PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 148, 834–837 (1975)

Effects of Several Antianginal Agents on Pacing-Induced S-T Segment Depression in the Atherosclerotic Rabbit (38643)

SHERRIN H. BAKY AND ROBERT J. LEE
(Introduced by M. E. GOLDBERG)

Department of Pharmacology, Squibb Institute for Medical Research, Princeton, New Jersey 08540

Increasing myocardial demand for oxygen by right atrial pacing causes ischemic S-T segment depression in the electrocardiogram of the unanesthetized, atherosclerotic rabbit (1). Unlike the S-T segment depression induced in the same animal model by administration of ergonovine (2) or by "anoxia" due to breathing an atmosphere containing 10% oxygen (3), the S-T depression induced by atrial pacing was prevented by prior administration of nitroglycerin, but not of dipyridamole. The present study describes the effects of several clinically tested antianginal agents, including chromonar, papaverine, pentaerythritol tetranitrate, isosorbide dinitrate, and propranolol, on pacing-induced S-T segment depression in the same animal model.

Methods. The methods employed were the same as those previously described (1). Male New Zealand white rabbits, 2 kg, were fed a diet containing 2% cholesterol for 10–14 wk. At that time, a 14 g polyvinyl chloride catheter was implanted in the right external jugular vein under local anesthetic. Twenty-four hours later, a bipolar pacing electrode was passed into the right atrium of the unanesthetized, catheterized animal. Surface leads were placed on the spine and sternum for recording the electrocardiogram (ECG) on a direct-writing recorder and on magnetic tape for subsequent computer analysis. Stimuli were supplied at approximately one and half times threshold voltage at a frequency of at least 100 beats/min greater than the rabbit's intrinsic heart rate, to a maximum of 420 beats/min. Readings were taken every 15 sec during the 90-sec pacing period. When two successive reproducible episodes of S-T segment depression of at least 0.5 mm (sensitivity = 1 mV/cm) at a given pacing rate were obtained, a drug was administered via the marginal vein of the left ear. Pacing at the same rate as during control periods was instituted at 1, 5, and 30 min after drug administration to determine if protection against S-T segment depression occurred.

The drugs tested in these experiments were chromonar (2, 4 mg/kg; dissolved in water), papaverine (0.5, 1 mg/kg; water), pentaerythritol tetranitrate[1] (Peritrate, 250, 500 μg/kg; polyethylene glycol-400), isosorbide dinitrate[2] (25–600 μg/kg; dilute polyethylene glycol-400), and propranolol[3] (Inderal, 100–500 μg/kg; water).

The statistical significance of the effect of each drug on the response to pacing was determined by Student's t test (4).

Results. Of the agents tested in this study, only isosorbide dinitrate (ISD) protected against the S-T segment depression induced by pacing. The magnitudes of the pacing-induced S-T segment depression in 13 animals were compared before and after administration of the various doses of ISD (Fig. 1). The mean values of S-T segment depression ± 1 SEM for each 15-sec period are plotted for 26 control pacing periods; these control depressions averaged 0.91 ± 0.07 mm at 90 sec. Standard errors are shown at the 90-sec reading for the various doses of the drug. The protection afforded by pretreatment with ISD was dose-related, with almost complete prevention of pacing-induced S-T segment depression at the 600-μg/kg dose ($P < .001$). S-T segment depressions after the 100- and 400-μg/kg doses were also significantly different from that for the control pacing periods ($P < .005$) although they were not different from each other.

Electrocardiographic tracings from a rep-

[1] Dissolved according to instructions kindly furnished by Dr. M. Winbury of Warner-Lambert Co.

[2] Supplied by Ives Laboratories; 25% isosorbide dinitrate, 75% lactose.

[3] Supplied by Ayerst Laboratories.

