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Effects of lignocaine and propranolol on experimental cardiac arrhythmias

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Summary

1. The effects of intravenous injection of lignocaine and propranolol were studied in dogs.

2. Ventricular ectopic beats produced by intravenous injection of adrenaline in anaesthetized dogs respired with halothane were abolished in four out of six dogs by lignocaine. Propranolol was effective in all three dogs tested.

3. Intravenous infusion of lignocaine at (0·2 and 1·0 mg/kg)/min to total doses of $3{\cdot}0 \pm 1{\cdot}0$ and $2{\cdot}2 \pm 0{\cdot}5$ mg/kg, respectively, abolished the ventricular tachycardia produced in anaesthetized dogs by ouabain. A similar effect was produced by infusion of propranolol at (0·2 mg/kg)/min to a total dose of $1{\cdot}9 \pm 0{\cdot}4$ mg/kg. Intravenous injection of single doses of lignocaine (4·0–8·0 mg/kg) also abolished the arrhythmia.

4. The frequency of the ventricular ectopic beats occurring in conscious dogs 20–44 h after ligation of the anterior descending branch of the left coronary artery was reduced, with an increase in the number of sinus beats, after intravenous injection of lignocaine (8·0 mg/kg). Larger doses produced excitement. Propranolol (4·0 mg/kg) had a greater effect than the same dose of lignocaine but after 8·0 mg/kg, three of the four dogs died.

5. Propranolol was more effective than lignocaine in abolishing the three different types of arrhythmia.

6. Dose-response curves showed that lignocaine was more active in abolishing the ouabain induced arrhythmia than the halothane-adrenaline arrhythmia and was least active on the arrhythmia caused by ligation of the coronary artery.

Introduction

The local anaesthetic agent lignocaine is widely used in the treatment of ventricular arrhythmias following myocardial infarction. Although its mode of action is poorly understood, few studies have been made of its effects on arrhythmias experimentally produced in animals (Mendez & Kabela, 1970). In normal dogs pretreatment with lignocaine increases the dose of ouabain required to produce ventricular arrhythmias (Usubiaga, Wikinski, Vestal & Moya, 1967) and its intravenous administration can abolish the arrhythmias produced by cardiac glycosides (Katz & Zitnik, 1966 ; Hilmi & Regan, 1968).

Although ventricular arrhythmias induced by sympathomimetic amines and by coronary artery ligation in animals have been widely used in the evaluation of β-adrenoceptor blocking drugs (Dunlop & Shanks, 1968 ; Barrett & Cullum, 1968 ; Lucchesi & Iwami, 1968), the antiarrhythmic properties of lignocaine have not been

previously studied by these methods. However, the electrophysiological effect of lignocaine on isolated canine Purkinje fibres and ventricular muscle have been studied in detail (Davis & Temte, 1969 ; Bigger & Mandel, 1970a, b). Its effects have been compared with those of propranolol (Davis & Temte, 1968). Allen, Pantridge & Shanks (1970), reported that lignocaine raised the threshold for ventricular fibrillation produced by high energy electric shocks across the intact chest wall of dogs. Propranolol and bretylium had no such effect.

The effects of propranolol have been studied on arrhythmias induced in dogs in three ways: by halothane and adrenaline, by ouabain and by coronary artery ligation. In this paper, the effects of lignocaine are compared with the effects of propranolol.

Methods

Observations were made in greyhounds weighing 20–33 kg, anaesthetized by subcutaneous injection of morphine sulphate (0·5 mg/kg) followed 1 h later by intravenous injection of pentobarbitone sodium (20 mg/kg). A cuffed endotracheal tube was inserted and the dogs were artificially respired with room air using a Starling Ideal pump at a rate of eighteen strokes/min and a stroke volume of 13 ml/kg body weight. Drugs were injected through a polythene catheter in a foreleg vein. Arterial pressure was measured in mmHg (1 mmHg≡1·333 mbar) through a cannula inserted into the left carotid artery or a femoral artery and attached to a pressure transducer (Consolidated Electrodynamics ; Type 4-327-L221). Electrocardiograms (Lead II and aVL) were obtained from subcutaneous needle electrodes. Arterial pressure, the electrocardiograms and instantaneous heart rate (Nielsen cardiotachometer) were recorded on a Devices recorder (Type M8 or M4) and displayed on a four channel oscilloscope (Airmec).

