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EFFECTS OF PROPRANOLOL AND PINDOLOL ON PLASMA LIGNOCAINE CLEARANCE IN MAN

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1 Steady state concentrations and clearance of lignocaine were determined in eight healthy volunteers during 360 min continuous lignocaine infusion (2 mg/min). Before the infusion propranolol (0.18 mg/kg i.v.), pindolol (0.023 mg/kg i.v.) or placebo were administered in a random double-blind, cross over design.

2 During the infusion of lignocaine heart rate, cardiac output and arterial blood pressure were measured every 60 min.

3 Propranolol decreased heart rate and cardiac output significantly by 10–20%, while pindolol or lignocaine did not change cardiac output or heart rate significantly. None of the drugs changed the arterial blood pressure.

4 Propranolol pretreatment decreased lignocaine clearance significantly by 14.7% and the steady state concentration was increased by 22.5%. Pindolol produced no significant change in steady state concentration or clearance of lignocaine.

Introduction

Lignocaine is a drug with a high hepatic extraction ratio and its clearance is therefore linked closely to the hepatic blood flow (Stenson *et al.*, 1971). It has been shown that in patients with low cardiac output administration of normal doses of lignocaine result in very high blood concentrations (Thomson *et al.*, 1973). This has been explained by a decreased lignocaine clearance due to a reduction in hepatic blood flow caused by the low cardiac output.

During treatment with propranolol it has been reported that the splanchnic-hepatic blood flow is reduced by about 20–30% (Price *et al.*, 1967; Trap-Jensen *et al.*, 1976). Thus lignocaine clearance may be expected to be decreased during co-administration with propranolol. This has been confirmed by Ochs *et al.* (1980).

In contrast to propranolol, which reduces cardiac output by 20–30%, pindolol produces only very small changes in cardiac output (Svendsen *et al.*, 1979, 1980, 1981). Consequently it is to be expected that during treatment with pindolol hepatic blood flow and lignocaine clearance will not be decreased.

The purpose of this study was to assess the influence of pindolol and propranolol on lignocaine elimination.

Methods

Eight healthy volunteers, all male with a mean age of 23 years, range 20 to 29 years, were studied after their informed consent had been obtained. Each subject was studied three times with an interval of at least 2 weeks between investigations. On each occasion the subject received a continuous infusion of lignocaine. Either propranolol, pindolol or placebo were administered as an intravenous infusion, at random in a double-blind design. The study was performed in the morning with the patient resting supine and having fasted overnight.

Two short catheters were introduced into the cubital veins. A microphone for phonocardiography and electrodes for ECG and impedance cardiography were applied to the chest and a sphygmomanometer cuff was placed around the arm.

After 30 min rest the control values of heart rate and cardiac output were determined in duplicate with an interval of 10 min.

Thereafter either propranolol (0.18 mg/kg body weight), pindolol (0.023 mg/kg body weight) or placebo (0.9% NaCl) were administered i.v. over 2 min, as an injection in a volume of 20 ml. Five min later a continuous infusion of 0.2% lignocaine at a rate of 2 mg/min was started.

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The infusion of lignocaine was continued for 360 min. Blood samples for estimation of plasma concentrations of lignocaine were taken at 30 min intervals. The above mentioned haemodynamic variables were determined every 60 min.

After the lignocaine infusion was finished, an exercise test was performed.

The degree of β-adrenoceptor blockade was estimated by comparing the heart rate responses to exercise with those obtained in a similar test carried out 2–3 days before the first study.

The heart rate was continuously recorded from a precordial lead. Arterial blood pressure was measured with a standard sphygmomanometer. Cardiac output was determined by impedance cardiography. The plasma lignocaine concentration was determined in duplicate using a modified gaschromatographic technique (Steiness, in preparation). Lignocaine clearance was calculated from the dose of lignocaine administered per min divided by the steady state concentration of lignocaine. It was assumed that steady state concentrations were attained after 300 min, and the steady state concentration was calculated as the mean of the last three plasma concentrations of lignocaine.

Results are given as mean values ± s.e.mean. Statistical evaluation was performed using Student's *t*-test for paired observations. Differences were considered to be statistically significant if *P*-values less than 0.05 were obtained.

Results

Haemodynamic effects

The changes in cardiac output and heart rate are shown in Figures 1 and 2. Lignocaine induced only small, statistically insignificant changes in heart rate and cardiac output. Pindolol did not change heart rate and cardiac output significantly compared to the placebo values.

Propranolol reduced heart rate and cardiac output by about 10 and 20% respectively. These reductions were statistically significant. During exercise propranolol and pindolol reduced heart rate to the same extent (17 and 18% respectively), thus showing that equipotent doses had been administered.

Neither pindolol, propranolol or lignocaine changed the arterial blood pressure significantly.

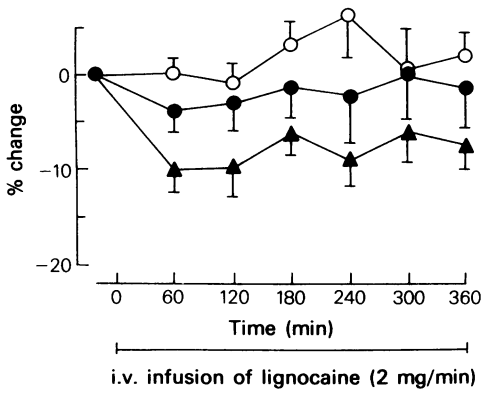

Figure 1 Changes (mean ± s.e.mean) in heart rate during continuous infusion of lignocaine and coadministration of either placebo (○), pindolol (●) or propranolol (▲).

