Effects of Betaxolol on Cardiohemodynamics and Coronary Circulation in Anesthetized Dogs: Comparison with Atenolol and Propranolol

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Abstract—Effects of betaxolol, a cardioselective β-adrenoceptor antagonist, on cardiohemodynamics and coronary circulation were investigated in two kinds of anesthetized open-chest dog preparations in comparison with those of atenolol and propranolol. When administered intravenously, betaxolol, atenolol and propranolol produced dose-dependent decreases in the heart rate (HR), maximum left ventricular dP/dt (+(+)dP/dt), cardiac output (CO) and mean arterial pressure (MAP). Although all three drugs were almost equipotent in decreasing HR, betaxolol was much less potent than atenolol and propranolol in decreasing (+(+)dP/dt). Betaxolol decreased the total peripheral resistance (TPR), whereas atenolol and propranolol increased it. In another series of experiments, when administered intravenously, betaxolol, atenolol and propranolol all produced a decrease in the myocardial oxygen consumption (MVO₂) and an increase in the atrioventricular conduction time (AVCT). All three drugs were nearly equipotent in decreasing MVO₂, although betaxolol was less potent than the other two drugs at higher doses (>300 μg/kg). Prolongation of AVCT with propranolol was stronger than those with betaxolol and atenolol. These results suggest that, unlike atenolol and propranolol, the decrease in TPR as well as β₁-adrenoceptor blockade may be responsible for both the hypotensive effect of betaxolol and the decrease in MVO₂ with betaxolol. The result that the cardiodepressant effect of betaxolol was much less potent than those of atenolol and propranolol suggests that betaxolol would be more beneficial than the others in the treatment of ischemic heart disease.

Since β-adrenoceptor antagonists were first introduced in the 1960s (1), they have received major attention. They have been demonstrated to be useful in the management of cardiovascular diseases, including hypertension, cardiac arrhythmias and angina pectoris (2).

Because nonselective β-adrenoceptor antagonists have some undesirable effects through blocking β₂-adrenoceptors such as contraction of bronchial smooth muscle and inhibition of glycogenolysis, these drugs are usually not used in patients with bronchial asthma and must be used cautiously in diabetics who are receiving insulin. As a consequence, drugs that exhibit selectivity for β₁-adrenoceptors have been developed. In fact, metoprolol or practolol, cardioselective β-adrenoceptor antagonists, are less likely to increase airway resistance in asthmatic patients than propranolol (3, 4).

Betaxolol is a cardioselective β-adrenoceptor antagonist devoid of partial agonist activity, with little membrane stabilizing activity (5). Like atenolol, betaxolol exhibited a high β₁-adrenoceptor selectivity in isolated tissues (5–7) and had a hypotensive effect in SHR (8). In patients with coronary artery disease, acute intravenous administration of betaxolol did not increase the systemic arte-
rial resistance at all (9), suggesting that the effect of betaxolol on the total peripheral resistance is different from those of other \(\beta\)-adrenoceptor antagonists (10). Furthermore, administration of betaxolol significantly decreased the myocardial oxygen demand, estimated from the double product (heart rate \(\times\) systolic pressure), in patients with ischemic heart disease (11). The present study was designed to investigate the effects of betaxolol on cardiohemodynamics and coronary circulation in comparison with those of atenolol, a cardioselective \(\beta\)-adrenoceptor antagonist, and propranolol, a nonselective one.

