 ℃, purity > 99 %) and Sop (white crystal, M_r 248, mp 109 ℃, purity > 99 %) were dissolved in K-H solution before use. Aconitine (Aco) was the product of E Merck. Ouabain (Oua) was the product of Sigma.

Animals Animals were purchased from Animal Center, Beijing Medical University. Kunming strain mice (Grade Ⅱ, Certificate № 01-1058); Wistar rats (Grade Ⅱ, Certificate № 01-1051).

Drug-induced arrhythmias Kunming strain

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mice of either sex ($n = 60$, weighing 24 g ± s 3 g) were divided into 3 groups and anesthetized with urethane 1 g·kg^{-1} ip. Five min after Oxy 500 mg·kg^{-1}, Sop 10 mg·kg^{-1} or equal volume of saline (NS) were injected ip, Aco (0.001 %, 50 μg·kg^{-1}) was injected via caudal vein. the changes of cardiac rhythm were recorded by oscilloscope and ECG for 30 min.

Wistar rats of either sex ($n = 21$, weighing 380 g ± s 66 g) were divided into 3 groups randomly and anesthetized with urethane 1.2 g·kg^{-1} ip. Ten min after NS, Oxy, Sop were injected ip, $BaCl_2$ 2 mg·kg^{-1} was infused via femoral vein in 4 s, Lead Ⅱ ECG was monitored and recorded.

Rabbits of either sex ($n = 15$, weighing 1.6 kg ± s 0.2 kg) were selected. After inhalation of chloroform and iv epinephrine (0.01 %, 0.5 mL·kg^{-1}), the ECG of the selected rabbits appeared ventricular tachycardia (VT). After VT lasted 205 s ± 52 s, sinus rhythm restored. The selected rabbits were divided into 3 groups. After iv Oxy 250 mg·kg^{-1}, Sop 10 mg·kg^{-1}, or NS, the rabbits inhaled chloroform and were injected epinephrine in the same way and same doses, the changes of cardiac rhythm were recorded by oscilloscope and ECG for 30 min.

Guinea pigs of either sex ($n = 18$, weighing 346 g ± s 43 g) were divided into 3 groups and anesthetized with urethane. Ten min after iv Oxy, Sop, or equal volume of NS, Oua 50 μg·kg^{-1} was injected iv in 1 min. After that, Oua (0.05 %, 5 μg·kg^{-1}) was infused at a constant rate of 5 μg·min^{-1}. Lead Ⅱ ECG was monitored to record the appearance of ventricular premature (VP), VT, ventricular premature (VF), and cardiac arrest (CA).

Myocardial ischemia-induced arrhythmias Wistar ♀ rats ($n = 24$, weighing 337 g ± s 30 g) were divided into 3 groups. After Oxy, Sop, or NS was injected via femoral vein, the pericardium was incised to expose the left anterior descending coronary artery, which was ligated at the level of the left atrial appendage. Lead Ⅱ ECG was recorded for 30 min.

Isolated preparations Guinea pigs of either sex ($n = 26$, weighing 439 g ± s 76 g) were stunned by a blow to the head. The left or right atria were suspended vertically under 1.0 g of tension, and incubated in a bath containing 20 mL of Tyrode's solution (pH 7.3 – 7.4). The solution was gassed with 95 % O_2 + 5 % CO_2, and maintained at 30 ℃ or 37 ℃.

Determination of physiologic properties of isolated heart atria Left atria preparations were stimulated through a pair of stainless steel electrodes and stimulus set at frequency of 1.0 Hz, duration of 3 ms, 2 times of threshold voltage to induce heart atria contraction. After 60-min equilibration, Oxy or Sop was added into the solution by accumulated method until the contractile altitude increased no more[5]. The final concentrations of Oxy and Sop were 7.2 mmol·L^{-1} and 240 μmol·L^{-1}, respectively. The contractile altitude curve was recorded.

The threshold concentration of epinephrine inducing automaticity on left atria preparations were determined[6]. The preparations ($n = 7$) were exposed to serial concentration of epinephrine for 3 min to determine the minimal concentration of inducing automaticity. If no contraction was induced, electric stimulation was given for 30 s at the end of the third min. The lowest epinephrine concentration of inducing contraction was threshold concentration. Only preparations for which the threshold concentration of epinephrine was identical on two successive trials were used for further tests. The preparations were washed and equilibrated for 15 min, then exposed to Oxy or Sop for 10 min. Adrenaline concentration of inducing automaticity was determined.