Halothane-adrenaline arrhythmias

After preparation the dogs were artificially respired with room air and 1% halothane. Ten minutes later adrenaline (0·2 μg/kg) was injected intravenously during a period of 5 seconds. The dose of adrenaline was increased progressively from 0·4 μg/kg by increments of 0·4 μg/kg, with an interval of 7–10 min between each dose, until a ventricular arrhythmia was produced. In most dogs this arrhythmia consisted of repetitive multifocal ventricular ectopic beats or ventricular tachycardia but in some it was ventricular bigeminy. The dose of adrenaline required to produce arrhythmia was between 0·8 and 6·4 μg/kg ; the mean effective challenge dose for the ten experiments was $3{\cdot}5 \pm 0{\cdot}7$ (S.E.M.) μg/kg. Occasionally, adrenaline produced ventricular fibrillation which was terminated by external direct current counter-shock delivered from an American Optical defibrillator. After such defibrillation, halothane was discontinued for 10 min and the adrenaline challenge was repeated 20 min later but initially with a dose less than that which produced fibrillation.

Following determination of the dose of adrenaline required to produce arrhythmia in any one dog, increasing doses of either lignocaine or propranolol were given by intravenous injection at 10 min intervals and the effective adrenaline challenge was repeated after each dose of the two drugs.

Ouabain-induced arrhythmias

Observations were made on eighteen dogs prepared as described above. The right vagus nerve was exposed in the neck and divided. Bipolar electrodes were applied to its distal end ; stimulation was for periods of 10 s with shocks of 1 ms duration at a frequency of 25 Hz and a voltage which was progressively increased to produce the maximal sinus slowing possible without loss of sinus dominance. This voltage was determined for each animal before the administration of any drug and was in the range 2–10 V. Arrhythmias were produced by intravenous injection of ouabain (40 μg/kg) followed after 30 min by 20 μg/kg and then every 15 min by 10 μg/kg until ventricular tachycardia was produced. After establishment of the ventricular arrhythmia, stimulation of the vagus nerve had no effect on the ventricular rate, an observation indicating complete ventricular dominance. In fourteen dogs, when the arrhythmia had been established for 10 min, either 0·9% sodium chloride solution or solution of the compound under test was infused intravenously from a motor driven syringe. The infusion was continued until the return of sinus rhythm. In the drug studies, the vagus nerve was then stimulated with the previously determined test voltage and, if sinus slowing occurred without the appearance of ventricular ectopic beats, the infusion was stopped. If vagal stimulation exposed ventricular ectopic beats the infusion was continued until vagal stimulation produced slowing of the sinus rhythm without the occurrence of ventricular ectopic beats. The amounts of drug required (1) to produce a return to sinus rhythm and (2) to prevent the appearance of ventricular ectopic beats on vagal stimulation after the return of sinus rhythm were determined in each experiment.

In some dogs, the ventricular ectopic rhythm recurred spontaneously after a variable period of sinus rhythm ; in the other dogs, it could be induced by stimulation of the right vagus nerve or by intravenous injection of insulin (80–180 U). The restoration of the ventricular arrhythmia by these procedures showed the continued presence in the heart of toxic doses of ouabain.

In four dogs, the electrocardiogram was recorded continuously when ventricular tachycardia had been produced by ouabain. After a 10 min control period, lignocaine was given intravenously in increasing doses at 5 min intervals. From the continuous electrocardiogram the ventricular rate and number of sinus beats for each 5 min period were counted. Sinus beats were defined as QRS complexes of normal duration and vector, preceded by a P wave.

Arrhythmias after ligation of the coronary artery

Dogs weighing 20–28 kg were anaesthetized by intravenous injection of thialbarbitone sodium (50 mg/kg) or methohexitone sodium (10 mg/kg) and respired through a cuffed endotracheal tube with room air and halothane (0·5–1·0%). Under aseptic conditions, the heart was exposed through the fifth left interspace. Two ligatures were placed around the anterior descending branch of the left coronary artery at a level 2 cm distal to the tip of the left atrial appendage or immediately distal to the origin of the second major branch from the artery to the anterior surface of the left ventricle. The ligatures were tied in two stages as described by Harris (1950). The first ligature was tied around the coronary artery and a 21 gauge needle which was later removed. Thirty minutes later the second ligature was tied tightly around the artery. After a further 30 min the chest was closed in

layers and the animals allowed to recover. The development of myocardial infarction after ligation of the coronary artery was demonstrated by the appearance of a persistent elevation of the ST segment in the electrocardiogram recorded from a unipolar platinum electrode in the ischaemic area of the left ventricle. This electrode was removed before closure of the chest.

Observations were made 20–44 h later when the dogs were conscious. Electrocardiograms (Leads II and aVL) were recorded by means of subcutaneous needle electrodes on a direct writing instrument (M4 or M8, Devices Ltd.) for at least 5 min before the administration of any drug and during the time when a series of increasing doses of lignocaine or propranolol were given by intravenous injection at 5 min intervals. Each electrocardiogram was examined and the total number of ventricular complexes in a 5 min period was counted (V.R.) and the number of the complexes originating in the sinus node was determined (S.B.).

The presence of continued coronary arterial obstruction was confirmed after death by perfusion of the coronary arteries with a 0·9% NaCl solution and a suspension of barium sulphate in a mixture containing KI, gelatine and distilled water (Schlesinger, 1957).

