PHARMACOLOGY OF SCH 11973,
N-(2-PHENYLISOPROPYL)-N-P-TOLUENE SULFONYL UREA,
A POTENTIAL NEW ANTIANGINAL AGENT

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Abstract—Antianginal drugs were evaluated on the basis of their ability to protect against subepicardial electrogram changes induced by local ventricular ischemia in anesthetized dogs. Sch 11973 [N-(2-phenylisopropyl)-N-p-toluene sulfonyl urea], a potential new antianginal agent, was also effective against local ventricular ischemia with its maximum effect appearing at 1 mg/kg, i.v. or i.d. and with a duration of at least 2 hours. Nitroglycerin, at a dose of 0.04 mg/kg given bucally, exerted less protection, lasting on the average less than 15 minutes. Protection by propranolol at 1 mg/kg, i.v., was not better than nitroglycerin, but lasted up to one hour, while dipyridamole was ineffective when given in a dose range of 0.1-10 mg/kg, i.v. Sch 11973 differed from standard antianginal agents which may act via beta-adrenergic blocking activity or alteration of cardiac or circulatory dynamics since no acute pharmacological changes were observed after Sch 11973 was administered.

Sch 11973 [N-(2-phenylisopropyl)-N-p-toluene sulfonyl urea] was synthesized originally in a series of compounds whose basic structural moiety, the sulfonyl urea nucleus, was of interest for potential hypoglycemic action. The structure of this drug is:

Since previous reports (1) suggested the possible use of tolbutamide as an antianginal agent, Sch 11973 was tested in a new animal model (2) of angina pectoris. The purpose of this paper is to expand the description of this method and to characterize the cardiovascular pharmacology of Sch 11973.

Angina pectoris has been described as a condition in which the oxygen demand of the myocardium exceeds the available oxygen supply. As early as 1928, Keefer and Resnick (3) recognized that patients with angina pectoris had either coronary artery disease or some derangement of cardiac hemodynamics, and that the common denominator for all was hypoxia of a discrete area of the ventricle. Since myocardial ischemia is present during...
anginal episodes (4) methods for evaluating new antianginal agents have centered around blood flow studies in vitro and in vivo as well as oxygen and metabolic measurements (5). The local ventricular ischemia (LVI) model utilizes monopolar electrical changes directly recorded from an ischemic area of the myocardium. The degree and duration of ischemia induced by a transient occlusion of the left anterior descending coronary artery may be controlled to reproduce some of the causes and sequelae of clinical angina. These may include decreased regional coronary flow and myocardial electrical changes associated with a lack of oxygen in a circumscribed area of the ventricle.

MATERIALS AND METHODS

Local ventricular ischemia (LVI) model

Mongrel dogs (15-25 kg) of either sex were anesthetized i.v. with 0.6 ml·kg-1 dial-urethane solution composed of 4 parts urethane to 1 part diallylbarbituric acid. A cuffed endotracheal tube was inserted and the dog maintained on positive pressure artificial respiration using room air through a Harvard respirator. The femoral vein on either side was cannulated and connected to saline infusion tubing for drug injection and anesthetic supplement, and the femoral artery on either side was cannulated for systemic blood pressure measurement using a Statham P23 AA transducer. The left chest was opened at the fourth intercostal space, and the pericardium exposed and opened. At this point, the branches given off by the left anterior descending coronary artery (LAD) were examined, and one that supplied a relatively small area of epicardium was selected by gross observation for cannulation. The extent of the involved area could be validated by lack of change in limb lead ECG during an ischemic challenge as well as the extent of localized color change seen on the myocardium.

