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Developmental Cellular Electrophysiologic Effects of *d*-Sotalol on Canine Cardiac Purkinje Fibers

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ABSTRACT. *d*-Sotalol may be a clinically useful class III antiarrhythmic agent for controlling ventricular arrhythmias in children. Because age-related differences in repolarization currents may contribute to developmental differences in response to antiarrhythmic agents that primarily affect repolarization, the electrophysiologic effects of *d*-sotalol were compared in Purkinje fibers from neonatal and adult dogs. Significant age-related changes characterized the antiarrhythmic profile of *d*-sotalol. *d*-Sotalol (10^{-4} M) significantly prolonged the action potential duration of adult Purkinje fibers (310 ± 8 to 380 ± 7 ms, $p < 0.01$) and neonatal fibers (247 ± 5 to 342 ± 9 ms, $p < 0.01$). However, the lengthening of action potential duration was significantly greater in the immature age group. *d*-Sotalol had no significant effect on maximum diastolic potential, action potential amplitude, or phase zero upstroke velocity in normally polarized fibers. In contrast, different electrophysiologic effects were observed in K^+-depolarized Purkinje fibers. Superfusion of adult K^+-depolarized fibers with *d*-sotalol suppressed excitability in five (38%) of 13 fibers and significantly decreased action potential amplitude (88 ± 2 to 83 ± 1 mV, $p < 0.05$) and phase zero upstroke velocity (180 ± 14 to 105 ± 3 V/s, $p < 0.01$) in the other eight fibers. The membrane depressant effects observed in the younger age group were significantly less [no suppression of excitability and a smaller decrease in phase zero upstroke velocity (121 ± 22 to 101 ± 23 V/s, $p < 0.05$). The magnitude of action potential duration prolongation by *d*-sotalol in K^+-depolarized fibers was less than in normally polarized fibers. These results suggest that at the clinical level the mechanism of *d*-sotalol's antiarrhythmic action will depend not only on the developmental maturity, but also on the resting membrane potential of the tissue treated. (*Pediatr Res* 29: 104–109, 1991)

Abbreviations

APA, action potential amplitude
APD_{50}, action potential duration to 50% repolarization
APD_{100}, action potential duration to full repolarization
MDP, maximum diastolic potential
$\dot{V}_{max}$, phase zero upstroke velocity

Arrhythmia control by lengthening of cardiac repolarization has emerged as an effective antiarrhythmic mechanism (1). A high therapeutic success rate in the treatment of ventricular arrhythmias with antiarrhythmic drugs that significantly prolong repolarization, class III effect, has broadened clinical interest in their use (2, 3). The electrophysiologic effects of class III antiarrhythmic agents have been studied in mature animals and adult humans (4–7), but little is understood of their effects in younger subjects (8–11). Furthermore, important insights into the ionic events regulating cardiac repolarization in the immature may be learned through study of the electrophysiologic effects of class III antiarrhythmic agents that inhibit specific potassium currents. Selective inhibition of specific potassium currents may underscore their role in the overall repolarization process.

Previous developmental studies of the cellular electrophysiologic effects of antiarrhythmic drugs have observed age-related differences in responsiveness. Cardiac tissues from immature animals demonstrate little inhibition of $\dot{V}_{max}$ (an indirect measurement of fast sodium channel activity) after exposure to concentrations of local anesthetic drugs that depress adult tissues (12, 13). Similarly, the sensitivity of slow-response action potentials to calcium channel blockers is diminished in the neonatal age group (14, 15).

Sotalol is a β-adrenergic blocking agent that prolongs action potential duration and cardiac refractoriness. Its *d*-isomer has little β-adrenergic blocking activity, except at extremely high concentrations (16). The purpose of this study was 2-fold: first, to assess age-related differences in the cellular electrophysiologic effects of *d*-sotalol, an antiarrhythmic drug that predominantly inhibits potassium currents (17, 18). Because the electrophysiologic effects of many antiarrhythmic drugs are dependent on the experimental conditions and state of health (level of membrane potential) of the tissue studied (19), the second purpose was to determine whether *d*-sotalol exerted antiarrhythmic actions in depolarized tissue not recognized in previous electrophysiologic studies on healthy myocardium with a normal resting membrane potential.

