Progestin Permeation through Polymer Membranes II: Diffusion Studies on Hydrogel Membranes

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Abstract □ The potential use of hydrogels in controlled-release drug delivery systems for contraceptive steroids was investigated. The permeabilities, diffusion coefficients, and partition coefficients for progesterone were determined for hydrogels made from hydroxyethyl methacrylate containing varying amounts of ethylene glycol dimethacrylate and tetraethylene glycol dimethacrylate. In addition, copolymers of hydroxyethyl methacrylate with methoxyethyl methacrylate and methoxyethoxyethyl methacrylate were investigated. The results were interpreted in terms of the mechanisms of permeation of progesterone through the hydrogels. This study showed that progesterone permeated these membranes primarily through loose pores in the hydrogel network except at high concentrations of the cross-linker, ethylene glycol dimethacrylate, where dissolution and diffusion of the progesterone in the polymer network was the dominant mechanism.

Keyphrases □ Polymer membranes—permeabilities, diffusion coefficients, and partition coefficients for progesterone permeation through various hydrogels, potential for use as controlled-release drug delivery devices □ Progesterone—permeabilities, diffusion coefficients, and partition coefficients for permeation through various hydrogels □ Hydrogels, various—permeabilities, diffusion coefficients, and partition coefficients for progesterone permeation, potential for use as controlled-release drug delivery devices □ Delivery devices, controlled release—various hydrogel membranes evaluated, permeability to progesterone □ Diffusion coefficients—for progesterone permeation through various hydrogels □ Dosage forms—controlled-release delivery devices, various hydrogel membranes evaluated, permeability to progesterone □ Progestins—progesterone, permeabilities, diffusion coefficients, and partition coefficients for permeation through various hydrogels

Hydrogels are polymeric materials that absorb large quantities of water while remaining insoluble. These polymers exhibit low interfacial free energies with aqueous solutions and only a weak tendency to adsorb biological species such as platelets and proteins. As a result, hydrogels show good biocompatibility and are strong candidates for use as biomedical implant devices (1).

Hydrogels have potential for use in the controlled release of drugs and were investigated in delivery systems for antibiotics (2, 3), steroids (4), inorganic fluoride (5), antitumor agents (6), and narcotic antagonists (7). Hydrogels can be used to control the release of both hydrophobic and hydrophilic drugs, and the release rate can be controlled by variations in the nature and concentration of the cross-linker and by the use of copolymers.

In the present study, the use of hydrogels in the delivery of contraceptive steroids was investigated with progesterone as a model hydrophobic drug. Hydrogels were prepared from hydroxyethyl methacrylate containing varying amounts of ethylene glycol dimethacrylate and tetraethylene glycol dimethacrylate as cross-linking agents. Copolymers of hydroxyethyl methacrylate, methoxyethyl methacrylate, and methoxyethoxyethyl methacrylate also were prepared. The permeability of these polymers to progesterone was determined, and the results were interpreted in terms of the mechanisms of drug permeation through the hydrogels. These studies should provide insight into the general mechanism of permeation of hydrophobic drugs through hydrogels as well as valuable information for the development of these polymers for drug delivery systems.

EXPERIMENTAL

Materials—All hydrogels were prepared by free radical polymerization, using azobis(methylisobutyrate) at a concentration of 7.84 mmoles/liter of monomer as the initiator. The preparation of the initiator followed the procedure given by Mortimer (8). Hydroxyethyl methacrylate[1] was used as received. Methoxyethyl methacrylate and methoxyethoxyethyl methacrylate were synthesized from methyl methacrylate[2] by transesterification with the appropriate alcohol (9). Ethylene glycol dimethacrylate[3] and tetraethylene glycol dimethacrylate[4] were purified by base extraction to remove inhibitors and then distilled prior to use.

The hydrogel membranes prepared from hydroxyethyl methacrylate were synthesized by mixing the required amount of cross-linker and monomer with 45% (v/v) deionized water prior to polymerization between sealed glass plates at 60° for 24 hr. The copolymers of hydroxyethyl methacrylate with methoxyethyl methacrylate or methoxyethoxyethyl methacrylate were prepared by mixing the required amount of monomer with deionized water and polymerizing under the same conditions. The amounts of water added were the maximum amounts that would yield a single solubilized phase as reported by Gregonis *et al.* (9).