After selection of the appropriate coronary branch the common carotid artery on either side was cannulated and its blood flow was shunted through an extra-corporeal circuit containing a square wave electromagnetic flow probe (Carolina Medical Electronics) to an INTRAMEDIC Luer-end catheter into the coronary branch artery. Prior to the cannulation the dogs were given 605 units·kg-1 (5 mg·kg-1) i.v. sodium heparin. Flow and perfusion pressure were measured and could be controlled by the investigator. A second flow probe, 30 to 35 mm in circumference previously calibrated with dog blood, was placed around the ascending aorta to monitor cardiac output (minus coronary flow). Two platinum electrodes 0.1 mm in diameter each recording from a separate site, were inserted 3 mm into the epicardium supplied by the cannulated artery to detect monopolar ventricular electrical activity from this area. Each electrode, insulated along its entire length except at the tip, was connected through a V lead (Wilson central terminal) to a standard ECG amplifier. A miniature Brody-Walton strain gauge arch (6) was sewn to the ventricular surface as close as was practical to the electrodes but not within the partially ischemic area to monitor force per beat. When instrumentation was complete, the following measurements were made: (1) Monopolar myocardial electrograms, (2) Systemic blood pressure, (3) Cardiac output, (4) Coronary branch artery flow and pressure, (5) Contractile force per beat, and
Heart rate.

The following additional cardiovascular parameters could be obtained either by measurement with the existing instrumentation or by calculations: (1) Limb lead ECG's, (2) Peripheral and regional resistances, and (3) Cardiac work.

Control experiments performed to demonstrate the validity of the model started with a 30 min stabilization period to allow myocardial injury currents to subside. After electrogram stability was demonstrated, a one min control occlusion was performed by clamping the cannulated branch of the LAD. At 15 sec intervals, recordings of 5 sec durations each were made. After this control occlusion, flow was restored by removing the clamp and observations made at 30 sec and then at one min intervals until the electrograms returned to control configurations.

The alterations in the electrograms were reproducible at a confidence level of p<0.01 and were reversible during consecutive LVI challenges over a four hour period. After a minimum of two control challenges, 0.04 mg/kg of nitroglycerin (NG tablet, Lilly, 1/100 grain) was given buccally and the dog was again challenged. Buccal administration was accomplished by gently massaging the tablet on a previously wetted oral mucous membrane. The response to NG was used as the standard of effectiveness against which all other agents were compared. When the NG response was dissipated, a test drug was given and the LVI challenge repeated at suitable intervals. As indicated then, only two drugs were ever given to each dog.

All data were tested by Analysis of Variance for repeat measure (7) comparing responses after drug administration to the animal's own control responses. A percent protection for any drug at any dose was calculated using the following equation: Percent protection equals 100 minus the ratio of ischemia-induced T-wave change in mm after drug to the same measure before drug.

Experiments on cardiovascular and autonomic effects

The effects of 5 and 25 mg/kg of Sch 11973, i.v., were compared to that of 3 mg/kg of propranolol, i.v., on ventricular function in morphine-chloralose anesthetized dogs using a modified method of Sarnoff (8). Changes in developed tension of ventricular muscle as a function of increased myocardial segment length were observed before and after i.v. administration of test drugs.

Beta-adrenergic blocking activity in vivo was assessed in pentobarbital anesthetized dogs using heart rate and diastolic blood pressure responses to isoproterenol (ISO). Dose response curves were constructed with doses of ISO increasing from 0.01 to 10 ug/kg in 10 fold increments. Beta adrenergic blocking activity was compared to the effects of propranolol using a standard Analysis of Variance procedure.

Conscious animals: Indirect blood pressure (9), heart rate, ECG, and gross behavior were observed for at least six hours after Sch 11973 was administered to unanesthetized dogs at 5–100 mg/kg. orally.
RESULTS

1. Effects of local ventricular ischemia (LVI) in anesthetized dogs
   a) Control observations

   Fig. 1 illustrates the typical configuration of a ventricular electrogram and compares it with a simultaneous recording of limb lead II during a stabilization period. The electrogram differs from lead II in that it reflects only ventricular depolarization and repolarization. The repolarization phase, T-wave, always appears as a biphasic wave of relatively high voltage (20 mV total amplitude) and was the area in which major changes were observed during LVI. The depolarization wave-form, QRS, did not consistently change during the LVI episode, but a marked decrease in voltage of the negative component of the T-wave was determined from the isoelectric line to the point of maximum negative deflection. A reversible decrease in negative voltage produced by LVI was clearly indicated (see Fig. 1). During 10 control experiments, occlusions of 1 min duration were repeated at 30 min intervals over a 4 hour observation period. During 4 hours of LVI challenges, the amplitude of the ischemia-induced T-wave change became variable, probably as a function of the deterioration

