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Diphenylhydantoin and Lidocaine Modification of A-V Conduction in Halothane-anesthetized Dogs

John L. Atlee, III, M.D., Louis D. Homer, M.D., Ph.D.,†*
CAPT Raymond E. Tobey, MC, USN‡

The effect of halothane on A-V conduction was evaluated in dogs during atrial pacing using the technique of His-bundle electrocardiography. In addition, the effects of lidocaine and diphenylhydantoin (DPH) on A-V conduction were examined during halothane anesthesia. Effects of these drugs on three subintervals of A-V conduction were compared. These included the P-H (stimulus artifact to His-bundle deflection—atrioventricular conduction), H-Q (His-bundle deflection to onset of QRS complex—His–Purkinje conduction), and H-S intervals (His-bundle deflection to end of QRS complex—total intraventricular conduction). Linear regression best described the relationship between duration of interval (P-H, H-V, and H-S) and heart rate during incremental increases in the atrial paced rate. Data from these experiments were fitted to a multiple linear regression model that predicted the effects of increasing concentrations of halothane, lidocaine, and DPH on slope and intercept coefficients. Increasing concentrations of halothane (30 and 45 mg/100 ml arterial) prolonged all three subintervals of A-V conduction to more than control (15 mg/100 ml arterial). Both lidocaine and DPH further depressed conduction at all levels of halothane anesthesia. The P-H interval was particularly sensitive to drug effects. This may represent potentiation of the normal slowing of conduction through the AV node in response to incremental increases in heart rate (fatigue response). We conclude that both lidocaine and DPH fail to reverse the depressant effect of halothane on A-V conduction. This may explain their ineffectiveness in treating certain types of arrhythmias during halothane anesthesia. (Key words: Heart, arrhythmias and conduction; Anesthetics, volatile, halothane; Anesthetics, local, lidocaine; Pharmacology, diphenylhydantoin.)

* Staff Anesthesiologist, United States Naval Hospital, National Naval Medical Center, Bethesda, Maryland 20014. Present address: Department of Anesthesiology, 418-D University Hospitals, University of Wisconsin, Madison, Wisconsin 53706.

† Medical Officer, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland 20014.

‡ Head, Division of Experimental Anesthesia and Pharmacology, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland 20014.

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Address requests for reprints to Dr. John L. Atlee, Department of Anesthesiology, 418-D University Hospitals, University of Wisconsin, Madison, Wisconsin 53706.

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IN A PREVIOUS STUDY in dogs, a concentration-dependent depression of A-V conduction by halothane was demonstrated with the aid of catheter electrocardiography.[1] Depression of conduction was most pronounced proximal to the bundle of His. Vagal block with atropine did not significantly alter the halothane effect, but beta-adrenergic receptor block with propranolol further slowed conduction. It was suggested that arrhythmias during halothane anesthesia were in part due to impaired conduction. This conclusion is further substantiated by several *in-vitro* studies that demonstrate the ability of halothane to suppress automaticity in both dominant and latent pacemaker cells.[2–5] In addition, studies in an intact dog heart preparation have shown that halothane consistently depressed ventricular escape pacemaker activity during vagal stimulation and suppressed ventricular automaticity following toxic doses of ouabain.[6]

Lidocaine and diphenylhydantoin (DPH) are often used to treat arrhythmias during anesthesia. While their antiarrhythmic effects are related to suppression of automaticity, both drugs also influence conduction. Some electrophysiologic properties of DPH suggest that it might improve A-V conduction, especially where depressed conduction already exists.[7] Because lidocaine has electrophysiologic properties similar to those of DPH,[7] it too might improve conduction.

The present study was designed to test the hypothesis that either one or both of these drugs would reverse the effects of halothane on A-V conduction. Drug effects on three subintervals of A-V conduction were evaluated during incremental increases in atrial paced rate. Catheter electrocardiography was used to record potentials from the bundle of His. Total A-V conduction was subdivided into intra-atrial and AV node (P-H interval), His–Purkinje (H-Q interval), and total intraventricular (H-S interval) conduction. Rapid atrial pacing was chosen to differentiate rate- from non-rate-dependent drug effects on conduction. The results do not demonstrate reversal of halothane effects on A-V conduction by lidocaine or DPH; in fact, conduction is prolonged by these two compounds, especially with respect to the P-H interval. This may represent a potentiation of the normal "fatigue" response of the AV node. The fatigue response is responsible for the progressive prolongation of the P-H interval (His-bundle electrogram) or P-R interval (surface electrocardiogram) found with incremental increases in paced heart rate.[8]

