Research Article

Comparative Electrophysiological Effects of the Second Generation Antihistamines, Astemizole and Ebastine, in a Canine Myocardial Infarction Model

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Strategy, Management and Health Policy				
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ABSTRACT In this study, the effects of the histamine H_1 receptor antagonists, astemizole, and ebastine on RT intervals, ventricular action, effective refractory periods (ERPs), and programmed electrical stimulation (PES)-induced ventricular arrhythmias were investigated in canine hearts with myocardial infarction produced by two-stage ligation of the left anterior descending coronary artery. Seven days postligation, bipolar electrodes were sutured on the ventricular surface in infarcted and intact zones to either electrically stimulate or record ventricular activation. The RT interval was measured in the intact zone. The ERPs in infarcted and intact zones were determined during atrial pacing. Ventricular activation delay was measured during premature excitation produced by stimulation at a coupling interval between 120 and 300 ms on the ventricular surface in the intact zone. The RT interval was significantly ($P < 0.05$) prolonged by astemizole. In addition, the prolongation of the RT interval was greater at longer coupling intervals. In contrast, ebastine did not affect the RT interval. Astemizole at doses of 0.3–3.0 mg/kg significantly ($P < 0.05$) prolonged the ERP; ebastine at a dose of 3.0 mg/kg also prolonged the ERP in both intact and infarcted zones. Astemizole at doses of 0.3–3.0 mg/kg prolonged ventricular activation delay; ebastine at a dose of 3.0 mg/kg also prolonged it in both infarcted and intact zones. Astemizole was more effective than ebastine in prolonging the ERP and ventricular activation delay. Astemizole (0.3–3.0 mg/kg), but not ebastine, induced proarrhythmias in the PES-induced ventricular arrhythmia model. In conclusion, astemizole was proarrhythmic in the RT interval prolongation model while ebastine was not proarrhythmic in the canine myocardial infarcted heart. Drug Dev. Res. 50:163–169, 2000.

Key words: astemizole; ebastine; canine myocardial infarction; activation delay; ERPs; RT intervals; reverse-use-dependent

INTRODUCTION

Astemizole and ebastine are second-generation histamine H_1 receptor antagonists widely prescribed for allergic and upper respiratory tract diseases. The popularity of these newer H_1 antihistamines results from their ability to relieve symptoms of allergy without the sedation commonly associated with first-generation H_1 receptor antagonists such as diphenhydramine. In recent clinical studies, the second-generation, nonsedating histamine H_1 receptor antagonists terfenadine and astemizole showed the potential for inducing life-threatening ventricular arrhythmias. In contrast, ebastine, another second-generation histamine H_1 receptor antagonist, had minimal effects on cardiac function especially, life-threatening ventricular arrhythmias. Terfenadine and astemizole induce QTc interval prolongation and ventricular arrhythmias including *torsades de points* [Snook et al., 1988; Nightingale, 1992; Honig et al., 1993; Pohjola-Sintonen

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et al., 1993; Sakemi and VanNatte, 1993; Koh et al., 1994]. The prolongation of QTc interval by these drugs has also been observed in experimental animals at doses higher than those used in the clinic [Hey et al., 1995, 1996]. QTc prolongation is a primary risk factor and a probable cause of drug-induced ventricular arrhythmias [Hey et al., 1995; Lacroix et al., 1999]. However, the electrophysiological actions of those H_1 receptor antagonists in ischemic hearts have not yet been studied.

In the present study, the effects of astemizole and ebastine were examined for their effects on RT intervals, ventricular action, effective refractory periods (ERPs), and programmed electrical stimulation (PES)-induced ventricular arrhythmias using a canine heart model with myocardial infarction.

MATERIALS AND METHODS

Animal Preparation

Myocardial infarction was produced in 14 mongrel dogs weighing 7.0 to 13.0 kg by two-stage ligation of the left anterior descending coronary artery according to a previously described procedure [Harris et al., 1950]. 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, ERP_S, and RT Intervals, Presence of Reverse-Use-Dependent, Incidence of PES-Induced Arrhythmias

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., USA). 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 intact 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 (183.2 ± 6.29 beats/min) and this was fixed throughout the electrophysiological study. All examinations were determined during atrial pacing (300 ms).

The RT interval in intact zone during atrial pacing and sinus rhythm or after a premature stimulation was measured in dogs treated with either astemizole or ebastine. The RT interval was defined as the time interval between the largest deflection and the peak of the T-wave.

