Toxic Effects of Lignocaine on the Circulation

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There is little doubt concerning the efficacy of lignocaine (Xylocaine) in the treatment of many cardiac arrhythmias, particularly during cardiac catheterization (Southworth *et al.*, 1950), during intubation and induction of anaesthesia and cardiac surgery (Weiss, 1960), and after myocardial infarction (Lown *et al.*, 1967; Jewitt *et al.*, 1968; Spracklen *et al.*, 1968). In spite of the apparent value of the drug there is little information on its haemodynamic effects, and this communication is concerned with evaluating its effect in small doses in man and much larger doses in dogs. This investigation was done to determine whether a continuous infusion of lignocaine could be used in all patients after myocardial infarction to suppress the common ventricular ectopic beats, and possibly act as a prophylactic measure to prevent arrhythmias causing further myocardial deterioration. Lown *et al.* (1967) expressed the opinion that antiarrhythmic drugs might jeopardize survival after myocardial infarction by reducing myocardial contractile force.

Methods

Patients

Four patients (weight 40.6-79.8 kg.) undergoing cardiac catheterization under light barbiturate anaesthesia with a view to possible surgery were investigated. Measurements were taken before and after an intravenous dose of lignocaine (1 mg./kg.) given over a two-minute period, and 10, 20, 30, and 60 minutes after starting a lignocaine infusion given with a home-made constant infusion pump (1 mg./min. in a volume of 2 ml. of isotonic saline; total dose was approximately 120 mg. of lignocaine). Conventional catheters were used and transeptal left atrial catheterization was performed with a modified Brockenbrough needle; in one instance left ventricular pressure was measured with a transeptal catheter through the mitral valve (the maximum rate of rise of left ventricular pressure, dp/dt, was measured and taken as the average of five values determined by a tangent drawn on the steepest part of the pressure tracing; the rate at which ventricular pressure is developed reflects a fundamental property of contracting myocardium and may be used to study myocardial contractility (Gleason and Braunwald, 1962)). Pressures were measured with Sanborn transducers 5 cm. below the sternal angle and recorded on a Sanborn 560-series polyanalyser. Cardiac output was measured by using indocyanine green dye injected into the pulmonary artery or right ventricle with arterial blood being withdrawn by a Gilford 105-S pump through a Gilford 103-IR densitometer and recorded on a Southern Instruments ultraviolet recorder. Haemodynamic changes are given as percentage changes from control values ($\Delta\%$).

Dogs

Six dogs (weight 21.8-29.0 kg.) were anaesthetized with sodium pentobarbitone (30 mg./kg. body-weight) and the experiment was started two hours later, when the cardiovascular

system is known to be in a stable state (Binnion and Hatcher, 1963). Cardiac output was determined by the dye-dilution method with the use of indocyanine green dye injected into the central venous circulation; arterial blood was withdrawn from the femoral artery by a Gilford 105-S constant withdrawal pump through a Cambridge Instruments cuvette coupled to a Cambridge dye dilution recorder. Central aortic blood pressure was measured through a polyethylene catheter (Portex PP260) by means of a Consolidated Electrodynamics strain gauge transducer (type 4-327-L221) attached to a Devices M.4 recorder. The arterial blood pressure and lead II of the electrocardiogram were recorded during the inscription of the dye curve. Mean arterial blood pressure was calculated from the diastolic pressure plus one-third of the pulse pressure. The Q-T interval was measured with callipers from lead II of the electrocardiogram, and the rate of rise of the central aortic pulse (dp/dt) was measured from a tangential line drawn on the steepest part of the upstroke and the average of no fewer than five measurements taken (this measurement may be related to myocardial contractility).

An intravenous infusion of lignocaine (10-13.5 mg./min.) was given with a constant infusion pump, and cardiac output, central aortic pressure, and the electrocardiogram were recorded after 10, 20, and 30 minutes of infusion. After a rest period these measurements were recorded before and after a rapid intravenous injection of 200 and 400 mg. of lignocaine (given as a 2% solution), and in one instance after 500 mg.

