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The effect of Kö 1173, a new anticonvulsant agent on experimental cardiac arrhythmias

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Summary

1. The effects of the intravenous injection of Kö 1173, a new anticonvulsant drug, phenytoin and procainamide were studied on three types of cardiac arrhythmia in dogs.

2. Ventricular ectopic beats produced by intravenous injection of adrenaline in anaesthetized dogs respired with halothane were abolished by Kö 1173, $0{\cdot}6 \pm 0{\cdot}1$ mg/kg, phenytoin, $1{\cdot}1 \pm 0{\cdot}3$ mg/kg and procainamide, $4{\cdot}1 \pm 1{\cdot}8$ mg/kg.

3. Ventricular tachycardia was produced in anaesthetized dogs by the intravenous injection of ouabain and the three drugs infused intravenously at 0·2 (mg/kg)/min until sinus rhythm returned. Kö 1173 was effective in 8 out of 9 dogs after a mean dose of $1{\cdot}3 \pm 0{\cdot}3$ mg/kg; phenytoin in all 3 dogs after $2{\cdot}7 \pm 0{\cdot}6$ mg/kg and procainamide in the 3 dogs tested after $16{\cdot}6 \pm 1{\cdot}3$ mg/kg.

4. The intravenous injection of Kö 1173, 8·0 mg/kg, greatly reduced the number of ventricular ectopic beats occurring in conscious dogs 18–44 h after ligation of the anterior descending branch of the left coronary artery, with a resultant increase in the number of sinus beats. Phenytoin, 8·0 mg/kg, had a similar effect but procainamide was much less effective.

5. These results indicate that Kö 1173 is effective in abolishing experimental cardiac arrhythmias and suggest that its effects should be studied in patients.

Introduction

All drugs which are effective in the treatment of cardiac arrhythmias may cause serious side-effects when administered on a long-term basis. Hence procainamide has been shown to produce a syndrome like systemic lupus erythematosis (Ladd, 1962 ; McDevitt & Glasgow, 1967) ; the β-adrenoceptor blocking drugs, propranolol and practolol, may produce cardiac failure or bradycardia (Stephen, 1966 ; Allen, Pantridge & Shanks, 1971), and phenytoin (also widely used as an anticonvulsant agent) may cause ataxia, nystagmus, tremor and diplopia as well as hyperplasia of the gums on long-term administration (Toman, 1965). There is, therefore, still a place for new effective antiarrhythmic drugs which will not have deleterious results when used over a prolonged period.

Recently a new anticonvulsant agent, Kö 1173, has become available. The purpose of this study was to evaluate its action on experimental cardiac arrhythmias and to compare its actions with those of phenytoin and procainamide. The

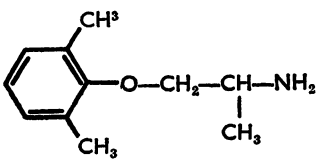
structure of the three drugs is given in Fig. 1. Some of the results of the present experiments have been described to the British Pharmacological Society (Allen, Kofi Ekue, Shanks & Zaidi, 1970).

Methods

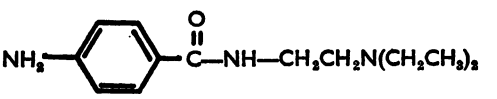
Observations were made in dogs anaesthetized by the subcutaneous injection of morphine sulphate, 0·5 mg/kg, followed one hour later by the intravenous injection of pentobarbitone, 20 mg/kg. A cuffed endotracheal tube was inserted and the dogs were respired with room air from a Starling Ideal pump at a rate of 18 strokes per minute and a stroke volume of 13 ml/kg body weight. Arterial pressure was measured through a metal cannula inserted in the left carotid artery and attached to a pressure transducer (Consolidated Electrodynamics Type 4-327-L 221). Arterial pressure and the electrocardiogram (Lead II) were recorded on a Devices recorder (Type M8 or M4) and displayed on a four-channel oscilloscope (Airmec). Drugs were injected through a polythene catheter inserted in a foreleg vein.