**Materials and Methods**

**Cardiohemodynamic profile:** Experiments were performed on 21 mongrel dogs of either sex weighing 7–15 kg. The animals were anesthetized initially with 30 mg/kg, i.v., of sodium pentobarbital, followed by an infusion of 4 mg/kg/hr, i.v. Following tracheal intubation, artificial respiration was performed with room air in a tidal volume of 20 ml/kg at 18 breaths/min. The left chest was opened at the fifth intercostal space. The pericardium was cut to expose the heart. A micro-tip catheter pressure transducer (Millar, PC-350) was introduced through the left carotid artery into the left ventricle to measure the left ventricular pressure (LVP). The maximum rate of change in LVP (\(+(\end{enumerate}dP/dt)\)) was obtained with an electronic differentiator (Nihon Kohden, EQ-45764). A catheter was inserted into the left femoral artery and connected to a pressure transducer (Nihon Kohden, MPU-0.5) to measure the mean arterial pressure (MAP). The heart rate (HR) was measured with a cardiotachometer (Nihon Kohden, AT-601G) triggered by LVP. Non-canulating probes of an electromagnetic flow meter (Nihon Kohden, MFV-1200) were placed around the ascending aorta to measure the cardiac output (CO). The total peripheral resistance (TPR) (dyn·sec·cm\(^{-5}\)) was calculated as:

\[
TPR = 80 \times \frac{MAP}{CO}
\]

All these variables were recorded on a thermal pen recorder (Nihon Kohden, WT-687) throughout the experiment. The animals were divided into three groups. The animals received betaxolol (\(n=7\)), atenolol (\(n=7\)) and propranolol (\(n=7\)) in the first, second and third group, respectively. After a control period, the drugs were injected intravenously at 15 min intervals in cumulative doses of 3, 10, 30, 100, 300, 1000 and 3000 \(\mu g/kg\) through the cannula inserted into the left femoral vein. The administration interval of 15 min was chosen because all parameters measured in this experiment became stable 10 to 30 min after drug injection.

**Effects on coronary circulation:** Experiments were performed on 21 mongrel dogs of either sex weighing 9–17.5 kg. The preparation was basically the same as that used by Narimatsu et al. (12). The animals were anesthetized, and artificial respiration was performed in the same way as that in the above experiment. The right chest was opened at the fourth and fifth intercostal spaces, and the fifth costa was removed. The pericardium was cut to expose the heart. After the animal was given sodium heparin at a dose of 500 units/kg, i.v., a Morawitz cannula was introduced into the coronary sinus. The other end of the cannula was introduced into the right jugular vein to form a extracorporeal circuit made of rubber tubing. Coronary sinus outflow was returned to the main venous system through the circuit. A probe of the electromagnetic flow meter (Nihon Kohden, MFV-1200) was interposed in the circuit to measure the coronary sinus outflow (CSF). Samples of coronary sinus blood were obtained from the Morawitz cannula and those of arterial blood from the extracorporeal circuit in the right carotid artery. The oxygen content and pH of the blood samples were measured using a blood gas analyzer (Instrumental Laboratory, model 213). The coronary arteriovenous oxygen difference (A-V \(O_2\)) was determined from arterial and coronary sinus blood samples obtained simultaneously. After each experiment, the heart was removed, rinsed, blotted and weighed. The myocardial oxygen consumption (M\(VO_2\)) was calculated on the basis of the assumption that about 70% of the total coronary blood flowed out of the coronary sinus. Two pairs of bipolar recording Pt electrodes were sutured on the sinus node area and on the right ventricular wall to obtain atrial and ventricular bipolar electrograms, respectively. The atrio-ventricular conduction
time (AVCT) was measured as the interval between the atrial and ventricular electrogram by an A-V interval meter (Data-Graph, HT-11) with an analysis pitch of 1 msec. MAP and HR were measured in the same way as that described for the above experiment. All the variables were recorded on a thermal pen recorder throughout the experiment.

The dogs were divided into three groups. The animals received betaxolol (n=7), atenolol (n=7) and propranolol (n=7) in the first, second and third group, respectively. The drugs were injected intravenously at 30-min intervals in cumulative doses of 3, 30, 300 and 3000 μg/kg, through the cannula inserted into the left femoral vein. All the variables were measured 5 min before and 10 min after the drug injection.

**Drugs:** Drugs used were as follows: betaxolol hydrochloride (Synthelabo), atenolol (Sigma) and propranolol hydrochloride (Sigma). All drugs were dissolved in saline (0.9% NaCl).

**Statistical analysis:** All data shown in the figures are expressed as the mean±S.E. For statistical analysis, Student’s t-test for paired observations was utilized. Values of P<0.05 were considered significant.

