ANTI-ARRHYTHMIC EFFECT OF NADOLOL IN EXPERIMENTAL ARRHYTHMIAS: COMPARISON WITH PROPRANOLOL AND ALPRENOLOL

MITSUYOSHI NAKASHIMA, YOSHIHARU TAKIGUCHI, KATSUNORI OGURO, KEIZO SOGABE AND HISAKUNI HASHIMOTO

Department of Pharmacology, Hamamatsu University School of Medicine, Hamamatsu, 431-31, Japan
(Received March 26, 1984)

The effects of nadolol on experimental arrhythmias were investigated and compared with those of propranolol and alpenolol. The arrhythmias were induced by either ouabain, halothane plus adrenaline or acute coronary occlusion in anesthetized dogs. All three β-blocking drugs in a dose range of 10 to 200 μg/kg inhibited halothane plus adrenaline-induced arrhythmias. These drugs also attenuated coronary occlusion-induced ventricular arrhythmias as well as other electrical abnormalities such as electrical alternation and conduction delay. Among the three drugs, nadolol was the most potent in suppressing both types of arrhythmias. Contrary to the potent effects on these arrhythmias, nadolol was ineffective against ouabain-induced arrhythmias even in a dose of 3 mg/kg, while propranolol and alpenolol were significantly effective in a dose of 100 μg/kg. It is probable that the anti-arrhythmic effect of nadolol is exclusively due to its β-blocking activity.

Keywords — nadolol; propranolol; alpenolol; adrenaline-induced arrhythmia; ouabain-induced arrhythmia; coronary occlusion-induced arrhythmia

INTRODUCTION

Various β-adrenergic blocking drugs have been shown to be useful in clinical cases of arrhythmias. In general, β-blocking drugs are estimated to be more effective in the treatment of supraventricular than ventricular arrhythmias. Nadolol is a non-cardioselective β-adrenergic blocking drug which lacks both membrane stabilizing and intrinsic sympathomimetic activity, and has a long duration of action. It was also reported to possess anti-arrhythmic property in experimental animals. The present study was undertaken to examine the anti-arrhythmic activities of nadolol and to compare with those of propranolol and alpenolol. The arrhythmias examined were ouabain-induced, halothane plus adrenaline-induced and coronary occlusion-induced arrhythmias in anesthetized dogs. In the coronary occlusion study, effects of drugs on electrical alternation of the ST-T complex of epicardial electrograms and on delayed conduction which was recorded with a bipolar electrode were also determined, because these electrical abnormalities have been reported to contribute to manifestation of arrhythmias during coronary occlusion.

METHODS

1. General — Ninety eight mongrel dogs of both sexes, weighing 6—17 kg, were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and were artificially ventilated. A femoral vein and artery were cannulated for drug administration and blood pressure monitoring, respectively, and needle electrodes were inserted subcutaneously for recording the Lead II of electrocardiogram (ECG) and heart rate.

2. Halothane Plus Adrenaline-Induced Arrhythmias — Mongrel dogs were anesthetized with pentobarbital, and bilateral vagotomy was performed. Halothane (1%) was introduced with pure oxygen gas using a general anesthesia apparatus (Shin-ei Kogyo) which was connected to the respirator. After equilibration with halo-
thane, arrhythmia was induced by adrenaline injection (3 or 5 μg/kg, i.v.). Before the administration of a drug, adrenaline injection was repeated two to four times until the degree of arrhythmias was not so much different between two successive injections. A low dose of a β-blocking drug was then administered intravenously through the femoral vein 10 min prior to the next adrenaline injection. After 2 h, a high dose of the same drug was administered, and the adrenaline injection was performed again. To determine the degree of arrhythmias, the ventricular beats were counted during 0 to 0.5, 0.5 to 1, 1 to 2, 2 to 3, and 3 to 4 min after the adrenaline injection.

