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THE EFFECTS OF A NEW β-ADRENOCEPTOR BLOCKING COMPOUND, TOLAMOLOL, ON HAEMODYNAMICS AND MYOCARDIAL FUNCTION IN MAN

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1 The effects of tolamolol on haemodynamics and myocardial contractility were investigated in two groups of six patients undergoing diagnostic cardiac catheterization.

2 The intravenous administration of tolamolol (0.15 mg/kg) produced a significant fall in heart rate from a control value (87 ± 7 to 62 ± 3 beats/min) 5 min after administration and a concomitant fall in cardiac output from 4.7 ± 0.9 to 3.5 ± 0.8 litres/minute. There was no significant change in systemic blood pressure, pulmonary artery blood pressure or stroke volume.

3 There was no change in left ventricular end diastolic pressure after tolamolol. There was a fall in the maximum rate of rise of the left ventricular pressure (LV dp/dt_{max}) and the derived index of the left ventricular contractile state (V_{max}).

4 These results suggest that tolamolol has a predominantly negative chronotropic but also a lesser negative inotropic action on the heart.

Introduction

β-Adrenoceptor blockade is frequently used in the clinical management of certain cardiac dysrhythmias and coronary heart disease. β-Adrenoceptor blockade can have undesirable additional effects such as bronchospasm (McNeil, 1964) and myocardial depression (Sowton & Hamer, 1966). There is need therefore for the continuing development and assessment of β-adrenoceptor blocking compounds such as tolamolol (4-[2-(hydroxy-3-*o*-tolyloxypropylamino) ethoxy] benzamide hydrochloride) which has been shown to have cardio-selective properties in animal preparations (Augstein, Cox, Ham, Leeming & Snare, 1973). The purpose of the present study was to investigate, in man, the cardiovascular effects of tolamolol with reference to both haemodynamics and myocardial contractility.

Methods

Twelve patients, aged 27 to 56 years, were studied in the fasting state during cardiac catheterization carried out for diagnostic purposes and assessment for cardiac surgery. Permission for the use of tolamolol was given by each patient. Clinical details of the patients studied are shown in Table 1.

The effect of tolamolol was investigated in two groups of six patients. The first group had haemodynamic measurements made before and after tolamolol administration. All were in sinus rhythm and had no clinical evidence of congestive cardiac failure. The second group of six patients had studies of myocardial contractility performed. All were in sinus rhythm, had no evidence of congestive cardiac failure and were not receiving digoxin. Premedication was not used. Tolamolol (Pfizer Ltd) was administered intravenously in a dosage of 0.15 mg/kg body weight. The heart rate was obtained from a continuously recorded electrocardiogram. Pulmonary artery pressure was recorded by means of a Goodale-Lubin catheter (length 100 cm, end and side aperture, internal diameter 1.42 mm) introduced from a median antecubital vein. Aortic pressure was recorded from a Gensini catheter (length 100 cm, end and side aperture, internal diameter 1.47 mm; United States Catheter and Instrument Corporation) which was inserted into the femoral artery by the Seldinger technique and advanced to the ascending aorta. All pressures were measured by capacitance

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transducers (Sanborn 267) and recorded on a multi-channel photographic recorder at paper speeds of 10 and 25 mm/second. Mid-thorax was taken as zero level with the patient supine. Mean pressures were obtained by electronic integration. Pressures were recorded each minute for 10 min before the injection of tolamolol and similarly for 20 min following the administration of the drug.

Cardiac output was measured by the dye dilution technique using indocyanine green as the indicator. Injections were made into the pulmonary artery and blood was withdrawn from the descending aorta through a Waters densitometer at a rate of 20 ml/min with a Harvard constant speed withdrawal pump. Cardiac output measurements were made 5 and 1 min before the injection of tolamolol and then 3, 5, 10 and 15 min after the drug was administered.