Results

Infusion into Patients.—There were no consistent changes in any of the cardiovascular measurements (Table I), and the total dose of lignocaine given within the hour varied from 110 to 140 mg. There were no subjective or other objective changes in these patients.

TABLE I.—Haemodynamic Changes Produced in Four Patients by 1 mg. of Lignocaine per Minute After Loading Dose of 1 mg./kg. Body-weight

	Cardiac Output ($\Delta\%$)	Heart Rate ($\Delta\%$)	Stroke Volume ($\Delta\%$)	Mean Arterial Blood Pressure ($\Delta\%$)	Total Systemic Resistance ($\Delta\%$)
10 min. of infusion ..	-2.4	-0.5	-4.7	-0.6	+2.4
20 min. of infusion ..	-0.7	-3.2	-3.3	+2.4	+3.8
30 min. of infusion ..	+1.7	+1.9	+2.0	+1.3	-0.5
60 min. of infusion ..	-8.2	-1.3	-6.5	-4.9	-0.8

Infusion into Anaesthetized Dogs.—The dose was approximately 25 times greater than that given to the patients, and this caused a small fall in arterial blood pressure which was progressive (11% fall in mean pressure at end of the 30-minute infusion) and a progressive bradycardia (fall of 18.4% in heart rate at end of infusion). There was an increase in cardiac output, but total peripheral resistance fell only after 30 minutes' infusion. The increase in the Q-T interval of the electrocardiogram was small, but there was a distinct fall in central aortic dp/dt (Tables II and III). However, in spite of the large doses used the cardiovascular changes produced were not severe.

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Injection of Lignocaine in Patients.—An injection of 1 mg. of lignocaine per kg. body-weight produced no effect on the measurements except in one patient where there was a transient fall in left ventricular dp/dt from 1,518 to 1,363 mm. Hg/sec. This dose of lignocaine given over a two-minute period causes a small reduction in myocardial contractility.

TABLE II.—Effect of Infusing Lignocaine at 10–13.5 mg./min. Into Anaesthetized Dogs

Dog		Arterial Blood Pressure (mm. Hg)			E.C.G. Rate (Complexes/min.)	Q-T Interval (sec.)	Max. Aortic dp/dt (mm. Hg/sec.)
		Systolic	Mean	Diastolic			
47	Control	170	154	146	130		
	10 min. of infusion	176	156	146	120		
	20 "	171	152	142	114		
	30 "	172	152	142	111		
55	Control	205	165	145	167	0.22	1,550
	10 min. of infusion	200	160	140	159	0.20	1,760
	20 "	174	141	124	148	0.20	1,347
	30 "	150	122	108	140	0.22	1,127
56	Control	223	202	190	195	0.21	1,297
	10 min. of infusion	231	204	191	161	0.22	790
	20 "	225	198	185	140	0.22	673
	30 "	205	183	172	138	0.22	466
57	Control	234	211	199	187	0.19	1,951
	10 min. of infusion	235	208	194	183	0.20	1,877
	20 "	227	201	188	174	0.20	872
	30 "	218	194	182	159	0.22	764
58	Control	213	189	177	168	0.23	963
	10 min. of infusion	218	190	176	154	0.24	945
	20 "	221	192	177	148	0.26	898
	30 "	216	189	175	146	0.27	831

TABLE III.—Haemodynamic Changes Induced in Anaesthetized Dogs Infused with Lignocaine (13.5 mg./min.)

