Original Article

Antiarrhythmic Effects of Possible Anti-Ischemic Drugs

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Abstract: Direct antiarrhythmic effects of intravenously administered coronary vasodilators, metabolically acting drugs and a Ca activated neutral protease inhibitor were examined using two canine ventricular arrhythmia models, adrenaline and digi- talis arrhythmias. Two dihydropyridine Ca antagonists, nifedipine and nisoldipine in the dose range of 10 to 20 μg/kg, suppressed adrenaline arrhythmia, while they did not affect digitalis arrhythmia. Similar effects were observed using 80 μg/kg nitroglycerin. Caffeine (10 mg/kg) also had no antiarrhythmic effect on digita- lis arrhythmia, while it aggravated adrenaline arrhythmia, inducing ventricular fibrillation. 1-Carnitine chloride in a high dose of 600 mg/kg transiently decreased the blood pressure and suppressed only adrenaline arrhythmia. Coenzyme Q₁₀, 10 mg/kg, did not show antiarrhythmic effects. A new Ca activated neutral protease inhibitor, NCO-700 (3 mg/kg), had a prominent hypotensive effect and transiently suppressed adrenaline arrhythmia. All these drugs had no Na channel blocking action, thus it is understandable that they were not effective on digitalis arrhythmia. Adrenaline arrhythmia may be generated by increased Ca current, but the effective drugs used in the present study, except nifedipine and nisoldipine, are not known as direct depressants of the Ca channel.

Key words: Ventricular arrhythmia, coronary vasodilators, 1-carnitine, coenzyme Q₁₀, NCO-700

INTRODUCTION

Ischemic coronary heart diseases are often complicated by arrhythmias of various types, which are usually treated successfully with antiarrhythmic drugs of class 1, Na channel blockers. However drugs effective in treating myocardial ischemia by dilating coronary artery or relieving vasospasm, or by improving myocardial metabolism may have antiarrhythmic effects. We have been interested in antiarrhythmic effects of drugs used to treat myocardial ischemic diseases, and recently reported antiarrhythmic effects of coronary vasodilators on canine ventricular arrhythmia models¹⁰). The arrhythmia models used in that study were digitalis and adrenaline induced ventricular arrhythmias. Only class 4 antiarrhythmic drugs, Ca antagonists including verapamil, diltiazem and bepridil, were effective in suppressing adrenaline arrhythmia. They were not effective in suppressing digitalis arrhythmia. Also in the study, another coronary vasodilator, nicorandil, was not effective in suppressing either ventricular arrhythmia. It seemed that antiarrhythmic effects of drugs at least as judged by the immediate disappearance of existing arrhythmia after drug treatment depend on their ability to suppress cardiac Na or Ca channels⁵,¹⁸).

In order to verify this hypothesis, we extended our study to include dihydro-
pyridine Ca antagonists and the so-called anti-ischemic drugs. These were the coronary vasodilators, nitroglycerin, nifedipine, nisoldipine and caffeine, the metabolically acting drugs, 1-carnitine chloride and coenzyme Q₁₀, and the Ca activated neutral protease inhibitor, NCO-700(20). Some of these drugs have been successfully used in the treatment of myocardial ischemic diseases, and all of these drugs have been shown to protect myocardial cell damage under ischemia in vivo and in vitro conditions, and to decrease infarct size after coronary ligation(6,13-15,17,20,21). We examined whether these drugs have acute anti-arrhythmic effects in canine digitalis and adrenaline arrhythmia models, and not ischemia induced arrhythmia models, for example the two-stage coronary ligation arrhythmia, because 1) digitalis arrhythmia is a more appropriate model to detect class 1 antiarrhythmic drugs(5) and 2) pure anti-arrhythmic effects might be modified by their effects to improve myocardial ischemia. As for the second reason, however, anti-ischemic effects do not appear to add any favorable immediate antiarrhythmic effects, since verapamil and several beta blockers were not effective on the two-stage coronary ligation arrhythmia(4).

Methods

1) Production of digitalis arrhythmia

Mongrel dogs of either sex, weighing 7 to 15 kg, were anesthetized with pentobarbital sodium 30 mg/kg. As reported earlier(5), 40 μg/kg ouabain was injected intravenously and then followed by an additional 10 μg/kg every 20 min until stable ventricular arrhythmia was produced. Drugs were injected intravenously through a cannula in the femoral vein.

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

2) Production of adrenaline arrhythmia

Mongrel dogs of either sex, weighing 7 to 15 kg, were anesthetized initially with thiopental sodium. As reported earlier(18), after intubation, 1.0% halothane, vaporized with 100% O₂, was administered with a volume-limited ventilator. Adrenaline was infused through the left femoral vein at a rate of 2.5-7 μg/kg/min, to produce sustained multifocal ventricular tachycardia. After 3 min of adrenaline infusion, drugs were injected from the right femoral vein.

The lead II ECG, atrial electrogram and blood pressure were continuously recorded.