Drugs

Drugs used were: (−)-adrenaline bitartrate (C. Zimmerman & Co.), (±)-propranolol hydrochloride ('Inderal', I.C.I.), ouabain (May & Baker), lignocaine hydrochloride ('Xylocaine', Astra-Hewlett). Drugs were dissolved in 0·9% NaCl solution at the required concentration; doses are expressed in terms of the salt. Halothane ('Fluothane', I.C.I.) was administered using a Blease Universal anaesthetic vaporizer.

Results

Halothane-adrenaline arrhythmias

Effect of lignocaine. Six dogs were given lignocaine following determination of the dose of adrenaline required to produce a ventricular arrhythmia. The dose of lignocaine was increased geometrically from 0·4 mg/kg until it prevented the adrenaline arrhythmia or until a maximum dose of 6·4 mg/kg had been given. The adrenaline challenge was given 2 min after intravenous administration of each dose of lignocaine. Some of the results of a typical experiment are shown in Fig. 1. In the control period intravenous injection of 1·6 μg/kg of adrenaline increased arterial pressure; a transient reduction in heart rate was followed by a burst of ventricular ectopic beats which began 17 s after injection of adrenaline and lasted for 34 seconds. Similar responses were seen after intravenous administration of 0·4 and 1·6 mg/kg of lignocaine but these are not reproduced in the figure. After the administration of 3·2 mg/kg of lignocaine, the number of ectopic beats was reduced and no ectopic beats were produced by adrenaline given after lignocaine (6·4 mg/kg). In one experiment the administration of lignocaine (0·8 mg/kg) and in two experiments, 3·2 mg/kg, prevented the ectopic response to adrenaline. In the remaining two dogs the highest dose of lignocaine (6·4 mg/kg) did not prevent the adrenaline arrhythmia although the number of ectopic beats was reduced.

In the four dogs in which lignocaine prevented the ventricular ectopic response to adrenaline, it did not significantly reduce resting heart rate (134 ± 19 to 121 ± 14), or

mean arterial pressure (130 ± 23 to 101 ± 20 mmHg). At this effective dose of lignocaine, the maximum mean arterial pressure after adrenaline administration (158 ± 15 mmHg) was similar to that at the onset of the arrhythmia produced by the same dose of adrenaline during the control period (168 ± 22 mmHg).

Effect of propranolol. The effects of propranolol were studied in four dogs. In all four propranolol (0·05 mg/kg) abolished the ectopic response to adrenaline. Propranolol significantly reduced resting heart rate from 131 ± 19 to 113 ± 14 ($P<0·05$ by paired analysis) but did not reduce resting arterial pressure (107 ± 24 to 106 ± 26 mmHg).

Ouabain arrhythmias

In five dogs ventricular tachycardia was produced by a mean dose of ouabain (68·0 ± 4·9 μg/kg). Isotonic NaCl solution was infused intravenously at a rate of 2 ml/min after the arrhythmia had been established. Sinus rhythm returned in four of these dogs after 90, 150, 160 and 187 min, although ventricular ectopic beats recurred during stimulation of the peripheral end of the cut vagus nerve. In the fifth dog the ouabain-induced ventricular tachycardia changed to atrial fibrillation 107 min after the last dose of ouabain. Atrial fibrillation persisted for a further 210 min, during which time vagal stimulation induced ventricular ectopic beats.

Effect of lignocaine. Observations were made in three dogs in which lignocaine was given by constant intravenous infusion at the rate of (0·2 mg/kg)/min and in three dogs in which it was given at (1·0 mg/kg)/min after the ouabain-induced ventricular tachycardia had been established.

The results of a typical experiment are shown in Fig. 2. Before the administration of ouabain, stimulation of the peripheral end of the cut vagus nerve caused