Ouabain arrhythmias

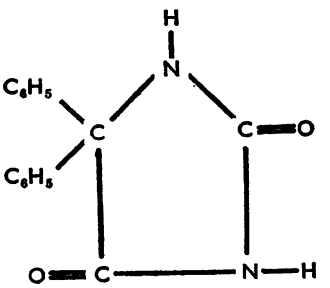
Observations were made on 18 dogs prepared as described above. In 15 dogs the right vagus nerve was exposed in the neck and divided. Bipolar electrodes were applied to the distal end of the nerve which was stimulated for periods of 10 s with shocks of 1 ms duration at a frequency of 25 Hz and a voltage sufficient to produce maximal sinus slowing without loss of sinus dominance. This voltage was determined for each animal before the administration of any drug and was in the range of 2–10 volts. Ventricular tachycardia was produced by the intravenous injection of ouabain, 40 μg/kg, followed after 30 min by 20 μg/kg and by



KÖ 1173



Procainamide



Phenytoin

FIG. 1. Chemical structure of Kö 1173, procainamide and phenytoin.

10 μg/kg every 15 min until ventricular tachycardia was produced. Stimulation of the vagus nerve, with the previously established voltage, had no effect on the ventricular tachycardia; this indicated complete loss of sinus dominance. When the arrhythmia had been established for 10 min the test compound was infused intravenously from a motor driven syringe at the rate of 0·2 or 1·0 mg/kg per minute. The infusion of each drug was continued until the return of sinus rhythm which slowed, without the occurrence of any ectopic beats, on vagal stimulation with the previously determined voltage. After this end-point had been achieved, insulin (80–160 u) was given intravenously to induce ventricular tachycardia, the appearance of which indicated the continued presence in the heart of toxic doses of ouabain. In 3 dogs the vagus nerve was not divided and was not stimulated. Ventricular tachycardia was produced by ouabain, as described above, and the test compound infused until the return of sinus rhythm which was taken as the end-point after which insulin was given to induce ventricular tachycardia.

Halothane–adrenaline arrhythmias

Observations were made on 13 dogs. After preparation, the dogs were artificially respired with room air and 1% halothane. Fifteen minutes later adrenaline, 0·2 μg/kg, was injected intravenously. The dose of adrenaline was then progressively increased from 0·4 μg/kg, in 0·4 μg/kg increments, with an interval of 7–10 min between each dose, until ventricular tachycardia or multifocal ventricular ectopic beats had been produced. In some dogs adrenaline produced ventricular fibrillation which was corrected by external direct current countershock delivered from an American Optical Defibrillator (Model 10645). After such defibrillation, halothane was discontinued for 10 min and the adrenaline challenge was not repeated until 20 min later but with a dose less than that which had produced fibrillation. After the dose of adrenaline which produced an arrhythmia had been established, the test compound was injected intravenously. Five minutes later the adrenaline challenge, using the same dose, was repeated. Increasing doses of the test compound were given to determine the minimum dose that prevented the adrenaline challenge from producing any ectopic beats.

Arrhythmias after coronary artery ligation

Dogs were anaesthetized by the intravenous injection of methohexitone, 10 mg/kg, and respired through a cuffed endotracheal tube with room air and halothane (0·5–1·5%). The heart was exposed through an incision in the fourth or fifth left intercostal space. The left anterior descending coronary artery was dissected free 2 cm below the tip of the left atrial appendage and was ligated at this level in two stages as described by Harris (1950). Two ligatures were placed round the artery and a 21 gauge needle. The first ligature was tied around the artery and the needle which was then removed. Thirty minutes later the second ligature was tied tightly around the artery. The chest was closed in layers 30 min after the second ligature had been tied and the dog was allowed to recover. Further observations were made 18 to 44 h after ligation of the coronary artery when the dogs were conscious. Lead 2 of the electrocardiogram was continually recorded on a direct writing instrument (M2 or M4, Devices Ltd.) for 5 to 30 min before the administration of Kö 1173, phenytoin or procainamide and during their administration. A series of increasing doses of each drug was given at 5 min

intervals. The ventricular rate was obtained from the electrocardiogram by counting the total number of sinus beats and ectopic beats during each successive 5 min period. Post-mortem examination in all dogs showed the presence of an acute myocardial infarction.