MATERIALS AND METHODS

Neonatal (0 to 10 d) and adult dogs (1 to 5 y, weighing 15 to 25 kg) were anesthetized with 35 mg/kg sodium pentobarbital, given i.v. to adults and intraperitoneally to neonates. The heart was quickly removed and placed in cold oxygenated Tyrode's solution. Free-running Purkinje fiber bundles were dissected from the right and left ventricle (disconnected from any muscle attachments) and placed in a Lucite tissue bath superfused with Tyrode's solution containing (mmol/L): NaCl, 131; $NaHCO_3$, 18; $CaCl_2$, 2.7; $MgCl_2$, 0.5; NaH_2PO_4, 1.8; KCl, 4.0, and dextrose, 5.5. The Tyrode's solution was bubbled with 95% O_2-5% CO_2 and warmed to 37°C, (pH 7.33 ± 0.15).

Stimuli were delivered with bipolar silver wires that were insulated to the tips with Teflon. The stimulus pulse width was

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2 ms and the amplitude was 1.5 to 2.0 times diastolic threshold. The Purkinje fibers were impaled with 3 M KCl-filled glass capillary microelectrodes having tip resistances of 10–30 M ohms. The Purkinje fibers were paced at a cycle length of 500 ms and allowed to stabilize for 1 h before control measurements were made. After equilibration, the following transmembrane action potential characteristics were measured from photographic recordings: MDP; APA; $\dot{V}_{max}$, which was differentiated electronically; plateau height (measured from 0 potential to the peak of the plateau); APD_{50}; and APD_{100}. The slopes of phases 2 and 3 of repolarization were measured digitally from photographic enlargements of recorded transmembrane action potentials. Plateau duration was measured from the end of phase 1 to the beginning of phase 3. The methods used for measuring transmembrane action potential characteristics, calibrating the equipment, and recording the action potential data have been described previously (20).

The cellular electrophysiologic effects of *d*-sotalol were studied in three groups of Purkinje fibers: adult free-running, adult subendocardial, and neonatal free-running fibers. To assess age-related differences in the electrophysiologic effects of *d*-sotalol in similar regions of the conduction system, the response of free-running Purkinje fibers from adult and neonatal animals was compared. Previous microelectrode studies have shown adult Purkinje fibers to have significantly longer action potential durations, compared to neonatal fibers (14). In an attempt to minimize differences in action potential duration as a variable explaining developmental differences in drug response, comparison of the electrophysiologic effects of *d*-sotalol superfusion was made between adult subendocardial Purkinje fibers (shorter action potential than adult free-running fibers) and neonatal free-running Purkinje fibers (21).

The Purkinje fibers were superfused with graded concentrations of *d*-sotalol hydrochloride (Bristol-Myers Squibb, Wallingford, CT): 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, and 1×10^{-4} M. Transmembrane action potential characteristics were recorded after an initial equilibration period of 60 min, and 25 min after each change in superfusate concentration. Steady state effects were achieved within 25 min of onset of *d*-sotalol superfusion.

To explore whether the effect of *d*-sotalol on depolarized Purkinje fibers was different from that noted in healthy tissue with a normal MDP, neonatal and adult Purkinje fibers were superfused with Tyrode's solution containing a higher KCl concentration. MDP was depolarized from −92 mV (adult Purkinje fibers) and −85 mV (neonatal Purkinje fibers) to −64 ± 1 mV, using KCl, 11 ± 1 mM/L. The superfusate potassium concentration was changed in stepwise increments until MDP decreased to − 64 ± 1 mV.

Toxic effects of d-sotalol. Thirty min after superfusion with *d*-sotalol 10^{-4} M, external pacing was terminated and spontaneous activity observed. After attaining a steady state spontaneous cycle length, each Purkinje fiber was paced for a 3-min period at cycle lengths between 2000 and 500 ms, beginning at a cycle length 10% less than the spontaneous cycle length. The paced rate was decremented by 200-ms intervals. At each paced cycle length, early afterdepolarizations and triggered activity were searched for.

Data analysis. Only results from experiments in which a continuous impalement was maintained throughout the superfusion protocol were analyzed. A nested analysis of variance was used to assess statistically significant differences between the two age groups (22). When significance was found ($p < 0.05$), comparisons between groups were made using Bonferroni's modification of the *t* test. Significance was determined at $p < 0.05$. Results are expressed as the mean ± SEM.

