Actions of a Newly Synthesized Compound (711389-S) on Various Types of Experimentally Induced Arrhythmias in Mammalian Species In Situ

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Abstract—We examined effects of 711389-S, a new antiarrhythmic agent, on ouabain-induced arrhythmias in dogs and guinea-pigs, aconitine-induced arrhythmias in dogs and mice, adrenaline-induced arrhythmias in dogs under anesthetized condition, and arrhythmias induced by coronary artery ligation and occlusion by a glass bead in dogs under conscious and un-restrained conditions. 711389-S (1–3 mg/kg, i.v.) decreased the number of ventricular extrasystoles induced by ouabain in dogs, and the doses of ouabain required to induce various types of arrhythmias were increased by pretreatment of guinea-pigs with intraduodenal application of 711389-S (5–10 mg/kg). In mice, 711389-S (3 mg/kg, i.v. or 10 mg/kg, p.o.) significantly prolonged the time to onset of arrhythmias induced by aconitine infusion. Atrial fibrillation induced by a topical application of aconitine on the atrium was blocked by 711389-S (1 mg/kg, i.v.) in dogs. 711389-S (1–3 mg/kg, i.v.) depressed arrhythmias induced by adrenaline and restored the sinus rhythm by significantly decreasing the number of ventricular ectopic beats induced by coronary ligation or occlusion in dogs. Oral administration of 711389-S (10–30 mg/kg) in dogs markedly depressed the ventricular ectopic beats induced by coronary ligation. The half decay time of 711389-S after a single bolus injection of 711389-S ranged from 60 to 80 min. Results indicate that 711389-S has similar antiarrhythmic effects to those of other Class I antiarrhythmic agents in situ, and they suggest that this compound might have potential usefulness as a new type of antiarrhythmic agent for clinical use.

While searching for new cardiovascular active agents having an imidazole moiety, we found that 1-{1-[2-(3-isopropylamino-2-hydroxypropoxy)-3,6-dichlorophenyl]-vinyl}-1H-imidazole hydrochloride (711389-S) possessed antiarrhythmic activity against aconitine-induced arrhythmias in mice (1), ouabain arrhythmias in guinea-pigs and dogs and ischemic arrhythmias in dogs (1, 2). The compound was found to exert Class I antiarrhythmic effects on intracellular action potentials of the papillary muscle of guinea-pigs, mainly suppressing the maximal upstroke velocity (V_{max}) of action potentials and showing a potent use-dependent decrease of V_{max}, similar to disopyramide (3). In spite of the similarity among currently available antiarrhythmic agents with Class 1 effects, it is not universally agreed that these effects per se are responsible for their antiarrhythmic actions (4). Furthermore, the clinical use of currently available antiarrhythmic drugs for...
antiarrhythmic therapy still has some limitations because of their various side effects (see refs. 4–7 for reviews). Therefore, it is important to examine the potential actions of newly introduced compounds on various types of experimentally-induced arrhythmias in situ. Along this line of thought, the present experiments were designed to extend the previous work and to further characterize the mode of action of 711389-S by comparing its action with other antiarrhythmic agents.

The results reported here show that either intravenous or oral administration of the compound at relatively low doses suppresses various types of experimentally-induced arrhythmias in mammalian hearts, and provides evidence suggesting that the compound might have potential clinical usefulness.

**Materials and Methods**

The present experiments were done using adult dogs, mice and guinea-pigs. Four different types of arrhythmias were induced in different mammalian species: ouabain-induced arrhythmias in dogs and guinea-pigs, aconitine-induced arrhythmias in dogs and mice, adrenaline-induced arrhythmias in dogs, and arrhythmias induced by coronary arterial ligation and occlusion by a glass bead in dogs.

**Ouabain-induced arrhythmias:** Adult dogs of either sex (weighing 8–15 kg) were anesthetized with sodium pentobarbitone (30 mg/kg, i.v.). Arterial blood pressure was recorded from the femoral artery with a Statham-type pressure transducer. Blood pressure, electrocardiogram (lead II and V1), and instantaneous heart rate were recorded on the pen-writing recorder of a polygraph (Nihon Kohden, RM-6000). A cannula was inserted into the femoral vein and another one, into the duodenum for administration of drugs. Ouabain was administered intravenously at an initial dose of 40 µg/kg, followed later by 20 µg/kg, and then by 10 µg/kg at intervals of 15 min until a ventricular tachycardia was induced. After the ventricular tachycardia had been established for 10 min, increasing doses of test-drugs were administered intravenously or intraduodenally until the return of sinus rhythm occurred.