Comonomer solutions capable of solubilizing 20% water or greater on a volume basis were prepared similarly. Comonomer solutions solubilizing less than 20% water were polymerized under the same conditions except that polyethylene plates were used in place of the glass plates to facilitate polymer removal from the mold. All hydrogels were equilibrated with water prior to use. For the diffusion experiments, unlabeled progesterone[5], radiolabeled progesterone[6] (1,2-^{3}H-progesterone), and the scintillation fluid[7] were used as received.

Methods—The diffusion experiments were carried out at room temperature, 24 ± 1°, in an all-glass cell composed of two compartments of equal volume (176 ml). The membrane was clamped in place between these compartments. Each compartment was continuously stirred at 1600 rpm by externally mounted constant-speed synchronous motors[8]. A 10% change in the stirring rate did not affect the observed permeabilities.

For each experiment, one compartment was filled initially with deionized water. The remaining compartment was filled with an aqueous solution containing unlabeled progesterone at 11.2 μg/ml and an appropriate amount of the labeled steroid. The increase in radioactivity in the initially progesterone-free compartment was followed by withdrawing microliter quantities of solution. The solution withdrawn was placed in tared scintillation vials and weighed, 10 ml of scintillation fluid was added, and the samples were counted in a scintillation counter[9].

Partition coefficients were determined by a solution depletion technique in which 15 ml of a labeled solution of progesterone was allowed to equilibrate with a known volume of membrane. The equilibrium concentrations of progesterone in the bulk solutions were obtained as already described.

Membrane thicknesses, ~0.07 cm, were measured on water-swollen membranes using a lightwave micrometer[10]. The measurements were made at the minimum allowable pressure for this instrument (60 g). The

[1] Courtesy of Hydron Laboratories, New Brunswick, N.J.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] Monomer Polymer Laboratories, Philadelphia, Pa.
[4] Polysciences, Warrington, Pa.
[5] Steraloids, Inc., Pauling, N.Y.
[6] New England Nuclear, Boston, Mass.
[7] Aquasol, New England Nuclear, Boston, Mass.
[8] Precision stirrer, Curtis Matheson Scientific, Denver, Colo.
[9] Model 3385, Packard Instrument Co., Downers Grove, Ill.
[10] Van Kueren Co., Watertown, Mass.

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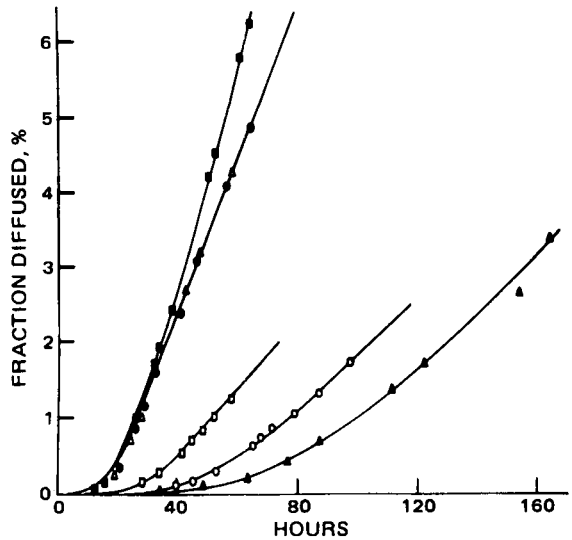

Figure 1—*Fraction of progesterone released* versus *time for progesterone permeation through hydroxyethyl methacrylate cross-linked with ethylene glycol dimethacrylate. Key (mole percent cross-linker):* ■, *0;* ●, *0.56;* △, *0.75;* □, *2.30;* ○, *3.75; and* ▲, *5.25.*

error resulting from these measurements probably varies depending on the properties of the hydrogel but is believed to be small.

Hydration and water fraction values were obtained using the technique described by Wisniewski *et al.* (10).

RESULTS

Figures 1 and 2 show the effects of the cross-linker percentage on the fraction of drug diffused *versus* time for polyhydroxyethyl methacrylate membranes containing varying amounts of ethylene glycol dimethacrylate and tetraethylene glycol dimethacrylate as cross-linking agents. As the cross-linker percentage increased, the fraction of drug diffused decreased. At equivalent mole percents, membranes cross-linked with tetraethylene glycol dimethacrylate showed greater permeabilities than membranes cross-linked with ethylene glycol dimethacrylate.