The left atrium preparations were stimulated by a series of square wave of different width (0.2, 0.5, 1, 3, 5, 10 ms), and the maximal voltage inducing contraction was determined, according to the proctocal, intensive-time curve was drawn[7].

The left atrium preparations ($n = 7$) were stimulated by 2 strong stimulus of 3 ms, 0.5 Hz, 5 times as threshold voltage. The shortest interval between the driving stimulus and testing one which just produced a premature contraction of the muscle was taken to be the functional refractory period[7].

RESULTS

Acute toxicity In 100 Kunming mice (20 g ± 1.5 g), LD_{50} (95 % confidence limits) of Oxy and Sop were 3391 (2799 – 3565) mg·kg^{-1} and 58 (57 – 59) mg·kg^{-1}, respectively.

Arrhythmias induced by Aco in mice In all

mice of the control group ($n = 20$) serious arrhythmias occurred. But in Sop or Oxy group, only 7 mice developed arrhythmia ($P < 0.01$).

Arrhythmias induced by $BaCl_2$ in rats Oxy 250 mg · kg^{-1} shortened the duration of ventricular arrhythmias from (7.8 ± 2.5) min to (2.8 ± 2.2) min ($P < 0.01$). Sop 10 mg · kg^{-1} shortened the duration of ventricular arrhythmias from (7.8 ± 2.5) min to (2.9 ± 1.1) min ($P < 0.01$).

Arrhythmias induced by chloroform-epinephrine in rabbits In control group, the appearance time of VT was 5 s ± 2 s, the duration of VT was 191 s ± 47 s. The onset of VT was 24 s ± 17 s in Oxy group and 11 s ± 4 s in Sop group; the duration of VT was 100 s ± 20 s in Oxy group and 60 s ± 28 s in Sop group (All $P < 0.01$).

Arrhythmias induced by Oua in guinea pigs In Oxy and Sop group, the doses of Oua inducing VP, VT, VF, and CA were different from those of control (Tab 1).

Tab 1. Effects of oxysophoridine and sophoridine on ouabain-induced ventricular premature (VP), ventricular tachycardia (VT), ventricular fibrillation (VF), and cardiac arrest (CA). $n = 6$ guinea pigs. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

Drug/ mg·kg^{-1}		Ouabain dose/mg·kg^{-1} VP	VT	VF	CA
NS		130 ± 5	161 ± 36	199 ± 35	226 ± 33
Oxy	500	206 ± 34^b	238 ± 55^b	304 ± 56^c	342 ± 62^c
Sop	10	174 ± 26^b	237 ± 40^c	298 ± 223^c	336 ± 14^c

Myocardial ischemia-induced arrhythmias In Oxy and Sop groups the appearance time of VP was delayed; the total numbers of EB, the total time of VT, and the incidence of VF were decreased, compared with those of the control (Tab 2).

Effect on contractility Oxy and Sop produced concentration-dependent positive inotropic effects, and the doses of 50 % increasing contractile amplitude were 3.5 mmol · L^{-1} and 102 μmol · L^{-1}, respectively (Tab 3).

Effect on automaticity The threshold concentration of epinephrine inducing automaticity was (96 ± 37) μmol·L^{-1}. In Oxy group, it was (48 ± 18) μmol·L^{-1} ($P < 0.05$); in Sop group, it was (57 ± 27) μmol·L^{-1} ($P < 0.05$). Both Oxy and Sop decreased the thresholds of epinephrine.

Tab 2. Effects of Oxy and Sop on arrhythmias after acute coronary artery ligation in rats. $n = 8$ rats. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

Drug/ mg·kg^{-1}		Onset time of VP/s	Number of ectopic beats in 30 min	Duration of VT/s	VF /%
NS		330 ± 135	1406 ± 975	59 ± 28	75
Oxy	500	397 ± 90^a	483 ± 413^b	17 ± 13^c	12.5
Sop	10	450 ± 84^a	404 ± 291^b	22 ± 14^c	12.5

Tab 3. Effects of Oxy and Sop on myocardial contraction of left and right atria isolated from guinea pigs. $n = 6$ guinea pigs. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$, *vs* control.