Methods

Experimental Procedure

Unpremedicated beagle dogs were anesthetized with inhaled concentrations of halothane leading to arterial anesthetic concentrations of 15, 30 and 45 mg/100 ml. These concentrations are approximately equivalent to 1, 2, and 3 MAC (minimum alveolar concentration) in the dog. Data pertaining to halothane effects on A-V conduction were obtained at each halothane concentration during stepwise increases in arterial concentration from 15 to 30 to 45 mg/100 ml. These control data were compared with similarly obtained data following the administration of lidocaine (without preservatives) or DPH (dissolved in commercial diluent) during a stepwise decrease in halothane concentration from 45 to 30 to 15 mg/100 ml. Lidocaine was administered as an initial intravenous dose of 2–5 mg/kg and blood levels maintained with a continuous infusion of 0.25 mg/kg/min. DPH was administered as an initial intravenous dose of 10 mg/kg and blood levels maintained with a continuous infusion of 35 μg/kg/min. These methods of administration were chosen to achieve antiarrhythmic serum levels of lidocaine[9] and DPH.[10] Often the same animal was anesthetized on separate occasions, usually a week later, but at least two days later. At this time the second antiarrhythmic drug was evaluated; the sequence of halothane concentrations remained the same—15, 30, and 45 mg/100 ml for controls, and 45, 30, and 15 mg/100 ml in the presence of drug. Thirty-nine experiments were carried out in 26 animals. In 21 experiments lidocaine was evaluated, while DPH was studied in the remaining 18. A total of 1,045 observations was made during the 39 experimental sessions. An observation consisted of measurements of the P-H, H-Q, and H-S intervals at each paced heart rate for each anesthetic concentration with or without the addition of lidocaine or DPH.

Anesthetic Procedure

Halothane and oxygen were delivered to a nonrebreathing system (Reuben valve) from a Fluomatic vaporizer. Respiration was controlled (Bird, Mark 4 anesthesia ventilator) to maintain Pa_{CO_2} between 28 and 35 torr. Arterial blood oxygen tension and *p*H determinations were made at each anesthetic concentration prior to A-V conduction measurements. Oxygen tensions in excess of 200 torr and *p*H values of 7.30 to 7.50 were maintained during all studies. Decamethonium, 0.5 mg/kg, iv, was used both to facilitate tracheal intubation and to prevent spontaneous movement or respirations during anesthesia. Additional doses of 1–2 mg

were given intravenously as necessary during the course of the experiment. Arterial halothane concentrations were determined by gas chromatography.[11] Halothane concentrations were maintained within 10 per cent of the 15, 30, and 45 mg/100 ml levels for at least 10 minutes prior to the recording of A-V conduction data. Serum lidocaine§ and DPH[12] levels were measured at each of the three halothane concentrations for ten of the 21 lidocaine and nine of the 18 DPH experiments. The duration of every experiment was less than four hours.

Technique for Evaluating Drug Effects on A-V Conduction

Under fluoroscopic guidance a hexapolar electrode catheter for recording His-bundle potentials (Electro-Catheter Corporation, Rahway, New Jersey) was positioned across the tricuspid valve after being passed proximally from the femoral vein according to the technique of Scherlag *et al.*[13] A bipolar catheter was fluoroscopically positioned midway in the right atrial cavity and was used for electrically pacing the atria (Grass S44 stimulator). The electrodes of the His-bundle catheter were connected through a three-channel switch box (which allowed recording from any two of six electrodes) to a differential amplifier (Type 1A7A—Tetronix) of a dual-beam oscilloscope (Tetronix 555). The output from this amplifier was passed to a low-gain D-C amplifier (CEC—Bell and Howell, Type 1-163) used to drive the galvanometer of a recording oscillograph (CEC—Bell and Howell, Type 5-124). The surface ECG was recorded from needle electrodes positioned under the skin of each extremity. The surface ECG signal was split so that one output went to a high-gain amplifier (Tetronix, Type L) on the oscilloscope, the other to a high-gain D-C amplifier (CEC—Bell and Howell, Type 1-165) used to drive the galvanometer of the recording oscillograph. Records were made on photographic paper at a speed of 16 inches/sec (0.406 mm = 1 msec) to facilitate the detection of small differences between conduction intervals.

§ Measured for us by Dr. R. N. Boyes, Research Department, Astra Pharmaceutical Corporation, Worcester, Massachusetts.

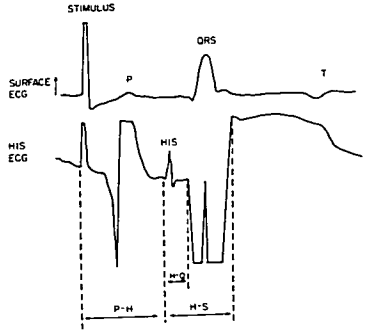

FIG. 1. Tracing from record of one experiment. The top recording is Lead II of the surface electrocardiogram. The bottom recording is the His-bundle electrogram. The P-H interval is measured from the stimulus artifact to the His potential. The H-Q interval is measured from the His potential to the first evidence of ventricular depolarization in the His electrogram. The H-S interval is measured from the His potential to the end of ventricular depolarization.

Measurements of the P-H, H-Q, and H-S intervals of A-V conduction (fig. 1) were made during paced experiments in which the heart rate was incrementally increased to 100 beats/min above an initial paced rate slightly greater than the unpaced sinus rate. The P-H interval, measured from the stimulus artifact to the beginning of the His-bundle potential, represents conduction through the atria and the A-V node to the bundle of His (atrioventricular conduction time).[14] The H-Q interval, measured from the His-bundle potential to the first evidence of ventricular depolarization in the His-bundle electrogram (which coincided with the Q wave of Lead II of the surface ECG), represents His–Purkinje conduction time.[14] The H-S interval, measured from the His-bundle potential to the end of ventricular depolarization (return of the QRS complex to baseline in the His-bundle electrogram), represents total intraventricular conduction.[14] The duration of each interval was estimated from several (generally six to eight) complexes during each paced run.