The ERP in intact and infarcted zones was measured during atrial pacing. For measuring the ERP, the ventricle was prematurely stimulated at twice the threshold strength at progressively shorter coupling intervals. The ERP was defined as the shortest coupling interval at which conduction was successful.

Ventricular activation delay was measured in both intact and infarcted zones after premature ventricular stimulation of the intact zone. The time interval from the artifact of premature stimulation to the most delayed measurable wave was measured using an epicardial bipolar electrocardiogram (ECG) and this value was determined as the activation delay. The coupling interval of the ventricular stimulation was varied between 120 and 300 ms. Lead II ECG, femoral arterial blood pressure, and epicardial bipolar ECG were recorded on a multichannel thermal-array recorder (Nihon Kohden, WS-682G) at a paper speed of 100 mm/s.

PES-induced ventricular arrhythmias were examined to study the proarrhythmic effects of astemizole and ebastine. ES was produced by triple ventricular extra stimuli during atrial pacing. The coupling interval of the extra stimuli was 130 ms. When these stimuli caused arrhythmias during pretreatment the coupling interval was increased to 140 ms. This extra stimuli did not produce arrhythmias before drug administration. Ventricular premature beats (VPBs) were defined as three or less successive ventricular beats. Ventricular tachycardia (VT) was defined as four or more successive ventricular beats.

Compound Administration

After 1-h equilibration, control data were obtained and astemizole and ebastine were then administered in cumulative doses of 0.1, 0.3, 1.0, and 3.0 mg/kg via the femoral vein at intervals of 15 min. Measurements were started 10 min after compound administration.

Astemizole and ebastine were dissolved in a vehicle containing DMSO which by itself did not affect any monitoring parameters at 6 min after administration. Changes in ECG parameters were measured for up to 5 h after open-heart surgery of dogs. In the absence of compounds for up to 5 h after the start of thoracotomy, no change in ECG parameters was observed (data not shown).

Statistical Analysis

All data are expressed as arithmetic means ±SEM. Comparison between control and compound values of the ventricular activation delay, RT interval, ERPs were performed by analysis of variance followed by Dunnet's test ($n = 7$). Comparisons of basal values of ERPs and RT intervals between normal and infarcted zones were

made by paired Student's *t*-test; χ^2 analysis was used to compare the incidence of PES-induced ventricular arrhythmias. The criterion for statistical significance was $P < 0.05$.

RESULTS

Effects of Astemizole and Ebastine on Blood Pressure and Heart Rate

Astemizole and ebastine at doses of 0.1–3.0 mg/kg had no effect on blood pressure. Astemizole at doses of 1.0 and 3.0 mg/kg and ebastine at 3.0 mg/kg significantly decreased the heart rate (data not shown)

Effects of Astemizole and Ebastine on RT Interval

Representative ECGs for astemizole and ebastine recorded in intact and infarcted zones are shown in Figure 1. The RT interval in the intact zone was prolonged from 150 to 185 ms by astemizole at 3.0 mg/kg with a coupling interval of 240 ms (striped arrow). The RT interval was prolonged from 150 to 168 ms by astemizole at 1 mg/kg with coupling interval of 140 ms. Astemizole at doses 0.3–3.0 mg/kg significantly prolonged the RT interval during atrial pacing and sinus rhythm in dose-dependent manner (Fig. 2a). Prolongation of the RT interval during sinus rhythm by astemizole was significantly greater than that produced by ebastine during atrial pacing. Furthermore, astemizole (3.0 mg/kg) prolonged the RT interval by 42.1 ± 5.9 ms or 18.6 ± 6.6 ms with coupling intervals of 240 ms or 140 ms, respectively. These changes in the RT interval occurred in a reverse-use-dependent manner (Fig. 2b). Ebastine at the doses used in this study did not prolong the RT interval during both atrial pacing and sinus rhythm (striped arrows in Fig. 1).

