ACUTE EFFECTS OF ACEBUTOLOL ON CARDIOVASCULAR FUNCTION IN MAN

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- 1 The acute cardiovascular effects of acebutolol were measured at constant paced heart rate in thirteen patients investigated for possible coronary artery disease, six of whom showed significant coronary stenosis with regional myocardial dysfunction, seven of whom proved normal. Acebutolol 0.75 mg/kg i.v. was given to three patients with coronary artery disease and three normals, and 1 mg/kg i.v. to the other patients.
- 2 Measurements were made of cardiac output, left ventricular and arterial pressures, and left ventricular angiography. Isovolumic and ejection phase parameters of left ventricular function, and systemic vascular resistance were derived. Plasma levels of acebutolol were measured.
- 3 The acute effects of acebutolol were a slight fall in cardiac output, LV dp/dt and dP/dt/P. There was no change in LV or arterial pressures, no consistent change in LVEDP or EDV, and no consistent change in ejection fraction or mean V_{CF} . These changes imply a small negative inotropic effect, more marked at the higher dose.
- 4 The effects of acebutolol differed in patients with ischaemic heart disease compared with normals in that LVEDP and EDV increased, mean V_{CF} decreased and cardiac output was lowered more.
- 5 These data are consistent with myocardial and vascular effects of β -adrenoceptor blockade more marked at the higher dose and more marked in patients with ischaemic heart disease.

Introduction

Acebutolol is a β -adrenoceptor antagonist which has some partial agonist activity and some cardio-selectivity (Basil, Jordan, Loveless & Maxwell, 1973). Despite its now widespread use, there is relatively little published data on its clinical haemodynamic effects. One study reported that intravenous doses of 10-30 mg acebutolol reduced 'isovolumic indices of contractility' (Lewis, Bakst, Mitha, Purdon & Gotsman, 1973). In another study acebutolol, given to patients with coronary vein grafts in the larger dose of 1 mg/kg body weight, reduced ejection fraction and mean circumferential shortening velocity and increased end diastolic volume (Mason, Specter, Ingels, Daughters, Ferris & Alderman, 1978). In a third study, a similar dose of acebutolol reduced cardiac index (Wollam, Cody, Tarazi & Bravo, 1979). In none of the studies was heart rate kept constant. We accordingly studied the acute effects of 0.75 mg/kg and of 1 mg/kg acebutolol, given intravenously, on left ventricular function and haemodynamic measurements at constant heart rates in patients being investigated for coronary artery disease (CAD).

Methods

Thirteen patients (nine males, four females, aged 35 to 65 years) undergoing cardiac catheterisation for suspected ischaemic heart disease were selected for the study after giving their informed consent. Six patients had severe narrowing (> 70%) of one or more coronary arteries with regional ventricular dysfunction, and seven patients had no coronary artery or myocardial disease. All drugs were withdrawn 7 days before catheterisation. Oral diazepam 10 mg was given as premedication. The first part of the study (Study I) comprised six patients given 0.75 mg acebutolol/kg body weight. The second part of the study (Study II) comprised seven patients given 1.0 mg acebutolol/kg.

Cardiac catheterisation was performed through a percutaneous femoral artery puncture or a brachial arteriotomy, using Judkins or Sones technique respectively for coronary arteriography. Intravascular pressures were measured with a No. 7 Millar catheter-tip transducer with dye injection lumen (Model

Table 1 Study I Effect of acebutolol 0.75 mg/kg i.v. ($n=6$, mean $\pm$ s.e. mean) on left ventricular function and haemodynamic measurements at constant heart rates in patients being investigated for coronary artery disease

		Control	Acebutolol	% change	P value
Femoral arterial pressure (mmHg)	Systolic	162.2 $\pm$ 9.0	164.8 $\pm$ 10.3	+ 2	NS
	Diastolic	91.5 $\pm$ 3.3	93.2 $\pm$ 4.1	+ 2	NS
	Mean	115.8 $\pm$ 4.3	118.5 $\pm$ 6.0	+ 2	NS
LV pressure (mmHg)	Systolic	153.5 $\pm$ 7.0	152.7 $\pm$ 6.6	- 1	NS
	End Diastolic	9.1 $\pm$ 2.1	8.8 $\pm$ 1.9	- 3	NS
Peak LV dP/dt (mmHg s ⁻¹)	+ ve	1683 $\pm$ 12	1561 $\pm$ 99	- 7	NS
	- ve	1516 $\pm$ 76	1488 $\pm$ 80	- 2	NS
LV dP/dt/P (s ⁻¹)	+ ve	27.5 $\pm$ 2.4	24.8 $\pm$ 2.6	-10	< 0.05
CI (l min ⁻¹ m ⁻²)		5.0 $\pm$ 0.7	4.8 $\pm$ 0.4	- 4	NS
SVR (dyn s cm ⁻⁵)		1095 $\pm$ 135	1125 $\pm$ 102	+ 3	NS
Plasma acebutolol* (μ g ml ⁻¹)	10 min		1.2 $\pm$ 0.1		
	20 min		0.6 $\pm$ 0.1		

* Plasma levels of diacetolol were undetectable ($< 0.02 \mu\text{g ml}^{-1}$) at these times.

