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Cardiovascular Effects of Controlled Lidocaine Overdosage in Dogs Anesthetized with Nitrous Oxide

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The circulatory responses to a 200-minute infusion of a large dose (333 μg/kg/min) of lidocaine were studied in dogs anesthetized with nitrous oxide. Control animals showed evidence of cardiovascular depression with time. Lidocaine infusion had a positive inotropic effect which was reversed by pretreatment with hexamethonium. The data suggest that lidocaine has both a direct depressant effect and an indirect stimulant effect on the cardiovascular system. There is evidence that the indirect stimulant effect is mediated by the autonomic nervous system, as demonstrated by the responses of dogs with ganglionic blockade. The addition of central nervous system depressants and other drugs depressing autonomic function may modify the stimulant action of lidocaine in addition to their own cardiovascular depressant effects. (Key words: Lidocaine; Local anesthetics; Nitrous oxide; Ganglionic blockade; Cardiovascular system.)

LIDOCAINE is considered a clinically safe, effective antiarrhythmic agent which does not depress cardiovascular performance when blood levels remain below 3.5 μg/ml.[1, 2, 3] Data are available to show that low levels of lidocaine depress myocardial contractility in isolated hearts[4] and in some perfused animal preparations.[5] Most previous studies of the toxicity of lidocaine have been directed toward the central nervous system manifestations of relative overdosages and the pharmacology of treating or preventing these effects. This study, performed in dogs with intact cardiovascular systems, was designed to elucidate some of the cardiovascular effects of blood levels of lidocaine which would be expected to cause convulsions. In an attempt to avoid the myocardial depressant effects of barbiturate anesthetics used in most previous studies, the dogs used for this study were anesthetized with a nitrous oxide–relaxant technique.

Methods

Seventeen mongrel dogs weighing 11–18 kg were selected without regard to sex or age and divided into three groups. After an overnight fast, each animal was restrained in the supine position, and anesthesia was induced with nitrous oxide, 6 l/min, and oxygen, 2 l/min, using a snug-fitting dog mask. Following induction, each animal was paralyzed with 0.3 to 0.6 mg/kg of succinylcholine injected into a hind-limb vein and the trachea was intubated with a cuffed endotracheal tube. Gas flows were then changed to nitrous oxide, 2 l/min, and oxygen 1 l/min. Ventilation was controlled throughout the experiment, and the *p*H's of random arterial blood samples were 7.40 ± 0.05 in all cases. Paralysis was maintained by the intermittent injection of 0.3 to 0.5 mg/kg of succinylcholine.

The left carotid artery was cannulated for recording arterial pressure from a tip position in the aortic arch, and the right carotid artery

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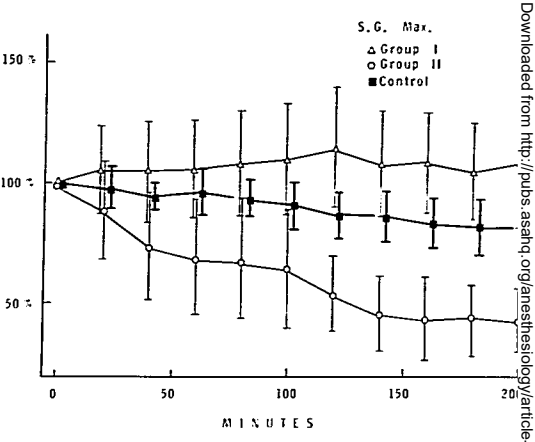

FIG. 1. Relative changes in strain-gauge amplitude ($S.G._{max}$) with time in dogs anesthetized with nitrous oxide. Each point represents an average value for one minute. Vertical bar represents ± one standard deviation of the mean. Lateral displacement was used to prevent obscuring of the symbols.

was cannulated with a catheter which was advanced until recordings characteristic of left ventricular pressure were obtained. An external jugular vein was cannulated for the recording of central venous pressure and for injection of drugs. Both the arterial pressure catheter and the ventricular pressure catheter were connected to saline solution-filled Statha P23db pressure transducers, and the veno catheter was connected to a saline solutio filled P23BB pressure transducer. Care w taken to use large-bore saline solution-fille catheters of the same length.