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**Fig. 1.** Upper two panels illustrate typical ventricular electrogram compared with limb lead II ECG. As indicated, the components can be broken down to the following: 1-2 isoelectric line, period of no electrical activity; 2-3 Q wave, 3-4 R wave, 4-5 S wave, standard wave forms which, when taken as a unit, indicate ventricular depolarization; 5-6 T wave; 8-9 completion of ventricular repolarization. Lower two panels illustrate unipolar electrograms in the anesthetized dog simultaneously recorded with limb lead II ECG. The control panel, recorded during the stabilization period, indicates a normal ventricular myocardium. The center panel shows an electrogram response to local ventricular ischemia (LVI) with a decreased T wave amplitude but no ischemia-induced alteration in the limb lead. The post-challenge panel illustrates control conditions are restored within one minute after coronary flow is reinstituted. Note that no change indicative of myocardial ischemia, i.e., S-T segment depression, appears in lead II during the partial ischemic challenge. This would indicate that the area of ventricle involved is too small to change the vector sum of electrical activity recorded by the surface lead.
Fig. 2. Change in negative component of T-wave over time in a series of control experiments in 10 dogs.

of the preparation (Fig. 2). Finally, challenges at 4 hours or later produce no changes. Because of the change in T-wave amplitude response to LVI over time no drug studies were extended for a period in excess of four hours following initial (control) challenges.

b) Effects of nitroglycerin

Nitroglycerin attenuated the electrogram change induced by LVI challenge. Fig. 3 illustrates electrogram responses before and after NG, and shows that, after 0.04 mg/kg was dissolved buccally, there was a significant protection against LVI-induced reduction of T-wave voltage during the challenge. Other changes observed after NG administration (also seen in Fig. 3) were a 10-30 mm Hg fall in systemic and coronary artery perfusion pressure and variability but essentially no change in heart rate recorded within 2 min after NG was administered (Panel B). All responses including attenuated T-wave change in response to LVI (protective effects) returned to control values within 10-15 min.

c) Effect of other standard agents

Propranolol: In 10 dogs intravenous doses of 0.5 to 4.0 mg/kg of propranolol conferred a dose-related degree of protection against ischemia-induced electrogram changes (Fig. 5.) Propranolol slowed heart rate about 30%, reduced blood pressure 15-40% below control with a 25% decrease in contractile force after 1 mg/kg. At a maximal protective dose of 4 mg/kg, the potentially toxic signs of cardiac depression were observed.

Dipyridamole: Administration of dipyridamole, i.v. to 10 dogs in doses of 0.5 to 10.0
FIG. 3. Cardiovascular effects of bucally administered nitroglycerin in the dog. Panel A illustrates the changes produced by a control LVI challenge. Note the decreased amplitude in electrogram T wave during the ischemic episode. Panel B shows 0.04 mg/kg of nitroglycerin not only decreased systemic blood pressure but also coronary flow. Coronary flow decrease is probably a function of decreased cardiac output and carotid flow. Panel C shows the attenuated response to LVI 2 minutes after nitroglycerin was administered. Occlusion occurs during the period of slow paper speed of 25 mm of paper minute. A slight but non-significant rise in systemic blood pressure was observed between recording Panel A and B. After NG was administered a slight but non-significant decrease was observed in heart rate.

FIG. 4. Effect of Sch 11973 on electrogram response to local ventricular ischemia. As shown in Fig. 3, Panel A illustrates the decreased T wave of control electrograms produced by a LVI challenge. Panel B shows the lack of acute effects of Sch 11973 on systemic blood pressure, coronary branch flow and electrograms. Panel C indicates the protective effect of Sch 11973 30 minutes after administration by almost complete attenuation of T wave change during the LVI challenge. Paper speed change is the same as in Fig. 3.

mg/kg did not protect against electrogram changes during a LVI challenge.

