Cardio-circulatory Effects of Beta-adrenergic Blockade in Organic Heart Disease

Comparison between Propranolol and CIBA 39,089-Ba

T. GRANDJEAN AND J. L. RIVIER

From the Département de Cardiologie, Hospital Cantonal, Lausanne, Switzerland

Beta-adrenergic blockers are increasingly used in the treatment of angina pectoris (Hamer *et al.*, 1964, 1966; Srivastava, Dewar, and Newell, 1964; Gillam and Prichard, 1965, 1966; Keelan, 1965; Rabkin *et al.*, 1966; Wolfson *et al.*, 1966), cardiac arrhythmias (Stock and Dale, 1963; Fiene, Griffin, and Harrison, 1965; Ginn, Irons, and Orgain, 1965; Harrison, Griffin, and Fiene, 1965; Bath, 1966; Harris, 1966; Rowlands, Howitt, and Markman, 1965; Schamroth, 1966; Szekely *et al.*, 1966), and some other less common conditions (Harrison *et al.*, 1964). The danger of inducing or aggravating heart failure by beta-blockade remains a matter of controversy (Stephen, 1966). Whereas this risk has been considered as relatively small and acceptable by Snow (1965, 1966), undesirable side-effects and sometimes severe complications related to the depressant action of propranolol on myocardial contractility have been reported, in isolated instances with fatal outcome (Fleckenstein *et al.*, 1964; Vogel, 1965; Scheu, 1966; Lüthy and Hegglin, 1966). This risk undoubtedly represents an important drawback to this kind of therapy.

In the present study, propranolol was given intravenously to patients with organic disease of the left heart, and its circulatory effects were assessed during the course of standard pre-operative catheterization of the heart. In a second stage of this study, these effects were compared with those of CIBA 39,089-Ba, a new specific beta-adrenergic blocking agent. Fig. 1 shows the chemical structures of isoprenaline, propranolol, and CIBA 39,089-Ba. Fig. 2 shows that the two drugs are apparently equipotent beta-blockers in terms of their negative chronotropic effect. This study

suggests that propranolol depresses myocardial contractility, and this effect correlates well with the severity of the heart disease. CIBA 39,089-Ba has a negative chronotropic effect fairly similar to that of propranolol, but produces a significantly less marked depression of myocardial contractility.

FIG. 1.—Chemical structure of isoprenaline, propranolol, and CIBA 39,089-Ba.

Received March 30, 1967.

FIG. 2.—Comparative effects of propranolol and CIBA 39,089-Ba on resting and exercising heart rate in a patient with aortic valve disease. The negative chronotropic effect of the two drugs is very similar.

PATIENTS AND METHODS

Studies were made on 12 patients with propranolol (Group I) and on 22 patients with CIBA 39,089-Ba (Group II). Tables I and II sum up the clinical data of these patients. The study includes 8 patients with aortic stenosis, 7 with aortic incompetence, 3 with mixed aortic valve disease, 9 with moderate to severe mitral incompetence, 4 with mixed aortic and mitral valve disease (excluding mitral stenosis), 2 with mild primary myocardial disease, and 1 with ventricular septal defect.

Electrocardiographic evidence of left ventricular hypertrophy was shown by 24 patients and tracings indicating "left ventricular strain" were noted in another 24. In Group I, 5 patients and in Group II, 17 patients were or had previously been in overt heart failure and were digitalized at the time of the study. In all of them, the diagnosis was confirmed by left heart catheterization and angiocardiology, as well as in 16 patients by open-heart surgery.

Right heart catheterization was used, as this was thought more suitable for long-lasting studies with repeated exercise tests. A double-lumen Cournand catheter was wedged into the pulmonary capillary position, and a cannula was inserted into the brachial artery. Pressures were measured with Statham strain gauges P23Db and Philips Type 133-4-452 electromanometers, and recorded on a Cardiopan-6 multichannel recorder. Cardiac outputs were measured by the Fick method. The patients were exercised for 6 minutes in the supine position on a bicycle ergometer and then allowed to rest for 15 minutes. 5 mg. propranolol in Group I or 5 mg. CIBA 39,089-Ba in Group II were injected intravenously at a rate of 1 mg./min., with continuous monitoring of the pulmonary wedge and artery pressure. Ten minutes later, the same sequence was repeated. The usual haemodynamic parameters were recorded during the last 2 minutes of each exercise test and during the last 5 minutes of each resting steady state.

