Effects of Astemizole on Ventricular Activation Delay and RT Intervals in a Canine Myocardial Infarction Model

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In order to clarify the arrhythmogenic effects of nonsedating antihistamines, we examined the effects of astemizole, a nonsedating antihistamine, on ventricular activation and RT intervals in a canine myocardial infarction model. Myocardial infarction was produced by two-stage ligation of the left anterior descending coronary artery in dogs. Seven days after ligation, bipolar electrodes were sutured on the ventricular surface of the infarcted and normal zones to apply an electrical stimulation or record the ventricular activation. An electrical stimulation with coupling intervals between 300 and 140 ms was applied on the ventricular surface of the normal zone during atrial pacing, and the ventricular activation delay was measured. The effect of astemizole on the RT interval was also determined during atrial pacing, sinus rhythm or after premature stimulation. The ventricular activation delay increased after astemizole at doses of 0.3 to 3 mg/kg in the infarcted and at 3 mg/kg in the normal zones, and the effect of astemizole was greater in the infarcted zone. Astemizole increased the RT interval in the normal zone to a greater extent at a long coupling interval. The increase in the RT interval was greater in the infarcted zone compared with that in the normal zone. In conclusion, astemizole increased the activation delay in the infarcted zone, probably through prolongation of the repolarization time, and its effect on the activation delay may be arrhythmogenic.

Key words astemizole; ventricular activation; RT interval; canine myocardial infarction model

Clinical data have shown that nonsedating antihistamines, such as terfenadine and astemizole, produce prolongation of the QT interval and ventricular arrhythmias including *torsades de pointes*.^{1–5} Prolongation of the QT interval by these drugs has also been observed in experimental animals at doses higher than those seen clinically.^{6,7} There is strong evidence that QT prolongation is a primary risk factor and a probable cause of drug-induced ventricular arrhythmias.⁶ In isolated ventricular cells, these drugs inhibit K⁺ channels and prolong the action potential duration,^{8–10} which may cause QT prolongation in experimental animals and patients. In patients with ischemic heart diseases, the use of terfenadine or astemizole is contraindicated. However, the electrophysiological effects of nonsedating antihistamines in ischemic hearts have not yet been clarified. It has been reported that increases in ventricular activation delay enhance the incidence of reentrant arrhythmias.^{11,12} Several drugs which produce the QT prolongation cause ventricular arrhythmias.^{1–5,13} In the present study, the effects of astemizole on the ventricular activation delay and RT intervals were examined in dog heart following myocardial infarction.

MATERIALS AND METHODS

Animal Preparation Myocardial infarction was produced in 8 mongrel dogs weighing 7 to 13 kg by two-stage ligation of the left anterior descending coronary artery according to the procedure described previously.¹⁴ After surgery, the dogs recovered from anesthesia and were returned to the animal quarters for postoperative care. Seven days after surgery, the animals were used for the electrophysiological study.

Measurement of the Ventricular Activation Delay and RT Intervals Animals were reanesthetized with sodium

pentobarbital 20 mg/kg i.v. Body temperature was maintained at 36–37 °C with a heating-pad (American Pharmseal Co., U.S.A.). Each animal was intubated and ventilated 12 times/min with air at a tidal volume of 15 ml/kg. Left thoracotomy was performed, and the pericardium was opened. After the heart was cradled on the pericardium, bipolar stimulating electrodes were sutured on the left atrial appendage and right ventricle for atrial pacing and applying premature stimulation, respectively. To record ventricular activation, two or three bipolar electrodes were sutured on the infarcted zones of the left ventricle and the normal zones of the right ventricle. Electrical stimulation of the ventricle was performed using a 5 ms rectangular pulse with an electrical stimulator (SEN-7103, Nihon Kohden). Stimulus strength was kept at twice the diastolic threshold, and atrial pacing was performed at a rate slightly above the sinus rhythm before drug administration (172.1 ± 2.5 beats/min), and this was fixed throughout the electrophysiological study.

To study the effects of the drug on ventricular activation, we measured the activation delay in both normal and infarcted zones of the ventricle after premature ventricular stimulation of the normal zone. The time interval ranging from the artifact of the premature stimulation to the most delayed measurable wave was measured on the epicardial bipolar electrocardiogram (ECGs) and this value was estimated as the activation delay. The coupling interval of the ventricular stimulation was varied between 300 and 140 ms. Lead II ECG, femoral arterial blood pressure, and epicardial bipolar ECGs were recorded on a multichannel thermal-array recorder (Nihon Kohden, WS-682G) at a paper speed of 100 mm/s.

The effect of astemizole on the RT interval was determined by measuring the RT interval in the ECGs of the normal and infarcted zones during atrial pacing, sinus rhythm or after a premature stimulation. The RT interval

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in the infarcted zone was the time interval between the largest deflection and the peak of the T-wave.