Guinea-pigs of either sex weighing 450–670 g were used. The animals were anesthetized with urethane (1.2 g/kg, i.p.), and the lead II electrocardiogram was recorded on a polygraph (Nihon Kohden RM-6000, WI-641). An intravenous cannula was inserted into the external carotid vein and another one, into the duodenum for administration of drugs. Arrhythmias were induced by a continuous infusion of ouabain following the method described by Sekiya and Vaughan Williams (8). Ouabain was injected intravenously at a dose of 8 µg/kg at intervals of 2 min using a micro-infusion pump (Furue Science, Type JP-W-V) until ventricular tachycardia, ventricular extrasystole and other types of arrhythmias were induced. Test-drugs were administered into the duodenum 10 min before the start of the ouabain-infusion, and the total amount of infused ouabain required to induce the arrhythmias were compared between the control and pretreated animals.

**Aconitine-induced arrhythmias:** Dogs were anesthetized with sodium pentobarbitone (30 mg/kg, i.v.), and they were artificially ventilated with a positive-pressure respirator with a tidal volume of 13–16 ml/kg ventilation rate of 18/min so as to maintain arterial PO2, PCO2 and pH within a normal range. A left thoracotomy was performed in the fourth or fifth left intercostal space. The anterior surface of the heart was exposed, and the heart was suspended in a pericardial cradle. A small piece of filter paper (5x5 mm) immersed in aconitine solution at a concentration of 10^-6 M was placed on the surface of the left atrium. Within 1 min after the topical application of aconitine, atrial premature contraction started to occur and then was converted into atrial fibrillation. Immediately after the occurrence of the atrial fibrillation (AF), the filter paper was removed. AF, thus induced, persisted for more than 1 hr. Increasing doses of test-drugs were applied intravenously 10 min after the arrhythmia was established until sinus rhythm was restored.

Male mice weighing 25–36 g (SLC-ddy) were anesthetized with sodium pentobarbitone (30 mg/kg, i.p.), and the lead II electrocardiogram was recorded. Effects of test-drugs on aconitine-induced arrhythmias were determined following the method by
Nwangwu et al. (9): aconitine solution (5 μg/ml) was infused at a constant flow rate of 0.25 ml/min into the tail vein, and the time to onset of initial cardiac arrhythmia and the time to onset of ventricular tachycardia after the start of the aconitine infusion were determined in the animals without any drugs and ones pretreated with the test-drugs applied intravenously or per os, 3 min or 30 min before the aconitine administration, respectively.

Adrenaline-induced arrhythmias: Dogs were anesthetized with sodium pentobarbitone (30 mg/kg, i.v.) and a cannula was inserted into the femoral vein for drug administration. The electrocardiogram (lead II and aVF) was recorded. Adrenaline at an initial dose of 1 μg/kg was injected intravenously, and the dose was progressively increased with an interval of 10 min between each dose, until similar ventricular tachycardia or frequent multifocal ventricular ectopic beats was produced on two occasions, and then test-drugs were given intravenously. Five min later, the dose of adrenaline was administered again. Increasing doses of the test-drugs were given at every 10 min, followed by the test dose of adrenaline. The same procedure was repeated to determine the minimum dose that prevented the development of any ectopic beats.

