DRUG DEVELOPMENT RESEARCH 35:102–115 (1995)

Research Article

Canine Plasma Concentration-Cardiovascular Effect Relationships for Bidisomide, a New Antiarrhythmic Drug, and Disopyramide, Cibenzoline, and Propafenone

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Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Bidisomide (SC-40230) is a unique new antiarrhythmic agent. In this study the canine intravenous (i.v.) antiarrhythmic doses of bidisomide (9 ± 1 mg/kg), disopyramide (8 ± 1 mg/kg), cibenzoline (8 ± 2 mg/kg), and propafenone (6 ± 0.5 mg/kg) were established in a 24 h coronary ligation ventricular arrhythmia model. Based on the canine therapeutic doses of the four agents, three cumulative i.v. doses (load/maintenance infusions) of each of these drugs and placebo were then studied in normal anesthetized dogs to evaluate their general cardiovascular effects. Propafenone (0.7–3.0 μg/ml plasma concentration) caused potent reductions in cardiac output and increases in QRS duration relative to the other agents. Cibenzoline (0.9–7.0 μg/ml) and disopyramide (1.4–12.9 μg/ml), at matched plasma concentrations, caused very similar cardiac output reductions, but cibenzoline caused nearly double the QRS increase. Bidisomide (1.9–16.1 μg/ml) had the least potent effects on cardiac output and QRS duration. All four drugs increased PR and QT in addition to QRS, but only disopyramide and propafenone increased JT (QT-QRS). These experiments suggest that the antiarrhythmic plasma concentrations of bidisomide, in contrast to those of selected reference agents, do not cause prominent ventricular conduction slowing or prolongation of ventricular repolarization, and in addition, cause only modest hemodynamic effects in normal dogs. © 1995 Wiley-Liss, Inc.

Key Words: arrhythmia, cardiac output, dogs, electrocardiogram, coronary ligation

INTRODUCTION

Bidisomide is a unique new antiarrhythmic agent that causes substantial increases in atrial refractory period at doses or concentrations that cause only modest changes in electrocardiographic (ECG) intervals [Garthwaite et al., 1992, 1994]. Because of its profile, bidisomide seems well suited for treatment of supraventricular arrhythmias and is being clinically evaluated for prevention of paroxysmal supraventricular tachycardia (PSVT) and atrial fibrillation. However, bidisomide has been shown to be efficacious for ventricular in addition to supraventricular arrhythmias [Garthwaite et al., 1989b,c, 1994; Spinelli and Hoffman, 1989; Schmidt et al., 1992; Roy et al., 1992; Moreno et al., 1992; Zhenjiu et al., 1993; Frederick et al., 1993]. Because of its structural similarity to disopyramide (Fig. 1), a potent negative inotrope, the potential for bidisomide to cause undesirable hemo-

Received January 23, 1995; final version accepted March 12, 1995.

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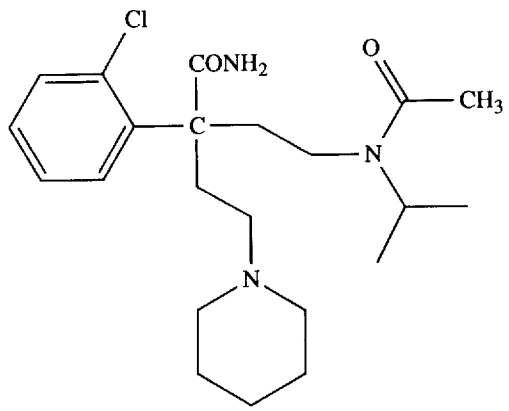

Figure 1. Bidisomide (SC-40230) is α-[2-[acetyl(1-methylethyl)-amino]ethyl]-α-(2-chlorophenyl)-1-piperidinebutanamide. It differs from disopyramide in the replacement of a 2-pyridyl function by the 1-piperidyl-ethyl function, the replacement of an isopropyl group by an acetyl group, and the substitution of chlorine for hydrogen in the ortho position of the phenyl group. The molecular weight of bidisomide is 408.

dynamic effects has been investigated with different types of dosing regimens in both normal and myocardial infarcted dogs [Frederick et al., 1989; Garthwaite et al., 1989c, 1992; Schmidt et al., 1992; Hackett et al., 1993; Zhenjiu et al., 1993] and also in early clinical studies [DeWitt et al., 1991; Moreno et al., 1992; Page et al., 1992; Roy et al., 1992]. In a previous canine study [Frederick et al., 1989], we have shown bidisomide to have only minor hemodynamic effects at its canine antiarrhythmic dose. For interpretation of those experiments, we relied upon previous experience with other drugs in the same model [Frederick et al., 1988], as the previous study of bidisomide did not include a direct and contemporary comparison with other antiarrhythmic agents or measurement of plasma concentrations of bidisomide.

In this study, we have directly compared the effect of bidisomide on cardiac output and ECG intervals with those of propafenone, cibenzoline, and disopyramide, antiarrhythmic agents that have all been shown to cause clinically important hemodynamic and ECG (especially ventricular conduction slowing) effects [Podrid et al., 1980; Baker et al., 1982; Block and Winkle, 1983; Ferro et al., 1983; Dangman and Miura, 1986]. We first determined the canine antiarrhythmic dose for these agents in the Harris [1950] dog model to ensure that our model, in which the canine dose of bidisomide was originally established [Garthwaite et al., 1989b], would also confirm the doses of the other agents as reported in the literature. Based on the canine therapeutic doses of the four test agents, three cumulative doses of each agent were infused using a load/maintenance protocol, as opposed to the constant rate infusion methods we previously used [Frederick et al., 1989] to study bidisomide. The load/maintenance protocol was designed to achieve periods of relatively constant plasma concentrations during which the cardiovascular parameters were measured. The importance of plasma concentration monitoring of antiarrhythmic drugs [Kates, 1981], particularly in the examination for adverse cardiovascular effects [Libersa et al., 1992], has been emphasized. We therefore included assays of the plasma concentrations of each of the agents in the design of the cardiac output experiments and used the results as an aid to interpreting the cardiovascular responses to the agents.

MATERIALS AND METHODS

All experiments were conducted according to recommended principles [National Institutes of Health, 1985] and Searle's institutional guidelines. Dogs were obtained from Bar-Wan (Crocker, MO) and Hazleton (Cumberland, VA).