RESULTS

Effects of d-sotalol on normally polarized Purkinje fibers. The predominant electrophysiologic effect of *d*-sotalol was to prolong repolarization (Fig. 1). *d*-Sotalol significantly prolonged APD_{50} in both adult and neonatal Purkinje fibers. The effect was similar for each age group. In the 12 adult fibers studied, *d*-sotalol 1×10^{-4} M significantly prolonged APD_{50} from a control value of 202 ± 8 to 229 ± 7 ms ($p < 0.01$). In the 12 neonatal fibers studied, *d*-sotalol prolonged APD_{50} from a control value of 151 ± 2 to 177 ± 11 ms ($p < 0.01$).

A significant age-related difference in response of full repolarization to *d*-sotalol was observed (Fig. 1). After exposure to *d*-sotalol 1×10^{-4} M, the APD_{100} of neonatal Purkinje fibers increased from a control value of 247 ± 5 to 342 ± 9 ms ($p < 0.01$). Although *d*-sotalol 1×10^{-4} M prolonged the APD_{100} of adult fibers significantly [310 ± 8 to 380 ± 7 ms ($p < 0.01$)], the degree of action potential prolongation was significantly different than that observed for the neonatal age group ($p < 0.01$). In the neonatal age group, *d*-sotalol 1×10^{-4} M prolonged APD_{100} by 27%, in contrast to only 18% in the older group of fibers.

Superfusion of Purkinje fibers with concentrations of *d*-sotalol that prolonged repolarization had no significant depressant effect on MDP, APA, or $\dot{V}_{max}$ (Table 1).

The response of plateau height, plateau duration, and the slope of phases 2 and 3 of repolarization to *d*-sotalol superfusion was analyzed to further characterize the age-related differences in repolarization observed. *d*-Sotalol superfusion had no significant effect on plateau height in either age group: adult fibers, 0 ± 1 mV (control) *versus* −2 ± 1 mV (*d*-sotalol 1×10^{-4} M); neonatal fibers, 11 ± 3 mV (control) *versus* 11 ± 3 mV (*d*-sotalol 1×10^{-4} M). Figure 2*A* demonstrates a concentration-dependent prolongation of plateau duration after *d*-sotalol superfusion in both age groups studied; however, the magnitude of increase in plateau duration was significantly greater for the younger age group ($p < 0.01$). In addition, the threshold concentration for prolonging plateau duration in the neonatal fibers was lower (*d*-sotalol 1×10^{-5} M). *d*-Sotalol had no significant effect on the slope of phase 2 repolarization in either age group (Fig. 2*B*). The change in the slope of late repolarization, phase 3, is shown in Figure 2*C*. *d*-Sotalol significantly slowed the slope of phase 3 in both age groups; however, the decrease in the slope of phase 3 was significantly greater in the neonatal fibers ($p < 0.01$) and occurred at a lower threshold concentration in the younger age group (*d*-sotalol 1×10^{-5} M).

To exclude the possibility that the enhanced responsiveness of the neonatal age group to *d*-sotalol was not secondary to the longer action potential duration of adult Purkinje fibers, similar experiments were performed using adult subendocardial Purkinje fibers. The APD_{100} of adult subendocardial Purkinje fibers (267 ± 7 ms) was shorter than that observed in free-running adult strands (310 ± 8 ms) and closer to neonatal fibers (247 ± 5 ms). The effect of *d*-sotalol on APD_{100} of adult subendocardial Purkinje fibers and neonatal fibers is presented in Figure 3. *d*-Sotalol significantly prolonged APD_{100} in adult subendocardial Purkinje fibers. Despite similar control action potential durations, neonatal fibers again exhibited a larger increase in APD_{100} compared with the adult group ($p < 0.01$). Action potential recordings from two experiments are shown in Figure 4.

Toxic effects of d-sotalol. Significant age-related differences in the toxic effects of *d*-sotalol were observed. A strip chart recording from an adult fiber superfused with *d*-sotalol 1×10^{-4} M is displayed in Figure 5. In these experiments, the adult and neonatal Purkinje fibers were paced at cycle lengths ranging from 2000 to 500 ms. Short, nonsustained runs of triggered activity initiated by early afterdepolarizations were evident in the adult fibers only. Triggered activity started within 10 s of a change in cycle length. *d*-Sotalol induced early afterdepolarizations and triggered activity in seven of 12 Purkinje fibers and in none of the 12 neonatal fibers studied.

