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Naloxone inhibits arrhythmias induced by coronary artery occlusion and reperfusion in anaesthetized dogs

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The intravenous administration of naloxone 2 min before coronary artery occlusion in anaesthetized dogs reduced the incidence and severity of cardiac arrhythmias during coronary occlusion (20 min) and reperfusion (120 min) in a dose-related manner. It also reduced the mortality. At a dose of 1 mg kg^{-1} (the maximum dose used in this study) naloxone abolished the appearance of the life threatening ventricular fibrillation (VF) and ventricular tachycardia (VT) and as a consequence all dogs in this group survived. The results suggest a possible involvement of endogenous opioid peptides in arrhythmogenesis during coronary occlusion and reperfusion in the dog.

Introduction It has been shown that naloxone inhibits the early arrhythmias resulting from acute coronary ligation in conscious and anaesthetized rats (Fagbemi *et al.*, 1982). This antiarrhythmic effect of naloxone in the rat was supported by our study using an isolated heart preparation (Zhan *et al.*, 1986) although this effect was found to be absent in anaesthetized pigs also subject to acute coronary ligation (Bergey & Beil, 1983). In order to determine whether the discrepancy in the action of naloxone on arrhythmias in the rat and pig is due to species difference or size of the heart, we have studied the effect of naloxone in anaesthetized dogs with arrhythmias induced by acute coronary ligation followed by reperfusion.

Methods Mongrel dogs of either sex weighing about 5–10 kg were used. They were anaesthetized with pentobarbitone sodium (25 mg kg^{-1}) intravenously into the lateral saphenous vein and artificially ventilated. The femoral artery was cannulated for recording blood pressure (BP) and heart rate (HR) and the cephalic vein for the administration of naloxone. Standard lead II electrocardiogram (ECG) was monitored continuously.

We used a similar procedure for coronary artery ligation in the dog as that described by Benfey *et al.* (1984). A left thoractomy was performed through the 5th rib. The heart was exposed by cutting open the pericardium. The left anterior descending coronary artery (LAD) was isolated for ligation. A suture with a short polyethylene tubing threaded around it was placed under the artery. The animal was allowed to stabilize for 30 min. Naloxone (Dupont Pharmaceutical) in 0.9% NaCl solution or 0.9% NaCl solution as control was then infused into the cephalic over a period of 5 min. At 2 min after the start of infusion, occlusion of the artery was performed by applying tension on the suture and clamping immediately above the tubing. Occlusion was maintained for 20 min followed by reperfusion by simply releasing the clamp above the polyethylene tubing surrounding the artery. The reperfusion period was 2 h.

Doses of naloxone used were 0.2, 0.4 and 1.0 mg kg^{-1}. They were dissolved in 5 ml of 0.9% NaCl solution. ECG, BP and HR were monitored throughout the experiment. Survival time was also recorded. Arrhythmias were assessed by recording the incidence of ventricular fibrillation (VF), ventricular tacycardia (VT) and other less severe atrial and ventricular arrhythmias including premature atrial contraction, paroxysmal atrial tachycardia, atrial fibrillation, A-V block and premature ventricular contraction etc. Chi squared test was used to analyse differences in the incidence of arrhythmias between control and naloxone-pretreated groups.

Results *Effects of naloxone on blood pressure and heart rate* In the doses used in this study naloxone had no significant effects on BP or HR. For example the BPs in the control groups before and after ligation were 91 ± 10 and 94 ± 13 mmHg ($n = 4$), respectively whereas the corresponding values in the group pretreated with naloxone (1 mg kg^{-1}) were 106 ± 8 and 115 ± 7 ($n = 6$), respectively. Similarly the HRs in the control group before and after ligation were 196 ± 9 and 203 ± 13 beats min^{-1} ($n = 3$) while the

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Table 1 Effects of naloxone on cardiac arrhythmias and survival during coronary occlusion and reperfusion

	Occlusion (20 min)						*Reperfusion* (120 min)					
	n	*VF*	*VT*	*Others*	*None*	*Survival*	n	*VF*	*VT*	*Others*	*None*	*Survival*
Control	7	1	2	6	1	6	6	6	6	6	0	0
Naloxone (mg kg^{-1})												
0.2	7	3	4	6	1	4	4	3	3	3	1	1
0.4	7	0	0	3	4	7	7	2**	3*	4	3	5**
1.0	7	0	0	2*	5*	7	7	0***	0***	0***	7***	7***

Figures represent number of animals; VF–ventricular fibrillation; VT–ventricular tacycardia; others include premature atrial contraction paroxysmal atrial tachycardia, atrial fibrillation, A-V block, premature ventricular contraction.
Statistical difference from the corresponding control values at the levels of $*P<0.05$, $**P<0.01$ and $***P<0.001$, by chi squared test.

corresponding values in the group receiving naloxone (1 mg kg^{-1}) were 180 ± 5 and 184 ± 4 ($n = 4$), respectively.

Effects of naloxone on arrhythmias and survival In the control group all dogs exhibited malignant ventricular arrhythmias namely VF and VT, leading eventually to death. In agreement with the previous findings (Penny & Sheridan, 1983; Zhan *et al.*, 1986), arrhythmias were more frequent and severe during the reperfusion period. Pretreatment with naloxone reduced the incidence of arrhythmias in both ischaemia and reperfusion periods in a dose-related manner (Table 1). The difference in arrhythmias and mortality between the control and the group pretreated with 0.2 mg kg^{-1} of naloxone was slight and statistically insignificant. However, in the group receiving the highest dose of naloxone, 1 mg kg^{-1}, there was no life-threatening VF in all 7 animals in either period and as a result all of them survived. The difference was statistically significant, which was more obvious in the reperfusion period (Table 1).

Discussion In this study, naloxone at doses that did not affect BP and HR, reduced cardiac arrhythmias induced by acute coronary occlusion and reperfusion and consequently mortality in anaesthetized dogs. The results are in agreement with those on the antiarrhythmic effect of naloxone in the rat subjected to acute coronary ligation (Fagbemi *et al.*, 1982). It is of interest to note that the doses of naloxone that produced antiarrhythmic effects in rats and dogs were of similar order of magnitude. These results suggest a possible involvement of endogenous opioid peptides in arrhythmogenesis due to myocardial ischaemia.

In the study on pigs by Bergey & Beil (1983), the body weights ranged from 7–14 kg, which are of a similar order of magnitude to that of the dogs used in this study (5–10 kg). Therefore, the sizes of heart in the two experimental animals used in these two studies are not greatly different. The discrepancy in the effect of naloxone in the pig and the dog probably reflects species difference. An interesting analogy was reported by Benfey and his colleagues in 1984. They found that during coronary artery occlusion and reperfusion, prazosin and propranolol had antiarrhythmic effects in the dog, but not in the pig (Benfey *et al.*, 1984). They speculated that the different efficacy in the pig may be due to a different anatomy of the coronary circulation with less collateral flow (Schaper, 1971). Our results, however, do not allow us to make any comment on this.

From this study we found two things that make naloxone a potentially useful antiarrhythmic agent. Firstly, it is antiarrhythmic in the dog which has a heart size more similar to man than the rat. Secondly, naloxone at the doses used in this study produces an antiarrhythmic effect without affecting BP or HR, suggesting that naloxone at the doses that produce antiarrhythmic effects may not produce undesirable effects due to alteration in haemodynamics. Further studies are needed to determine the application of this drug in man for the prevention and treatment of ischaemic heart diseases.

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