Chinese Journal of Physiological Sciences
1986, 2 (2), 154 — 157

Short Communication

PROTECTIVE EFFECTS OF NALOXONE AGAINST CARDIOTOXICITY INDUCED BY ACUTE ADMINISTRATION OF A LETHAL DOSE OF OUABAIN IN THE GUINEA PIG

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Naloxone has been shown to possess protective and antiarrhythmic effects against intoxication after slow infusion of ouabain in the guinea pig, both prophylactically and therapeutically (Lee *et al.* 1986). However, it is well known that mortality associated with acute ingestion of massive doses of digitalis either accidentally or due to suicidal attempt remains extremely high despite all current therapeutic efforts (Rodensky & Wasserman, 1961; Beller *et al.* 1971). It is therefore of clinical interest to determine whether or not naloxone is effective for the reversal of the very acute and far advanced digitalis toxicity after a single bolus of a uniformly lethal dose of ouabain. In this communication, we report an investigation on the above mentioned problem.

Toxicity studies in pentobarbital-anaesthetized guinea pigs were carried out as previously described (Lee *et al.* 1986), except that ouabain at the dose 189 μg/kg, which is the lethal dose previously determined by Lee *et al.* (1986), was administered intravenously as a bolus within one minute.

Female guinea pigs weighing 400-500 g were anaesthetized with pentobarbital sodium (47 mg/kg i.p.), tracheotomized and artificially ventilated. Both jugular veins were cannulated, one for the administration of ouabain, the other for the administration of naloxone or saline. The electrocardiograms (ECG) (Lead II) was continuously monitored throughout the experimment.

Two series of experiments were performed. In the first, we adopted the method of Ciofalo *et al.* (1967). Naloxone (Dupont) at doses of 0.67 and 2.2 mg/kg in 0.1 ml of 0.9% NaCl solution, or 0.1 ml of 0.9% NaCl solution alone as controls were administered intravenously 5 minutes before injection of ouabain. In the second series of experiment, we adopted the procedure of Lloyd *et al.* (1978). After injection of ouabain, naloxone at doses 2.2, 6.6 and 20 mg/kg in 0.1ml of 0.9% NaCl solution, or 0.1 ml of 0.9% NaCl solution alone as controls were administered intravenously at the onset of multifocal ventricular premature contraction (VPC) or ventricular tachycardia (VT) in the absence of the former. The times of onset of VPC, ventricular fibrillation (VF) and cardiac arrest were recorded.

Chi-square test was employed to test the difference in the number of animals exhibiting VPC, VF, cardiac arrest, recovery or unsuccessful recovery after administration of ouabain between the control and naloxone-treated groups. Student's test was used to analyse difference in the times of onset of VPC, VF, cardiac arrest and recovery after ouabain administration between the control and naloxone-treated groups.

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Table 1 shows the effects of prophylactic administration of naloxone on acute ouabain-induced cardiotoxicity. In the control group, a bolus lethal dose of ouabain invariably produced VPC, VF, cardiac arrest in succession and consequently death in all animals. All animals in the naloxone-pretreated groups also produced VPC, but the time of onset of VPC was significantly increased in the group receiving 2.2 mg/kg naloxone. Both the times of onset of VF and cardiac arrest were also significantly delayed in the naloxone-pretreated groups compared with that of the control. Moreover, in the naloxone-pretreated groups, the number of animals going to cardiac arrest was significantly decreased in a dose-dependent manner. Subsequently, only 4 and 1 out of 8 guinea pigs in the groups pretreated with 0.67 and 2.2 mg/kg naloxone, respectively exhibited VF and died. All these animals, however, showed transient improvement of cardiac rhythm with episodes of sinus rhythm, followed by idioventricular beats, ventricular asystoles and cardiac arrest. This is in contrast to the control group in which all animals died of VF without showing any attempt to recover. Recovery in the naloxone-treated groups also increased significantly in a dose related manner, the percentage being 50 and 88 in the groups treated with 0.67 and 2.2 mg/kg of naloxone, respectively whereas there was no recovery in the control group.