Canine Antiarrhythmic Dose Experiments

The canine antiarrhythmic doses of bidisomide, disopyramide, cibenzoline, and propafenone were assessed using the Harris [1950] dog model. The methods and criteria for efficacy have been described previously [Garthwaite et al., 1989a,b] and are summarized briefly. Approximately 24 h before the antiarrhythmic drugs were given, the dogs were anesthetized with sodium pentobarbital (32.5 mg/kg i.v.) and then a two-stage ligation of their left anterior descending coronary arteries was performed. The dogs were allowed to recover for 18–24 h with appropriate postsurgical care. Antiarrhythmia testing was done with conscious dogs monitored (Gould Instruments, Cleveland, OH) continuously with a lead II ECG. Each dog received only one test drug and was utilized only once. Bidisomide, disopyramide, and cibenzoline were all administered as a 5 mg/kg i.v. dose (given as 1 mg/kg/min), followed by a second 5 mg/kg dose, depending on the result of the first dose. If the first 5 mg/kg of one of these drugs reduced the ventricular ectopic rate by ≥25% for a minimum duration of 10 min, no more drug was given. If the first 5 mg/kg dose did not reduce the ectopic rate according to these criteria, the second 5 mg/kg dose was given 15 min after the first one. Because literature reports [Karagueuzian et al., 1982; Philipsborn et al., 1984] indicated that repeated 5 mg/kg dose increments might be inappropriately large for propafenone, it was administered in 1 mg/kg/min i.v. doses up to a total of 7

mg/kg until a ≥25% reduction of the ectopic rate occurred and was sustained for at least 10 min. For each drug, the mean total i.v. dose required for an ectopic rate reduction of ≥25% for a minimum of 10 min was considered to be the canine antiarrhythmic dose.

Cardiac Output (CO) Experiments

Dogs were anesthetized with a combination of sodium pentobarbital (15 mg/kg) and barbital sodium (300 mg/kg) given i.v. They were intubated and mechanically ventilated with room air. A lead II ECG was continuously recorded (Gould Instruments) for measurements of heart rate (HR) and ECG intervals (PR, QRS, QT). Mean arterial pressure (MAP) was recorded via a catheter in a femoral artery. A femoral vein was cannulated for the administration of test agents. Blood samples were withdrawn via a cannula in the femoral artery contralateral to the treatment administration site. Body temperature was continuously monitored and maintained at 37–38°C using a heating pad.

For CO measurements, a balloon-tipped, heparin-coated thermodilution catheter was positioned in the pulmonary artery via the right jugular vein and connected to a commercially available computerized CO system (Com-2P-115, Baxter Edwards, Irvine, CA). The standard thermodilution technique [Forrester et al., 1972] was used for determining CO. A 5 ml bolus of ice-cold normal saline (0.9% NaCl) was rapidly injected into the right atrium via the proximal lumen of the catheter. The subsequent change in pulmonary artery blood temperature was detected via a thermistor at the catheter tip. CO was calculated by the computerized system based on the area under the temperature-time curve, the amount of saline injected, and the Stewart-Hamilton indicator dilution equation [Forrester et al., 1972]. For pretreatment control and for each dose within the dose-response curve (see below), three CO measurements 1 min apart were averaged to obtain the reported value for that experiment step.

Total peripheral resistance (TPR) was calculated from the measured values for MAP and CO based on the following relationship [Dustan, 1982]:

$$MAP = CO \times TPR.$$

Stroke volume (SV) was calculated from the measured values for HR and CO based on the following relationship [Grover et al., 1982]:

$$CO = HR \times SV.$$

After a period of stabilization, the pretreatment control measurements were made. Each dog then received three different and cumulative doses of one test agent (or an equivalent volume of saline). Bidisomide (Searle, Skokie, IL), disopyramide (Searle), and cibenzoline (Hoffman-LaRoche, Nutley, NJ) were administered i.v. as loading doses followed by maintenance infusions according to the protocol below:

Low Dose
Loading dose = 0.35 mg/kg/min for 1 min
Maintenance infusion = 0.065 mg/kg/min
Medium Dose
Loading dose = 2.25 mg/kg/min for 1 min
Maintenance infusion = 0.30 mg/kg/min
High Dose
Loading dose = 0.5 mg/kg/min for 10 min
Maintenance infusion = 0.26 mg/kg/min

For reference, the high dose loading infusion (0.5 mg/kg/min) would be equivalent to 1.23 μMol/kg/min (bidisomide), 1.47 μMol/kg/min (disopyramide free base), or 1.91 μMol/kg/min (cibenzoline).

Propafenone (Knoll, Whippany, NJ), which had the lowest canine antiarrhythmic dose (see Results), was given as follows:

Low Dose
Loading dose = 0.27 mg/kg/min for 1 min
Maintenance infusion = 0.051 mg/kg/min
Medium Dose
Loading dose = 1.75 mg/kg/min for 1 min
Maintenance infusion = 0.23 mg/kg/min
High Dose
Loading dose = 0.39 mg/kg/min for 10 min
Maintenance infusion = 0.20 mg/kg/min

For reference, the high dose loading infusion (0.39 mg/kg/min) of propafenone would be equivalent to 1.46 μMol/kg/min.

All experimental measurements were begun 10 min after each maintenance infusion had been initiated. Every attempt was made to complete the measurements within the same length of time each time they were done, thus keeping the length of the maintenance infusions virtually the same from dose to dose and from dog to dog. The maintenance infusions were stopped upon completion of experimental measurements. A 10 min "washout" period followed the low and medium dose maintenance infusions, and a 20 min "washout" period followed the high dose maintenance infusion. HR, MAP, and plasma concentrations of the test agents were also measured at the 10 and 20 min time points during the final washout.

Blood samples (3–5 ml) for analysis of test agent plasma concentrations were taken before and after

TABLE 1. Antiarrhythmic Activity of Bidisomide, Disopyramide, Cibenzoline, and Propafenone in Dogs With Coronary Ligation-Induced Arrhythmias

Drug	Initial total HR (beats/min)	Initial ectopic rate (beats/min)	Average duration of activity (min)[a]	Maximum % reduction of ectopic rate (%)	Average effective dose (mg/kg i.v.)	No. of dogs
Bidisomide	202 ± 17	198 ± 19	21 ± 4	89 ± 7	9 ± 1	5
Disopyramide	172 ± 15	169 ± 15	15 ± 2	87 ± 10	8 ± 1	6
Cibenzoline	185 ± 18	185 ± 18	19 ± 6	92 ± 5	8 ± 2	3[b]
Propafenone	169 ± 15	160 ± 15	19 ± 4	98 ± 2	6 ± 0.5	5

[a]Average time from onset of ≥25% reduction of ectopic rate (sustained for at least 10 min) to the first period of inactivity, i.e., <25% reduction of ectopic rate.
[b]N = 3 for cibenzoline due to limited compound supplies.

each loading dose and before and after the series of CO measurements at each dose level and during the washout periods described above. Blood was withdrawn into cold 5 ml heparinized vacutainer tubes. Samples were kept in ice, transferred to a cold centrifuge, and spun for 8 min at 2,300*g*. Plasma was kept in ice until frozen. Analyses of test agents in plasma were performed by Searle's Department of Pharmacokinetics, Bioanalytical, and Radiochemistry using standardized assays.

Test agent infusates were prepared fresh daily. Compounds were dissolved in distilled water by slight warming or addition of HCl and adjusted to neutral pH with NaOH as necessary. Solutions were brought to volume with saline.

