concentrations of the cross-linking agent ethylene glycol dimethacrylate must be to decrease the size of these fluctuating pores with ethylene glycol dimethacrylate, producing a much greater effect than tetraethylene glycol dimethacrylate. This conclusion is consistent with the fact that tetraethylene glycol dimethacrylate is a longer chain length cross-linker. The abruptly increasing slope in the plot of mole percent cross-linker *versus* D for ethylene glycol dimethacrylate shown in Fig. 5 suggests that a change in mechanism occurs in this region such that at high concentrations of this cross-linker the solution–diffusion mechanism is dominant. As discussed in the section on the mechanism of solute permeation through polymer membranes, when the solution–diffusion mechanism is dominant, the diffusion coefficient is controlled primarily by interactions between the solute and the polymer segments of the membrane. The relative constancy of the diffusion coefficients for progesterone with variations in the ethylene glycol dimethacrylate cross-linker percentage in the high concentration region of the plot in Fig. 5 is consistent with this behavior. At intermediate concentrations of this cross-linker, both mechanisms of solute permeation probably contribute to the observed permeability of these membranes.

It is not possible to provide direct proof of the mechanisms outlined for the effects of cross-linker percentage on solute permeation through these membranes. Proof of the proposed mechanisms can only arise from an extensive study of the permeation of a wide variety of solutes in which both the physical-chemical nature and the molar volume of the solute are varied. However, the interpretations presented here are consistent with the shapes of the curves shown in Fig. 5 and with previous studies of the mechanism of solute permeation through polymer membranes (12–14) including hydrogels (10, 15, 16, 18).

REFERENCES

(1) J. D. Andrade, *Med. Instrum.*, **1**, 110 (1973).

(2) M. Tollar, M. Stol, and K. Kliment, *J. Biomed. Mater. Res.*, **3**, 305 (1969).

(3) V. Majkus, F. Horakova, F. Vymola, and M. Stol, *ibid.*, **3**, 443 (1969).

(4) J. M. Anderson, T. Koinis, T. Nelson, M. Horst, and D. S. Love, in "Hydrogels for Medical and Related Applications," J. D. Andrade, Ed., Symposium Series 31, American Chemical Society, Washington, D.C., 1976, p. 167.

(5) D. R. Cowsar, O. R. Tarwater, and A. C. Tanquary, in *ibid.*, p. 180.

(6) J. Drobnik, P. Spacek, and O. Wichterle, *J. Biomed. Mater. Res.*, **8**, 45 (1974).

(7) R. A. Abrahams and S. H. Ronel, *ibid.*, **9**, 355 (1975).

(8) G. A. Mortimer, *J. Org. Chem.*, **30**, 1632 (1964).

(9) D. E. Gregonis, C. M. Chen, and J. D. Andrade, in "Hydrogels for Medical and Related Applications," J. D. Andrade, Ed., Symposium Series 31, American Chemical Society, Washington, D.C., 1976, p. 88.

(10) S. J. Wisniewski, D. E. Gregonis, S. W. Kim, and J. D. Andrade, in *ibid.*, p. 80.

(11) M. Y. Mah, Master's thesis, University of Utah, Salt Lake City, Utah, 1972.

(12) L. C. Craig and W. Konigsberg, *J. Phys. Chem.*, **65**, 116 (1961).

(13) D. J. Lyman and S. W. Kim, *J. Polym. Sci., Symp.*, **41**, 139 (1973).

(14) D. J. Lyman and S. W. Kim, *Biomater. Med. Devices Artif. Organs*, **1**, 431 (1973).

(15) H. Yasuda, C. E. Lamaze, and L. D. Ikenberry, *Makromol. Chem.*, **118**, 19 (1968).

(16) H. Yasuda, C. E. Lamaze, and A. Peterlin, *J. Polym. Sci., A-2*, **9**, 1117 (1971).