Table 1. Effects of pre-treatment of naloxone on cardiotoxicity induced by acute administration of a lethal dose of ouabain (189 μg/kg) in the guinea pig

	N	VPC		VF		Cardiac arrest		Recovery to sinus rhythm		No of guinea pigs with VF showing transient improvment of cardiac rhythm
		No	Time of onset (min)	No	Time of onset (min)	No	Time of onset (min)	No	Time onset (min)	
Control	8	8	1.75 ± 0.16	8	2.38 ± 0.18	8	21.63 ± 3.75	0	—	0
Naloxone (mg/kg) pretreated										
0.67	8	8	2.0 ± 0.19	7	3.0 ± 0.15	4**	46.3 ± 3.12	4*	33.0 ± 1.29	4*
2.2	8	8	3.5 ± 0.33***	5	4.9 ± 0.93*	1***	54	7***	33.6 ± 3.41	1

Values are presented as mean ± SEM

VPC — ventricular premature contraction
VT — ventricular tachycardia
VF — ventricular fibrillation

*, **, *** signifies statistical difference to the control group to the level $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively by Chi-square test.

*, *** signifies statistical difference to the control group to the level $P < 0.05$ and $P < 0.001$, respectively by Student's test.

Table 2 shows the effects of post-treatment with naloxone on arrhythmias and survival in the guinea pig after acute administration of ouabain. Animals in all groups invariably died of ventricular arrhythmias and cardiac arrest. There was no difference between the control and naloxone-treated groups in times of onset of VPC, VF and cardiac arrest. Nor was there any difference in the proportions of death or recovery to normal sinus rhythm. The only exception is that in the group post-treated with naloxone at the dose, 20 mg/kg, there was significantly more animals exhibiting transient episodes of sinus rhythm, followed by idioventricular beats, ventricular asystoles and cardiac arrest.

Table 2. Effects of post-treatment of naloxone on cardiotoxicity induced by acute administration of a lethal dose of ouabin (189 μg/kg) in the guinea pig

	N	Time of onset of multifocal VPC or VT (min)	VF		Cardiac arrest		Recovery to sinus rhythm		No of guinea pigs with VF showing transient improvment of cardiac rhythm
			No	Time of onset (min)	No	Time of onset (min)	No	Time onset (min)	
Control	8	1.75 ± 0.16	8	2.25 ± 0.16	8	17.6 ± 1.92	0	—	0
Naloxone (mg/kg) post-treated									
2.2	8	2.06 ± 0.06	8	2.63 ± 0.18	7	18.3 ± 1.15	1	36	0
6.6	8	2.13 ± 0.16	8	2.88 ± 0.30	6	28.8 ± 4.88	2	38.5 ± 3.5	3
20	8	2.0 ± 0.16	8	2.63 ± 0.23	6	26.2 ± 6.66	2	27.5 ± 2.5	5**

Values are presented as mean ± SEM

VPC — ventricular premature contraction
VT — ventricular tachycardia
VF — ventricular fibrillation

** signifies statistical differences to the control group to the level $P < 0.01$ by Chi-square test.

In agreement with our previous findings (Lee *et al.* 1986), in this study we found that prophylactic administration of naloxone markedly attenuates the fatal cardiac arrhythmias resulting from acute administration of a lethal dose of ouabain (Table 1), confirming that naloxone produces an antiarrhythmic effect. However, naloxone even at much higher doses, when given at the onset of malignant arrhythmias following acute massive ouabain administration, does not effectively restore the cardiac rhythm to normal (Table 2). This is contrary to our previous findings that naloxone administrated at the onset of similar arrhythmias induced by slow intravenous infusion of same dose of ouabain effectively reverses the advanced and fatal cardiotoxicity (Lee *et al.* 1986). Since the onset of action of naloxone by intravenous route is 2 minutes (Osol and Pratt, 1973), and the occurrence of VF is less than 1 minute, the injected naloxone can hardly reach the heart after the onset of VF when the blood circulation is poor. On the other hand, the interval between naloxone administration and the occurrence of VF in our previous study is 4-5 minutes, which provides sufficient time for the injected naloxone to reach the heart.

Thus, our present study suggests that naloxone is only effective for the reversal of very acute and far advanced digitalis toxicity if administered prophylactically, but not therapeutically. Only when the onset of VF is not so rapid, post-treatment of naloxone may be useful as a therapeutic antiarrhythmic agent as shown in our previous study (Lee *et al.* 1986). Further studies are needed to determine the clinical value of naloxone in the treatment of patients suffering from acute and massive digitalis poisoning.

Acknowledgement: The study was supported by a Hong Kong University Research Grant. Naloxone was kindly supplied by DuPont Pharmaceutical Co.

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