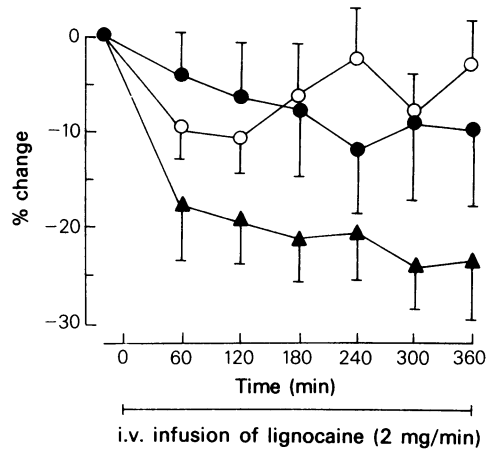

Figure 2 Changes (mean ± s.e.mean) in cardiac output during continuous infusion of lignocaine and coadministration of either placebo (○), pindolol (●) or propranolol (▲).

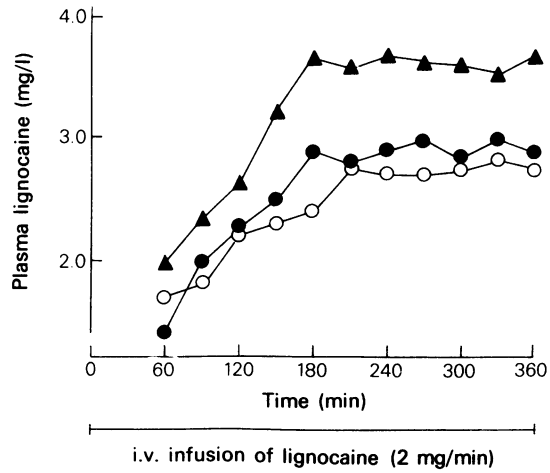

Figure 3 A typical example of plasma lignocaine concentrations when placebo (○), pindolol (●) and propranolol (▲) were coadministered.

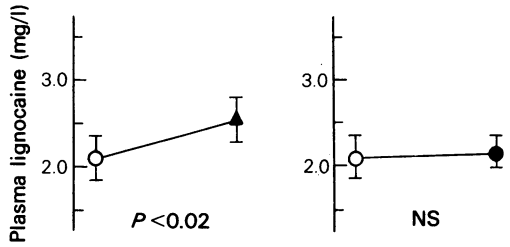

Figure 4 Steady state concentrations (mean ± s.e.mean) of lignocaine after placebo (○), pindolol (●) and propranolol (▲).

Elimination of lignocaine

Figure 3 shows a typical example of the plasma lignocaine concentrations during the 6 h of lignocaine infusion, with coadministration of placebo, pindolol or propranolol. The steady state concentration of lignocaine after placebo, propranolol and pindolol are shown in Figure 4. The steady state concentration was 2.26 ± 0.72 mg/l after placebo, 2.35 ± 0.13 mg/l after pindolol and 2.77 ± 0.25 mg/l after propranolol. The steady state concentration was significantly increased after propranolol but not after pindolol.

Lignocaine clearance decreased significantly after propranolol but not after pindolol (Figure 5). Lignocaine clearance was 1.02 ± 0.07 l/min in the placebo study, 0.95 ± 0.06 l/min after pindolol and 0.83 ± 0.07 l/min after propranolol.

Discussion

The results show that when lignocaine and propranolol are administered together, the clearance of lignocaine is decreased and the steady state plasma concentrations of lignocaine are increased.

This finding supports the theoretical consideration of Nies *et al.* (1974) and is in accordance with the results of Ochs *et al.* (1980). Presumably the interactions are caused by the reductions in cardiac output and hepatic blood flow induced by propranolol.

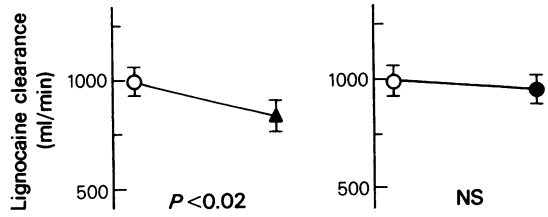

Figure 5 Lignocaine clearance (mean ± s.e.mean) during coadministration of placebo (○), pindolol (●) and propranolol (▲).

Why pindolol did not reduce the cardiac output as did propranolol may be explained by the marked intrinsic sympathomimetic activity possessed by pindolol (Svendsen *et al.*, 1981). Coadministration of lignocaine and pindolol did not change the steady state concentration or clearance of lignocaine. This supports the suggestion that pindolol did not change the hepatic blood flow.

As a consequence of this interaction between lignocaine and propranolol clinicians should exercise caution if lignocaine and propranolol are coadministered since lignocaine has a narrow therapeutic index and small increases in plasma lignocaine concentrations may lead to intoxication.

This haemodynamic interaction between propranolol and lignocaine may be expected to occur also after coadministration of other β-adrenoceptor blocking drugs without a high degree of intrinsic sympathomimetic activity. This suggestion is prompted by the study of Svendsen *et al.* (1981) who showed that the reductions in cardiac output and heart rate induced by β-adrenoceptor antagonists are dependent on the degree of intrinsic sumpathomimetic activity, whereas β-selectivity did not modify the reduction in heart rate and cardiac output.

The present findings suggest a possible risk of lignocaine intoxication, if lignocaine and propranolol are coadministered without reduction in the dosage of the former drug, whereas coadministration of lignocaine and pindolol seems to be without this risk. However this study was carried out in healthy volunteers, and investigations should be made in patients with acute myocardial infarction before a final conclusion is made.

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