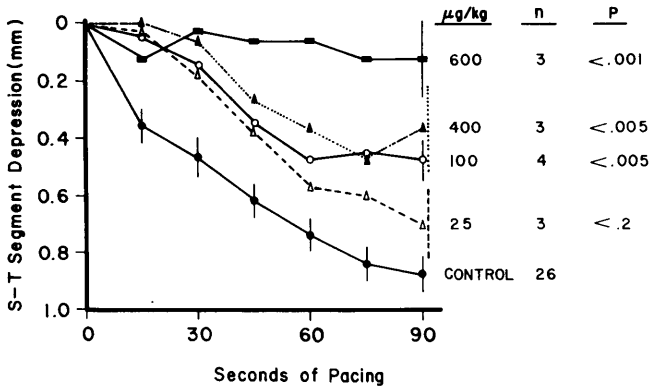

FIG. 1. Alteration of pacing-induced S-T segment depression by isosorbide dinitrate. Mean values ± 1 SEM are shown for each time period for the 26 control pacings and at the 90-sec period for the various doses of the drug. The 600-μg/kg dose completely prevented the occurrence of depression ($P < 0.001$). The values for the S-T segment depressions are those obtained during that pacing challenge (1 or 5 min af ter drug administration) where maximal drug protection was achieved.

resentative experiment are shown in Fig. 2. The S-T segment was isoelectric with the P-R interval in the control state at a heart rate of 200 beats/min. Computer analysis of the ECG at a paced rate of 390 beats/min revealed an S-T segment depression of 0.9 mm. One minute after iv administration of ISD, 600 μg/kg, pacing at the same rate did not induce S-T segment depression. The effect of this dose of ISD is comparable to that observed after nitroglycerin (GTN) at 100 μg/kg, iv (1). In this model then, GTN is approximately six times more potent than ISD on a weight basis.

The effects of the other four agents tested are summarized in Table I.

Pentaerythritol tetranitrate (PETN), was tested in five animals at 250 μg/kg and in four others at 500 μg/kg. There was little change in S-T segment depression after the drug had been administered from that during the control pacing periods. The average depression in this group was 0.8 ± 0.005 mm at 90 sec.

The two vasodilating agents, papaverine and chromonar, were ineffective in preventing pacing-induced S-T segment depression, as dipyridamole had been in the previous study (1). A total of seven animals received papaverine. There was no protection afforded by the 500-μg/kg dose in five animals (average control depression: 1.14 ± 0.2 mm at 90 sec). A dose of 1 mg/kg was administered to two other animals and also had no beneficial effect. Chromonar, tested at 2 and 4 mg/kg in a total of six animals, appeared to cause an exacerbation of the depression seen during the control pacing periods (0.88 ± 0.09 mm at 90 sec).

The beta-adrenergic receptor blocking agent, propranolol, caused a significant exacerbation ($P < .025$) of the pacing-induced depression in four animals (average control depression 0.81 ± .17). The effect of 100 μg/kg is reported because it was the highest dose after which pacing was consistently possible. Attempts to pace after administration of propranolol at 200 or 300 μg/kg were unsuccessful, due to depression of atrioventricular conduction.

Discussion. Anginal pain occurs secondary to an imbalance between myocardial oxygen supply and demand. Therapy for this condition has evolved through several concepts of pharmacological management. Increasing the oxygen supply by coronary vasodilatation was once thought to be of singular importance, and several drugs with this property have been tested in patients with angina pectoris. Chromonar is a potent, long-acting coronary vasodilator with no effect on cardiac output, work of the heart, or myocardial oxygen consumption; however, it has not gained wide usage in the treatment of angina (5). Dipyridamole has similar properties, but is ineffective when tested under double-blind conditions (6). Papaverine is another potent coronary vasodila-