Arrhythmias induced by coronary artery ligation or occlusion by a glass bead: Ischemic arrhythmias were produced by two different methods following Harris' method (10) and the glass bead-occlusion methods (11, 12). Mongrel dogs of either sex weighing 8-15 kg, were anesthetized with sodium pentobarbitone (30 mg/kg, i.v.) in the occlusion experiments by Harris' method. The animals were ventilated with a positive pressure respirator. Under an aseptic condition, the anterior descending branch of the left coronary artery was exposed through left thoracotomy and ligated in two stages as described previously (10). Thereafter, the chest was closed in layers and the animals were allowed to recover. In the occlusion of the coronary artery by the other method, beagles of either sex weighing 6.5–10.5 kg were used. While blood pressure and lead II electrocardiogram were monitored, a coronary cannula was inserted into the coronary orifice via the left carotid artery, and a glass bead (diameter, 1.5 mm) was flushed into the left coronary artery (12). The next day, 24 hr after the operation, the electrocardiogram (lead II) was recorded under conscious and non-restrained conditions before, during and after administration of increasing doses of test-drugs. Ventricular rate was obtained from the electrocardiogram by counting the number of sinus beats and ectopic beats during each successive 3-min period.

Determination of 711389-S in dog plasma: Heparinized blood samples taken from dogs were centrifuged immediately, and the plasma was stored at −20°C until required for high performance liquid chromatographic (HPLC) assay. One-tenth ml of 5 N NaOH and 5 ml of diethylether were added to 0.5 ml of the serum in a screw-cap tube. The mixture was shaken well and centrifuged. The organic phase was transferred to another tube and then allowed to evaporate to dryness at ambient temperature under a gentle stream of nitrogen. The residue was dissolved in 0.5 ml of the mobile phase, which was prepared by mixing 20 parts of acetonitrile with 80 parts of 0.05 M phosphate buffer (pH 3.0); and then 20 μl of the mixture was injected into the chromatograph. A standard curve was constructed by injecting serum extracts simulating concentrations of 711389-S from 0.5 to 10.0 μg/ml. The amount of 711389-S was calculated by comparison with standards prepared daily. HPLC was done on a Waters "u Bondapak C18" column. The flow rate was 1.0 ml/min. Absorbance was monitored at a wavelength of 214 nm. The retention time of 711389-S was 7.5 min (Fig. 1).

Drugs used: The drugs used in the present experiments were as follows: 711389-S (Shionogi), disopyramide (Chugai Seiyaku), quinidine sulfate (Merck), lidocaine hydrochloride (Sigma), ouabain octahydrate (Sigma), g-strophanthin (Merck), aconitine (Sigma), and adrenaline injection B.P. (Sankyo). Capsules filled with 711389-S (Nihon Elanco Capsule KK, Elanco capsule 00/S) and lactose were given to conscious dogs for oral administration. All drugs were dissolved in physiological saline in the appropriate concentrations just before use.
Doses were expressed as the respective salt, unless otherwise stated.

Results

Ouabain-induced arrhythmias: Effects of 711389-S on ouabain-induced arrhythmias in dogs are shown in Fig. 2. During the control period, the intravenous injection of ouabain produced a rapid ventricular tachycardia interspersed with a few sinus beats. The dose required to induce ventricular tachycardia varied in each of the 12 dogs examined, ranging from 40 to 65 μg/kg. About 90% of the heart beats consisted of multifocal ventricular extrasystoles. When the arrhythmias had been established for 10 min, 711389-S was administered either intravenously or intraduodenally. Within 1 min after an intravenous injection of the agent (1 mg/kg), a significant increase of the number of sinus beats was observed, and a further increase in the dose (3 mg/kg) restored sinus rhythm, but not completely, in 4 dogs examined; there was a reduction of 70–90% in the number of ventricular ectopic beats compared with the control before the administration of 711389-S. The effects lasted for 30–50 min. However, in 2 experiments, the rate of sinus rhythm gradually decreased about 30 min after the injection of the agent, and the second degree of atrio-ventricular block developed. A representative example of the effects of 711389-S (3 mg/kg, i.v.) on ouabain-induced arrhythmias, shown in Fig. 2, demonstrates that by 2 min after its administration, the agent completely restored the sinus rhythm. The time course of effects of the intraduodenal administration of the agent is illustrated in Fig. 3. The intraduodenal administration of 0.3 mg/kg had
no effect, but 1 mg/kg gradually increased the number of sinus beats. Thirty min after the administration, about a 50% reduction in the number of ventricular ectopic beats was observed, and the depressant effects on ventricular ectopic beats lasted for another 90 min. Effects of intraduodenal administration of various doses of the agent on mean arterial blood pressure of dogs during ouabain administration are summarized in Table 1. The absolute value of the mean arterial blood pressure varied in individual cases, but in each case, the administration of 711389-S did not affect the time course of the arterial blood pressure. Effects of intraduodenal administration of disopyramide (3 and 10 mg/kg) on ouabain induced-arrhythmias were examined in 6 dogs. Intraduodenal administration of disopyramide at the dose of 10 mg/kg exerted effects similar to that of 1 mg/kg 711389-S.

