Effects of OPC-18790, a New Positive Inotropic Agent, on Canine Ventricular Arrhythmias

Wu Zhenjiu, Takeo Awaji, Humiaki Abe, Shigeru Motomura and Keitaro Hashimoto*

Department of Pharmacology, Yamanashi Medical University, Tamaho-cho, Yamanashi 409-38, Japan

Received June 18, 1993 Accepted August 23, 1993

ABSTRACT—OPC-18790 is a positive inotropic and vasodilating agent that increases intracellular cyclic AMP and stimulates Ca currents. We examined its direct electrophysiological effects in isolated blood-perfused canine cardiac preparations. OPC-18790 caused an acceleration of the intraventricular conduction in association with an increase of the contractile force and the coronary blood flow. We also examined the effects of OPC-18790 on ventricular arrhythmias in canine ventricular tachycardia (VT) models. OPC-18790 in doses producing submaximal inotropic effects, 3 mg/kg, i.v., increased the total heart rate, atrial rate and decreased the blood pressure, but did not suppress or aggravate 24- and 48-hr coronary ligation VTs. OPC-18790 up to 3 mg/kg, i.v. also did not suppress or aggravate digitalis-induced VTs. However, this dose of OPC-18790 aggravated halothane-adrenaline induced VT into ventricular fibrillation and eventually death, but a lower dose of 0.3 mg/kg did not aggravate this VT. These results in canine VTs indicate that OPC-18790 is similar to other positive inotropic agents, vesnarinone, amrinone, milrinone and sulmazole. The absence of an aggravating effect of this new positive inotropic agent on digitalis and coronary ligation VTs may be advantageous in a clinical setting of combined therapy with digitalis for myocardial ischemia.

Keywords: OPC-18790, Positive inotropic agent, Ventricular tachycardia, Animal model

OPC-18790 is a newly synthesized positive inotropic agent with vasodilator activity and reported to be devoid of digitalis-like and catecholamine-like actions (1, 2). Its chemical structure, (±)-6-[3-(3,4-dimethoxybenzylamino)-2-hydroxypropoxy]-2(1H)-quinolinone, is similar to that of vesnarinone (OPC-8212), a positive inotropic drug without vasodilating action, and phosphodiesterase (PDE) inhibiting action is one of the common positive inotropic mechanisms between the two drugs (3–5). Since the Ca channel opening effect is expected to occur from the PDE inhibiting actions of OPC-18790, alterations in the cardiac electrophysiological properties such as increasing latent pacemaker activities or aggravation of delayed afterdepolarizations may occur and initiate or aggravate arrhythmias. On the other hand, OPC-18790 has been reported to prolong the action potential duration (1), which may cause an antiarrhythmic action. Since the occurrence of arrhythmias is deleterious in the treatment of cardiac failure, the present experiment was designed to examine the effects of OPC-18790 on blood-perfused isolated canine sinoatrial (SA) node and papillary muscle (PM) preparations and on various types of canine ventricular arrhythmias. The ventricular tachycardia (VT) models chosen for the present study were produced by two-stage coronary ligation, digitalis intoxication and adrenaline infusion. The effects of OPC-18790 were compared with those of vesnarinone, amrinone, milrinone and sulmazole (AR-R 115) previously reported by us (6, 7).

MATERIALS AND METHODS

Cross circulated blood-perfused cardiac preparations

As reported earlier (8, 9), 2 mongrel dogs of either sex were used for one experiment. One dog, weighing 10–15 kg, was used as a blood donor; and from the other dog, weighing approximately 10 kg, isolated preparations were obtained. The SA node preparation consisted of the entire right atrium, and the sinus node artery was cannulated via the right coronary artery. The sinoatrial rate (SAR) was measured.

The PM preparation consisted of an anterior papillary muscle attached to the interventricular septum, and the

* To whom correspondence should be addressed.
Production of adrenaline-induced VT

As reported earlier (10), 6 mongrel dogs, weighing 10–12 kg, were anesthetized initially with thiopental sodium (30 mg/kg, i.v.) and then with 1.0% halothane vaporized with 100% oxygen. A left thoracotomy was performed, and the left anterior descending coronary artery (LAD) was ligated by a two-stage ligation technique. One catheter in the left carotid artery and the other in the superior vena cava via the left jugular vein were exteriorized at the nape of the neck and used for recording the blood pressure and intravenous injection of OPC-18790, respectively. Bipolar electrodes were sutured on the left atrium for recording the atrial electrogram.

Experiments were done about 24- and 48-hr after coronary ligation under a conscious state. The lead II electrocardiogram (ECG), atrial electrogram and blood pressure were recorded continuously for 60 min by telemetry systems (Nihon Kohden, Tokyo). OPC-18790 was administered into the right jugular vein as a bolus injection through the cannula inserted into the vein.