All measurements were determined from the mid point of an injection of 0.15 mg/kg body weight of tolamolol in 10 ml 0.9% w/v NaCl solution (saline) injected into a peripheral vein over a 2 min period. The following data were derived:

$$\text{Systemic vascular resistance (dynes s}^{-1}\text{ cm}^{-5}) = \frac{\text{mean arterial pressure (mmHg)} \times 80}{\text{Cardiac output (l/min)}}$$

$$\text{External cardiac work (kg m}^{-1}\text{ min}^{-1}) = \frac{\text{mean arterial pressure (mmHg)} \times 13.6 \times \text{cardiac output (l/min)}}{1{,}000}$$

Changes in myocardial contractility have been shown to be rate related (Wallace, Skinner & Mitchell, 1963) and in assessing this it was therefore necessary to maintain a constant heart rate before and after tolamolol administration. This was done by the method of atrial pacing using a NIBH bipolar pacing catheter (United States Catheter and Instrument Corporation) introduced from an antecubital vein and positioned at the junction of the superior vena cava and right atrium. Throughout the study the heart rate was maintained at 10 beats/min above the resting level. Left ventricular pressure was measured from a Gensini catheter introduced retrogradely through the aortic valve. The frequency response of the catheter system was over 30 Hz. The intraventricular pressure was continuously differentiated by means of an analogue differentiating circuit (Sanborn 350-17 pressure derivative); the rate of rise of left ventricular pressure (dp/dt) was recorded and the peak value obtained (LV dp/dt_{max}). In some studies pressure in the aortic arch was measured at paper speeds of 100 and 200 mm/s to confirm that the dp/dt_{max} occurred

Table 1 Clinical details of patients studied

	Age (years)	*Diagnosis*	*Disability**	*Cardiac rhythm*
Group I Haemodynamic studies:				
Patient 1	27	Minor aortic incompetence	Asymptomatic	Sinus
2	46	Mitral stenosis	II	Sinus
3	39	Minor aortic incompetence	I	Sinus
4	27	Innocent systolic murmur	Asymptomatic	Sinus
5	33	Mitral stenosis	I	Sinus
6	32	Mitral stenosis	II	Sinus
Group II Myocardial contractility studies:				
Patient 1	36	Aortic stenosis (gradient 20 mmHg)	I	Sinus
2	47	Congestive cardiomyopathy	II	Sinus
3	44	Mitral stenosis Insignificant mitral incompetence	II	Sinus
4	28	Innocent systolic murmur	Asymptomatic	Sinus
5	56	Coronary heart disease	II	Sinus
6	42	Coronary heart disease	II	Sinus

*New York Heart Association classification.

prior to the opening of the aortic valve. The isovolumic segment of the left ventricular pressure tracing was used to calculate force velocity curves from the formula (Mason, 1969)

$$\frac{LV\ dp/dt\ s^{-1}}{KP + C}$$

where P = LV pressure mmHg; LV dp/dt = simultaneously measured rate of rise of LV pressure; K and C are constants ($K = 40$: $C = 80$) (Parmley & Sonnenblick, 1967).

An index of the contractile state of the myocardium was then obtained by extrapolation of the isovolumic segment of the force velocity curve back to zero pressure load, this value being described as V_{max}. Statistical analysis of the results was done by the paired t test.

Results

The haemodynamic results in the first group of six patients are shown in Table 2. The heart rate fell significantly within 3 min of injection and this reduction persisted throughout the study. The cardiac output fell significantly from 4.7 ± 0.9 litres/min to 3.5 ± 0.9 litres/min at 3 and 5 min after the injection, but was returning towards control levels after 10-15 minutes. Stroke volume did not alter significantly suggesting that the decrease in cardiac output was rate related. There was no significant change in systemic arterial or pulmonary artery pressures. There was a reduction in external cardiac work and a rise of approximately 25% in systemic vascular resistance after tolamolol administration. Table 3 shows the effect of tolamolol on the indices reflecting the contractile state of the left ventricle in the second group of six patients. Following the administration of tolamolol there was no significant change in the left ventricular end diastolic pressure. A significant fall occurred in the left ventricular dp/dt_{max} at 5 min after injection which remained reduced at 10-15 minutes. A similar fall occurred in the V_{max} calculated on 10 minutes.

Discussion

Haemodynamic studies in a group of six patients requiring diagnostic cardiac catheterization showed that the intravenous administration of approximately 10 mg tolamolol (0.15 mg/kg) resulted in a significant fall in heart rate and cardiac output but that changes in stroke volume, mean systemic arterial pressure and pulmonary artery pressure were slight and not significant.

