

CARDIAC CONTROLLED RELEASE FOR ARRHYTHMIA THERAPY: LIDOCAINE-POLYURETHANE MATRIX STUDIES

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Cardiac arrhythmias are the principal cause of sudden death due to heart disease, and current therapy is inadequate. A novel approach for formulating a lidocaine-polyurethane controlled release matrix and implanting this drug delivery system directly onto the arrhythmic epicardium is reported. Lidocaine-HCl-polyurethane matrices (28% w/w) were fabricated and studied for their in vitro drug release into physiologic buffer, and their in vivo pharmacologic effectiveness in rapidly converting ouabain-induced ventricular tachycardia in dogs to normal sinus rhythm. In vitro lidocaine release was successfully modulated as a result of variations in fabrication: compression molding, and stirring during polymer synthesis. Lidocaine release in vitro from the most rapidly releasing matrix formulation delivered more than 40% of the contained drug delivered after only 20 minutes, and the remainder slowly released over one week or more. Direct epimyocardial placement of this formulation resulted in the prompt conversion of ouabain-induced ventricular tachycardia to normal sinus rhythm in all experimental animals (n=6) studied in 1.5 ± 0.77 min (mean \pm standard error), while controls (n=4) had persistent ventricular tachycardia for more than 60 min. Site-specific therapy was as rapid as intravenous administration, but with lower plasma lidocaine levels after comparable dosages. It is concluded that lidocaine-polyurethane controlled release matrices can be fabricated with a broad range of initial release profiles, and that these matrices can rapidly initiate the conversion of ouabain-induced ventricular tachycardia to normal sinus rhythm.

INTRODUCTION

Ventricular arrhythmias are the principal cause of sudden death in acute myocardial infarction, and frequently complicate the medical and surgical treatment of a wide array of cardiac diseases [1]. However, conventional therapy is often ineffective in either preventing or

rapidly treating life-threatening ventricular arrhythmias, due to inadequate myocardial drug concentrations and adverse effects [2]. Lidocaine is a widely used antiarrhythmic agent for the therapy of ventricular tachycardia [3]. Nevertheless, this compound is only effective clinically when given intravenously, and its use is frequently associated with untoward drug effects [3].

Implantable controlled release drug delivery systems have received increasing attention over the past decade [4-7], and represent an impor-

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tant and emerging area of research, which may be useful in the therapy of a wide variety of disease processes, including cardiac arrhythmias. The primary goal of this type of site-specific drug administration is the prolonged delivery of a medication into a particular body compartment at effective, but minimal local therapeutic concentrations, while reducing the risk of generalized toxic effects. However, it should be noted that ventricular tachycardia is life-threatening and its rapid conversion within minutes to sinus rhythm is a prerequisite for any dosage form.

The present study examined lidocaine-polyurethane controlled release matrix formulations *in vitro* and tested the novel hypothesis that lidocaine could be effectively administered transmurally by a polymeric matrix, placed on the epicardial surface in dogs, for the rapid conversion of ouabain-induced ventricular to normal sinus rhythm. The objectives of these studies were to investigate methodology for modulating matrix release of lidocaine, and then to study the efficacy and mechanisms of onset of action of these formulations in a canine model of ouabain-induced ventricular tachycardia.

MATERIALS AND METHODS

Lidocaine-HCl (Abbott Inc., Chicago, Ill.) was sieved to a particle size of 75–150 μm (U.S.A. standard sieve nos. 100–200, ASTM designation E11, Newark Wire Cloth Co., Newark, N.J.). Matrices were fabricated using the Tecoflex 2-80A polyurethane two component system (Thermedics, Inc., Woburn, Mass.) combined with lidocaine-HCl (28%w/w lidocaine-polyurethane) and catalyzed by the addition of FeCl_3 , 0.74 $\mu\text{mol/g}$ polyether (as 5 mg/ml solution in acetone). Typically, 4 parts of lidocaine were combined with 10 parts of Tecoflex 2-80A using 0.21 parts of the diisocyanate monomer and 0.79 parts of the polyether monomer. Polymeric matrices were formed by film casting (2 mm thickness) of the reaction

mixture, and polymerization for 48 hours at 55°C with or without a 2 minute period of stirring (50 rpm) after two hours of polymerization. Another series of matrices was polymerized with compression molding (0.01 ton) of the lidocaine-monomers mixture at 55°C with the bonding of reinforced Silastic sheeting (501-1 Dow Corning Corp., Midland, Mich.) onto one of the planar surfaces in order to seal it from drug release. Matrices (1 cm \times 1 cm samples) were released into 10 ml of buffer (pH 7.4, 0.05 *M* potassium phosphate, 37°C) in polyethylene vials on an orbit shaker (100 rpm). The solubilized lidocaine was monitored by absorbance at 260 nm, and the data were expressed as the means of duplicate measurements.