(17) N. F. H. Ho, L. Suhardja, S. Hwang, E. Owada, A. Molokhia, G. L. Flynn, W. I. Higuchi, and J. Y. Park, *J. Pharm. Sci.*, **65**, 1578 (1976).

(18) R. Y. S. Chen, *Polym. Prepr.*, **15** (2), 387 (1974).

ACKNOWLEDGMENTS

Presented in part at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, New Orleans meeting, April 1976.

Supported by National Institutes of Health Grant HD-09791.

The authors thank Dr. D. E. Gregonis and Dr. J. D. Andrade for their contributions and Mr. Darryl D. Ivanson for assistance.

Comparison of Effects of Quinidine and Dihydroquinidine on Canine Heart

TIBOR BALAZS *x, EUGENE HERMAN *, and JOHN ATKINSON ‡

Received August 22, 1977, from the **Division of Drug Biology and the* ‡*Division of Mathematics, Food and Drug Administration, Washington, DC 20204.* Accepted for publication January 26, 1978.

Abstract □ Various cardiac effects of quinidine and dihydroquinidine were tested in isolated dog hearts and *in vivo* in dogs. No significant differences were found in the negative inotropic, chronotropic, and dromotropic effects. Dihydroquinidine was more potent than quinidine in decreasing coronary arterial pressure.

Keyphrases □ Quinidine—various cardiac effects on isolated heart and *in vivo* in dogs, compared to dihydroquinidine □ Dihydroquinidine—various cardiac effects on isolated heart and *in vivo* in dogs, compared to quinidine □ Cardiac effects, various—quinidine and dihydroquinidine compared in isolated heart and *in vivo* in dogs □ Antiarrhythmic agents—quinidine and dihydroquinidine, various cardiac effects compared in isolated heart and *in vivo* in dogs

Pharmaceutical preparations of the antiarrhythmic quinidine may contain other cinchona alkaloids, of which dihydroquinidine is present in the highest concentration. The dihydroquinidine content of 40 tested commercial samples of quinidine ranged from 3 to 22% (1). USP XIX specifies that the dihydroquinidine content of quinidine gluconate or sulfate USP should not exceed 20% of the total alkaloids.

Both quinidine and dihydroquinidine have qualitatively similar cardiac pharmacological actions (2–5), but their potencies may differ. The intravenous median lethal dose of dihydroquinidine in mice was about 18% lower than that of quinidine (4). The hypotensive effects of the alkaloids after intravenous administration were about equal in anesthetized cats. The threshold dose of dihydroquinidine required to raise the intensity of electrical stimulation to produce ventricular fibrillation in cats was about one-third of that of quinidine. A recent study with these alkaloids in rats revealed no differences in acute intravenous toxicities or in potencies to suppress electrically induced ventricular fibrillation (6). Limited clinical data indicate that dihydroquinidine has a greater antiarrhythmic effect (2, 3).

Since both alkaloids have several cardiac effects that

0022-3549/78/1000-1355$01.00/0

Table I—Average Values (Percent of Control) by Dose Level for Contraction Force, Arterial Pressure, and Heart Rate in Isolated Dog Hearts: Quinidine Tartrate (I) and Dihydroquinidine Tartrate (II)

Dose, mg	Contraction Force		Arterial Pressure		Heart Rate	
	I	II	I	II	I	II
5	106.8	106.8	98.7	93.8	85.9	85.5
10	82.2	95.5[a]	84.8	73.8	80.2	86.5
20	84.8	78.2	81.4	65.4[a]	86.9	87.9
LSD[b]	10.1		11.6		5.7	

[a] Difference between drugs is statistically significant ($p = 0.05$) at this dose level. [b] Least significant difference.

have not been compared previously, the effects on heart rate (chronotropic), force of contraction (inotropic), ventricular conduction velocity (dromotropic), and coronary arterial pressure were chosen as ways to compare their potencies.