Effects of d-sotalol on K^+-depolarized Purkinje cells. In contrast to its limited electrophysiologic effect on repolarization in normally polarized Purkinje cells, *d*-sotalol exhibited membrane depressant activity in K^+-depolarized Purkinje fibers (Table 2).

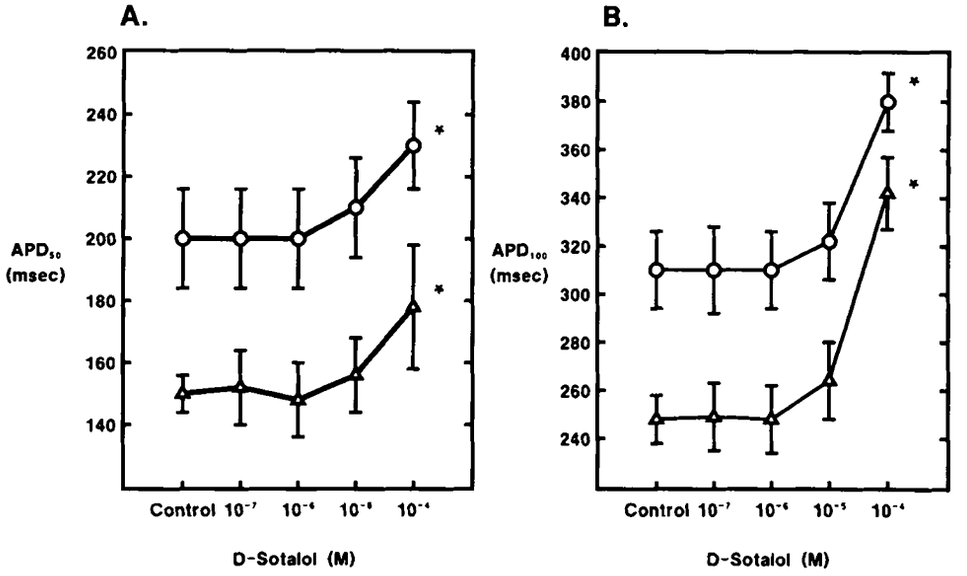

Fig. 1. The influence of *d*-sotalol on repolarization of adult (n = 12) and neonatal (n = 12) free-running Purkinje fibers. The concentrations (M) of *d*-sotalol superfused are shown on the abscissa; the responses of APD_{50} (*A*) and APD_{100} (*B*) measured in ms are illustrated on the ordinate. *d*-Sotalol significantly prolonged action potential duration at 50% and full repolarization. See text for discussion. O, adult fibers; Δ, neonatal fibers; *, $p < 0.01$ compared with control.

Table 1. *Effects of d-sotalol on action potential characteristics of normally polarized adult and neonatal Purkinje cells**

DS concentration	MDP (−mV)	APA (mV)	$\dot{V}_{max}$ (V/s)
Adult Purkinje fibers (n = 12)			
Control	92 ± 1	137 ± 1	610 ± 13
DS 10^{-7} M	92 ± 1	136 ± 1	608 ± 15
DS 10^{-6} M	93 ± 1	137 ± 1	612 ± 11
DS 10^{-5} M	93 ± 1	137 ± 1	614 ± 13
DS 10^{-4} M	93 ± 1	137 ± 1	602 ± 14
Neonatal Purkinje fibers (n = 12)			
Control	85 ± 1	121 ± 1	411 ± 10
DS 10^{-7} M	85 ± 1	121 ± 2	406 ± 11
DS 10^{-6} M	84 ± 1	120 ± 2	404 ± 11
DS 10^{-5} M	85 ± 1	120 ± 1	397 ± 10
DS 10^{-4} M	85 ± 1	119 ± 2	396 ± 9

* Values are mean ± SEM. DS, *d*-sotalol.

KCl (11 ± 1 mM) was used to produce depressed fast-response action potentials in adult and neonatal fibers. After equilibration, action potential characteristics remained stable for at least 2 h after increasing the extracellular potassium concentration (preliminary results). Once depolarized, 13 adult and 12 neonatal fibers were superfused with *d*-sotalol: 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, and 1×10^{-4} M.