Evaluation of antiarrhythmic effects on VTs

The severity of VT was expressed by the arrhythmic ratio: the number of ventricular ectopic beats divided by the total heart beats in a 5-sec strip of ECG (i.e., the number of ventricular ectopic beats and conducted beats). The ventricular beats were judged by the difference in the shape of the ventricular complex from the normal QRS complex. For the three VTs, the arrhythmic ratios before drug injection were about 0.8–1, and there were no spontaneous improvements in these ratios. If the arrhythmic ratio after drug administration decreased or increased significantly from the 0 time value, the drug was considered to have an antiarrhythmic or proarrhythmic effect, respectively.

Statistics

In cross-circulated, blood-perfused experiments, data are expressed as the mean±S.E. The doses of OPC-18790 that produced a 15% or 50% change in the parameters of the cross circulated blood-perfused cardiac preparations were determined from the dose-response curves. The doses that produced a 15% or 50% decrease were determined from dose-response curves fitted by the least squares method.

Data are expressed as the mean±S.D. in the experiments for two-stage coronary ligation-, digitalis- and adrenaline-induced VTs. Analysis of variance (ANOVA) and the Dunnett’s test for paired data were used for the determination of statistically significant differences between the mean values obtained at various times after treatment and the pretreatment, 0 time, values. A P value of 0.05 or less was considered statistically significant. All statistical calculations were done with a Macintosh IICX computer with Statview 512+ (Abacus Concepts, Inc., Berkeley, CA, USA) and Excel (Microsoft Corporation, USA) software. All experiments were performed in accordance with the Guidelines for Animal Experiments, Yamanashi Medical University.
RESULTS

Direct cardiac effects of OPC-18790 on blood-perfused isolated canine cardiac preparations

OPC-18790 given intraarterially through the rubber tube connected to the coronary artery cannula increased the DT (control value: 4.0±0.9 g, n=5) dose-dependently (1-300 μg). The effective positive inotropic dose producing a 50% increase was calculated to be 160 μg (Fig. 1). OPC-18790 also increased the flow rate of the ASA (control value: 8±3 ml/min, n=5), and the effective dose producing a 50% increase in the coronary blood flow was 150 μg. IVCT (control value: 70±5 msec, n=6) was decreased by OPC-18790, and the effective dose producing a 15% decrease was calculated to be 320 μg. In the SA node preparation, OPC-18790 in lower doses increased initially and then decreased the SA rate (control value: 76±9 beats/min, n=6). Higher doses had negative chronotropic effects, and only the steady state negative chronotropic effects are plotted in Fig. 1. These effects except for those on the IVCT were almost the same as those reported previously (1).

Effects of OPC-18790 on two-stage coronary ligation-induced VT

Conscious beagles 24 hr after coronary ligation showed sustained VT. Application of OPC-18790 at a dose of 3 mg/kg to such dogs caused a significant increase in the total heart rate and a significant decrease in the blood pressure. However, the treatment produced no significant changes in the arrhythmic ratio (Fig. 2). The dogs did not show any appreciable side effects in their central nervous systems.

The same dogs were used the next day for the study of OPC-18790 effects on the 48-hr VT. The arrhythmic ratio became lower, about 0.8 at -5 and 0 min, indicating that the 48-hr VT was less severe. At the same dose (3 mg/kg), OPC-18790 tended to increase the arrhythmic ratio and decreased the conducted beats soon after injection. The total heart rate also increased, but there were no decreases in the blood pressure, and there was no appearance of more severe ventricular fibrillation (VF).

Effects of OPC-18790 on digitalis-induced VT

After injection of a total dose of 70–90 μg/kg ouabain, almost all the beats were of ventricular origin (Fig. 3). This VT continued for at least 1 hr. The maximum dose of OPC-18790 (3 mg/kg) did not aggravate this VT, but instead showed a tendency to suppress this VT, namely increasing the number of conducted beats and decreasing the arrhythmic ratio, although this was not statistically significant. This dose of OPC-18790 barely altered the other parameters, except for a late decrease in the blood pressure. Such blood pressure decreases might have been produced by the discontinuation of ouabain after OPC-18790 injection, because a similar late decrease of the blood pressure was observed in dogs treated with many other drugs (11).

Effects of OPC-18790 on adrenaline-induced VT

Adrenaline infusion at a rate of 2.5 to 3 μg/kg/min induced VT as shown by the sudden increase in the number of ventricular ectopic beats (Fig. 4). Because OPC-17890 at 1 and 3 mg/kg aggravated this adrenaline VT and induced VF, a lower dose, 0.3 mg/kg, was examined. Though 2 out of 8 dogs fibrillated after OPC-18790 at this dose, 6 dogs did not show VF; Figure 4 summarizes the results from these 6 dogs, showing the effect of 0.3 mg/kg OPC-18790 on adrenaline VT. This low dose of OPC-18790 had a minimal effect on the total heart rate, atrial rate and blood pressure and did not aggravate adrenaline VT.
Fig. 2. Effects of intravenous bolus injection of OPC-18790 on 24-hr coronary ligation arrhythmia. The arrhythmic ratio did not change after OPC-18790. *: P<0.05, **: P<0.01.