The chest was opened through a media

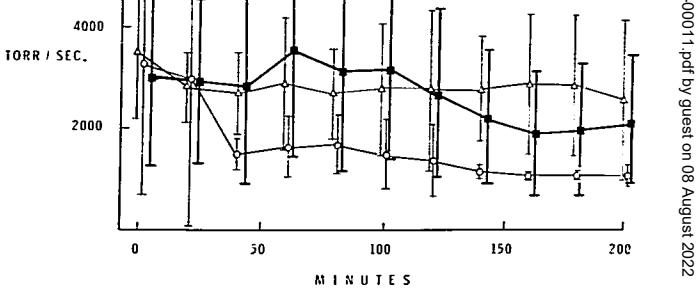

FIG. 2. Changes in dP/dt_{max} with time in dogs anesthetized with nitrous oxide. Each point represents an average value for one minute. Lateral displacement was used to prevent obscuring of the symbols.

TABLE 1. Significance* of Changes of Values within Groups as a Function of Time

	Control	Group I Lidocaine	Group II Hexamethonium plus Lidocaine
Heart rate	NS	<0.0001↓	<0.0001↓
Strain gauge amplitude	<0.001↓	NS	<0.001↓
Strain gauge baseline deviation	NS	NS	NS
Left ventricular end-diastolic pressure	NS	<0.0001↑	NS
Pulse pressure	<0.005↓	NS	NS
Systolic arterial pressure	NS	<0.001↑	<0.005↓
Diastolic arterial pressure	NS	<0.005↑	<0.005↓
dP/dt	NS	NS	<0.005↓
Central venous pressure	NS	NS	NS

* Numbers indicate level of significance. NS indicates lack of significance ($P > 0.05$). Arrows indicate direction of change.

sternotomy, the pericardium was incised, and the cut edges of the pericardium were loosely sutured to the anterior chest wall to support the heart. A Walton-Brodie strain gauge arch was sutured onto the anterior surface of the left ventricle. A thermistor was placed in the esophagus to monitor body temperature, which was maintained at 37.2 ± 0.5 C with a circulating-hot-water blanket. The electrocardiogram (ECG) was recorded from subcutaneous needle electrodes.

The outputs of the ECG amplifier, the strain gauge arch transducer, and the pressure transducers were connected to an Electronics for Medicine DR-8 recorder and displayed on its oscilloscope screen. The output of each amplifier was interphased into an Ampex SP-300 tape recorder and recorded in the frequency-modulated mode.

At a later time, the magnetic tapes were replayed through analog-to-digital conversion equipment, and data were returned in the following format: Average systolic arterial blood pressure (SAP), average diastolic arterial blood pressure (DAP), average arterial pulse pressure (PP), average left ventricular end-diastolic pressure (LVEDP), maximal first derivative of ventricular pressure (dP/dt_{max}), average maximal strain-gauge signal amplitude ($S.G._{max}$) expressed as per cent of the initial control value, and average strain-gauge signal baseline deviation ($S.G._{dev}$) expressed as per cent of initial control strain-gauge amplitude. These values were determined for one-minute periods at 20-minute intervals throughout each experiment. Heart rate (HR) and central venous pressure (CVP) were manually determined for the same sample periods.

GROUP I

Following application of the various monitoring devices and the recording of control measurements, lidocaine infusion was started at the rate of 20 mg/kg/hr (333 μg/kg/min) and maintained for 200 minutes in seven dogs.

GROUP II

Five dogs were given 0.1 mg/kg of tetramethylammonium chloride intravenously following application of the monitoring devices. This agent produced tachycardia and hypertension in all animals. After all variables being monitored had returned to their initial values (usually within 5 minutes) and remained stable for 10 minutes, each animal was given 10 mg/kg of hexamethonium to induce ganglionic blockade. CVP fell in every dog, and sufficient balanced salt solution (20–50 ml/kg) was given to return it to the preganglionic-blockade level and then discontinued. After a 30–45-minute period of stabilization, 0.1 mg/kg of tetramethylammonium chloride was administered iv. The lack of response to this dose, which had caused marked cardiovascular stimulation before hexamethonium, verified total ganglionic blockade. Control measurements were then made, and a lidocaine infusion was started at 20 mg/kg/hr as in Group I. At 45-minute intervals throughout the course of the 200-minute experiment, ganglionic blockade was verified by the administration of 0.1 mg/kg of tetramethylammonium chloride. If tachycardia or hypertension was observed, an additional 5 mg/kg dose of hexamethonium was given; the animal was then retested with 0.1 mg/kg of tetramethylammonium chloride to confirm ganglionic blockade.

Control Group

Five dogs were treated identically to those in Group I except that following application of the monitoring devices and the recording of control values, an infusion of balanced salt solution was started. The volume per hour of salt solution infused was identical to the volume per hour of lidocaine solution infused in Group I and Group II.