Lidocaine measurements utilized a Waters high performance liquid chromatograph (Model 6000A, Waters Inc., Bedford, Mass.) with a prepacked C18 column (particle size 5 μm), Altex Ultrasphere-ODS 25 cm \times 4.6 mm I.D. (Beckman Inc., San Ramon, Calif.), and an isocratic mobile phase of 0.1 *M* sodium phosphate buffer pH 3.0 with 0.7% v/v triethylamine-acetonitrile (50:50). Chromatographic absorbance was monitored at 210 nm [9,10]. Net *in vivo* polymeric lidocaine delivery was determined by Soxhlet methanolic extraction of the residual drug remaining in the polymeric matrices after use, followed by subsequent high performance liquid chromatographic (HPLC) analyses [9,10].

Scanning electron micrographs were taken on cross-sections of the lidocaine-polyurethane matrices. Specimens were sputtered with gold-palladium to suppress electron beam-induced charging, and were examined with an ISI-DSI30 scanning electron microscope (ISI Inc., Mountain View, Calif.).

Ventricular tachycardia was induced with ouabain administration [8] in 12 male mongrel dogs (12–14 kg), which had undergone a left thoracotomy and pericardotomy under pentobarbital anesthesia. Bipolar platinum tip electrodes (Ethicon, Somerville, N.J.) were sewn to the left atrial appendage, right ventricle, and

left ventricular free wall for electrocardiographic recording. Ouabain (Sigma Inc., St. Louis, Mo.) was administered at an initial dose of 40 $\mu\text{g}/\text{kg}$ intravenously at a rate of 40 $\mu\text{g}/\text{min}$, and at subsequently halved dosages until sustained ventricular tachycardia was documented on the electrocardiogram (AR6, Honeywell, Inc., Wellesley, Mass.). The electrocardiogram lead configuration utilized standard surface limb leads, II and AVR as well as atrial and ventricular leads (see Fig. 3). Ten dogs were used in the epicardial polymer studies and two were given intravenous lidocaine. In each epicardial administration animal, the polymeric matrix, either control (non-drug containing) or containing lidocaine, was left in place on the left ventricular myocardium for the time needed to initially convert the ventricular tachycardia to normal sinus rhythm, or for one hour. When sinus rhythm reappeared, the matrix was removed after one additional minute, and the experiment was continued in order to detect the return of the arrhythmia. Periodic blood sampling was carried out to monitor the resulting plasma lidocaine levels. Two animals were given intravenous lidocaine over 1.5 minutes at dosages equivalent to the extremes (25 and 45 mg/kg) delivered by the lidocaine-polyurethane patches as determined by Soxhlet analysis (as described, above) and these animals were studied for comparisons with respect to their lidocaine plasma levels.

RESULTS

Controlled release of lidocaine from polyurethane matrices was achieved with an array of formulations possessing a broad range of kinetic profiles. In addition, lidocaine polyurethane matrices successfully and rapidly converted ouabain-induced ventricular tachycardia in dogs to sinus rhythm.

Control release of lidocaine: *In vitro* results

Sustained cumulative release of lidocaine from the polyurethane matrices was comparable between all formulations, however the early phase of release could be modulated depending upon the synthetic technique used (Fig. 1). Matrices formulated with compression molding and sealing demonstrated with lowest bulk release rates in the first sixty minutes of *in vitro* incubation, compared with polymers fabricated by simple film casting techniques and polymerized over 48 hours. These latter matrices released nearly 40% of their contained lidocaine after only 20 minutes. Polymers synthesized with a disruptive stirring step demonstrated an early release phase, which was intermediate in rate compared with the previous two approaches.