	Cardiac Output (Δ%)	Heart Rate (Δ%)	Stroke Volume (Δ%)	Mean Arterial Blood Pressure (Δ%)	Total Systemic Resistance (Δ%)
10 min. of infusion ..	+10.3	-8.0	+21.2	-0.4	+2.5
20 min. of infusion ..	+3.9	-14.6	+15.8	-4.8	+9.3
30 min. of infusion ..	+14.3	-18.4	+39.1	-10.8	-15.4

Large Doses of Lignocaine Injected into Dogs.—Rapid injections of 200 and 400 mg. caused a marked reduction in both arterial blood pressure and maximum aortic dp/dt (Table IV), but this is of a relative transient nature. In dog 54 an injection of 500 mg. of lignocaine intravenously caused a fall in heart rate from 135 to 102/min. after 50 seconds and of 105/min. after 180 seconds. Shortly after this the previously normal sinus rhythm changed suddenly to an idioventricular rhythm, and at 225 seconds this deteriorated into coarse ventricular fibrillation and then rapidly to ventricular asystole (Table IV).

Discussion

This communication and the work of others (Harrison *et al.*, 1963; Jewitt *et al.*, 1968) show that lignocaine given as an intravenous infusion of 1 mg./min. does not have any noticeable haemodynamic effects in man. This dose is capable of reducing the incidence of ventricular ectopic beats after myocardial infarction (Jewitt *et al.*, 1968); hence it is appropriate now to consider whether clinical trials should be instituted in which all patients in an intensive care unit after myocardial infarction are given an infusion of lignocaine to determine whether it will prevent the occurrence of ventricular arrhythmias. These arrhythmias are known to have a deleterious effect on the circulation (McIntosh and Morris, 1966) and would tend to compound the myocardial damage. Lown *et al.* (1967) stated that owing to the myocardial depression produced by antiarrhythmic drugs their prophylactic use in myocardial infarction is not justified. This article shows that this statement

is not justified. Lignocaine infusions should be given at a constant rate (preferably by a constant infusion pump), for even 1 mg. of lignocaine per kg. body-weight given over a two-minute period can reduce left ventricular contractility slightly.

Even when infused at a rate 25 times greater the deterioration in arterial blood pressure and heart rate in anaesthetized dogs is only moderate, and if ventricular arrhythmias cannot be controlled with 1 mg. of lignocaine per minute it would appear safe to increase this dose, but only with arterial blood pressure being constantly monitored, especially if large injections of lignocaine are used (this is necessary in view of the sudden change from sinus rhythm to ventricular fibrillation which occurred in one dog). Severe depression of the arterial blood pressure is seen in anaesthetized dogs given a sudden injection of 400 mg. of lignocaine, which is just less than 20 mg./kg. body-weight. The reduction of arterial blood pressure is short-lived, so there is a large safety factor present when using this drug. The electrocardiogram is not a good guide to the presence of a severe toxic depression of the circulation, for an idioventricular rhythm and ventricular fibrillation can occur suddenly from preceding normal sinus rhythm. If large doses are to be infused, arterial blood pressure measurements are mandatory.

Summary

In man an infusion of intravenous lignocaine in a dose of 1 mg./min. has no noticeable cardiovascular effects when given for up to 60 minutes. In anaesthetized dogs 10–13.5 mg./min.