Drug Administration After a one-hour-equilibration, control data were obtained, and then astemizole was administered in cumulative doses of 0.1, 0.3, 1 and 3 mg/kg *via* the femoral vein at intervals of 15 min. The measurements were started 10 min after drug administration. Astemizole was dissolved in a solution containing 4% Tween 80 and 2% ethanol. The vehicle did not affect any monitoring parameters five minutes after administration.

Statistical Analysis All data are expressed as arithmetic means $\pm$ S.E.M. Comparison between control and drug values of ventricular activation delay and the RT interval was performed by analysis of variance followed by Dunnett's test. The criterion for statistical significance was $p < 0.05$.

RESULTS

Effects of Astemizole on Blood Pressure and Heart Rate Astemizole at doses of 1 and 3 mg/kg significantly reduced blood pressure. The heart rate also fell after astemizole doses higher than 0.1 mg/kg (Fig. 1).

Effects of Astemizole on Ventricular Activation Representative ECGs recorded from the normal and infarcted zone are shown in Fig. 2. At the basic cycle length, the ECG from a normal zone consisted of deflection with a duration of less than 50 ms, whereas most of the ECGs from an infarcted zone were fractionated potential, indicating that the activation in the infarcted zone was delayed. The delayed activation was further delayed during a premature stimulation-induced excitation.

Typical effects of astemizole on ventricular activation are shown in Fig. 2. Astemizole at a dose of 3 mg/kg increased the delay in premature stimulation-induced activation from 128 ms to 165 ms in the infarcted zone,

when the premature stimulation was applied at a coupling interval of 160 ms. At a coupling interval of 140 ms, astemizole 3 mg/kg blocked the delayed activation. The activation of the normal zone was not significantly affected. The RT interval in the normal zone was prolonged from 150 to 175 ms by astemizole at 3 mg/kg. The RT interval of the premature stimulation-induced excitation increased from 132 to 143 ms with astemizole.

Figures 3 and 4 summarize the effects of astemizole on the ventricular activation delay in eight animals. Astemizole, at doses of 0.3 to 3 mg/kg, significantly increased the activation delay in the infarcted zone to a greater extent at the shorter coupling interval (Fig. 3); the increases in the activation delay produced by 3 mg/kg of astemizole at coupling intervals of 250 and 150 ms were 11.8 ± 3.7 ms and 25.6 ± 3.7 ms, respectively ($p < 0.05$). In the normal zone, the activation delay was also increased at a coupling interval of 150 ms by 3 mg/kg of astemizole, but to a lesser extent compared with that in the infarcted

Fig. 1. Effects of Astemizole on Blood Pressure and Heart Rate in Eight Anesthetized Dogs with Myocardial Infarction

*; $p < 0.05$ vs. control.

Fig. 2. Effects of Astemizole (3 mg/kg) on Ventricular Activation and RT Intervals in Dog Hearts with Myocardial Infarction

L-II; Standard limb lead II ECG. NZeg, IZeg; ECGs of the normal and infarcted zones. The arrows pointing up indicate premature stimulation with a coupling intervals of 160 ms (right panel) and 140 ms (left panel). The basic cycle length was 370 ms. The arrows pointing down indicate delayed activation (IZeg) and the T-wave (NZeg). The numbers in the NZeg and IZeg are the RT intervals and the activation delay, respectively. The open arrow indicates block of delayed activation.

Fig. 3. Effects of Astemizole on the Ventricular Activation Delay in the Infarcted Zone

Values are the mean $\pm$ S.E.M. ($n=8$). *, **, statistically significant at $p < 0.05$, and 0.01 vs. control.

Fig. 4. Effects of Astemizole on the Ventricular Activation Delay in the Normal Zone

Values are the mean $\pm$ S.E.M. ($n=8$). *, statistically significant at $p < 0.05$ vs. control.

zone (Fig. 4); the increases produced by 3 mg/kg in the normal and the infarcted zones were 15.0 ± 3.6 and 25.6 ± 3.7 ms ($p < 0.05$), respectively.

Effects of Astemizole on the RT Interval Astemizole at doses higher than 0.3 mg/kg significantly prolonged the RT interval during atrial pacing as well as during sinus rhythm, which was consistent with clinical observations (Fig. 5). Prolongation of the RT interval by 1 and 3 mg/kg of astemizole was significantly greater during sinus rhythm than that during atrial pacing. The RT interval in the excitation induced by premature stimulation with a coupling interval of 160 ms was shorter than that during atrial pacing or sinus rhythm, and it also increased after astemizole at doses of 1 and 3 mg/kg. However, the increase was lesser than that during atrial pacing. The effect of astemizole on the RT interval in the infarcted zone was compared with that in the normal zone (Fig. 6). The RT interval was measured in the premature stimulation-induced excitation at a coupling interval of 250 ms. Under these conditions, an artifact of the stimulation did not overlap on the T-wave, and astemizole did not significantly affect the activation delay. Astemizole at doses higher than 0.1 mg/kg significantly increased the RT interval in the infarcted zone, and the increases were greater than those in the normal zone.

