A comparison of the effects of intravenous propranolol and nadolol on the renal response to hypertonic saline infusion

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- 1 Intravenous loading with 500 ml of 2.7% saline increased the clearance of PAH and inulin and urine sodium excretion in 14 healthy subjects.
- 2 Intravenous propranolol (0.075 and 0.15 mg/kg) did not alter PAH or inulin clearance at rest but abolished the increase expected during saline infusion. There was no consistent effect on urinary sodium excretion.
- 3 Intravenous nadolol (0.05 and 0.75 mg/kg) reduced resting PAH and inulin clearances by up to 25%. Both clearances fell significantly during saline infusion but natriuresis was not significantly reduced in spite of the changes in renal function.
- 4 There was no evidence from these studies in normal volunteers that nadolol confers any advantages over propranolol in its effects on renal function.

Keywords propranolol nadolol renal function

Introduction

Early studies using intravenous nadolol demonstrated a dose-related increase in renal blood flow (RBF) in both normotensive and hypertensive subjects (Hollenberg *et al.*, 1979; Foley *et al.*, 1981). These findings contrast with reported findings after propranolol (Schirmeister *et al.*, 1966; Sullivan *et al.*, 1976). However, there is little published information using doses of nadolol greater than 30 µg/kg body weight, a level at which the renal vasodilatory action of nadolol in man reached a plateau (Foley *et al.*, 1981).

In contrast, a study of a single oral dose of nadolol (2.5 mg/kg) in normal volunteers demonstrated a fall in glomerular filtration rate (GFR) of 17% (Leary *et al.*, 1979). Since autoregulation of RBF is closely linked to GFR, this suggests that a vasoconstrictor response (due probably to a reduced cardiac output) dominates at large oral doses of nadolol.

We have compared the effects of high intravenous doses of nadolol and propranolol on

renal blood flow in normotensive volunteers. In order to investigate whether any haemodynamic changes modified the ability of the kidney to adapt to variations in sodium delivery, the effects of these drugs were assessed on the renal response to an acute saline load.

Methods

Informed consent was obtained from all volunteers and the studies were approved by the Ethical Committee of the Portsmouth & South East Hampshire Health District.

Two studies were carried out. The first compared the effect of two doses of propranolol with a single dose of nadolol. The second study employed a lower dose of nadolol and extended the observations on the response to saline infusion.

All subjects avoided alcohol during the evening before the study and ate a light

breakfast without coffee or tea on the morning of the study.

Two cannulae were inserted into forearm veins. One was used for blood sampling, the other cannula for infusion of *p*-amino hippuric acid (PAH) in 5% dextrose at 4 ml/min to estimate effective renal plasma flow (ERPF) (Smith *et al.*, 1945).

Blood pressure was recorded using the Arteriosonde 1217 (Roche Medical Electronic Division) in the first study and the Sentry ASD 400 (Automated Screening Devices Inc) in the second. Mean arterial pressure was calculated by adding one-third of the pulse pressure to the diastolic blood pressure, and the average value during each study period obtained from readings taken at 5 min intervals. Heart rate was recorded from the digital display of an ECG monitor at 5 min intervals and an average value calculated for each study period.

Urine was collected by spontaneous voiding and the volume and exact time of voiding recorded. The plasma PAH concentration at the start and finish of the study period were plotted against time, and the interpolated value 5 min before the mid-point of each urine collection period was used for the clearance calculation.

Study 1

Eight healthy subjects (six male and two female) with an average age of 25.9 years (range 22–38 years) were studied. Four studies were undertaken, at least 1 week apart, in the order shown:

- (a) Control observations without drug
- (b) After propranolol 0.15 mg/kg intravenously (eight subjects)
- (c) After propranolol 0.075 mg/kg intravenously (six subjects)
- (d) After nadolol 0.075 mg/kg intravenously (eight subjects)

The drug was infused at a rate of 1 mg/min simultaneously with the priming dose of PAH, the latter given in 200 ml of 5% dextrose over 15 min. The subjects then rested semi-recumbent for a further 45 min, urine was voided and observations of pulse and blood pressure commenced. To encourage a diuresis, 250 ml water were drunk every 20 min throughout the study. There were two study periods each of 40 min duration: period 1, during which baseline observations were made; period 2 during which an intravenous infusion of 500 ml of 2.7% w/v saline (sodium—475 mmol/l) was given at a rate of 12–13 ml/min.