TABLE 1. Effects of Increasing Arterial Concentrations of Halothane with and without Lidocaine on the P-H, H-Q, and H-S Intervals in Response to Increased Heart Rate in One Experiment

	Heart Rate (Beats/Min)	P-H (msec)	H-Q (msec)	H-S (msec)
Halothane, 15 mg/100 ml	126	66	29	63
	160	68	29	65
	194	71	29	65
	215	75	29	65
Halothane, 15 mg/100 ml, + lidocaine	127	73	38	93
	159	76	39	95
	188	80	39	100
	222	95	39	103
Halothane, 30 mg/100 ml	130	68	32	68
	161	70	31	70
	183	76	33	80
	209	83	31	78
Halothane, 30 mg/100 ml, + lidocaine	106	74	36	95
	130	78	36	95
	164	81	38	100
	200	94	38	108
Halothane, 45 mg/100 ml	93	76	35	75
	123	80	35	78
	154	83	35	78
	186	93	35	78
Halothane, 45 mg/100 ml, + lidocaine	119	78	35	98
	138	80	38	100
	170	90	40	100
	196	99	38	103
	211	109	38	103

STATISTICAL TREATMENT OF RESULTS

The effects of increasing concentrations of halothane, and lidocaine or DPH, on the P-H, H-Q, and the H-S intervals were evaluated using multiple linear regression. Previous work has shown that the effect of a drug on conduction time is manifest either by a change in the mean conduction time or by a change in the rate dependence of the conduction time.[1]

The effect of the mean can be expressed as follows:

$$T = A_0 + A_D X$$

Where T is the conduction time, A_0 is the mean in the absence of the drug, $A_D X$ is the shift in the mean seen upon addition of the drug at concentration X. If the concentration is not precisely known, X can be given the value 0 in the absence of drug, or 1 in its presence.

The effect on the rate dependence can be added as follows:

$$T = A_0 + A_D X + (B_0 + B_D X)(R - 100)$$

The A coefficients may be recognized as the intercept of a line whose slope is given by the B coefficients. The B coefficients include both a drug-independent coefficient (B_0) and a drug-dependent one ($B_D X$), just as in the case of the A coefficients. The rate less 100 is used rather than the rate, simply because most of our pacing began near this rate and plotting of the results of our analysis in the range where most of our observations were made is somewhat more convenient with this form. Finally, it was also clear from previous work that the initial intercept A varies considerably from experiment to experiment, probably because of individual variation among animals. Accordingly, an additional refinement was made which allowed each

animal to have an individual drug-independent mean conduction time, a_j. The equation now assumes the form:

$$T = a_j + A_D X + (B + B_D X)(R - 100)$$

Realizing that drugs might well have interactions not described by independent linear relationships, we also included interactions for both the effect on mean conduction time and the rate dependence of conduction time. Details of the model so refined are presented in the appendix. One might correctly argue that the relationship between conduction time and drug dosage or heart rate can scarcely be expected to be linear, since dose–effect relationships rarely are. In the absence of detailed knowledge of a more exact relationship, however, a linear relationship may be justified as representing an approximation using the first two terms of a Taylor series expansion in the "true" relationship.

The model (see Appendix) devised by one of us (L.H.), was based on this approach. Drug effects were analyzed by determining their effects on the slope (B coefficients) and intercept (A coefficients) of that relationship. The individuality of each animal was in part accounted for by a different drug-independent intercept for each animal (a_j). The coefficients (a, A, and B) were estimated by the method of least squares.[15]

Least significant coefficients were removed from the model until each remaining coefficient was significant by a t test ($P < 0.05$). An F test was computed to con-

TABLE 2. Effects of Increasing Arterial Concentrations of Halothane with and without Diphenylhydantoin on the P-H, H-Q, and H-S Intervals in Response to Increased Heart Rate in One Experiment

	Heart Rate (Beats/Min)	P-H (msec)	H-Q (msec)	H-S (msec)
Halothane, 15 mg/100 ml	140	96	34	98
	169	98	33	95
	197	103	33	100
	222	105	34	98
	240	115	34	98
Halothane, 15 mg/100 ml, + diphenylhydantoin	91	100	35	98
	118	104	35	100
	144	105	40	103
	166	119	40	108
Halothane, 30 mg/100 ml	115	81	38	100
	132	90	35	95
	152	90	34	95
	174	95	34	96
	197	105	35	98
	211	115	34	98
Halothane, 30 mg/100 ml, + diphenylhydantoin	91	101	40	108
	109	104	40	110
	132	113	40	105
	149	126	40	115
	176	163	40	123
Halothane, 45 mg/100 ml	106	91	38	100
	130	94	38	101
	155	100	38	101
	182	124	38	104
	206	145	38	109
Halothane, 45 mg/100 ml, + diphenylhydantoin	92	123	44	116
	119	106	43	118
	145	120	43	118
	168	164	45	125

sider the possible cumulative significance of the dropped coefficients.

