Haemodynamics and myocardial function after sotalol

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The cardiovascular effects of the beta-adrenergic blocking agent, sotalol, have been assessed in a group of patients with heart disease. There was a significant reduction in heart rate and cardiac output, but stroke volume was unchanged. Systemic arterial and pulmonary artery pressures were not significantly altered. Indices of myocardial function (dp/dt max and V max) were also significantly reduced.

Though previous studies have reported that sotalol is devoid of myocardial depression associated with other beta-adrenergic blocking drugs, these results suggest that sotalol has both a negative chronotropic and a lesser negative inotropic action.

Beta-adrenergic blocking drugs are now widely used in clinical cardiology. In addition to beta-adrenergic blockade, however, undesirable effects such as myocardial depression may occur (Nakano and Kusakari, 1966; Blinks, 1967). Sotalol (M.J., 1999)¹ has been reported to be a beta-adrenergic blocking agent devoid of significant myocardial depression (Lish, Weikel, and Dungan, 1965; Levy and Richards, 1965). Though studies of sotalol in man have been reported (Brooks *et al.*, 1970; Svedmyr, Malmberg, and Häg-gendal, 1970), little is known of the effect of this drug on myocardial contractility in patients with heart disease. The purpose of the present study was to assess the cardiovascular effects of sotalol with particular reference to myocardial contractility.

Methods

Twelve patients, aged 24 to 52 years, were studied in the fasting state during cardiac catheterization carried out for diagnostic purposes and assessment for cardiac surgery (Table 1). Each patient gave permission for the use of sotalol. None of the patients was in cardiac failure at the time of the study. The effect of sotalol was investigated in 2 groups of 6 patients. The first group had haemodynamic measurements made before and after sotalol administration. Four of these patients were in sinus rhythm and 2 were in atrial fibrillation,

¹ dl 4-(2-isopropylamino-1-hydroxyethyl) methane sulphonanilide hydrochloride.

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receiving digoxin therapy. The second group had studies of myocardial contractility performed. All of these patients were in sinus rhythm and none was receiving digoxin. In each group sotalol was administered intravenously in a dosage of 0.2 mg/kg body weight.

The heart rate was obtained from a continuously recorded electrocardiogram. Pulmonary artery pressure was recorded using a Goodale-

TABLE 1 Clinical details of patients studied

	Age (yr)	Diagnosis	Disability grade (New York Heart Association)	Cardiac rhythm
Group I				
<i>Haemodynamic studies:</i>				
Patient 1	40	Mitral stenosis	II	Sinus
2	39	Mitral stenosis	II	Atrial fibrillation
3	48	Mitral stenosis	I	Sinus
4	41	Mitral stenosis	III	Atrial fibrillation
5	42	Mitral stenosis	II	Sinus
6	37	Mitral stenosis and incompetence	II	Sinus
Group II				
<i>Myocardial contractility studies:</i>				
Patient 1	28	Systolic murmur; no cardiac lesion found	I	Sinus
2	24	Mitral stenosis	II	Sinus
3	43	Mitral stenosis	II	Sinus
4	52	Aortic stenosis (gradient < 50 mmHg)	I	Sinus
5	29	Aortic incompetence	III	Sinus
6	37	Mitral stenosis	II	Sinus

Lubin catheter¹ (length 100 cm, end and side aperture; internal diameter 1.42 cm) inserted via an antecubital vein. Aortic pressure was recorded from a Gensini catheter¹ (length 100 cm, end and side aperture; internal diameter 1.47 mm) inserted into the femoral artery by the Seldinger technique and advanced into the ascending aorta. Pressures were measured by a capacitance transducer (Sanborn 267) and recorded on a multichannel photographic recorder at paper speeds of 10 and 25 mm/sec. The midthorax was taken as zero level with the patient supine. Mean pressures were obtained by electrical integration. Pressures were recorded for 10 minutes before injection of sotalol and similarly for 20 minutes after injection. Cardiac output was estimated by the dye dilution technique using indocyanine green as the indicator. All cardiac output measurements were made in duplicate. Control measurements were made 5 minutes and 1 minute before the injection of sotalol, and then 5, 10, and 15 minutes after the drug was administered. The appropriate dose of sotalol was injected over a 2-minute period and all measurements were timed from the mid point of injection. Derived measurements were:

