Effect of tolamolol versus propranolol on cardiovascular haemodynamics in patients with angina

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In a double-blind crossover study, 8 patients with angina and with angiographically documented coronary artery disease received two weeks apart 5 successive doses of 4 mg tolamolol (20 mg) and 5 successive doses of 2 mg propranolol (10 mg) administered intravenously within 25 minutes. After 20 mg tolamolol, a significant decrease occurred in heart rate (14%), in aortic systolic pressure (4%), in left ventricular systolic pressure (4%), in left ventricular dp/dt (25%), in cardiac index (18%), in stroke index (6%), in systolic ejection rate (11%), and in left ventricular work (24%), and a significant increase in left ventricular end-diastolic pressure (39%) and in systemic vascular resistance (17%). After 10 mg propranolol, a significant decrease occurred in heart rate (13%), in aortic systolic pressure (3%), in left ventricular systolic pressure (3%), in left ventricular dp/dt (28%), in cardiac index (22%), in stroke index (10%), in systolic ejection rate (16%), and in left ventricular work (27%), and a significant increase in left ventricular end-diastolic pressure (47%) and in systemic vascular resistance (25%). No significant difference in haemodynamics was observed between these equipotent doses of intravenous tolamolol and propranolol except that tolamolol caused a significantly smaller increase in systemic vascular resistance.

Tolamolol (UK 6558) is a new cardioselective beta-adrenergic blocking agent (Briant *et al.*, 1973) which was found (Hillis, 1974) not to have the direct depressant action of propranolol on myocardial contractility. We found both intravenous (Aronow *et al.*, 1972) and oral (Aronow *et al.*, 1973) tolamolol to be useful in the treatment of certain cardiac arrhythmias. Sood and Havard (1973) found that tolamolol increased the exercise tolerance of patients with angina. These investigators also found that doses of intravenous tolamolol capable of blocking cardiac sympathetic beta-receptors did not significantly affect the forced expiratory volume in 1 second in these patients.

A cardioselective beta-adrenergic blocking drug which produces less myocardial depression than propranolol would have therapeutic advantages over propranolol. Therefore, this double-blind crossover study was performed to evaluate the effects of equipotent doses of intravenous tolamolol versus propranolol on cardiovascular haemodynamics in the same patients.

Received 17 May 1974.

Subjects and methods

Studies were made on 8 men between the ages of 46 and 60 years (mean age, 51.1 years), with severe stable angina pectoris, who needed cardiac catheterization and coronary angiography; 5 had a history of a documented transmural myocardial infarction more than 1 year before and 1 patient had a history of a documented subendocardial myocardial infarction more than 1 year previously. None of the 8 patients had cardiomegaly present on physical examination or on their chest x-rays (PA and lateral), a previous history of congestive heart failure, or a third heart sound. None of the 8 subjects had pulmonary, haematological, hepatic, or renal disease. None of the 8 men had a systolic blood pressure less than 100 mmHg, atrioventricular block, a bundle-branch block, or sinus bradycardia. None of the 8 patients was a smoker at the time of the study and none received any medication except for sublingual nitroglycerin within at least 2 weeks of each of their 2 cardiac catheterizations. Informed consent was obtained in each of the 8 men who participated in this study after the nature of the procedures was fully explained.

A right and left heart cardiac catheterization was performed in the fasting state in each of the 8 patients 2 weeks apart. No premedication was given. None of the

subjects took any medication on the mornings of their 2 cardiac catheterizations. Pressures were measured with Statham model P23 Db catheter tip pressure transducers and recorded with an Electronics for Medicine recorder. The left ventricular dp/dt was calculated by electronic means with an Electronics for Medicine RC Differentiator model RC-1. After the pressures were obtained, the cardiac output was determined by the indocyanine green dye dilution method. Duplicate determinations were made.

After the control measurements were made between 8 a.m. and 9 a.m., in a double-blind randomized manner, 4 mg tolamolol (2 ml) or 2 mg propranolol (2 ml) were injected intravenously over 1 minute at 5-minute intervals until a total dose of 20 mg tolamolol or 10 mg propranolol was given. Two weeks later the other drug was administered. The order of treatments (tolamolol or propranolol) was randomly allocated using a pseudo random number generator. Pressures and left ventricular dp/dt measurements were obtained each minute for the 5 minutes after each dose of intravenous tolamolol or propranolol and the results averaged after each dose. The cardiac output was measured in duplicate between the fourth and fifth minute after the fifth dose of tolamolol or propranolol was administered.