RESULTS

The results are shown in Tables III and IV and in Fig. 3-7. Both drugs slowed the heart rate to much the same extent. At rest, the heart rate was reduced from 77 to 64 beats/min. (−16%) after

TABLE I
CLINICAL DATA OF PATIENTS IN GROUP I INVESTIGATED WITH PROPRANOLOL

Case No., sex, and age	Diagnosis	Class	Electrocardiogram		Congestive heart failure*	Digitalis*	Pulmonary wedge pressure (mm. Hg)
			Left ventricular hypertrophy	Strain			
1 F 26	Aortic stenosis	I B	+	+	—	—	7
2 M 64	Aortic stenosis	II C	+	+	—	—	6
3 M 37	Aortic regurgitation	II C	+	+	+	+	15
4 M 26	Aortic stenosis and regurgitation	I B	+	—	—	—	11
5 M 63	Aortic stenosis and regurgitation	II D	+	+	+	+	16
6 M 24	Mitral regurgitation	III C	+	+	+	+	28
7 F 27	Mitral regurgitation	III C	+	+	+	+	20
8 M 53	Mitral regurgitation and mild chronic cor pulmonale	II C	+	—	—	—	9
9 M 48	Mitral regurgitation and mild chronic cor pulmonale	I C	—	—	—	—	6
10 F 36	Mitral and aortic regurgitation	II C	+	+	+	+	10
11 M 54	Mitral and aortic regurgitation	II B	+	—	—	—	10
12 M 59	Primary myocardial disease	I B	—	(+)	—	—	6

*Past or present.

TABLE II
CLINICAL DATA OF PATIENTS IN GROUP II INVESTIGATED WITH CIBA 39,089-Ba

Case No., sex, and age	Diagnosis	Class	Electrocardiogram		Congestive heart failure*	Digitalis	Pulmonary wedge pressure (mm. Hg)
			Left ventricular hypertrophy	Strain			
13 M 34	Aortic stenosis	II B	+	-	-	-	5
14 M 61	Aortic stenosis	II C	+	-	-	-	8
15 M 42	Aortic stenosis	III C	+	+	+	+	15
16 F 64	Aortic stenosis	II C	+	+	+	+	22
17 M 53	Aortic stenosis	II C	+	+	+	+	10
18 F 55	Aortic stenosis	III C	+	+	+	+	16
19 F 47	Aortic regurgitation	I B	-	-	-	-	5
20 M 21	Aortic regurgitation	I C	+	+	+	-	16
21 M 29	Aortic regurgitation	I B	+	+	-	-	9
22 F 19	Aortic regurgitation	I C	+	+	-	-	7.5
23 M 34	Aortic regurgitation	I B	+	+	+	-	11
24 M 37	Aortic regurgitation	II C	+	+	+	+	14
25 M 56	Aortic stenosis and regurgitation	II C	+	+	+	+	6
26 F 68	Mitral regurgitation	IV D	+	+	+	+	20
27 M 24	Mitral regurgitation	III C	+	+	+	+	26
28 F 50	Mitral regurgitation	III C	+	+	+	+	24
29 M 48	Mitral regurgitation	I C	-	-	(+)	+	7.5
30 M 54	Mitral regurgitation, aortic stenosis and regurgitation	III D	+	+	+	+	14
31 M 53	Mitral regurgitation and aortic stenosis	II C	+	-	-	-	6
32 M 39	Mitral and aortic regurgitation	III D	+	+	+	+	28
33 M 50	Ventricular septal defect	I A	-	-	-	-	6
34 M 31	Primary myocardial disease	II C	-	(+)	-	-	9.5

* Past or present.

