Differential Modulation of Autonomic Activity by Ethmozin and Ethacizin (Analog of Ethmozin) on the Canine Sinus Node and Atrioventricular Junction

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The chronotropic and dromotropic actions of ethmozin and its diethylamine analog ethacizin were studied in the presence and absence of combined muscarinic, beta- and alpha-adrenoreceptor blockade in the intact canine heart in situ (n = 38). Injections of ethacizin, 5, 10 and 25 μg/ml, into the sinus node artery caused an immediate and significant (p < 0.001) sinus bradycardia of 2, 6 and 11%, respectively. Injection of 25 and 50 μg/ml of ethacizin into the atrioventricular (AV) node artery significantly (p < 0.001) prolonged AV conduction time with occasional second degree heart block. Conduction delay was located exclusively during the AH interval of the His bundle electrogram. Autonomic blockade did not alter the negative chronotropic or negative dromotropic effects of ethacizin. Ethacizin, 25 μg/ml, injected into the sinus node artery immediately reduced the sinus node response to vagal stimulations by 30% and the effect of acetylcholine, 0.1 μg/ml, injected into the sinus node artery by 50%. Ethacizin, 25 μg/ml, injected into the AV node artery immediately reduced the duration of complete AV block elicited by vagal stimulation or intranodal acetylcholine, 0.5 μg/ml, by 90%. Ethacizin caused a minor reduction in sinus node response to right stellate stimulations without, however, altering the sinus node response to intranodal norepinephrine. Ethacizin injections of up to 50 μg/ml into the sinus and AV node arteries had no chronotropic or dromotropic effects. Ethmozin had a minor and variable vagolytic action but significantly (p < 0.05) reduced the sinus node response to sympathetic nerve stimulation.

Hence, ethacizin, in contrast to ethmozin, has a direct depressing action on both the sinus node and the AV junction. Ethacizin also has a transient atropinic action together with a minor sympatholytic effect. Ethmozin has virtually no atropinic action but a moderate sympatholytic effect. Neither agent has any significant adrenolytic effect.

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Ethmozin, a phenothiazine derivative originally developed in the Soviet Union (1–3), is an effective, safe and well tolerated antiarrhythmic agent (4–13). The diethylamine analog of ethmozin, ethacizin (Fig. 1), promises to be an even more powerful antiarrhythmic agent because it can influence both the fast and the slow inward currents (14–18).

The importance of neurogenic factors in the development and maintenance of cardiac arrhythmias is well established (19–21), and most if not all currently available antiarrhythmic agents exert important effects on either one or both limbs of the autonomic nervous system. Because many antiarrhythmic drugs have direct cardiac actions that are opposed to autonomically mediated indirect effects on the heart (22,23), we examined the direct and indirect effects of ethmozin and ethacizin on sinus node automaticity and atrioventricular (AV) conduction.

Methods

Experimental preparation. Adult mongrel dogs of either sex, weighing 18 to 23 kg, were anesthetized with intravenous sodium pentobarbital, 30 mg/kg body weight. Ventilation was maintained through a cuffed endotracheal tube with intermittent positive pressure supplying room air. Cen-

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Figure 1. Chemical structure of ethmozin and ethacizin (diethylamine analog [DAA] of ethmozin).

Ethmozin

DAA-Ethmozin (Ethacizin)

Ethanolamine was measured with a catheter placed through the subclavian artery and attached to a transducer. A standard limb lead II electrocardiogram was also routinely recorded. The chest was opened in the fourth right intercostal space, and the sinus node artery or the AV node artery, or both, was isolated and cannulated with one or more small polyethylene catheters. The entire remaining coronary circulation and the normal innervation of the heart were preserved intact. Details of these procedures have been previously reported (24).

Recordings and measurements. Bipolar electrograms were recorded from electrodes sutured on or near the sinus node, and on the right ventricular outflow tract. A His bundle electrogram was obtained with a standard pacing electrode catheter (5F or 6F) (10 mm interpolar distance) advanced into the aortic root as previously described (24). A tachogram was derived from either the atrial or the ventricular electrogram. All measurements of AV conduction were made during continuous pacing (twice threshold) from the left atrial appendage to avert any possible effects of pacing-induced neurotransmitter release. Tracings were recorded at a paper speed of 200 mm/s on an eight channel Hewlett-Packard polygraph (model 7888-A).