EXPERIMENTAL

Materials—Quinidine tartrate and dihydroquinidine tartrate were prepared[1] as described by Smith *et al.* (1) and were found to contain 65 and 67% of the respective alkaloid. Quinidine was free of any dihydroquinidine and contained not more than traces of other cinchona alkaloids. Dihydroquinidine did not contain any quinidine.

Testing in Isolated Dog Hearts—Adult beagle dogs of each sex were anesthetized with pentobarbital sodium (30 mg/kg), and a polyethylene catheter was inserted into the right femoral artery for rapid blood removal. Clotting was prevented by injecting 1000 units of heparin sodium/kg into the femoral vein. Respiration was maintained with a positive pressure respirator[2].

The chest was opened by a midline incision, and all major branches of the ascending aorta except the brachiocephalic trunk were ligated. The latter vessel was cannulated with a short stainless steel cannula connected by tubing to a pump oxygenator system. The descending aorta was then ligated, and the heart was removed from the chest cavity quickly, placed into a chamber of the pump–oxygenator system, and perfused at a constant flow with approximately 500 ml of autologous blood maintained at 35°.

The perfusion pressure (coronary arterial pressure) was continuously monitored *via* a needle-tipped catheter inserted into the perfusion circuit and connected to a pressure transducer. Needle electrodes were inserted into the ventricles to monitor the heart rate. The contraction force was measured by a Walton–Brodie strain gauge sutured to the left ventricle.

After a 30-min stabilization period, the heart preparations were treated over a 30–60-sec period with 5, 10, or 20 mg of quinidine or dihydroquinidine, calculated as the free base, dissolved in 5 ml of physiological saline. These doses were chosen to cover the range from therapeutic to toxic levels. The effect of each level was determined in five separate experiments. All experiments were terminated 60 min after dosing. An analysis of variance was conducted for heart rate, contraction force, and coronary arterial pressure. In each of these three analyses of variance, the effects of drug dose and time were considered, together with the interactions of these effects.

Testing in Anesthetized Dogs—A pool of 12 beagle dogs of both sexes, 7–12 kg, was used. Eight dogs (Group 1) were used to compare the effects of the pure alkaloids in a crossover test. Four dogs from Group 1 and the four remaining dogs were used to compare the effects of a mixture of 25% dihydroquinidine and 75% quinidine with pure quinidine (Group 2). Nine dogs (Group 3) were used to test the effects of a mixture of equal concentrations of the alkaloids. At least 1 week elapsed before an individual dog was used again.

Dogs were anesthetized with pentobarbital sodium. One percent drug solutions of each drug in physiological saline, prepared by gentle heating, were infused into the cephalic vein in the foreleg at a rate of 5 mg/kg/min for 10 min. ECG's (lead II) were recorded at 50 mm/sec prior to and at 1-min intervals during the infusions. The duration of QRS complexes was calculated (mean of three values for each minute). A regression analysis of response *versus* time of infusion was conducted for each infusion.

RESULTS

Both alkaloids affected the contraction force of the isolated heart, resulting initially in a dose-related negative inotropic effect (Fig. 1). The recovery rates were comparable at each dose level for both alkaloids during the first 15 min. Thereafter, the contraction force increased above control levels at the 5-mg doses, remained close to the baseline level at the 10-mg doses, and tended to remain below control values at the 20-mg doses.

The inotropic effects of dihydroquinidine were greater at 10 mg and lower at 20 mg than those of quinidine. However, only the differences at 10 mg were statistically significant. A statistically significant interaction occurred between dose and drug. This result can be seen from the averages in Table I, since the lowest values occurred at 10 mg for quinidine (I) and 20 mg for dihydroquinidine (II). The effect of dose, therefore, was considered separately for each drug, and the least significant difference between drugs for a dose level was determined. The analysis of variance summary is shown in Table II.