TABLE III
HAEMODYNAMIC DATA BEFORE AND AFTER 5 mg. PROPRANOLOL

Case No.	At rest					During exercise			
	Heart rate per min.	Mean pulmonary wedge pressure (mm. Hg)	Mean pulmonary artery pressure (mm. Hg)	A-V difference in O ₂ content (ml. O ₂ %)	Stroke output (ml./sec.)	Load (watts)	Heart rate per min.	Mean pulmonary wedge pressure (mm. Hg)	A-V difference in O ₂ content (ml. O ₂ %)
1 { Before	79	7	11	3.5	93	60	115	13	5.75
	After 10	10	13	4.4	78		95	19	6.35
2 { Before	82	6	14	4.15	94	70	100	30	7.8
	After 67	8	17	5.15	91		94	35	8.5
3 { Before	74	15	21	6.3	55	50	102	28	8.2
	After 67	26	33	6.5	57		87	31	9.9
4 { Before	64	11	16	5.6	78	70	104	14	8.5
	After 58	13	18	5.3	89		98	20	9.8
5 { Before	72	16	18	4.65	78	60	102	18	8.7
	After 65	18	20	6.55	62		94	33	10.2
6 { Before	63	30	36	8.2	47	—	—	—	—
	After 47	39	50	10.2	51		—	—	—
7 { Before	84	20	28	5.4	53	—	—	—	—
	After 54	24	30	6	70		—	—	—
8 { Before	90	9	14	4.75	68	60	115	20	10.2
	After 66	8	13	5.5	80		110	28	10.8
9 { Before	79	6	19	7.5	48	60	116	14	12.2
	After 69	8	21	8.3	48		105	22	13
10 { Before	87	10	15	5.0	70	40	107	25	—
	After 73	17	21	5.2	77		103	37	—
11 { Before	83	10	26	5.2	52	60	111	16	9.8
	After 65	11	29	6.7	52		105	22	10.4
12 { Before	60	6	11	4.3	93	60	91	9	8.6
	After 60	6	10	5.5	73		80	16	10.5

TABLE IV
HAEMODYNAMIC DATA BEFORE AND AFTER 5 mg. CIBA 39,089-Ba

Case No.	At rest					During exercise			
	Heart rate per min.	Mean pulmonary wedge pressure (mm. Hg)	Mean pulmonary artery pressure (mm. Hg)	A-V difference in O ₂ content (ml. O ₂ %)	Stroke output (ml./sec.)	Load (watts)	Heart rate	Mean pulmonary wedge pressure (mm. Hg)	A-V difference in O ₂ content (ml. O ₂ %)
13 { Before After	68 60	5 5	12 10	4.72 4.3	91 112	— —	— —	— —	— —
14 { Before After	77 68	8 11	15 15	5.5 5.5	67 76	— —	— —	— —	— —
15 { Before After	89 70	15 15	18 17	5.45 4.95	60 80	— —	— —	— —	— —
16 { Before After	63 56	22 20	26 24	5.9 5.9	60 67	40 40	91 75	39 29	8.4 9
17 { Before After	80 75	10 6	17 16	5.5 5.7	57 59	50 50	112 100	26 25	7.6 9.4
18 { Before After	69 58	10 12	13 14	4.5 4.5	71 84	— —	— —	— —	— —
19 { Before After	72 61	5 6	10 9	5.25 5	67 81	— —	— —	— —	— —
20 { Before After	79 64	16 13	22 19	5.8 5.8	63 77	— —	— —	— —	— —
21 { Before After	76 72	9 9	12 11	3.62 3.8	104 101	— —	— —	— —	— —
22 { Before After	81 75	7.5 8	9 10	5.4 6.1	81 75	50 50	115 100	17 18	8.6 9.4
23 { Before After	68 63	11 11	18 14	5.6 5.5	95 99	60 60	90 78	14 12	8 9.8
24 { Before After	70 66	14 14	24 24	6.1 6.3	61 62	40 40	95 95	34 31	7.8 8.9
25 { Before After	80 68	6 6	13 13	5.4 5.9	75 79	50 50	110 98	16 20	8.3 9.3
26 { Before After	106 60	20 14	28 20	6.8 7.6	23 36	— —	— —	— —	— —
27 { Before After	82 63	26 24	49 43	8.6 8.9	39 46	— —	— —	— —	— —
28 { Before After	80 64	24 17	37 28	4.75 4.75	64 80	30 30	165 102	43 33	7 7.3
29 { Before After	69 60	7 7	18 18	8.5 7.5	48 63	60 60	113 91	14 17	12.4 11.8
30 { Before After	62 56	14 22	22 38	5 6.4	87 77	— —	— —	— —	— —
31 { Before After	100 93	6 8	12 13	4.55 5.7	65 56	60 60	136 119	14 24	9.2 9.9
32 { Before After	86 81	28 27	32 28	7.7 9.7	45 39	50 50	107 91	44 37	— —
33 { Before After	63 49	6 5	12 13	4.45 4.6	81 101	— —	— —	— —	— —
34 { Before After	78 69	9.5 7	12 12	4.55 3.9	84 106	60 60	115 102	12.5 16	7.7 8.1

propranolol and from 78 to 66 beats/min. (−15%) after CIBA 39,089-Ba. During exercise, it was decreased from 107 to 97 beats/min. (−9%) after propranolol, and from 114 to 96 beats/min. (−16%) after CIBA 39,089-Ba. The greater fall in heart rate noticed in response to CIBA 39,089-Ba during

exercise is not statistically significant. Both drugs reduced the resting cardiac output. After propranolol, there was no adjustment of the stroke volume to the lower heart rate, and cardiac output fell in direct proportion to the fall in heart rate, i.e. from 5.1 to 4.4 l./min. (−15%). After CIBA 39,089-