An age-related difference in the membrane depressant effect of *d*-sotalol was apparent, the depressant effect being greater in adult fibers. Five of thirteen adult fibers studied became inexcitable during *d*-sotalol 1×10^{-5} M exposure, even during maximum stimulation (100 V, 2 ms). None of the 12 *d*-sotalol-superfused neonatal fibers developed enough depression to become inexcitable. In the other eight adult fibers studied, *d*-sotalol 1×10^{-4} M significantly decreased APA from 88 ± 2 to 83 ± 1 mV ($p < 0.05$). The decrease in APA detected in neonatal fibers (81 ± 3 to 79 ± 3 mV) was not significant. *d*-Sotalol significantly decreased $\dot{V}_{max}$ in both adult and neonatal fibers; however, the change was significantly greater in adult fibers ($p < 0.01$). Decrease of $\dot{V}_{max}$ occurred at a lower threshold concentration in the adult age group (1×10^{-5} M).

d-Sotalol significantly prolonged both the APD_{50} and APD_{100} of K^+-depolarized fibers from both age groups in a concentration-dependent manner.

DISCUSSION

Age-related differences in cardiac tissue responsiveness to antiarrhythmic drugs that predominantly inhibit sodium or calcium channel activity have previously been demonstrated (12–14). Altered responsiveness of cardiac tissues from immature animals has important clinical implications for the therapeutic effectiveness and toxicity of antiarrhythmic agents in children. Implications deduced from experimental and clinical studies performed in mature animals or adult humans may have little validity for younger subjects. Thus, the clinical usage of antiarrhythmic agents in children may need to be modified depending on age-related differences in pharmacokinetics and tissue sensitivity.

Class III activity of d-sotalol: evidence for maturational changes. A significant age-related difference in the class III electrophysiologic effect of *d*-sotalol was observed in this study. *d*-Sotalol prolonged repolarization (APD_{50} and APD_{100}) in both neonatal and adult Purkinje fibers. However, the maximum extent of action potential lengthening was greater in the younger age group (27 *versus* 18%). Furthermore, the threshold concentration of *d*-sotalol that significantly prolonged plateau duration and decreased the slope of phase 3 repolarization was lower in the newborn age group (10^{-5} *versus* 10^{-4} M). The results are concordant with those of Xu *et al.* (9), who observed i.v. sotalol to prolong ventricular refractoriness in a dose-dependent manner in young puppy hearts.

Age-related differences in control action potential duration were eliminated as an explanation for these findings. In fact, the class III effect of *d*-sotalol on Purkinje fibers with shorter action potential durations was not invariably greater. Prolongation of action potential duration in adult subendocardial Purkinje fibers was less than that which occurred in adult free-running Purkinje fibers. Action potential duration in the control state was shorter in adult subendocardial Purkinje fibers than it was in adult free-running Purkinje fibers.

d-Sotalol lengthened action potential duration by slowing the terminal phases of repolarization. The absence of effect on early repolarization was evidenced by no change in plateau height or the slope of phase 2. *d*-Sotalol prolonged action potential duration by lengthening plateau duration and decreasing the slope of phase 3 repolarization. In a voltage clamp study by Carmeliet (17), sotalol was noted to decrease the time-dependent potassium current activated during the plateau of the action potential