Characteristic pharmacological effects of dipyridamole such as an increase in total coronary flow accompanied by a decrease in systemic and coronary perfusion pressure were observed.

d) Effect of Sch 11973

Action on LVI: When 1 mg/kg of Sch 11973 was administered to 30 anesthetized dogs i.v. or i.d. and the LVI challenge was performed, marked protection against electrogram alterations during ischemic periods were observed within 10 min with maximum effects from
Comparison with other standard agents: Fig. 5 summarizes and compares the percent protection of NG, propranolol and Sch 11973 and shows that 1 mg/kg of Sch 11973 is essentially equiactive to 4 mg/kg of propranolol. The duration for both of these drugs was greater than 2 hours. These dose response studies also show that the minimum effective dose of Sch 11973 was between 0.5 and 0.75 mg/kg, while doses of 1 and 5 mg/kg produced maximum responses. In contrast, propranolol did not produce a maximal effect until a cardiac depressant dose of 4 mg/kg was attained. The most effective dose of NG, 0.08 mg/kg, buccally, was equal in effect to 0.75 mg/kg of Sch 11973, but the duration of NG response

![Graph showing comparison of LV1 effects after buccally administered nitroglycerin and i.v. propranolol and Sch 11973](image)

**Fig. 5.** Comparison of LV1 effects after buccally administered nitroglycerin and i.v. propranolol and Sch 11973. Those dose-response curves indicate protection against ischemia-induced electrogram changes for the drugs indicated. Although propranolol protection (as defined in the text) is dose related, cardiodepressant activity appears at 4 mg/kg, i.v., and precludes testing at higher doses. Each point indicates a mean value and the bars indicate standard error of the mean.

### Table 1. Effect of Sch 11973 on selected cardiovascular dynamics in the anesthetized dog

<table>
<thead>
<tr>
<th>Dose, i.v. (mg/kg)</th>
<th>Mean B.P. (mm Hg)</th>
<th>Heart Rate (beats/min)</th>
<th>Contractile Force (gms, tension)</th>
<th>Cardiac Output (L/min)</th>
<th>Cardiac Work (gm-m/min)</th>
<th>Coronary Flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>40</td>
<td>112 ± 6</td>
<td>160 ± 6</td>
<td>16 ± 0.8</td>
<td>2.3 ± 0.3</td>
<td>3503 ± 400</td>
</tr>
<tr>
<td>0.50</td>
<td>4</td>
<td>119 ± 11</td>
<td>164 ± 16</td>
<td>16 ± 2.0</td>
<td>1.9 ± 0.1</td>
<td>3075 ± 200</td>
</tr>
<tr>
<td>1.0</td>
<td>36</td>
<td>109 ± 4</td>
<td>157 ± 5</td>
<td>16 ± 0.8</td>
<td>1.8 ± 0.6</td>
<td>2668 ± 900</td>
</tr>
<tr>
<td>5.0</td>
<td>8</td>
<td>127 ± 13</td>
<td>135 ± 12*</td>
<td>15 ± 1.0</td>
<td>NOT RECORDED</td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td>3</td>
<td>128 ± 14</td>
<td>153 ± 17</td>
<td>15 ± 2.0</td>
<td>2.4 ± 0.5</td>
<td>4178 ± 1000</td>
</tr>
<tr>
<td>25.0</td>
<td>6</td>
<td>137 ± 14*</td>
<td>148 ± 8</td>
<td>13 ± 0.7*</td>
<td>2.7 ± 0.6</td>
<td>5031 ± 1200</td>
</tr>
</tbody>
</table>

*1* All values expressed as ± S.E.M. * Significant different from control, *P* < 0.05
Cardiovascular effects: Most antianginal agents alter cardiovascular dynamics such as blood pressure or heart rate. Sch 11973 differed in this respect since i.v. doses of 0.5 to 25 mg/kg produced no significant dose-related changes in systemic blood pressure, heart rate, cardiac output, coronary flow and cardiac work. (Table 1). Contractile force decreased after the highest dose used.

