PHARMACOLOGY AND TOXICOLOGY

Effect of Suphan, Lidocaine, and Their Combination on Early Occlusion and Reperfusion Arrhythmias in Cats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 5, pp. 545-547, May, 1997
Original article submitted January 29, 1996

It is shown that the nonglycoside cardiotonic drug suphan exhibits antiarrhythmic and antifibrillatory activity, although less pronounced than that of lidocaine. When lidocaine was administered after suphan, the antifibrillatory effects of both preparations increased.

Key Words: *suphan; lidocaine; arrhythmias; treatment*

It is established that the most common variant of ischemic heart disease, angina pectoris, arises from regional transitory insufficiency characterized by consecutive periods of ischemia and restoration of circulation, i.e., reperfusion. The use of intense perfusion and oxygenation of the myocardium (aortocoronary bypass, coronary angioplastics, fibrinolysis, etc.) can also cause postischemic reperfusion syndrome. This is usually accompanied by ominous cardiac rhythm disturbances, reperfusion arrhythmias, such as ventricular fibrillation (VF), acute heart failure, etc. [5].

Recent investigation showed that the nonglycoside cardiotonic drug suphan (N-succine-dl-tryptophan dipotassium salt) exerts antihypoxic and antianginal effects in animals [4], and therapeutic effect in patients with ischemic heart disease complicated by congestive circulatory failure.

The aim of the present study was to compare antiarrhythmic and antifibrillatory activity of suphan with that of lidocaine and to evaluate the efficiency of their combination in modeled early occlusion (EOA) and reperfusion (RPA) arrhythmia, including VF.

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MATERIALS AND METHODS

Experiments were carried out on 140 male Wistar rats (0.155-0.210 kg) and 75 cats (2.6-3.4 kg).

Acute toxicity (mean lethal dose, LD_{50}) was determined by injecting the preparations intravenously to rats as described previously [6].

In cats narcotized with Nembutal (40 mg/kg, intraperitoneally) and artificially ventilated, the chest was opened and occlusion (30 min) and reperfusion (10 min) of the descendent branch of the left coronary artery at the level of lower edge of the auricula was performed [3]. The test preparations and their combinations were slowly injected intravenously in isotoxic doses (5, 10, 15, 20, and 30% of LD_{50}) 5-7 min prior to occlusion of the coronary artery. For evaluation of antiarrhythmic activity, the occurrences of EOA, RPA, and VF were recorded using an EKIT-04 electrocardiograph.

The data were processed statistically using χ^2 test [1].

RESULTS

As seen from Table 1, in the control series coronary occlusion led to EOA in 60% of cases, while RPA

0007-4888/97/0005-0474$18.00

TABLE 1. Effects of Suphan, Lidocaine, and Their Combination on EOA and RPA in Cats

Drugs and their combination	Dose		n	EOA (n without arrhythmia)	RPA (n)	
	mg/kg	% of LD_{50}			without arrhythmia	without fibrillation
Control			15	6	0	5
Suphan	15	10	6	2	2	3
	30	20	6	3	3	4
	45	30	7	4	5*	7*
Lidocaine	1.4	5	11	4	5	6
	2.8	10	6	6*	4	5*
	5.6	20	7	7*	7*	7*
Suphan+lidocaine	22.5	15				
	1.4	5	7	4	4	6*
Lidocaine+suphan	1.4	5				
	22.5	15	10	2	1	4

Note. n: number of animals; *$p<0.05$ compared with the control.

were observed in all cases and in 67% animals they transformed into VF.

Suphan in doses 15 and 30 mg/kg (10 and 20% of LD_{50}) did not prevent the development of EOA, RPA, and VF, however, at 45 mg/kg (30% LD_{50}) it caused a significant decrease in the occurrence of RPA (by 71.4% in comparison with the control), whereas antifibrillatory effect was observed in 100% of cases. In case of postocclusion arrhythmias suphan was less effective; EOA were noted in 42.9% animals *vs.* 60% in the control ($p>0.05$).

The reference preparation lidocaine administered in isotoxic doses (10 and 20% of LD_{50}) produced antiarrhythmic and antifibrillatory effects. For instance, being injected in a dose of 2.8 mg/kg the drug prevented EOA in 100%, RPA in 67%, and VF in 83% of animals. After increasing the dose to 5.6 mg/kg, no cases of EOA, RPA, and VF were noted. In a dose of 1.4 mg/kg (5% LD_{50}) lidocaine exhibited no antiarrhythmic and antifibrillatory activity.