The coronary arterial pressure decreased in a dose-related manner during the 1st min after dosing (Table I). Recovery occurred within 5 min at 5 mg but was slower for the 10- and 20-mg doses; only partial recovery occurred with dihydroquinidine. The mean coronary pressure values for the 1-hr experiment were lower, in a dose-related fashion, for dihydroquinidine and were significantly different from those for quinidine at 20 mg (Fig. 2). The analyses of variance are given in Table II.

The heart rate was decreased 10–20% throughout the 1-hr period at each level of each alkaloid (Tables I and II). These findings imply that

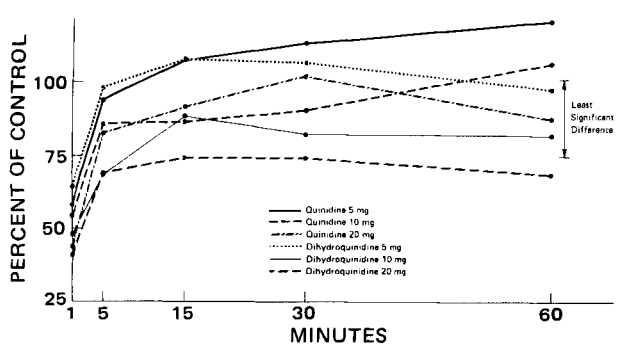

Figure 1—*Effects of the alkaloids on the contraction force in isolated dog hearts. (Each point represents mean values from five hearts.)*

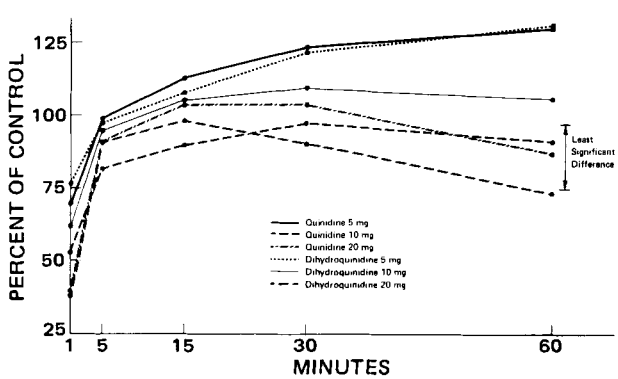

Figure 2—*Effects of the alkaloids on the coronary arterial pressure in isolated dog hearts. (Each point represents mean values from five hearts.)*

[1] The drugs were prepared by M. Maienthal, Division of Drug Chemistry, Food and Drug Administration, Washington, DC 20204, and analyzed by Susan Barkan of the same Division.

[2] Harvard.

Table II—Analysis of Variance [a] for Contraction Force, Arterial Pressure, and Heart Rate

Source of Variation	Degrees of Freedom	Force of Contraction		Arterial Pressure		Heart Rate	
		MS	*F*	*MS*	*F*	*MS*	*F*
Drug	1	182	—	4245	10.11**[b]	199	1.99
Dose	2	8468	6.54	7005	16.61***	212	2.12
Drug × dose	2	1294	4.08*	319	—	157	1.57
Time	4	13205	41.67***	10219	24.94**	76	—
Drug × time	4	44	—	461	1.10	3	—
Dose × time	8	838	2.64	190	—	9	—
Drug × dose × time	8	61	—	156	—	37	—
Error	120	317	—	420	—	100	—

[a] *MS* = mean square; *F* = *F* value. [b] As large or larger difference could occur from chance alone; * = less than 5% of the time, ** = less than 1% of the time, and *** = less than 0.1% of the time.

Table III—Effect of Quinidine Tartrate (I), Dihydroquinidine Tartrate (II), and Their Combinations on the Duration of QRS in Dogs

Group	Number of Dogs	I, %[a]	QRS Increase, msec		I + II		QRS Increase, msec	
			Mean	*SE*	%[a]	%[a]	Mean	*SE*
1	8	100	23.4	3.6	0	100	24.2	4.2
2	9	100	22.4	3.4	50	50	31.2	3.6
3	8	100	21.2	3.4	75	25	28.8	7.0

[a] The concentrations of the drugs are expressed as percentages of the salts.

the changes in the contraction force and coronary pressure are independent of the negative chronotropic effect.

