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Antiarrhythmic Potency of Naloxone Determined by a Screening Test Using the Isolated Ischaemic Perfused Rat Heart Preparation

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Abstract – The antiarrhythmic potency of naloxone was determined by a screening test using the isolated ischaemic perfused rat heart preparation. The cardiac antiarrhythmic potency CAP_{50} with 95 % confidence limit was 818 nmole/heart (646–985) and relative potency 0.22 compared with 0.35, 0.51 and 1.0 for lidocaine, quinidine and propranolol, respectively. These values are of clinical importance when considering the use of naloxone as an antiarrhythmic agent.

Introduction

Naloxone has been shown to block cardiac arrhythmias induced by myocardial ischaemia and reperfusion in the rat (Fagbemi *et al.*, 1982; Zhan *et al.*, 1985) and dog (Huang *et al.*, 1986), chloroform hypoxia in the young rat (Wong and Lee, 1985) and digitalis intoxication in the guinea-pig (Lee *et al.*, 1986). Since this antiarrhythmic effect is of clinical interest, it is important to know its antiarrhythmic potency as compared with the prototype antiarrhythmic drugs. We have recently developed a cardiac antiarrhythmic screening test using the isolated ischaemic perfused rat heart preparation (Lee *et al.*, 1985). In this communication we report the antiarrhythmic potency of naloxone using this preparation.

Methods

The procedure of the screening test has been described previously (Lee *et al.*, 1985). Female Sprague-Dawley rats of 210–230 g were used. The

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weight of the heart was in the range of around 1 g. They were decapitated, the heart was rapidly removed and mounted for perfusion by the Langendorff technique. The perfusion fluid was Krebs-Ringer at pH 7.4. The perfusion pressure was about 100 mmHg and flow rate 6–8 ml per min. The heart was kept at between 31° C–32° C by a water jacket. Electrocardiograms were recorded throughout the experiment with a positive electrode hooked at the apex of the heart, a negative electrode at the aorta and a ground electrode at the pericardial tissue.

Immediately after the heart had been mounted, perfusion was stopped for 10 min followed by reperfusion for 35 min. Naloxone dissolved in Krebs-Ringer was injected via an aortic cannula into the preparation 1 min after the appearance of ventricular fibrillation (VF) induced by ischaemia and reperfusion. The doses were 165, 550, 1650 and 4948 nmole/heart and the volume was 20 μl. In the control experiment 20 μl of Krebs-Ringer was injected.

The evaluation of the antiarrhythmic activity has also been described previously (Lee *et al.*, 1985). Naloxone was considered to have cardiac antiarrhythmic protection (CAP) if VF was converted into sinus rhythm after administration. Both the time course changes of CAP and dose-response relationship were studied. The regression line showing the latter was determined by the least square fit analysis with each regression point representing data from 10 hearts.

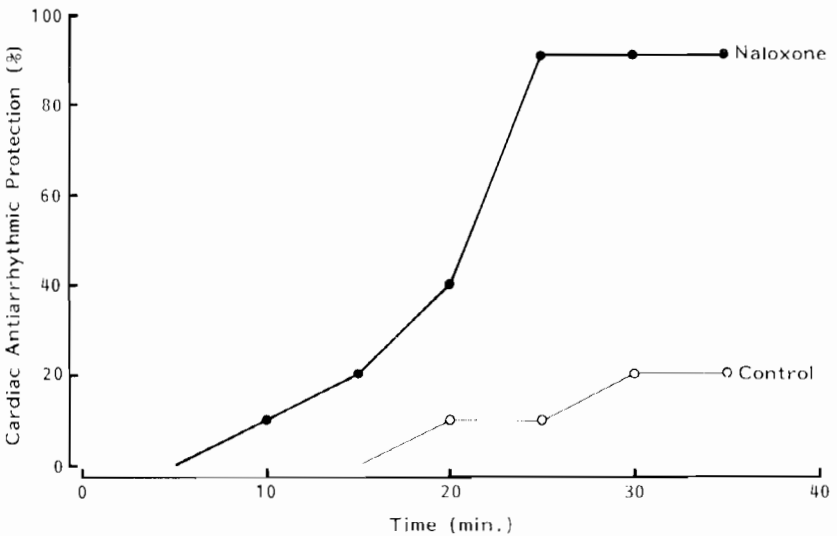

FIG. 1

Time course changes of conversions of ventricular fibrillation to sinus rhythm after administration of naloxone (4948 nmole/heart) in the isolated heart. Number of hearts for each group was 10.