Left ventriculography and coronary angiography were not performed until after completion of the above measurements. Coronary angiography revealed more than 75 per cent narrowing of one or more major coronary vessels in all 8 patients with angina.

The stroke index (ml/beat per m^2) was determined by dividing the cardiac index by the heart rate.

The systolic ejection rate (ml/sec per m^2) was determined by dividing the stroke index by the left ventricular systolic ejection time.

The left ventricular work (kg m/min per m^2) was calculated by the following formula:

$$LVW = (\text{mean LVSP (mmHg)} - \text{LVEDP (mmHg)}) \times \text{cardiac index (l./min per } m^2) \times 0.136.$$

The systemic vascular resistance (dynes sec cm^{-5}/m^2) was calculated by dividing 80 times the difference between the mean aortic pressure and mean right atrial pressure in mmHg, by the cardiac output in l./min.

Student's *t* test for paired data was used to determine the effect of each dose of tolamolol or propranolol on the control variables. Paired *t* tests were performed on the differences between tolamolol and propranolol. In addition, all observations were converted to natural logs, and paired *t* tests were performed on the log (baseline/final) measures (Snedecor and Cochran, 1967).

Results

No adverse effects occurred in any patient during this study.

Table 1 shows the effect of tolamolol on the mean values of 11 haemodynamic variables ± 1 standard deviation in the 8 anginal patients. Table 1 also shows whether, after each dose of tolamolol, the

TABLE 1 Effect of tolamolol on haemodynamics

Variable	Control	After 4 mg	After 8 mg	After 12 mg	After 16 mg	After 20 mg
Heart rate (beats/min)	71.5 ± 5.2	64.1* ± 3.9	62.8* ± 4.8	62.4* ± 1.8	62.3* ± 4.6	61.8* ± 4.7
Aortic systolic pressure (mmHg)	123.8 ± 14.9	120.5† ± 15.9	120.3† ± 15.5	119.5† ± 16.1	119.0† ± 15.9	119.0† ± 15.3
Aortic diastolic pressure (mmHg)	74.6 ± 9.1	72.9 ± 8.7	72.3 ± 8.0	72.3 ± 8.3	71.8 ± 8.6	72.3 ± 8.0
LV systolic pressure (mmHg)	123.8 ± 14.9	120.3† ± 16.2	120.0† ± 17.1	119.8† ± 15.8	119.0† ± 15.9	118.8† ± 15.3
LV end-diastolic pressure (mmHg)	8.0 ± 2.3	9.6* ± 3.0	10.0* ± 3.3	10.8* ± 3.0	10.9* ± 3.3	11.1* ± 3.5
LV dp/dt (mmHg/sec)	1416 ± 165	1216* ± 138	1151* ± 119	1113* ± 113	1094* ± 119	1059* ± 119
Cardiac index (l./min per m^2)	3.06 ± 1.3					2.51* ± 1.7
Stroke index (ml/beat per m^2)	43.1 ± 3.8					40.6† ± 4.0
Systolic ejection rate (ml/sec per m^2)	147.9 ± 11.6					132.0* ± 9.3
LV work (kg m/min per m^2)	4.82 ± 0.64					3.67* ± 0.53
Systemic vascular resistance (dynes sec cm^{-5}/m^2)	1187 ± 163					1390* ± 190

* $P < 0.001$, † $P < 0.01$, ‡ $P < 0.05$ compared to the control period.
LV = left ventricular.

mean value of each haemodynamic variable is significantly different from the control value.

After 20 mg intravenous tolamolol, the mean heart rate significantly decreased 14 per cent, the mean aortic systolic pressure significantly decreased 4 per cent, the mean aortic diastolic pressure did not significantly change, the mean left ventricular systolic pressure significantly decreased 4 per cent, the mean left ventricular end-diastolic pressure significantly increased 39 per cent, the mean left ventricular dp/dt significantly decreased 25 per cent, the mean cardiac index significantly decreased 18 per cent, the mean stroke index significantly decreased 6 per cent, the mean systolic ejection rate significantly decreased 11 per cent, the mean left ventricular work significantly decreased 24 per cent, and the mean systemic vascular resistance significantly increased 17 per cent.

Table 2 shows the effect of propranolol on the mean values of 11 haemodynamic variables ± 1 standard deviation in the 8 anginal patients. Table 2 also shows whether, after each dose of propranolol, the mean value for each haemodynamic variable is significantly different from the control value.