Results

Mean serum lidocaine level for the ten determinations made in the lidocaine experimental group was 5.64 ± 2.84 μg/ml (range 1.8–13.7 μg/ml). Mean serum DPH level for the nine determinations made in the DPH experiments was 11.27 ± 2.09 μg/ml (range 8–17 μg/ml). These values represent the average of lidocaine or DPH determinations at each of the three concentrations of halothane (15, 20, and 45 mg/100 ml).

Data on paced heart rates, with the corresponding values for the P-H, H-Q, and H-S intervals, are shown in table 1 for one of the 21 lidocaine experiments. Similar data are shown in table 2 for one of the 18 DPH experiments. These data are representative of those obtained from other experiments.

Results of the reduced regressions are depicted in tables 3 and 4. Estimates of the drug-related coefficients for intercepts of the P-H, H-Q, and H-S intervals are included in table 3, while estimates of similar coefficients for slopes of the same intervals are in table 4.

There was no evidence that any of the dropped coefficients was either individually or collectively different from zero ($P > 0.1$ for F test computed to test cumulative significance of dropped coefficients). Standard errors for the coefficients are also reported in tables 3 and 4. Standard deviations of the observations for the P-H, H-Q, and H-S intervals were 16, 1.7, and 5.2 msec, respectively. Approximate standard errors of the regression lines were 3.5, .38, and 1.0 msec, respectively.

Figures 2 and 3 show the fitted P-H intervals over a range of heart rates (100 to 200 beats/min). The 95 per cent confidence limits about these regression lines are slightly narrower at heart rates of 150 than at 100 or 200 beats/min. They also vary somewhat with the halothane concentration and the standard error of the coefficient a_j, but were within 10 per cent of the single interval shown in the figures. These confidence limits reflect primarily uncertainties in the a_j, rather than the pooled coefficients A and B. In figure 2, the effects of halothane alone (control), halothane with lidocaine, and halothane with DPH are compared at similar halothane

TABLE 3. Estimates of Drug-related Coefficients* for Intercepts of the P-H, H-Q, and H-S Intervals: Results of Reduced Regressions

Coefficients†	P-H Interval	H-Q Interval	H-S Interval
A_1 (lido)	0	4.15 ± .50	16.3 ± 1.2
A_2 (DPH)	0	2.54 ± .22	8.7 ± 1.1
A_3 (lido + halo)	0	−.063 ± .015	−.262 ± .032
A_4 (DPH + halo)	0	0	−.089 ± .033
A_5 (halo)	0	.1092 ± .0056	.187 ± .019

* Estimates of drug-related coefficients for equation 1 (Appendix) are shown ± their standard errors.
† Lido = lidocaine; DPH = diphenylhydantoin; halo = halothane.

TABLE 4. Estimates of Drug-related Coefficients* for Slopes of the P-H, H-Q, and H-S Intervals: Results of Reduced Regressions

Coefficients†	P-H Interval	H-Q Interval	H-S Interval
B_1 (lido)	.157 ± .018	.0400 ± .0063	.0472 ± .0081
B_2 (DPH)	0	.0174 ± .0036	0
B_3 (lido + halo)	0	−.00048 ± .00020	0
B_4 (DPH + halo)	.00256 ± .00053	−.00069 ± .00011	0
B_5 (halo)	.00254 ± .00038	0	0
B_6 (DI)	0	0	0

* Estimates of drug-related coefficients for equation 1 (Appendix) are shown ± their standard errors.
† Lido = lidocaine; DPH = diphenylhydantoin; halo = halothane; DI = drug-independent.

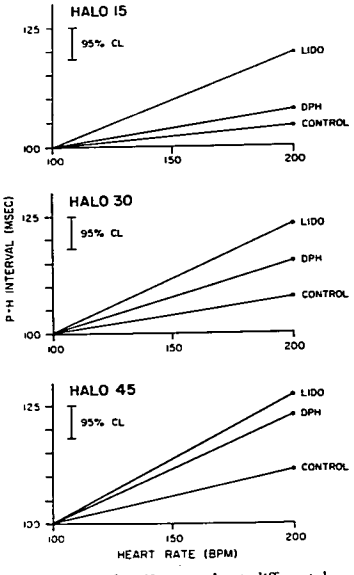

FIG. 2. Fitted P-H intervals at different heart rates: Comparison of lidocaine (LIDO) and diphenylhydantoin (DPH) effects at three arterial halothane concentrations (15, 30, 45 mg/100 ml). The bar indicates an approximate (± 10 per cent) 95 per cent confidence limit (CL) common to all regression lines (see text for discussion).