Adequacy of sinus node perfusion is routinely determined with a control injection of Ringer’s solution (2 ml) into the sinus node artery. The characteristic response of the sinus node to such a Ringer’s injection is an immediate but transient decrease in sinus rate, with a rapid return to control level. An immediate decrease in sinus rate of at least 20 beats/min was required for inclusion in these studies (25). Injection of drugs that elicit a negative chronotropic action not only prevents or slows the rapid return to control sinus rate, but also often exaggerates the immediate bradycardia induced by the injection.

To assess the accuracy of the response to AV junctional perfusion during sinus rhythm, 2 ml of acetylcholine chloride, 0.5 \( \mu \text{g} \)/ml, prepared in Ringer’s solution was injected into the AV node artery. The preparation can be considered adequate only if acetylcholine produces an immediate and complete AV block for at least 2 seconds.

Stimulation technique. When neural stimulations were performed, both cervical vagosympathetic trunks were exposed through a midline incision. The nerves were isolated and dissected free, leaving their fibrous sheath intact so as to avoid disruption of their blood supply. After fixing a double ligature, both vagi were severed. Both stellate ganglia were isolated and decentralized, thus removing virtually all tonic autonomic activity to the heart. Vagal and stellate stimulations were performed using stainless steel internal wire electrodes (26). Nerve stimulations were performed with a Grass S88 stimulator, a Grass SIU5 isolation unit and a Grass constant current unit. The stimulation frequencies were 8 Hz for the vagus and 4 Hz for the stellate ganglia. The duration of each individual pulse was 2 ms. The efficacy of this stimulation technique was evaluated during preliminary experiments in which changes in sinus rate were consistent and reproducible for at least 3 hours, the maximal duration of each experiment. The sinus node response to right stellate stimulation was studied as follows. Stimulation current (continuous 4 Hz) was steadily increased until further increases caused no further increments in sinus rate. At this point the current used was considered supramaximal. The current (constant current) was then selected to be 80% of the current that had previously elicited the supramaximal sinus rate increase. To study the responses to vagal stimulation, the current was selected in the preceding manner, but at 8 Hz.

Drug administration. Test solutions of ethmozin were prepared daily by diluting 10 mg of the drug in 1 ml distilled water (stock solution). To obtain prompt solution, a pH of 3 to 4 is required (achieved with the addition of small amounts of hydrochloric acid). Final concentrations of 5, 10, 25 and 50 \( \mu \text{g} \)/ml of ethmozin were then prepared by diluting appropriate amounts of the stock solution in Ringer’s solution. The pH of the perfusate with the highest concentration of ethmozin tested in this study was 7.10. Test solutions of ethacizin, 5, 10 and 25 \( \mu \text{g} \)/ml, were also prepared freshly every day. The drug readily dissolves in Ringer’s solution. In contrast to ethmozin, ethacizin does not require acidified distilled water as a primary diluent to prepare the stock solution. Acetylcholine chloride, 0.1 to 5 \( \mu \text{g} \)/ml, and noradrenaline bitartrate, 0.00625 to 0.2 \( \mu \text{g} \)/ml, were also prepared in Ringer’s solution. Muscarinic blockade was achieved with intravenous administration of atropine sulfate, 0.5 mg/kg body weight. Beta-adrenergic and alpha-adrenergic receptor blockade were accomplished by intravenous administration of propranolol hydrochloride, 1 mg/kg, and phentolamine mesylate, 1 mg/kg, respectively.

Statistics. The results are expressed as mean ± 1 SD. Analysis of variance using a randomized complete block over time, dose and dose × time effects were analyzed. At
each time point a comparison among the doses was done using Fisher's least significant difference test (tested at the p < 0.05 level) (27).

Results

Direct chronotropic effect of ethmozin and ethacizin perfused into the sinus node artery. In five dogs with nerves intact and a control sinus rate of 139 ± 18 beats/min, injection of ethmozin, 5, 10, 25 and 50 μg/ml (2 ml), into the sinus node artery had no detectable chronotropic effect. Also, there was no significant chronotropic action when the same amounts and concentrations of ethmozin were administered into the sinus node artery of the same dogs after pretreatment with a combined muscarinic, alpha- and beta-adrenoreceptor blockade.

