EFFECTS OF NICARDIPINE ON THE CROSS-PERFUSED CANINE ATRIUM

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Abstract—Effects of nicardipine, a newly synthesized dihydropyridine vasodilator exhibiting cyclic phosphodiesterase inhibitory properties, were studied in the isolated canine atrium which was cross-perfused with blood from a donor dog. When nicardipine (1.0–10 μg/kg) was administered intravenously to the donor dog, the systemic blood pressure decreased and the heart rate did not significantly change. However, the contraction and beat rate of the isolated atrium were only slightly decreased. At larger doses (30–100 μg/kg, i.v.), the systemic blood pressure fell markedly and was usually accompanied by marked bradycardia, which was greater than that of the isolated atrium. Nicardipine injected into the sinus node artery of the isolated atrium caused dose-related negative chronotropic and inotropic effects which were less pronounced than those of verapamil. In contrast, papaverine increased right atrial rate and contractile force. Nicardipine similarly to verapamil and unlike manganese ion caused greater inhibition of the right atrial contraction at higher than lower pacing frequencies. From these results, it is concluded that nicardipine may produce predominantly cardiac depressant properties as a calcium antagonistic, and that such may not be related to phosphodiesterase inhibition in cardiac tissues.

Nicardipine (2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[2-(N-benzyl-N-methylamino)]ethyl ester 5-methyl ester hydrochloride, YC-93) is a synthetic compound with potent vasodilative properties, as already reported (1–3).

Sakamoto et al. (4) reported that nicardipine inhibited cyclic AMP phosphodiesterase in the supernatant homogenate prepared from cranial arteries, or the beef heart. In 1980, Satoh et al. (5) reported that nicardipine has negative chronotropic, dromotropic and inotropic properties, as determined in various isolated, blood-perfused preparations of the dog.

Nifedipine, which is a potent calcium antagonistic anti-anginal drug, is also a dihydropyridine derivative. It was reported that nifedipine and verapamil, calcium antagonists, suppressed contraction to a much greater extent frequencies, in the dog atrial and ventricular preparations (6–8).

In the present experiments, direct and indirect cardiac effects of nicardipine were investigated by an intraarterial administration of nicardipine into the sinus node artery of the isolated atrium and by an intravenous administration to the donor dog (9, 10). Effects of nicardipine on the frequency-force...
relationship were also examined and the findings compared with those of verapamil and manganese chloride.

MATERIALS AND METHODS

Twenty mongrel adult dogs of either sex, weighing 10 to 18 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. After i.v. administration of sodium heparin, 500 units/kg, the right atrium was quickly excised and plunged into cold physiological salt solution at approximately 4°C. The right atrium was isolated and cross-circulated with heparinized arterial blood from a donor dog according to the procedure described previously (9, 10). Briefly, the sinus node artery of the isolated atrium was cannulated at its origin in the right coronary artery. All the arterial branches, except the sinus node artery, were carefully ligated. The excised right atrium was placed in a glass chamber and perfused with arterial blood from the carotid artery of the donor dog by using a peristaltic pump (Harvard Apparatus, Model 1210). Perfusion pressure was kept constant at 100 mm Hg. The perfusion rate at this pressure was approx. 3–6 ml/min and time delay from the donor dog to atria was 2 to 4 min. The glass chamber was filled with the blood of the dog and maintained at a constant temperature of 37°C. Bipolar platinum electrodes were placed in contact with the atrial epicardium. Sinus rate was measured with a tachometer triggered by atrial electrograms, and isometric tension development was measured with a force displacement transducer (Grass FT03B). The atrial muscle was maintained under a resting tension of 2 g. The donor dogs were respired artificially with room air by using a respirator (Harvard Apparatus, Model 607). The systemic blood pressure and heart rate of the donor dog and the sinus rate and tension development in the isolated atrium from another dog were simultaneously recorded on a polygraph (Nihon Kohden). Drugs used were as follows: nicardipine (2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[2-(N-benzyl-N-methylamino)]-ethyl ester 5-methyl ester hydrochloride, YC-93, Yamanouchi Seiyaku, Japan), dl-verapamil hydrochloride (Knoll A.G.), atropine sulfate, manganese chloride and dl-propranolol hydrochloride (Sumitomo Chemicals). All drug solutions were diluted with saline to the desired concentrations and were injected in a volume of 10 to 30 µl over a period of 4 sec by microinjectors into the rubber tubing which conducted the blood to the arterial cannula in the isolated atrium and in a volume of 0.1–1 ml over a period of 10 sec into the jugular vein of the donor dog.

RESULTS

Effects of nicardipine on anesthetized dogs and on isolated atria when given into the jugular vein of the donor dogs: Administration of nicardipine (1–100 µg/kg, i.v.) to the donor dog produced dose-related decreases in the systemic blood pressure. Heart rate was slightly changed, and positive or negative chronotropic responses were observed after relatively smaller doses (1–10 µg/kg) with a significant negative chronotropic response occurring after higher doses (30–100 µg/kg). In the isolated atria, negative chronotropic and inotropic responses were usually observed but the threshold dose for these effects was approx. 10 µg/kg, such being much lower than that inducing significant hypotension. Figure 1 shows tracings of an experiment. Summarized data are shown in Fig. 2.

