Comparative Action of Propranolol and Sotalol (MJ-1999) on Myocardial Oxygen Consumption in Dogs: Hemodynamic Correlates[1] (34420)

JOSEPH V. LEVY[2]

Research Laboratories, Presbyterian Hospital, Pacific Medical Center, San Francisco, California 94115

Propranolol has been shown to be a potent beta-adrenergic receptor blocking drug capable of reducing myocardial oxygen consumption ($M\dot{V}O_2$) in experimental animals and man (1–4). This effect is associated with decreases in heart rate and myocardial contractility, which are two of the main determinants of $M\dot{V}O_2$ (5). It is presumed that the decrease in $M\dot{V}O_2$ produced by this drug is primarily responsible for its therapeutic effect in relieving angina pectoris in ischemic heart disease (1–3). However, the well-known nonspecific myocardial depressant actions of propranolol may also be contributing to this therapeutic effect, particularly with large doses.

The availability of a variety of other beta-adrenergic receptor blocking drugs possessing specific myocardial beta-adrenergic blocking effects but devoid of local anesthetic or quinidine-like actions on the heart now allows their comparison with propranolol. Sotalol (racemic MJ-1999), recently introduced for clinical trials in man (6–8), appears to be uniquely suited for comparison with propranolol. In confirmation of a variety of experimental studies in animals (9–13), sotalol has been shown to have comparatively minimal cardiodepressant action in man in doses capable of blocking sympathetic stimulant effects on the heart (7, 8).

Because of the potential use of propranolol and sotalol in the treatment of ischemic heart disease, a comparison of their effects on $M\dot{V}O_2$ and various hemodynamic functions appeared desirable. An analysis of the hemodynamic and $M\dot{V}O_2$ effects of sotalol includes studies of its (+)-isomer, which is relatively inactive as a beta-adrenergic blocker, as well as experiments where heart rate was held constant during drug effects.

Methods. Experiments were performed on mongrel dogs anesthetized with 25 mg/kg of pentobarbital intravenously. Tracheal intubation was performed and constant ventilation was maintained with a Palmer respirator using room air. In some dogs, where control arterial pO_2 was less than 80 mm Hg, oxygen was also administered via the respirator inlet to increase the arterial pO_2. The heart was exposed by performing a right thoracotomy. The pericardium was incised, and a cradle was formed by suturing the edges of the pericardium to the thorax. A Honneywell strain gauge arch (14) was sutured to the right ventricle for the recording of right ventricular contractile force (RVCF). A catheter was placed into the coronary sinus and held in place by passing sutures around the terminal portion of the greater coronary vein at the coronary sinus. The right atrium was opened during a brief period of inflow occlusion, and the other end of the coronary sinus catheter was inserted and secured in place. Thus, the coronary sinus blood flow (CSBF) was exteriorized, permitting measurement of CSBF and sampling of coronary sinus blood for blood gas analysis via an appropriately placed three-way stopcock. A femoral artery and vein were cannulated for the recording of femoral arterial blood pressure and injection of drugs. A catheter was placed directly into the left ventricle and connected to a Statham transducer for recording left ventricular

[1] Results of these studies were presented in part at a Colloquy on Sotalol held in Atlantic City, April 15, 1968.

[2] Recipient of a Research Career Program Award from the National Heart Institute.

TABLE I. Myocardial and Hemodynamic Effects of Propranolol (0.5 mg/kg) in Open Chest Dogs ($N = 5$).[a]

	Control (mean ± SEM)	Percentage change after propranolol (mean ± SEM) (min): 5	30	p[b] 5	30
$M\dot{V}O_2$ (ml of O_2/min/100 g)	4.96 ± .46	−17.1 ± 5	−11.4 ± 9	<.025	>.40
CSBF (ml/min/100 g)	41.3 ± 6.8	−18.7 ± 6	−13.7 ±10	<.05	>.4
HR (beats/min)	152 ± 9	−14.6 ± 3	−13.6 ± 7	<.025	>.10
MABP (mm Hg)	90 ± 6	−1.2 ± 5	−3.0 ± 8	>.50	>.50
LVBP (mm Hg)	100 ± 5	−4.5 ± 3	−8.6 ± 6	>.40	>.20
RVCF (mm)	16.2 ± 2.8	−15.4 ± 9	−18.0 ± 8	>.10	>.05

[a] $M\dot{V}O_2$ = myocardial oxygen consumption; CSBF = coronary sinus blood flow; HR = heart rate; MABP = femoral mean arterial blood pressure; LVBP = left ventricular blood pressure; and RVCF = right ventricular contractile force.