TABLE IV.—Effect of Rapid Intravenous Injection of Lignocaine

Dog	Time after Injection (min.)	Arterial Blood Pressure (mm. Hg)			E.C.G. Rate (Complexes/min.)	Q-T Interval (sec.)	Max. Aortic dp/dt (mm. Hg/sec.)
		Systolic	Mean	Diastolic			
200 mg. Lignocaine							
55	Control	170	137	120	137	0.21	1,320
	End of injection	104	79	66	135		
	1	110	91	81	123	0.23	511
	2	118	99	89			
	3	128	107	97			
	5	139	115	103			
	7	149	123	110	132	0.21	893
56	Control	225	198	184	134	0.23	682
	End of injection	173	155	146	136		668
	3	210	186	174	124	0.24	632
	6	226	199	185	126		642
	10	209	186	174	122	0.24	800
	15	211	187	175	130	0.24	692
							2,165
57	Control	231	206	194	178	0.20	
	1	172	151	141	145	0.22	1,137
	2	193	173	163	151	0.22	1,483
	5	221	198	186	157	0.21	824
58	Control	208	183	170	153	0.25	810
	1	203	188	166	141	0.26	714
	2	209	179	164	137	0.26	730
	5	216	189	175	140	0.26	746
10	216	189	176	141	0.28	764	
400 mg. Lignocaine							
56	Control	225	200	187	131	0.24	730
	1	112	101	96	105	0.27	376
	3	156	139	131		0.26	452
	5	193	172	162	111	0.26	426
	8	232	201	186	113	0.26	617
	12	204	179	166	110	0.25	620
57	Control	232	209	196	192	0.19	1,469
	1	103	91	85	133	0.22	731
	2	115	104	98	133	0.25	706
	5	179	164	156	135	0.25	780
	10	208	187	177	144	0.22	1,013
60	Control	216	186	171	187	0.21	2,610
	1	107	88	79	137	0.28	885
	3	129	108	98	143	0.27	1,232
	5	174	145	131	150	0.26	1,553
	10	196	164	148	155	0.25	1,847
		217	186	170	163	0.24	1,781
500 mg. Lignocaine							
54	Control				135		
	1				102		
	3				105		
	3½						
	4½						
					Sinoatrial block with idioventricular rhythm. Idioventricular rhythm terminating in ventricular fibrillation and then ventricular asystole		

causes a moderate reduction in heart rate, arterial blood pressure, and central aortic dp/dt, but a reduction in total systemic resistance occurred only at 30 minutes of infusion. A slight reduction in left ventricular dp/dt was seen in one patient given 1 mg./kg. body-weight over a two minute period. Doses of 200–500 mg. of lignocaine given as a rapid injection into anaesthetized dogs cause a marked fall in arterial blood pressure and maximum aortic dp/dt, and in one instance ventricular fibrillation was produced suddenly and without warning. The electrocardiogram is a poor guide to toxic effects, and arterial blood pressure is more useful and probably mandatory when larger doses are infused. Lignocaine infusion (1 mg./min.) should be given a clinical trial in all patients with myocardial infarction, for it has no marked haemodynamic effects in this dose and may well suppress the onset of potentially harmful ventricular arrhythmias.

ADDENDUM.—A 200-mg. rapid injection of lignocaine (dog 68) caused a fall in maximum left ventricular dp/dt from 2,122

mm. Hg/sec. to 1,492 (15 seconds later), 1,673 (30 seconds later), and 2,143 (two minutes later). In one patient an injection of lignocaine 1 mg./kg. over two minutes caused a fall in left ventricular dp/dt from 1,920 to 1,495 mm. Hg/sec. ($\Delta\% = -22.1$).

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Medical Memoranda

Hyperkalaemic Periodic Paralysis Starting at Age 48

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Three main types of periodic paralysis are recognized—hypokalaemic (the commonest), hyperkalaemic, and the sodium-responsive normokalaemic variety.

Hyperkalaemic periodic paralysis, or adynamia episodica hereditaria, was described in full by Gamstorp (1956). It is a hereditary disease that starts in infancy or childhood, is at its worst during adolescence, and, apart from pregnancy, tends to subside later in life (McArdle, 1963). It is characterized by periodic attacks of paralysis lasting 30 to 40 minutes, and typically occurring during rest after exercise. Attacks are usually diurnal and frequent, though nocturnal attacks of longer duration and greater severity may also occur. They are often precipitated by fasting, emotional states, cold weather, and intercurrent infections (Layzer, Lovelace, and Rowland, 1967). Episodes may be aborted by exercise or at times by ingestion of carbohydrate (van't Hoff, 1962). Unlike the hypokalaemic variety death never occurs during a spontaneous attack of hyperkalaemic periodic paralysis (Helweg-Larsen, Hauge, and Sagild, 1955).