Effects of nicardipine on sinus rate and developed tension in the isolated atrium: When nicardipine at a dose range of 0.1–100 µg was administered into the cannulated sinus node artery of the isolated atrial preparation, a negative chronotropic and inotropic effect was dose-dependently
Fig. 1. Effects of nicardipine injected into the jugular vein of a donor dog at doses of 1–100 μg/kg on the blood pressure and heart rate in a donor dog (A), and the developed tension and atrial rate in an isolated atrium (B). The isolated atrium was perfused with arterial blood led from the donor dog.

Fig. 2. Effects of nicardipine given into the jugular veins of the donor dogs at doses of 3–100 μg/kg in five experiments. The control blood pressure, heart rate, developed tension and atrial rate were 102±9 mm Hg, 160±3 beats/min, 1.9±0.2 g, 110±7 beats/min (mean±S.E.M.), respectively. Vertical lines represent the standard errors of the mean.
induced. Figure 3 shows records from an experiment in which increasing doses of nicardipine were used. Summarized data are shown in Fig. 4. The threshold dose of nicardipine for inducing a negative effect was approx. 0.3 µg. Over 30 µg, nicardipine frequently caused sudden sinus arrest in 5 out of 9 preparations.

Effects of nicardipine, verapamil and manganese of the frequency-force relationship: When electrical stimulation of atrial muscle was given in the range of 2–3.5 Hz, a positive staircase phenomenon was

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**Fig. 3.** Negative chronotropic and inotropic effects of nicardipine injected into the sinus node artery of an isolated atrium.

**Fig. 4.** Negative chronotropic and inotropic effects of nicardipine injected into the sinus node arteries of isolated atria. Vertical lines represent the standard errors of the mean, and the numbers in parentheses indicate the number of observations. **Injection of nicardipine at a dose of 30 µg caused cardiac arrest in two atrial preparations.**

**Fig. 5.** Effects of nicardipine (10–100 µg) on the frequency-force response pattern of isometrically contracting dog atrial muscle, stimulated at 2.0 to 3.5 Hz.

**Fig. 6.** Steady-state frequency-force relationship of isometrically contracting dog atrial muscle: influence of nicardipine (Nica), manganese chloride and (+)-verapamil (Ver). These results were obtained from 5 experiments each. Standard errors are all less than 15% of the mean, but S.E.M. values are omitted for clarity.
observed, as reported previously (7). Nicardipine caused a greater suppression of the contraction at a higher frequency, as shown in Fig. 5. Verapamil also suppressed contraction far more at higher frequencies than at lower frequencies, as reported previously (7). On the other hand, manganese chloride produced an almost uniform suppression of contraction at 2.0–3.0 Hz. Summarized data of nicardipine, verapamil and manganese chloride are shown in Fig. 6.

DISCUSSION

It has been reported that nicardipine caused a vasodilatation not only in cerebral and coronary but also in general systemic blood vessels (2) and produced a hypotension when given intravenously (11). It was also reported that the vasodilating effect was not influenced by pretreatment with propranolol, atropine or diphenhydramine (2). In the present experiments, we confirmed that nicardipine caused a dose-related hypotension, and relatively small doses of nicardipine produced slight changes in heart rate, with a significant hypotension, while significant bradycardia was seen in the case of larger doses given to the donor dog. This bradycardia was greater than that observed in the isolated atrium. The plasma concentration of nicardipine required to induce marked bradycardia in the donor dog caused a lesser degree of bradycardia in the isolated atrium. These results might be due to different controls of the heart rate between the intact dog and isolated atrial preparations. In pentobarbital-anesthetized intact dog preparations the control heart rate was usually over 150 beats/min but in isolated atria was less than 120 beats/min.

When nicardipine was given into the sinus node artery of the isolated atrium, negative chronotropic and inotropic effects were dose-relatedly induced. As reported by Satoh et al. (5), large doses of nicardipine produced on atrial standstill. It was reported that nicardipine had cyclic phosphodiesterase inhibitory properties (1). However, nicardipine did not produce positive effects in atrial muscle, thereby indicating cardiac effects different from those of papaverine which produced positive chronotropic and inotropic effects (12). With regard to inotropism, nicardipine produced dose-relatedly negative inotropic effects on dog papillary muscle preparations (5), and even in the present study using atrial muscle preparations, nicardipine caused a dose-related decrease in contraction.

On the frequency-force relationship, Chiba et al. (6, 7) showed that verapamil and/or nifedipine suppressed contraction to a greater extent at higher frequencies, whereas manganese chloride or pentobarbital produced a rather uniform depression of contractile amplitude, at all frequencies examined. In the present work, we demonstrated that the effect of nicardipine on the frequency-force relationship was similar to effect of verapamil, indicating that nicardipine acts as a calcium antagonistic drug, as does verapamil or nifedipine. Terai et al. (13) reported that nicardipine inhibited KCI-induced 45Ca uptake in the rabbit aorta. From these results, it is concluded that nicardipine may produce predominantly cardiac depressant properties which are unrelated to phosphodiesterase inhibition.

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