In a few pilot studies we had observed that small amounts of ethacizin, 5 and 10 μg/ml, injected into the sinus node artery often caused a brief and moderate sinus rate increase and that this tachycardia was absent after administration of atropine. Hence, unless otherwise indicated, all subsequent studies examining the effect of ethacizin were performed in the presence of intravenous muscarinic blockade. In 10 dogs, injection of ethacizin into the sinus node artery had an immediate negative chronotropic action. The maximal injection bradycardia observed after Ringer’s solution and ethacizin occurred at the same time (between 4.1 ± 0.66 and 4.2 ± 0.63 seconds). However the magnitude of this bradycardia was significantly more pronounced after the administration of 5 (p < 0.0188), 10 (p < 0.0001) and 25 μg/ml (p < 0.0001) of ethacizin than after the injection of Ringer’s solution (Fig. 2). The maximal postinjection tachycardia caused by 5 μg/ml of ethacizin was indistinguishable from that seen after administration of Ringer’s solution but it was significantly diminished (p < 0.001) after the administration of 10 and 25 μg/ml of ethacizin (Fig. 2). Also, when compared with Ringer’s control solution, administration of 10 and 25 μg/ml of ethacizin into the sinus node artery had a significant negative chronotropic effect (p < 0.0001) 1, 2, 3 and 4 minutes after injection, and 25 μg/ml was significantly (p < 0.0001) more effective in depressing the sinus node activity than 10 μg/ml. Return to control sinus rate after 25 μg/ml of ethacizin required 19 ± 3 minutes (Fig. 2).

In four dogs ethacizin, 5, 10 and 25 μg/ml, was injected into the sinus node artery after combined muscarinic, alpha- and beta-adrenoreceptor blockade. The responses observed were not significantly different from those observed when ethacizin was administered in the presence of atropine alone. We interpret these observations to mean that ethacizin has a direct depressiv effect on sinus node automaticity.

Effect of ethmozin and ethacizin on the cholinergic control of the sinus node. 1) Parasympathetic nerve. In five dogs injection of 25 μg/ml of ethmozin into the sinus node artery had no effect on the sinus node response to serial vagal stimulation. Injection of 50 μg/ml, however, transiently diminished the extent of the sinus bradycardia in three dogs but had no effect in the remaining two dogs. The vagolytic action of ethmozin was very brief. Its extent did not exceed 7% and it was only detectable within the first minute after injection.

Figure 3 summarizes the time course and the extent of the vagolytic action of three increasing concentrations of ethacizin injected into the sinus node artery of six dogs and...
Figure 3. Summary of the extent and time course of the vagolytic action of three increasing doses of ethacizin administered directly into the sinus node artery. After 5 μg/ml of ethacizin (squares) the control sinus bradycardia achieved by a given vagal stimulation was significantly diminished (maximum of 6%) for a duration of 5 minutes. After 10μg/ml of ethacizin (maximal vagolytic action of 15%), significant differences from control were observed for 8 minutes, and after 25 μg/ml of ethacizin (maximal vagolytic action of 30%), return to control bradycardia required 30 minutes.

Figure 4 is a characteristic example of such an experiment. One minute after injection of ethacizin, 5, 10 and 25 μg/ml, there is a dose-dependent reduction in the amount of vagally mediated sinus bradycardia by 13 (p < 0.002), 29 (p < 0.002) and 63% (p < 0.0001), respectively. Recovery of vagal responses required 7 minutes after injection of 5 μg/ml of ethacizin, 9 minutes after injection of 10 μg/ml and 30 minutes after injection of 25 μg/ml.

2) Direct administration of acetylcholine. In five dogs 0.01, 0.05 and 0.1 μg/ml of acetylcholine injected into the sinus node artery caused an average bradycardia that was 9 ± 3, 15 ± 5 and 35 ± 10%, respectively, greater than that induced by the control injection of Ringer's solution. Intranaoral ethmozin of up to 25 μg/ml had no significant effect on the negative chronotropic action of acetylcholine. In two dogs injection of 50 μg/ml of ethmozin reduced the effect of 0.1 μg/ml of acetylcholine by half; in the remaining three dogs it had no significant effect.

Injection of ethacizin, 10 and 25 μg/ml, into the sinus node artery (n = 6) reduced the negative chronotropic action of acetylcholine injected into the sinus node artery. Doses of 10 μg/ml of ethacizin abolished the responses to 0.01 of acetylcholine and diminished the responses to 0.05 and 0.1 μg/ml of acetylcholine by 60 and 40%, respectively. Doses of 25 μg/ml of ethacizin abolished the responses to both 0.01 and 0.05 μg/ml of acetylcholine and reduced the responses to 0.1 μg/ml of acetylcholine by 50%. In four of these six dogs ethacizin, 25 μg/ml, prevented the transient pause and the brief episodes of atrial fibrillation that are elicited by the administration of 1 μg/ml into the sinus node artery.