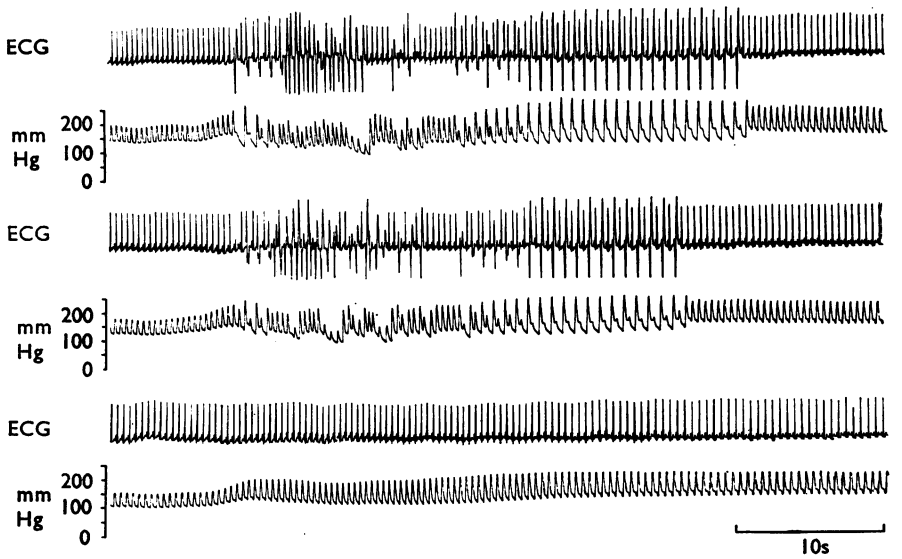

FIG. 1. Records of the electrocardiogram (Lead II) and arterial pressure in a dog respired with 1% halothane. The effects of the intravenous injection of adrenaline (1·6 μg/kg) are shown during a control period (upper pair of records) and 2 min after intravenous injection of lignocaine (3·2 (middle pair of records) and 6·4 mg/kg (lowest pair of records)). Adrenaline was injected 10 s before the start of each of the three traces.

marked slowing of the sinus rate (A). Intravenous injection of ouabain (60 μg/kg) produced ventricular tachycardia which was unaffected by vagal stimulation (B). Ten minutes later lignocaine was infused at a rate of (1 mg/kg)/minute. Sinus rhythm was restored after the infusion of 1·3 mg/kg of lignocaine, and after 3 mg/kg, ventricular ectopic activity did not occur on vagal stimulation (C). The infusion was stopped after 3·5 mg/kg had been given. Ten minutes after stopping the lignocaine infusion, sinus rhythm was present but vagal stimulation produced ventricular tachycardia (D). Intravenous injection of 180 U of soluble insulin resulted in ventricular tachycardia (F). Similar results were obtained in two other dogs in which lignocaine was given at (1·0 mg/kg)/minute.

The mean doses for reversion to sinus rhythm and for complete suppression of ectopic pacemaker activity are given in Table 1. Lignocaine was infused at a rate of (0·2 mg/kg)/min in three animals. The ouabain-induced ventricular tachycardia was reverted to sinus rhythm in all three dogs after the administration of a mean dose of lignocaine of 3·0±1·0 mg/kg. Administration of lignocaine at this

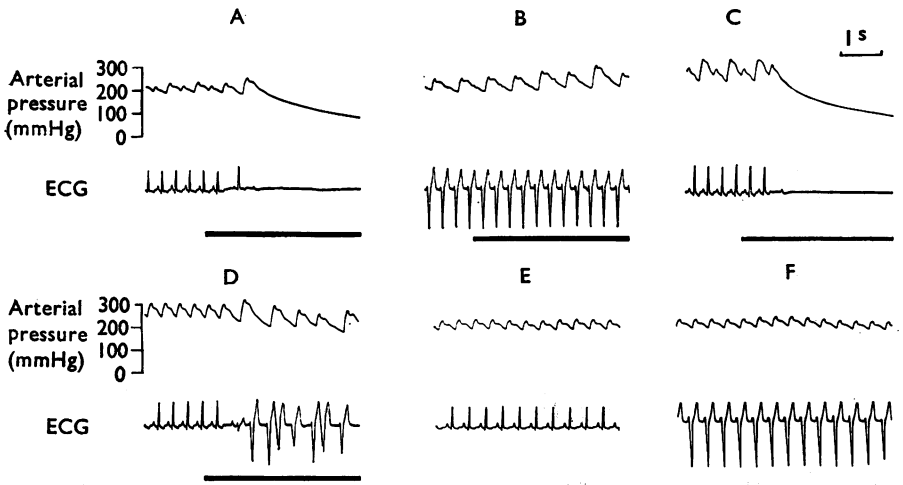

FIG. 2. Effect of lignocaine on ventricular tachycardia produced by ouabain in an anaesthetized dog. Records of arterial pressure and the electrocardiogram (Lead II) are shown. The peripheral end of the right vagus nerve was stimulated during the period indicated by the solid bar (3·5 V, 1 ms, 25 Hz). A, Control; B, after intravenous injection of ouabain (60 μg/kg); C, after intravenous infusion of lignocaine ((1 mg/kg)/min for 3 min); D, 10 min later; E and F, before and after intravenous injection of insulin (180 U).