Systemic vascular resistance

(dynes sec cm⁻⁵)

$$= \frac{\text{Mean arterial pressure (mmHg)} \times 80}{\text{Cardiac output (l./min)}}$$

External cardiac work

(kg m/min)

$$= \frac{\text{Mean arterial pressure (mmHg)} \times 13.6 \times \text{cardiac output (l./min)}}{1000}$$

Since changes in myocardial contractility may be rate related, it was necessary to maintain a constant heart rate before and after sotalol administration. This was done by atrial pacing using a NBIH bipolar pacing catheter¹ introduced from an antecubital vein and positioned at the superior vena cava-right atrial junction. Throughout the study, the heart rate was maintained at 10 beats a minute above its resting level. Left ventricular pressure was measured from a Gensini catheter introduced retrogradely through the aortic valve. The first derivative of left ventricular systolic pressure was measured electronically using a differentiating circuit (Sanborn 350-16 pressure derivative) and the maximum value recorded - LV dp/dt max. Left ventricular end-diastolic pressure and the first derivative of left ventricular systolic pressure were recorded at a paper speed of 200 mm/sec and the isovolumic segment of the left ventricular pressure tracing was used to calculate force velocity curves from the formula (Mason, 1969):

$$\frac{\text{LV dp/dt sec}^{-1}}{\text{K.P.} + \text{C}}$$

where P = LV pressure (mmHg)

LV dp/dt = simultaneously measured rate of rise of LV pressure (mmHg).

K and C are constants (K = 40; C = 80) (Parmley and Sonnenblick, 1967).

¹ United States Catheter and Instrument Corporation.

TABLE 2 *Haemodynamic measurements before and after intravenous administration of sotalol*

Variables	Control	5 min	10 min	15 min
Heart rate	83 ± 6	69 ± 5‡	70 ± 5‡	72 ± 5‡
Aortic systolic pressure (mmHg)	130 ± 9	118 ± 8†	118 ± 9†	117 ± 8†
Aortic diastolic pressure (mmHg)	71 ± 7	68 ± 7	65 ± 6	68 ± 6
Mean aortic pressure (mmHg)	89 ± 4	86 ± 3	87 ± 3	88 ± 3
Mean pulmonary artery pressure (mmHg)	26 ± 4	27 ± 4	25 ± 4	25 ± 4
Cardiac output (l./min)	5.0 ± 0.3	3.9 ± 0.2*	4.0 ± 0.4*	4.2 ± 0.2
Stroke volume (ml/beat)	58 ± 5	54 ± 5	55 ± 7	56 ± 5
Systemic vascular resistance (dynes sec cm ⁻⁵)	1466 ± 130	1834 ± 128†	1748 ± 149*	1526 ± 140
External cardiac work (kg m/min)	6.2 ± 0.2	4.6 ± 0.5*	4.7 ± 0.3*	5.6 ± 0.4

± = 1 SE of the mean.

* = P < 0.05.

† = P < 0.01.

‡ = P < 0.001.

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.

Results

Haemodynamic results are shown in Table 2. Heart rate decreased significantly during the study from a control value of 83 ± 6 beats a minute to 69 ± 5 beats a minute. The cardiac output fell significantly from 5.0 ± 0.3 l./min to 3.9 ± 0.2 l./min while the stroke volume was unchanged, suggesting that the decrease in cardiac output was rate related. The mean systemic arterial pressure fell slightly but not significantly and the mean pulmonary artery pressure was unaltered. There was a significant reduction in the derived variable of external cardiac work and a rise of approximately 25 per cent in systemic vascular resistance after sotalol administration. The changes in left ventricular dp/dt max and V max are shown in Table 3 and Fig. 1, 2, and 3. There was a significant reduction in both variables. There

TABLE 3 *Myocardial function before and after intravenous administration of sotalol*

Variable	Control	5 min	10 min
LV end-diastolic pressure (mmHg)	6.4 ± 2.1	7.2 ± 1.6	7.0 ± 1.8
LV dp/dt max (mmHg/sec)	918 ± 87	690 ± 57*	633 ± 63*
V max	0.44 ± 0.04	—	0.39 ± 0.03

± = 1 SE.