In a preliminary study of six dogs, the lidocaine infusion rate which could be tolerated for 200 minutes was determined. Dogs were given 4, 8, 16, 20, 32, or 50 mg/kg/hr after having the various monitoring devices applied. Doses of 20 mg/kg/hr and lower were tolerated without profound changes in the cardiovascular measurements; 32 and 50 mg/kg/hr proved rapidly fatal in two dogs.

An analysis of variance [6] was performed on the data, utilizing an RCA Spectra 70-46 time-sharing computer. This method allowed the statistical evaluation of the changes observed in the individual variables in each group as a function of time from the start of the lidocaine or saline solution infusion. It also allowed the statistical comparison of time-dependent responses between the groups. In the determination of levels of significance when all groups were compared with each other, Scheffé's criterion [7] was applied.

Results

Control Group

All five animals given infusions of saline solution survived the study. $S.G._{max}$ (fig. 1), the maximal tension developed by a segment of the left ventricular musculature, decreased significantly ($P < 0.001$) with time. At the end of the experiment this value averaged 80.6 ± 9.06 (SD) per cent of the initial value. This decline was steady and progressive. Pulse pressure also fell significantly ($P < 0.005$) with time and at 200 minutes was 80 per cent of the initial value. Changes in the other variables with time were not significant.

Group I

All seven animals given lidocaine at 20 mg/kg/hr survived the study. HR progressively decreased ($P < 0.0001$) to 69 per cent of control. LVEDP increased from 5.31 ± 8.67 torr to 9.0 ± 8.02 torr (SD) at 200 minutes ($P < 0.0001$). Both SAP ($P < 0.001$) and DAP ($P < 0.005$) increased significantly over the course of the experiment. $S.G._{max}$, $S.G._{dev}$, CVP, PP, and dP/dt_{max} (fig. 2) did not change significantly.

Table 2. Significance* of Changes of Values between Groups as a Function of Time

	Control ⇅ Group I	Control ⇅ Group II	Group I ⇅ Group II
Heart rate	NS	NS	NS
Strain gauge amplitude	<0.05	<0.025	<0.0001
Strain gauge baseline deviation	NS	NS	NS
Left ventricular end-diastolic pressure	NS	NS	NS
Pulse pressure	NS	NS	NS
Systolic arterial pressure	NS	NS	<0.001
Diastolic arterial pressure	NS	NS	<0.001
dP/dt	NS	NS	NS
Central venous pressure	NS	NS	NS

* Numbers indicate level of significance. NS indicates lack of significance ($P > 0.05$).

Group II

Of five dogs pretreated with hexamethonium, two died before the end of the study. One dog died after 40 minutes of infusion, having received less than 15 mg/kg of lidocaine. This animal manifested progressive cardiovascular depression from the start of the lidocaine infusion. The other dog that died developed a bradycardia followed by asystole at 125 minutes. Data from these two animals were eliminated from the group means. In the surviving three animals, HR decreased 31 per cent ($P < 0.0001$), and SG_{max} progressively declined 57.2 per cent ($P < 0.001$). Both SAP and DAP decreased significantly ($P < 0.005$) over 200 minutes. The changes within each group as a function of time are summarized in table 1.

In the comparison of the time-dependent changes in Group I with those in Group II, significant differences were noted in $S.G._{max}$, SAP, and DAP. Since the directions of change of the variables in Group I and Group II were