In guinea-pigs, doses of ouabain required to induce ventricular ectopic beats, ventricular tachycardia, ventricular fibrillation and cardiac arrest were compared with those of animals pretreated with 711389-S or other anti-arrhythmic agents. In the control animals, ventricular extrasystole, ventricular tachycardia, ventricular fibrillation and cardiac arrest occurred at a total amount of infused ouabain of 95.7±4.1 mg/kg (n=12), 132.2±6.7 mg/kg (n=12), 152.8±9.9 mg/kg (n=12) and 174.0±9.7 mg/kg (n=12), respectively. The intraduodenal administration of 5 mg/kg
Table 1. Effects of intraduodenal administration of 711389-S and disopyramide on the mean carotid blood pressure of dogs under ouabain-induced arrhythmias

| Compounds       | Dose (mg/kg) | n  | before | 15         | 30         | 45         | 60         | 75         | 90         | 105        | 120        |
|-----------------|--------------|----|--------|------------|------------|------------|------------|------------|------------|------------|------------|
| 711389-S        | 0.3          | 3  | 111.7±23.3 | 107.5±23.2 | 105.0±24.7 | 103.3±23.2 | 104.2±20.2 | —          | —          | —          | —          |
|                 | 1            | 5  | 67.0±8.3  | 73.5±7.3   | 78.5±7.1   | 79.5±7.8   | 77.5±6.9   | 77.0±6.2   | 80.5±7.1   | 78.5±7.6   | 80.0±8.0   |
|                 | 3            | 3  | 93.3±1.7  | 98.3±2.2   | 97.5±5.2   | 97.5±5.2   | 96.7±6.0   | 96.7±7.9   | 97.5±7.2   | 96.7±7.3   | 96.7±7.3   |
| Disopyramide    | 3            | 3  | 80.0±15.3 | 81.7±14.2  | 86.7±14.2  | 88.3±10.2  | 90.8±12.3  | —          | —          | —          | —          |
|                 | 10           | 3  | 100.0±23.1 | 115.0±20.2 | 120.8±18.3 | 119.2±19.9 | 119.2±17.2 | 115.0±15.3 | 110.7±15.7 | 108.3±15.9 | 108.3±10.1 |
| Distilled water | 1 ml/kg      | 3  | 100.0±18.0 | 88.3±16.9  | 85.0±15.3  | 86.7±15.9  | 85.0±17.6  | 85.0±15.0  | 83.3±14.2  | 88.3±16.9  | 83.3±17.6  |

Mean arterial blood pressure was measured just before intraduodenal administration of each test drug under a condition in which consistent and persistent arrhythmias had been induced by ouabain (before) and 15, 30, 45, 60, 75, 90, 105 and 120 min after the drug administration. Numerals in each column show mean carotid arterial blood pressure (mean±S.E., mmHg).
of 711389-S significantly increased the total amounts of ouabain to produce ventricular extrasystole, ventricular fibrillation and cardiac arrest, as shown in Fig. 4. A further increase in the dose of 711389-S (10 mg/kg) induced tolerance for ouabain to induce the arrhythmias except for ventricular tachycardia. These effects were almost comparable to those of disopyramide. In the case of disopyramide, however, the dose of ouabain to induce ventricular tachycardia increased significantly at a dose of 10 mg/kg. Quinidine even at a relatively large dose (100 mg/kg) did not alter the threshold dose of ouabain to induce arrhythmias, as compared with the control.

Aconitine-induced arrhythmias: Effects of intravenous injections of 711389-S on arrhythmias induced by topical application of aconitine on the surface of the left atrium were examined in 4 dogs. Ten min after the establishment of stable atrial fibrillation, 711389-S was injected intravenously. Within 1 min after the injection of the agent (1 mg/kg), sinus rhythm was restored in all cases examined (Fig. 5). The effects lasted for 30–40 min.