Results

Figure 1 shows the time course changes in the conversion of VF into sinus rhythm after administration of naloxone at the dose of 4948 nmole/heart, the highest dose used in this study. The conversion rate increased with time after administration of the drug up to 25 min. In agreement with our previous study (Lee *et al.*, 1985), there was no more change in cardiac rhythm after 25 min. The maximum CAP was 90 %. It is of interest to note that in the control-group there was 10–20 % anti-arrhythmic potency, indicating a spontaneous recovery from arrhythmias to normal sinus rhythm in small rats.

Figure 2 shows the dose-response (maximum CAP) relationship. As expected, the response was directly proportional to the dose of naloxone. The CAP_{50} with 95 % confidence limit of naloxone was 818 (646–985) nmole/heart.

Discussion

In our previous report we have described this antiarrhythmic screening test using the isolated ischaemic perfused rat heart and have also deter-

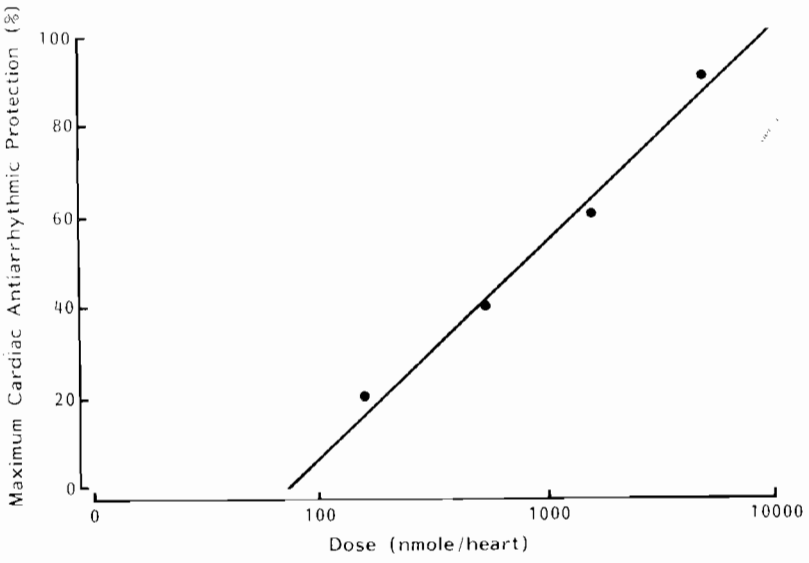

FIG. 2

The dose-maximum cardiac antiarrhythmic protection relationship for naloxone ($y = 46.77 \log X - 86.24$, $r = 0.99$). Each point represents data from 10 hearts.

mined the antiarrhythmic potencies of 3 prototype antiarrhythmic agents: propranolol, lidocaine and quinidine (Lee *et al.*, 1985). Based on the CAP_{50} values the relative potencies of these drugs are found to be comparable with the results by previous workers (Lee *et al.*, 1985). In this study we found that the CAP_{50} with 95 % confidence limit of naloxone was 818 nmole/heart (646–985) and the relative antiarrhythmic potency of naloxone was 0.22 compared with 0.35, 0.51 and 1.0 for lidocaine, quinidine and propranolol, respectively.

Since the antiarrhythmic effect of naloxone has been demonstrated in the rats (Fagbemi *et al.*, 1982; Zhan *et al.*, 1985; Wong and Lee, 1985), guinea-pigs (Lee *et al.*, 1986) and dogs (Huang *et al.*, 1986), it is a likely candidate to be used as an antiarrhythmic agent. Its relative potency compared with other antiarrhythmic drugs is important in consideration of its use in the prevention and treatment of diseases related with cardiac arrhythmias. Further studies are however needed to define its therapeutic value.

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