Statistical Analyses

In the canine arrhythmia experiments, the drugs were infused to achieve preestablished endpoints and to confirm previously reported effective doses. Therefore, it was not considered appropriate to subject these data to statistical analysis.

Data from the CO experiments were analyzed using a repeated measures analysis of variance, followed by contrast t-tests to compare pretreatment control values with the low, medium, and high dose values of the parameters measured. Group (drug or placebo) by dose interaction effect (instead of main effects) was tested because dose effects in the drug-treated groups were adjusted for placebo effects. The Greenhouse-Geisser adjustment for degrees of freedom was used. $P < 0.05$ was considered to be statistically significant.

RESULTS

Canine Antiarrhythmic Dose

The results of confirming the canine antiarrhythmic doses of bidisomide, disopyramide, cibenzoline, and propafenone are summarized in Table 1. The pretreatment ectopic rate averaged 95–100% of the total HR in all four treatment groups, thus the dominant cardiac rhythm in the pretreatment phase was ventricular tachycardia. The maximum percent reduction in the ectopic rate was ≥87% following all four drugs, thus the dominant cardiac rhythm (for at least a few minutes) in the posttreatment phase was normal sinus rhythm. Each of the drugs tested reduced the ectopic rate by at least 25% for ≥15 min.

The i.v. canine antiarrhythmic dose of bidisomide, disopyramide, or cibenzoline was 8–9 mg/kg. The canine antiarrhythmic dose of propafenone was somewhat lower, i.e., 6 mg/kg i.v. or about 67–75% the dose of the other drugs tested. We have previously demonstrated that placebo treatments had no effect on ventricular ectopy in this model [Garthwaite et al., 1989a,b]. All of the drugs were well tolerated (except for minor emesis) by the conscious dogs with myocaridal infarctions.

Dose Administered (CO)

During the treatment phase of the CO experiments, the cumulative doses (mg/kg) of bidisomide, disopyramide, and cibenzoline administered were 1.4 (low dose), 8.4 (low + medium doses), and 17.6 (low + medium + high doses). The cumulative doses (mg/kg) of propafenone administered were 1.1 (low dose), 4.2 (low + medium doses), and 11.3 (low + medium + high doses). For each agent, therefore, the total cumulative dose administered was roughly double the canine effective antiarrhythmic dose, i.e., was a supratherapeutic dose. The low doses for all agents were well below the doses needed for antiarrhythmic activity in the Harris [1950] dog model, i.e., were subtherapeutic. The medium doses were in the approximate canine therapeutic range for each agent, including propafenone (see Discussion), based on the above results (Table 1) and/or similar experiments reported in the literature [Karagueuzian et al., 1982; Hinsch et al., 1983; Dangman, 1984; Philipsborn et al., 1984; Hashimoto et al., 1987; Frederick et al., 1988; Garthwaite et al., 1989b].

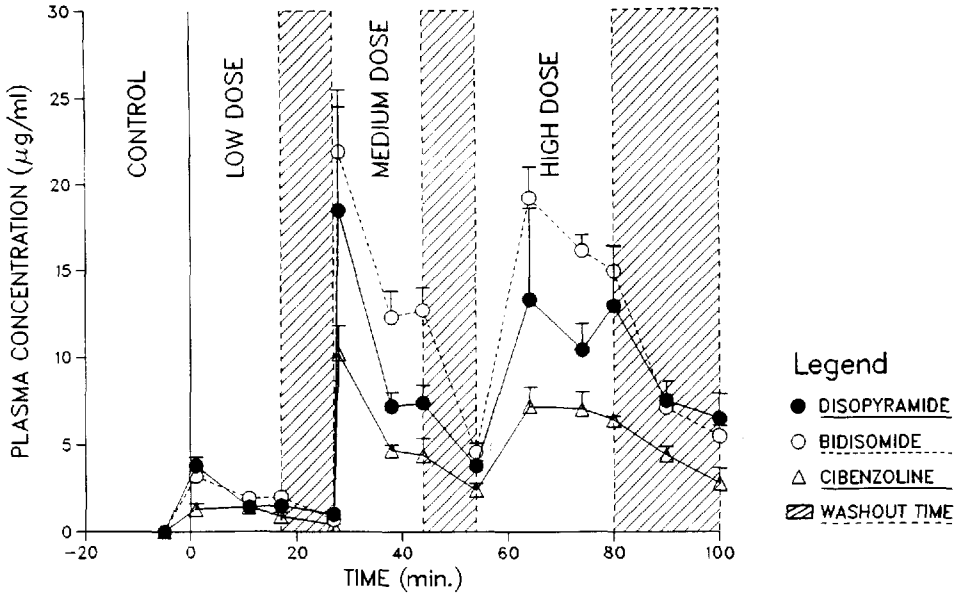

Figure 2. The plasma concentrations (mean ± s.e.m., μg/ml) of disopyramide, bidisomide, and cibenzoline achieved during infusion of three cumulative doses of each drug. At each dose level, a loading dose was followed by a maintenance infusion. Cardiovascular parameters were measured during the several minutes of maintenance infusion preceding each washout period (hatched areas). Note the low concentrations of cibenzoline achieved relative to disopyramide and especially to bidisomide. N = 5 for disopyramide, bidisomide; N = 4 for cibenzoline.

Plasma Concentrations

The plasma concentration-time graphs for each test agent are shown in Figures 2 and 3. Despite the similarities in dosing regimens and total doses for bidisomide, disopyramide, and cibenzoline, there were differences in the plasma concentrations achieved. The medium and high dose plasma concentrations of cibenzoline were low, whereas those of bidisomide were high relative to the disopyramide concentrations achieved. Based on the data shown in Figure 2, the loading dose for cibenzoline was insufficient to achieve the peak plasma concentrations achieved with the other agents. The concentrations of propafenone achieved were lower than those for the other drugs, as was expected based on the different dosing regimen used. The CO, blood pressure, and ECG measurements which were taken during the low doses were done when the plasma concentrations (μg/ml) were 1.9–2.0 (bidisomide), 1.4–1.5 (disopyramide), 0.9–1.4 (cibenzoline), and 0.7–0.8 (propafenone). During medium dose measurements the plasma concentrations (μg/ml) were 12.3–12.7 (bidisomide), 7.2–7.4 (disopyramide), 4.4–4.7 (cibenzoline), and 1.9–2.4 (propafenone). During high dose measurements the plasma concentrations (μg/ml) were 14.9–16.1 (bidisomide), 10.4–12.9 (disopyramide), 6.4–7.0 (cibenzoline), and 2.2–3.0 (propafenone). For each test agent and each dose level, therefore, the plasma concentrations were held relatively constant during the time the cardiovascular parameters were measured. For propafenone, in contrast to the other test agents, the dose-concentration relationship was "flatter." The washout periods between doses and at the end of the last infusion resulted in declines in plasma concentrations for all four agents. The declines in concentration did not necessarily result in a reduced effect on HR or MAP, however (see below).