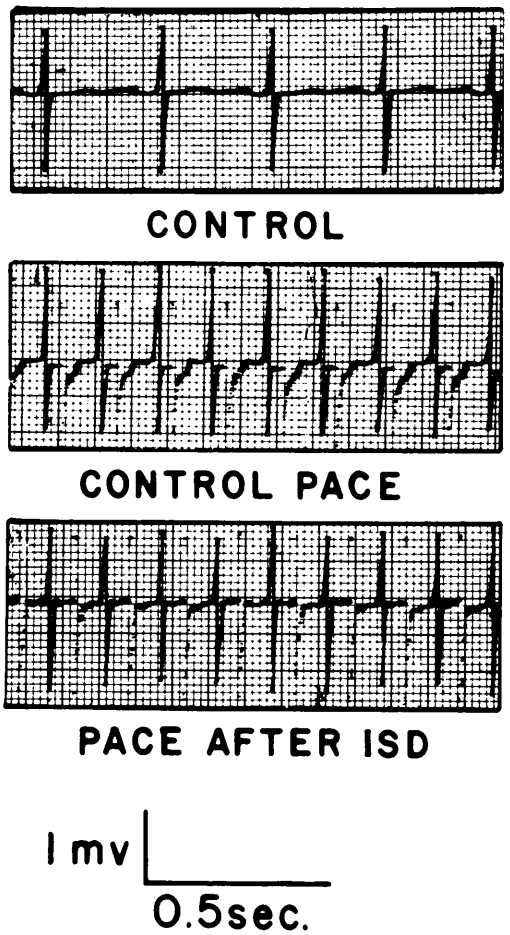

FIG. 2. ECG tracings from an atherosclerotic rabbit. Intrinsic heart rate was 200 beats/min, paced rate was 390 beats/min. Control pacing caused an S-T segment depression of 0.9 mm which was prevented by isosorbide dinitrate, 600 μg/kg, iv. The ventricular complex was darkened for clarity but not the stimulus artifact. Paper speed was 50 mm/sec; sensitivity was 1 mV/cm.

tor, once promoted as an effective antianginal agent, but now of only historical interest (7). Thus, coronary vasodilation *per se* does not produce a therapeutic effect in angina, and may cause exacerbation by diverting blood flow from ischemic regions of myocardium to normal areas, i.e., the "coronary steal" effect (8).

Efforts to improve on the antianginal effects of nitroglycerin led to the development of the so-called long-acting nitrates. Their chief advantages are purported to be efficacy after oral administration and prolonged duration of action. However, there is strong evidence that the claims for oral efficacy cannot be supported for any of these agents. Furthermore, it has not been clearly established that these compounds offer any advantage over GTN when given sublingually (10). PETN, perhaps the best known of the long-acting nitrates, has had limited success in controlled therapeutic studies. One report (11) states that PETN is not effective in decreasing the severity and frequency of exercise-induced ischemic S-T segment depression or in increasing the duration of effort in anginal patients. On the other hand, ISD has been found to be useful in the long-term treatment of angina. ISD is said to increase exercise tolerance and to have a longer duration of effect than GTN when administered sublingually (5).

Blockade of beta-adrenergic receptors is the newest approach to the medical management of anginal patients. The major beneficial effect of propanolol is the reduction in cardiac work brought about by a decrease in resting heart rate and the prevention of stress-induced tachycardia (12). Cardiac output and myocardial oxygen consumption are also reduced (5, 13). Possible deleterious effects of propranolol include an increase in myocardial wall tension (14) and increased coronary vascular resistance, causing a reduction in coronary flow (13, 15) and an increase in oxygen extraction by the myocardium (5). These latter properties, in combination with the masking of its beneficial effects (i.e., reduction of heart rate and cardiac work) by pacing, may explain why propranolol was ineffective in this rabbit model. Similarly, Muiesan *et al.* (16) reported that beta-adrenergic blockade with oxprenolol failed to inhibit the severity and duration of pain precipitated by atrial pacing in anginal patients.