Drugs

Ouabain (May & Baker); (−)-adrenaline bitartrate (C. Zimmerman & Co.); Kö 1173 (Boehringer Ingelheim); phenytoin (Parke Davis) and procainamide (Squibb). 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 by means of a Blease Universal anaesthetic vaporizer.

Results

Ouabain arrhythmias

Observations were made in 18 dogs in which the intravenous administration of ouabain produced ventricular tachycardia. The mean dose of ouabain which produced this arrhythmia in each group of animals is given in Table 1. Kö 1173, phenytoin and procainamide were administered by constant intravenous infusion after establishment of the ventricular tachycardia in each dog.

Effect of Kö 1173

The effects of the intravenous infusion of Kö 1173 were studied in 2 groups of dogs consisting of 6 and 3 animals. The results of part of one experiment from the first group are shown in Figure 2. Stimulation of the distal end of the right vagus nerve before the administration of ouabain produced slowing of sinus rate without any ectopic beats (A). After the administration of ouabain, 40 μg/kg, followed by 20 μg/kg, a ventricular tachycardia developed; this rhythm was unaltered by vagal stimulation (B). The constant intravenous infusion of Kö 1173 at 0·2 (mg/kg)/min was then started. Sinus rhythm returned after the infusion of 0·6 mg/kg Kö 1173, but ectopic beats occurred during vagal stimulation (C). After infusion of 1·5 mg/kg, ectopic beats did not occur on vagal stimulation (D). The

TABLE 1. *Effects of Kö 1173, phenytoin and procainamide on ouabain-induced arrhythmias. Ventricular tachycardia was produced by intravenous administration of ouabain. After arrhythmia had been present for 10 min, Kö 1173, phenytoin, or procainamide was infused*

Drug		No. of dogs	Mean dose of ouabain mg/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	To prevent ectopic beats on stimulation of vagus nerve
Kö 1173	a	5	77·0± 6·9	0·2	1·3±0·6	3·9±1·8 (4 dogs)
	b	3	70·0± 5·8	0·2	1·3±0·08	—
Phenytoin	a	3	66·6± 3·3	0·2	2·7±0·6	13·4 (1 dog)
Procainamide	a	3	63·3± 3·3	0·2	16·6±1·3	22·2 (2 dogs)
	a	3	63·3±12·1	1·0	2·5 (1 dog)	9·0 (1 dog)

a—Vagal stimulation performed. b—No vagal stimulation.

continued presence of toxic amounts of ouabain in the heart was shown by the appearance of a ventricular tachycardia following the intravenous injection of insulin 120 units (E). Similar results were obtained in a total of 4 dogs and are shown in Table 1 which gives the mean doses of Kö 1173 for reversion to sinus rhythm and for complete suppression of ectopic pacemaker activity. In the fifth dog, Kö 1173 restored sinus rhythm but ectopic beats occurred on vagal stimulation and after the administration of 2 mg/kg (i.e. 10 min of infusion) spontaneous ventricular ectopic beats recurred and within 20 min, despite the infusion of Kö 1173, ventricular fibrillation developed. In the sixth dog in this group ventricular fibrillation occurred five minutes after the start of the infusion of Kö 1173, before any change in the ventricular tachycardia had occurred. The results from this dog are not included in Table 1. In the second group of dogs the end-point was taken as the return of sinus rhythm as vagal stimulation was not carried out. The mean dose of Kö 1173 which restored sinus rhythm in this group was $1{\cdot}3 \pm 0{\cdot}3$ mg/kg.