Effects of Astemizole and Ebastine on Ventricular Activation

At the basic cycle length, the ECG in the intact zone consisted of a deflection with a duration of less than 50

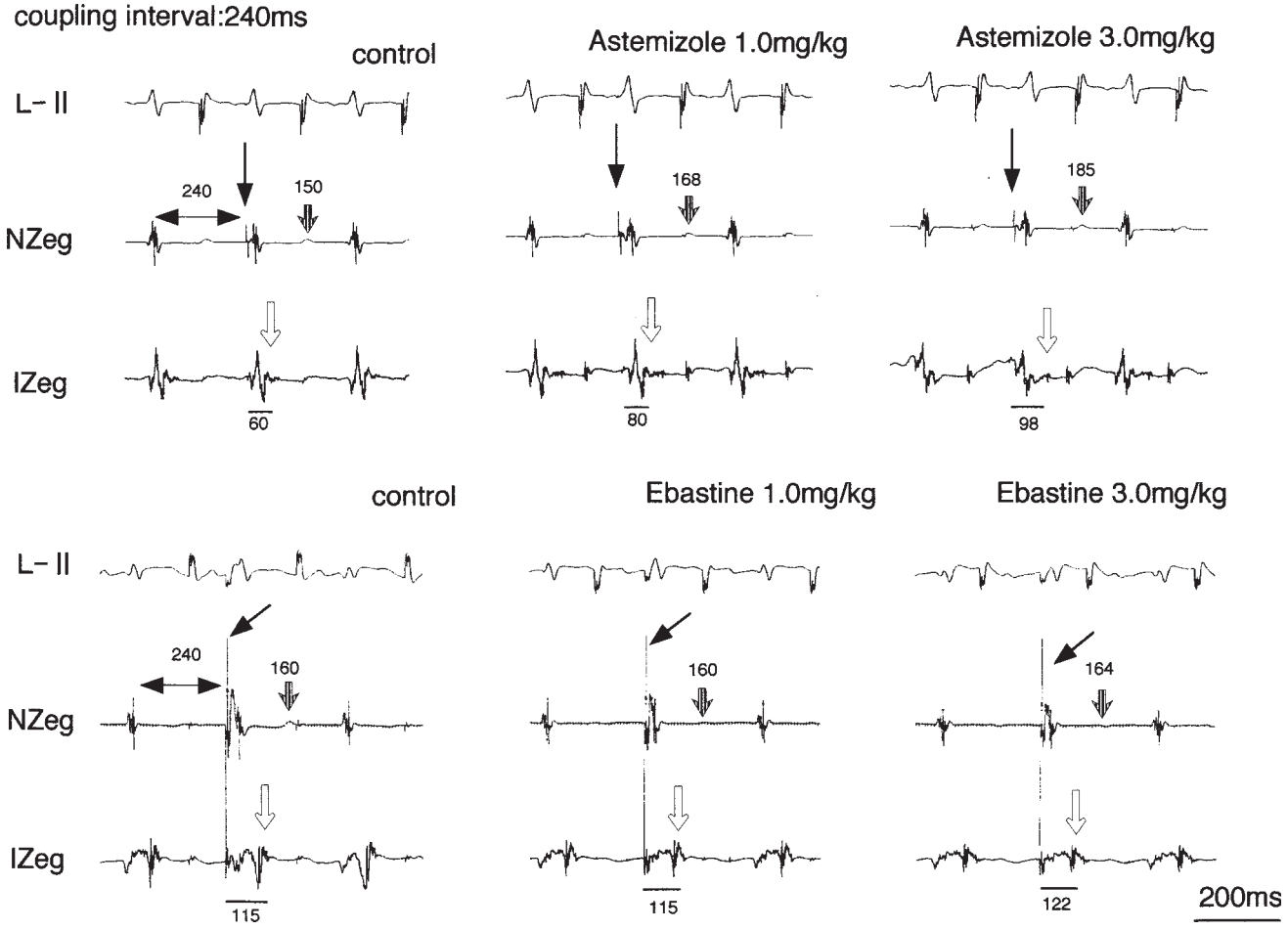

Fig. 1. Effect of astemizole (1 and 3 mg/kg) and ebastine (1 and 3 mg/kg) on ventricular activation and RT intervals in dog hearts with myocardial infarction. L-II: standard limb lead II; Nzeg, Izeg: ECGs of normal (intact) and infarcted zones, respectively. Black arrows indicate the premature stimulation with coupling intervals of 240 ms. Open arrows indicate delayed activations (Izeg). Striped arrows indicate RT intervals in the intact zone. The numbers in Nzeg and Izeg are the RT intervals and activation delay, respectively.