3) Evaluation of the antiarrhythmic effects

The severity of arrhythmia was expressed by the arrhythmic ratio: number of ventricular ectopic beats divided by the total heart rate. For the two arrhythmias, the arrhythmic ratios before drug injection were almost 1 and there were no spontaneous improvements in these ratios. If the arrhythmic ratio after drug administration was decreased significantly from the 0 time value, as judged by the Student’s t-test for paired data, the drug was judged as having an antiarrhythmic effect.

4) Drugs

Intravenous preparations used were as follows; nitroglycerin ampoules (Nippon Kayaku), 5 mg/10 ml; nifedipine ampoules for animal experiment (Bayer), 0.2 mg/2 ml; nisoldipine (Bayer), 10 mg dissolved in 18 ml ethanol, 14 ml polyethylene glycol, and 70 ml distilled water; caffeine (Wako), dissolved in distilled water; 1-carnitine chloride solution (Earth Chemical), dissolved in distilled water at a concentration of 20% w/v and pH 6.8 adjusted with 1 N NaOH; coenzyme Q₁₀ solution (Eisai), 12.5 mg/5 ml; and NCO-700 (Nippon Chemiphar), dissolved in distilled water.
NCO-700 is a calcium activated neutral protease inhibitor, having the following chemical formula, bis (ethyl (2R, 3R)-3-((S)-3-methyl-1-(4-(2, 8, 4-trimethoxyphenyl methyl) piperazin-1-ylcarbonyl) butylcarbamoyl) oxiran-2-carboxylate) sulfate.

5) Drug plasma assay

Plasma concentrations of nifedipine and nisoldipine were assayed using a gas chromatographic method in the digitalis arrhythmia experiment. Venous samples were drawn from the right external jugular vein 5 min before and 0, 1, 3, 5, 10, 15, 30 and 60 min after the drug injection.

Results

Nitroglycerin (Fig. 1)

As shown in Fig. 1, doses of 0.3 mg/kg induced a long-lasting decrease in the arrhythmic ratio, i.e. antiarrhythmic effects, on adrenaline arrhythmia for 18 min, while the hypotensive effect lasted less than 1 min. There were also decreases in the total heart rate and the number of ventricular beats.

Doses of 0.1 and 0.3 mg/kg were examined on digitalis arrhythmia and as shown in Fig. 1, 0.3 mg/kg transiently decreased the blood pressure, but there were no antiarrhythmic effects and no changes in the total heart rate or atrial rate.

Nifedipine (Fig. 2)

A hypotensive dose of 10 μg/kg gradually decreased the arrhythmic ratio and the significant decrease lasted until the end of adrenaline infusion. Decrease of the total heart rate and the number of ventricular beats, and increase in the atrial rate occurred soon after injection. In the digitalis arrhythmia, doses up to 20 μg/kg did not have any antiarrhythmic effects, but showed a long-lasting hypotensive effect. The plasma concentration of nifedipine decreased as predicted by the two compartment open model theory and the parameters of the curve, concentration = Ae^{-αt} + Be^{-βt} were: A = 88 ± 169 ng/ml, α = 0.74 ± 1.18/min, B = 16 ± 18 ng/ml and β = 0.027 ± 0.022/min (n = 6). The peak plasma concentration of nifedipine 1 min after injection was 32 ± 9 ng/ml (n = 6).

Nisoldipine (Fig. 3)

Nisoldipine had qualitatively and quantitatively almost the same effects as nifedipine and showed long-lasting antiarrhythmic effect only on adrenaline arrhythmias. In the digitalis arrhythmia, the peak plasma concentration of nisoldipine 1 min after injection was about 29 ± 17 ng/ml. Unlike nifedipine, the plasma concentration of nisoldipine did not decrease as might be predicted by the two-compartment open model.

Caffeine (Fig. 4)

Caffeine aggravated adrenaline tachycardia, inducing ventricular fibrillation. Three mg/kg induced ventricular fibrillation in 4 out of 7 dogs and 10 mg/kg induced it in all 6 dogs within 1 min of injection. Ten mg/kg had a transient hypotensive effect, but had no antiarrhythmic effect on digitalis arrhythmia. The atrial rate increased after injection and the effect lasted about 1 hr.

L-Carnitine Chloride (Fig. 5)

A large dose of 600 mg/kg, as compared to the 300 mg/kg, dose which is sufficient to suppress the two-stage coronary ligation arrhythmia17 showed a transient hypotensive effect and suppressed adrenaline arrhythmia just after injection and later from the 7th min to the end of adrenaline infusion. The same dose had no effect on digitalis arrhythmia.

Coenzyme Q10 (Fig. 6)

A dose of 10 mg/kg, higher than the dose (5 mg/kg) that improves vulnerability after coronary reperfusion19, had almost no effects on cardiovascular or arrhythmic
Fig. 1. Effects of nitroglycerin on adrenaline arrhythmia (left) and digitalis arrhythmia (right). *: p less than 0.05, **: p less than 0.01 from the 0 time value. Bars represent the S.D.

Fig. 2. Effects of nifedipine on adrenaline and digitalis arrhythmias.
Fig. 3. Effects of nisoldipine on adrenaline and digitalis arrhythmias.