The differences in release kinetics may be explained in part by the surface sealing effects of the bonded silastic sheeting, and by the diminished ultrastructural porosity noted in the stirred matrices compared with that seen in the films polymerized by casting at 55°C. These important differences in matrix porosity are evident in the scanning electron microscopic studies of the polymers carried out prior to their release (Fig. 2). However, it is of interest that post-release scanning electron micrographs revealed qualitatively greater depletion of the granular lidocaine from the non-stirred matrices compared with either the stirred or compression molded-sealed matrices. The sealing of 50% of the matrix surface in the compression molded group probably explains its relatively lower release rate.

Rapid conversion of ventricular tachycardia to sinus rhythm in dogs with lidocaine-polyurethane matrices

Ouabain-induced ventricular tachycardia in dogs was successfully and quickly resolved (Table 1 and Fig. 3) using the most rapidly releasing matrix formulation (non-stirred, see

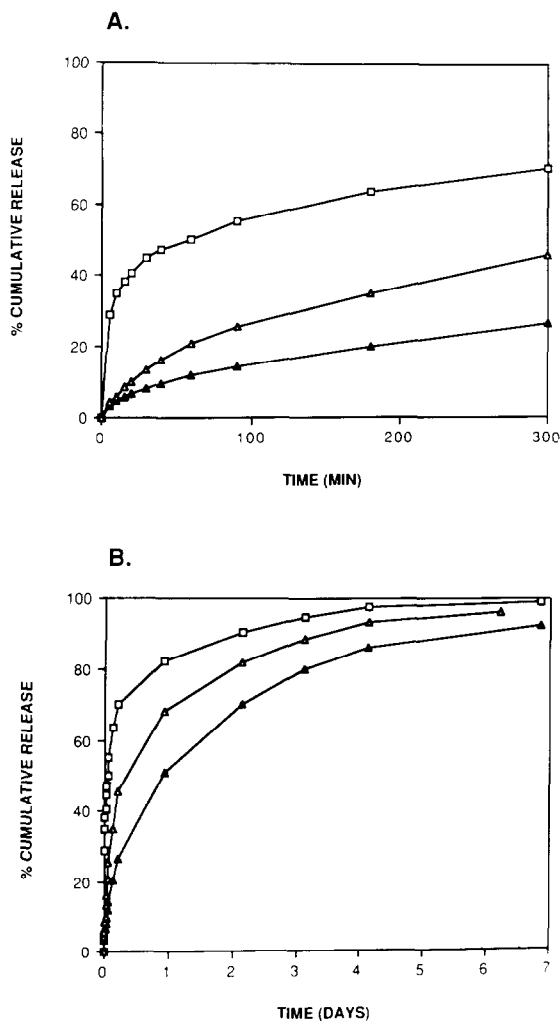


Fig. 1. Cumulative *in vitro* drug delivery (monitored by absorbance at 260 nm) of lidocaine-HCl (28% w/w loading) from polyurethane matrices into pH 7.4 buffer (0.05 M potassium phosphate), showing short term (A) and sustained release (B) characteristics. Lidocaine release was affected by the following variations in fabrication: □ = polymerization at 55°C without stirring, △ = at 55°C with brief stirring after 2 hours of polymerization, and ▲ = compression molding at 55°C with silastic sealing at one side.

Methods) applied to the left ventricular epicardium. Ventricular tachycardia was converted to sinus rhythm in all treated dogs after 1.5 ± 0.77 min. In contrast, control polymer (drug-free polyurethane) applications had no effect on the

course of the ventricular tachycardia, which persisted for more than one hour in all experimental animals. After conversion of ventricular tachycardia to sinus rhythm, matrices were removed after one minute, and plasma lidocaine levels were noted to typically exhibit a delayed peak (after 1 to 5 minutes), which was four fold or more reduced in magnitude compared with intravenous administration. The net lidocaine dose delivered by the matrices over the brief duration of application was quite high, ranging from 24.1 to 48.9 mg/kg. Despite this, plasma levels of 8.75 to 25.5 $\mu\text{g}/\text{ml}$ were noted, compared with 36.7–101.2 $\mu\text{g}/\text{ml}$, respectively, when the same doses were administered intravenously (Fig. 4). Thus, transmyocardial drug delivery appears to result in extravascular compartmentalization of lidocaine, and relatively lower plasma levels compared with intravenous administration.