2. Ventricular function studies

Sch 11973 had no effect on ventricular function during a 2-hour test period after 5 or 25 mg/kg, i.v. These doses are 5 and 25 times greater than the dose needed to protect against electrogram changes during a LVI challenge. Fig. 6 shows that, in 5 vagotomized dogs, with increasing myocardial fiber lengths, the responses to Sch 11973 were not different from control, in contrast to propranolol at 3 mg/kg, i.v., which markedly depressed ventricular function.

3. Tests for beta-adrenergic blocking activity

These studies showed that there were no differences from control in heart rate or blood pressure responses to ISO at 90 min after 25 mg/kg of Sch 11973, i.v., when the protective effect of the drug in the LVI model would still be at a maximum level. This dose is 25 times greater than that effective against LVI. In contrast, propranolol significantly blocked both responses to isoproterenol after 3 mg/kg, i.v. Fig. 7 illustrates the responses of diastolic pressure and heart rate respectively in these studies.

![Graph showing comparison of Sch 11973 and propranolol effects on ventricular function curves using 4 dogs per drug and dose. After i.v. doses of 1, 5, or 25 mg/kg of Sch 11973, no differences in developed tension with increasing fiber length are observed compared to control measurements. After 3 mg/kg of propranolol, i.v., cardiac depression was observed.](image-url)
Fig. 7. Comparison of effects of Sch 11973 and propranolol on heart rate and diastolic blood pressure responses to isoproterenol. Note lack of beta-adrenergic blockade after Sch 11973. Each point is a mean value with bars indicating standard error of the mean.

Table 2. Cardiovascular effects of oral Sch 11973 in the unanesthetized dog

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Dose (mg/kg)</th>
<th>Blood Pressure (mm Hg)</th>
<th>Heart Rate (beats/min)</th>
<th>P-R (SEC)</th>
<th>ECG QRS (SEC)</th>
<th>Q-T (SEC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Syst.</td>
<td>Diast.</td>
<td>Mean¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>145 ± 2</td>
<td>106 ± 6</td>
<td>119 ± 4</td>
<td>63 ± 3</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>138 ± 10</td>
<td>80 ± 8</td>
<td>106 ± 9</td>
<td>55 ± 6</td>
<td>0.07</td>
</tr>
<tr>
<td>96</td>
<td>Control</td>
<td>166 ± 6</td>
<td>100 ± 2</td>
<td>122 ± 4</td>
<td>118 ± 4</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>167 ± 8</td>
<td>109 ± 10</td>
<td>128 ± 9</td>
<td>95 ± 10</td>
<td>0.06</td>
</tr>
<tr>
<td>GA43</td>
<td>Control</td>
<td>142 ± 5</td>
<td>71 ± 2</td>
<td>95 ± 3</td>
<td>86 ± 7</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>148 ± 6</td>
<td>78 ± 5</td>
<td>101 ± 8</td>
<td>53 ± 5</td>
<td>0.07</td>
</tr>
<tr>
<td>AD70</td>
<td>Control</td>
<td>142 ± 3</td>
<td>91 ± 4</td>
<td>108 ± 3</td>
<td>76 ± 4</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>150 ± 10</td>
<td>105 ± 10</td>
<td>120 ± 10</td>
<td>82 ± 5</td>
<td>0.07</td>
</tr>
</tbody>
</table>

¹ Mean blood pressure calculated as equal to diastolic - 1/3 pulse pressure. One dose trial per dog.

It appears from these data that Sch 11973 exerts its protective effects against LVI by a mechanism other than beta-adrenergic blockade or depression of ventricular function.

4. Cardiovascular studies in unanesthetized dogs

Four trained normotensive dogs observed over 24 hours after oral doses of 5–100 mg/kg
of Sch 11973 showed no changes in overt behavior, heart rate, blood pressure, or lead II of the ECG. (Table 2).