[b] Paired (correlated mean) t test, 5 and 30 min vs. control.

blood pressure (LVBP). Volume replacement of blood obtained for various blood sampling procedures was made by suitable administration of isotonic saline, and reinfusion of blood. Blood gas measurements were made using a Beckman model 160 gas analyzer system. Hematocrit, hemoglobin, and pH were also measured. Heart rate (HR) in beats/min was measured from a lead II ECG. Recordings of RVCF, LVBP, mean femoral arterial blood pressure (MABP) were made with an Electronics for Medicine multichannel recorder. In those experiments where heart rate was to be controlled, platinum electrodes were attached to the right atrium, and the heart paced, using a model 198A American Electronics Laboratory stimulator. All $M\dot{V}O_2$ and CSBF values were expressed per 100 g of heart weight. The individual effects produced by propranolol, sotalol, and saline treatments were analyzed for statistical significance by comparison of paired observations (correlated means) t test. Comparison of mean effects produced by any two different treatments was done using Student's t test for uncorrelated means. Statistical significance was defined when p equaled or was less than 0.05.

Results. Table I summarizes the myocardial and hemodynamic effects produced by slow (1 min) intravenous injection of 0.5 mg/kg of propranolol in 5 dogs. Significant decreases in $M\dot{V}O_2$, CSBF, and HR were observed 5 min after giving the drug. Although RVCF was reduced by 15–18%, these changes were not significant. No significant changes in MABP or LVBP were observed. Thirty min after propranolol none of the measured func-

TABLE II. Myocardial and Hemodynamic Effects of Propranolol (1.0 mg/kg) in Open Chest Dogs ($N = 5$).[a]

	Control (mean ± SEM)	Percentage change after propranolol (mean ± SEM) (min): 5	30	p 5	30
$M\dot{V}O_2$ (ml of O_2/min/100 g)	3.84 ± 0.29	−21.4 ± 5.5	−18.5 ± 7.9	<0.025	<0.05
CSBF (ml/min/100 g)	31.5 ± 2.8	−21.7 ± 4.6	−17.3 ± 4.8	<0.020	<0.05
HR (beats/min)	154 ± 5	−18.7 ± 2.7	−21.3 ± 2.8	<0.01	<0.01
MABP (mm Hg)	95 ± 5	−0.5 ± 1.8	−0.2 ± 4.0	>0.8	>0.9
LVBP (mm Hg)	103 ± 4	−1.5 ± 1.8	+1.6 ± 3.5	>0.4	>0.2
RVCF (mm)	26.0 ± 5.6	−18.0 ± 5.1	−11.1 ± 4.0	=0.05	=0.05

[a] Abbreviations same as in Table I.

TABLE III. Myocardial and Hemodynamic Effects of Sotalol (5.0 mg/kg) in Open Chest Dogs ($N = 5$).[a]

	Control (mean ± SEM)	Percentage change after sotalol (mean ± SEM) (min): 5	30	p 5	30
$M\dot{V}O_2$ (ml of O_2/min/100 g)	5.69 ± 0.33	−33.4 ± 5	−34.6 ± 6	<.005	<.005
CSBF (ml/min/100 g)	51.0 ± 5	−33.6 ± 6	−37.1 ± 8	<.01	<.025
HR (beats/min)	162 ± 6	−30.2 ± 2	−34 ± 3	<.001	<.001
MABP (mm Hg)	118 ± 5	−9 ± 7	−9 ± 5	>.10	>.10
LVBP (mm Hg)	135 ± 8	−8 ± 6	−11 ± 5	>.20	>.10
RVCF (mm)	31.3 ± 3.9	−19.3 ± 6	−20.6 ± 4	<.025	<.005

[a] Abbreviations same as in Table I.

tions were significantly different than the preinjection values.

Table II indicates the changes produced by a 1.0 mg/kg dose of propranolol. Greater decreases in $M\dot{V}O_2$, CSBF, and HR were noted with this dose. Heart rate and CSBF were still significantly lower than controls 30 min after drug administration. This is in contrast to the effects seen with the lower dose. The decreases in RVCF at 5 and 30 min were barely significant compared to predrug control values.