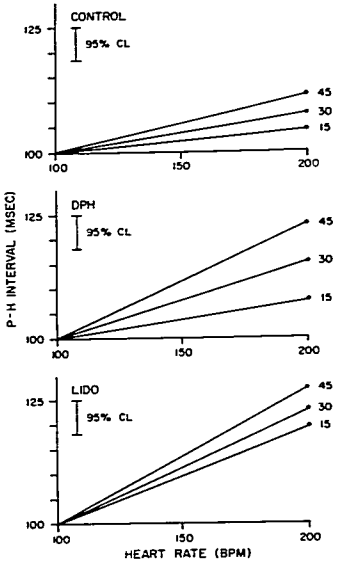

FIG. 3. Fitted P-H intervals at different heart rates: Effects of lidocaine (LIDO) and diphenylhydantoin (DPH) at arterial halothane concentrations of 15, 30 and 45 mg/100 ml. The bar indicates an approximate (± 10 per cent) 95 per cent confidence limit (CL) common to all regression lines. See text for discussion.

levels. Note that the regression lines are separated by more than the 95 per cent confidence limit only at rates in excess of 150 beats/min. This means that the response of a single animal to these drugs at lower heart rates would be undetectable even with many measurements. Lidocaine significantly prolongs the P-H interval compared with controls at all three halothane concentrations. With DPH the lines are well separated only with the deepest halothane anesthesia (45 mg/100 ml). It is also apparent that lidocaine gives more depression of conduction than DPH at each concentration of halothane. In figure 3 the effect of halothane concentration on prolongation of the P-H interval is shown for each of the three experimental groups. Note that within the control and lidocaine groups increasing the concentration of halothane would probably not give clinically detectable prolongation of the P-H interval for heart rates to 200 beats/min. However, with the DPH group, noticeable prolongation of the P-H interval occurs at heart rates above 150 beats/min when the halothane level is 45 mg/100 ml as opposed to 15 mg/100 ml.

Drug effects on His–Purkinje conduction (H-Q interval) predicted by fit of our data to the model are displayed in figure 4. Increasing depth of halothane anesthesia prolongs the H-Q interval in all three groups (controls, DPH, and lidocaine). At comparable levels of anesthesia, the addition of lidocaine or DPH

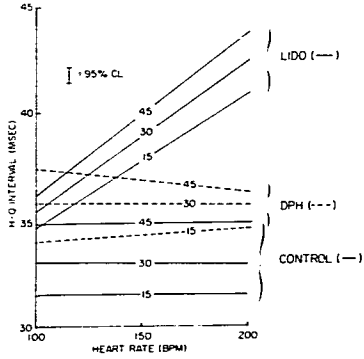

FIG. 4. Fitted H-Q intervals at different heart rates: Effects of lidocaine (LIDO) and diphenylhydantoin (DPH) at arterial halothane concentrations of 15, 30 and 45 mg/100 ml. Control (——) = halothane alone. DPH (- - -) = halothane plus DPH. Lido (——) = halothane plus lidocaine. The bar indicates an approximate (± 10 per cent) 95 per cent confidence limit (CL) common to all regression lines (see text for discussion).

further prolongs the H-Q interval. A rather marked dependence of the prolongation on heart rate is apparent in the lidocaine group, but not in the DPH or control groups. This suggests an additional effect of lidocaine on conduction, as opposed to DPH.

Regression lines for the H-S interval (total intraventricular conduction) shown in figure 5 resemble in a qualitative fashion those for the H-Q interval. Again, adding lidocaine or DPH to any of the three concentrations of halothane further prolongs conduction. Also, a rate-dependent prolongation of the H-S interval is apparent with lidocaine (as with the H-Q interval). The only difference between drug effects on the H-S and H-Q intervals is the somewhat smaller effect of increased halothane concentration on rate dependence of the H-S interval compared with the H-Q interval over the range of heart rates from 100 to 200 beats/min.

Discussion

The present study demonstrated prolongation of the three subintervals of A-V conduction by halothane, alone and in combination with DPH or lidocaine. Drug-related changes in conductivity were estimated from differences in regression lines describing a linear relationship between heart rate and duration of interval studied. Changes in the slope of this relationship were most characteristic of drug effects on the P-H interval (figs. 2 and 3). Changes in the intercept for a range of heart rates from 100 to 200 beats/min were most pronounced for the H-Q and H-S intervals (figs. 4 and 5). The ensuing discussion is organized under three topics: drug-related slope effects, drug-related intercept effects, and mechanisms of arrhythmias and therapeutic implications.

Drug-Related Slope Effects

Slope changes for the P-H interval may represent alterations in the "fatigue" response that has been attributed to conduction delays within the AV node.[8,16] As the pacing frequency increases, the P-H interval lengthens. If the rate that establishes critical 1:1 propagation to the bundle of His is surpassed, conduction with Wenkebach periodicity is observed; that is, the ratio of atrial to His-bundle responses is greater than 1. With faster pacing rates, 2:1 and 3:1 ratios are established. Continued stimulation at the

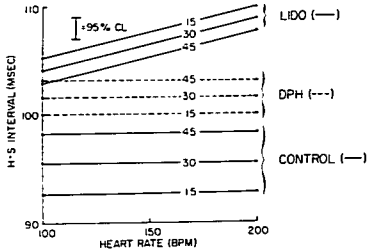

FIG. 5. Fitted H-S intervals at different heart rates: Effects of lidocaine (LIDO) and diphenylhydantoin (DPH) at arterial concentrations of 15, 30, and 45 mg/100 ml. Control (——) = halothane alone. DPH (- - -) = halothane plus DPH. Lido (——) = halothane plus lidocaine. The bar indicates an approximate (± 10 per cent) 95 per cent confidence limit (CL) common to all regression lines (see text for discussion).

rate critical for 1:1 propagation across the AV node will also cause eventual "fatigue" and a greater than 1:1 transmission ratio.

