Do Antiarrhythmic Drugs Act on the Site of Abnormal Impulse Generation or Act on the Normal Myocardium?

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Locally-induced digitalis arrhythmia was produced to study whether antiarrhythmic drugs suppress arrhythmia by directly acting on the abnormal impulse generation or by suppressing Na channels of normal myocardium to make it unresponsive to abnormal impulses. Dogs were thoracotomized and the anterior descending artery (ADA) was isolated and autoperfused with arterial blood from the carotid artery. Forty μg and an additional 10 μg every 20 min of ouabain was injected directly into the ADA produced ventricular tachycardia originating from the digitalis intoxication. Locally injected class 1 antiarrhythmic drugs, including tetrodotoxin, were effective in suppressing this arrhythmia. However, when intravenously applied lidocaine was prevented from reaching the ADA area, lidocaine was not effective in suppressing this arrhythmia. We conclude that class 1 drugs produce antiarrhythmic effect by directly suppressing the digitalis toxicated area, not by suppressing the normal myocardium.

MECHANISMS of generation of arrhythmias and antiarrhythmic mechanisms of drugs have been subjects of research for many electrophysiologists and electropharmacologists. Though recent cellular and membrane cardiac electrophysiological studies have revealed precise ionic mechanisms of generation of both normal and pathological cardiac impulses,^{1,2} antiarrhythmic mechanisms of clinically useful drugs for cardiac arrhythmias have not yet been clearly elucidated.

In order to understand better the drug actions on cardiac cell membrane and drug effects on arrhythmias occurring in the whole heart, we have been studying effects of antiarrhythmic drugs on canine ventricular arrhythmia models, while at the same time trying to determine their minimum effective plasma concentrations.³⁻⁷ We chose three different canine ventricular arrhythmias

induced by different mechanisms of generation, and compared drug actions with its drug plasma concentration data more quantitatively. They were induced by (a) two-stage coronary ligation in beagle dogs and subsequent electrocardiographic evaluation in conscious animals, (b) intravenous administration of ouabain, 40 $\mu\text{g}/\text{kg}$ prime followed by 10 $\mu\text{g}/\text{kg}$ every 20 min, to mongrel dogs under pentobarbital anesthesia, and (c) adrenaline infusion of 2 to 3 $\mu\text{g}/\text{kg}/\text{min}$ to mongrel dogs under 1% halothane anesthesia.

Summary of our already published results³⁻⁷ are shown in Fig. 1. As can be seen, antiarrhythmic drugs of class 1, Na channel inhibitors according to Vaughan Williams,⁸ all suppressed digitalis-induced arrhythmia and, except for lidocaine, also coronary ligation-induced arrhythmias. The minimum effective plasma concentrations of each drug were almost equal to the concentration in vitro that suppressed the Na channel of isolated normal canine cardiac ventricular tissues.⁵ Class 2 antiarrhythmic drugs,

Key words:

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Drugs	Effects on canine ventricular arrhythmias (min. effective plasma conc. $\mu\text{g/ml}$)		
	Digitalis arrhythmia	Coronary ligation arrhythmia	Adrenaline arrhythmia
Phenytoin	▼ (12.1)	▼ (9.8)	▼ (11.3)
E-0747	▼ (1.4)	▼ (1.6)	▼ (1.8)
Aprindine	▼ (0.8 [*])	▼ (1.6)	▼ (1.0 [*])
Mexiletine	▼ (1.8 [*])	▼ (1.9 [*])	▼ (3.7)
Tocainide	▼ (6.2 ^{**})	▼ (11.4 [*])	▼ (23.7)
Cibenzoline	▼ (0.6 ^{***})	▼ (1.9 [*])	▼ (3.5)
Propafenone	▼ (1.8 [*])	▼ (3.5)	▼ (0.6 ^{**})
Disopyramide	▼ (1.7 [*])	▼ (5.3)	
Procainamide	▼ (10.1 [*])	▼ (26.4)	
SUN-1165	▼ (0.9 [*])	▼ (2.5)	
Lidocaine	▼ (3.5)		
Propranolol	▼ (1.7)		▼
N-696		▼ (7.6)	▼
Pindolol	▼ (1.0 [*])	▼ (2.4)	▼
Verapamil			▼ (0.03)
Diltiazem			▼ (0.02)
Bepridil			▼ (0.38)
Nifedipine			▼
Nisoldipine			▼
Nitroglycerin			▼
Nicorandil			▼
Dilazep	▼ (0.6)		▼ (0.2)
Trimetazidine			▼ (7.0)
L-Carnitine			▼
Coenzyme Q ₁₀			▼
NCO-700			▼