* = P < 0.01.

FIG. 1 The effect of intravenous administration of sotalol on the dp/dt (max).

was a small but non-significant increase in left ventricular end-diastolic pressure from 6.4 ± 2.1 to 7.2 ± 1.6 mmHg.

Discussion

Sotalol has been shown to be an effective beta-adrenergic blocking agent in isolated cardiac muscle preparations (Lish *et al.*, 1965) and in closed chest anaesthetized dogs (Puri and Bing, 1969). Levy and Richards (1965) and Lish *et al.* (1965) found no evidence of myocardial depression after sotalol when studying an isolated cardiac muscle preparation. Blinks (1967), on the other hand, reported that sotalol did produce some depression of myocardial function in isolated guinea-pig atria though less than that found after propranolol. Brooks *et al.* (1970) studied the effects of sotalol in a group of patients with rheumatic heart disease of varying severity and including patients in congestive cardiac failure. They suggested that the haemodynamic effects of sotalol

FIG. 3 Force velocity curves obtained from a patient before and after the intravenous administration of sotalol.

lol were due to a negative chronotropic action. They reported that sotalol did not have any negative inotropic action though this finding was mainly based on a study of anaesthetized, apparently healthy, dogs.

In the present study the intravenous administration of sotalol to a group of patients with valvular heart disease of varying severity (Table 2) but free from cardiac failure resulted in a significant fall in heart rate and cardiac output, while changes in stroke volume, mean systemic arterial pressure, and pulmonary artery pressure were slight and not significant. These results are consistent with a negative chronotropic action in keeping with a beta-adrenergic blocking drug but differ from the haemodynamic changes found after propranolol (Sowton and Hamer, 1966), where a fall in stroke volume as well as cardiac output occurred. The increase in the calculated systemic vascular resistance found after sotalol is thought possibly to be secondary to reflex vasoconstriction in response to the decrease in cardiac output.

These data do not provide definitive evidence of the effect of sotalol on myocardial contractility. Furnival, Linden, and Snow (1970) suggested that the dp/dt max is a quantitative index of inotropic changes in the left ventricle and that though influenced by ventricular preload and after-load is useful in the assessment of directional changes of contractility in response to an inotropic drug or other

FIG. 2 The effect of intravenous administration of sotalol on the V max.

intervention in an individual patient. Though there are a number of technical and theoretical limitations in the derivation of the velocity of shortening of the contractile element to zero load ($V_{\max}$), Falsetti *et al.* (1971) assessed myocardial contractility by several methods and concluded that $V_{\max}$ was the most sensitive. In the present series, the left ventricular pressure measurements were obtained from a fluid-filled catheter system similar to that used by Hugenholtz *et al.* (1970) who compared a fluid-filled catheter system with a catheter tipped transducer and obtained comparable values for dp/dt and $V_{\max}$. In the present study a constant heart rate was obtained by atrial pacing, thus allowing the effects of sotalol on myocardial contractility to be assessed independently of its negative chronotropic action. After injection of sotalol, the left ventricular end-diastolic pressure remained unchanged. There was, however, a reduction in myocardial contractility as shown by a significant decrease in left ventricular $dp/dt_{\max}$ and a downward shift of the force-velocity curve with a resultant fall in $V_{\max}$.

External cardiac work represents energy associated with myocardial shortening and is one of the factors determining myocardial oxygen consumption (Sonnenblick, Ross, and Braunwald, 1968). The significant reduction in external cardiac work in addition to the effect on the heart rate and the reduction in the velocity of myocardial contraction suggests that, in common with other beta-adrenergic blocking drugs, sotalol decreases myocardial oxygen consumption.

The above results are consistent with a beta-adrenergic blocking drug which has a predominant rate-dependent effect but in addition has a modest depressant action on the myocardium. Further clinical evaluation of sotalol appears to be indicated.

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