Effects of Betaxolol, a New Beta 1 Selective Blocker, on Canine Ventricular Arrhythmias

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Abstract—Antiarrhythmic effects of a new beta 1 selective adrenoceptor blocker, betaxolol, were examined in comparison with those of atenolol using two canine ventricular arrhythmia models (adrenaline arrhythmia and digitalis arrhythmia). Both betaxolol and atenolol suppressed adrenaline arrhythmia, and the minimum effective plasma concentration of betaxolol for this arrhythmia model was determined to be less than 10 ng/ml. However, on digitalis arrhythmia, both beta blockers were ineffective, even though the high doses used in these experiments, 3 mg/kg for betaxolol and 5 mg/kg for atenolol, showed significant hypotensive effects. The present results suggest that betaxolol and atenolol may be expected to be clinically effective on arrhythmias related to increased sympathetic tone.

Betaxolol, (±)-1-(isopropylamino)-3-[p-(2-cyclopropyl-methoxyethyl)-phenoxy]-2-propanol HCl, is a new beta 1 selective adrenoceptor blocker which has been reported to be devoid of intrinsic sympathomimetic activities and membrane-stabilizing properties (1-4). Many animal and clinical studies have indicated that its plasma half-life is long and its hepatic first-pass extraction after oral administration is low (5-7) and that its intravenous or oral potencies were similar to or much higher than those of propranolol (1, 8).

A large number of beta blockers have been investigated in relation to their antiarrhythmic effects as well as their antihypertensive and antiangiinal activities, and their antiarrhythmic properties are generally considered to stem from their antagonistic activities against increased cardiac automaticity and conductivity. We examined the antiarrhythmic effects of several beta blockers using canine ventricular arrhythmia models (digitalis-, adrenaline- and two-stage coronary ligation-induced arrhythmias) and demonstrated that most of them were effective only on adrenaline arrhythmia when beta blocking doses were used (9-12).

Although many studies concerning pharmacokinetics, pharmacodynamics and antihypertensive effects of betaxolol have already been reported (5-7, 13-19), almost no study about its effect on arrhythmias has been presented yet. Therefore, in the present study, we examined the effects of betaxolol on canine ventricular arrhythmias, in comparison with atenolol which seemed to be the most similar beta blocker to betaxolol, and studied whether beta 1 selective drugs have different profiles of antiarrhythmic effects from other beta blockers.

Materials and Methods
Production of adrenaline-induced arrhythmia: Twelve mongrel dogs of either sex, weighing 7–15 kg, were anesthetized initially with thiopental sodium. As reported earlier (9, 20), after intubation, 1.0% halothane, vaporized with 100% oxygen, was administered with a volume-limited ventilator. Adrenaline was infused through the left femoral vein at a rate of 2.5–4.5 µg/kg/min for 18 min. After 3 min of adrenaline infusion and when stable and severe ventricular arrhythmia was produced, 0.05 mg/kg betaxolol or 0.1 mg/kg atenolol was injected into the right femoral vein.

The lead II ECG and blood pressure were
continuously recorded. Venous blood samples were taken from the jugular vein 1 min before and 1, 3, 5, 10 and 15 min after betaxolol injection.

Production of digitalis-induced arrhythmia: Twelve mongrel dogs of either sex, weighing 7–15 kg, were anesthetized with pentobarbital sodium, 30 mg/kg. As reported earlier (10, 20), 40 μg/kg ouabain was injected intravenously into the femoral vein and then followed by an additional dose of 10 μg/kg every 20 min until stable ventricular arrhythmia of more than 1 hr duration was produced. Betaxolol, 3 mg/kg, and atenolol, 5 mg/kg were injected intravenously through a cannula in the femoral vein within seconds.

The lead II electrocardiogram (ECG), atrial electrogram from catheter tip electrodes in the right atrium, and blood pressure were continuously recorded.

Plasma betaxolol assay: Venous blood samples were centrifuged, and the plasma was stored in a freezer at about -25°C before plasma betaxolol concentration analysis.

The plasma betaxolol assay was carried out at the Research Center, Mitsubishi Chemical Industries, Ltd. using a high-performance liquid chromatographic (HPLC) method with fluorescence detection according to the method of Muriel and Bernard (21).