TABLE 1. *Effects of lignocaine and propranolol on ouabain-induced arrhythmia*

Drug	No. of dogs	Mean dose of ouabain μg/kg±S.E.M.	Rate of infusion (mg/kg)/min	Mean dose of antiarrhythmic drug (mg/kg±S.E.M.) required: To restore sinus rhythm	Mean dose of antiarrhythmic drug (mg/kg±S.E.M.) required: To prevent ectopic beats on stimulation of vagus nerve
Control	5	68±4·9	—	—	—
Lignocaine	3	63±3·3	0·2	3·0±1·0	4·4±0·7 (2 dogs)
	3	70±5·8	1	2·2±0·5	5·6±1·3
Propranolol	3	56·7±9·0	0·2	1·9±0·4	3·6±0·7

Ventricular tachycardia was produced by intravenous administration of ouabain. After arrhythmia had been present for 10 min, 0·9% NaCl solution, lignocaine or propranolol was infused.

rate prevented the appearance of ventricular ectopic beats on stimulation of the vagus nerve in two of the three dogs. For either infusion rate of lignocaine, the heart rate and mean arterial pressure after reversion to sinus rhythm were not significantly different from the values observed before injection of ouabain (Table 2).

In four dogs with ouabain-induced ventricular tachycardia, a series of increasing doses of lignocaine were given by intravenous injection at intervals of 5 min (Fig. 3). In the first minute after the administration of the lowest dose (0·5 mg/kg), the number of sinus beats was increased significantly as compared with the preceding control period of 1 min ($P<0·05$). This was a transitory effect and the number of sinus beats was less during the periods 2, 3, 4 and 5 min after injection of lignocaine. The next highest dose (1·0 mg/kg), increased the total number of sinus

TABLE 2. *Effects of lignocaine and propranolol on heart rate and mean arterial pressure after restoration of sinus rhythm in ouabain-induced arrhythmias*

		Heart rate (beats/min±S.E.M.)		Mean arterial pressure (mmHg±S.E.M.)	
Drug	No. of dogs	Before ouabain	After return of sinus rhythm	Before ouabain	After return of sinus rhythm
Control	5	172±8	157±13 (n=4)	170±6	151±20 (n=4)
Propranolol 0·2 (mg/kg)/min	3	159±9	110±3	187±10	226±11
Lignocaine 0·2 (mg/kg)/min	3	155±5	145±3	165±17	213±5
1·0 (mg/kg)/min	3	159±5	161±13	216±16	254±7

Ventricular tachycardia was produced by intravenous administration of ouabain. Mean values (±S.E.M.) are given for heart rate and mean arterial pressure during a period of sinus rhythm before administration of ouabain, and after the spontaneous return of sinus rhythm (controls) or after suppression of the arrhythmias by intravenous infusion of lignocaine or propranolol. The only significant effects were a slowing of the sinus rate ($P<0·05$) and an increase in arterial pressure ($P<0·01$) on the return of sinus rhythm after the administration of propranolol.

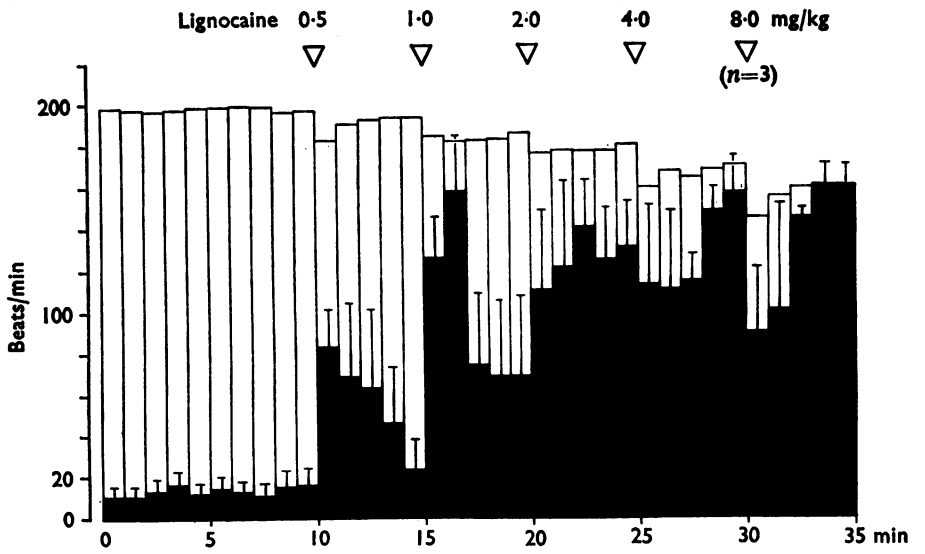

FIG. 3. Mean ventricular rate (clear columns), mean number of sinus beats (black columns) and standard error of the mean number of sinus beats (T-bars) are shown for each minute before and after administration of increasing doses of lignocaine in four dogs with ouabain-induced ventricular tachycardia. The mean dose of ouabain was 64±4·2 μg/kg.

beats for the 5 min period in all dogs ($P<0.02$, when compared with paired control values). The two highest doses (4·0 and 8·0 mg/kg) produced initial transient atrio-ventricular dissociation in two dogs but further increased the proportion of sinus beats in the 5 min period.