Table III shows the changes in cardiovascular functions produced by 5.0 mg/kg of sotalol. Significant decreases in $M\dot{V}O_2$, CSBF, HR, and RVCF were noted at 5 and 30 min following drug administration. Percentagewise, the decrease in CSBF produced at 5 min by sotalol was greater than that seen with the 0.5 mg/kg dose of propranolol (33.6 ± 6% vs. 18.7 ± 6%, mean ± SEM). A similar magnitude of difference was noted when comparing 30-min values. The decrease in $M\dot{V}O_2$ produced by sotalol was nearly twice as great as that of 0.5 mg/kg propranolol (33.4 ± 5% vs. 17.1 ± 5% at 5 min). The difference between the two drugs was even greater at 30 min. The differences between sotalol and propranolol on CSBF and $M\dot{V}O_2$ were associated with differences in HR changes. Thus sotalol produced over twice as great a decrease in HR as propranolol at 5 and 30 min. The greater decrease in $M\dot{V}O_2$ seen is primarily reflected by greater differences in magnitude and persistence of HR and CSBF changes.

In order to further characterize the mechanisms involved in the metabolic and hemodynamic changes produced by sotalol, experiments were done using the (+)-isomer

TABLE IV. Myocardial and Hemodynamic Effects of (+)-Sotalol (5.0 mg/kg) on Open Chest Dogs ($N = 5$).[a]

	Control (mean ± SEM)	Percentage change after drug (mean ± SEM) (min): 5	30	p 5	30
$M\dot{V}O_2$ (ml of O_2/min/100 g)	3.93 ± 0.29	−13.2 ± 4.3	+2.6 ± 11.5	<.05	>.50
CSBF (ml/min/100 g)	31.8 ± 2	−10.2 ± 6.9	+4.1 ± 12.0	>.10	>.50
HR (beats/min)	153 ± 14	−26.4 ± 3.8	−16.2 ± 3.9	<.01	<.025
MABP (mm Hg)	111 ± 10	−6.1 ± 6.6	+0.2 ± 6.5	>.20	>.20
LVBP (mm Hg)	125 ± 12	−8.4 ± 6.7	−3.1 ± 7.0	>.20	>.50
RVCF (mm)	25.8 ± 0.9	−12 ± 5.6	+2 ± 7.2	>.05	>.50

[a] Abbreviations same as in Table I.

of the drug. Previous work has shown that the (+)-isomer is approximately one-eleventh as potent as the racemic form of the drug in terms of its beta-adrenergic blocking action (10, 11). Table IV summarizes the results of these experiments, using a 5.0 mg/kg dose of the (+)-isomer of sotalol. Several features are evident from these data. First, the only significant changes from control values produced by (+)-sotalol were in $M\dot{V}O_2$ and HR. Secondly the decrease in $M\dot{V}O_2$ seen at the 5-min period was not evident at 30 min. However, the HR decrease did persist for the 30-min period of observation. These data would suggest that the 13.2 ± 4.3% decrease in $M\dot{V}O_2$ produced by this isomer at 5 min was probably determined by the concomitant decreases in HR (26.4 ± 3.8%) and contractility (12 ± 5.6%). When the HR had recovered to 84% of control and RVCF was above control at 30 min, the $M\dot{V}O_2$ effect was no longer significant.

To gain further information on the influence of HR changes on the $M\dot{V}O_2$ effect produced by sotalol, four experiments were performed in which heart rate was held constant by electrical pacing (150–200 beats/-min). The results of these experiments showed that when HR was not allowed to change with administration of a 5.0 mg/kg dose of racemic sotalol, no significant change in $M\dot{V}O_2$ was seen at 5 or 30 min. This lack of effect on $M\dot{V}O_2$ was associated with insignificant changes in RVCF, MABP, and LVBP.

Saline-injected controls, comparably treated as the propranolol and sotalol groups, showed no significant changes in any of the measured functions over the 30-min experimental period. None of the functions changed by more than ± 5% during the course of the experiments.

Discussion. Various studies have shown that propranolol is approximately 4–10 times more potent than sotalol in terms of its myocardial beta-adrenergic blocking action (6, 9, 15). In this study, comparison of the two drugs was made using 0.5 and 1.0 mg/kg doses of propranolol and 5.0 mg/kg of sotalol. The adequacy of these doses in producing myocardial beta-adrenergic blockade in the dog has been described elsewhere (11–13, 15, 16, 23–25).