3. Ouabain-Induced Arrhythmias — Cardiac arrhythmias were induced by ouabain infusion at a rate of 1 μg/kg/min through femoral vein with an infusion pump until the animal died with ventricular fibrillation. A drug was administered 10 min before ouabain infusion. The effects of drugs were determined by measuring the time required for appearance of cardiac arrhythmias induced by ouabain, i.e. first extrasystole, frequent extrasystole (more than 10 beats/min), ventricular tachycardia and ventricular fibrillation.

4. Electrical Alternation, Conduction Delay and Arrhythmias Induced by Acute Coronary Occlusion — Under artificial respiration, a left lateral thoracotomy was performed through the fifth left intercostal space and the heart was cradled in the opened pericardium. Epicardial unipolar electrocardiogram (UPEG) and epicardial bipolar electrocardiogram (BPEG) were recorded according to Hashimoto and Nakashima.6) UPEG and BPEG were recorded from the center of the ischemic area. To produce transient ischemia, the left anterior descending artery was occluded for 3 to 10 min. The time interval of two successive occlusions was 20 min. Before drug administration, coronary occlusion was performed at least twice and it was determined that the time course and the degree of the electrical alternation and of ventricular arrhythmias were not so much different in the two successive occlusions. The last occlusion before a drug is a control occlusion. Drugs were administered via the femoral vein. Occlusion was again performed 10 min after drug administration. A β-blocking drug was administered only once in each dog.

The degree of STTA and of conduction delay were measured at 30 s intervals (T1, T2, and T3) after the start of occlusion and also 2 min after T3 (T4). T1, T2, and T3 were timed to correspond to 30, 60 and 90 s after the appearance of

![Graph of total beats and ventricular beats/total beats](image)

**FIG. 1. Effects of β-Adrenoceptor Blocking Drug, Nadolol, on Adrenaline-Induced Arrhythmias in Halothane Anesthetized Dogs**

Nadolol (1, 10 μg/kg) was administered intravenously through the femoral vein 10 min prior to infusion of adrenaline (3 or 5 μg/kg, i.v.) after equilibration with halothane. Total beats (sinus beats and ventricular beats) were counted during the indicated periods, and represented in terms of beats/min (upper panel). The ratio of ventricular beats to total beats were represented at lower panel: Control ○ --- ○, 1 μg/kg ● - - - ● (n=6), 10 μg/kg ● --- ● (n=6). a) p<0.01, b) p<0.05 vs. control.
STTA in the control occlusion. For instance, when STTA appeared at 2 min after the start of the control occlusion, $T_1$, $T_2$, $T_3$ and $T_4$ were determined at 2.5, 3.5 and 5.5 min after the start of each occlusion. The parameters at $T_4$ were measured only during occlusions after a drug.

The degree of STTA was represented in terms of the difference in the ST-segment elevation of two adjacent potentials in the UPeG. When alternation was 3:1 pattern, the degree of STTA was measured in two potentials which were a potential with a negative deflection of the ST-T complex and the next one. The ST-segment elevation was measured 180 ms after the onset of the QRS complex. The degree of conduction delay which was reflected as a delayed deflection in BPeG was represented as the time from the onset of an initial deflection to a final rapid deflection in BPeG. Because conduction delay in most cases changed alternately, the longer delay was regarded as "max. conduction delay."

In order to determine the effect of a drug on the arrhythmias, a number of the animals in which the arrhythmias were observed during the period of $T_1$ to $T_3$ or $T_1$ to $T_4$ was compared before and after the drug. No arrhythmias appeared before $T_1$ in any animal. A quantitative

**FIG. 2. Effects of Alpranolol on Adrenaline-Induced Arrhythmias in Halothane Anesthetized Dogs**

Alpranolol (10, 100 $\mu$g/kg) was administered intravenously 10 min prior to adrenaline injection. The results were represented as in Fig. 1: Control ○ ○ $10 \mu$g/kg $\bullet$ $\bullet$ $\bullet$ (n=6), 100 $\mu$g/kg $\bullet$ $\bullet$ $\bullet$ (n=6). $a)$ $p<0.01$, $b)$ $p<0.05$ vs. control.