CO

The placebo treatment (not shown) had no statistically significant effect on CO (2.97 ± 0.35 l/min) of that group. The percent decrease in CO vs. plasma concentration is illustrated for each agent in Figures 4–6. For each agent, a dose- and concentration-dependent reduction of CO was observed. The data indicate that propafenone had a relatively "steep" plasma concentration-response relationship for CO reduction (Fig. 4); i.e., small increases (1–2 μg/ml) in the plasma concentration of propafenone resulted in very substantial, nonproportional increments (4–8×) in CO reduction. Propafenone plasma concentrations ≥1.9 μg/ml caused a statistically significant decrease in CO from the pretreatment value of 3.81 ± 0.32 l/min in this group.

At the opposite end of the spectrum of potency was bidisomide (Fig. 5), for which a 6× increase in

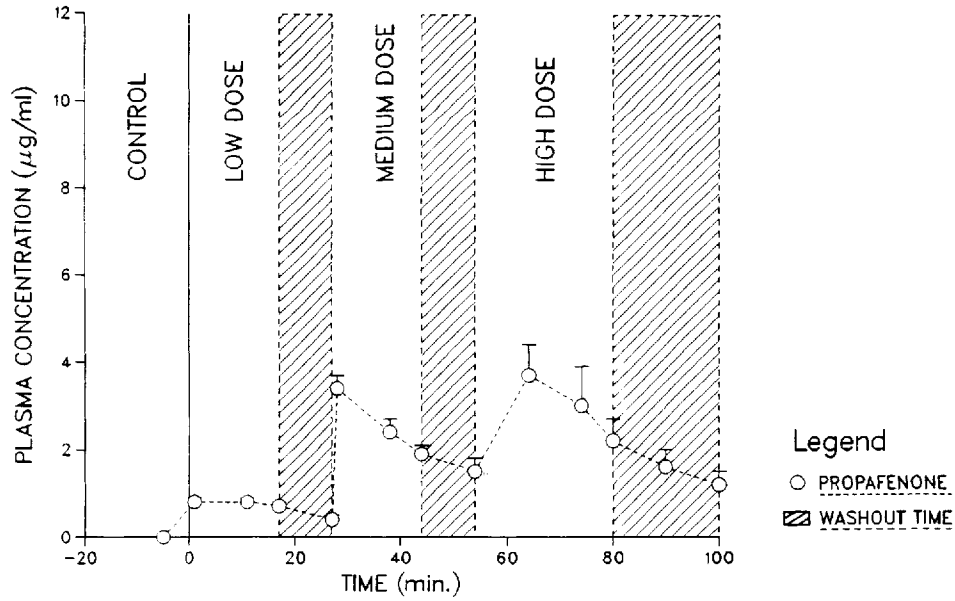

Figure 3. The plasma concentrations (mean ± s.e.m., μg/ml) of propafenone achieved during infusion of three cumulative doses. At each dose level, a loading dose was followed by a maintenance infusion. The cardiovascular effects of propafenone were assessed during the maintenance infusions preceding each washout period (hatched areas). N = 5.

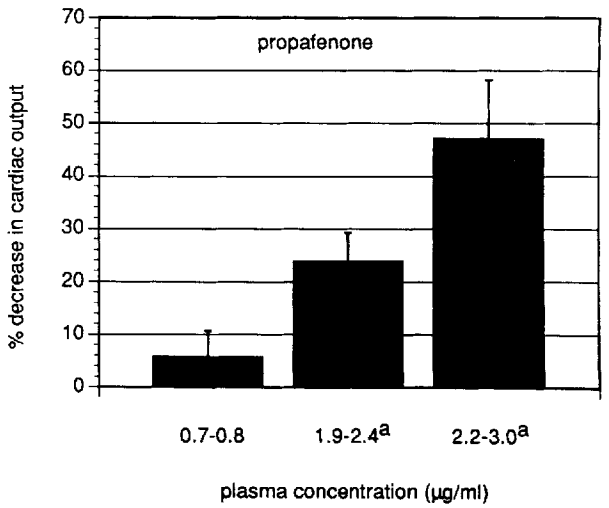

Figure 4. Propafenone caused a concentration-dependent decrease in CO. The 24% reduction in CO at a plasma concentration of 1.9–2.4 μg/ml was statistically significant, as was the 47% decrease at the 2.2–3.0 μg/ml concentration. Based on the large decrease in CO within a relatively narrow plasma concentration range, the effects of propafenone on this parameter were potent relative to the other agents. $^{a}P < 0.05$; n = 5.

plasma concentration (from 2 to 12 μg/ml) caused the percent decrease in CO to change less substantially from −4.6 to −19%. When the bidisomide plasma concentration increased to about 15–16 μg/ml (8× the low dose concentration), however, the incremental change in CO was more pronounced (7× the low dose effect). Bidisomide plasma concentrations ≥12.3 μg/ml were required to cause a statistically significant reduction in CO from the control value of 3.17 ± 0.35 l/min for this group.

Disopyramide's concentration-response relationship for CO (Fig. 6) was less steep than that of propafenone, but not nearly so flat as that of bidisomide. A change in disopyramide plasma concentration from 7 to approximately 12 μg/ml caused the percent decrease in CO to change from −18 to −37%. At a comparable plasma concentration of 12 μg/ml, the effect of bidisomide on CO was only half that of disopyramide. The reduction from these dogs' control output of 2.61 ± 0.24 l/min was statistically significant when the disopyramide plasma concentration was ≥7.2 μg/ml.

Concentrations of cibenzoline higher than 6–7 μg/ml were not achieved (Fig. 2). Cibenzoline, like disopyramide (Fig. 6) had a concentration-response relationship for CO intermediate to those of propafenone and bidisomide. Cibenzoline, at plasma concentrations of about 7 μg/ml, reduced CO about 20%. Cibenzoline plasma concentrations ≥6.4 μg/ml caused a statistically significant reduction in CO from the control value of 2.60 ± 0.12 l/min for this group.

Based on Figures 4–6 and on estimates from log concentration-response curves (not shown), the concentrations (μg/ml) of these drugs which resulted in 20% decreases (i.e., the EC_{20} values) in CO were approximately 1.8 (propafenone), 6.2 (cibenzoline),

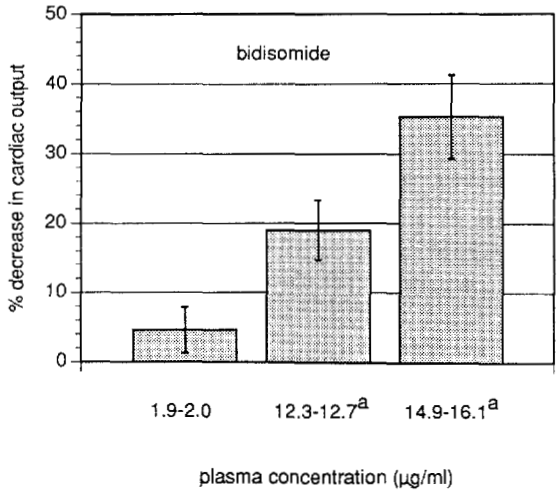

Figure 5. High plasma concentrations (>12 μg/ml) of bidisomide caused statistically significant reductions in CO. A 14.9–16.1 μg/ml concentration of bidisomide caused a 35% decrease in CO. [a]$P < 0.05$; N = 5.