Fig.1 Summary of the effects of antiarrhythmic drugs on three canine ventricular arrhythmias. Downward arrows indicate possession of antiarrhythmic effects. Numbers in parenthesis indicate minimum effective plasma concentrations.

beta-blockers, and class 4 drugs, Ca channel blockers, had common features of effectiveness where they suppressed adrenaline arrhythmia in relatively low concentrations or doses.

This conclusion led us to propose a new classification of model arrhythmias as follows.

Na channel dependent arrhythmia
digitalis and coronary ligation arrhythmias
Ca channel dependent arrhythmia
adrenaline arrhythmia

Also our results showing that drugs suppressing Na channels of normal ventricular myocardium could suppress digitalis- and coronary ligation-induced arrhythmia, led us to speculate that class 1 antiarrhythmic drugs may act to suppress normal cardiac tissue to respond to abnormal impulse generation.

In order to test this hypothesis, we developed a "locally induced digitalis arrhythmia model", where arrhythmia originates in the digitalis toxicated myocardial area which is supplied by

Fig.2. Experimental scheme of the ADA auto-perfusion system. The arterial blood from the carotid artery was introduced to a extracorporeal circuit connecting the carotid artery and the anterior descending artery. An electromagnetic flowprobe and rubber tube for drug injection was inserted in the circuit. Ao = aorta, RV = right ventricle, ADA = anterior descending artery, LCX = left circumflex artery, LV = left ventricle.

the anterior descending artery (ADA) and there exists a substantial amount of normal, not digitalis toxicated myocardium in the same heart. In this model arrhythmia, we could examine the drug effect on either abnormal myocardium by directly injecting drugs to the ADA or normal myocardium by intravenous injection.

METHODS

Mongrel dogs of both sexes weighing from 10 to 18 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and right vagotomy was performed at the midcervical level. Lead II ECG and atrial electrogram directly from the bipolar electrodes sutured on the left atrial appendage were continuously recorded on a jet recorder (Nihon Kohden RIJ-2104). The femoral blood pressure, heart rate triggered by the R wave of ECG and the blood flow of the anterior descending artery described below were also continuously recorded on a pen recorder (Nihon Denshi Sanei 362, 8K-22).

Animals were artificially respired with room air using a volume limited respirator. The left thoracotomy was performed at the fifth intercostal space, and the heart was suspended in the

Locally induced digitalis arrhythmia

Fig.3. Epicardial mapping of a ventricular ectopic beat induced by local injection of ouabain into the ADA. The right panel shows electrograms of the ventricular beats recorded from the corresponding 20 electrodes. The first ectopic beat was analysed and the isopotential maps was obtained. Vertical bars show the manually determined time of the arrival of the ectopic beat. Numbers in the isopotential maps represents time (in msec) after the breakthrough of the ectopic beat at the epicardial surface. See text for further explanation.

pericardial cradle. The anterior descending artery was carefully dissected, and after injection of calcium heparin (initially 500 U/kg and additional 100 U/kg every hour), the left carotid artery was cannulated in order to drain the blood into the perfusion system with an electromagnetic flow probe (Nihon Kohden MFV 1100). A polyethylene cannula was inserted into the anterior descending artery (Fig. 2). Ouabain 40 μ g was injected directly into the perfusion circuit, and 10 μ g was added every 20 min until ventricular arrhythmia was induced. Antiarrhythmic drugs were directly injected into the rubber tube connecting the cannula and the flowmeter probe or injected intravenously into the femoral vein.