Fig. 5. Increases in the RT Intervals of the Normal Zone Produced by Astemizole in Dog Hearts Following Myocardial Infarction

Values are the mean $\pm$ S.E.M. ($n=8$). #, statistically significant at $p < 0.05$ vs. sinus rhythm and premature stimulation. The increases in RT intervals at all doses are statistically significant at $p < 0.05$ under all three conditions.

Fig. 6. Increases in the RT Interval Produced by Astemizole in the Infarcted Zone in Comparison with Those in the Normal Zone

Values are the mean $\pm$ S.E.M. ($n=7$). The increases in the RT interval are statistically significant at all doses. #, statistically significant at $p < 0.05$ vs. the normal zone.

DISCUSSION

The present study showed that astemizole increased the ventricular activation delay in both normal and infarcted zones. The RT interval in the normal zone was prolonged by astemizole. These actions of astemizole may be caused by increases in the action potential duration, which was observed in *in vitro* studies.^{7,8,10} The increase in the activation delay produced by astemizole was observed at a shorter coupling interval but not at a longer coupling interval. It is probable that the increase in the activation delay may be caused by the increase in the action potential duration; premature stimulation with a short coupling interval will produce an excitation during incomplete repolarization, which may cause a slow maximal rate of depolarization, resulting in slow conduction. This idea is supported by other investigators.¹⁵ The increase in the activation delay was greater in the infarcted zone.

Depolarization as well as repolarization in the infarcted zone may not be homogenous, even within small regions. We could not measure the RT interval in the infarcted zone in one of the eight animals because there was no obvious T-wave. Nevertheless, in the other seven animals, a significant increase in the RT interval was observed after astemizole, suggesting that prolongation of the repolarization phase may be involved in the increase in the activation delay. The increase in the activation delay was greater in the infarcted zone, probably because the increase in the RT interval, *i.e.* time for repolarization, was greater in the infarcted zone. However, it is not clear why prolongation of the RT interval after astemizole was greater in the infarcted zone.

It is also probable that the increase in the activation delay produced by astemizole is caused by Na⁺ channel inhibition. Several investigators observed Na⁺ channel blockade by terfenadine in ventricular myocytes, Purkinje fibers and myocardium.¹⁶⁻¹⁸ They showed that terfenadine blocks Na⁺ channels more markedly at a membrane potential of -40 mV than -90 mV, and that the effect of terfenadine is greater at short coupling intervals. Astemizole may have similar effects on Na⁺ channels, which may cause a marked increase in the activation delay in infarcted zones at short coupling intervals.

It is well known that the increase in the activation delay in the infarcted zone may cause a risk of reentrant arrhythmias.^{11,12} Class I antiarrhythmic drugs also block the delayed activation or increase the activation delay^{12,19}; the former contributes to their antiarrhythmic effects and the latter may be an arrhythmogenic action.²⁰⁻²² Astemizole either increased the activation delay or blocked the delayed activation. Therefore, astemizole may produce both antiarrhythmic and arrhythmogenic actions by affecting the activation delay. In a fact, antiarrhythmic effects of astemizole have already been reported.²³

In the present study, astemizole increased the RT interval to a greater extent at longer coupling intervals. In *in vitro* studies with myocytes, the increases in action potential duration produced by terfenadine are greater when myocytes are driven at a lower frequency.¹⁰ Marked prolongation of the repolarization phase at driving rates by terfenadine produces delayed afterdepolarization, which is supposed to be a cause of ventricular tachyarrhythmias in clinical situations.²⁴ It has been reported that the effect of astemizole on the repolarization phase may be similar to that of terfenadine.¹⁰ Thus, astemizole may have arrhythmogenic effects. Astemizole reduced the heart rate, which may enhance the arrhythmogenic effects.

The electrophysiological effects of astemizole were observed at doses greater than 0.3 or 1 mg/kg *i.v.*, which are larger than the clinical doses. Plasma concentrations of these nonsedating antihistamines in humans are usually low because of rapid metabolism.^{25,26} Therefore, astemizole may produce the electrophysiological effects observed in the present study under conditions that lead to increased plasma levels of astemizole such as overdose, liver disease or concomitant treatment with drugs which

interfere with the metabolism of astemizole.^{2,9,26-28} Because the electrophysiological effects of astemizole are similar to those of other nonsedating antihistamines,^{7,10,24} these drugs may have similar electrophysiologic effects on ischemic hearts.