Three of the six lidocaine controlled release animals, which demonstrated conversion of ventricular tachycardia to sinus rhythm, experienced a resumption of the arrhythmia after 15 to 25 minutes. These animals had plasma lidocaine levels of 0.64–7.94 $\mu\text{g}/\text{ml}$ at the time of the resumption of ventricular tachycardia compared with plasma levels of 1.2–2.9 $\mu\text{g}/\text{ml}$ in the three animals with persistent sinus rhythm after 45–60 minutes. Thus, plasma lidocaine proved to be an insensitive index of the duration of the effectiveness of an initially effective dose of transmyocardial lidocaine.

DISCUSSION

The present study has investigated the formulation and modulation of lidocaine-polyurethane controlled release matrices, as well as the effectiveness of short term *in vivo* release of lidocaine for the rapid site-specific conversion of ventricular tachycardia to sinus rhythm. Epicardially placed lidocaine matrices were rapidly effective for site-specific therapy of

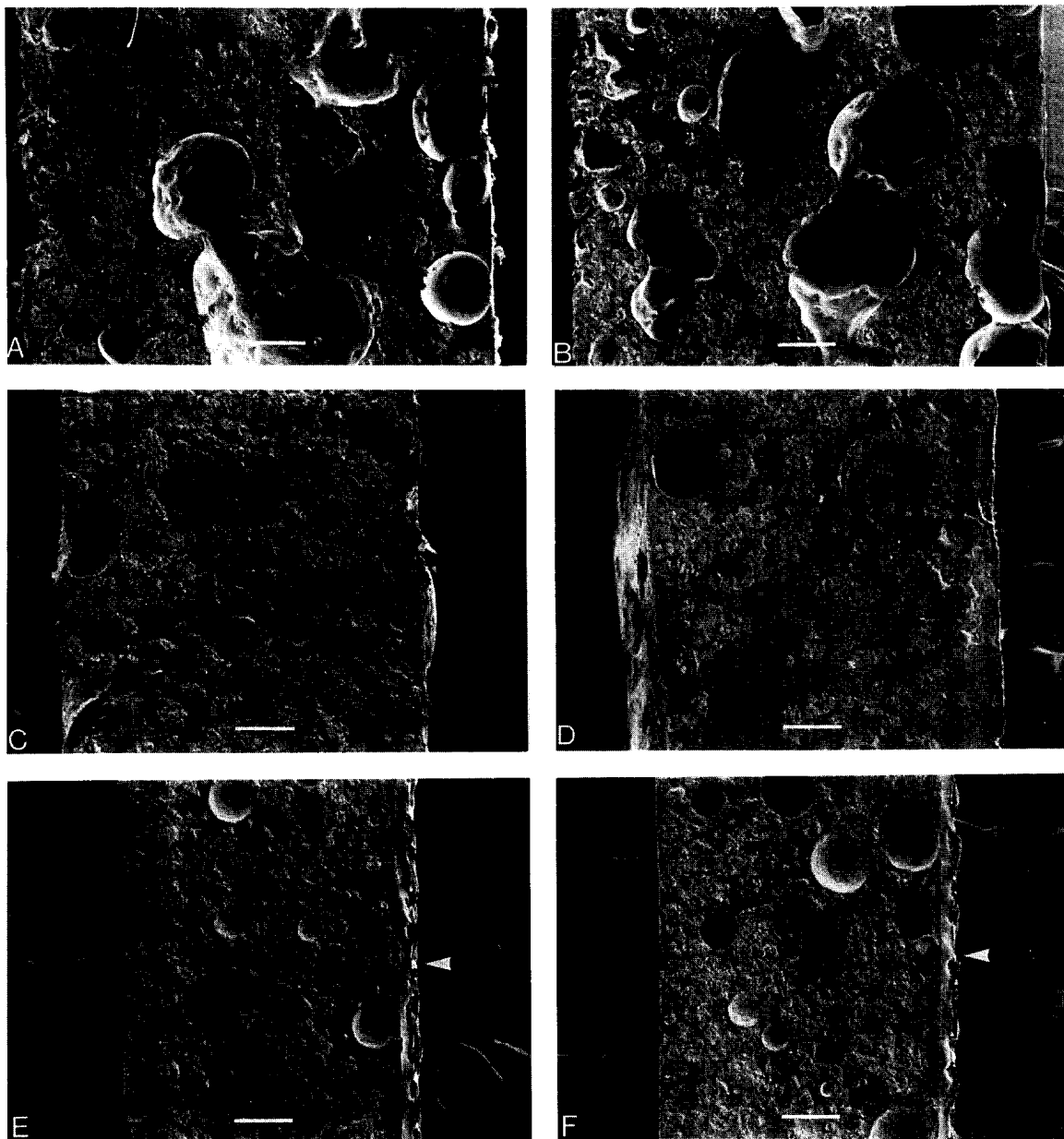


Fig. 2. Scanning electron micrographs (bar = 500 μm) of lidocaine-polyurethane (28% w/w) matrices before and after five minutes release into a physiologic buffer. Lidocaine release from non-stirred matrices is shown before (A) and after release (B), illustrating extensive depletion of granular lidocaine via rapid permeation through the open porous