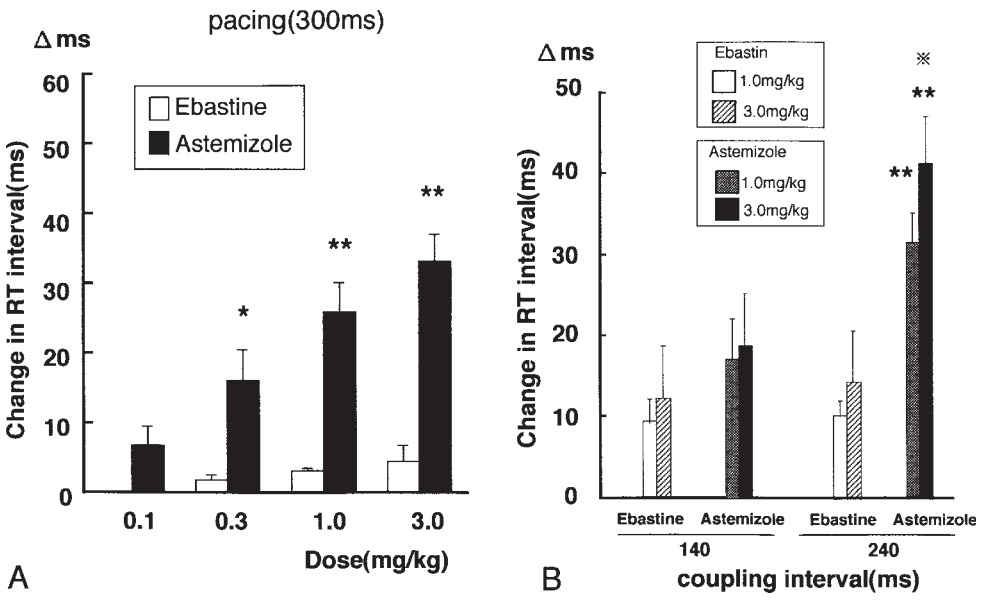

Fig. 2. Effects of astemizole and ebastine on the RT intervals and reverse-use-dependent in dog hearts with myocardial infarction. Left panel indicates change in RT interval of astemizole and ebastine in the intact zone under the pacing. Light panel indicates difference of change in RT interval with short coupling interval (140 ms) and long coupling interval (240 ms). Values expressed as mean ±SEM of seven animals. *Increases are statistically significant at $P < 0.05$; **$P < 0.01$ compared with each control. $P < 0.01$ compared with 140 ms coupling interval value.

ms, whereas most of the ECGs in the infarcted zone showed a 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 Figure 1. Astemizole (3.0 mg/kg) increased the activation delay from 60–98 ms in the infarcted zone (open arrow), when the premature stimulation was applied at a coupling interval of 240 ms. At a coupling interval of 140 ms, the activation delay was prolonged from 95–135 ms in the infarcted zone. Ebastine (3.0 mg/kg), prolonged the activation delay from 115–122 ms in the infarcted zone with a coupling interval of 240 ms (open arrow).

The effects of astemizole and ebastine on the ventricular activation delay in each group of seven animals is shown in Figure 3. Astemizole at doses of 0.3–3.0 mg/kg significantly prolonged the activation delay in both intact and infarcted zones to a greater extent at the shorter coupling interval (Fig. 3). In the intact zone, prolongation of the activation delay by astemizole at a dose of 3.0 mg/kg at coupling intervals of 240 and 140 ms were 22.1 ± 7.1 ms and 49.3 ± 9.8 ms, respectively ($P < 0.05$ and $P < 0.01$). In the infarcted zone, the prolongation at coupling intervals of 240 and 140 ms were 38.6 ± 10.8 and