A high serum potassium during attacks is diagnostic of the condition. Other electrolyte values are usually normal; a few otherwise typical cases of hyperkalaemic periodic paralysis do have hypocalcaemia during attacks (Layzer *et al.*, 1967).

CASE HISTORY

A 48-year-old man, the second of a family of 10 children, was admitted to hospital in January 1966 with an acute anterior infarct for which he was treated. He was discharged four weeks later. During his stay in hospital he was found to be diabetic, and accordingly was put on a diabetic diet.

Some time after discharge he started having attacks of generalized weakness at the rate of one a week. They usually occurred a short time after exertion. He noticed that when he stuck to his diabetic diet attacks tended to be more frequent. As they were occurring in a background of conjugal troubles a hysterical origin was not excluded. Attacks persisted, and he was asked to call at the clinic, where he obliged by having an attack while sitting in the waiting-room. Admission to hospital was recommended but he was not restricted to bed. Further diurnal paralytic attacks occurred without any special rhythm. However, when an attack occurred he usually had one or two similar episodes on the same day.

He was conscious of an impending attack, because it was preceded by paraesthesiae and weakness ascending both lower limbs, and by a sensation of precordial discomfort. Weakness soon involved trunk muscles, upper limbs, and neck muscles. He became terrified during attacks but never lost consciousness, and had full control of sphincters. Speech and respiratory muscles were always spared. He found difficulty in moving his eyes. Episodes were over within 20 to 30 minutes, and the lower limbs were the last to recover. During attacks he was unable to raise the lower and upper limbs and the head. Tendon reflexes were diminished but not absent. Both plantars were flexor. Muscles were not painful or tender. Cranial nerves were not involved. Sensation was unimpaired.

Investigations were carried out in three separate attacks. On 2 November 1966 the serum Na was 130 mEq/l., serum K 9 mEq/l., plasma Cl 94 mEq/l., serum Ca 4.5 mEq/l., and blood glucose 155 mg./100 ml. At 12 noon on 25 May 1967 the serum Na was 133 mEq/l., serum K 10 mEq/l., plasma Cl 102 mEq/l., serum Ca 4.5 mEq/l., and blood glucose 171 mg./100 ml. At 4 p.m. on 25 May the serum Na was 140 mEq/l., serum K 7.3 mEq/l., plasma Cl 108 mEq/l., serum Ca 4.8 mEq/l., and blood glucose 109 mg./100 ml.

Between attacks the patient showed no evidence of residual weakness. Investigations carried out between attacks showed: haemoglobin 15.1 g./100 ml., blood urea 33 mg./100 ml., serum Na 132–146 mEq/l., serum K 3.7–5 mEq/l., and plasma Cl 90–100 mEq/l. X-ray examination of chest showed no appreciable disease. Muscle biopsy (taken from the gastrocnemius muscle between attacks) showed no evidence of vacuoles, the only slightly unusual features being a few areas where there seemed to be a possible excess of intracellular nuclei and a single "ringed" fibre (*Ring-binden*). In the pathologist's view the findings were within normal limits. Electromyography was not carried out, as facilities were not available locally.

The patient was given chlorothiazide 2 g. daily from December 1966 to the end of March 1967, and during that period he had no attacks. When treatment was stopped, a recurrence followed. In the beginning of May he became incapacitated once more, and admission to hospital was again suggested. Further attacks occurred during this latter period. He was restarted on chlorothiazide, and has remained well controlled.

DISCUSSION

Hyperkalaemic periodic paralysis is a very uncommon condition, for the diagnosis of which certain criteria have to be fulfilled. We believe that the above case satisfies these criteria. The periodic attacks which occur during rest after exercise, and their precipitation by emotional states, are typical. The duration of attacks and their spontaneous remission after 30 to 40 minutes are also characteristic.