In order to examine whether the ectopic beats originate from the ADA area, epicardial mapping of normal beats and digitalis induced ectopic beats was performed in some of the experiments, using a computerized single beat epicardial mapping system (Fukuda Denshi HPM-6500).

Twenty simultaneous electrograms were recorded using a sock type multiple bipolar electrodes to draw isopotential maps of the anterior left ventricular surface, including the area perfused by the ADA.

RESULTS

In the first 25 experiments, the body weight of the dogs used were 10 ± 2 kg (mean $\pm$ standard deviation) and the cumulative dose of ouabain inducing sustained ventricular tachycardia was 63 ± 14 μ g. The origin of such ventricular ectopic beats could not be accurately determined by the standard ECG recordings, so an isopotential map of the ventricular ectopic beats was drawn by the computerized mapping system (lower left side of Fig. 3). The arrangement of the electrodes (upper left side of the figure) shows that the area below the line connecting electrode number, 3, 6, 10, 14 and 19 was per-

Fig.4. Effects of locally injected antiarrhythmic drugs on locally induced digitalis arrhythmia. BP = blood pressure, HR = heart rate, CF = coronary flow, TTX = tetrodotoxin.

fused by the anterior descending artery and intoxicated by intraarterial injection of ouabain. The ectopic beats slowly propagated concentrically from the points near 11 and 15. Normal beats propagated nearly twice as fast as from somewhere outside of the area recorded by the 20 electrodes (figures not shown).

Effects of drugs injected directly into the anterior descending artery

Class 1 Na channel blocking antiarrhythmic drugs, including tetrodotoxin, were all effective in suppressing the locally induced digitalis arrhythmia. As shown in Fig. 4, tetrodotoxin, which cannot be injected systemically because of its strong effect on nerve excitation and its hypotensive effect, could be administered as a bolus of 1 or 3 μ g directly into the anterior descending artery and it immediately suppressed the arrhythmia as shown in the lowest trace of the fast speed recording of ECG (lead II). Usually antiarrhythmic effect appeared as a sudden dis-

appearance of the tachycardia, and recurrence also occurred suddenly as shown in the slow speed ECG trace of Fig. 4. Other class 1 drugs, phenytoin (2.5 mg), mexiletine (0.5–1 mg), lidocaine (1–2 mg), disopyramide (0.5–3 mg) and procainamide (5–10 mg) were all effective in suppressing this arrhythmia. The antiarrhythmic effects were observed as the sudden disappearance of arrhythmia, not as a gradual decrease in the severity of arrhythmia, and the dose related effects were observed as the longer duration of the disappearance of the arrhythmia.

The Ca channel blockers used were verapamil (0.03–1 mg), nifedipine (0.01–0.1 mg) and nisoldipine (3–30 μ g) and they were given in supramaximal doses for dilating the anterior descending artery before ouabain injection. Figure 4 shows lack of antiarrhythmic effects of verapamil and nisoldipine. However in about half of the experiments, the Ca channel blockers also showed antiarrhythmic effects. It was concluded that the Class 4 Ca channel blockers

Fig. 5. Effect of lidocaine injected intraarterially into the ADA (left) and intravenously (right). Note that antiarrhythmic effect of intravenous lidocaine appeared about 2 min after injection, while that of intraarterial lidocaine appeared just after injection.

showed variable effects.

KCl solution, which is known to suppress digitalis automaticity *in vitro*,⁹ was also injected directly. About 0.25–0.4 ml KCl (in a 1 molar solution) suppressed the arrhythmia soon after injection but it did not affect the normal beat probably because it was diluted in the whole blood.

Comparison of the effects of lidocaine directly injected into the ADA and injected intravenously

In order to examine whether the locally induced digitalis arrhythmia could be suppressed by lidocaine given to the normal myocardium, the length of the autoperfusion circuit was increased so that the time for the blood to reach the ADA area from the carotid artery took longer. Using this perfusion system, intravenous lidocaine reached normal myocardium soon after injection, but the lidocaine containing arterial blood reached the ADA area at least 2 min later.