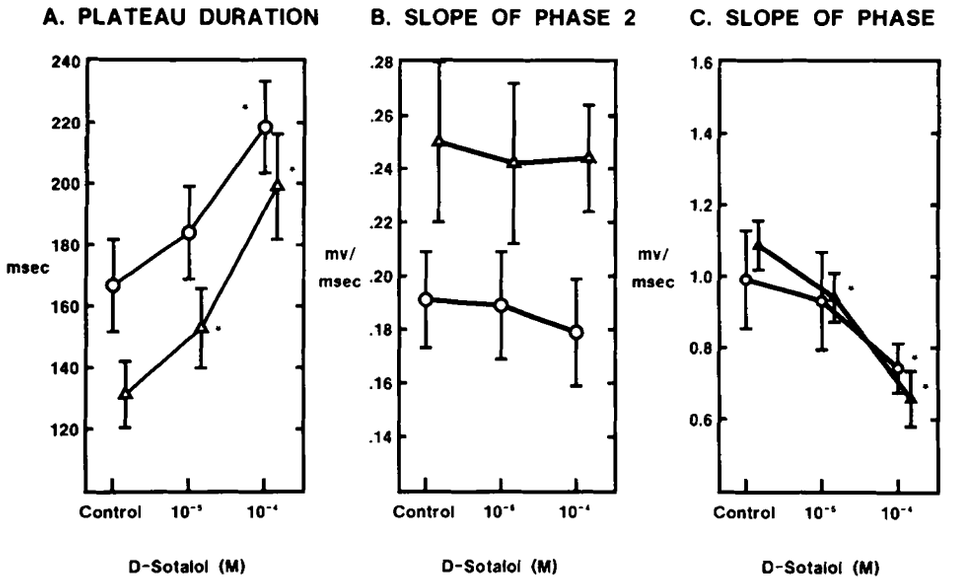

Fig. 2. The effect of *d*-sotalol on different phases of Purkinje fiber repolarization. The concentrations (M) of *d*-sotalol superfused are shown on the abscissa; the responses of the plateau duration (*A*), slope of phase 2 (*B*), and slope of phase 3 (*C*) are illustrated on the ordinate. See text for discussion. O, adult fibers; Δ, neonatal fibers; *, $p < 0.01$ compared with control.

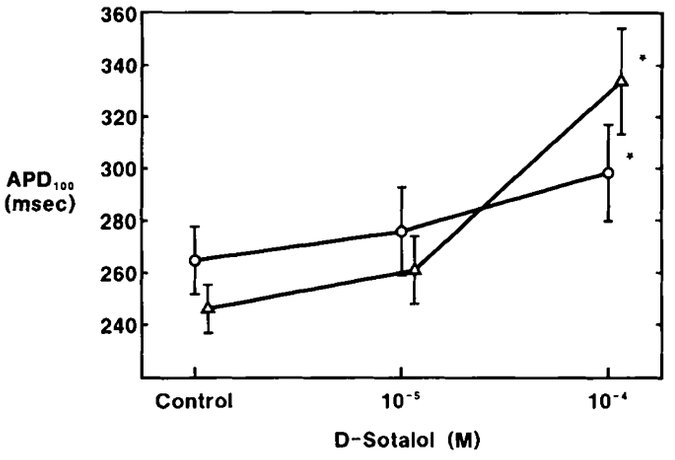

Fig. 3. The effect of *d*-sotalol on APD_{100} of adult subendocardial and neonatal free-running Purkinje fibers. The concentrations (M) of *d*-sotalol superfused are shown on the abscissa; the responses of APD_{100} are displayed on the ordinate. See text for discussion. O, adult fibers; Δ, neonatal fibers; *, $p < 0.01$ compared with control.

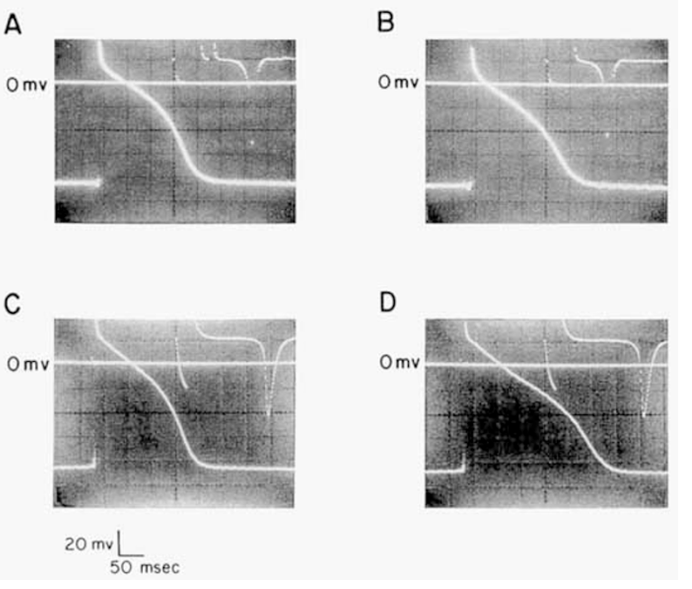

Fig. 4. Effects of *d*-sotalol on action potential configuration and $\dot{V}_{max}$ of Purkinje cells. *A*, control adult subendocardial Purkinje fiber; *B*, after superfusion with *d*-sotalol 1×10^{-4} M, APD_{100} increased 25 ms; *C*, control neonatal Purkinje fiber; *D*, after superfusion with *d*-sotalol 1×10^{-4} M, APD_{100} increased 85 ms. The magnitude of action potential prolongation is larger in the younger age group. Calibrations: *horizontal bar*, 50 ms; *vertical bar*, 20 mV. $\dot{V}_{max} = 200$ V/s. (Note difference in gain of $\dot{V}_{max}$ calibration between neonatal and adult Purkinje fibers).