Effect of ethmozin and ethacizin on the adrenergic control of the sinus node. 1) Sympathetic nerve stimulation. In five dogs right stellate stimulations were performed before and after injections of 10, 25 and 50 μg/ml of ethmozin into the sinus node artery (Fig. 5). Increasing doses of ethmozin had a dose-dependent, transient sympatholytic action. The decrease in sinus node response to stellate stimulation was modest but significant 1 minute after injection of 10 μg/ml of ethmozin. After 25 and 50 μg/ml, maximal sympatholytic action, averaging 11 ± 4 and 14 ± 5%, respectively, was observed 1 minute after injection. Recovery was rapid and complete because the responses to the stellate stimulation were not significantly different from control 7 minutes after the injection of ethmozin.

In five other dogs right stellate stimulation was performed before and after injection of 10 and 25 μg/ml of ethacizin into the sinus node artery (Fig. 6). Injection of 10 μg/ml of ethacizin had no significant effect on the sinus node response to stellate stimulation whereas injection of 25 μg/ml caused a modest, transient but significant reduction in sinus node response to sympathetic stimulations.

b) Direct administration of norepinephrine. In five dogs 0.0125, 0.025, 0.05 and 0.1 μg/ml of norepinephrine was administered into the sinus node artery before and after
ethmozin, 5, 10, 25 and 50 μg/ml, respectively. In none of these experiments did the phenothiazine derivative alter the sinus node response to norepinephrine. In six other dogs the same amounts and concentrations of norepinephrine were injected into the sinus node artery before and after ethacizin, 5, 10 and 25 μg/ml. In none of these experiments did ethacizin have any influence on the magnitude of the sinus node response to catecholamine administration.

Taken together these results indicate that both phenothiazine derivatives (but ethmozin more than ethacizin) have a minor transient sympatholytic effect that is neuronally mediated and that neither phenothiazine derivative interferes with the stimulatory actions mediated by beta-adrenoreceptors.

Direct dromotropic effect of ethmozin and ethacizin directly perfused into the AV node artery. In six dogs with nerves intact and a control sinus rate of 140 ± 17 beats/min, continuous pacing from the left atrial appendage was instituted at a frequency selected to be 15% above the control sinus rate at rest. Injection of ethmozin, 5, 10 and 25 μg/ml, into the AV node artery had no dromotropic effect. Administration of 50 μg/ml also had no detectable action on AV conduction in four dogs, but in two dogs it caused a minor transient prolongation of the PR interval of 5 and 10 ms, respectively, with a return to control status within 3 minutes. The slowing of AV conduction was entirely due to a prolongation of the AH interval of the His bundle electrogram.

In four dogs the same amounts and concentrations of ethmozin were administered into the AV node artery after complete autonomic blockade. The results of these experiments were indistinguishable from those obtained before

Figure 5. Summary of the extent and time course of the sympatholytic action of ethmozin (10, 25 and 50 μg/ml) injected into the sinus node artery. At each concentration there was a significant decrease in sinus node response to right stellate stimulation. The effect was transient and dose-dependent and full recovery was observed in each of the five dogs used in this study.

Figure 6. Ethacizin, 10 μg/ml, did not diminish the sinus node response to right stellate stimulation; however, injection of 25 μg/ml did cause a transient, significant reduction of sinus node response to sympathetic stimulation.
the autonomic blockade, indicating that ethmozin has little or no direct negative dromotropic effect on the AV node region.

In 10 dogs injections of ethacizin, 5 and 10 µg/ml, into the AV node artery had no effect on AV conduction. Injection of the next higher concentration, 25 µg/ml, caused a small but significant prolongation (p < 0.001) of the PR interval in 6 of these 10 dogs. In the His bundle electrogram the prolongation of AV conduction time always occurred during the AH interval (from a control of 57 ± 10 to 72 ± 11 ms). The HV interval remained constant throughout each experiment (30 ± 5 ms). In 8 of these 10 dogs injections of 50 µg/ml of ethacizin into the AV node artery caused a rapidly progressing but transient prolongation of the AH interval (from 56 ± 9 to 112 ± 16 ms). Peak effect was observed within 2 minutes and return to control level occurred within 18 ± 3 minutes. In the two remaining dogs a brief period of second degree AV block developed within 1 minute from onset of injection (2:1 and 3:2 Wenckebach periodicity) with return to 1:1 conduction and first degree AV block within the next minute. Full recovery of AV conduction, however, required 18 and 25 minutes, respectively.