Effect of propranolol. Observations were made in three dogs in which propranolol was infused intravenously at (0·2 mg/kg)/min after ouabain-induced arrhythmia had been established. Propranolol restored sinus rhythm in all three dogs after the administration of a mean dose of $1·9 \pm 0·4$ mg/kg; a larger dose was required to suppress ventricular ectopic activity on vagal stimulation (Table 1). Heart rate at the return of sinus rhythm was significantly less than the value before ouabain and the mean arterial pressure was elevated (Table 2).

Ventricular arrhythmias after coronary artery ligation

Observations were made in thirteen dogs 20–44 h after two-stage ligation of the anterior descending branch of the left coronary artery. All dogs had severe ventricular arrhythmia which consisted of a multifocal ventricular tachycardia interspersed with normal sinus beats. Although the frequency of sinus beats varied between different dogs and in the same dog at different times, the number occurring in consecutive 5 min intervals was fairly constant (Table 3). Five dogs were used as controls—no drug was given and the electrocardiogram was recorded continuously for 30 min after the initial period of observation. The results show that the total ventricular rate and the number of sinus beats remained remarkably constant during the period of observation; the values were similar to those observed during the control period in the dogs which afterwards received lignocaine or propranolol (Table 3).

TABLE 3. *Effects of lignocaine and propranolol on the ventricular dysrhythmia induced by ligation of a coronary artery in dogs*

Period of observation	0–5 min		5–10 min		10–15 min		15–20 min		20–25 min		25–30 min	
	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.
Control ($n=5$)	987 ±9	45 ±11	924 ±31	66 ±19	912 ±43	81 ±22	925 ±32	80 ±26	974 ±36	66 ±30	949 ±76 ($n=3$)	55 ±39 ($n=3$)
Dose of drug (mg/kg)	0		0·5		1·0		2·0		4·0		8·0	
	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.	V.R.	S.B.
Lignocaine	933	0	934	0	965	0	936	0	793	49	749	254
	1,083	10	1,058	8	1,038	17	946	27	924	26	802	447
	1,084	62	1,133	16	1,088	25	1,060	3	959	133	894	793
	973	21	1,014	30	977	16	1,000	41	896	81	824	166
Mean	1,018	23	1,035	14	1,017	20	986	18	893	72	817	415
S.E.M.	±39	±14	±42	±7	±29	±2	±29	±10	±36	±23	±30	±139
Propranolol	930	0	857	1	773	4	604	0	474	229	*	—
	920	48	949	11	952	4	929	0	909	7	861	41
	783	280	699	288	624	222	638	250	539	487	*	—
	976	26	927	77	962	35	845	68	713	215	*	—
Mean	902	89	858	94	828	66	754	80	659	235	—	—
S.E.M.	±42	±65	±57	±67	±81	±57	±79	±59	±98	±88	—	—

The anterior descending branch of the left coronary artery was ligated 20–44 h before the drugs were administered to the conscious dogs. The ventricular rate (V.R.) and the number of sinus beats (S.B.) are given for consecutive 5 min periods (beats/5 min) in five control dogs given no drug, and in the treated dogs for 5 min periods before and after intravenous injection of the drugs. Mean values and S.E.M. are also shown. The only significant effects were a depression of V.R. after lignocaine (4 and 8 mg/kg; $P<0.01$) and an increase in S.B. after lignocaine (4 mg/kg; $P<0.05$).
* Died, ventricular fibrillation.

Effect of lignocaine. The effect of intravenous injection of a series of doses of lignocaine (0·5, 1·0, 2·0, 4·0 and 8·0 mg/kg) given by intravenous injection at 5 min intervals was observed in four dogs. Some of the results of one experiment are given in Fig. 4. During the control period a multifocal ventricular tachycardia was present with occasional ectopic beats. This pattern was unaltered by the administration of lignocaine (0·5 and 1·0 mg/kg). After 2·0 and 4·0 mg/kg of lignocaine, the ventricular arrhythmia became more stable at a slower rate and there were transient increases in the number of sinus beats. Within 2 min of intravenous injection of 8 mg/kg there was almost complete suppression of the arrhythmia with a return to sinus rhythm. This effect of lignocaine was of short duration and 9 min after injection, ventricular tachycardia had returned.

Similar results were obtained in the other three dogs (Table 3). Suppression of the ventricular arrhythmia with an increase in the number of sinus beats occurred after 4·0 and 8·0 mg/kg ; the effect was of short duration. All dogs became excited and restless after 8 mg/kg of lignocaine so that greater doses could not be administered.