At the conclusion of the study, the subjects exercised on a motor driven treadmill at a speed of 4 km/h. Heart rate was recorded when it had become stable. Subsequently (about 3 h after the drug) the subjects performed a more strenuous exercise test, mounting an 8 inch step once every 2 s for 2 min and heart rate was recorded at the conclusion.

Study 2

The protocol for the second study was similar to that in Study 1, except that the carrier solution for PAH was 0.9% w/v saline, and inulin clearance was simultaneously measured (Smith *et al.*, 1938). Baseline observations were made over two 20 min urine collection periods and observations were continued for two additional 40 min collection periods after saline loading (Periods 3 and 4). The subjects were not exercised at the conclusion of the study. Six healthy volunteers (four male and two female) average age 22.7 years (range 21–28 years) were studied on three occasions, at least 1 week apart.

- (a) Control observations with no drug
- (b) After propranolol 0.15 mg/kg intravenously
- (c) After nadolol 0.05 mg/kg intravenously

Analytical methods

All plasma and urine samples were stored at –20°C until analysis. PAH analysis was by the method described by Bratton & Marshall (1939). Inulin was assayed according to the method of Davidson & Sacker (1961). Urine sodium concentrations were analysed using flame photometry.

Statistical analysis

Results are expressed as the mean $\pm$ s.e. mean. Paired observations within a study were assessed by a two-tailed Student's *t*-test. All comparisons between different treatments were tested by two-way analysis of variance.

Results

1. The effects of saline loading on renal function

Heart rate and mean arterial pressure There were no significant changes in either heart rate or mean arterial pressure during saline loading in either study.

PAH clearance (Figures 1 and 2) The resting PAH clearance during the control observations

Table 1 Study 2. Mean inulin clearance (ml/min) on control day and after β -adrenoceptor antagonists

	Baseline	Salt load
Control	104 $\pm$ 7	111 $\pm$ 10
Propranolol	97 $\pm$ 6	75 $\pm$ 5†
Nadolol	85 $\pm$ 4*	72 $\pm$ 4††

* $P < 0.05$ compared to control

† $P < 0.05$, †† $P < 0.01$ percentage change from baseline compared to control

in study 1 was increased by a mean of 32% during saline loading ($P < 0.005$). In study 2, resting PAH clearance, measured during two consecutive 20 min collections showed a within-subject coefficient of variation of 3.1%. The resting PAH clearance on the control day in study 2 showed a mean increase of 15% during saline loading, but this was not statistically significant.

Inulin clearance (Table 1) The intra-individual coefficient for variation of consecutive baseline inulin clearance was 9.5%. The resting inulin clearance on the control day was increased by a small but statistically insignificant amount during saline loading.

Sodium excretion (Table 2) Increments in urinary sodium excretion occurred during and after saline loading in both studies.

2. The effect of β -adrenoceptor antagonists on baseline measurements

Heart rate (Table 3) and mean arterial pressure Resting heart rate was significantly reduced after all β -adrenoceptor antagonist infusions,

compared to control measurements. There were no significant differences between resting heart rates after any of the drug treatments.

During treadmill exercise in study 1, heart rate was reduced by all the drug doses when compared to control. Exercise heart rate after nadolol was also significantly lower than after the higher propranolol dose ($P < 0.005$). Exercise heart rate after step test in study 1 was reduced to a similar extent by all the drug infusions.

Mean arterial pressure was not significantly altered by drug treatment.

PAH clearance (Figures 1 and 2) Resting PAH clearance was unchanged after both doses of propranolol in study 1 when compared to control but reduced by 25% after nadolol. The clearance after nadolol was significantly lower than that after twice the dose of propranolol ($P < 0.05$).

In study 2, there were mean reductions in resting PAH clearance of 10% after propranolol and 16% after nadolol, but these were not statistically significant.

Inulin clearance (Table 1) There was no significant difference in the resting inulin clearance after propranolol when compared to control. After nadolol, the clearance was reduced by 18% ($P < 0.05$), although the difference between clearances after nadolol and propranolol did not reach significance.

Sodium excretion (Table 2) There were no significant differences between baseline urinary sodium excretion rates in study 1. In study 2, baseline sodium excretion was significantly reduced after nadolol but not propranolol.