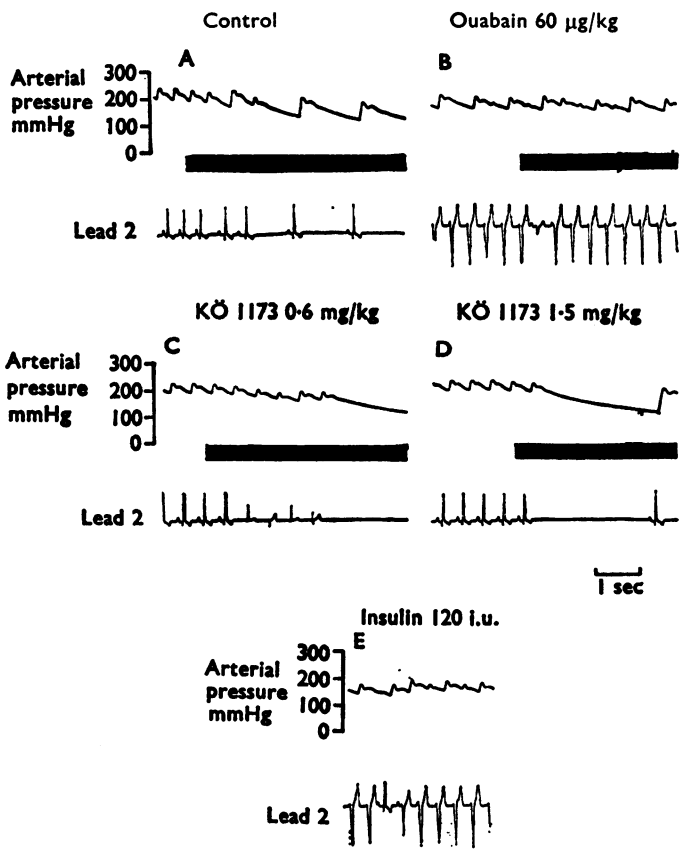


FIG. 2. The effect of Kö 1173 on ventricular tachycardia produced by ouabain in an anaesthetized dog. Records of arterial pressure and the electrocardiogram (Lead 2) are shown. The peripheral end of the right vagus nerve was stimulated during the period indicated by the solid bar. A, Control: B, after intravenous injection of ouabain (60 μg/kg); C, D, after the intravenous infusion of Kö 1173 at 0·2 (mg/kg)/min for 3 min, and 7·5 min respectively; E, after the intravenous injection of insulin, 120 units.

Effect of phenytoin

The effects of phenytoin were studied in 3 dogs in which the drug was infused at the rate of 0·2 (mg/kg)/min. Sinus rhythm developed in all 3 dogs after the administration of a mean dose of $2·7 \pm 0·6$ mg/kg; slowing of this rhythm on vagal stimulation without the appearance of ectopic beats occurred in one out of the 3 dogs (Table 1).

Effect of procainamide

The effects of the infusion of procainamide on the ouabain-induced ventricular tachycardia were studied in 6 dogs. In 3 dogs, in which the rate of infusion was 0·2 (mg/kg)/min, sinus rhythm was restored after a mean dose of $166 \pm 1·3$ mg/kg (Table 1). Absence of ectopic beats on vagal stimulation occurred in 2 of these 3 dogs after a mean dose of 22·2 mg/kg had been infused. In another 3 dogs procainamide was given at a rate of 1·0 (mg/kg)/min. In one dog the ventricular tachycardia was abolished after infusion of 2·5 mg/kg and after 9·0 mg/kg ventricular ectopic beats did not occur on vagal stimulation (Table 1). In the second of these dogs the ventricular tachycardia was still present after administration of procainamide, 30 mg/kg, after which the infusion was stopped. In the third dog the ventricular tachycardia was converted to a nodal tachycardia after the infusion of 60 mg/kg of procainamide.