(delayed rectifier current) and the time-independent background potassium current. Inhibition of these two potassium currents occurred at sotalol concentrations greater than 10^{-7} M and probably accounts for the results observed in this study. Carmeliet did note that at concentrations greater than 10^{-4} M, sotalol depressed the sodium window current. No significant effect of sotalol was evident on the slow inward calcium current.

Lengthening of plateau duration and decrease in the slope of phase 3 repolarization were greater in the younger age group and occurred at a lower *d*-sotalol concentration. Possible explanations for the greater effect of *d*-sotalol noted in immature Purkinje fibers include: *1*) a larger contribution of the delayed rectifier potassium current to action potential repolarization in the neonate (23), *2*) smaller contribution of the sodium window current to action potential duration in the neonatal age group, *3*) maturational differences in the membrane binding of *d*-sotalol (greater in the newborn age group), and *4*) maturational differences in the access of drug to receptor sites. Voltage clamp and drug-membrane binding studies will be required to resolve these possibilities.

Torsade de pointes. Torsade de pointes has been reported as a proarrhythmic complication in several clinical trials with sotalol (24, 25). Bradycardia-dependent triggered activity has been suggested by Brachmann *et al.* (26) as one possible mechanism for drug-induced multiformed ventricular tachycardia. A high incidence (58%) of early afterdepolarizations and triggered activity was observed in this study when adult Purkinje fibers were exposed to high concentrations of *d*-sotalol (10^{-4} M). In contrast, no triggered phenomenon occurred in the immature age group. If early afterdepolarizations and triggered activity are the underlying mechanism for drug-induced torsade de pointes, we may

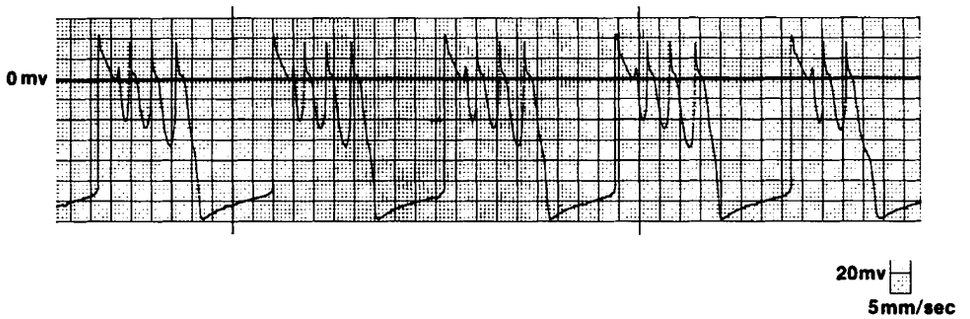

Fig. 5. Toxic effects of *d*-sotalol. Superfusion of adult free-running Purkinje fiber with *d*-sotalol 1×10^{-4} M induced early afterdepolarizations and triggered activity. Spontaneous activity is displayed on strip chart recording. Calibrations: *horizontal bar*, 5 mm/s; *vertical bar*, 20 mV.

Table 2. *Effects of d-sotalol on action potential characteristics of K^+-depressed adult and neonatal Purkinje fibers**

DS concentration	MDP (−mV)	APA (mV)	$\dot{V}_{max}$ (V/s)	APD_{50} (ms)	APD_{100} (ms)
Adult Purkinje fibers ($n = 8$)					
Control	65 ± 1	88 ± 2	180 ± 14	110 ± 2	195 ± 7
DS 10^{-7} M	64 ± 1	87 ± 2	168 ± 17	107 ± 3	188 ± 3
DS 10^{-6} M	64 ± 1	85 ± 2	158 ± 17	103 ± 4	189 ± 3
DS 10^{-5} M	65 ± 1	85 ± 2	105 ± 3†	105 ± 3	194 ± 4
DS 10^{-4} M	64 ± 1	83 ± 1‡	138 ± 16‡	125 ± 2†	225 ± 5
Neonatal Purkinje fibers ($n = 12$)					
Control	63 ± 1	81 ± 3	121 ± 22	75 ± 4	141 ± 7
DS 10^{-7} M	63 ± 1	80 ± 3	115 ± 23	75 ± 4	140 ± 6
DS 10^{-6} M	63 ± 1	80 ± 3	115 ± 24	78 ± 4	141 ± 7
DS 10^{-5} M	63 ± 1	80 ± 3	108 ± 23	83 ± 5	150 ± 6
DS 10^{-4} M	63 ± 1	79 ± 3	101 ± 23‡	103 ± 7†	183 ± 9†

* Values are mean ± SEM. DS, *d*-sotalol.
† $p < 0.01$ compared with control.
‡ $p < 0.05$ compared with control.

anticipate that *d*-sotalol treatment of children may be less likely to produce new onset arrhythmias (27, 28).