**FIG. 3. Effects of Propranolol on Adrenaline-Induced Arrhythmias on Halothane Anesthetized Dogs**

Propranolol (10, 100 $\mu$g/kg) was administered intravenously 10 min prior to adrenaline injection. The results were represented in Fig. 1: Control ○ ○ $10 \mu$g/kg $\bullet$ $\bullet$ $\bullet$ (n=5), 100 $\mu$g/kg $\bullet$ $\bullet$ $\bullet$ (n=4). $a)$ $p<0.01$, $b)$ $p<0.05$ vs. control.
analysis of ventricular arrhythmia (VA) was not tried, because the incidence of VA was not frequent during each coronary occlusion.

Arterial blood pressure and heart rate were measured just before each occlusion.

5. Drugs and Statistics — The drugs used were as follows: ouabain octahydrate (Merck), nadolol (Dainippon), propranolol (Sumitomo), alpranolol (Fujisawa) and adrenaline (Dai-ichi). These drugs were dissolved in 0.9% saline solution.

Results were represented in terms of means ± S.E., and Student’s paired t-test was used for statistical comparison.

RESULTS

1. Adrenaline-Induced Arrhythmias under the Halothane Anesthesia

When adrenaline in a dose of 3 or 5 μg/kg was injected i.v. within 1 min, systolic blood pressure (SBP) was gradually elevated and sinus tachycardia occurred. At 30 s after the injection, the bigeminy appeared and continued for about 10 s and then it was followed by multifocal ventricular arrhythmia (VA). Between 1 and 3 min after the injection, ventricular rhythm was dominantly observed. After that, VA and SBP were gradually decreased and sinus rhythm became dominant. After the administration of nadolol in a dose of 1 μg/kg, alpranolol or propranolol in a dose of 10 μg/kg, heart rate (HR) and SBP decreased slightly. But these treatments did not show the protecting effect on halothane plus adrenaline-induced arrhythmias (figs. 1, 2 and 3). When the dose of each drug was elevated by ten-fold, all of the three drugs markedly suppressed the incidence of VA. Thus, nadolol was about ten times as potent as alpranolol or propranolol in suppressing halothane plus adrenaline-induced arrhythmias.

2. Ouabain-Induced Arrhythmias

When ouabain was infused intravenously at a rate of 1 μg/kg/min, SBP was gradually elevated and HR was increased. In ten control dogs, the first extrasystole (FE), frequent extrasystole (EX), ventricular tachycardia (VT) and ventricular fibrillation (VF) appeared at 36.4 ± 3.3, 41.1 ± 3.7, 51.9 ± 4.8 and 74.1 ± 4.6 min, respectively (Table I). The pretreatment with alpranolol in a dose of 0.1 mg/kg significantly delayed the appearance of FE and EX. The appearance of VT or VF was also slightly delayed but not significantly. The pretreatment of propranolol in the same dose also significantly delayed the appearance of FE, EX and of VF. Nadolol, on the other hand, did not show any protective effect against ouabain-induced arrhythmias even in a dose of 3 mg/kg. Thus, nadolol was the least potent among the three drugs.

| Table 1. The Protective Effects of Beta-blocking Drugs, Nadolol, Alpranolol and Propranolol, on Cardiac Arrhythmias Induced by Ouabain Infusion |
|-----------------|-----------------|-----------------|-----------------|
| Dose (mg/kg)    | Toxic effect (min) | Lethal effect (min) |                  |
|                 | First extrasystole | Frequent extrasystole | Ventricular tachycardia | Ventricular fibrillation |
| Ouabain control | 36.4 ± 3.38      | 41.4 ± 3.75      | 51.9 ± 4.87      | 74.2 ± 4.63     |
| Nadolol         | 43.6 ± 4.14      | 45.1 ± 4.62      | 49.0 ± 4.95      | 66.7 ± 4.73     |
|                 | 39.0 ± 7.15      | 47.4 ± 5.00      | 51.5 ± 3.83      | 100.0 ± 13.5    |
| Alpranolol      | 54.3 ± 3.44a)    | 54.5 ± 3.27b)    | 61.9 ± 5.53      | 96.5 ± 12.6     |
|                 | 51.1 ± 4.69b)    | 48.5 ± 3.32b)    | 58.8 ± 3.35      | 102.0 ± 9.52a) |