FIG. 3.—Circulatory effects of beta-adrenergic blockade in organic heart disease. ●—▷—● = effect of 5 mg. propranolol; ○—▷—○ = effect of CIBA 39,089-Ba. B, before; A, after. HR=heart rate per min. CVP=central venous pressure (mm. Hg). PCP=pulmonary capillary pressure (mm. Hg). PAP=pulmonary arterial pressure (mm. Hg). A-V-Diff.=arterio-venous difference (O₂%). CO=cardiac output (l./min.). SV=stroke volume (ml.). * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

FIG. 4.—Comparative effects of propranolol and CIBA 39,089-Ba on resting and exercising pulmonary capillary pressure. *Left*: effect of 5 mg. propranolol. *Right*: effect of 5 mg. CIBA 39,089-Ba. After propranolol, there was a 4.3 mm. Hg increase at rest and a 7.1 mm. Hg increase during exercise. After CIBA 39,089-Ba, the pulmonary capillary pressure decreased by 0.6 mm. Hg at rest, and by 1.2 mm. Hg during exercise.

Ba, the decline in heart rate was to a large extent offset by a 10 per cent increase in stroke volume, and the fall in resting cardiac output was only 3 per cent from 5.0 to 4.8 l./min. This difference in the effects of propranolol and of CIBA 39,089-Ba on the resting cardiac output is significant

($p < 0.01$). Following exercise, both cardiac rate and stroke volume decreased after propranolol, resulting in a 17 per cent fall in cardiac output from 9.9 to 8.3 l./min. After CIBA 39,089-Ba, the lower heart rate was still offset to a small degree by a slight rise in stroke volume, resulting in a 10 per cent

reduction in the cardiac output from 9.1 to 8.2 l./min.

At rest, there was no change in the arterial pressure after propranolol and a 7 per cent increase after CIBA 39,089-Ba. With respect to the lower cardiac output, this means a 17 per cent increase in total peripheral vascular resistance after propranolol and a 9 per cent increase after CIBA 39,089-Ba. During exercise, neither drug affected the total peripheral vascular resistance, both arterial pressure and cardiac output having been reduced to a similar extent by both beta-blockers.

There was a difference in the effects of the two drugs on the pulmonary wedge pressure (Fig. 4). Propranolol increased this pressure from 12 to 16 mm. Hg (+4 mm. Hg, or +35%) at rest, and from 19 to 26 mm. Hg (+7 mm. Hg, or +37%) during exercise. At rest, there was a good correlation between this effect and the severity of the underlying heart disease. The increase was slight in mildly diseased, well-compensated subjects with normal resting pulmonary capillary pressure, but was conspicuous in 4 patients (Case 3, +11 mm. Hg; Case 6, +12 mm. Hg; Case 7, +4 mm. Hg; and Case 10, +7 mm. Hg). These four patients were or had previously been in frank heart failure and were digitalized at the time of this investigation. During exercise, the pulmonary capillary pressure was increased by propranolol in all subjects, irrespective of the presence or absence of heart decompensation.

After CIBA 39,089-Ba, a single patient (Case 30) showed an increase of 8 mm. Hg in his resting pulmonary wedge pressure from 14 to 22 mm. Hg. This patient died 3 months after the study from intractable heart failure. Necropsy showed a maximally damaged heart weighing over 900 g. In all the other patients in this group, the drug produced only minor changes, with an average decrease of 1 mm. Hg from 13 to 12 mm. Hg at rest, and from 25 to 24 mm. Hg during exercise. This difference in the effects of the two drugs on the resting and exercising pulmonary wedge pressure is highly significant ($p < 0.001$).