structure. Release of lidocaine from matrices stirred during polymerization is shown pre-(C) and post-release (D), revealing an extensive granular depletion from the matrix structure, although from a less intrinsically porous matrix than noted in (A) and (B). Lidocaine release from compression-molded matrices, sealed with Silastic sheeting (arrow), demonstrated the least depletion in granular lidocaine comparing matrices before (E) and after release (F), due to the compact matrix structure and bonded Silastic sealing of one of the potential releasing surfaces.

TABLE 1

Ventricular tachycardia (ouabain-induced) response to lidocaine-polyurethane matrices applied to the left ventricular epicardium in dogs

Route of lidocaine administration	No. of animals converted to SR	Time of conversion to SR (min)	Duration of drug application (min)	Time of return of VT (min)	% drug delivered from matrix	Lidocaine dose (mg/kg)	Peak plasma level ($\mu\text{g/ml}$)
Intravenous	1/1	0.5	1.5	—	—	24.0	36.7
Intravenous	1/1	0.5	1.5	—	—	45.0	101.2
Drug-free polymer (control)	0/4	—	—	—	—	—	0
Lidocaine-polyurethane	6/6	1.5 ± 0.77^a	2.5 ± 1.73	15-25 ^b	43.8 ± 10.5	39.2 ± 8.8	16.5 ± 8.0

^aMean \pm standard error, $p < 0.001$ compared with control with Student's *t*-test.

^bReturn of ventricular tachycardia (VT) was noted in 3 animals, with the remainder continuing in normal sinus rhythm (SR) for > 60 minutes.