For example, a 0.5 mg/kg dose of propranolol produced approximately the same inhibition of isoproterenol-induced increases in RVCF as a 3–4 mg/kg dose of sotalol (15). The pharmacological half-life of a 0.5 mg/kg dose of propranolol in terms of inhibition of isoproterenol tachycardia is of the order of 60 min (24). A 0.8 mg/kg dose of propranolol produces complete blockade of isoproterenol tachycardia for a period in excess of 90–100 min (24). A 2.0 mg/kg dose of sotalol produces a maximum 85% inhibition of isoproterenol effects on RVCF. This inhibition is still more than 75% 30 min after giving the drug (25). A cumulative dose of 3.0 mg/kg of sotalol produced nearly complete antagonism of isoproterenol-induced changes in femoral blood flow, RVCF, and HR in anesthetized dogs (23).

An important point to emphasize is that the inhibition of these adrenergic responses is considered a more valid pharmacological criterion of specific beta-adrenergic blockade than observations on spontaneous HR changes that are attributed to beta-blockade. Moreover, the similar (or dissimilar) changes in RVCF or HR do not necessarily mean that beta-adrenergic blockade is equal (or unequal) in other organs and tissues (23). However, sotalol does appear to affect all beta-receptor-mediated systems equally in any given species (11, 12, 23).

The significant and sustained lowering of $M\dot{V}O_2$ produced by racemic sotalol observed in this study can largely be attributed to the HR and contractility decreases caused by its beta-adrenergic blocking action. This view is supported by the finding that the (+)-isomer, which is only one-eleventh as potent a beta-blocker as the racemic form, produced less than one-half the $M\dot{V}O_2$ decrease seen with racemic sotalol. A shorter duration of action was also noted. Moreover, if HR was held constant, racemic sotalol failed to significantly lower $M\dot{V}O_2$. Thus, these results are consistent with the findings with beta-adrenergic

blockade in animals and man, indicating that the HR and contractility decreases produced by these drugs are mainly responsible for the observed lowering of $M\dot{V}O_2$ (1–3). Sotalol does not possess any significant quinidine or local anesthetic-like properties which would contribute to these changes.

A primary (direct) effect of beta-adrenergic blockers on basal $M\dot{V}O_2$ is lacking as evidenced by failure of these drugs to affect myocardial O_2 uptake of quiescent cardiac muscle, even with concentrations several hundred times greater than effective beta-blocking levels (9).

Sotalol, like propranolol, produced a decrease in coronary blood flow, although the effect of the former drug is greater in magnitude and longer lasting. Again, as with $M\dot{V}O_2$ changes, the decrease in CSBF produced by sotalol is associated with its beta-blocking and HR action since, in the (+)-sotalol and HR-controlled experiments, no significant changes in this function were seen. Hence, evidence has been obtained supporting the concept that the secondary reduction in $M\dot{V}O_2$ produced by beta-adrenergic blockade may be largely responsible for diminished coronary flow (17). However, contrary to this interpretation is the reported ability of direct intracoronary injection of sotalol (3 mg/kg) to produce a 5–20% increase in coronary vascular resistance under constant coronary arterial perfusion (18). This effect was attributed to a vasoconstriction resulting from the primary beta-blocking action of the drug. Other studies have shown that the decrease in coronary blood flow observed with propranolol is the result of its negative inotropic and chronotropic effects (19). Similar interpretations of propranolol effects on coronary blood flow are supported by studies on dogs on total cardiopulmonary bypass (20). The evidence reported here, coupled with these latter reports, thus favors the contention that the decrease in coronary blood flow produced by beta-adrenergic blocking drugs such as sotalol and propranolol is mainly the result of reduced O_2 needs of the heart brought about by other pharmacological consequences of the drugs (*i.e.*, HR, and contractility changes). The contributing effect of inhibition of sympathetic vasodilator tone produced by these drugs (21) cannot be ignored, however.

Investigations in normal man suggested that sotalol, in doses capable of producing sufficient blockade of isoproterenol responses, did not reduce cardiac output or work below predrug values (8). It was speculated that if it could be verified that myocardial oxygen consumption was reduced at the time cardiac function was not impaired, cardiac efficiency would be increased as the result of the drug. The present data obtained in dogs demonstrated the potent effect of sotalol in lowering $M\dot{V}O_2$. The potentially greater oxygen-sparing effect of sotalol compared to propranolol could be the result of its greater effect on other ventricular and cardiovascular determinants of $M\dot{V}O_2$ (22). Whether or not these experimental results in dogs and normal man can be extrapolated to clinical therapeutics remains to be determined.