TABLE 3. Values for Variables (Mean ± SD) as a

		Time (Minutes)			
		0	20	40	60
Heart rate (/min)	Control	112 ± 30	122 ± 26	120 ± 32	130 ± 25
	Group I	160 ± 40	141 ± 26	134 ± 25	136 ± 19
	Group II	130 ± 25	124 ± 37	123 ± 36	115 ± 30
Strain-gauge amplitude (per cent of control)	Control	100 ± 0	98 ± 9	94 ± 6	96 ± 10
	Group I	100 ± 0	105 ± 18	105 ± 21	105 ± 20
	Group II	100 ± 0	88 ± 20	72 ± 24	68 ± 25
Strain-gauge baseline deviation (per cent of control)	Control	0 ± 0	1 ± 9	−2 ± 16	−10 ± 22
	Group I	0 ± 0	−2 ± 10	−11 ± 22	−13 ± 23
	Group II	0 ± 0	−10 ± 32	−10 ± 20	−18 ± 15
Left ventricular end-diastolic pressure (torr)	Control	18 ± 17	15 ± 18	18 ± 20	16 ± 19
	Group I	5 ± 8	4 ± 9	8 ± 7	8 ± 7
	Group II	17 ± 5	16 ± 4	18 ± 3	18 ± 3
Arterial pulse pressure (torr)	Control	35 ± 8	33 ± 9	35 ± 10	32 ± 10
	Group I	27 ± 7	26 ± 6	28 ± 8	28 ± 7
	Group II	33 ± 9	27 ± 8	30 ± 8	30 ± 7
Systolic arterial pressure (torr)	Control	138 ± 31	131 ± 26	134 ± 29	136 ± 26
	Group I	130 ± 25	128 ± 29	133 ± 27	138 ± 30
	Group II	104 ± 40	92 ± 44	80 ± 11	80 ± 7
Diastolic arterial pressure (torr)	Control	102 ± 36	97 ± 19	98 ± 30	104 ± 23
	Group I	102 ± 21	102 ± 27	105 ± 24	108 ± 27
	Group II	69 ± 36	65 ± 48	50 ± 8	49 ± 8
dP/dt (torr/second)	Control	3,092 ± 1,894	2,933 ± 1,724	2,833 ± 1,843	3,560 ± 2,179
	Group I	3,532 ± 1,339	2,806 ± 687	2,743 ± 758	2,947 ± 1,253
	Group II	3,360 ± 2,579	3,040 ± 3,169	1,580 ± 389	1,650 ± 640

generally opposite, few significant differences were noted when these two groups were compared with the control group (table 2). The absolute values for each variable are presented in table 3.

Discussion

The cardiovascular toxicity of lidocaine is modified by the ability of the autonomic nervous system to respond. Extremely high doses of this drug cause no significant depression of the functional activity of the cardiovascular system in the dog with an intact autonomic nervous system. Blockade of ganglia greatly increases the cardiovascular depressant effects of lidocaine.

Lidocaine appears to have both a direct depressant effect on the myocardium and an indirect stimulant effect mediated by the autonomic nervous system. The degree of predominance of one over the other appears to be a function of the blood level of the agent. With increased blood levels, the depressant effects predominate, as demonstrated by the dogs receiving 32 and 50 mg/kg/hr in a pilot study, whereas dogs receiving 20 mg/kg/hr in this study and lesser amounts in the pilot study showed little evidence of cardiovascular depression.

Kao and Jalar [5] reported increases in cardiac output and arterial pressure in a cross-circulation study using dogs whose heads were being perfused with blood containing lidocaine. Circulatory depression was observed in decerebrate dogs given lidocaine, and no stimulant effect was noted when lidocaine was given

Function of Time for Each Group

Time (Minutes)						
80	100	120	140	160	180	200
128 ± 25	123 ± 27	117 ± 40	121 ± 37	132 ± 35	130 ± 27	135 ± 26
136 ± 15	130 ± 19	127 ± 15	123 ± 19	123 ± 15	117 ± 18	115 ± 24
125 ± 26	112 ± 22	108 ± 23	92 ± 20	88 ± 20	89 ± 18	87 ± 18
93 ± 8	90 ± 10	86 ± 9	86 ± 10	83 ± 10	80 ± 11	80 ± 9
108 ± 22	110 ± 23	115 ± 25	108 ± 22	108 ± 21	105 ± 20	108 ± 27
68 ± 28	64 ± 27	52 ± 14	48 ± 19	44 ± 21	44 ± 20	44 ± 16
−12 ± 34	−18 ± 42	−17 ± 41	−18 ± 43	−21 ± 42	−23 ± 39	−22 ± 40
−19 ± 34	−14 ± 25	−10 ± 21	−6 ± 17	−1 ± 20	1 ± 29	0 ± 34
−32 ± 16	−24 ± 16	−32 ± 17	−33 ± 18	−37 ± 32	−32 ± 20	−40 ± 20
16 ± 18	17 ± 18	17 ± 19	19 ± 17	18 ± 18	17 ± 16	19 ± 18
8 ± 7	8 ± 6	9 ± 7	9 ± 8	9 ± 6	9 ± 8	9 ± 7
19 ± 4	19 ± 3	19 ± 4	20 ± 4	19 ± 3	19 ± 4	19 ± 3
31 ± 10	27 ± 15	30 ± 6	30 ± 5	27 ± 3	30 ± 8	28 ± 7
28 ± 7	29 ± 8	29 ± 7	29 ± 8	29 ± 5	28 ± 8	29 ± 8
27 ± 6	30 ± 8	27 ± 6	28 ± 8	27 ± 7	27 ± 6	30 ± 9
135 ± 30	108 ± 63	131 ± 35	134 ± 30	130 ± 37	124 ± 45	126 ± 35
143 ± 29	151 ± 25	158 ± 28	151 ± 23	151 ± 27	152 ± 29	149 ± 33
80 ± 10	72 ± 14	72 ± 18	72 ± 18	68 ± 16	72 ± 16	68 ± 20
103 ± 28	81 ± 49	101 ± 33	104 ± 34	103 ± 37	94 ± 44	97 ± 31
114 ± 27	121 ± 22	129 ± 23	122 ± 19	121 ± 24	123 ± 24	125 ± 25
53 ± 11	42 ± 12	45 ± 18	44 ± 12	41 ± 10	45 ± 9	38 ± 10
3,169 ± 2,125	3,189 ± 1,933	2,683 ± 1,730	2,219 ± 1,374	1,875 ± 1,282	2,032 ± 1,347	2,165 ± 1,368
2,749 ± 903	2,774 ± 1,348	2,838 ± 1,630	2,838 ± 1,000	2,851 ± 1,389	2,936 ± 1,397	3,910 ± 2,584
1,549 ± 702	1,436 ± 629	1,457 ± 652	1,043 ± 128	1,040 ± 78	1,128 ± 152	1,104 ± 253