In this regard, it is of interest to analyse separately the effects of the two beta-blockers in patients with severe, pure mitral incompetence (Fig. 5-7). In 3 such patients (Cases 26-28 in Table II), CIBA 39,089-Ba decreased the resting pulmonary capillary pressure on an average by 5 mm. Hg from 23 to 18 mm. Hg, by reducing the frequency and the height of the V waves, suggesting decreased mitral regurgitation, and also by lowering the levels of the Y dips, indicating decreased left ventricular diastolic pressures (Fig. 6). In 3 similar patients (Cases 6, 7, and 10 in Table I), propranolol pro-

FIG. 5.—Comparative effects of CIBA 39,089-Ba and propranolol on the resting pulmonary capillary pressure in cases of severe mitral incompetence. *Left*: in 3 patients (Cases 26, 27, and 28, Table II, with average resting pulmonary wedge pressure of 23.3 mm. Hg), CIBA 39,089-Ba reduced this pressure considerably with less frequent and less tall V waves, and with lower levels of the Y depressions. *Right*: in 3 equally severe cases of mitral insufficiency (Cases 6, 7, and 10, Table I, with an average resting pulmonary wedge pressure of 20.0 mm. Hg), propranolol produced the opposite effect: the drug increased this pressure by 6.6 mm. Hg with taller V waves and an increase in the levels of the Y depressions.

duced an opposite effect. Despite full digitalization in all 3, the drug increased the resting pulmonary wedge pressure by 7 mm. Hg from 20 to 27 mm. Hg, with a rise in the height of the V waves and in the levels of the Y dips (Fig. 7).

DISCUSSION

Effects of Propranolol. The slowing effect of this drug on the heart rate at rest and during exercise is well known and does not require further comment. A significant reduction in cardiac output after propranolol is a constant finding in man, both in health and in heart disease (Hamer and Sowton, 1965; Sowton and Hamer, 1966; Paley, McDonald, and Peters, 1965; Robinson *et al.*, 1965; Harris *et al.*, 1966), and in animals (Black and Rolett, 1965; Nakano and Kusakari, 1965). Our findings are closely similar to those of Wolfson *et al.*

FIG. 6.—Electrocardiographic and resting pulmonary capillary pressure curves before (*above*) and 10 minutes after 5 mg. CIBA 39,089-Ba (*below*) in Case 26 (Table II). Before injection of the drug, prominent V waves reaching 30 to 35 mm. Hg and a mean pulmonary wedge pressure of 22 mm. Hg were recorded; in spite of maximal digitalization, there was a poorly controlled ventricular rate of over 120/min. *Below*: the drug produced a dramatic fall in heart rate down to 60–65/min., a decrease in the height of the V waves, and a drop in the mean pulmonary wedge pressure down to 14 mm. Hg. In spite of the smaller V waves, the forward stroke output was increased from 23 to 38 ml./systole, thereby offsetting to a large extent the effect of bradycardia. The tip of the catheter was not displaced between the two readings.

(1966), who found no changes in stroke output after propranolol, and therefore a directly proportional decrease in cardiac rate and output. The mechanism underlying this reduction is not entirely clear. Both increased and decreased heart sizes have been observed in response to beta-adrenergic blockade. An increase in systolic and diastolic heart size following treatment with beta-blockers has been ascribed both to longer diastolic filling period due to the lowered heart rate and to impaired myocardial contractility (Chamberlain, 1966). Decreased systolic and diastolic heart volumes after propranolol have been related to a possible nitroglycerin-like venous pooling and to impaired venous return (Wolfson *et al.*, 1966). In the present study, changes in heart volumes following beta-blockade have not been measured. Yet, in spite of the lower heart rate, no significant change in right ventricular filling pressure was found after propranolol, which may account for the unchanged stroke output. In addition, it must be stressed that no correlation

became evident between the amount of fall in cardiac output and the severity of the underlying heart disease. This suggests that the depressant effect of propranolol on myocardial contractility plays only a minor role in its effect on resting cardiac output, at least in healthy subjects and in well-compensated heart patients.

The effect of propranolol on the pulmonary capillary pressure is of interest. After propranolol the left ventricle produced an unchanged stroke work, at least in cases without aortic obstruction, but probably at the expense of some rise in its filling pressure, since the pulmonary wedge pressure was increased by 4 mm. Hg at rest and by 7 mm. Hg during exercise (which probably reflects a similar increase in the left ventricular telediastolic pressure). This effect was minimal in mildly diseased patients without heart failure, but was clearly evident in the more severely ill patients. It also became obvious in all subjects during exercise. These findings are somewhat similar to those

FIG. 7.—Resting and exercising pulmonary capillary pressure curves before (*left*) and 10 minutes after 5 mg. propranolol (*right*) in Case 10, Table I. After the drug, there was an increase in the height of the V waves and in the mean pulmonary wedge pressure. At rest (*above*), this pressure was increased by 7 mm. Hg, and during exercise (*below*), by 12 mm. Hg by the drug.

noticed in patients with ischaemic heart disease (Sowton and Hamer, 1966). They are even more significant in view of the fact that pulmonary artery and capillary pressures are expected to be lower during the second of two identical periods of exercise a short time apart (Widimsky, Berglund, and Malmberg, 1963; Burkart, Barold, and Sowton, 1967). Hence, it must be concluded that propranolol depresses myocardial contractility to some extent and may aggravate cardiac decompensation in patients with latent or overt heart failure.

