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PREVENTION AND REVERSAL OF OUABAIN-INDUCED CARDIOTOXICITY BY NALOXONE IN THE GUINEA-PIG

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SUMMARY

1. The effects of pre- and post-treatment with naloxone on the cardiotoxicity of ouabain in the guinea-pig were studied.

2. After pretreatment with naloxone, the dose of ouabain required to induce ventricular arrhythmias and cardiac arrest were significantly increased, in a dose-dependent manner, compared with the control, indicating a protective effect of naloxone against digitalis intoxication.

3. Administration of naloxone at the onset of cardiac arrhythmias induced by a lethal dose of ouabain restored the cardiac rhythm and consequently saved life in seven out of eight animals, indicating an antiarrhythmic effect of naloxone in digitalis-intoxicated guinea-pigs.

4. The protective and antiarrhythmic effects of naloxone against digitalis intoxication have clinical implications.

Key words: digitalis-intoxication, guinea-pig, naloxone, ouabain, ventricular arrhythmias.

INTRODUCTION

Naloxone has been shown to possess an antiarrhythmic property in the rat *in vivo* (Fagbemi *et al.* 1982; Wong & Lee 1985) and *in vitro* (Zhan *et al.* 1985). It is known that digitalis intoxication manifests in cardiac arrhythmias (Bircher *et al.* 1963; Lathers & Roberts 1980). It is of interest to study whether or not naloxone also blocks the digitalis-induced arrhythmias. In this communication we report the results of a study on the protective and antiarrhythmic effects of naloxone in ouabain-induced cardiotoxicity in the guinea-pig.

METHODS

Preparation

Female guinea-pigs weighing 400–500 g were used. They were anaesthetized with pentobar-

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bitone sodium (47 mg/kg, i.p.), tracheotomized and artificially ventilated. Both jugular veins were cannulated, one for the infusion of ouabain, the other for the administration of naloxone or saline. ECG (lead II) was continuously monitored throughout the experiment.

Experimental procedure

Two series of experiments were performed. In the first we adopted the procedure of Saito *et al.* (1974). Naloxone (Dupont) dissolved in 0.1 ml of 0.9% NaCl solution in doses of 2.2 and 11 mg/kg, or 0.1 ml of 0.9% NaCl solution alone as control were administered intravenously 5 min before administration of ouabain. Ouabain (Sigma) dissolved in 0.9% NaCl solution at a concentration of 85 μg/ml was infused at a rate of 0.007 ml/min using a peristaltic pump (Harvard). The times of infusion of ouabain necessary to produce premature ventricular contractions (VPC), ventricular fibrillation (VF) and cardiac arrest were recorded. The amounts of ouabain needed to produce these changes were calculated by multiplying the rate and time of infusion and concentration of the drug.

In the second series of experiments the procedure of Lechat *et al.* (1984) was used. A lethal dose of ouabain (85 μg/ml at a rate of 0.077 ml/min for 13 min) was infused into the animal to produce intoxication. This dose was the mean lethal dose determined in the first series of experiments. Naloxone at a dose of 2.2 mg/kg was administered intravenously as a bolus at the onset of multifocal VPC or ventricular tachycardia (VT) in the absence of the former. The pattern and time course changes in cardiac rhythm were recorded.

Statistical analyses

Analysis of variance (one-way ANOVA) was used to test the difference in dose of ouabain required to cause cardiac arrhythmias and cardiac standstill between the control and naloxone pretreated groups. The test gives an indication of the overall effect of the drug.

Chi-square test was employed to test the difference in number of animals exhibiting VF, recovery or death after administration of ouabain between the control and naloxone post-treatment groups.