This result may seem paradoxical at first. Lengthening of action potential duration by *d*-sotalol was greater in the neonatal age group; however, the incidence of potentially toxic proarrhythmic effects was lower in the younger age group. The mechanism underlying drug-induced early afterdepolarizations, although not fully understood, involves a critical balance between depression of outward potassium current(s) and an increase in inward calcium current (29). Calcium release from the sarcoplasmic reticulum has been thought to be one important source for inward current in the genesis of early afterdepolarizations (30). Developmental morphologic data has, however, suggested that the t-tubule system and sarcoplasmic reticulum are underdeveloped in the neonatal heart (30, 31). Despite decreasing outward potassium current in the younger age group, the insignificant contribution of the sarcoplamic reticulum as a source for inward current may explain the lower incidence of toxic effects in the neonatal group after *d*-sotalol exposure.

Class I activity of d-sotalol. Before this study, Cobbe *et al.* (32) studied the electrophysiologic actions of sotalol in a conscious canine model of myocardial infarction. These investigators found a significant increase in ischemic zone refractoriness, the mechanism of which could not be explained. The results of the present study, however, suggest that the electrophysiologic effects of *d*-sotalol in depolarized cardiac tissue differ from normally polarized cells.

The experiments reported on in this study using K^+-depolarized Purkinje fibers provide evidence that *d*-sotalol manifests weak depressant effects on the sodium current. This action of *d*-sotalol, although not apparent in normally polarized tissue, was evident in the studies on K^+-depolarized adult Purkinje fibers. *d*-Sotalol (10^{-5} M) suppressed electrical excitability in 38% of adult Purkinje fibers depolarized with KCl and decreased APA, as well as $\dot{V}_{max}$, in the other fibers without altering membrane potential. The voltage clamp studies of Carmeliet provide an understanding for these observations (17). At high concentrations ($>10^{-4}$ M), sotalol was demonstrated to inhibit the sodium current in rabbit Purkinje fibers.

In accord with previous developmental studies of antiarrhythmic drugs that depress the sodium current, the electrophysiologic effects of *d*-sotalol were significantly less in the neonatal age group (12, 13). None of the K^+-depolarized neonatal fibers became inexcitable. Depression of APA and $\dot{V}_{max}$ was significantly less in the younger age group. This result may possibly be explained by: *1*) a larger contribution of the sodium current to APA and $\dot{V}_{max}$ in the adult Purkinje fiber, *2*) maturational differences in the membrane binding of *d*-sotalol to sodium channels, or *3*) maturational differences in the access of drug to receptor sites.

Clinical implications. The contribution of different elements of *d*-sotalol's electrophysiologic profile to its antiarrhythmic action is complex and needs to be interpreted in light of the developmental maturity and "health" (level of membrane potential) of the cardiac tissue treated. In the younger age group, *d*-sotalol exerts little depressant effect on the sodium current (and presumably conduction) in either normal or depolarized cardiac tissue. Its antiarrhythmic action would thus predominantly depend upon prolongation of cardiac refractoriness.

In normally polarized adult cardiac tissue, the insignificant depressant effect on the sodium current limits the antiarrhythmic action of *d*-sotalol to prolongation of refractoriness. In contrast, both depression of membrane activity (sodium current) and prolongation of repolarization may contribute to the antiarrhythmic action of *d*-sotalol. Given our observation that the class III effect of *d*-sotalol is significantly attenuated in depressed cardiac tissue, the local anesthetic effects of *d*-sotalol, although weak, take on therapeutic advantage for suppressing arrhythmias

arising in diseased tissue in adult subjects. However, the almost absent local anesthetic effects observed in the immature age group may limit the therapeutic effectiveness of *d*-sotalol in this age group to arrhythmias arising in normally polarized tissue.

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