Thus the first 2 min of the lidocaine effect was only of the normal myocardium. As shown in Fig. 5, lidocaine directly injected into the ADA suppressed this locally induced digitalis arrhythmia. On the other hand, lidocaine given intravenously showed known hypotensive effect soon after injection, but the arrhythmia persisted for 2 min after injection.⁵ Similar experiments were performed on 6 animals and although sometimes arrhythmia was not completely suppressed after 2 min of i.v. lidocaine, 2–3 mg/kg, arrhythmia was not suppressed soon after i.v. lidocaine injection. Similar experiments using mexiletine and disopyramide also showed similar results.

DISCUSSION

The present experiment was designed to examine the possibility that an antiarrhythmic drug may act on the normal myocardium to suppress

the excitability responding to abnormal impulse generation. For this purpose we chose canine digitalis arrhythmia for the following reasons: 1) digitalis arrhythmia was usually thought to occur from digitalis toxicated myocardium where increased automaticity or triggered activity was induced,^{10,11} 2) digitalis arrhythmia was suppressed by class 1 Na channel blocking drugs and is considered to be a good model arrhythmia to detect Na channel blocking activity of drugs.⁵

The locally induced abnormality of rhythm was confirmed by using a multichannel epicardial surface mapping technique, and in the present study ectopic beats were shown to originate from the ADA perfused area. All the class 1 antiarrhythmic drugs were effective in suppressing this arrhythmia and even an experimental, though prototype Na channel blocker, tetrodotoxin, could be used in this experiment and was quite effective. These results are consistent with our proposal that digitalis arrhythmia is Na channel dependent, and unlike in vitro cardiac tissue, Ca channel blockers were not quite effective. The ineffective period of about 2 min soon after intravenous injection of lidocaine indicates that only the Na channel suppression of normal myocardium by the drug does not suppress this digitalis induced arrhythmia. This is in contrast to our previous study using arrhythmias induced by intravenously injected ouabain where the same dose of i.v. lidocaine was effective soon after injection.⁵ Therefore, we conclude from our study that it may be quite impossible for normal myocardium to become irresponsive to abnormal impulse generation when injected with antiarrhythmic drugs. Another question from our results which must be solved in the future is why Ca antagonists are not effective in suppressing digitalis arrhythmia. It may be possible that our sustained type digitalis arrhythmias are not generated by the same mechanism that produce triggered activity in isolated in vitro cardiac tissues, or that all the abnormalities of rhythm produced by digitalis are more related to Na channels than to Ca channels.

As for the general conclusion of the direct antiarrhythmic drug effect on the site of abnormal impulse generation, using only the digitalis arrhythmia may not be appropriate. However we think that coronary ligation arrhythmia is not a good model for such study, because the locus of abnormal impulse generation might be the border of ischemic and normal myocardium and there is no way to selectively apply the drug there in

vivo. Also as for the third arrhythmia models we used, adrenaline arrhythmia can be generated locally,¹² so it should be studied in the future, but the selectivity of responsiveness of the adrenaline arrhythmia to antiarrhythmic drugs is not so good when compared with that of digitalis arrhythmia. Thus our conclusion of low possibility of drug effects to suppress normal myocardial Na channel as their antiarrhythmic mechanism must be quite general, regardless of using only one arrhythmia model.

From a clinical stand point, our results may indicate that the drug effects on the normal myocardium only relate to the drug's side effects and that drugs, having a less depressing effect on normal myocardial Na channels (fast kinetic class 1 drugs, according to Hondeghem and Katzung¹³), may be more appropriate than those depressing normal myocardium (slow kinetic drugs). It is an open question whether the kinetics of the interaction between class 1 antiarrhythmic drugs and their binding sites really determine their drug efficacy in clinical or in vivo animal arrhythmias.

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