In mice, the times to the onset of the initial cardiac arrhythmia and ventricular tachycardia after the start of the continuous infusion of aconitine were measured in the control group and the animals pretreated with intravenous or oral administration of 711389-S. In the control animals, about 90 sec after the start of the aconitine-infusion, the first discernible sign of persistent deviation from normal sinus rhythm was observed; and then another 20–30 sec later, a sudden transition from the cardiac arrhythmia (ventricular extrasystole) to ventricular tachycardia occurred. These

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**Fig. 4.** Effects of 711389-S, disopyramide and quinidine on the doses of ouabain required to induce arrhythmias in guinea-pigs. *P<0.05, **P<0.01, ***P<0.001, significantly different from the control values. The numerals in parentheses indicate the numbers of animals subjected to the experiments. Doses of antiarrhythmic agents are shown in terms of the respective bases. See the text for detailed descriptions.
results were consistent with those described by Nwangwu et al. (9). Neither 1 mg/kg, i.v. nor 3 mg/kg, p.o. of 711389-S affected the time to onset of aconitine-induced arrhythmias, as compared with the control. However, a further increase in the doses (3 mg/kg, i.v. and 10 mg/kg, p.o.) significantly prolonged the time to onset of arrhythmias (Fig. 6). Disopyramide (10 mg/kg, i.v. and 30 mg/kg, p.o.) and quinidine (10 mg/kg, i.v. and mg/kg, p.o.) exerted effects comparable to those of 711389-S, significantly prolonging the time to onset of the aconitine-induced arrhythmias.

Adrenaline-induced arrhythmias: Intravenous injections of the test dose of adrenaline induced an increase in the heart rate and elevation of arterial blood pressure before the onset of arrhythmias. The dose of adrenaline to produce severe and reproducible multifocal ventricular extrasystoles varied in individual animals, ranging from 2 to 10 μg/kg, i.v., in 6 dogs examined. Five min after an intravenous injection of 711389-S, the test dose of adrenaline was given. The agent at the dose of 1 mg/kg decreased the number of ventricular ectopic beats produced by adrenaline in 2 cases, but did not prevent the occurrence of the arrhythmias. Pretreatment of the animals with a dose of 3 mg/kg, however, completely depressed the incidence of the arrhythmias in all cases examined. The depressant effects of 711389-S on adrenaline-induced arrhythmias lasted for 30–50 min.

Arrhythmias after ligation of the coronary or occlusion by a glass bead: One day after ligation of the anterior descending branch of the left coronary artery, there was a rapid multiform ventricular tachycardia in all of the 5 dogs subjected to experiments. There were a few sinus beats interspersed in the multifocal ventricular ectopic beats. The intravenous injections of 711389-S in successive doses (0.1–1 mg/kg) exerted no significant effects on the occurrence of ectopic beats except in 1 dog, in which 711389-S (1 mg/kg, i.v.) increased the number of sinus beats to about 50% of the control. After a dose of 3 mg/kg, there was a 90–100% reduction of the occurrence of the ventricular ectopic beats, and thus, sinus rhythm was regained. The depressant effects of 711389-S on the ventricular tachycardia for 30–60 min (Fig. 7). Under a conscious condition, there was no development of atrioventricular block and no ventricular fibrillation in all cases examined after a dose of 3 mg/kg. The effects of 711389-S in a dose of 3 mg/kg were almost comparable to those of disopyramide (10 mg/kg, i.v.) (data not shown). All dogs showed no sign of any toxic effects such as vomiting or convulsions. On the other hand, an intravenous injection of lidocaine (1 mg/kg) did not produce any significant depressant effects on the occurrence of the ventricular ectopic beats in dogs.