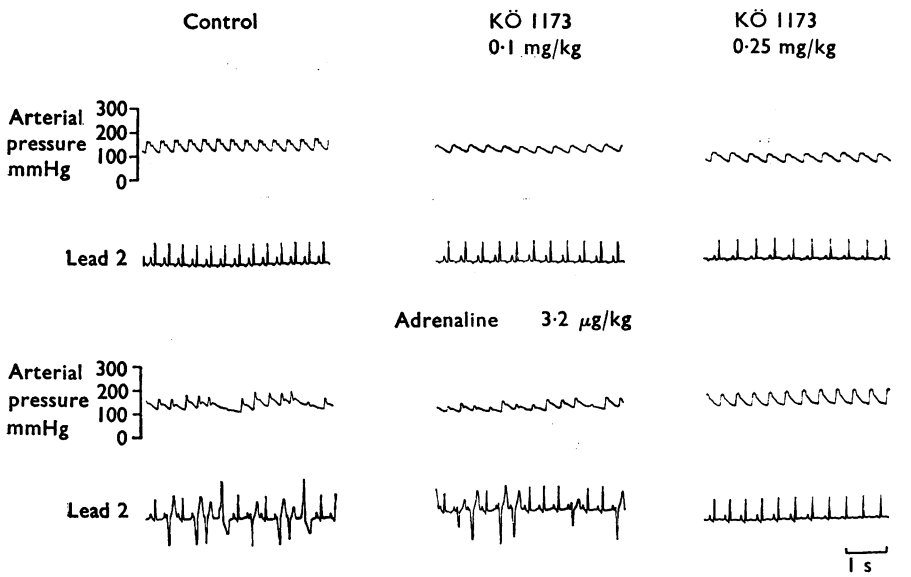


FIG. 3. The effect of the intravenous injection of Kö 1173 on the ventricular arrhythmia produced by the intravenous injection of adrenaline in an anaesthetized dog respired with 1% halothane. Records of arterial pressure and the electrocardiogram (Lead 2) are shown. The upper pair of records were obtained before and the lower pair after the intravenous injection of adrenaline 3·2 μg/kg. The responses to the administration of adrenaline before (control) and after 0·1 and 0·25 mg/kg Kö 1173 are shown.

Halothane–adrenaline arrhythmias

Effect of Kö 1173

Five dogs were given Kö 1173 following determination of the dose of adrenaline required to produce a ventricular arrhythmia. Increasing doses of Kö 1173, 0·1, 0·25, 0·5 and 1·0 mg/kg were given by intravenous injection at 15 min intervals until the adrenaline arrhythmia was prevented. The adrenaline challenge was given 5 min after the intravenous administration of each dose of Kö 1173. Portions of the records from one experiment are shown in Fig. 3. During the control period, the intravenous injection of adrenaline, 3·2 μg/kg, produced a burst of ventricular ectopic beats followed by a return to sinus rhythm. The administration of adrenaline after Kö 1173, 0·1 mg/kg, produced fewer ectopic beats and after Kö 1173, 0·25 mg/kg, adrenaline produced no ectopic beats. Similar results were obtained in the other 4 dogs but higher doses of Kö 1173 were required to prevent the arrhythmias. The mean dose of Kö 1173 that abolished the adrenaline arrhythmias in the 5 dogs was $0{\cdot}6 \pm 0{\cdot}1$ mg/kg.

Effect of phenytoin

The effects of increasing doses of phenytoin, 0·1, 0·25, 0·5, 1·0 and 2·0 mg/kg were studied in 4 dogs. The adrenaline-induced arrhythmia was abolished in all 4 dogs, after the administration of a mean dose of phenytoin of $1{\cdot}1 \pm 0{\cdot}3$ mg/kg.

Effect of procainamide

Procainamide abolished the adrenaline-induced arrhythmia in the 4 dogs in which observations were made. The mean effective dose of procainamide in the 4 dogs was $4{\cdot}1 \pm 1{\cdot}8$ mg/kg.

Coronary artery ligation arrhythmias

Observations were made in 12 dogs 18–44 h after two-stage ligation of the anterior descending branch of the left coronary artery. All dogs had a severe ventricular arrhythmia consisting of multifocal ventricular tachycardia interspersed with normal sinus beats. After the initial period of observation the electrocardiogram was recorded continuously in 4 dogs for 30 min before the administration of any drug; this period of observation in these dogs was used as a control. The results in these 4 dogs showed that the total ventricular rate and the number of sinus beats in each 5 min period during this 30 min period of observation varied slightly (Table 2). The values for each of these 5 min periods were similar to those observed during the 5 min control period in the three groups of dogs which received Kö 1173, phenytoin and procainamide.