DISCUSSION

The LVI challenge procedure in the anesthetized dog mimics some of the pathophysiologic changes that occur during an anginal episode, including decreased regional blood flow and ischemia induced myocardial electrical changes. In addition, the model is sensitive to such commonly used antianginal drugs as NG and propranolol while it shows no response to a coronary vasodilator such as dipyridamole. The results with dipyridamole agree with those reported by Lee and Baky (10) who used a different animal model of angina and also with clinical observations (11) on the lack of efficacy of the agent. Most investigators agree that in patients with uncomplicated angina, the same sensitivity to these three drugs is observed.

Sch 11973 was the most promising drug tested in this procedure since the duration of action was considerably longer than NG and its lack of side effects considerably greater than propranolol. While mechanisms of activity can be postulated reasonably well for most antianginal drugs, the beneficial effects of Sch 11973 are not easily explainable. Antianginal drugs presumably are effective, in part, by modifying cardiac dynamics in such a way that either work or oxygen utilization is decreased while cardiac efficiency is increased. Thus, after a sublingual dose of NG in the dog, observed changes and their time course correlated well with the previous findings of Gorlin et al. (12) in angina patients compared to subjects with normal coronary artery circulation. The decreased rather than increased coronary branch flow after NG administration was as expected, when the experimental method is carefully considered, since NG is a smooth muscle relaxant and the overall effect on circulation would be reflected as a decrease in systemic blood pressure. Since the coronary blood flow depends on perfusion pressure the decreased systemic blood pressure produces the decreased coronary branch flow. In patients, venous return (preload), left ventricular end diastolic pressure, and coronary flow decrease, with a net effect of decreased cardiac work and attenuation of anginal pain. On the other hand, propranolol decreases cardiac work via reduction of heart rate, contractile force of the heart (inotropy) and systemic blood pressure (after load). In contrast to NG and propranolol, Sch 11973 does not alter cardiovascular dynamics. However, all of these agents are active in protecting against electrogram changes observed in the LVI model. Thus, we conclude that changes in coronary flow, cardiac output, heart rate or systemic blood pressure are not necessarily required for protection. Indeed, dipyridamole, which markedly increased total coronary flow, had no protective effect in the LVI challenge.

Sulfonyl ureas exhibit hypoglycemic activity which can be associated with more efficient tissue utilization of glucose. Possibly this could make the myocardium less prone to the effects of ischemia by increasing the availability of substrate. This rationale is questionable though, since Sch 11973 is only a weak hypoglycemic agent. In addition, tolbutamide, which is five times more potent than Sch 11973 as a hypoglycemic has been tested and
was found to be inactive in the LVI model.

Sch 11973 has an unusual lack of pharmacologic activity, and along with this, a very high degree of safety. Unlike beta-adrenergic blocking agents, no decreased cardiac function is observed in the dog after Sch 11973 up to 600 times the therapeutic dose. Because of this lack of acute change in any of the measurable cardiovascular parameters, changes in metabolic or enzymic activity may be the underlying mechanism of drug activity.

Changes in myocardial metabolism allowing for more efficient utilization of available oxygen during ischemic periods can account for the lack of electrical changes in the subepicardium during LVI. In fact there are data which support the hypothesis that Sch 11973 may act similarly to oxygen or by causing increased availability of oxygen to tissues (13).

No long term harmful effects have been observed during 13 week toxicity studies in animals. Clinical studies are underway in patients with angina. The compound will be further evaluated against standards for possible beneficial effects on electrocardiogram and onset of chest pain in patients undergoing exercise tolerance testing.

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REFERENCES

1) SINGH, I. AND BARDHAN, P.M.: Lancet 2, 1141 (1952)
4) ZOLL, P.M. AND NORMAN, L.R.: Circulation 6, 832 (1952)
12) GORLIN, R., BRACHFELD, N., MACLIND, C. AND BOO, P.: Circulation 19, 705 (1959)