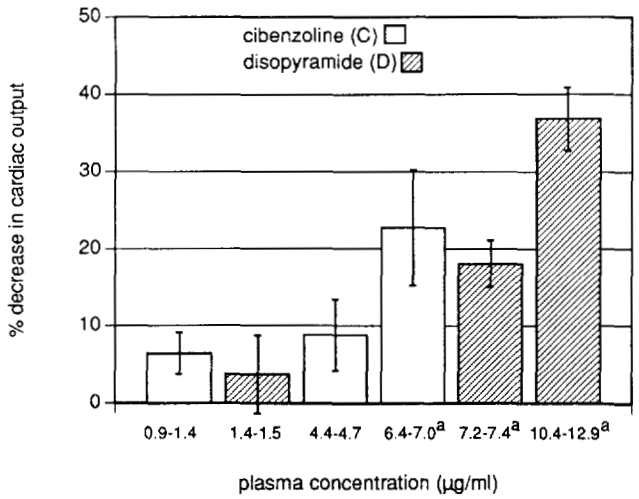

Figure 6. Disopyramide (n = 5) caused a statistically significant reduction in CO at plasma concentrations ≥7 μg/ml. A 37% reduction in CO was observed at disopyramide plasma concentrations of 10.4–12.9 μg/ml. The highest maintenance plasma concentrations of cibenzoline (n = 4) achieved were only 6.4–7.0 μg/ml, at which a 23% reduction in CO occurred, similar to the effect of the same concentration of disopyramide. [a]$P < 0.05$.

7.8 (disopyramide), and 13.0 (bidisomide). On the basis of plasma concentration achieved, therefore, bidisomide had about three-fifths to one-half the potency of disopyramide and cibenzoline in decreasing CO.

HR and SV

HR and SV vs. plasma concentration are shown for each agent in Figures 7–10. Neither HR (155–160

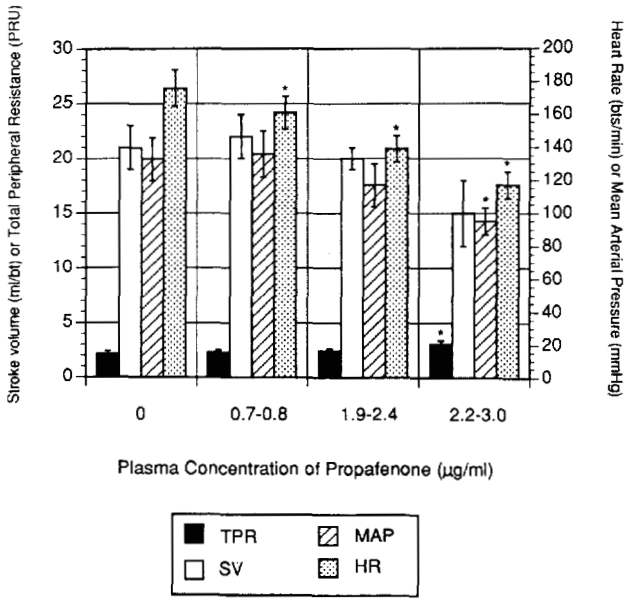

Figure 7. Propafenone significantly ($P < 0.05$) increased TPR, decreased MAP, and decreased HR, but did not significantly change SV. N = 5.

beats/min) nor SV (19 ± 2 ml/beat) was significantly affected by the placebo treatment (not shown). All plasma concentrations of propafenone significantly decreased HR but not SV (Fig. 7). HR remained at 114 beats/min in the propafenone group at the end of the final washout period. Cibenzoline did not significantly affect HR and significantly decreased SV only at plasma concentrations ≥6.4 μg/ml (Fig. 8). Bidisomide significantly decreased both HR and SV at plasma concentrations ≥12.3 μg/ml (Fig. 9). When HR was measured at the end of the final 20 min washout period, the effects of bidisomide were no longer evident (Fig. 9). Disopyramide significantly decreased HR but not SV at each of the plasma concentrations achieved (Fig. 10). HR remained depressed (106 beats/min) in response to disopyramide at the end of the final 20 min washout period (not shown).

MAP and TPR

MAP increased significantly from a pretreatment control value of 112 ± 8 mmHg to a value of 125 ± 7 mmHg at the end of the placebo treatment (not shown). Disopyramide, at plasma concentrations ≥10.4 μg/ml, and propafenone, at plasma concentrations ≥2.2 μg/ml, significantly decreased MAP (Figs. 7, 10). At the end of the final washout period, MAP was 109 mmHg (disopyramide) and 99 mmHg (propafenone). There were no other statistically significant effects of the test agents on MAP (Figs. 8, 9). Placebo treatment did not significantly change TPR,

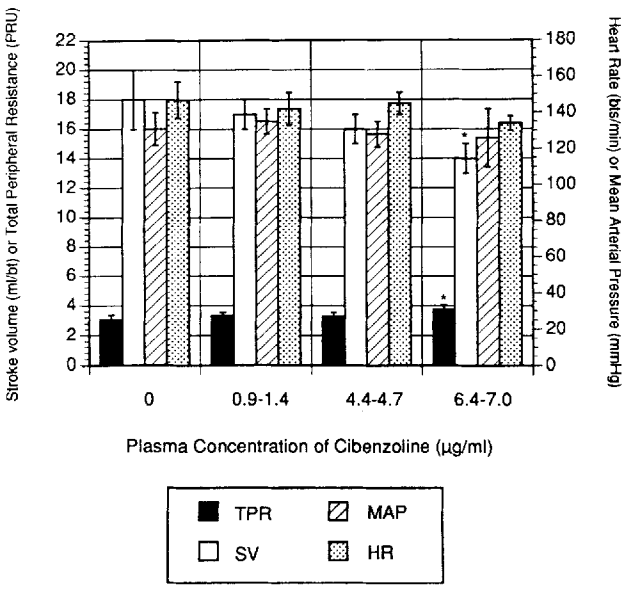

Figure 8. Cibenzoline, over the 0–7 μg/ml plasma concentration range studied, significantly ($P < 0.05$) increased TPR and decreased SV, but did not significantly change HR or MAP. N = 4.