Effect of propranolol. Observations were made in four dogs after intravenous injection of propranolol (0·5, 1·0, 2·0, 4·0 and 8·0 mg/kg) at 5 min intervals (Table 3). In three of the four dogs propranolol (0·5–2·0 mg/kg) appeared to reduce the total ventricular rate with little effect on the number of sinus beats. After propranolol (4 mg/kg) there was a further reduction in the ventricular rate and an increase in the number of sinus beats. The largest dose of propranolol (8 mg/kg) produced a reduction in ventricular rate and arterial pressure ; the animals died in less than

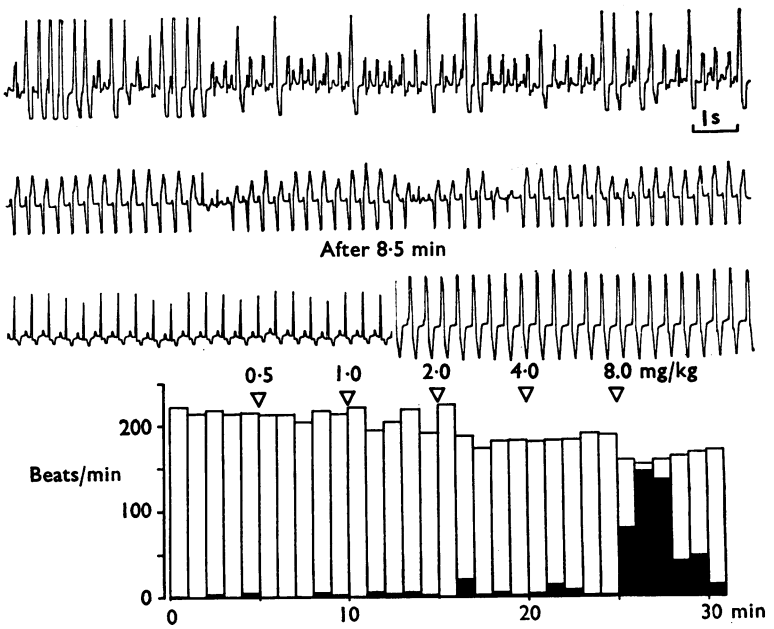

FIG. 4. Multifocal ventricular tachycardia present before and after intravenous administration of increasing doses of lignocaine in a dog 20 h after coronary artery ligation (electrocardiogram, lead II). (Upper record, control ; middle record, lignocaine (4 mmg/kg) ; lowest record, lignocaine (8 mg/kg).) The histogram indicates the ventricular rate (clear columns) and number of sinus beats (black columns) for each minute. The point of administration of each dose of lignocaine is shown.

5 min due to ventricular asystole or fibrillation. In the fourth dog, propanolol had no consistent effect on total ventricular rate or on the number of sinus beats. Although propranolol (4 mg/kg) reduced the total ventricular rate and increased markedly the number of sinus beats in three dogs, these changes were not significant for the group as a whole, and were not significantly different from the effects of the same dose of lignocaine. This may be due to the rather small number of observations made.

Lignocaine dose-response curves for ventricular arrhythmias

The effects of administering increasing doses of lignocaine on the three types of arrhythmias used in these experiments are shown in Fig. 5. In the ouabain-induced arrhythmias and in those occurring after ligation of a coronary artery, the number of ectopic beats in the 5 min period following the administration of each dose of lignocaine has been expressed as a percentage of the number present in the 5 min control period preceding the first dose of the drug. For the arrhythmia induced by halothane and adrenaline the total number of ectopic beats in response to the adrenaline challenge after each dose of lignocaine has been expressed as a percentage of the total number produced by adrenaline before the first dose of lignocaine. The dose of lignocaine required to produce a 50% reduction in the number of ventricular ectopic beats was 0·9 mg/kg for the ouabain arrhythmia, 3·0 mg/kg for the halothane-adrenaline arrhythmia, and 7·0 mg/kg for the arrhythmia induced by coronary artery ligation.

Discussion

In the halothane-adrenaline arrhythmias lignocaine reduced the ectopic response of all six dogs in which it was tested, but it only prevented the arrhythmia in four dogs. As was to be expected from previous work (Barrett & Cullum, 1968 ; Dunlop & Shanks, 1968), small doses of propranolol (0·05 mg/kg) inhibited this type of arrhythmia completely, an action which results from its specific effect in blocking β-adrenoceptors.

These observations confirm the report of Hilmi & Regan (1968) who showed in anaesthetized dogs that intravenous administration of a mean dose of 12 mg/kg