Determination of the minimum effective plasma concentration: The severity of arrhythmia was expressed by the arrhythmic ratio: the number of ventricular ectopic beats divided by the total heart rate. The total heart rate is the number of all beats counted from the 5 sec strip of lead II ECG (i.e., the number of ventricular ectopic beats plus the number of conducted beats), and ventricular beats were judged by the different shape of the ventricular complex from the normal QRS complex. For both adrenaline and digitalis-induced arrhythmias, the arrhythmic ratios before drug injection were almost 1, and there were no spontaneous improvements in these ratios. As reported earlier (10, 11), drugs producing statistically significant (P<0.05) reduction in the arrhythmic ratio were judged as effective antiarrhythmic drugs. The minimum effective plasma concentration of a drug was determined as follows: the last minute of statistically significant decrease (P<0.05) in the arrhythmic ratio compared with that at 0 time was determined. Then the corresponding plasma concentration was calculated from the experimentally derived plasma concentration-time equations, and this was regarded as the minimum effective plasma concentration.

Results

Effects of betaxolol and atenolol on adrenaline-induced arrhythmia: As reported previously (9), adrenaline infusion for 3 min at a rate of 2.5–4.5 μg/kg/min induced ventricular tachycardia with almost all the beats consisting of ventricular ectopic beats. Doses of betaxolol, 0.01, 0.05 and 0.1 mg/kg,
i.v., were examined in the preliminary study; and since a 0.01 mg/kg dose did not completely suppress the arrhythmia and a 0.05 mg/kg dose seemed to be sufficient to suppress this arrhythmia compared to a higher dose of 0.1 mg/kg, a 0.05 mg/kg dose was used in the present experiment. As for atenolol, many comparative studies have suggested that the potency of the drug was about half that of betaxolol (1, 5, 8), so a 0.1 mg/kg dose was examined in the preliminary study, and since it was effective on the arrhythmia, this dose was used in the present experiment. As shown in Fig. 1, betaxolol decreased the total heart rate, number of ventricular beats, and arrhythmic ratio one or two min after injection, and this antiarrhythmic effect lasted up to 15 min.

![Adrenaline arrhythmia](n=5)

The blood pressure was gradually reduced, but the change was not significant. As shown in Fig. 2, the effects of 0.1 mg/kg atenolol on this arrhythmia were almost similar to those of betaxolol, although it did not completely suppress the arrhythmia compared to betaxolol. The plasma concentration-time curve of betaxolol fitted well with that predicted by the one-compartment, open-model theory. The parameters of the equation, expressed as concentration = \( A e^{-\alpha t} \), were: \( A = 41.6 \pm 35.3 \; \mu g/ml \) and \( \alpha = 0.13 \pm 0.06/\min \) \((n=6)\); where \( A \) is the concentration at 0 time, and \( \alpha \) is the time constant. Since the antiarrhythmic effect of betaxolol lasted up to the last minute of adrenaline infusion, the minimum antiarrhythmic betaxolol plasma concentration for canine halothane-adrenaline-induced arrhythmia was determined as less than 10 ng/ml.

![Fig. 2. Summary of the effects of atenolol, 0.1 mg/kg, i.v., on halothane-adrenaline-induced arrhythmia. The effects were almost similar to those of betaxolol, although atenolol did not completely suppress the arrhythmia compared to betaxolol. *P<0.05, **P<0.01.](image1)

![Fig. 3. Summary of the effects of betaxolol, 3 mg/kg, i.v., on digitalis-induced arrhythmia. Betaxolol did not suppress the arrhythmia, even though this dose showed a significant hypotensive effect soon after injection. *P<0.05.](image2)
Effects of betaxolol and atenolol on digitalis-induced arrhythmia: After injection of a total dose of 70–80 µg/kg ouabain, almost all the beats were of ventricular origin. As shown in Figs. 3 and 4, 3 mg/kg betaxolol and 5 mg/kg atenolol were ineffective on digitalis arrhythmia, even though these doses showed significant hypotensive effects. A dose of 3 mg/kg betaxolol reduced total heart rate and atrial rate, but the changes were not significant, and a slight decrease of arrhythmic ratio in the later part of the observation period must have been due to a decrease in the concentration of ouabain, because no supplement of ouabain was given after injection of beta blockers in the present experiments. As the plasma concentration-time curve did not fit the two compartment open model, we could not calculate the pharmacokinetic parameters of the drug. The maximum concentration of betaxolol reached up to 2.38±0.93 µg/ml at 1 min after the injection.