An important determinant of conductivity in excitable tissues is the relationship between the maximum rate of rise of the cell membrane potential (dV/dt_{max}) during the period of rapid depolarization (phase 0), and the level of cell membrane potential.[17] A schematic representation of the relationship between dV/dt_{max} and the level of membrane potential is shown in figure 6. Drugs and changes in ionic composition can alter this relationship. A shift to the right of the curve represents impaired conductivity, while a shift to the left represents enhanced conductivity.

"Fatigue" in the AV node may relate to changes in conductivity produced by alterations in membrane responsiveness. During rapid atrial pacing, if impulses arrive at the AV node before the membrane has had time to repolarize to a level sufficient for normal conduction, dV/dt_{max} of the resulting action potential would be of insufficient magnitude for propagation. The effect of halothane on the relationship between dV/dt_{max} and membrane potential for cells of the conduction system has apparently not been reported. We postulate that this agent shifts this relationship to the right, an action that would be in keeping with its observed effects on the P-H interval in the present and earlier studies. The additional increase in slope for the P-H interval (figs. 2 and 3) with lidocaine and DPH during halothane anesthesia is more difficult to explain. This is because both drugs at therapeutic concentrations tend to improve conductivity by shifting the curve relating dV/dt_{max} to membrane potential to the left.[18-24]

Changes in slope for the H-Q and H-S intervals (figs. 4 and 5) following lidocaine indicate a difference between the effect of this drug and that of halothane or DPH on His–Purkinje and total intraventricular conduction. A possible explanation for this may relate to the demonstration by Davis and Temte[22] of the action of lidocaine to impair the responses of both Purkinje and ventricular muscle fibers to rapid stimuli. We are not aware of any reports on the effect of DPH on such responses.

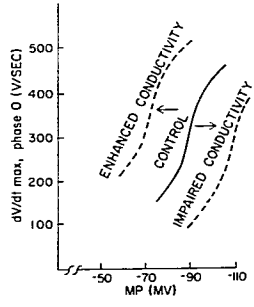

FIG. 6. Schematic drawing of relationship between maximum rate of rise of the cell membrane potential (dV/dt_{max}—ordinate) during the period of rapid depolarization, and level of cell membrane potential (MP—abscissa). A shift to the right represents impaired conductivity. A shift to the left represents enhanced conductivity.

DRUG-RELATED INTERCEPT EFFECTS

Alterations in the relationship between dV/dt_{max} and membrane potential offer an attractive explanation for the observed slope-related effects on the P-H interval of drugs in this study. However, changes in intercept constituted the most frequently observed drug effects for the H-Q and H-S intervals. A prolongation of conduction that was not rate-dependent could produce the latter effect. The most likely explanation for this is an increase in the time or current required to reach threshold potential (the level to which the cell membrane must be depolarized for a self-propagating action potential). Changes in the time and current required to reach threshold potential could be brought about by decreasing the threshold potential (less negative) while keeping the resting potential constant. Alternatively, the resting potential could be increased (more negative) while the threshold was held constant. Either of these would satisfy the criteria suggested above.

Halothane does increase (make more negative) the resting membrane potential of Purkinje fibers, while exerting little effect on that of atrial or ventricular muscle fibers.[3] Its influence on the threshold potential of Pur-

kinje or ventricular muscle cells has not been reported, although it appears to have an insignificant effect on the threshold potential of sinoatrial node cells.[2] The action of this agent to increase the resting membrane potential of Purkinje fibers may explain our observation of non-rate-dependent prolongation of the H-Q and H-S intervals.

At therapeutic levels neither DPH nor lidocaine has a significant effect on the resting membrane potential of atrial, Purkinje, or ventricular muscle cells.[18,19,21-23] DPH increases (makes more negative) the threshold potential of Purkinje fibers without altering the resting potential, therefore increasing excitability.[10] For this reason, with DPH less current should be required to achieve an action potential capable of propagation (improved conductivity). This has been reported for both atrial and ventricular muscle in the presence of DPH.[10] It is interesting that the commercial diluent for DPH has an opposite effect on these variables, and when used as a vehicle for DPH, offsets some of the decrease in threshold current requirements seen with the drug alone.[10] The diluent consists of 10 per cent ethanol and 40 per cent propylene glycol with the *p*H adjusted to 12 with NaOH. Diluent and DPH effects were indistinguishable in this study. We are not aware of any published observations concerning the effect of lidocaine on threshold potential, although it has been reported to increase diastolic threshold current requirements in dogs.[23]