systemically to dogs whose heads were isolated. Austen and Moran [5] have shown myocardial depression in *in-situ* dog hearts which were isolated and perfused with blood containing lidocaine. Isolated-heart studies have confirmed the myocardial depressant effects of low levels of lidocaine.[4] These studies and our results show that lidocaine does not cause its cardiovascular stimulation at the medullary level or below. Wagman *et al.*[9] have shown that lidocaine-induced seizures may originate in the limbic system. Therefore, we suggest that stimulation of limbic or other higher centers is responsible for the lack of obvious cardiovascular toxicity from large doses of lidocaine in the animal with an intact autonomic nervous system. This explanation of the cardiovascular effects of lidocaine is further supported by our previous study [10] showing depression of $S.G._{max}$, SAP, and DAP in dogs anesthetized with pentobarbital and given lidocaine.

Some clinical correlations are suggested by these results. The treatment of local anesthetic-induced convulsions with barbiturates or other depressants should be assessed carefully with regard to potential cardiovascular depression. Central nervous system depressants may block the mechanism of cardiovascular stimulation found with lidocaine. In addition, central nervous system depressants may have myocardial depressant effects of their own, and these effects may be additive with the effects of lidocaine. Even more important, patients receiving agents with autonomic depressant or inhibitory actions, such as some antihyperten-

sive agents, would be expected to be much more sensitive to the direct myocardial effects of lidocaine.

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Respiration

ENDOTRACHEAL INTUBATION This study reports the histopathologic changes in 19 infants who had been intubated (almost all via the oral route) for periods ranging from 15 minutes to 152 hours (one infant for nine weeks). The endotracheal tubes used were of the disposable uncuffed variety, made of polyvinyl chloride, with external diameters from 3 to 5 mm. *En-bloc* specimens of esophagus, main bronchi, trachea, and larynx were removed and examined. No gross lesion was present except in one instance in which a small ulcer was found over the cricoid.

In 14 of the 19 infants, there was histologic evidence of necrosis of the airway epithelium; in 11 there were areas of focal necrosis over the arytenoids, cricoid, and vocal cords, associated with extensive necrosis of the tracheal mucosa in six; an additional two infants also had extensive tracheal mucosal necrosis, but laryngeal sections were not obtainable. There were three instances of squamous metaplasia below the vocal cords. The tracheal lesions were considerably more extensive than the more anatomically superior focal lesions—whole stretches of epithelium and underlying lamina propria were necrotic and basophilic.

The single most important causative factor for these changes was the duration of intubation. Intubation for more than an hour resulted in some focal mucosal necrosis. Extensive necrosis of tracheal mucosa occurred in six of seven infants intubated for than six hours, in contrast to nine infants intubated less than six hours, of whom only two developed tracheal necrosis. Squamous metaplasia occurred in three infants intubated for more than 100 hours, and subglottic fibers occurred in the infant intubated for nine weeks. (*Raschke, R. F. H., and Kuhns, L. R.: Histopathologic Changes in Airway Mucosa of Infants after Endotracheal Intubation. Pediatrics 50: 632–637, 1972.*) ABSTRACTER'S COMMENT: This revealing study indicates that mucosal lesions can occur even during the time course of the usual operative procedure. It is comforting to know, as the author points out, that nearly similar degrees of mucosal damage occur with upper respiratory tract infections without permanent sequelae.