Each drug was administered intravenously 10 min prior to ouabain infusion (1 μg/kg/min, i.v.). The time required for the appearance of cardiac arrhythmias was measured.

a) Significance (p < 0.01) vs. ouabain control, b) significance (p < 0.05) vs. ouabain control.
3. Electrical Alternation, Conduction Delay and VA Induced by Acute Coronary Occlusion

The occurrence of VA during a period of STTA is shown in Figs. 4 and 5. In the case

FIG. 4. Ventricular Arrhythmias Observed during the Period of Electrical Alternation of the ST-T Complex of U Peg

A. control

B. after nadolol 200 μg/kg

FIG. 5. Effects of Nadolol in 200 μg/kg on the Electrical Alternation, Conduction Delay and the Incidence of VA
FIG. 6. Effect of Nadolol on the Electrical Abnormalities during Acute Coronary Occlusion

A: alternation of the ST-T complex (STTA). B: max. conduction delay. C: incidence of ventricular arrhythmias (VA). D: systolic blood pressure (SBP) and heart rate (HR). The effect of the drug on VA was represented in terms of the number of animals in which VA occurred during the period of $T_1$ to $T_3$ or of $T_1$ to $T_4$. Nadolol (10, 200 µg/kg) was administered 10 min prior to coronary occlusion. ○, control for 10 µg/kg. ●, after 10 µg/kg. □, control for 200 µg/kg. ■, after 200 µg/kg. Six or eight animals were used for each dose. a) $p<0.05$, b) $p<0.01$ vs. control.
shown in Fig. 4, slight STTA appeared 2 min after the start of occlusion in area-2. At 3 min, typical STTA appeared in the same area, which was followed by VF. No VA preceded VF in this

FIG. 7. Effect of Alpenolol on the Electrical Abnormalities during Acute Coronary Occlusion
For details, see Fig. 6. Alpenolol (10, 100 μg/kg) was administered 10 min prior to coronary occlusion. ○, control for 10 μg/kg. ●, after 10 μg/kg. □, control for 100 μg/kg. ■, after 100 μg/kg. Six animals were used for each dose. a) p < 0.05, b) p < 0.01, vs. control.
case. VF followed the negative deflection of the ST-T complex in UPeG in the area-2. During the period of STTA, delayed conduction was also observed.

FIG. 8. Effect of Propranolol on the Electrical Abnormalities during Acute Coronary Occlusion
For details, see Fig. 6. Propranolol (10, 200 μg/kg) was administered 10 min prior to coronary occlusion. ○, control for 10 μg/kg. ●, after 10 μg/kg. □, control for 200 μg/kg. ■, after 200 μg/kg. a) p < 0.05, b) p < 0.01 vs. control.
Anti-arrhythmic Effects of Nadolol

In the case shown in Fig. 5, UPeq shows 3:1 alternation. Ventricular premature beats followed a sinus beat with a negative deflection of the ST-T complex 4 min after the start of occlusion. Markedly delayed conduction was observed after the sinus beat with a negative deflection of the ST-T complex. After 200 μg/kg of nadolol, HR was lowered, and both STTA and conduction delay were attenuated. No VA appeared even after a longer period of occlusion.