In conclusion, astemizole at doses higher than those seen clinically produced increases in ventricular activation delay and RT intervals in the heart following myocardial infarction. The increase in the ventricular activation delay by astemizole was greater in the infarcted zone than in the normal zone, which may lead to enhanced cardiac toxicity in patients with ischemic heart diseases.

REFERENCES

- 1) Snook J., Boothman-Burrell D., Watkins J., Colin-Jones D., *Brit. J. Clin. Pract.*, **42**, 257-259 (1988).
- 2) Honig P. K., Woosley R. L., Zamani K., Conner D. P., Cantilena L. R., Jr., *Clin. Pharmacol. Ther.*, **52**, 231-238 (1992).
- 3) Pohjola-Sintonen S., Vitasalo M., Toivonen L., Neuvonen P., *Eur. J. Clin. Pharmacol.*, **45**, 191-193 (1993).
- 4) Sakemi H., VanNatte B., *Am. Heart J.*, **125**, 1436-1438 (1993).
- 5) Koh K. K., Rim M. S., Yoon J., Kim S.S., *J. Electrocardiol.*, **27**, 343-346 (1994).
- 6) Hey J. A., Del Prado M., Cuss, F. M., Egan R.W., Sherwood, J., Lin C. C., Krutner W., *Clin. Exp. Allergy*, **25**, 974-984 (1995).
- 7) Hey J. A., Del Prado M., Sherwood J., Kreutner W., Egan R. W., *Arzneim.-Forsch./Drug Res.*, **46**, 153-159 (1996).
- 8) Rampe D., Wible B., Brown A. M., Dage R. C., *Mol. Pharmacol.*, **44**, 1240-1245 (1993).
- 9) Woosley R. L., Chen Y., Freiman J. P., Gillis R. A., *J. Am. Med. Assoc.*, **269**, 15432-1536 (1993).
- 10) Salata J. J., Jurkiewicz N. K., Wallace A. A., Stupinski R. F., Guinasso P. J., Lynch J. J., Jr., *Circ. Res.*, **76**, 110-119 (1995).
- 11) El-Sherif N., Scherlag B. J., Lazzara R., Hope R. R., *Circulation*, **55**, 686-702 (1977a).
- 12) Bigger J. T., Hoffman B. F., "Antiarrhythmic Drugs: Goodman and Gilman's The Pharmacological Basis of Therapeutics," ed. by Gilman A. G., Rall T. W., Nies A. S., Taylor P., Macmillan, New York, 1990, pp. 840-873.
- 13) Zhuo J., Casley D., Murone C., Mendelshon F. A. O., *J. Cardiovasc. Pharmacol.*, **29**, 297-310 (1997).
- 14) Harris A. S., *Circulation*, **1**, 1318-1328 (1950).
- 15) Koller B. S., Krasik P. E., Solomon A. J., Franz M. R., *Circulation*, **91**, 2378-2384 (1995).
- 16) Lang D. G., Wang C. M., Wenger T. L., *J. Cardiovasc. Pharmacol.*, **22**, 438-442 (1993).
- 17) Ming Z., Nordin C., *J. Cardiovasc. Pharmacol.*, **26**, 761-769 (1995).
- 18) Tanaka H., Masumiya H., Kato Y., Shigenobu K., *Gen. Pharmacol.*, **27**, 337-340 (1996).
- 19) El-Sherif N., Scherlag B. J., Lazzara R., Hope, R. R., *Circulation*, **56**, 395-402 (1977).
- 20) Vildmair V., Podrid P., Lown B., Cohn B., Graboyes T. B., *Circulation*, **65**, 886-894 (1982).
- 21) The Sicilian Gambit, *Eur. Heart J.*, **12**, 1112-1131 (1991).
- 22) Kidwell G. A., Gonzalez M. D., *J. Cardiovasc. Pharmacol.*, **21**, 621-632 (1993).
- 23) Sanchez P. J., Zaldivar H. M., *Archivos del Instituto de Cardiologia de Mexico*, **63**, 185-189 (1993).
- 24) Berul C. I., Morad M., *Circulation*, **91**, 2220-2225 (1995).
- 25) Oonishi A., Oosawa N., Nakai Y., Naha H., *J. Clin. Ther. Med.*, **7**, 1437-1465, (1991).
- 26) Honig P. K., Wortham D. C., Zamani K., Conner D. P., Mullin J. C., Cantilena L. R., *JMAM*, **269**, 1513-1518 (1993).
- 27) von Moltke L. L., Greenblatt D. J., Duan S. X., Harmatz J. S., Shader R. I., *J. Clin. Pharmacol.*, **34**, 1222-1227 (1994).
- 28) Kamisako T., Adachi Y., Nakagawa H., Yamamoto T., *Internal Medicine*, **34**, 92-95 (1995).