Bearing in mind that combined administration can provide a reserve for elevation of drug efficiency (potentiation) [2], we examined antiarrhythmic activity of a combination of suphan and lidocaine taken in subthreshold (half-effective) doses equal to 22.5 and 1.4 mg/kg, respectively. In some experiments, suphan injection followed after 1-2 min by lidocaine, while in others, this order was reversed. It was found that the combination suphan+lidocaine exhibited no considerable antiarrhythmic activity (EOA and RPA occurred in 43% of cases), however, it produced a pronounced antifibrillatory effect (VF were noted only in 14% animals). The combination lidocaine+suphan had no antiarrhythmic and antifibrillatory effect (EOA were recorded on 80%, RPA in 90, and VF in 60% animals). Thus, the sequence of the preparations is very important for realization of their antiarrhythmic effect.

For evaluation of the effect of combined administration on the toxicity of suphan and lidocaine we performed two experimental series.

To find out how combined administration of suphan and lidocaine affects the toxicity of these drugs, we determined LD_{50} of the test preparations under conditions of their consecutive administration. In series I, suphan served as a background substance and was injected first, while lidocaine was the test substance, i.e., injected last. In series II this sequence was reverted. Against the background of 22.5 mg/kg suphan, LD_{50} of lidocaine was 30.5 (26.0-35.0) mg/kg, while in the absence of suphan it was 28.0 (22.5-31.5) mg/kg, i.e., the difference was insignificant. By contrast, against the background of lidocaine (1.4 mg/kg), LD_{50} of suphan increased 1.8-fold and constituted 266.4 (223.8-309.0) *vs.* 148.0 (121.6-174.4) mg/kg in the absence of lidocaine. These findings suggest that lidocaine reduces the toxicity of suphan, which probably determines the decrease in antiarrhythmic and antifibrillatory activity of their combination in the cases when lidocaine is injected first.

Thus, suphan in a dose of 45 mg/kg possesses antiarrhythmic and antifibrillatory activity in RPA and VF although less pronounced than the effect of isotoxic dose of lidocaine. Combination of suphan and lidocaine exhibits a higher antifibrillatory effect than individual preparations; however, the sequence of preparations is very important. Potentiation of the antifibrillatory effect is observed only when suphan

is injected against the background of lidocaine injection. These data are important for choosing the strategy of the treatment of the postischemic reperfusion syndrome.

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Autostimulation of Prolactin Receptors in Adrenal Cortex of Guinea Pigs

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 5, pp. 548-550, May, 1997
Original article submitted February 12, 1996

Prolactin injected to male guinea pigs for 7 days considerably enhanced binding of ^{125}I-prolactin by adrenal cortex microsomes. Scatchard analysis showed that this rise is due to an increase in the receptor binding capacity but not in their affinity.

Key Words: *prolactin; prolactin receptors; adrenal cortex; autoregulation of receptors*

Adrenal cortex contains a considerable number of prolactin receptors (PRL). In some animal species (for example, rabbits) binding of PRL to the adrenal cortex membranes is higher than its binding to mammary glands and ovaries [10]. After this phenomenon had been described, the high affinity of PRL binding and abundance of PRL receptors in the adrenal gland were repeatedly confirmed [1,7,8,14]. Intense expression of the long form of PRL receptor in the adrenal cortex in rats has been recently demonstrated [9]. The biological role of abundant PRL receptors in adrenocorticocytes remains unclear.

The study of the prolactin postreceptory signal transduction system in the adrenal cortex provides an insight into the role of this hormone in cellular regulation in steroidogenic tissues. This system includes phosphatidylcholine hydrolysis to diacylglycerols and phosphorylcholine and activation of protein kinase C in different cell fractions [2,11,12]. This mechanisms of signal transduction is most typical for proliferative stimuli.

Prolactin receptors in standard target organs (mammary gland, gonads, and liver) are the subject of hormone regulation, and first of all, self-regulation [4,6]. However, hormone regulation and self-regulation of PRL in the adrenal cortex has been poorly investigated [3,5].

In the present study we explore the effect of long-term PRL treatment *in vivo* on PRL binding in microsomes from the adrenal cortex of male guinea pigs.

MATERIALS AND METHODS

Experiments were carried out on adult male guinea pigs weighing 300-400 g. Bovine PRL in a dose of 2 U/100 g (Kaunas endocrine plant) in 500 μl physiological saline was subcutaneously injected to the experimental animals for 7 days. Control animals received physiological solution. The purity of PRL

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0007-4888/97/0005-0476$18.00