The four patients whose resting pulmonary wedge pressure was much increased in response to propranolol were fully digitalized at the time of the study. Thus, digitalization may sometimes fail to protect decompensated patients against a deleterious effect of propranolol on myocardial function.

No unpleasant subjective side-effects were produced by propranolol nor did any patient become aware of the changes in haemodynamic conditions induced by the drug.

Effects of CIBA 39,089-Ba. The reduction in heart rate following treatment with CIBA 39,089-Ba was closely similar to that produced by the same dose of propranolol. Therefore, CIBA 39,089-Ba and propranolol may be considered as practically equipotent beta-adrenergic inhibitors in terms of their negative chronotropic effects. Yet, the two drugs differed significantly as regards their effect on the resting cardiac output. Whereas after propranolol there was no adjustment of the stroke output to the lowered heart rate, the reduction in heart rate following injection of CIBA 39,089-Ba was almost entirely offset by a 10 per cent increase in stroke output, thus resulting in a mere 3 per cent decrease in cardiac output. During exercise, the same effect was observed in response to CIBA 39,089-Ba, but the increase in stroke volume was small and hence incapable of compensating for the fall in heart rate.

There was a highly significant difference in the effects of the two drugs on the pulmonary wedge

pressure. Propranolol produced a rise in this pressure, but no such change occurred after CIBA 39,089-Ba. After this latter drug, the 10 per cent increase in left ventricular stroke work in response to the lowered heart rate was apparently achieved without there being any rise in left ventricular filling pressure. With the exception of Case 30, already discussed, comparable findings were obtained after CIBA 39,089-Ba in all subjects of Group II, irrespective of the presence or absence of heart failure. These data suggest that, in most instances, this drug does not depress myocardial contractility to the same extent as does propranolol.

Since propranolol sometimes produced an alarming rise in pulmonary wedge pressure in patients with heart failure, despite full digitalization, such patients were excluded from further experimentation with this drug. This restriction did not apply to CIBA 39,089-Ba, since this latter drug did not affect the pressures in the lesser circulation. Consequently, Group II (patients studied with CIBA 39,089-Ba) included on an average more severely ill patients than those in Group I. This difference was evident from the exercising pulmonary capillary pressure, which was 19 mm. Hg in Group I and 25 mm. Hg in Group II. Yet, this difference favours propranolol and tends to enhance the difference in the effects of the two beta-blockers on myocardial contractility.

The mechanism underlying this difference is not evident. Brunner *et al.* (1967), working with catecholamine-depleted cats, noticed a positive inotropic effect of CIBA 39,089-Ba. This suggests that this drug has some intrinsic sympathomimetic action which, at the doses used in the present study, may remain effective as regards the inotropic function of the myocardium, while it is overcome by the beta-blocking properties of the drug as regards the chronotropic functions of the heart. Recently, Levy and Richards (1966), comparing the inotropic and chronotropic effects of 6 beta-adrenergic blocking drugs and of their optical isomers*, showed that some of these compounds (dl-Kö-592 and dl-propranolol), while having almost equipotent beta-adrenolytic properties, differed widely with respect to their inotropic effects on the heart. They found that pronethalol and propranolol had an intrinsic depressant effect on myocardial contractile force unrelated to their beta-adrenergic blocking potency, possibly connected with their chemical structures, i.e. with the naphthyl-nucleus characteristic of these two drugs. In view of these findings, the

different chemical structures of propranolol and of CIBA 39,089-Ba may explain the difference in their inotropic effect on the heart muscle.

The data presented suggest that CIBA 39,089-Ba acts as a potent beta-adrenergic receptor inhibitor in terms of its effects on the regulation of the heart rate, but differs from propranolol in that it depresses myocardial contractility to a significantly less pronounced extent. If confirmed in further experimentation, this evidence would have important therapeutic implications, since with CIBA 39,089-Ba, full benefit of beta-adrenergic blockade may be given to patients at a definitively lower risk of aggravating heart failure. Up to the present, over 50 patients have been treated in this hospital with this drug with satisfactory results and no detectable side-effects. The compound is regularly effective by the oral route, and seems to represent an appreciable advance in the therapeutic scope of beta-adrenergic blocking drugs.