Infusion of the drug solution in anesthetized dogs produced a slight tachycardia during the 1st min, followed by a slight bradycardia throughout the dosing period. Sinus rhythm was maintained, and arrhythmia did not occur. The duration of the QRS complex increased throughout the infusions. Response *versus* time of infusion curves constructed for each of the individual dog exposures from Group 1 revealed that all regressions were significant, with the highest values reached or maintained at the end of dosing. The mean time for maximal effect on the QRS duration was 8.9 min for quinidine and 9.0 min for dihydroquinidine. The maximum QRS less the predose QRS was used to assess the effect (Table III). Differences in effects of dihydroquinidine and quinidine solutions were not statistically significant.

DISCUSSION

Some cardiac effects of quinidine and dihydroquinidine alkaloids were used to compare their potencies. The effect on ventricular conduction velocity, a negative dromotropic effect, as measured by the duration of the QRS complex, represents a major pharmacological action, which is correlated with blood levels of quinidine (7). The negative inotropic effect is, in part, a consequence of the decreased conduction rate since it leads to a reduction of the synchrony of contraction. This effect and also the effect on the coronary pressure represent toxic and, in part, independent effects. This autonomy may explain the greater potency of dihydroquinidine in one parameter, coronary pressure, in the *in vitro* assay.

Similarly, such an explanation might also be applicable to the findings of Scott *et al.* (4) who reported that dihydroquinidine produced a greater antifibrillatory, *i.e.*, negative bathmotropic, effect in cats. Their data demonstrate that the two alkaloids can induce equal systemic hypotensive effects but with different bathmotropic effects. However, the recent data of Dietmann *et al.* (6) on the lack of significant differences in the negative bathmotropic effects of these two alkaloids in rats raise the possibility of species differences in sensitivity. Differences in the pharmacokinetic patterns of dihydroquinidine and quinidine might be one mechanism to explain divergent species effects.

While data are not available for cats and rats, no significant differences were found in humans in the distribution and elimination kinetics of these two alkaloids (8). In view of previous data (6, 8) and the data reported here, a level of 20% dihydroquinidine in pharmaceutical preparations of quinidine is acceptable pharmacologically. However, in view of the earlier data for cats (4) and humans (3) indicating a significantly greater antiarrhythmic potency of dihydroquinidine, a reexamination of the therapeutic effects of these alkaloids in humans appears to be in order.

REFERENCES

(1) E. Smith, S. Barkan, B. Ross, M. Maienthal, and J. Levine, *J. Pharm. Sci.*, **62,** 1151 (1973).

(2) T. Lewis, A. N. Drury, A. M. Wedd, and C. C. Iliescu, *Heart*, **9,** 207 (1922).

(3) F. Alexander, H. Gold, L. N. Katz, R. L. Levy, R. Scott, and P. D. White, *J. Pharmacol. Exp. Ther.*, **90,** 191 (1947).

(4) C. Scott, R. C. Anderson, and K. K. Chen, *ibid.*, **84,** 184 (1945).

(5) W. Model, S. J. Shane, C. Dayrit, and H. Gold, *Fed. Proc. Fed. Am. Soc. Exp. Biol.*, **8,** 320 (1949).

(6) K. Dietmann, W. Bartsch, and M. Gutekunst, *Arzneim.-Forsch.*, **27,** 589 (1977).

(7) R. H. Heissenbuttel and J. T. Bigger, *Am. Heart J.*, **80,** 453 (1970).

(8) C. T. Ueda, B. J. Williamson, and B. S. Dzindzio, *Res. Commun. Chem. Pathol. Pharmacol.*, **14,** 215 (1976).

ACKNOWLEDGMENTS

The authors thank Mr. Joseph Levine (retired), formerly Director, Division of Drug Chemistry, Food and Drug Administration, for bringing the problem to their attention.