Summary. The two beta-adrenergic receptor blocking drugs, propranolol and sotalol (MJ-1999), were studied for their effects on myocardial oxygen consumption ($M\dot{V}O_2$) and hemodynamic functions in anesthetized, open chest dogs. Propranolol (0.5 and 1.0 mg/kg) and sotalol (5.0 mg/kg) iv produced a significant decrease in $M\dot{V}O_2$, although the effect of the latter drug was greater in magnitude and persisted longer. No significant effects on arterial or left ventricular blood pressure were produced by either drug.

The decreases in $M\dot{V}O_2$ were associated with a negative chronotropic and inotropic effect, the former change being more pronounced with sotalol. Coronary sinus blood flow (CSBF) also was decreased by both drugs, with sotalol having a greater effect than either of the doses of propranolol. The lowering of $M\dot{V}O_2$ by sotalol can be attributed largely to its negative chronotropic effect. This is supported by studies with the (+)-isomer (relatively weaker as a beta-blocker) showing significantly less change in $M\dot{V}O_2$ compared to the recemic drug. In

addition, racemic sotalol failed to significantly lower $M\dot{V}O_2$ in heart rate-controlled experiments. The decrease in CSBF could be explained by the lowering of the oxygen demands of the heart accompanying heart rate and contractility changes, although a direct coronary vasoconstriction mechanism may also contribute to the observed decrease in CSBF. These results are discussed in terms of the possible application of these drugs to the treatment of ischemic heart disease.

Data and statistical computations were provided by the Research Data Facility, Pacific Medical Center (Dir., R. Abbott). Sotatol was donated by the Mead Johnson Research Center, Evansville, Ind.

1. Epstein, S. and Braunwald, E., Med. Clin. N. Am. **52**, 1031 (1968).

2. Krasnow, N. and Barbarosh, H., Anesthesiology **29**, 814 (1968).

3. Wolfson, S., Heinle, R., Herman, M., Kemp, H., Sullivan, J., and Gorlin, R., Am. J. Cardiol. **18**, 345 (1966).

4. Ahlquist, R., Ann. Rev. Pharmacol. **8**, 259 (1968).

5. Sonnenblick, E., Ross, J., and Braunwald, E., Am. J. Cardiol. **22**, 328 (1968).

6. Lish, P., Shelanski, M., La Budde, J., and Williams, W., Current Therap. Res. **9**, 311 (1967).

7. Svedmyr, N. and Lundholm, L., Life Sci. **6**, 21 (1967).

8. Frankl, W. and Soloff, L., Am. J. Cardiol. **22**, 266 (1968).

9. Levy, J. V. and Richards, V., J. Pharmacol. Exptl. Therap. **150**, 361 (1965).

10. Levy, J. V., European J. Pharmacol. **2**, 250 (1968).

11. Lish, P., Weikel, J., and Dungan, K., J. Pharmacol. Exptl. Therap. **149**, 161 (1965).

12. Stanton, H., Kerchgessner, T., and Parmenter, K., J. Pharmacol. Exptl. Therap. **149**, 174 (1965).

13. Schmid, J. and Hanna, C., J. Pharmacol. Exptl. Therap. **156**, 331 (1967).

14. Sutfin, D. and Lefer, A., Med. Electron. Biol. Eng. **1**, 371 (1963).

15. Hoffman, R. and Grupp, G., Diseases Chest **55**, 229 (1969).

16. Shanks, R., Am. J. Cardiol. **18**, 308 (1966).

17. Berne, R., Physiol. Rev. **44**, 1 (1964).

18. Folle, L. and Aviado, D., J. Pharmacol. Exptl. Therap. **149**, 79 (1965).

19. Whitsitt, L. and Lucchesi, B., Circulation Res. **21**, 305 (1967).

20. Nayler, W., McInnes, I., Swann, J., Carson, V., and Lowe, T., Am. Heart J. **73**, 207 (1967).

21. Klocke, F., Kaiser, G., Ross, J., and Braunwald, E., Circulation Res. **16**, 376 (1965).

22. Puri, P. and Bing, R., Diseases Chest **55**, 235 (1969).

23. Wilkenfeld, B. and Levy, B., Arch. Intern. Pharmacodyn. **176**, 218 (1968).

24. Black, J., Duncan, W., and Shanks, R., Brit. J. Pharmacol. **25**, 577 (1965).

25. Somani, P., Fleming, J., Chan, G., and Lum, B., J. Pharmacol. Exptl. Therap. **151**, 32 (1966).

Received Sept. 8, 1969. P.S.E.B.M., 1970, Vol. 133.