Mechanisms of Arrhythmias and Therapeutic Implications

An understanding of the underlying mechanisms for cardiac arrhythmias is necessary for rational drug therapy. Cardiac arrhythmias may be attributed to disturbances of automaticity, conduction, or both.[26] Any factor that decreases the automaticity (intrinsic rate) of the normal sinus pacemaker while increasing the automaticity of a latent pacemaker may cause an arrhythmia.[26] Disturbed conduction may contribute to a number of mechanisms cited for arrhythmias, including re-entry of excitation, summation, inhibition, parasystole, and oscillatory depolarizations.[26]

Arrhythmias during halothane anesthesia are commonly attributed to suppression of primary pacemaker foci with enhancement of automaticity at latent pacemaker sites (escape phenomena). However, *in-vitro*[4] and *in-vivo*[6] evidence that halothane suppresses automaticity in latent pacemaker foci casts some doubt on this concept. The present and earlier[1] results indicating that halothane impairs A-V conduction suggest that disturbed conduction may be an additional mechanism responsible for arrhythmias. If the arrhythmia during halothane anesthesia were related to enhanced ventricular automaticity, the decision to treat with lidocaine or DPH would be justified. However, the use of these drugs for the treatment of an arrhythmia due to impaired conduction may be problematical, since they further depress conduction during halothane anesthesia in dogs.

Despite our knowledge of the exact contribution of disturbed automaticity or conduction to an arrhythmia, clinical experience with both DPH and lidocaine points to their effectiveness in treating ventricular arrhythmias during anesthesia. A possible explanation for this requires the understanding of an additional mechanism that has been offered to explain ventricular arrhythmias. Myerburg and colleagues called attention to the marked disparity between times of recovery of adjacent Purkinje fibers in the distal conducting system.[27] Prolonged action potential durations and refractoriness in some Purkinje fibers could prevent the propagation of premature impulses across these fibers. These fibers were thought to function as a "gate," and it was the hypothesis of these authors that if sufficient fibers were refractory, and conduction velocities such that the premature impulse reentered the conduction pathway before the next normal impulse arrived, conditions for re-entry of excitation would be present. If re-entry occurred during the vulnerable period in areas of the myocardium that had achieved sufficient repolarization, ventricular fibrillation could be triggered. Lidocaine has been shown to reduce the disparity in action potential durations that exists between adjacent Purkinje cells in the distal conduction system.[28] This action of lidocaine would tend to minimize conditions for re-entry of excita-

tion, acording to the hypothesis of Myerburg *et al.*[27] While DPH shares with lidocaine the ability to shorten the duration of the action potential and the refractory period for Purkinje cells,[19] its ability to reduce the disparity in action potential durations of adjacent cells in the distal conduction system has not been established. It is also not certain that halothane or other anesthetics increase the disparity in recovery times of adjacent Purkinje fibers in the distal conducting system.

We conclude that neither DPH nor lidocaine reverses the depressant effects of halothane on conduction. The greatest drug-related prolongation of conduction occurs with the P-H interval at rapid heart rates, and probably represents a potentiation of the normal "fatigue" response of the AV node. The exact clinical significance of these results must remain uncertain until the contribution of depressed conduction to arrhythmias during halothane anesthesia is further clarified.

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References

1. Atlee JL, Rusy BF: Halothane depression of A-V conduction studied by electrograms of the bundle of His in dogs. ANESTHESIOLOGY 36:112–118, 1972
2. Hauswirth O, Schaer H: Effects of halothane on the sino-atrial node. J Pharmacol Exp Ther 158:36–39, 1967
3. Hauswirth O: Effects of halothane on single atrial, ventricular, and Purkinje fibers. Circ Res 24:745–750, 1969
4. Reynolds AK, Chiz JF, Pasquet AF: Halothane and methoxyflurane—a comparison of their effects on cardiac pacemaker fibers. ANESTHESIOLOGY 33:602–610, 1970
5. Reynolds AK, Chiz JF, Pasquet AF: Pacemaker migration and sinus node arrest with methoxyflurane and halothane. Can Anaesth J 18:137–144, 1971
6. Logic RL, Morrow DH: The effect of halothane on ventricular automaticity. ANESTHESIOLOGY 36:107–111, 1972
7. Bassett AL, Hoffman BF: Antiarrhythmic drugs: Electrophysiological actions. Annu Rev Pharmacol 11:143–170, 1971
8. Mendez C, Moe GK: Electrical Phenomena in the Heart. Edited by WC De Mello. New York, Academic Press, 1972, pp 263–291
9. Smith ER, Duce BR, Boyes RN: Antiarrhythmic effects in dogs of lidocaine administered orally and intravenously. Am Heart J 83:365–372, 1972
10. Bigger FT, Weinberg, DI, Kovalik TW, *et al.*: Effects of diphenylhydantoin on excitability and automaticity in the canine heart. Circ Res 26:1–15, 1970
11. Lowe HJ: Flame ionization detection of volatile organic anesthetics in blood, gases and tissues. ANESTHESIOLOGY 25:808–814, 1964
12. MacGee J: Rapid determination of diphenylhydantoin in blood plasma by gas–liquid chromatography. Anal Chem 42:421–422, 1970
13. Scherlag BF, Helfaut RH, Damato AN: A catheterization technique for His bundle stimulation and recording in the intact dog. J Appl Physiol 25:425–428, 1968
14. Hecht HH, Kossman CE: Atrioventricular and intraventricular conduction: Revised nomenclature and concepts. Am J Cardiol 31: 232–244, 1973
15. Graybill FA: An Introduction to Linear Statistical Models. New York, McGraw-Hill, 1961
16. Damato AN, Lau SH, Bobb GA, et al: Recording of A-V nodal activity in the intact dog heart. Am Heart J 80:353–366, 1970
17. Weidmann S: The effect of the cardiac membrane potential on the rapid availability of the sodium-carrying system. J Physiol (Lond) 127:213–224, 1955
18. Strauss HC, Bigger JT, Bassett AL, et al: Actions of diphenylhydantoin on the electrical properties of isolated rabbit and canine atria. Circ Res 23:463–477, 1968
19. Bigger JT, Bassett AL, Hoffman BF: Electrophysiological effects of diphenylhydantoin on canine Purkinje fibers. Circ Res 22:221–236, 1968
20. Bassett AL, Bigger JT, Hoffman BF: "Protective" action of diphenylhydantoin on canine Purkinje fibers during hypoxia. J Pharmacol Exp Ther 173:336–343, 1970
21. Bigger JT, Mandel WJ: Effect of lidocaine on the electrophysiological properties of ventricular muscle and Purkinje fibers. J Clin Invest 49:63–77, 1970
22. Davis LD, Temte JV: Electrophysiological actions of lidocaine on canine ventricular muscle and Purkinje fibers. Circ Res 24:639–655, 1969
23. Mandel WJ, Bigger JT: Electrophysiologic effects of lidocaine on isolated canine and rabbit atrial tissue. J Pharmacol Exp Ther 178:81–93, 1971
24. Bigger JT, Heisenbuttel RH: The use of procaine amide and lidocaine in the treatment of cardiac arrhythmias. Prog Cardiovasc Dis 11:515–534, 1969
25. Sugimoto T, Schaal SF, Dunn NM, et al: Electrophysiologic effects of lidocaine in