In six dogs injection of ethacizin, 5 and 10 µg/ml, into the AV node artery after complete autonomic blockade had no significant effect on AV node conduction. Injection of 25 µg/ml of ethacizin caused a minor prolongation of the AH interval from 60 ± 9 to 75 ± 7 ms. Injection of 50 µg/ml of ethacizin resulted in a transient second degree AV block in two dogs and prolonged the AH interval from 59 ± 11 to 124 ± 14 ms in the four remaining dogs. These experiments demonstrate that ethacizin exerts a negative dromotropic effect and that this effect is independent of either cholinergic or adrenergic influences. Furthermore we can also conclude that, in contrast to ethmozin, ethacizin has a direct negative dromotropic effect on the AV node.

Effect of ethmozin and ethacizin on the cholinergic control of the AV junction. 1) Parasympathetic nerve. Assessment of changes in AV conduction was performed during continuous left atrial pacing at a frequency 15% above the control sinus rate. Under these conditions submaximal left vagal stimulation regularly causes second or third degree AV block. In four dogs, left vagal stimulation was performed before and after administration of 25 µg/ml of ethmozin into the AV node artery without altering the extent or duration of the AV block. Intranaal ethmozin, 50 µg/ml, however, reduced the extent of AV block in response to the same vagal stimulation by transiently converting episodes of third degree AV block into episodes of second degree AV block in two dogs, while in the two remaining dogs it had no detectable effect on the vagally mediated AV block.

In five dogs vagal nerve stimulations were performed before and after intranodal ethacizin, 25 µg/ml. In each dog ethacizin immediately abolished the vagally mediated AV block and return to preinjection (ethacizin) AV block required at least 30 minutes.

2) Direct administration of acetylcholine. Figure 7 summarizes the results obtained in five dogs and Figure 8 shows a characteristic experiment in which serial AV block (produced by the injection of acetylcholine into the AV node artery) was examined before and after intranodal administration of ethacizin, 25 µg/ml. Injection of acetylcholine, 0.5 µg/ml, into the AV node artery causes an immediate complete AV block followed by a brief period of second degree and then first degree block before the return of control AV conduction. The total number of blocked beats when the atrium is paced at a rate 15% above control sinus rate can vary between 8 and 30 beats, but in each dog the duration of AV block is remarkably reproducible and virtually constant. The maximal number of blocked beats (obtained from the average of at least three injections) was considered to be the 100% response to acetylcholine. As illustrated in Figures 7 and 8, ethacizin, 25 µg/ml, immediately reduced the extent of AV block by some 90%. The figures also show that restoration of the negative dromotropic action of acetylcholine requires 30 minutes.

Effect of ethmozin and ethacizin on the adrenergic control of the AV junction. 1) Sympathetic nerve. During left atrial pacing at 15% above control sinus rate, submaximal (50% of the supramaximal current) left stellate stimulation abbreviates the duration of the AH interval (45 ± 10%). When supramaximal stimulations are applied (4 Hz, constant current), AV junctional tachycardia usually ensues (junctional rate exceeds pacing rate). In five dogs, sub-
maximal left stellate stimulation was performed before and after intranodal ethmozin, 25 µg/ml. This intervention resulted in a 14 ± 5% prolongation of the AH interval. After administration of 50 µg/ml of ethmozin, the response to left stellate stimulation was further diminished because the AH interval was lengthened by 21 ± 4%. These responses to left stellate stimulation after ethmozin are virtually identical to the decrease in sinus node response to right stellate stimulation after administration of the same volumes and concentrations of ethmozin into the sinus node artery.

Ethacizin, 25 µg/ml, injected into the AV node artery had no effect on the abbreviation of the AV conduction time caused by left stellate stimulation in four of the five dogs in which this experiment was performed. In the remaining dog, ethacizin prevented the AH interval shortening due to left stellate stimulation. Injection of 50 µg/ml of ethacizin reduced the positive dromotropic effect of left stellate stimulation by 9 ± 3% (p < 0.05).

2) Direct administration of norepinephrine. In 4 dogs 0.0125 and 0.025 µg/ml of norepinephrine was injected into the AV node artery before and after ethmozin, 25 and 50 µg/ml. Norepinephrine, 0.0125 and 0.025 µg/ml, reduced the AH interval by 14 ± 5 and 29 ± 7%, respectively, and neither concentration of ethmozin had any significant action on these effects of norepinephrine. In the same four dogs the same volumes and concentrations of norepinephrine were given into the AV node artery before and after ethacizin, 25 and 50 µg/ml. These concentrations of ethacizin also had no effect on the abbreviations of AV conduction time caused by intranodal norepinephrine.