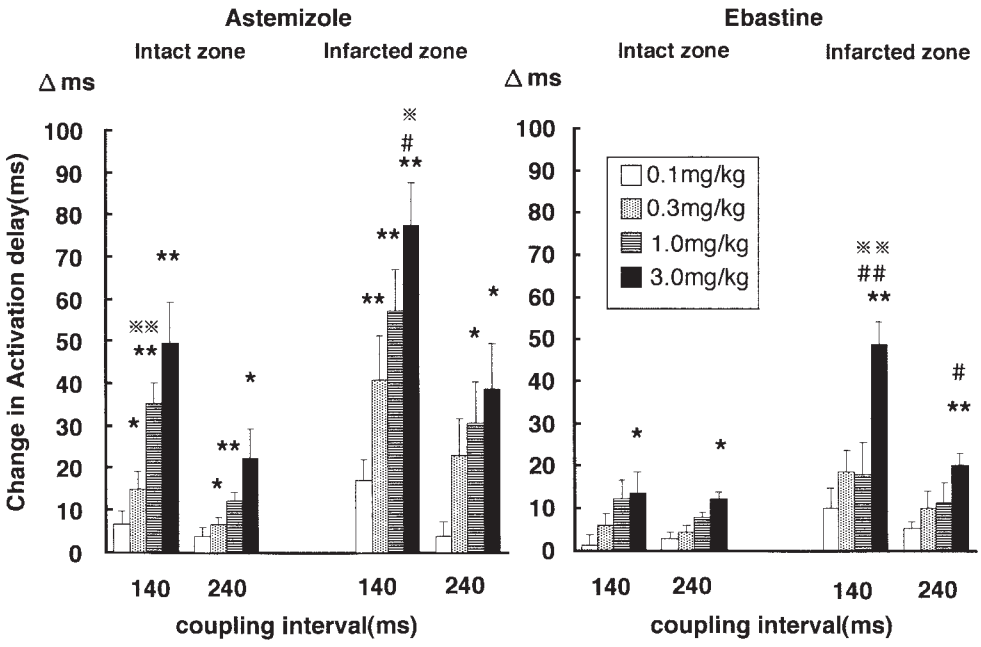

Fig. 3. Effects of astemizole and ebastine on the activation delay of premature excitation in the intact and infarcted zones in seven animals each. *$P < 0.05$; **$P < 0.01$ compared with each control values. #$P < 0.05$; ##$P < 0.01$ compared with intact zone. $P < 0.05$; $P < 0.01$ compared with 240 ms coupling interval values.

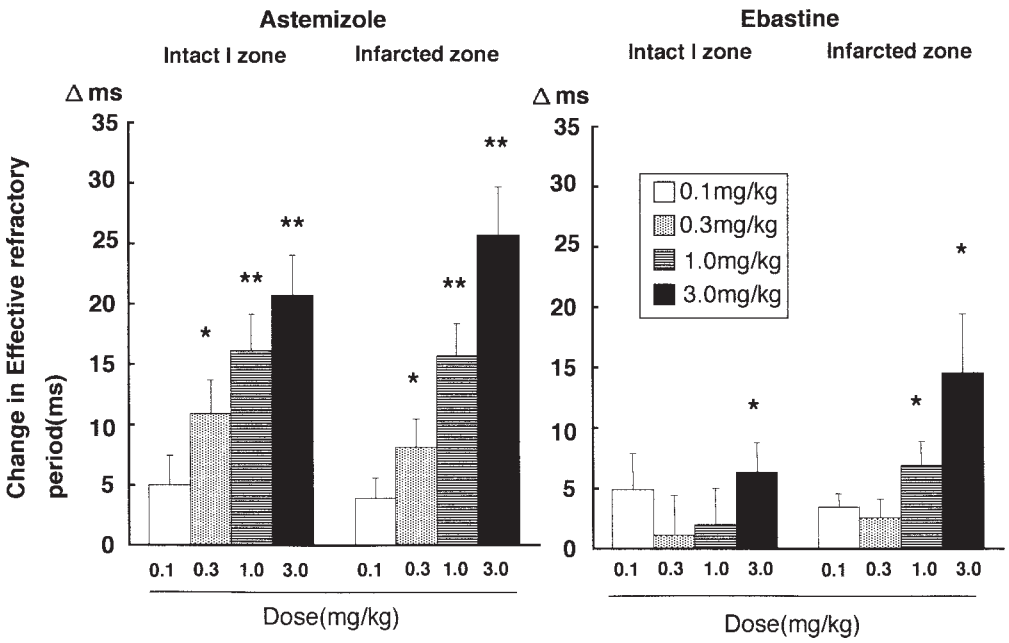

Fig. 4. Effects of astemizole and ebastine on ERP in the intact and infarcted zones in seven animals each. *$P < 0.05$; **$P < 0.01$ compared with control values.

77.1 ± 10.4 ms ($P < 0.05$ and $P < 0.01$), respectively. The prolongation of ventricular activation delay in the infarcted zone was thus greater than that in the intact zone.