Effect of Kö 1173

The effects of the intravenous injection of a series of doses of Kö 1173 (0·5, 1·0, 2·0, 4·0 and 8·0 mg/kg) given at 5 min intervals on the arrhythmias which occur spontaneously 18–44 h after coronary artery ligation were studied in 5 conscious dogs. Some of the results of one experiment are shown in Fig. 4. The predominant rhythm during the 5 min control period, before administration of Kö 1173, was ventricular tachycardia with ventricular ectopic beats; nodal beats and sinus beats occurred irregularly at infrequent intervals. There was little change

in the number of ectopic or sinus beats following the administration of Kö 1173, 0·5 and 1·0 mg/kg, but a slight increase in the number of sinus beats occurred after 2·0 mg/kg. After the administration of 4·0 mg/kg there was a slight fall in total ventricular rate and a marked reduction in the number of ectopic beats so that sinus rhythm became the predominant rhythm. After 8·0 mg/kg there was a further increase in the number of sinus beats with almost complete suppression of the ectopic foci, so that long runs of sinus rhythm without any ectopic beats occurred. This effect of the drug was still present 30 min after administration.

The results obtained in the 4 other dogs which were given Kö 1173 are shown in Figure 5. The total ventricular rate was reduced by the drug in 3 dogs. The ventricular ectopic beats were reduced in all 4 dogs by 4 mg/kg and almost completely abolished by 8·0 mg/kg. This effect lasted till the end of each experiment which was 10–30 min after the last dose of Kö 1173. Following the administration of 8·0 mg/kg of Kö 1173, all dogs had transient tonic convulsions which lasted for a few seconds. The mean results from these 5 dogs are given in Table 2.

Effect of phenytoin

Observations were made in 4 dogs which were given phenytoin (0·5, 1·0, 2·0, 4·0 and 8·0 mg/kg) by intravenous injection at 5 min intervals after an initial control period of at least 5 minutes. The mean results are shown in Table 2. Phenytoin had no effect on total ventricular rate. Administration of 0·5 mg/kg

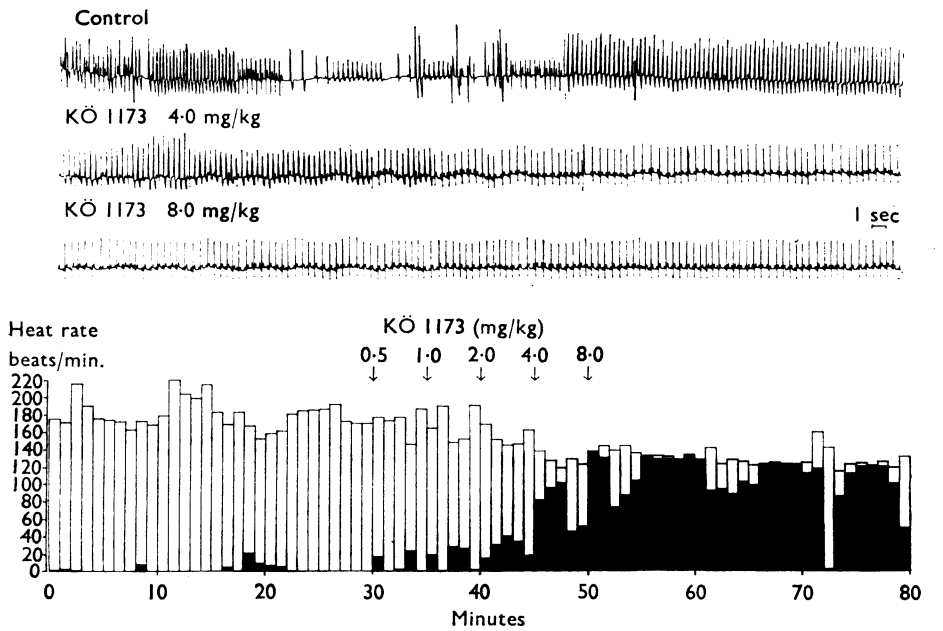


FIG. 4. The effect of Kö 1173 on the ectopic beats occurring in a conscious dog 22 hours after coronary artery ligation. Top half of the record shows samples of the electrocardiogram (lead II) obtained during the control period and after the intravenous injection of Kö 1173, 4·0 and 8·0 mg/kg. The histogram indicates the ventricular rate (clear columns) and number of sinus beats (black columns) for each minute. The point of administration of each dose of Kö 1173 is shown.

increased the number of sinus beats. Further increases in the number of sinus beats occurred after 2·0, 4·0 and 8·0 mg/kg. After the largest dose of phenytoin the dominant rhythm was sinus rhythm interspersed with a few ectopic beats. The dogs became transiently breathless and restless following both 4·0 and 8·0 mg/kg of phenytoin.