Table 2 Mean urinary sodium excretion on control day and after β -adrenoceptor antagonists

Study 1	Baseline (mmol/40 min)		Salt load (mmol/40 min excess sodium)	
	n = 6	n = 8	n = 6	n = 8
Control	9.89 $\pm$ 0.94	8.79 $\pm$ 1.00	+0.92 $\pm$ 1.66	+2.47 $\pm$ 1.60
Propranolol 0.75 mg/kg	7.08 $\pm$ 1.18	—	+1.65 $\pm$ 1.07	—
Propranolol 0.15 mg/kg	—	7.01 $\pm$ 0.94	—	+2.93 $\pm$ 1.35
Nadolol 0.075 mg/kg	—	6.64 $\pm$ 0.96	—	+2.11 $\pm$ 1.60

Study 2	Baseline (mmol/40 min)	During and after salt load (mmol/120 min excess sodium)
Control	12.71 $\pm$ 1.45	41.65 $\pm$ 12.50
Propranolol 0.15 mg/kg	9.80 $\pm$ 1.55	44.03 $\pm$ 11.36
Nadolol 0.05 mg/kg	7.27 $\pm$ 1.40*	33.62 $\pm$ 6.00

* $P < 0.05$ compared with control.

Table 3 Heart rate (beats/min) on control day and after β -adrenoceptor antagonists

Study 1	Baseline		Treadmill exercise		Step test	
	n = 6	n = 8	n = 6	n = 8	n = 6	n = 8
Control	60.7 $\pm$ 1.8	65.5 $\pm$ 3.9	93.9 $\pm$ 2.3	104.2 $\pm$ 6.9	151 $\pm$ 5	153 $\pm$ 4
Propranolol 0.075 mg/kg	54.0 $\pm$ 3.3	—	84.7 $\pm$ 2.5	—	124 $\pm$ 4	—
Propranolol 0.15 mg/kg	52.4 $\pm$ 2.6	55.5 $\pm$ 2.8	83.9 $\pm$ 1.5	88.0 $\pm$ 2.9	118 $\pm$ 5	122 $\pm$ 5
Nadolol 0.075 mg/kg	—	54.8 $\pm$ 2.1	—	82.0 $\pm$ 3.6	—	118 $\pm$ 4
Study 2						
Control	60.6 $\pm$ 2.8					
Propranolol 0.15 mg/kg	53.2 $\pm$ 2.5					
Nadolol 0.05 mg/kg	54.5 $\pm$ 2.2					

3. The effect of β -adrenoceptor antagonists during saline loading

Heart rate and mean arterial pressure No changes in heart rate or mean arterial pressure were recorded during saline loading in either study.

PAH clearance (Figures 1 and 2) In study 1, the expected rise in PAH clearance during saline loading was converted to a fall of 5% after the lower dose of propranolol, 9% after the highest dose of propranolol and 17% after nadolol. There were no significant differences between the percentage reductions from baseline after any drug infusion.

In study 2, the reductions in PAH clearance during salt loading of 13% after propranolol and 14% after nadolol were significantly different from the change in clearance on the control day.

Inulin clearance (Table 1) With reference to baseline measurements, inulin clearance was significantly reduced during salt loading by 21% after propranolol and 17% after nadolol.

Sodium excretion (Table 2) When compared to control values, there were no significant differences in the cumulative sodium excretion during and after saline loading following any drug infusion.

Discussion

Both doses of propranolol (0.075 and 0.15 mg/kg body weight) and of nadolol (0.05 and 0.075 mg/kg) produced a significant reduction in heart rate. Observations by Le Winter *et al.* (1979) suggested that the relative potency for intravenous nadolol was on average six times more than for propranolol on cardiac receptors.

Figure 1 Study 1. Effective renal plasma flow (PAH clearance) at rest and during salt loading on (a) control and two doses of propranolol ($n = 6$) and (b) control, propranolol and nadolol ($n = 8$).

● control, ■ propranolol 0.075 mg/kg, ○ propranolol 0.15 mg/kg and ◆ nadolol 0.075 mg/kg. Values are mean $\pm$ s.e. mean.

† $P < 0.05$ compared with control, * $P < 0.05$, ** $P < 0.005$ and *** $P < 0.001$ % change from baseline compared with control.

Figure 2 Study 2. Effective renal plasma flow (PAH clearance) at rest and during salt loading on the control day and after β -adrenoceptor antagonist treatments. ● control, ○ propranolol 0.15 mg/kg and ◆ nadolol 0.05 mg/kg. Values are mean $\pm$ s.e. mean. *** $P < 0.001$ % change.

However, the choice of equipotent oral doses of β -adrenoceptor antagonists presents certain problems. Intravenous administration eliminates 'first-pass' metabolism of propranolol (Shand, 1974). Propranolol, however, has a shorter elimination half-life after intravenous administration (Shand *et al.*, 1970) than nadolol (Dreyfuss *et al.*, 1977). This may not be a problem in studies lasting up to 4 h (Vucovich *et al.*, 1979); the equal suppression of heart rate by both drugs during the step test at the end of study 1 supports this contention. Nevertheless, during the treadmill exercise in study 1, nadolol consistently reduced the tachycardia to a greater extent than twice the dose of propranolol. For this reason, a lower dose of nadolol was used in study 2.