Ebastine had a similar effect as astemizole in the activation delay, but was less efficacious than astemizole. In the intact zone, the prolongation of the activation delay by 3.0 mg/kg ebastine at coupling intervals of 240 and 140 ms were 12.1 ± 1.8 ms and 13.6 ± 5.3 ms, respectively ($P < 0.05$ and $P < 0.01$). In the infarcted zone, the prolongation at coupling intervals of 240 ms and140 ms were 20.0 ± 2.9 and 48.6 ± 5.4 ms ($P < 0.05$ and $P < 0.01$), respectively. The prolongation of activation delay in the infarcted zone was greater in comparison with that in the intact zone.

Effects of Astemizole and Ebastine on ERP

Astemizole at a dose of 3.0 mg/kg significantly ($P < 0.01$) prolonged ERP by 20.7 ± 3.3 and 25.7 ± 4.0 ms in the intact and infarcted zone, respectively (Fig. 4). Ebastine had a similar effect to astemizole in the ERP, but again was less efficacious. Ebastine (3.0 mg/kg) prolonged the ERP in infarcted and intact zones by 14.6 ± 4.8 ms and 6.3 ± 2.5 ms, respectively.

Incidence of PES-Induced Arrhythmias

Typical ECGs for the PES-induced ventricular arrhythmias produced by astemizole and ebastine are shown in Figure 5. Astemizole (0.1–1.0 mg/kg) caused VT and ventricular fibrillation (VF). Astemizole induced VT and VF in 4/7 animals and VPB in 2/7 animals. In contrast, ebastine induced VT and VF in 2/7 animals and VPB in 1/7 animals. Astemizole significantly ($P < 0.05$) increased the incidence of ventricular arrhythmias induced by PES, but ebastine was without effect (Fig. 6).

DISCUSSION

In this study, astemizole was shown to prolong the RT interval in a reverse-use-dependent manner and also induced PES-induced ventricular arrhythmias. In contrast, ebastine did not affect the RT interval and did not induce arrhythmias.

A number of reports suggest that the arrhythmogenic effects of terfenadine and astemizole result from the prolongation of the QT interval secondary to suppression of K^+ channel conduction [Salata et al., 1995; Charles et al., 1995; Taglialateja et al., 1998; Valenzuela et al., 1997; Rampe et al., 1993; Ming et al., 1995]. These drugs inhibited the I_{k1} in both guinea pig and rat ventricular myocytes. In rat myocytes, terfenadine and astemizole also blocked a component of the I_{to} [Charles et al., 1995]. Arrhythmias, including *torsades de points*, result from an increase of trigger activity induced by the prolongation of action potential duration due to blockade of K^+ channels. Ebastine is no less effective in inhibiting K^+ currents in vitro than terfenadine [Ko et al., 1997]. Based on the present observations and previous reports, astemizole appears to induce arrhythmias via inhibition of K^+ currents. In contrast, ebastine did not affect the RT interval, suggesting that ebastine inhibited K^+ currents less than astemizole and, as a result, did not induce arrhythmias.

The increase in the activation delay produced by astemizole and ebastine occurred to a greater extent at a shorter coupling interval and were greater in the infarcted