Effects of intravenous or oral administration of 711389-S on the arrhythmias induced by occlusion of the coronary by a glass bead

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Fig. 5. Effects of 711389-S on aconitine-induced arrhythmias in dogs. Two min after topical application of aconitine, atrial fibrillation occurred, and 10 min after establishment of atrial fibrillation, 711389-S was injected intravenously, which converted atrial fibrillation to normal sinus beats. HR: heart rate (beats/min) at the points of the respective ECG-recordings. See the text for detailed descriptions.
Fig. 6. Effects of 711389-S, disopyramide and quinidine on the time required to induce arrhythmias by aconitine infusion in mice. i.v.: intravenous injections of test drugs. At 3 min after the injection of each test drug, aconitine infusion was started. p.o.: oral administration of test drugs. At 30 min after the administration, aconitine infusion was started. Levels of significance are indicated as in Fig. 4. The numerals in parentheses indicate the number of animals. Doses of antiarrhythmic agents are expressed in terms of the respective bases. See the text for detailed descriptions.

Aconitine arrhythmias in mice

Fig. 7. Effects of 711389-S and lidocaine on arrhythmias induced by coronary artery ligation in dogs. Each column indicates the mean heart rate (beats/min) counted in a 1 min-period in each dog. The dotted column shows the number of sinus beats, and the empty column, non-sinus beats. The vertical bar on each column indicates standard errors. 711389-S was injected intravenously at the points indicated by arrows. The numerals under the arrows indicate doses of 711389-S.
were examined in 3 dogs, respectively. One day after the coronary occlusion, ventricular tachycardia similar to that induced by the coronary ligation was observed. An intravenous injection of 711389-S (3 mg/kg) was effective for converting the ventricular ectopic beats to ones of sinus origin. Disopyramide (10 mg/kg, i.v.) produced effects similar to those of 711389-S, but no significant antiarrhythmic action was observed at 3 mg/kg, i.v. One hour after oral administration of 10 mg/kg of 711389-S, a significant increase in sinus beats started to occur, and this effect lasted for 120 min. A dose of 30 mg/kg per os markedly depressed the ventricular ectopic beats. A significant increase in the sinus beats was observed for more than 6 hr (Fig. 8). Disopyramide and quinidine in a dose of 60 mg/kg per os were not as effective for suppressing the ventricular ectopic beats, as compared to 711389-S at a dose of 30 mg/kg.

**Plasma concentration of 711389-S:** 711389-S (3 mg/kg) was given intravenously to 4 anesthetized dogs, and the plasma concentrations of the agent were determined for 90 min after the injection. The time course of changes in the plasma concentrations of 711389-S is shown in Fig. 9. The half decay time of 711389-S ranged from 60 to 80 min (72.3±7.8 min, mean±S.D.). In one case in which coronary ligation had been performed,

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Fig. 8. Effects of oral administration of 711389-S, disopyramide and quinidine on arrhythmias induced by occlusion of the coronary artery with a glass bead in dogs. Each column shows the heart rate (beats/min) evaluated in a 3 min-period. The striped column indicates the number of sinus beats and the empty column, non-sinus beats. B: the control period. The numerals under the horizontal lines indicate the time after oral administration of the test drugs (hr). Doses of antiarrhythmic agents are shown in terms of the respective bases.

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Ischemic arrhythmias in dogs
the plasma concentration was determined after cumulative administration of 711389-S. The plasma concentrations together with depressant effects of the agent on arrhythmias are illustrated in Fig. 10. Four min after an intravenous injection of 711389-S, almost complete restoration of the sinus rhythm was attained at a plasma concentration of 3.1 μg/ml.

Discussion

In the present experiments, it was demonstrated that 711389-S can prevent arrhythmias due to a variety of causes in different mammalian species. The mode of action of the agent bore some resemblance to that of disopyramide, but 711389-S was more potent than disopyramide. The relative potency of the antiarrhythmic action of 711389-S to that of disopyramide and quinidine was estimated and summarized in Table 2. Administration of 711389-S per os was 7-10 times more effective for suppressing arrhythmias induced by ouabain or by coronary artery occlusion than disopyramide, while intravenous injections of 711389-S was about 3 times more potent than disopyramide. The results indicate that 711389-S could be more easily absorbed from gastrointestinal tracts than disopyramide. Effective plasma concentrations of 711389-S in suppressing
arrhythmias induced by coronary artery ligation or occlusion in dogs would be within the range of 2–3 μg/ml, as judged from one experiment shown in Fig. 10. Further characterization of the pharmacokinetic properties of 711389-S in comparison with other antiarrhythmic agents would be necessary.