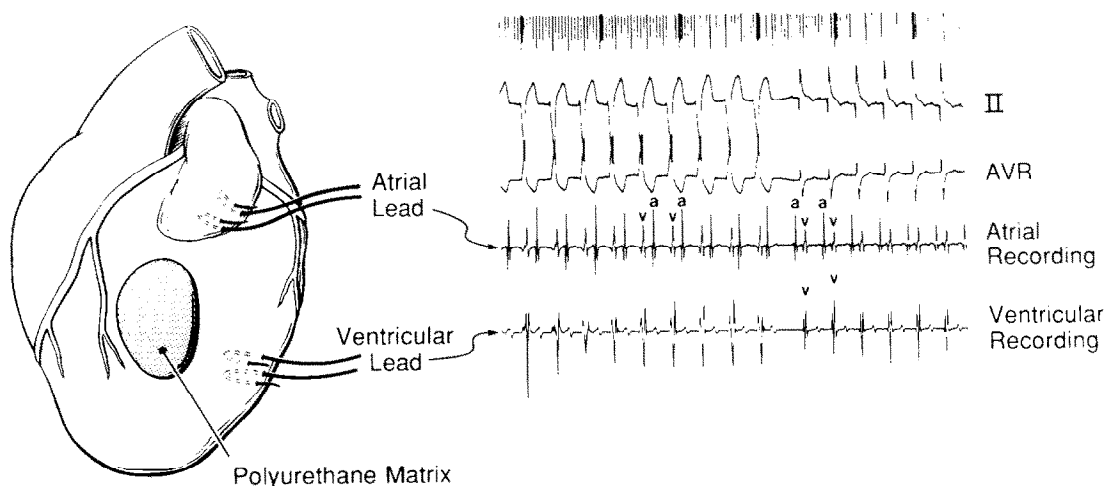


Fig. 3. Ouabain-induced ventricular tachycardia in canines (via a left thoracotomy): experimental polymeric patches ($3 \times 3 \times 0.2$ cm), either a control (non-drug containing) or a lidocaine-polyurethane matrix, were separately applied to the epicardial left ventricular myocardium 1-2 cm to the left of the anterior descending coronary artery 1-2 cm below the circumflex coronary. Atrial and ventricular deflections are indicated as "a" and "v", respectively, with 0.04-second time markings. Conversion of ventricular tachycardia after placement of a lidocaine-polyurethane matrix to normal sinus rhythm is clearly observed.

ouabain-induced ventricular tachycardia in dogs.

Polyurethane controlled release matrices containing hydrophilic compounds have been the subject of relatively little previous research. The reasons for this include dispersant-matrix

incompatibility, incomplete polymerization, and the insolubility of many hydrophilic compounds in the organic solvents used to process polyurethane. These problems have been successfully addressed in the present study. Lidocaine-HCl proved to be completely compatible

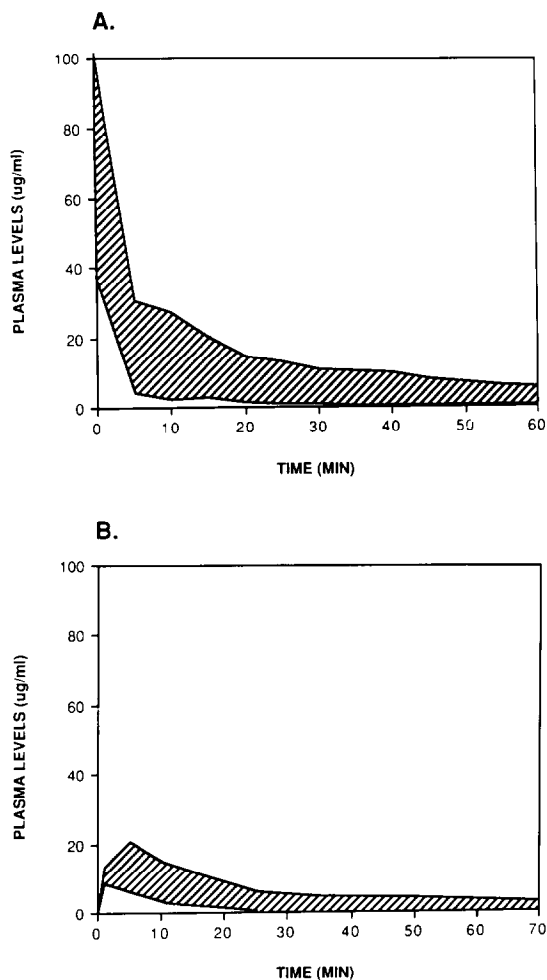


Fig. 4. Lidocaine plasma levels (ranges) determined by high performance liquid chromatography (HPLC) in canine studies of ouabain-induced ventricular tachycardia reflecting the means of duplicate measurements: (A) The range of plasma levels ($N=2$) following intravenous administration of 25 and 45 mg/kg lidocaine, which were doses corresponding to the epicardial administration achieved in (B), which illustrates the range of plasma levels ($N=6$) and their time-dependent decay after epicardial lidocaine-polyurethane therapy (see Table 1).

and well dispersed in the bulk reagents and was stable under the polymerization reaction conditions used. In addition, the polymerization proceeded faster with the addition of a FeCl_3 catalyst.

Minor modifications in the polymerization

procedures proved to have potent effects on the observed release kinetics in the early phases of controlled release. Polymers formed at 55°C for 48 hours demonstrated the most rapid releasing characteristics during the initial phase of the incubations. However, stirring of the polymers during their formulation, which enhanced reactive crosslinking, resulted in a relative diminishing of the early phase of release, and this effect was probably due to the partial elimination of cavities created during the polymerization. Furthermore, compression molding with sealing resulted in an even greater limiting of the early phase of release, and this was probably due to further reduction of these cavities, and limiting the releasing surface by bonding of impermeable Silastic sheeting.