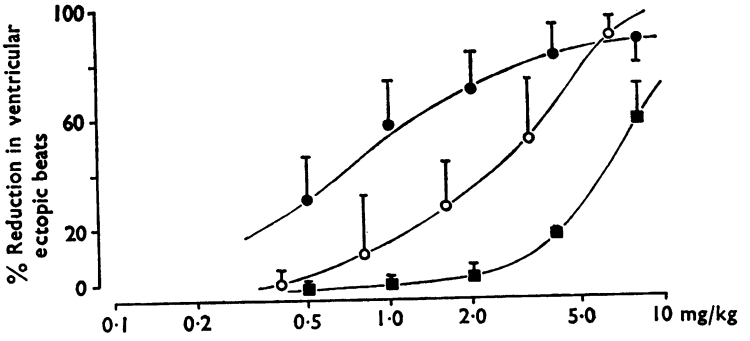

FIG. 5. Dose-response curves for the effects of lignocaine on ventricular ectopic beats. Abscissa: dose of lignocaine injected intravenously. Ordinate: reduction in ectopic beats/5 min, expressed as % of number of ectopic beats before administration of lignocaine. Arrhythmia due to ouabain (●), to coronary artery ligation (■) (mean of four experiments), or to halothane and adrenaline (○) (mean of six experiments). Vertical bars indicate S.E. of mean.

of lignocaine converted the ventricular tachycardia induced by lanatoside C to sinus rhythm. The large dose of lignocaine found necessary in their study was probably in part due to their requirement that sinus rhythm should persist for at least 30 min after the last dose of lignocaine. In our experiments, the doses of lignocaine and propranolol required to abolish the ouabain-induced arrhythmia were similar. As the two drugs have comparable potency as local anaesthetics (Morales-Aguilera & Vaughan Williams, 1965), our observations support the suggestion that the effect of propranolol on ouabain-induced arrhythmias is due to a combination of its β-adrenoceptor blocking action and its local anaesthetic action (Barrett & Cullum, 1968).

Harris, Aquirre y Guerra, Liptak & Brigham (1956) reported that intravenous infusion of lignocaine (50 mg/kg in divided doses), reduced by an unspecified extent the frequency of ventricular ectopic beats which occurred spontaneously in two conscious dogs 24 h after two-stage ligation of the anterior descending branch of the left coronary artery. Further observations were made in five dogs which received phenobarbitone sodium (25–40 mg/kg) before the administration of lignocaine. As phenobarbitone reduced the ventricular ectopic rate by itself, it is difficult to evaluate the effect of lignocaine. These observations are not strictly comparable to those made in our experiments in which increasing doses of lignocaine were injected intravenously at regular intervals and the ectopic rate was not reduced by doses of less than 4·0 mg/kg and only by 60% by 8 mg/kg of lignocaine. The latter dose of lignocaine is comparable to that required to raise the threshold to electrically induced ventricular fibrillation in the intact dog (Allen *et al.*, 1970). While transient toxic effects on cardiac rhythm were noted with lignocaine (4 and 8 mg/kg) in the dogs with ouabain arrhythmia, such effects were not seen at these doses in the dogs after coronary artery ligation.

In our experiments propranolol (4 mg/kg) reduced the ventricular rate and increased the number of sinus beats in dogs 20–44 h after coronary artery ligation. Shanks & Dunlop (1967) showed that this arrhythmia was unaffected by propranolol (1 mg/kg), but did not give detailed results for larger doses. Lucchesi, Whitsitt & Stickney (1967) reported that propranolol (3·5–7·5 mg/kg) was without effect on the ventricular arrhythmia present 24 h after coronary artery ligation but in a dose of 7·5–10 mg/kg, abolished the ventricular arrhythmias in two dogs 48 h after coronary artery ligation. In our experiments, the effect of propranolol was unrelated to the time at which it was administered after coronary artery ligation. The cause of death after 8 mg/kg of propranolol is not clear. The development of ventricular fibrillation appeared to be a terminal phenomenon following cardiac depression. It is of interest to note that lignocaine (8 mg/kg) did not lead to death of the animals.

The duration of the effect of lignocaine on arrhythmias is brief. In man, the mean half time of the blood concentration of lignocaine is approximately 20 min (Ettinger, Hayes, Forde, Wanat & Killip, 1967). Hence, although there is fairly rapid metabolism of the drug, the very transitory duration of the effects of a rapid intravenous injection of lignocaine on the arrhythmia induced by ouabain or ligation of the coronary artery cannot be due solely to metabolism. Rapid tissue washout and redistribution of lignocaine may affect the duration of its antiarrhythmic action, as has been observed for procaine (Boullin & Sullivan, 1969). The brief duration of the effects of lignocaine on cardiac arrhythmias causes difficulty in comparing lignocaine with drugs of longer metabolic half life, such as propranolol which, in the dog, has a half life of 50 min (Black, Duncan & Shanks, 1965).

Our observations indicate that lignocaine is effective in suppressing to a varying extent, ventricular ectopic beats produced in three different ways. It is unlikely that a common mechanism is involved in the genesis or abolition of these arrhythmias. On the one hand, β-adrenoceptor blocking drugs are much more effective in inhibiting the ectopic response to adrenaline than that to ouabain or myocardial infarction, while, on the other hand, lignocaine is more effective in controlling the arrhythmia due to ouabain than the arrhythmias due to halothane-adrenaline or ligation of the coronary artery.

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