### Results

**Cardiohemodynamic profile:** The control values of 5 cardiohemodynamic variables in 21 dogs are presented in Table 1. Dose-response curves for the effects of betaxolol, atenolol and propranolol on cardiohemodynamics are presented in Fig. 1.

Betaxolol, atenolol and propranolol decreased HR and MAP in a dose-dependent manner. They were almost equipotent in decreasing HR. No atrial standstill, sinoatrial block nor atrioventricular block occurred in any dogs. When compared at the doses producing a 20% decrease in MAP, betaxolol and atenolol were equipotent, both being about 3 times more potent than propranolol. Betaxolol, atenolol and propranolol all decreased (+)dP/dt and CO. However, betaxolol produced significant decreases in both (+)dP/dt and CO over 100 μg/kg, whereas atenolol and propranolol significantly decreased them at the lowest dose (3 μg/kg) tested. When compared at the doses producing a 20% decrease in (+)dP/dt, betaxolol was less potent than atenolol and propranolol by 60 and 105 times, respectively. When compared at the doses producing a 20% decrease in CO, betaxolol was less potent than atenolol and propranolol by 21 and 42 times, respectively. Betaxolol significantly decreased TPR at the doses of 100 and 3000 μg/kg. In contrast, propranolol increased TPR at all doses tested. Atenolol significantly increased TPR at doses of 100 and 300 μg/kg.

**Effects on coronary circulation:** The control values of 4 variables in 21 dogs are presented in Table 2. In this series of experiments, betaxolol, atenolol and propranolol were administered cumulatively at 30-min intervals to anesthetized dogs. No atrial standstill, sinoatrial block nor atrioventricular block were observed in any of the dogs. The changes in CSF, AVCT, A-V O₂ and MVO₂ are shown in Fig. 2. There were clear dose-response relations for all the variables.

Betaxolol, atenolol and propranolol decreased CSF. When compared at the doses producing a 30% decrease in CSF, betaxolol was less potent than atenolol and propranolol by 19 and 2.8 times, respectively.

### Table 1. Control values of cardiohemodynamic variables in 21 dogs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean±S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>153±6</td>
</tr>
<tr>
<td>(+)dP/dt (mmHg/sec)</td>
<td>2655±141</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>1125±87</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>121±5</td>
</tr>
<tr>
<td>TPR (dyne·sec·cm⁻⁵)</td>
<td>9330±909</td>
</tr>
</tbody>
</table>

HR; heart rate, (+)dP/dt: maximum left ventricular dP/dt, CO: cardiac output, MAP: mean arterial pressure, TPR: total peripheral resistance. Body weight was 10.3±0.5 (mean±S.E.) kg.
Fig. 1. Comparison of the hemodynamic effects of betaxolol (●), atenolol (△) and propranolol (□) in anesthetized dogs. HR: heart rate, (+)dP/dt: maximum left ventricular dP/dt, CO: cardiac output, MAP: mean arterial pressure, TPR: total peripheral resistance. Asterisks indicate P<0.05 vs. control by a paired t-test.

Table 2. Control values of four hemodynamic variables in 21 dogs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean±S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF (ml/min)</td>
<td>24.8±2.0</td>
</tr>
<tr>
<td>AVCT (msec)</td>
<td>116±3</td>
</tr>
<tr>
<td>A-V O₂ (%)</td>
<td>68±3</td>
</tr>
<tr>
<td>MVO₂ (ml/min/100 g)</td>
<td>4.5±0.4</td>
</tr>
</tbody>
</table>

CSF: coronary sinus outflow, AVCT: atrioventricular conduction time, A-V O₂: arteriovenous oxygen difference, MVO₂: myocardial oxygen consumption. Body weight was 13.2±0.5 (mean±S.E.) kg.