Figure 3 shows the effects of variations in the monomer composition on the fraction of progesterone diffused as a function of time. Variations in the monomer composition led to changes in the water content, W_f, defined as the weight fraction of water in the swollen gel. The water contents of these membranes are shown in Table I. As the water content

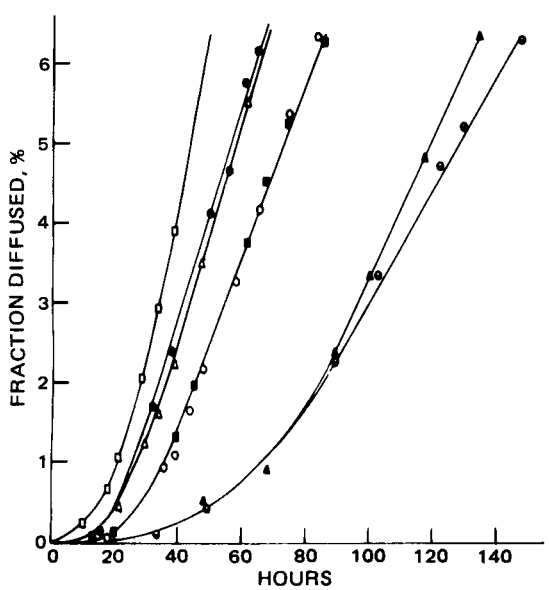

Figure 2—*Fraction of progesterone released* versus *time for progesterone permeation through hydroxyethyl methacrylate cross-linked with tetraethylene glycol dimethacrylate. Key (mole percent cross-linker):* ●, *0;* □, *0.25;* △, *0.46;* ○, *0.92;* ■, *1.84;* ▲, *3.22; and* ⊖, *4.60.*

Table I—Diffusion Coefficients, Partition Coefficients, Water Contents, and Permeabilities for Progesterone in Copolymers of Hydroxyethyl Methacrylates

Membrane	$D \times 10^9$, cm²/sec	K_d	W_f	$U \times 10^7$, cm²/sec
Methoxyethoxyethyl methacrylate	12.7	130	0.723	16.6
34% Hydroxyethyl methacrylate–66% methoxyethoxyethyl methacrylate	7.67	129	0.504	9.86
Hydroxyethyl methacrylate	4.38	129	0.423	5.63
80% Hydroxyethyl methacrylate–20% methoxyethyl methacrylate	0.98	156	0.340	1.53
67% Hydroxyethyl methacrylate–33% methoxyethyl methacrylate	0.90	192	0.308	1.75

of the membrane increased, the fraction of drug diffused also increased.

The diffusion coefficients for progesterone in these membranes were obtained through the use of (11):

$$\ln\left(1 - \frac{2C_t}{C_0}\right) = -\left(\frac{1}{V_1} + \frac{1}{V_2}\right)\frac{AUt}{l} \qquad \text{(Eq. 1)}$$

where C_t is the concentration of progesterone at time t, C_0 is the initial progesterone concentration, V_1 and V_2 are the compartment volumes (176 ml), A is the membrane area (14.2 cm²), l is the wet membrane thickness, and U is the permeability, which is defined as:

$$U = DK_d \qquad \text{(Eq. 2)}$$

where D is the diffusion coefficient and K_d is the partition coefficient. The permeability, U, can be obtained from the linear portion of a plot of $\ln(1 - 2C_t/C_0)$ *versus* t. The effects of variations in the monomer composition of the membrane on the diffusion coefficient, D, are shown in Table I; D decreased as the water content of the membrane decreased. The effects of variations in the cross-linker percentage on D are shown in Table II; D decreased as the cross-linker percentage increased. As seen from Tables I and II, the partition coefficients for progesterone were not strongly dependent on the composition of the membrane.

DISCUSSION

Mechanisms of Solute Permeation through Polymer Membranes—Solute transport through polymeric membranes is generally