Fig. 3. Effects of intravenous bolus injection of OPC-18790 on digitalis induced-arrhythmia. The arrhythmic ratio tended to decrease and the number of conducted beats tended to increase, but these antiarrhythmic responses were not statistically significant. *: P<0.05, **: P<0.01.
**DISCUSSION**

The present experiments have shown that the positive inotropic agent OPC-18790 aggravates adrenaline VTs, but not digitalis and two-stage coronary ligation VTs. Our previous experiments using three VT models showed that coronary ligation-induced and digitalis-induced VTs are Na channel-dependent, because they are suppressed by class I antiarrhythmic drugs, while adrenaline VT is Ca channel-dependent, because it is suppressed by class II β-blockers and class IV Ca channel blockers (13). Like other new positive inotropic agents (6, 7), which are phosphodiesterase inhibitors and increase cardiac Ca current, OPC-18790 was shown to aggravate adrenaline VTs. The 1–3 mg/kg OPC-18790 did not aggravate digitalis and two-stage coronary ligation VTs; the maximum tolerable dose for adrenaline VT was 0.3 mg/kg. In our previous study (6), vesnarinone up to 3 mg/kg did not aggravate digitalis VT, but aggravated adrenaline VT, and the maximum tolerable dose for adrenaline VT was 0.5 mg/kg. Also 3 mg/kg amrinone and sulmazole did not aggravate digitalis VT, but the maximum tolerable dose for adrenaline VT was 1 mg/kg. This aggravation of adrenaline VTs may be explained simply by the additive increasing effect of OPC-18790 on the Ca current, which had already been increased by adrenaline and caused the arrhythmia.

OPC-18790 had no deleterious effect on the digitalis VT, and it is consistent with our previous proposal that the occurrence of digitalis VT is not influenced by the Ca channel activities (11, 13). The practical importance of this result is that this new positive inotropic agent can be used in combination with digitalis without increasing the risk of arrhythmia, and this is a common observation among new positive inotropic drugs in our previous study (6). In the present in vitro electrophysiological study of OPC-18790, it slightly shortened IVCT of the canine isolated blood-perfused PM preparation, which is a unique effect but is probably not related to the drug effect on the Na channels. We reported that the lengthening effect of class I antiarrhythmic drugs on IVCT correlated well with the antiarrhythmic potency of these drugs on digitalis and coronary ligation VTs. In an in vivo study (1), OPC-18790 decreased the AV conduction time, but had no effect on the intraventricular conduction. We do not know the reason for the discrepancy between the two results, but as judged by the high doses needed to produce these effects, they may not play a significant role in their effect on the arrhythmias.

The effect of OPC-18790 on coronary ligation-induced VTs was similar to vesnarinone, because it tended to aggravate 48-hr coronary ligation VTs, but was different from that of vesnarinone in that OPC-18790 had no statistically significant effect on 24- and 48-hr coronary ligation VTs and did not induce ventricular fibrillation.
Vesnarinone (3 mg/kg) had no deleterious effect on 24-hr coronary ligation VT, but the same dose increased the arrhythmic ratio of 48-hr coronary ligation VT. These results indicate that OPC-18790 may be used for the treatment of cardiac failure caused by myocardial damage. However, it should always be borne in mind that this drug is potentially arrhythmogenic, because of its Ca current and/or intracellular Ca concentration increasing effects that may generate or aggravate arrhythmia by inducing delayed afterdepolarizations (14, 15).

In conclusion, the new positive inotropic drug OPC-18790 was similar to the other new positive inotropic drugs we examined; i.e., it aggravated adrenaline induced VT, but did not change the digitalis and two-stage coronary ligation VTs. This may indicate that there are electrophysiological differences among these new positive inotropic drugs: some have a negative inotropic effect; and some, like OPC-18790, have class III antiarrhythmic action to prolong action potential duration or an additional positive inotropic mechanism, such as the Ca sensitizing effect of sulmazole, and do not have a strong influence on ventricular arrhythmias.

Acknowledgments
The authors thank Otsuka Pharmaceutical Co., Ltd. for supplying us with OPC-18790 and thank Miss Mie Yamada for preparing the manuscript. This study was supported by a Grant-in-Aid for Scientific Research 03253103 from the Japanese Ministry of Education, Science and Culture.

REFERENCES