Effects of nadolol, alpenrolon and propranolol are summarized in Figs. 6, 7 and 8, respectively. Nadolol in doses of 10 and 200 μg/kg attenuated STTA and conduction delay at T1, T2 and T3 (Fig. 6). The incidence of VA during the period of T1 to T3 was completely inhibited by nadolol in 10 μg/kg. Suppression of the incidence of VA was more marked with 200 μg/kg. HR was lowered with nadolol in both doses. SBP was lowered with nadolol in 200 μg/kg. Alpenrolon also attenuated STTA and conduction delay, but in a less extent than did nadolol (Fig. 7). The suppression of VA by alpenrolon was also less prominent. Alpenrolon did not lower HR in a dose of 10 μg/kg. As shown in Fig. 8, attenuation of STTA and of conduction delay and suppression of VA with propranolol were also less prominent. Propranolol in 10 μg/kg lowered HR, but in a less extent than did nadolol. The effect of 200 μg/kg of propranolol on the incidence of VA was not shown, because a number of animals in which VA occurred was too small.

DISCUSSION

The present study demonstrated that nadolol was effective against cardiac arrhythmias induced by halothane plus adrenaline and by coronary occlusion, but less effective against ouabain-induced arrhythmias. Propranolol and alpenrolon, on other hand, had protective effects against all three types of experimentally induced arrhythmias. In general, anti-arrhythmic activity of β-adrenergic blocking drugs is ascribed to two important properties of the drugs. The first major property is β-adrenergic receptor blockade, that would antagonize the ability of catecholamines to induce arrhythmias by alteration of cardiac automaticity and conductivity. The second is what has been termed “quinidine-like” or membrane stabilizing action. According to Gibson et al. and others, nadolol in a concentration range of 10^{-8}—10^{-4}M did not alter membrane electrical properties of isolated canine Purkinje fibers, atrial muscle or of ventricular muscle, suggesting that nadolol does not possess the membrane stabilizing effect.

In the present study, nadolol was ineffective against ouabain-induced arrhythmias even in a dose of 3 mg/kg, while propranolol and alpenrolon which possess membrane stabilizing activity were significantly effective in the ouabain-induced arrhythmias, although the effects of the two drugs were slight in the dose tested. The ineffectiveness of nadolol against digoxin-induced arrhythmias has also been reported by Evans et al. 3) Oubain-induced arrhythmias, in general, were resistant to β-blocking drugs with a weak membrane stabilizing activity, whereas they were inhibited by β-blocking drugs with a more marked membrane activity. Therefore, the ineffectiveness of nadolol against ouabain-induced arrhythmias is probably due to lack of the membrane stabilizing activity.

In contrast to the weak effects of ouabain-induced arrhythmias, all three β-blocking drugs showed marked protective effects against halothane plus adrenaline-induced arrhythmias, which is consistent with the idea that β-blocking drugs generally show a potent anti-arrhythmic activity against this type of arrhythmias. Among the three β-blocking drugs, nadolol showed the most potent anti-arrhythmic effect. As compared with propranolol or alpenrolon, nadolol is two to four times potent in a β-blocking activity, which probably contributes to its potent anti-arrhythmic activity against halothane plus adrenaline-induced arrhythmias.

The electrical abnormalities including VA during acute coronary occlusion were also attenuated by all of the three β-blocking drugs. The beneficial effects of β-blocking drugs in acute myocardial infarction have been observed in ex-
peribalional animals and in clinical cases. It has been considered that the $\beta$-blocking effect mainly contributes to the beneficial effects.\textsuperscript{11–16} In the present study, nadolol was the most potent in attenuating the electrical alternation, conduction delay and the incidence of arrhythmias, which is parallel to the potency in a $\beta$-blocking action. The fact that the reduction in the heart rate was the most remarkable with nadolol may suggest the highest degree of $\beta$-blockade with nadolol in the present study. It is probable that the $\beta$-blocking drugs observed in the present study are caused by their $\beta$-blocking actions which may reduce the myocardial oxygen requirement and therefore result in attenuation of the coronary occlusion-induced electrical abnormalities.

In conclusion, nadolol was effective against halothane plus adrenaline-induced and acute coronary occlusion-induced arrhythmias, but was ineffective against ouabain-induced arrhythmias. It is probable that the anti-arrhythmic effect of nadolol is mainly due to its potent $\beta$-blocking activity.

REFERENCES