Betaxolol, atenolol and propranolol decreased A-V O₂ and MVO₂. When compared at the doses producing a 30% decrease in MVO₂, betaxolol was almost equipotent with atenolol, but was 2.6 times less potent than propranolol. Betaxolol, atenolol and propranolol increased AVCT. The dose-response curve for the increase in AVCT with propranolol was steeper than those with betaxolol and atenolol. The increase in AVCT with propranolol was greatest among the three drugs at the same dose.

Discussion

As expected from previous experiments using isolated cardiac muscle of guinea pig (5-7), betaxolol exerted a potent β-adrenoceptor antagonistic effect in anesthetized...
dogs. In the present study, betaxolol, atenolol and propranolol produced dose-dependent decreases in HR, (+)dP/dt, CO and MAP. However, some of our findings indicated that betaxolol is qualitatively different from the other two drugs.

The first finding is that betaxolol decreased TPR, whereas both atenolol and propranolol increased it. This decrease in TPR with betaxolol is of great interest because it is generally thought that most β-adrenoceptor antagonists increase TPR as a result of compensatory sympathetic reflexes. Our present result is in agreement with the previous report by Powell that propranolol, when acutely administered to the anesthetized dog, increased TPR (13). The mechanism by which betaxolol decreases TPR is not clear at present. It is well-known that β-adrenoceptor antagonists with either partial agonist activity or α-adrenoceptor antagonist activity produce little or no increase in TPR (14, 15). It seems unlikely that partial agonist activity is responsible for the decrease in TPR with betaxolol because betaxolol has no such activity (5). However, betaxolol, when injected intra-arterially, increased the femoral artery blood flow in anesthetized dogs, the potency of which was about one-thirds that of papa- verine (16). These data suggest that betaxolol has a vasodilator property that may contribute to the decrease in TPR. The extent to which the reflex increases TPR is proportional to the degree of the decrease in CO. Therefore, there is another possibility that the decrease in CO with betaxolol was not sufficient to produce the reflex increase in TPR. However, such a possibility can be excluded because betaxolol at a dose of 3000 μg/kg and atenolol at a dose of 100 μg/kg, which produced nearly the same extent of decrease in CO, produced opposite changes in TPR. The increase in TPR with propranolol is probably due to the reflex caused by the decrease in CO and its β2-adrenoceptor blocking effect since β2-adrenoceptor blockade produces a contraction of the vascular smooth muscle, which leads to the increase in TPR. Increase in TPR with atenolol may be due to the reflex and no vasodilatory effect.

The second finding in the present experiments is that betaxolol is much less potent than atenolol and propranolol in decreasing (+)dP/dt, although all the drugs were almost equipotent in decreasing HR. The reason why such a discrepancy occurs is not known. However, the less depressant effect on cardiac contractility was also observed in the canine ischemic heart model by Abe et al. (17). This property may be advantageous for subjects with limited cardiac functional reserve.

The effectiveness of β-adrenoceptor an-
tagonists in the treatment of exertional angina is attributable to a fall in myocardial oxygen consumption during exertion (18, 19). In the present study, betaxolol decreased MVO₂₂ as did atenolol and propranolol. This suggests that betaxolol also has a beneficial effect on the ischemic myocardium. Recently, betaxolol was found to improve the myocardial acidosis due to coronary artery ligation in anesthetized dogs (17). Increase in AVCT with propranolol at the highest dose (3000 μg/kg) was approximately two times those with betaxolol or atenolol. Although the β-adrenoceptor antagonistic effect of propranolol is thought to be the major mechanism of slowing A-V conduction (20), a direct depressant effect on atrioventricular transmission, including a membrane stabilizing action, may further increase AVCT at higher doses (21–23). Propranolol can cause A-V dissociation and cardiac arrest in patients with preexisting partial heart block due to digitalis or other factors. In this respect, betaxolol and atenolol are less likely to induce A-V block than propranolol since betaxolol and atenolol were less potent in increasing AVCT.

In conclusion, betaxolol exhibited the profile of a cardioselective β₁-adrenoceptor antagonist, with decreasing effect on TPR. The decrease in TPR with betaxolol is likely to benefit the reduction in myocardial oxygen consumption as well as hypotensive effect.

References