Table 2 Haemodynamic measurements before and after the intravenous administration of tolamolol

Variables	*Control*	*3 min*	*5 min*	*10 min*	*15 min*	*20 min*
Heart rate (beats/min)	81 ± 7	67 ± 5**	62 ± 3**	66 ± 5**	69 ± 5**	71 ± 5*
Systolic blood pressure (mmHg)	123 ± 5	122 ± 6	117 ± 6	118 ± 5	113 ± 6	116 ± 8
Diastolic blood pressure (mmHg)	66 ± 2	68 ± 3	64 ± 3	65 ± 2	63 ± 1	68 ± 2
Mean blood pressure (mmHg)	87 ± 2	88 ± 3	84 ± 4	87 ± 2	85 ± 3	85 ± 4
Mean pulmonary artery pressure (mmHg)	25 ± 7	24 ± 6	23 ± 7	26 ± 7	24 ± 6	25 ± 7
Cardiac output (l/min)	4.7 ± 0.9	3.5 ± 0.9**	3.5 ± 0.8**	4.1 ± 0.9	4.4 ± 0.7	—
Stroke volume (ml)	59 ± 7	54 ± 8	58 ± 6	64 ± 7	63 ± 6	—
External cardiac work (kg m^{-1})	5.5 ± 0.4	4.2 ± 0.4†	4.2 ± 0.4†	4.8 ± 0.4	5.1 ± 0.3	—
Systemic vascular resistance (dynes s^{-1} cm^{-5})	1547 ± 115	2113 ± 195**	1996 ± 171*	1758 ± 134	1578 ± 115	—

± s.e. mean
* = $P < 0.05$
** = $P < 0.01$
† = $P < 0.001$

Table 3 Measurements of left ventricular function before and after the intravenous administration of tolamolol

Variables	*Control*	*5 min*	*10 min*	*15 min*
LV end diastolic pressure (mmHg)	5.3 ± 0.6	5.0 ± 1.2	5.0 ± 1.1	5.0 ± 1.2
LV dp/dt_{max} (mmHg/s)	1019 ± 57	780 ± 53**	793 ± 49**	771 ± 56**
V_{max}	0.5002 ± 0.003	–	0.4213 ± 0.02†	–

± s.e. mean
** = $P < 0.01$
† = $P < 0.001$

These results are consistent with a negative chronotropic action due to β-adrenoceptor blockade.

The effect of tolamolol on the contractile state of the left ventricle was assessed using the left ventricular dp/dt_{max} and V_{max}. Furnival, Linden & Snow (1971) have suggested that LV dp/dt_{max}, although influenced by ventricular pre-load and after-load, is of value in the assessment of directional changes of contractility in individual patients in response to an inotropic drug or other intervention. V_{max} as an index of left ventricular contractile state is independent of ventricular pre-load and after-load (Mason, 1969). It is, however, rate-related since it has been shown that the first derivative of ventricular pressure rises with increasing heart rate (Wallace *et al.*, 1963). In the present study a constant heart rate was achieved by atrial pacing. In addition, the initial haemodynamic investigations demonstrated that tolamolol had no significant effect on systemic arterial pressure suggesting that after-load was unaltered. The left ventricular end diastolic pressure was not altered significantly after tolamolol, a finding which is consistent with the drug having no major effect on ventricular pre-load. For these reasons and since each patient was used as their own control we believe that in the present study changes in left ventricular dp/dt_{max} and V_{max} are likely to reflect alterations in myocardial contractility. Following injection of tolamolol there was a decrease in left ventricular dp/dt_{max} at 5 min which persisted through the time of study. There was a downward shift of the force velocity curve with a resultant fall in V_{max}. These results are consistent with a decrease in the inotropic state of the left ventricle and could be due to direct myocardial depression or β-adrenoceptor blockade (Fitzgerald, Wale & Austin, 1972).

External cardiac work represents energy associated with myocardial shortening and is one of the factors determining myocardial oxygen consumption (Braunwald, 1971). A significant reduction in external cardiac work in addition to the effect in heart rate and a reduction in the velocity of myocardial contraction would suggest that in common with other β-adrenoceptor drugs tolamolol decreases myocardial oxygen consumption.

Overall the results obtained after intravenous administration of tolamolol are consistent with those of a β-adrenoceptor blocking drug which has a predominantly negative chronotropic action but which in addition at the dose used has a depressant effect on myocardial contractility. Further clinical evaluation of tolamolol with respect to its action on cardiac dysrhythmias and in coronary heart disease would appear to be indicated.

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