Summary. Several agents used clinically in the treatment of angina pectoris were studied in an atherosclerotic rabbit model previously shown to be useful in differentiating antianginal drug activity. Intravenously administered isosorbide dinitrate afforded protection against pacing-induced S-T segment depression in a dose-related manner. Drugs with no protective effect included penta-

TABLE I. EFFECT OF SEVERAL AGENTS ON PACING-INDUCED S-T SEGMENT DEPRESSION.

Drug	Dose mg/kg	No. of Rabbits	S-T Segment changes from control pacing period[a] (mm) 15 seconds of pacing	30	45	60	75	90
Pentaerythritol tetranitrate	0.25	5	0.17	0.15	0.01	0.01	0.11	0.01
	0.5	4	0.06[b]	0.03	0.02	0.11	0.03[b]	0.09[b]
Papaverine	0.5	5	0.05[b]	0.07[b]	—	0.06	—	0.12[b]
	1.0	2	0.2	0.15	0.22	0.2	0.12	0.15
Chromonar	2.0	5	0.08	0.07	0.07	0.14[b]	0.32[b]	0.48[b]
	4.0	1	—	0.35[b]	0.37[b]	0.34[b]	0.32[b]	0.52[b]
Propranolol	0.1	4	0.49[b, c]	0.6[b, c]	0.7[b, c]	0.75[b, c]	0.69[b, c]	0.67[b, c]

[a] = For each drug, the mean values of pacing-induced S-T segment depression at each time period are compared to the mean values of all control pacing prior to that drug administration at the corresponding time period.

[b] = Exacerbation of depression when compared to control.

[c] $P < 0.05$.

erythritol tetranitrate, chromonar, and papaverine. Propranolol also did not prevent pacing-induced S-T segment depression, due in part to the overriding of the beneficial negative chronotropic effect of this drug by pacing.

1. Lee, R. J., and Baky, S. H., J. Pharmacol. Exp. Ther. **184,** 205, (1973).
2. Rinzler, S., Travell, J., Karp, D., and Charleson, D., Amer. J. Physiol. **184,** 605, (1956).
3. Winbury, M., Wolf, J. K., and Cronin, M. T. I., Amer. J. Physiol. **200,** 642, (1961).
4. Snedecor, G. W., "Statistical Methods", 5th ed., Iowa State College Press, Ames (1956).
5. Charlier, R., "Antianginal Drugs", 442 pp. Springer-Verlag, New York (1971).
6. DeGraff, A. C., and Lyon, A. F., Amer. Heart J. **65,** 423, (1963).
7. Simon, A. J., Dolgin, M., Solway, A. J. L., Hirschmann, J., and Katz, L. N., J. Lab. Clin. Med. **34,** 992, (1949).
8. Fam, W. M., and McGregor, M., Circ. Res. **22,** 649, (1968).
9. Needleman, P., and Johnson, E. M., Jr., J. Pharmacol. Exp. Ther. **181,** 489, (1972).
10. Goldstein, R. E., and Epstein, S. E., Prog. Cardiovasc. Dis. **14,** 382, (1972).
11. Dagenais, G. R., Pitt, B., Mason, R. E., Friesinger, G. C., and Ross, R. S., Amer. J. Cardiol. **25,** 90, (1970).
12. Gianelly, R. E., and Harrison, D. C., Clin. Med. **77,** 29, (1970).
13. Wolfson, S., Heinle, R. A., Herman, M. V., Kemp, H. G., Sullivan, J. M., and Gorlin, R., Amer. J. Cardiol. **18,** 345, (1966).
14. Sonnenblick, E. H., Braunwald, E., Williams, J. F. Jr., and Glick, G., J. Clin. Invest. **44,** 2051, (1965).
15. Parratt, J. R., and Grayson, J., Lancet I, 338, (1966).
16. Muiesan, G., Valori, C., Agabiti-Rosei, E., Nigri, A., Gioffrè, P., Motolese, M., and Reale, A., Amer. J. Cardiol. **31,** 149, (1973).

Received July 24, 1974. P.S.E.B.M. 1975, Vol. 148.