PAH and inulin clearance

The subjects were water loaded to induce a high urine flow rate and to minimise the effects of incomplete bladder emptying. Previous workers have not found any significant trend in renal plasma flow over a wide range of urine flow rates (Chapman & Henschel, 1949). In spite of fluid loading, the urine flow rate dropped substantially after intravenous hypertonic saline infusion; therefore, clearance measurements were not analysed after this period.

The mean baseline PAH clearance was not significantly different from control values after propranolol. In contrast nadolol reduced the baseline PAH clearance by up to 25% when compared to control observations.

Reductions in RBF have been reported after acute administration of propranolol to both normotensive volunteers (Schirmeister *et al.*, 1966; Sullivan *et al.*, 1976) and hypertensive patients (Falch *et al.*, 1979; O'Connor *et al.*, 1979). In contrast, recent studies have not shown any reduction in RBF after treatment of hypertension with propranolol (de Leeuw & Birkenhager, 1982; Pasternack *et al.*, 1982). The reduction in PAH clearance after nadolol conflicts with data from most published reports. Hollenberg *et al.* (1979) and Foley *et al.* (1981) demonstrated a dose-related increase in RBF in both normotensive and hypertensive subjects, using intravenous nadolol up to 10 μ g/kg. Subsequent studies have investigated the effect of long-term oral therapy with nadolol on renal haemodynamics in hypertensive subjects. Most report an increased (Britton *et al.*, 1981; Danesh *et al.*, 1984) or unchanged (O'Connor *et al.*, 1982; Textor *et al.*, 1982; Pessina *et al.*, 1982) RBF, but it was reduced after nadolol in the elderly population studied by O'Callaghan *et al.* (1982).

Cardiac depression after intravenous nadolol, increases until a dose of 50 μ g/kg is reached (Canepa-Anson *et al.*, 1982). It may be that direct renal vasodilatation occurs after intravenous nadolol up to 10 μ g/kg but that at higher doses this is overcome by a fall in cardiac output and reduced renal perfusion pressure. This concept gains further support from the fall in GFR reported in normal volunteers following a large oral dose of 2.5 mg/kg nadolol (Leary *et al.*, 1979).

The rise in PAH clearance that occurred during hypertonic saline infusion on the control day was similar in magnitude to that in earlier reports (Baldwin *et al.*, 1958). After both propranolol and nadolol this response was abolished and a significant reduction occurred during saline infusion. Krauss *et al.* (1972) found that propranolol did not alter the rise in renal plasma flow during saline infusion in their hypertensive subjects. However, they found that the pre-treatment rise in cardiac output induced by saline infusion was abolished by propranolol. The results from the present study suggest that β -adrenoceptor mediated responses must be intact for the increase in RBF during salt loading to occur.

The changes in inulin clearance tended to parallel those of PAH clearance throughout study 2.

In both studies plasma renin activity (unreported data) was low on the control day as well as after the drugs, probably as a consequence of prolonged recumbency and intravascular volume expansion. The data suggest that differences in the effects of the drugs on renin release are not the explanation for the observed changes in PAH clearance.

Urinary sodium excretion

Baseline sodium excretion was lower after all drugs in these studies when compared to the control day, although only significantly reduced after nadolol in study 2. The reduction is difficult to explain on the basis of changes in mean arterial pressure or RBF. The lack of consistent changes in sodium excretion may reflect the small numbers of subjects involved and the influence of wide day to day variations in sodium excretion in the absence of rigid dietary control (Lee, 1981). However, animal studies have demonstrated that moderate reductions in GFR do not contribute significantly to sodium retention (Levinsky, 1966).

During and after intravenous saline loading, the degree of natriuresis showed wide inter-individual variation, and represented only a small proportion of the total administered sodium load. This delay in the excretion of a saline load in normotensive subjects is well described (Cottier *et al.*, 1958). Neither propranolol nor nadolol significantly reduced the natriuresis after saline infusion even though both reversed the trend for RBF to increase during saline loading. Thus, an increase in RBF or GFR is not essential for the natriuresis of volume expansion, and β -adrenoceptor stimulation is not required for the response.

This study, therefore, provides no evidence that nadolol has advantageous effects on renal function when compared to propranolol after acute dosing in normotensive volunteers.

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