SUMMARY

In order to evaluate the risk of precipitating heart failure with beta-adrenergic blocking drugs, 34 patients with organic disease of the left heart were given either 5 mg. propranolol or 5 mg. CIBA 39,089-Ba, a new specific beta-receptor antagonist, during the course of pre-operative catheterization. Propranolol slowed the heart rate by 16 per cent at rest and by 9 per cent during exercise, and reduced the cardiac output by 15 per cent at rest and by 17 per cent during exercise. While the left ventricular stroke work remained practically unchanged, there was a 4 mm. Hg increase in pulmonary wedge pressure at rest and a 7 mm. Hg increase during exercise following treatment with propranolol. This finding is considered as evidence of a depressant effect of the drug on myocardial contractility. This effect was slight in well-compensated patients, but was considerable in patients with increased resting pulmonary wedge pressure.

CIBA 39,089-Ba produced an effect very similar to that of propranolol as regards heart rate, which was lowered by 15 per cent at rest and by 16 per cent during exercise, but produced only a small decrease in the resting cardiac output, the drug-induced bradycardia being to a large extent offset by a higher stroke output. Furthermore, this drug did not significantly change the resting or exercising pulmonary wedge pressure even in severely disabled patients in frank heart failure. It is concluded that CIBA 39,089-Ba is a potent beta-receptor blocker in terms of its negative chronotropic effect, but differs from propranolol in that it produces a significantly less conspicuous decrease in myocardial

* Pronethalol, propranolol, dichloroisoproterenol, MJ-1998, MJ-1999 (Mead Johnson Research Center, Indiana), and Kö-592 (Boehringer Sohn, Ingelheim).

contractile force. It is suggested that this difference may be ascribed to the difference in the chemical structures of the two drugs.

The authors are indebted to Geistlich Ltd., Wolhusen, Switzerland, for the generous gift of propranolol. They are also grateful to Dr. P. Imhof of CIBA Ltd., Basle, Switzerland, for kindly supplying CIBA 39,089-Ba.