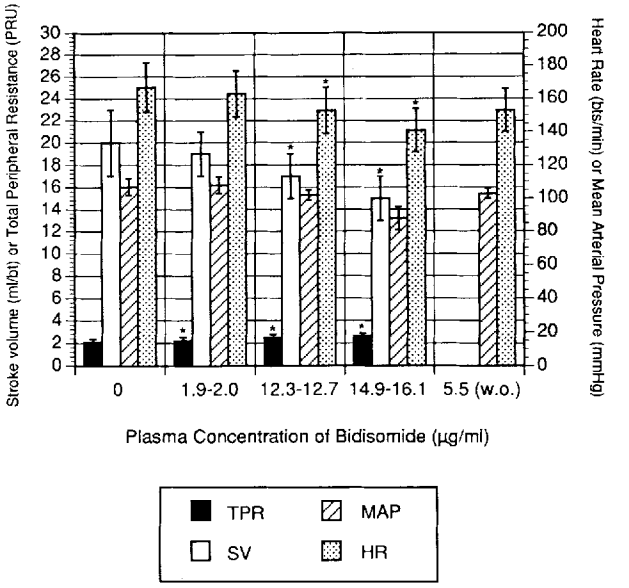

Figure 9. Bidisomide's modest effects on TPR were statistically significant ($P < 0.05$), as were the decreases bidisomide caused in SV and HR. The decrease in MAP was only of borderline statistical significance ($P = 0.051$). After a 20 min washout (W.O.) period toward the end of the experiment, the plasma concentration of bidisomide had fallen to 5.5 μg/ml and both HR and MAP approached pretreatment values. N = 5.

although TPR was increased to 2.62 ± 0.23 peripheral resistance units (PRU) at the end of the experiments vs. 2.31 ± 0.17 PRU at the beginning of placebo ad-

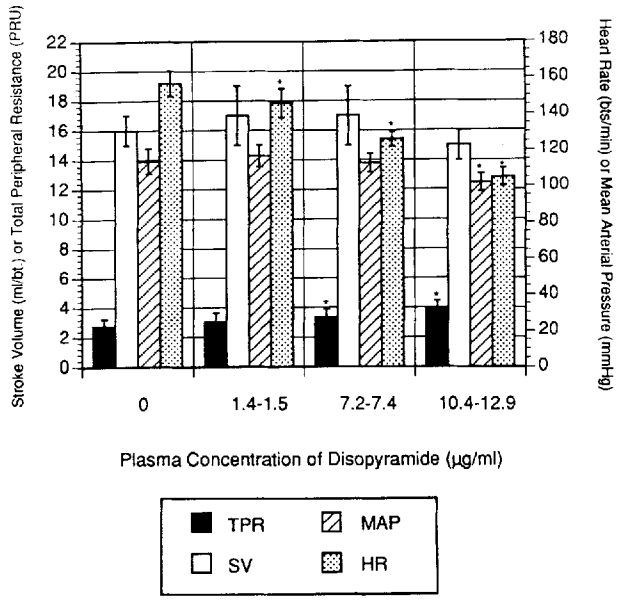

Figure 10. Disopyramide significantly ($P < 0.05$) increased TPR, more so than any of the other test agents. MAP and HR were significantly ($P < 0.05$) reduced by disopyramide.

ministration. All test agents significantly increased TPR at one or more of the plasma concentrations achieved (Figs. 7–10). Bidisomide increased TPR by 0.54 at the high dose, i.e., only 0.23 PRU more than was observed in response to the placebo. High dose propafenone (+0.97 PRU) and high dose disopyramide (+1.13 PRU) had the greatest effects on TPR.

ECG Intervals

Table 2 summarizes the ECG data recorded from limb lead II before and during test agent administration. Placebo treatment was without effect on the surface ECG intervals. Each of the test agents significantly increased PR interval at the medium (+13–22 msec) and high (+29–36 msec) doses. Cibenzoline and propafenone significantly increased QRS duration by 17 msec (medium doses) and by 25–33 msec (high doses). Disopyramide and bidisomide significantly increased QRS duration also, but the increases were much smaller (by one-half to two-thirds) in magnitude than those caused by cibenzoline and propafenone. Disopyramide (all doses) and propafenone (medium and high doses) were the only agents that significantly increased JT interval. The significant QT increases caused by bidisomide and cibenzoline were therefore secondary to the effect of these two drugs on QRS duration and not to JT prolongation.

DISCUSSION

Both the antiarrhythmic and the general cardiovascular effects of bidisomide, disopyramide, ciben-

TABLE 2. Plasma Concentrations and Effects on ECG Intervals of Propafenone, Cibenzoline, Bidisomide, Disopyramide, and Placebo

Treatment[a] or ECG interval[b]	Control	Plasma concentration (μg/ml) 0.7–0.8	0.9–2.2	2.3–4.7	6.4–7.4	10.4–12.9	14.9–16.1
Propafenone							
PR	96 ± 4	103 ± 5	119 ± 8*	133 ± 11*			
QRS	56 ± 3	62 ± 4*	73 ± 4*	81 ± 9*			
QT	199 ± 14	210 ± 15*	236 ± 20*	258 ± 22*			
JT	143 ± 12	148 ± 11	163 ± 11*	177 ± 18*			
Cibenzoline							
PR	100 ± 11		108 ± 14	115 ± 10*	135 ± 10*		
QRS	75 ± 6		80 ± 5	92 ± 5*	108 ± 14*		
QT	220 ± 8		223 ± 7	238 ± 17*	260 ± 16*		
JT	145 ± 7		143 ± 10	149 ± 14	153 ± 6		
Bidisomide							
PR	98 ± 2		97 ± 2			113 ± 4*	130 ± 9*
QRS	44 ± 2		45 ± 1			49 ± 2*	57 ± 3*
QT	207 ± 9		208 ± 10			216 ± 10*	222 ± 9*
JT	162 ± 10		162 ± 10			167 ± 11	163 ± 10
Disopyramide							
PR	88 ± 2		92 ± 3		102 ± 4*	118 ± 5*	
QRS	49 ± 2		51 ± 2		59 ± 4*	67 ± 5*	
QT	209 ± 8		223 ± 8*		248 ± 11*	283 ± 12*	
JT	160 ± 9		172 ± 10*		189 ± 13*	216 ± 18*	
Placebo							
PR	103 ± 4		100 ± 3		100 ± 3		98 ± 3
QRS	51 ± 3		50 ± 2		47 ± 2		45 ± 1
QT	216 ± 7		216 ± 7		214 ± 7		211 ± 6
JT	165 ± 8		166 ± 9		167 ± 7		166 ± 5

[a]N = 5 for propafenone, bidisomide, disopyramide; N = 4 for cibenzoline due to limited compound supplies.
[b]ECG intervals are expressed in msec. JT = QT-QRS.
*$P < 0.05$, statistically significant vs. pretreatment control value for same test agent.