After 10 mg intravenous propranolol, the mean

heart rate significantly decreased 13 per cent, the mean aortic systolic pressure significantly decreased 3 per cent, the mean aortic diastolic pressure did not significantly change, the mean left ventricular systolic pressure significantly decreased 3 per cent, the mean left ventricular end-diastolic pressure significantly increased 47 per cent, the mean left ventricular dp/dt significantly decreased 28 per cent, the mean cardiac index significantly decreased 22 per cent, the mean stroke index significantly decreased 10 per cent, the mean systolic ejection rate significantly decreased 16 per cent, the mean left ventricular work significantly decreased 27 per cent, and the mean systolic vascular resistance significantly increased 25 per cent.

Excluding systemic vascular resistance, no significant difference on the other 10 haemodynamic variables was observed between equipotent doses of intravenous tolamolol and propranolol. Significantly less of an increase in systemic vascular resistance occurred after 20 mg intravenous tolamolol than after 10 mg intravenous propranolol ($t=2.430$; $P<0.05$). This significant difference was found by performing paired t tests on the log (baseline/final) measures.

TABLE 2 Effect of propranolol on haemodynamics

Variable	Control	After 2 mg	After 4 mg	After 6 mg	After 8 mg	After 10 mg
Heart rate (beats/min)	69.5 ± 4.1	63.1* ± 5.7	61.4* ± 6.2	61.0* ± 6.0	60.6* ± 5.9	60.4* ± 5.6
Aortic systolic pressure (mmHg)	124.6 ± 18.6	121.9† ± 19.6	121.3† ± 19.2	121.4† ± 19.4	121.1‡ ± 19.4	120.9† ± 19.1
Aortic diastolic pressure (mmHg)	75.4 ± 11.5	74.1 ± 12.2	73.5 ± 11.9	73.3 ± 12.0	73.5 ± 12.5	73.0 ± 11.9
LV systolic pressure (mmHg)	124.6 ± 18.6	122.0† ± 19.5	121.8† ± 19.1	121.5† ± 19.3	121.1† ± 19.4	121.1† ± 18.8
LV end-diastolic pressure (mmHg)	8.5 ± 2.3	9.9* ± 3.2	10.6* ± 3.4	11.5* ± 3.3	11.9* ± 3.4	12.5* ± 3.7
LV dp/dt (mmHg/sec)	1406 ± 216	1156* ± 141	1076* ± 154	1043* ± 151	1025* ± 147	1013* ± 158
Cardiac index (l./min per m ²)	2.99 $\pm .23$					2.33* $\pm .24$
Stroke index (ml/beat per m ²)	43.1 ± 4.3					38.6† ± 5.4
Systolic ejection rate (ml/sec per m ²)	145.8 ± 14.5					122.6* ± 16.0
LV work (kg m/min per m ²)	4.71 $\pm .74$					3.44* $\pm .69$
Systemic vascular resistance (dynes sec cm ⁻⁵ /m ²)	1237 ± 281					1542* ± 330

* $P<0.001$, † $P<0.01$, ‡ $P<0.05$ compared to the control period.
LV=left ventricular.

Discussion

Our data on the effect of intravenous propranolol on heart rate, aortic pressure, left ventricular systolic and end-diastolic pressure, left ventricular dp/dt, cardiac index, stroke index, systolic ejection rate, left ventricular minute work, and systemic vascular resistance agree in general with those previously reported (Sowton and Hamer, 1966; Nakano and Kusakari, 1966; Wolfson *et al.*, 1966; Bloomfield and Sowton, 1967; Robin *et al.*, 1967; Parker, West, and Di Giorgi, 1968; Lewis and Brink, 1968). Our data also indicate that equipotent doses of intravenous tolamolol and propranolol produce similar changes in heart rate, aortic pressure, left ventricular systolic and end-diastolic pressure, left ventricular dp/dt, cardiac index, stroke index, systolic ejection rate, and left ventricular minute work.

Briant and associates (1973) showed that practolol and tolamolol produced greater antagonism of the chronotropic and inotropic responses to intravenous isoprenaline than of the vasodilator response to either intravenous or intra-arterial isoprenaline and, therefore, produced cardioselective beta-receptor blockade. Our data indicate that after equipotent doses of intravenous tolamolol and propranolol are used, significantly less rise in systemic vascular resistance occurs after intravenous tolamolol than after intravenous propranolol. These findings are consistent with a selective action of tolamolol on the cardiac beta-adrenoceptors.

In conclusion, tolamolol is a new beta-adrenergic blocking drug which, like propranolol, may produce depression of myocardial activity. However, tolamolol may have a therapeutic advantage over propranolol by virtue of a cardioselective beta-adrenergic blocking action.

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