Table 2 Study II Effect of acebutolol 1 mg/kg ($n=7$, mean $\pm$ s.e. mean) on left ventricular function and haemodynamic measurements at constant heart rates in patients being investigated for coronary artery disease

		Control	Acebutolol	% change	P value
Femoral arterial pressure (mmHg)	Systolic	143.7 $\pm$ 7.9	137 $\pm$ 6.2	- 5	< 0.05
	Diastolic	81.7 $\pm$ 3.6	80.6 $\pm$ 4.9	- 1	NS
	Mean	105.4 $\pm$ 5.1	104 $\pm$ 6.2	- 1	NS
LV pressure (mmHg)	Systolic	137.1 $\pm$ 6.6	130.3 $\pm$ 5.1	- 5	NS
	End diastolic	3.5 $\pm$ 0.6	2.6 $\pm$ 1.4	-26	NS
Peak LV dP/dt (mmHg s ⁻¹)	+ ve	1593 $\pm$ 219	1285 $\pm$ 183	-19	< 0.02
	- ve	1594 $\pm$ 331	1354 $\pm$ 289	-15	NS
LV dP/dt/P (s ⁻¹)	+ ve	58.4 $\pm$ 9.6	51.7 $\pm$ 11.0	-11	NS
CI (l min ⁻¹ m ⁻²)		3.6 $\pm$ 0.4	3.0 $\pm$ 0.5	-16	< 0.02
SVR (dyn s cm ⁻⁵)		1292 $\pm$ 120	1435 $\pm$ 111	+11	NS
Ejection fraction		0.61 $\pm$ 0.02	0.60 $\pm$ 0.02	- 2	NS
Mean V _{CF} (circ s ⁻¹)		1.4 $\pm$ 0.1	1.3 $\pm$ 0.1	- 7	NS
End diastolic volume (ml)		185.2 $\pm$ 12.5	196.0 $\pm$ 14.2	+ 6	NS
Plasma acebutolol* (μ g ml ⁻¹)	5 min		2.2 $\pm$ 0.5		
	10 min		0.9 $\pm$ 0.1		

* Plasma levels of diacetolol were undetectable ($< 0.02 \mu\text{g ml}^{-1}$) at these times

PC471), and recorded on a Siemens signal processor incorporating pressure amplifier (Type 863) linked to a Siemens Contractility Unit (Type 868). Cardiac output was measured in triplicate using indocyanine green by indicator dilution method.

Study II also included left ventricular (LV) cine angiography performed in the 45° right anterior oblique position. This was used to measure end diastolic volume (EDV) (Kasser & Kennedy, 1969), ejection fraction (EF), and mean circumferential fibre shortening velocity (V_{CF}) (Karliner, Gault, Eckberg, Mullins & Ross, 1971).

Heart rate was kept constant at 100 beats/min by right atrial pacing throughout the study. Left ventricular pressures, rate of pressure change (dP/dt) and dP/dt/P, cardiac output and systemic arterial pressure

were measured before and 10 min (Study I) or 5 min (Study II) after acebutolol given intravenously over 5 min. LV angiography was performed 30 min before control haemodynamic measurements and repeated immediately after the post-treatment haemodynamic measurements. Acebutolol and diacetolol levels were measured in blood samples taken 10 and 20 min after injection in Study I, and 5 and 10 min after injection in Study II. The assay was performed on stored frozen plasma by May and Baker Ltd using a specific high pressure liquid chromatography fluorescence method (Lewellen, 1977). Selective coronary angiography was then performed in all cases.

Data, given as mean $\pm$ s.e. mean, are compared between groups by *t*-test, *P* value < 0.05 being taken as the limit of statistical significance.

Results

Study I (Table 1)

With the lower dose of acebutolol (0.75 mg/kg), no significant changes were seen in measurements of haemodynamic state or left ventricular function, except that left ventricular peak dP/dt/P decreased by 10%, suggesting a slight decline in inotropic state. These measurements were performed at a time when the plasma acebutolol level was $1.2 \mu\text{g ml}^{-1}$.