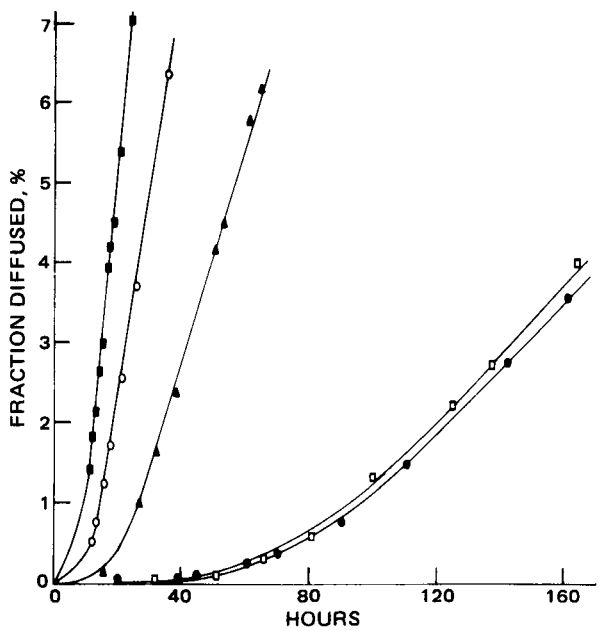

Figure 3—*Fraction of progesterone released* versus *time for progesterone permeation through methoxyethoxyethyl methacrylate* (■), *34% hydroxyethyl methacrylate–66% methoxyethoxyethyl methacrylate* (○), *hydroxyethyl methacrylate* (▲), *80% hydroxyethyl methacrylate–20% methoxyethyl methacrylate* (□), *and 67% hydroxyethyl methacrylate–33% methoxyethyl methacrylate* (○).

Table II—Diffusion Coefficients, Partition Coefficients, Water Contents, and Permeabilities for Progesterone in Cross-Linked Hydroxyethyl Methacrylate Membranes

Mole Percent Cross-Linker	$D \times 10^9$, cm²/sec	K_d	W_f	$U \times 10^7$, cm²/sec
	Ethylene Glycol Dimethacrylate			
0	4.38	129	0.423	5.62
0.56	2.57	151	0.410	3.89
0.75	2.57	151	0.403	3.89
2.30	1.08	151	0.376	1.63
3.75	0.72	161	0.355	1.16
5.25	0.64	232	0.348	1.48
	Tetraethylene Glycol Dimethacrylate			
0	4.38	129	0.423	5.62
0.25	4.76	147	0.414	6.99
0.46	3.82	149	0.418	5.70
0.92	3.28	137	0.408	4.48
1.84	3.30	140	0.398	4.63
3.22	2.10	152	0.383	3.20
4.60	1.27	184	0.368	2.34

described in terms of two mechanisms (12–14). In the "pore" mechanism, solutes are presumed to permeate the membrane by diffusion through microchannels or pores within the membrane structure. The rate at which solutes permeate the membrane is controlled primarily by the pore size of the membrane and the molecular volume of the solute (12). Cellulosic membranes exhibit this type of flow (12–14).

The other mechanism is the solution–diffusion or partition mechanism. In this type of permeation, solutes transverse the membrane by a process involving solute dissolution in the membrane structure followed by solute diffusion along and between the polymer segments that make up the membrane structure (13). The physical–chemical properties of the solute and the membrane play a dominant role in determining membrane permeability; the molecular volume of the solute is of secondary importance. Polyether urethane exhibits this type of permeation (13, 14).

These two mechanisms represent the extreme or limiting types of permeation. For any given membrane, permeation probably occurs by both mechanisms; however, one of the two will usually dominate. The permeation of progesterone through hydrogel membranes can be described in terms of the mechanisms described and, depending on the membrane composition, either the pore mechanism or the partition mechanism dominates.

Effects of Equilibrium Water Content—The effects of the equilibrium water content on the mechanism of progesterone permeation through hydrogel membranes were analyzed according to the methods outlined by Yasuda *et al.* (15, 16). When solutes permeate water-swollen membranes primarily by a porous mechanism, the following relationship should hold (15, 16):

$$\ln \frac{D}{D_0} = \frac{-\beta X(1-\alpha)}{1+\alpha X} \qquad \text{(Eq. 3)}$$

where $X = (1-H)/H$, $\alpha = V_f/V_w$, $\beta = V^*/V_w$, D_0 is the diffusion coefficient of progesterone in pure water, V_w is the free volume in a unit volume of pure water, V_f is the free volume in a unit volume of polymer, V^* is a characteristic volume parameter that describes the diffusion of the permeant molecule in the membrane, and H is the membrane hydration defined by the ratio (concentration of water in membrane/concentration of water in bulk). Equation 3 can be rearranged as follows to yield a linear plot:

$$\left(\ln \frac{D}{D_0}\right)^{-1} = \frac{-1}{\beta(1-\alpha)} X^{-1} - \frac{\alpha}{\beta(1-\alpha)} \qquad \text{(Eq. 4)}$$

A plot of the experimental values for the copolymer membranes according to Eq. 4 is shown in Fig. 4. A value of 7×10^{-6} cm²/sec was used for D_0 (17). As discussed by Yasuda *et al.* (15, 16), the linearity of the plot shown in Fig. 4 suggests that the structural factors for these water-swollen hydrogels are similar and that the permeation of progesterone occurs predominately through the porous regions of the network. Based on this plot, it appears that the dominant mechanism for the hydrogel membranes listed in Table I is the porous mechanism. However, as pointed out by Yasuda *et al.* (15, 16), this result does not imply that these membranes contain rigid pores of the type normally attributed to cellulosic membranes; rather, it suggests that the network is loose and that "fluctuating pores" are present.