Figure 8. The powerful atropinic action of intranodal ethacizin. A shows that the control AV block in response to acetylcholine (ACh), 0.5 µg/ml, injected into the AV node artery (AVNA) is completely abolished 1 minute after ethacizin, 25 µg/ml (2 ml), injected through the same route. After 2 minutes acetylcholine caused a single blocked atrial beat. B and C. Time course of recovery of the effect of acetylcholine on the AV node after the ethacizin (ETZ) injection. Ao = aortic pressure.
Discussion

Effects of ethmozin. Since its introduction in clinical practice in the Soviet Union about 10 years ago (4–6, 9), ethmozin has also been used in patients in the United States (7,8,11,12). Initial electrophysiologic studies demonstrated that ethmozin causes minor prolongation of ventricular refractory period and that it increases ventricular diastolic excitability threshold (28). Ethmozin diminishes reflex sympathetic activity to the heart (29). It markedly slows conduction in the ischemic myocardium (28), and in voltage clamp studies it was shown to have a powerful depressant effect on the rapid inward sodium current (15). In several recent studies (9,11–14,17) ethmozin has proved very effective in the prevention and therapy of both supraventricular and ventricular arrhythmias. Also, in most patients with the Wolff-Parkinson-White syndrome, ethmozin successfully terminated induced supraventricular tachycardias and prevented the induction of sustained supraventricular tachycardias by depressing conduction in the accessory pathway (13,17).

Effects of ethmozin on sinus and AV nodes. When injected directly into either the sinus node artery or the AV node artery, ethmozin, in concentrations up to 50 μg/ml, had virtually no detectable chronotropic or dromotropic effects. After appropriate muscarinic, beta- and alpha-adrenoreceptor blockade the sinus node and AV junctional responses were indistinguishable from those observed before cholinergic and adrenergic blockade. These observations indicate that ethmozin has no direct stimulatory or depressant action on the sinus node and AV node. These results are in accord with a previous report (28) in which the compound had also been administered intranodally. We agree with the interpretation that the slight prolongation in the PR interval observed by others (30) was probably due to an effect of the drug on non-nodal tissue. At the highest concentration studied, ethmozin had a minor peripheral atropinic activity. Furthermore, it significantly diminished the sinus node and AV junctional responses to stellate stimulation. Because neither the chronotropic responses of the sinus node nor the dromotropic responses of the AV junction to directly administered norepinephrine were influenced by intranodal ethmozin, we also conclude that ethmozin exerts some direct peripheral presynaptic sympathetic neuronal blocking action.

Effects of ethacizin. Like ethmozin, its diethyamine analog ethacizin depresses the fast inward sodium current (15). However, in contrast to ethmozin, ethacizin also depresses the slow inward current (15). In Purkinje fiber preparations ethacizin exerts its most prominent effect on the rate of increase of the action potential front (15) and it appears that the sensitivity of the fast sodium channel to ethacizin is an order of magnitude greater than its sensitivity to equimolar concentrations of ethmozin (15). Based on observations obtained in humans (17), and in dogs with experimental myocardial infarction (18), ethacizin was found to have a much longer duration of action than ethmozin and was considerably more powerful than ethmozin in preventing and suppressing supraventricular and ventricular tachycardias.

Effects of ethacizin on sinus and AV nodes. On selective injection into the sinus and AV node arteries, ethacizin produced an immediate negative chronotropic and dromotropic effect. These effects were equally demonstrable in the presence of cholinergic and adrenergic blockade, indicating that ethacizin has a direct negative chronotropic and dromotropic action. Ethacizin interferes with the slow inward current (15), so it is likely that these depressing actions on sinus node automaticity and AV conduction are mainly mediated through a decreased activity of the “slow current-dependent cells” of the sinus node and AV node. Like ethmozin, ethacizin did not alter the sinus node or the AV junctional responses to directly administered catecholamines, indicating that neither phenothiazine significantly interfered with the recruitment of receptor operated channels. In contrast to ethozin, however, ethacizin had an immediate, powerful and lasting peripheral atropinic action and it appears that the transient removal of vagal restraint could largely minimize the direct negative chronotropic and dromotropic actions of ethacizin. Because ethacizin in doses that consistently abolished ectopic ventricular activity in the late stage of experimental myocardial infarction had little or no net negative inotropic action (18), we can further conclude that because of and in spite of its multiple modes of action, ethacizin is a remarkably safe antiarrhythmic compound.

References

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