Fig. 4. Effects of caffeine on digitalis arrhythmia. Caffeine at dose of 3 and 10 mg/kg aggravated adrenaline arrhythmia.
Fig. 5. Effects of 1-carnitine chloride on adrenaline and digitalis arrhythmias.

Fig. 6. Effects of coenzyme Q₁₀ on adrenaline and digitalis arrhythmias.
parameters of dogs of both adrenaline and digitalis arrhythmias. The significant decrease in the blood pressure after 24th min in the digitalis arrhythmia experiment might have been due to the decrease in the plasma concentration of ouabain.

NCO-700 (Fig. 7)

A hypotensive dose of 50 mg/kg, higher than the dose that decreases infarct size in rabbits (20 mg/kg)\(^\text{20}\), had transient anti-arrhythmic effects on adrenaline arrhythmia, but no antiarrhythmic effect was observed in digitalis arrhythmia. The decrease in the blood pressure in digitalis experiment was long-lasting.

**DISCUSSION**

Among the possible antianginal and anti-ischemic drugs we examined, two dihydropyridine Ca antagonists, nifedipine and nisoldipine, have been shown to selectively suppress Ca channels of smooth muscles and to have a weak direct myocardial depressant effect\(^\text{3,9}\). However their antiarrhythmic effects were similar to those of other Ca antagonists we examined, verapamil, diltiazem and bepridil\(^\text{10}\), i.e. they were effective only on adrenaline arrhythmia. A recent study reported an antiarrhythmic effect of nifedipine on cat digitalis arrhythmia, but it was only effective when given before arrhythmogenic ouabain infusion\(^\text{16}\). This is quite reasonable that the two dihydropyridines with weak but definite depressant effects on cardiac Ca channels, suppress arrhythmogenic increase in Ca current via activation of beta-receptors by adrenaline. The only difference between the dihydropyridines and other Ca blockers was that the effects of the former did not appear soon after injection but lasted longer.

The effect of nitroglycerin on adrenaline
arrhythmia was not expected, because a similar coronary vasodilator, nicorandil, did not have the effect even though it had a hypotensive effect\(^{10}\). The conclusion in the previous paper was that only the Ca antagonist had antiarrhythmic effects on adrenaline arrhythmia among coronary vasodilators, but the present results indicate that not only nitroglycerin, but also l-carnitine and NCO-700 with hypotensive effects had antiarrhythmic effects on adrenaline arrhythmia. Since these three drugs are not Ca antagonists, it is necessary to examine whether high doses or a large volume of the vehicles have some Ca antagonistic effects.

Caffeine is a phosphodiesterase inhibitor and may also be a catecholamine releaser, therefore, it is understandable that it would aggravate adrenaline arrhythmia. Caffeine is known to suppress the oscillatory current of digitalis intoxicated Purkinje fibers\(^2\) or aftercontractions\(^8\). Therefore, caffeine may have an antiarrhythmic effect on digitalis arrhythmia by a mechanism different from those of class 1 Na channel blockers\(^5\). However, its hypotensive effect limited the dose usable in the in vivo study and possibly for this reason it was not able to suppress the digitalis arrhythmia. There may be another explanation that the digitalis arrhythmia we produced might not be produced by oscillatory current\(^11,12\) or transient depolarization\(^2\), but by a Na channel dependent increased automaticity.

As for the effects of the drugs used in the present study on digitalis arrhythmia, we obtained further support for our conclusion that digitalis arrhythmia is Na channel dependent, and is suppressed only by Na channel blockers\(^5\). None of the present drugs have been found to possess class 1 activity\(^1,3\).

The present results indicate that anti-ischemic drugs have only limited efficacy on ventricular arrhythmias. However, the possible direct protection of ischemic myocardium by these drugs may have favorable effects on long term treatment of arrhythmia not by the suppression of myocardial ionic channels, as in the case of l-carnitine where it suppressed the two-stage coronary ligation arrhythmia\(^7\).

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References


Anti-ischemic Drugs and Arrhythmia


心筋虚血改善薬の抗不整脈作用

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血管拡張薬、心筋代謝改善薬、Ca 依存性中性蛋白分解酵素抑制薬 NCO-700 のイズ、ジギタリスおよびアドレナリン誘発心室性不整脈に対する作用を検討した。ジヒドロビリジン系 Ca 拮抗薬のニフェジピン、ニソルジピン、それにニトログリセリンはアドレナリン不整脈を抑制したが、ジギタリス不整脈には無効であった。塩化カルニチンと NCO-700 もアドレナリン不整脈に有効であった。コエンザイム Q_{10} は、両不整脈に無効であった。カフェインは、アドレナリン不整脈を悪化させ心室細動を誘発した。以上の結果は、従来から知られている様にこれらの薬物に Na チャネルを抑制する作用はなく、従ってジギタリス不整脈には無効だったと考えられる。アドレナリン不整脈はアドレナリンにより Ca 電流が増加したためと考えられるが、ニフェジピン、ニトログリセリン以外のものに Ca 拮抗作用があるかは不明で、今後の検討課題である。

キーワード 心室性不整脈、冠血管拡張薬、1-カルニチン、コエンザイム Q_{10}、NCO-700