REFERENCES

- Bath, J. C. J. L. (1966). Treatment of cardiac arrhythmias in unanesthetized patients. *Amer. J. Cardiol.*, **18**, 415.
- Black, W. L., and Rolett, E. L. (1965). Changes in cardiac performance following propranolol in anesthetized dogs. *Circulation*, **32**, Suppl. II, 52.
- Brunner, H., Hedwall, P., Meyer, M., and Wilhelm, M. (1967). Pharmakologische Untersuchungen mit CIBA 39,089-Ba, einem adrenergischen Beta-Rezeptoren Blocker. *Arzneimittel-Forsch.* In the press.
- Burkart, F., Barold, S., and Sowton, E. (1967). Patient as his own control in exercise studies. *Amer. J. Cardiol.* In the press.
- Chamberlain, D. A. (1966). Effects of beta adrenergic blockade on heart size. *Amer. J. Cardiol.*, **18**, 321.
- Fiene, T. J., Griffin, J. R., and Harrison, D. C. (1965). Beta-adrenergic blockade with propranolol in atrial arrhythmias. *Circulation*, **32**, Suppl. II, 84.
- Fleckenstein, A., Freund, H. J., Kammermeier, H., and Döring, J. (1964). Akutes Myokardversagen infolge Sympathicus-Ausschaltung mittels β -Rezeptoren-Blockern. *Pflügers Arch. ges. Physiol.*, **279**, R 12.
- Gillam, P. M. S., and Prichard, B. N. C. (1965). Use of propranolol in angina pectoris. *Brit. med. J.*, **2**, 337.
- , and — (1966). Propranolol in the therapy of angina pectoris. *Amer. J. Cardiol.*, **18**, 366.
- Ginn, W. M., Jr., Irons, G. V., and Orgain, E. S. (1965). Use of propranolol in cardiac arrhythmias. *Circulation*, **32**, Suppl. II, 97.
- Hamer, J., Grandjean, T., Melendez, L., and Sowton, G. E. (1964). Effect of propranolol (Inderal) in angina pectoris: preliminary report. *Brit. med. J.*, **2**, 720.
- , —, and — (1966). Effect of propranolol (Inderal) on exercise tolerance in angina pectoris. *Brit. Heart J.*, **28**, 414.
- , and Sowton, E. (1965). Cardiac output after beta-adrenergic blockade in ischaemic heart disease. *Brit. Heart J.*, **27**, 892.
- Harris, A. (1966). Long term treatment of paroxysmal cardiac arrhythmias with propranolol. *Amer. J. Cardiol.*, **18**, 431.
- Harris, W. S., Schoenfeld, C. D., Brooks, R. H., and Weissler, A. M. (1966). Effect of beta-adrenergic blockade on the hemodynamic responses to epinephrine in man. *Amer. J. Cardiol.*, **17**, 484.
- Harrison, D. C., Braunwald, E., Glick, G., Mason, D. T., Chidsey, C. A., and Ross, J., Jr. (1964). Effects of beta-adrenergic blockade on the circulation with particular reference to observations in patients with hypertrophic subaortic stenosis. *Circulation*, **29**, 84.
- , Griffin, J. R., and Fiene, T. J. (1965). Effects of beta-adrenergic blockade with propranolol in patients with atrial arrhythmias. *New Engl. J. Med.*, **273**, 410.
- Keelan, P. (1965). Double-blind trial of propranolol (Inderal) in angina pectoris. *Brit. med. J.*, **1**, 897.
- Levy, J. V., and Richards, V. (1966). Inotropic and chronotropic effects of a series of β -adrenergic blocking drugs: Some structure-activity relationships. *Proc. Soc. exp. Biol.*, **122**, 373.
- Lüthy, E., and Hegglin, R. (1966). Zur Therapie mit β -adrenergischen Blockern. *Schweiz. Ärztesg.*, **47**, 381.
- Nakano, J., and Kusakari, T. (1965). Effects of propranolol on the cardiovascular performance. *Fed. Proc.*, **24**, 712.
- Paley, H. W., McDonald, I. G., and Peters, F. W. (1965). Effects of beta-adrenergic receptor suppression on left ventricular response to exercise in man. *Circulation*, **32**, Suppl. II, 167.
- Rabkin, R., Stables, D. P., Levin, N. W., and Suzman, M. M. (1966). The prophylactic value of propranolol in angina pectoris. *Amer. J. Cardiol.*, **18**, 370.
- Robinson, B. F., Kahler, R. L., Epstein, S. E., and Braunwald, E. (1965). Effects of beta-adrenergic blockade in man on the hemodynamic response to maximal exercise. *Fed. Proc.*, **24**, 590.
- Rowlands, D. J., Howitt, G., and Markman, P. (1965). Propranolol (Inderal) in disturbances of cardiac rhythm. *Brit. med. J.*, **1**, 891.
- Schamroth, L. (1966). Immediate effects of intravenous propranolol on various cardiac arrhythmias. *Amer. J. Cardiol.*, **18**, 438.
- Scheu, H. (1966). Therapie mit beta-adrenergischen Blockern. *Schweiz. med. Wschr.*, **96**, 127.
- Snow, P. J. D. (1965). Effects of propranolol in myocardial infarction. *Lancet*, **2**, 551.
- (1966). Treatment of acute myocardial infarction with propranolol. *Amer. J. Cardiol.*, **18**, 458.
- Sowton, E., and Hamer, J. (1966). Hemodynamic changes after beta adrenergic blockade. *Amer. J. Cardiol.*, **18**, 317.
- Srivastava, S. C., Dewar, H. A., and Newell, D. J. (1964). Double-blind trial of propranolol (Inderal) in angina of effort. *Brit. med. J.*, **2**, 724.
- Stephen, S. A. (1966). Unwanted effects of propranolol. *Amer. J. Cardiol.*, **18**, 463.
- Stock, J. P. P., and Dale, N. (1963). Beta-adrenergic receptor blockade in cardiac arrhythmias. *Brit. med. J.*, **2**, 1230.
- Szekely, P., Jackson, F., Wynne, N. A., Vohra, J. K., Batson, G. A., and Dow, W. I. M. (1966). Clinical observations on the use of propranolol in disorders of cardiac rhythm. *Amer. J. Cardiol.*, **18**, 426.
- Vogel, J. H. K. (1965). Propranolol therapy of cardiac arrhythmias. *New Engl. J. Med.*, **273**, 1052.
- Widimsky, J., Berglund, E., and Malmberg, R. (1963). Effect of repeated exercise on the lesser circulation. *J. appl. Physiol.*, **18**, 983.
- Wolfson, S., Heinle, R. A., Herman, M. V., Kemp, H. G., Sullivan, J. M., and Gorlin, R. (1966). Propranolol and angina pectoris. *Amer. J. Cardiol.*, **18**, 345.