Study II (Table 2)

With the higher dose of acebutolol (1 mg/kg), left ventricular dP/dt was significantly reduced by 19%, and dP/dt/P was similarly but not significantly reduced by 11%, suggesting a decline in inotropic state although mean V_{CF} showed only a negligible fall. Cardiac index was likewise significantly reduced by 16% without associated increase in systemic arterial pressure. There was a non-significant reduction of left ventricular end diastolic pressure but no parallel reduction in end diastolic volume was observed. The slight reduction of femoral artery systolic pressure was not associated with a fall in systemic vascular resistance and is therefore attributable to the reduction in cardiac index. Ejection fraction was unaltered, consistent with a decline in inotropic state balanced by a reduction in wall stress as is implied by the lower LV systolic pressure. These measurements were performed at a time when the plasma acebutolol level was $2.2 \mu\text{g ml}^{-1}$.

Patients with and without coronary artery disease

Table 3 compares the data obtained from the normal patients with those from the patients with CAD showing evidence of regional impaired myocardial function. Left ventricular end diastolic pressure and volume increased in patients with CAD whereas they decreased in normal patients. Aortic systolic pressure, mean V_{CF} and EF were all slightly decreased in CAD but not in normal patients. Cardiac index was lowered more in CAD. The responses of aortic diastolic pressure, systemic vascular resistance, +ve dP/dt, -ve dP/dt, and dP/dt/P showed no obvious differences between patients with and without CAD.

No side effects of acebutolol were noted and surface electrocardiograms remained unchanged.

Discussion

Therapeutic plasma levels of acebutolol of $0.5\text{--}2 \mu\text{g ml}^{-1}$ are recommended (Meffin, Harapat & Harrison, 1976), and were achieved in the present acute study. Changes in left ventricular function due to chrono-

Table 3 Comparison of normal patients and patients with coronary artery disease. (Results are shown as mean $\pm$ s.e. mean).

	Normals			Coronary artery disease		
	Control	Acebutolol (0.75 mg/kg) (n = 3)	Control (n = 4)	Control (n = 3)	Acebutolol (0.75 mg/kg) (n = 3)	Acebutolol (1.0 mg/kg) (n = 3)
Aortic pressure (mmHg)	166 $\pm$ 19	169 $\pm$ 20	159 $\pm$ 4.3	154 $\pm$ 10	145 $\pm$ 7	136 $\pm$ 11
LV pressure (mmHg)	10.7 $\pm$ 4.0	7.7 $\pm$ 0.8	3.3 $\pm$ 1.0	3.8 $\pm$ 0.7	4.7 $\pm$ 2.9	7.6 $\pm$ 2.0
LV end diastolic volume (ml)	4.5 $\pm$ 0.9	4.6 $\pm$ 0.7	173 $\pm$ 8.7	172 $\pm$ 8.8	163 $\pm$ 19.6	193 $\pm$ 17.3
CI ($\text{l min}^{-1} \text{m}^{-2}$)			3.7 $\pm$ 0.6	5.6 $\pm$ 1.1	4.9 $\pm$ 0.4	3.5 $\pm$ 0.6
Ejection fraction			0.60 $\pm$ 0.04	0.62 $\pm$ 0.01		0.60 $\pm$ 0.03
Mean V_{CF} (circ s^{-1})			1.4 $\pm$ 0.23	1.5 $\pm$ 0.26		1.3 $\pm$ 0.10
						2.7 $\pm$ 0.6
						0.58 $\pm$ 0.03
						1.1 $\pm$ 0.17

tropic effects of the drug were avoided by carrying out the study at constant paced heart rate. Both at higher ($2.2 \mu\text{g ml}^{-1}$) and lower ($1.2 \mu\text{g ml}^{-1}$) plasma levels, the data suggest a slight negative inotropic effect, more marked with the higher dose, and presumably attributable to blocking of endogenous sympathetic activity. At the higher dose cardiac index was also significantly reduced by 16%. The effect of acebutolol appeared to be slightly greater in patients with ischaemic heart disease and regional dysfunction than in normals, consistent with the higher initial level of sympathetic activity to be expected in these patients.

These findings are in broad agreement with those recorded after other β -adrenoceptor blocking drugs (Lund-Larsen, Sivertssen, Lorentsen, Bay & Hansteen, 1968; Bensaid, Scebat & Lenegre, 1970; Gibson & Coltart, 1972; Wollam *et al.*, 1979). Minor quantitative differences in relation to the secondary properties of different drugs cannot be excluded, though many of these may be related to heart rate effects.

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