zoline, and propafenone were dose-dependent. In conscious dogs with myocardial infarctions all of these drugs were well tolerated and consistently antiarrhythmic when judiciously infused to achieve a canine therapeutic dose. The arrhythmia experiments also confirmed the relative canine therapeutic potency of these drugs [Garthwaite et al., 1989b, 1994; Mokler and Van Arman, 1962; Patterson et al., 1979; Hashimoto et al., 1982; Bergey et al., 1983; Kaplan et al., 1984; Gomoll, 1987; Frederick et al., 1988; Hinsch et al., 1983; Dangman, 1984; Hashimoto et al., 1987]. As predicted from previous reports [Karagueuzian et al., 1982; Philipsborn et al., 1984], the canine antiarrhythmic dose of propafenone was lower than that of the other agents. It was 6 mg/kg i.v. in our experiments, which was a higher dose than the above referenced findings of 2–4 mg/kg i.v. Our model was a 24 h Harris model and not the 48 h Harris model used in the referenced experiments. We previously reported an ectopic rate of only 63 ± 11% in the 48 h Harris model [Schmidt et al., 1992] in contrast to the 95–100% ectopic rate in the 24 h Harris dogs used for the experiments in this study. A lower ectopic rate and/or differences in the infusion rate used may explain the lower propafenone antiarrhythmic doses reported by others.

For arrhythmia experiments, in which results can be readily observed via continuous ECG monitoring, "repeated bolus" dosing regimens have given a remarkable reproducibility of results from one laboratory to another despite the varied plasma half-lives of the drugs. We have shown that i.v. bolus dosing in Harris dogs results in rapid achievement of very high plasma concentrations of test agents, followed by very rapid declines in plasma concentrations [Garthwaite et al., 1989a,b]. In the i.v. bolus experiments, significant antiarrhythmic activity can persist despite the fact that plasma concentrations have plummeted [Garthwaite et al., 1989a,b], making it difficult to establish the relationship between plasma concentration and antiarrhythmic effect. With disopyramide, rapid bolus administration can lead to hemodynamic deterioration [Simpson et al., 1983] or poor tolerability and/or lethality [Schmidt et al., 1992], whereas slower infusions have an acceptable tolerability [Reddy et al., 1984]. Because of these considerations, the CO experiments were done with dosing regimens incorporating maintenance infusions after each loading dose,

as used for clinical electrophysiologic and/or hemodynamic studies of antiarrhythmic drugs [Horowitz et al., 1978; Roy et al., 1992].

The load/maintenance dosing in the CO experiments successfully achieved periods of reasonably constant plasma concentrations during which the cardiovascular measurements were made. Identical infusion protocols did not, however, produce similar plasma concentrations of these drugs. The plasma concentrations were reasonably consistent for each dog within a treatment group and were not uncharacteristic of these agents. It has been shown, e.g., that relatively high and fairly consistent bidisomide plasma concentrations could be sustained in anesthetized dogs using load/maintenance dosing [Garthwaite et al., 1992], including prolonged "drips" of ≤0.07 mg/kg/min [Hackett et al., 1993]. In contrast, minutes after infusing 4 mg/kg of cibenzoline into dogs, plasma concentrations <2 μg/ml have been observed [Sassine et al., 1984], suggesting that in dogs more "brisk" maintenance infusions of this drug may be necessary. Plasma concentrations of parent drug achieved in these experiments at the low doses of propafenone, bidisomide, disopyramide, and cibenzoline would result in ECG, electrophysiologic, and/or antiarrhythmic effects in humans [Naccarella et al., 1984; Dangman and Miura, 1986; Lynch and Horowitz, 1991; Steurer et al., 1991; Moreno et al., 1992; Page et al., 1992; Roy et al., 1992].

The CO experiments showed that propafenone was more potent than the other three agents in its general cardiovascular effects in addition to its antiarrhythmic effects. Since the 3 μg/ml plasma concentration of propafenone resulted in a 47% decrease in CO, it seems likely that higher concentrations, had we achieved them, might have been poorly tolerated. A 1 μg/ml increment (from 2 to 3 μg/ml) in the plasma concentration of propafenone resulted in a CO reduction of 47% vs. 24%, illustrating the importance of carefully controlling the plasma concentration of this drug. The highest concentration of bidisomide studied (15–16 μg/ml) was also approximately 30% greater than the highest concentration of disopyramide studied, and yet the effects of the two drugs on CO were similar. Since mean plasma concentrations of cibenzoline higher than 7 μg/ml were not achieved, its effects at high concentrations could not be determined. Even at 7 μg/ml, however, cibenzoline caused a 44% increase in QRS duration (see also below), suggesting that higher concentrations of this drug would not have a benign effect on ventricular conduction. Bidisomide proved to be the least potent of the four drugs studied in decreasing CO. The decreased CO caused by bidisomide, disopyramide, and propafenone may have been due in part to decreased HR. (Cibenzoline did not significantly decrease HR.) The positive relationship between rate and force (Bowditch effect) in the heart is well known [Schlant et al., 1982; Garthwaite et al., 1983; Hackett et al., 1990]. In normal dogs, the effect of rate on CO is particularly important over the 140–160 beats/min range [Tilley, 1985], which was the typical pretreatment rate in these experiments. Both propafenone and disopyramide caused statistically significant decreases in HR at all three dose levels. The other component to the decrease in CO caused by bidisomide and cibenzoline was decreased SV, i.e., the difference between the end-diastolic and end-systolic volumes. Cibenzoline has been shown to decrease SV but not to have important effects on end-diastolic volume or end-diastolic pressure [Verdouw et al., 1982; van den Brand et al., 1984; Humen et al., 1987]. The reduction in SV and CO caused by cibenzoline, then, seems likely to be due to an increase in end-systolic volume resulting from negative inotropism [Verdouw et al., 1982; van den Brand et al., 1984; Dangman and Miura, 1986; Humen et al., 1987; Matsuoka et al., 1991]. Bidisomide caused an increase in end-diastolic pressure at 15 mg/kg i.v. in dogs [Frederick et al., 1989], but did not significantly affect left ventricular systolic pressure in the same experiments. Bidisomide only modestly reduced max dP/dt in vivo and developed tension of papillary muscles in vitro [Frederick et al., 1989]. The depression of developed tension at high dose bidisomide, therefore, may be offset somewhat by increased ventricular filling.