awake dogs. J Pharmacol Exp Ther 166:146–150, 1969
26. Cranefield PF, Witt AL, Hoffman BF: Genesis of cardiac arrhythmias. Circulation 47:190–204, 1973
27. Myerburg RJ, Steward JW, Hoffman BF: Electrophysiological effects of canine peripheral A-V conducting system. Circ Res 26:361–378, 1970
28. Wittig J, Harrison LA, Wallace AG: Electrophysiological effects of lidocaine on distal Purkinje fibers of canine heart. Am Heart J 86:69–77, 1973

APPENDIX

The model used to describe the effects of lidocaine, DPH, halothane concentration, and heart rate on an assumed linear relationship between heart rate and the duration of the P-H, H-Q, or H-S interval was:

$$Y_i = \left(\sum_{j=1}^{39} a_j I_j\right) + A_1 L_i + A_2 D_i + A_3 L_i H_i + A_4 D_i H_i + A_5 H_i + (HR_i - 100) \times (B_1 L_i + B_2 D_i + B_3 L_i H_i + B_4 D_i H_i + B_5 H_i + B_6) \quad (1)$$

where:

Y_i = the interval to be analyzed, *i.e.*, . . . P-H, H-Q, or H-S, in msec

a = a drug-independent intercept coefficient for each animal experiment

$j = 1, 2 \ldots 39$ indicates one of the 39 animals in the study

$i = 1, 2 \ldots 1{,}045$ indicates one of the 1,045 observations made. An observation consisted of the simultaneous measurements of heart rate, P-H interval, H-Q interval, and H-S interval made with the different halothane concentrations with or without the addition of lidocaine or DPH

I_j = 1 if the observation is on the j^{th} animal, zero otherwise

A_{1-5} = drug-dependent intercept coefficients common to all animals

L_i = 1 if the i^{th} observation was made after lidocaine, zero otherwise

D_i = 1 if the i^{th} observation was made after DPH, zero otherwise

H_i = the halothane concentration in mg/100 ml

HR_i = the heart rate of the i^{th} observation in beats/min. An offset of 100 beats/min in the heart rate was used for convenience in reconstructing regression lines in the range of 100–200 beats/min where most of our observations were made

B_{1-5} = drug-dependent slope coefficients common to all animals

B_6 = drug-independent slope coefficient common to all animals

Obstetrics

OBSTETRIC MEDICATION This study investigated the effects of obstetric premedication on neonatal psychophysiologic functioning. A main sample of 25 babies whose mothers had received meperidine was examined in terms of rates of habituation to an auditory orienting reflex, the Neonatal Behavioral Assessment Scale, and Apgar scores. Scores on the first and third of these measures were also available for a supplementary sample of 19 babies whose mothers had received a variety of premedication agents. The results for both groups indicate not only that obstetric premedication affects neonatal functions but also that it affects these functions differentially. Premedication dosage was closely related not only to differences in infants' abilities to respond but, more importantly, to inhibition of response. Questions concerning the mediation of these effects, their duration, and their consequences for the developing organism are discussed. *(Brackbill, Y., and others: Obstetric Premedication and Infant Outcome, Am J Obstet Gynecol 18:377–384, 1974.)*