Discussion

The present experiments using two canine ventricular arrhythmia models demonstrated that both betaxolol and atenolol were effective on adrenaline induced arrhythmia but were ineffective on digitalis arrhythmia. According to our previous studies, almost all the beta blockers examined were effective on adrenaline arrhythmia in small doses ranging from 10 to 100 µg/kg (9, 10). Also in this study, small doses of 0.05 mg/kg and 0.1 mg/kg for betaxolol and atenolol, respectively, were used. Comparing the antiarrhythmic potencies of these two drugs, although the higher dose of 0.1 mg/kg was used for atenolol, it did not suppress adrenaline arrhythmia completely compared to 0.05 mg/kg betaxolol. Higher doses of atenolol must have induced a stronger antiarrhythmic effect, but the duration of action might have far exceeded the 18 min of adrenaline infusion time. It was reported that the pharmacokinetic features of these two drugs did not differ so much (1, 5, 8), so the data indicate that betaxolol was more potent than atenolol as a beta adrenoceptor blocker. We estimated the minimum effective plasma concentration of betaxolol for adrenaline arrhythmia to be less than 10 ng/ml. This concentration is almost the same as the minimum clinical beta blocking plasma concentration in man, estimated to be approximately 10 ng/ml.

Some specific properties of betaxolol and atenolol compared to beta blockers that we have already reported are the long duration of action and the lack of increase in the blood pressure soon after betaxolol or atenolol injection in the adrenaline arrhythmia. As for the long lasting effect of betaxolol, it has been reported to have a long plasma elimination half-life (5–7), and so it has also been reported to have a long duration of effect on exercise tachycardia and hypertension (2, 5, 6, 15, 22). As for the effects on the blood pressure, it is conceivable that the beta 1
selective property of these two beta blockers accounts for the lack of increase in the blood pressure. In other words, owing to their weaker beta 2 blocking effects, the blood pressure was not increased under residual beta 2 and alpha adrenergic stimulation by adrenaline. Except for these effects, the antiarrhythmic effects of betaxolol and atenolol were qualitatively similar to other nonselective beta blockers, and this may indicate that the well-known predominant beta 1 receptor population in the heart mediates adrenergic stimulation, including induction of arrhythmias.

In the digitalis arrhythmia experiment, betaxolol and atenolol were not effective. However, some beta blockers such as propranolol and pindolol were effective on digitalis arrhythmia at doses of a hundred or thousand times higher than their ordinary beta blocking doses, probably due to their membrane stabilizing action (9, 10). The betaxolol plasma concentration did not decline after bolus injection as predicted by the two compartment model theory. Our previous studies using not only beta blockers but also other antiarrhythmic drugs showed that most of the drug plasma concentrations declined as predicted by the two compartment model. We do not know the reason for the difference, but none the less, the maximum plasma concentration of betaxolol at 1 min after injection reached up to 2.4 μg/ml. Electrophysiological studies have indicated that betaxolol has little membrane stabilizing action (1). In in vitro experiments, however, the membrane stabilizing concentration of betaxolol, which was reflected by the IC50 of maximum upstroke velocity of action potential in rabbit ventricular muscle, was reported to be approximately 34 μg/ml (S. Katayama, personal communication). This concentration is significantly higher than the plasma concentration reached in our digitalis experiments. Thus it may be concluded that the ineffectiveness of betaxolol on digitalis arrhythmia is due to the lack of membrane stabilizing action.

Recently, much attention has been drawn to the involvement of catecholamines in cardiac arrhythmia in ischemic or reperfused myocardium (23–26), and both clinical and experimental studies have suggested that in such abnormal hearts, increased circulating catecholamine values might play an arrhythmogenic role (25–27). In this respect, it is necessary to examine the effects of beta blockers on arrhythmias related to myocardial ischemia. Atenolol has already been reported not to prevent reperfusion induced arrhythmia even in a high dose of 2 mg/kg, i.v. (23), although it was effective for the clinical treatment of supraventricular and ventricular arrhythmias (28). Also our previous studies indicated that beta blockers and Ca blockers were not effective on ischemia induced arrhythmia; in our cases, it was produced by two stage ligation of the coronary artery in the dog (11). We also examined the effects of betaxolol on three dogs with this arrhythmia, and we did not see any antiarrhythmic actions.

The aim of the present experiment was to examine whether beta 1 selective blockers have a specific antiarrhythmic effect, if any at all. In this regard, the conclusion is that the beta 1 selective blockers were similar to other types of beta blockers; thus they may be effective clinically mainly on supraventricular arrhythmias and some arrhythmias related to increased sympathetic tone.

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