No significant decrease in SV occurred in response to either disopyramide or propafenone, which was surprising in light of their well-known negative inotropic properties [Nayler, 1976; Philipsborn et al., 1984; Frederick et al., 1988; Hackett et al., 1990; Kondo et al., 1990]. Although disopyramide increased left ventricular end-diastolic pressure, it also very significantly decreased left ventricular systolic pressure and left ventricular dP/dt [Thadani et al., 1981; Block and Winkle, 1983; Cameron et al., 1984; Frederick et al., 1988], perhaps negating any beneficial effect of increased ventricular filling. Propafenone decreased rather than increased left ventricular end-diastolic pressure and reduced left ventricular pressure and left ventricular dP/dt [Winslow and Mason, 1992]. In the case of propafenone, decreased HR (as discussed above) was an important contributor to the reduction it caused in CO. It should be noted that propafenone's effects on SV were quite variable, ranging from an increase of 5 ml/beat in one dog to a decrease of 19 ml/beat in another dog by the end of dosing. In contrast, there was both little change and little variability

in the SV effects of disopyramide. In this model, in which a vagolytic anesthesia was used, the well-known anticholinergic effects of disopyramide [Cazes et al., 1990] did not manifest as increased HR; instead, disopyramide decreased HR (as discussed above), which contributed to decreased CO.

Besides HR and SV, the other principal components to CO are MAP and TPR, in particular the ratio of MAP to TPR (see equations in Materials and Methods). Bidisomide and cibenzoline did not significantly affect MAP. In the placebo group, MAP increased significantly in the simulated medium and high doses presumably due to changes in anesthetic state. In contrast, the high doses of disopyramide (−11%) and propafenone (−28%) significantly decreased MAP. Disopyramide and propafenone also had the most prominent effects on TPR. Bidisomide, in contrast, had relatively little effect on TPR, and cibenzoline was intermediate to bidisomide and propafenone in this regard. The data suggest that the decrease in MAP, increase in TPR, and decrease in MAP/TPR contributed to the reduction in CO by propafenone and disopyramide, and less so to that caused by cibenzoline and bidisomide. It has been proposed [Block and Winkle, 1983; Brogden and Todd, 1987] that negative inotropism combined with increased afterload explains the particular tendency of disopyramide to cause deleterious hemodynamic effects in some patients.

The data suggest there are plasma concentrations of all four agents which can potentially cause deleterious hemodynamic effects even in normal hearts. Clearly, propafenone had a particularly steep concentration-effect relationship (suggestive of a narrow safety margin), whereas bidisomide had a much "flatter" concentration-effect relationship (suggestive of a broader safety margin). Propafenone, disopyramide, and cibenzoline are all more likely to cause adverse hemodynamic effects in the presence of ventricular dysfunction [Podrid et al., 1980; Baker et al., 1982; Block and Winkle, 1983; Ferro et al., 1983; Shen et al., 1984; Dangman and Miura, 1986; Brogden and Todd, 1987; Ravid et al., 1989; Funck-Brentano et al., 1990; Winslow and Mason, 1992; Rankin, 1992; Birgersdotter-Green, 1992]. On several occasions, bidisomide has been studied for antiarrhythmic, electrophysiologic, and/or hemodynamic effects in dogs with left ventricular infarctions [Garthwaite et al., 1989b,c; Schmidt et al., 1992; Hackett et al., 1993; Zhenjiu et al., 1993] and was hemodynamically well tolerated in these models. A rapid infusion study [Schmidt et al., 1992] demonstrated that cardioactive effects (e.g., increased PR or QRS) could be achieved more rapidly with bidisomide than with disopyramide because of bidisomide's superior safety upon rapid i.v. administration. Canine therapeutic doses of bidisomide reduced max dP/dt 8% when infarct size was 11% of the left ventricle, and reduced it 21% when infarct size was 16% of the left ventricle [Garthwaite et al., 1989c], suggesting that the hemodynamic effect of bidisomide, although modest, may be greater with a more extensively damaged heart. In early clinical studies bidisomide did not significantly reduce ejection fraction in coronary artery disease patients [DeWitt et al., 1991] and was well tolerated by patients with ejection fractions as low as 25–30% [Roy et al., 1992].

All four drugs increased PR, QRS, and QT intervals of the lead II ECG. Only disopyramide and propafenone increased JT interval. QT increases caused by bidisomide and cibenzoline were secondary to increased in QRS duration, as neither drug increased JT interval. Propafenone, followed by cibenzoline, had the most potent effects on ECG intervals, as expected for class Ic agents. Disopyramide, as expected for a class Ia agent, caused significant changes in JT interval. Disopyramide's effects on PR and QRS were similar to the changes it caused in JT. The principal ECG effects of bidisomide were increased PR (15% medium dose, 33% high dose) and increased QRS (11% medium dose, 30% high dose), as previously described in dogs [Frederick et al., 1989; Spinelli and Hoffman, 1989; Schmidt et al., 1992; Garthwaite et al., 1992; Elrod et al., 1993; Hackett et al., 1993] and humans [Page et al., 1992; Moreno et al., 1992]. These changes were consistent with the slowing of A-V nodal and ventricular conduction observed in an in vivo canine electrophysiologic study of bidisomide [Garthwaite et al., 1992]. The lack of bidisomide effect on JT interval also agreed with its causing neither a consistent nor a prominent effect on ventricular refractory period in dogs [Garthwaite et al., 1992]. The antiarrhythmic effect of bidisomide in a canine atrial arrhythmia model was accompanied by only a modest (8–11 msec) increase in P, PR, and QRS [Garthwaite et al., 1994]. In a human premature ventricular contraction (PVC) suppression study, antiarrhythmic doses of bidisomide caused only 5–7% increases in PR and QRS [Moreno et al., 1992]. In contrast to propafenone and cibenzoline, therefore, bidisomide did not have prominent conduction slowing effects. For treatment of supraventricular arrhythmias, it is advantageous for a new drug such as bidisomide to cause little QRS or JT prolongation.

Bidisomide was of low potency in causing significant hemodynamic and ECG effects compared to propafenone, cibenzoline, and disopyramide. These data support previous conclusions that bidisomide's

supraventricular antiarrhythmic effect is largely due to increased atrial effective refractory period and not to potent conduction slowing [Garthwaite et al., 1992, 1994; Martin and Chinn, 1994]. The electrophysiologic profile of bidisomide has made it difficult to position this drug neatly into a single antiarrhythmic class or subclass. In an in vivo canine electrophysiologic study, an increase in atrial effective refractory period was the only statistically significant response (either electrophysiologic or hemodynamic) to bidisomide at the lowest dose studied (which achieved only a 2 μg/ml plasma concentration) [Garthwaite et al., 1992]. In the canine acute pericarditis atrial arrhythmia model, a plasma concentration of 6–8 μg/ml caused a substantial (30–40 msec) increase in atrial refractory period [Garthwaite et al., 1994]. The data from this CO study, therefore, also support the previous impressions that the antiarrhythmic effects of bidisomide are not likely to be accompanied by hemodynamic intolerability [Frederick et al., 1989; DeWitt et al., 1991; Moreno et al., 1992; Page et al., 1992].

ACKNOWLEDGMENTS

We thank the many Searle colleagues who assisted us: Bipin Desai (inventor of bidisomide), Devan Mehrotra (statistician), Minerva Gonzalez (typing and graphics), and the staff of Preclinical Bioanalytics who provided plasma assays of the drugs.

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