Effect of Cross-Linking Agent—Figure 5 is a plot of the mole percent of cross-linking agent *versus* the diffusion coefficient of progesterone

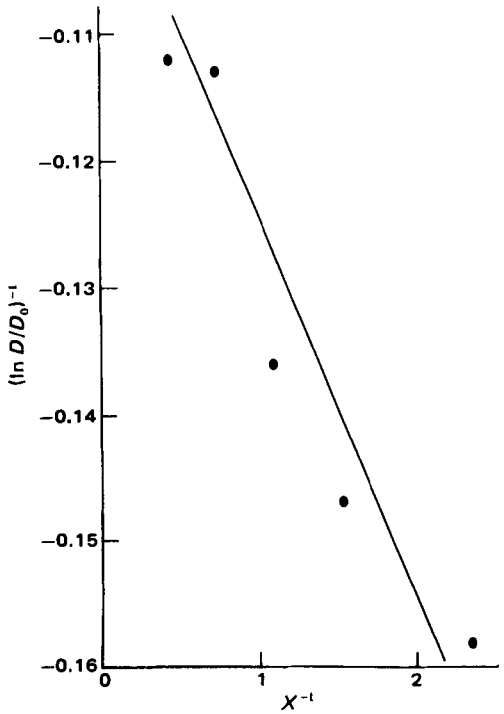

Figure 4—*Plot of* $(\ln D/D_0)^{-1}$ versus X^{-1} *for hydrogels swollen to different equilibrium water concentrations.*

for the hydrogel membranes described in Table II. As the mole percent of the cross-linking agent tetraethylene glycol dimethacrylate, decreased, the diffusion coefficient for progesterone increased linearly. The shape of this curve is in striking contrast to that shown for the cross-linking agent ethylene glycol dimethacrylate. At high concentrations of ethylene glycol dimethacrylate, the diffusion coefficient of progesterone was relatively independent of the mole percent of this cross-linker. However, at low concentrations of ethylene glycol dimethacrylate, the diffusion coefficient increased linearly with decreases in the concentration of the cross-linker. Thus, low concentrations of the cross-linker ethylene glycol dimethacrylate affect the diffusion coefficient of progesterone in the same way as the cross-linker tetraethylene glycol dimethacrylate.

As shown previously, the dominant mechanism of solute permeation through the uncrosslinked polyhydroxyethyl methacrylate membrane is permeation through "fluctuating pores" in the membrane. The effect of the cross-linking agent tetraethylene glycol dimethacrylate and low

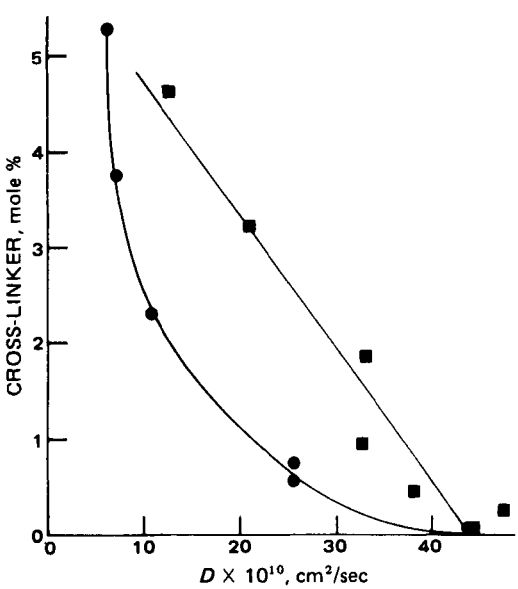

Figure 5—*Mole percent cross-linker* versus *diffusion coefficient. Key:* ●, *ethylene glycol dimethacrylate; and* ■, *tetraethylene glycol dimethacrylate.*

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).

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Comparison of Effects of Quinidine and Dihydroquinidine on Canine Heart

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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

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