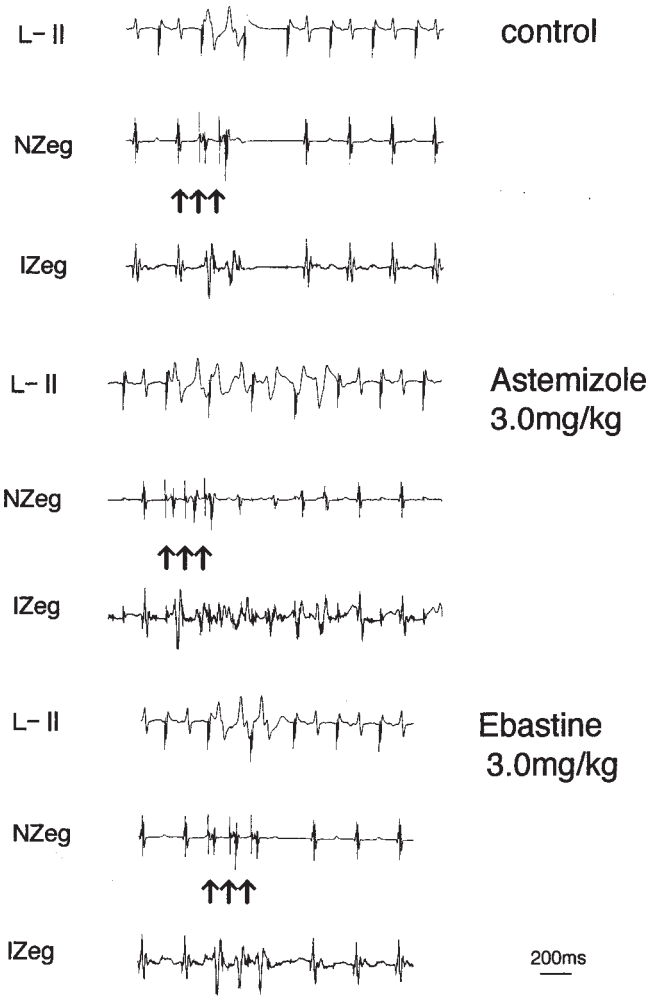

Fig. 5. Effects of astemizole and ebastine on the incidence of ventricular arrhythmias induced by PES. Before astemizole and ebastine were administered, extra stimuli did not cause any ventricular arrhythmia (control, upper panel). Astemizole, at a dose of 3 mg/kg (middle panel), produced ventricular tachycardia. Ebastine, at a dose of 3 mg/kg (lower panel), did not produce ventricular tachycardia. L-II: standard limb lead II; Nzeg, Izeg: ECGs of normal (intact) and infarcted zones, respectively. Arrows indicate the PES.

zone. Ebastine was less effective in producing an activation delay than astemizole.

It is well established that an increase in the activation delay in the infarcted zone is a risk for reentrant arrhythmias [El-Sherif et al., 1977a,b; Bigger and Hoffman, 1990]. It is probable that the increase in the activation delay results from an increase in the action potential duration; premature stimulation with a short coupling will then produce an excitation during incomplete repolarization, which may cause a slow maximal rate of depolarization, resulting in slow conduction. In the infarcted zone, repolarization and depolarization may not be homogenous, even within small areas. inducing reentrant arrhythmias. These findings suggest that ebastine might

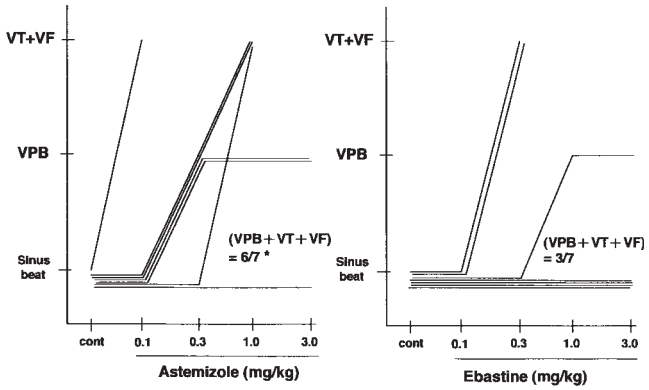

Fig. 6. Effects of astemizole and ebastine on the incidence of ventricular arrhythmias induced by PES in seven animals each. $*P < 0.05$ compared with control. VPB: ventricular premature beats, VT: ventricular tachycardia, VF: ventricular fibrillation.

be less prone to induce arrhythmias by reentry than astemizole.

Astemizole increased the RT interval in a reverse-use-dependent manner, but ebastine did not, indicating that serious arrhythmias may result during bradycardia. Prolongation in action potential duration by terfenadine are greater when myocytes are driven at lower frequency in vitro in myocytes [Salata et al., 1995]. Marked prolongation of the repolarization phase at low driving rates by terfenadine produces delayed after-depolarization, which may cause VT in clinic [Charles et al., 1995]. Astemizole has similar effects to terfenadine on the repolarization phase [Salata et al., 1995].

While ebastine is similar chemically to terfenadine and astemizole [Taglialateja et al., 1998; Ko et al., 1997] it differs from astemizole and terfenadine in its metabolic profile [Hashizume et al., 1998]. Astemizole and terfenadine are metabolized by CYP3A4. Thus, in the presence of ketoconazole, troleandomycin, and cyclosporin A, which inhibit CYP3A4, the plasma concentration of unchanged drug increases. In contrast, ebastine undergoes dealkylation and hydroxylation. When other drugs inhibit dealkylation, ebastine can be metabolized by hydroxylation [Matsuda et al., 1994].

In conclusion, in the present study astemizole induced arrhythmias in canine hearts with myocardial infarction, but ebastine did not, suggesting that the latter compound may be used more safely in patients with ischemic heart disease and patients taking other drugs which inhibit CYP3A4, and further in elderly patients, with reduced drug renal clearance, resulting in an increase in plasma drug concentrations.

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