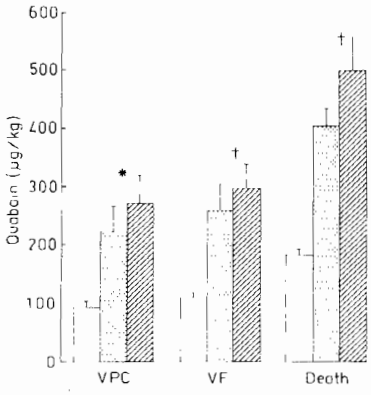

Fig. 1. Effects of prophylactic administration of naloxone on ouabain cardiotoxicity. (□ control; naloxone 2.2 mg/kg ▨ , 11.0 mg/kg ▨). Values are mean and s.e.m. of seven animals. *$P <$ 0.05, † $P <$ 0.01 significance compared to control (one-way ANOVA).

Table 1. Effects of post-treatment with naloxone on ouabain-induced arrhythmias and survival

	Time of onset of multifocal VPC or VT (min)			VF Time of onset (min)			Death Time (min)			Recovery to stable sinus rhythm Time (min)		
	mean	s.e.m	*n*	mean	s.e.m.	*n*	mean	s.e.m.	*n*	mean	s.e.m.	*n*
Control	8.63	0.46	8	10	0.46	8	13.71	0.84	7	45		1
Naloxone	8.75	0.49	8	12	0.86	6	15		1*	42.14	1.01	7*

VPC – Ventricular premature contraction, VT – Ventricular tachycardia, VF – Ventricular fibrillation.
*Signifies statistical difference to the control group to the level P 0.01 by chi-square test.

RESULTS

Figure 1 shows the effects of prophylactic administration of naloxone on ouabain cardiotoxicity. In the control group, the doses of ouabain required to induce VPC, VF and cardiac arrest were 93.50 μg/kg (s.e.m. = 9.44), 116.36 μg/kg (s.e.m. = 10.53) and 187 μg/kg (s.e.m. = 12.06), respectively, indicating that with increased amount of ouabain administered, cardiotoxicity increased. With prophylactic administration of naloxone, the doses of ouabain required to induce the above arrhythmias were significantly increased and the increase was dose related.

Table 1 shows the effects of post-treatment with naloxone on ouabain cardiotoxicity. Ouabain, at the dose (187 μg/kg) determined in the first experiment in this study as the mean lethal dose, invariably produced a succession of VPC, multifocal VPC or VT and VF. This was followed by cardiac arrest and consequently death in seven out of eight guinea-pigs. In the group treated with naloxone (2.2 mg/kg), all animals developed multifocal VPC or VT at a similar mean time as that of the control group. Only six out of eight animals progressed to VF also at a similar time as that of the control group. However, of the six 'fibrillating' animals, five subsequently reversed to stable sinus rhythm and only one died. Seven out of eight guinea-pigs recovered from arrhythmia to stable sinus rhythm and one out of eight died, whereas the corresponding numbers in the control group were one and seven out of eight, respectively. The difference was statistically significant.

DISCUSSION

The results show that with prophylactic administration of naloxone, the doses of ouabain required to induce ventricular arrhythmias and cardiac arrest were significantly greater than in control animals. This implies that when used prophylactically, naloxone may have a significant protective effect against digitalis intoxication.

Naloxone, when given at the onset of ventricular arrhythmias induced by a lethal dose of digitalis restored the cardiac rhythm to normal in seven out of eight guinea-pigs and consequently the animals survived. This result indicates that naloxone may be effective in reversing the advanced and otherwise fatal ouabain cardiotoxicity.

This antiarrhythmic effect of naloxone in the guinea-pig intoxicated by ouabain is in agreement with its antiarrhythmic effect in the ischaemic rat heart (Fagbemi *et al.* 1982; Zhan *et al.*

1985) and in chloroform hypoxia-induced fibrillating heart in the rat (Wong & Lee 1985). These findings suggest a possible involvement of endogenous opioid peptides in cardiac arrhythmogenesis due to different causes such as myocardial ischaemia, respiratory arrest or, as shown in this study, digitalis intoxication. However, the possibility of direct effect of naloxone on the heart other than opioid antagonism cannot be ruled out.

The protective and antiarrhythmic effects against digitalis intoxication have clinical implications. However, the therapeutic value of this drug in the treatment of patients suffering from digitalis intoxication awaits further study.

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