Table 2. Comparison of antiarrhythmic effects of 711389-S, disopyramide and quinidine in three experimentally-induced arrhythmias

| Types of arrhythmias                | 711389-S | Disopyramide | Quinidine |
|-------------------------------------|----------|--------------|-----------|
| Aconitine arrhythmia (mice)         | 3.3      | 1            | 3.3       |
| i.v.                                | 3        | 1            | 1         |
| p.o.                                |          |              |           |
| Ouabain arrhythmia (i.d.)           | 1        | 1            | 0.05      |
| guinea-pig                          |          |              |           |
| dog                                 | 10       | 1            | —         |
| Coronary occlusion arrhythmia (dog) | 2.5      | 1            | 0.85      |
| i.v.                                | 6.8      | 1            | 1.4       |
| p.o.                                |          |              |           |

Approximate relative potencies of 711389-S and quinidine to disopyramide were calculated in each experiment. In the aconitine and ouabain induced arrhythmias, significant antiharrhythmic doses of the compounds were compared, while in the coronary occlusion arrhythmias with a glass bead, anti-arrhythmic ED50 doses of disopyramide calculated from dose-response curves were divided by those of 711389-S and quinidine. i.v.: intravenous injection. p.o.: per os administration.

Possible explanations for the inhibitory action of 711389-S on aconitine-induced arrhythmias can be offered. It has been shown that in atrial and ventricular fibers after application of aconitine, a second plateau of the intracellular action potential develops at about −60 mV and from the potential level of this plateau, a volley of extrasystoles arises (24, 25). 711389-S would have prolonged the refractory period of the cardiac muscle, thereby abolishing extrasystoles occurring shortly after application of aconitine. In the presence of aconitine, due to the increase of sodium current, the positive repolarizing current at −60 mV is decreased, which in turn, retards the repolarization of the action potential; and at the plateau level where a depolarization rate is as low as 3 mV/sec, the negative sodium current is triggered (26). If this is also the case in the in situ situation, 711389-S would have contributed to suppression of the extrasystoles.
by inhibiting the negative current peak carried by sodium ion.

In the present experiments, 711389-S prevented occurrence of ventricular ectopic beats induced by adrenaline-injections. This effect of 711389-S presumed to be due to its direct inhibitory action on sodium current in cardiac muscle, rather than \( \beta \)-adrenoceptor blocking action, since the adrenoceptor and cholinergic blocking actions of the agent are 1/2000–1/4000 of those of propranolol and 1/4 of those of disopyramide (2, 3).

Relatively large doses of 711389-S (3 mg/kg, i.v.) were effective in reducing the frequency of ventricular ectopic beats 1 day after coronary artery ligation or occlusion of the artery by a glass bead. Effective plasma concentrations which depress the frequency of ventricular ectopic beats to about 50% of the control would be within the range of 2–3 \( \mu \)g/ml, as estimated from measurements of the plasma concentration of the agent after a single bolus injection of 3 mg/kg. The effective plasma concentration for this type of arrhythmias was lower than those of lidocaine, mexiletine and disopyramide (5–10 \( \mu \)g/ml) which frequently cause toxic effects on the central nervous system such as vomiting or convulsions in dogs (23, 27). Oral administration of the agent (30 mg/kg, p.o.) was also effective in depressing the arrhythmias, and the beneficial effects lasted for more than 6 hr after a single dose of the agent without showing any signs of toxic effects in the animals. The mechanisms responsible for the genesis of this type of arrhythmias are considered to be more complicated than those for other experimentally-induced arrhythmias. The depressant effects of the agent on the arrhythmias might have resulted from effects similar to those of other Class I antiarrhythmic agents on sodium currents and steady state inward currents carried by sodium ions in surviving Purkinje fibers in the endocardium after coronary occlusion (7, 27–29).

The newly synthesized compound 711389-S is effective for abolishing various types of experimentally induced arrhythmias. At this moment, it is premature to conclude from the present results that this agent may have wide clinical application, but the data suggest that 711389-S could be an effective and relatively safe drug for the control of ventricular arrhythmias in patients with myocardial infarction, when administered by either an intravenous or oral route.

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