The *in vivo* suppression of ouabain-induced ventricular tachycardia was studied using only the matrices with the most rapid releasing characteristics in order to demonstrate the effectiveness of this route of administration and the efficacy of the dosage form *per se*. A rapid onset of effect is a prerequisite of a controlled release system for the treatment of ventricular tachycardia, since this arrhythmia is often lethal and can, unless promptly treated, progress on to an even more dangerous arrhythmia, ventricular fibrillation. Of additional interest in the present results is the apparent late peaking of plasma lidocaine levels following transmucosal drug delivery, despite the rapid and brief period of exposure to the controlled release matrix. This suggests that a secondary phase of controlled release is taking place from the myocardium, which was exposed to the rapid-release polyurethane matrix.

The plasma lidocaine levels achieved in these experimental studies were well below those noted after intravenous administration of the same net lidocaine dose, but were nevertheless higher than those usually considered to be therapeutic in humans. It is likely that further studies of localized experimental arrhythmic foci, using perhaps programmed stimulation techniques rather than systemic ouabain toxicity,

will reveal that the dose needed via lidocaine matrix administration will be but a fraction of that used in the present study. Furthermore, the patterning of controlled release may in fact consist of two separate phases, one concerned with the short-term delivery of high levels of drug, similar to the approach of this work, in order to rapidly convert a life-threatening arrhythmia, and a chronically suppressive phase, using lower levels of antiarrhythmic agents to prevent the re-emergence of the arrhythmia.

Polymeric drug delivery of chronotropic agents was successfully carried out by others using myocardial implants of silicone rubber reservoirs containing a variety of compounds including digoxin, isoproterenol, and thyroid hormone, all of which could effectively accelerate cardiac rate when delivered directly into the myocardium [11]. Epicardial lidocaine has been used prior to these studies in experiments investigating decreased cardiac output due to an epicardial lidocaine drip [12]. This route of administration has also been used to effectively sympathetomize the heart, after filling the pericardial sac with a lidocaine solution [13]. Both of these previous approaches raise important questions about the mechanism of action of epicardial lidocaine and its adverse effects when administered by a controlled release matrix.

The eventual clinical utility of this experimental approach may require that the site of matrix placement and the duration of antiarrhythmia drug delivery be varied optimally to meet the needs of the disease process of interest. A number of potential clinical settings are possible, and these would include such applications as using a biodegradable epicardial polymer for suppression of post-operative arrhythmias during the first week following open heart surgery. Another application might be a drug delivery implant to be used instead of or as an adjunct to ablative arrhythmia surgery. Drug delivery implants could also be put in place via cardiac catheterization using screw-tip insertion techniques analogous to those used to

install pacemaker leads. This approach might prove to be beneficial to the hundreds of thousands of patients receiving ineffective conventional arrhythmia therapy.

Sustained site-specific cardiac drug delivery for periods ranging from weeks to years has been demonstrated experimentally for antibiotic therapy to prevent bacterial endocarditis [5], and the administration of diphosphonate compounds to prevent bioprosthetic heart valve calcification [7]. Furthermore, controlled drug delivery matrices are in clinical use in a steroid-eluting cardiac pacing catheter [6], in which site-specific dexamethasone administration is utilized to prevent fibrous tissue buildup. These drug delivery systems were all fabricated from polymeric-based matrices, which are directly analogous to those used in the present arrhythmia studies. However, the matrices which were investigated in the present work differ from these other examples in their ability to deliver quickly a relatively large amount of their contained drug, thereby providing the opportunity for immediate conversion of a life-threatening cardiac arrhythmia, ventricular tachycardia, to a normal sinus rhythm. These functional differences are due to the unique fabrication and formulation conditions used which optimize matrix surface area exposure during the early phases of release.

In conclusion, lidocaine-polyurethane controlled release matrices have been successfully formulated with a broad range of release rates, and have been shown to be efficacious via epicardial placement for the site-specific conversion of ouabain-induced ventricular tachycardia in dogs to normal sinus rhythm.

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