Concentration	Developed tension/mm Left atrium	Right atrium
Oxy/mmol·L^{-1}		
0	5.5 ± 0.6	3.7 ± 1.0
0.95	6.5 ± 0.7^b	4.4 ± 1.4^b
1.9	7.9 ± 2.0^b	4.8 ± 1.8^b
3.8	8.4 ± 2.2^b	5.4 ± 2.0^b
7.2	9.8 ± 2.8^c	6.1 ± 2.2^c
Sop/μmol·L^{-1}		
0	5.5 ± 2.3	4.0 ± 1.4
30	6.8 ± 2.7^c	4.9 ± 1.9^c
60	7.8 ± 3.3^c	5.7 ± 2.1^c
120	8.8 ± 3.7^c	6.1 ± 2.4^c
240	10.0 ± 5.0^c	6.6 ± 2.5^c

Effect on excitability After Oxy 1.9 and 3.8 mmol·L^{-1}, Sop 60 and 120 μmol·L^{-1} were added, the maximal voltages inducing myocardial contraction were increased ($P < 0.05$, or $P < 0.01$). The excitability of heart atria was decreased (Tab 4).

Effect on FRP Before Oxy and Sop were added, FRP were 140 ms ± 21 ms and 143 ms ± 14 ms, respectively. After the preparations were exposed to Oxy 1.9 and 3.8 mmol·L^{-1}, FRP were 164 ms ± 23 ms and 170 ms ± 23 ms ($P < 0.01$), respectively. In Sop 60 and 120 μmol·L^{-1} 10 min, FRP were 161 ms ± 18 ms and 165 ms ± 16 ms ($P < 0.01$), respectively.

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Tab 4. Effects of Oxy and Sop on minimal voltage inducing myocardial contraction by electric stimulus in left atrium. $n=6$ guinea pigs. $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$, *vs* control.

Duration/ms	Control	Intensity of stimulus/V			
		Oxy (mmol·L^{-1})		Sop (μmol·L^{-1})	
		1.9	3.8	60	120
0.2	1.6±0.6	2.1±0.6^a	2.4±0.8^b	1.8±0.5^a	2.0±0.6^b
0.5	1.2±0.4	1.7±0.3^c	1.9±0.9^b	1.4±0.4^a	1.6±0.5^b
1	1.0±0.2	1.3±0.3^c	1.6±0.6^b	1.3±0.3^c	1.3±0.3^c
3	0.8±0.2	1.2±0.3^b	1.3±0.4^c	1.1±0.3^c	1.1±0.3^b
5	0.7±0.2	1.0±0.4^b	1.1±0.4^c	0.9±0.3^b	1.0±0.3^b
10	0.6±0.2	0.9±0.3^b	1.0±0.4^b	0.8±0.3^c	0.9±0.3^b

DISCUSSION

Oxy and Sop belong to quinolizidine alkaloids, and have similar chemical structure. Sop produced the anti-arrhythmic effects by inhibiting Na^+ channel, prolonging ERP, increasing ERP/APD, and inhibiting β-adrenoceptors noncompetitively, and the mechanism is the same as that of amiodarone[2,4]. This study indicated that they had similar anti-arrhythmic effects and similar physiologic properties on isolated heart atria. But the toxicity of Oxy (oxidized product of Sop) was lower than that of Sop. In this study, Oxy at the dose of 1/6 LD_{50} and 1/13 LD_{50} produced the similar effects as Sop at the dose of 1/5 LD_{50}. In the study of Oxy and Sop on isolated heart atria, we found that Oxy and Sop decreased the threshold of epinephrine inducing heart atria contraction. It indicated that Oxy and Sop enhanced the automaticity of isolated heart atria, which is contrary to the anti-arrhythmic effects in whole animals. The mechanism of Oxy on arrhythmias and whether it has other effects need to be further studied.

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517-520

槐定碱和氧化槐定碱的抗心律失常作用

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关键词 槐定碱；氧化槐定碱；心律失常；心肌收缩；心房；心肌缺血；心室纤颤

目的：研究氧化槐定碱（Oxy）和槐定碱（Sop）对试验性心律失常的作用以及对心肌生理特性的影响. **方法**：应用各种心律失常模型观察药物对实验性心律失常的作用；离体心肌实验法观察药物对心房生理特性的影响. **结果**：Oxy 500 mg·kg^{-1} iv 对抗乌头碱，哇巴因和结扎冠状动脉左前降支诱发的室性心率失常，使室性异位搏动数减少（$P<0.05$），室速持续时间缩短（$P<0.01$），室颤的发生率由 75 % 减少到 12.5 %. 其作用与 Sop 10 mg·kg^{-1}产生的结果相似. Oxy 250 mg·kg^{-1} iv 对抗氯化钡和氯仿-肾上腺素诱发的心率失常，此作用与 Sop 10 mg·kg^{-1}产生的作用相似. Oxy，Sop 均有提高自律性、降低兴奋性及延长功能不应期的作用. **结论**：Oxy 与 Sop 在等效剂量时，有相似的抗心律失常作用. （责任编辑 杨雪芳）