The effect of phenytoin was similar to that of Kö 1173. The reductions produced in the number of ectopic beats by 4·0 mg/kg of Kö 1173 and of phenytoin were 61·3% and 62·2% respectively and after 8·0 mg/kg of the two drugs, 89·1% and 85·7% respectively.

Effect of procainamide

The effect of the intravenous injection at 5 min intervals of procainamide (0·5, 1·0, 2·0, 4·0, 8·0, 16·0 and 32·0 mg/kg) was observed in 3 dogs. The effect of procainamide was different in the 3 dogs. In one dog there was complete abolition of the ectopic beats after 32·0 mg/kg. In the second dog, procainamide had no effect on the number of ectopic beats. In the third dog, procainamide reduced the number of ectopic beats but did not abolish them. The mean results from the 3 dogs are given in Table 2. Procainamide reduced the total ventricular rate to a small extent.

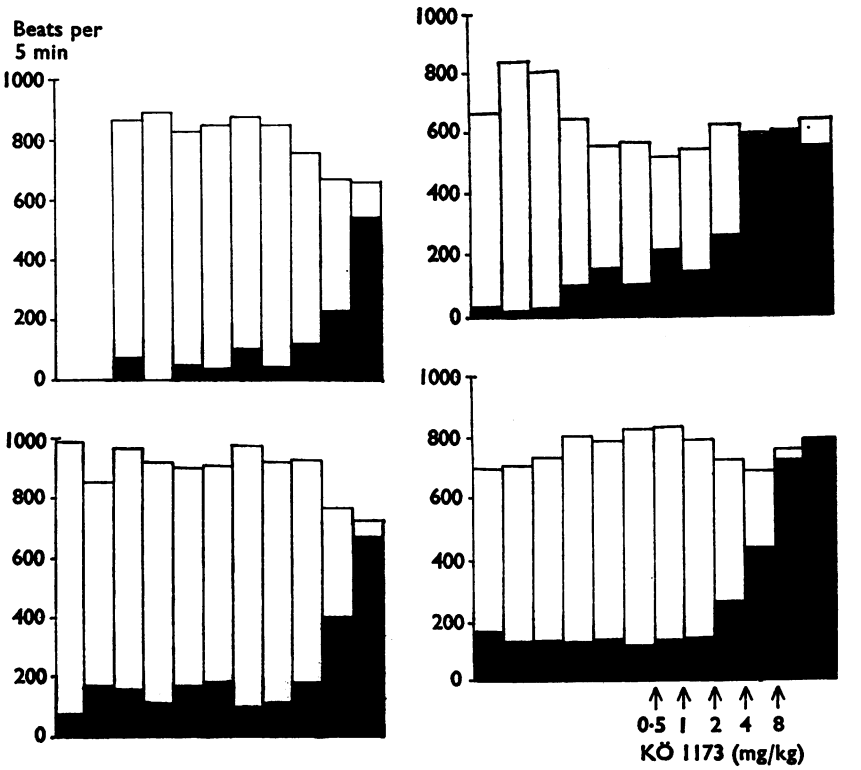


FIG. 5. Observations in 4 conscious dogs with multifocal ventricular tachycardia 18–44 h after ligation of the anterior descending branch of the left coronary artery. Each histogram refers to a separate dog and indicates the ventricular rate (clear columns) and number of sinus beats (black columns) for 5 min periods. After a control period of 30 min in 3 dogs and 20 min in the fourth dog, a series of doses of Kö 1173 were given at 5 min intervals as indicated.

TABLE 2. *Effects of Kö 1173, phenytoin and procainamide on the ventricular dysrhythmia induced by ligation of a coronary artery in dogs*

Time	0–5 min		5–10 min		10–15 min		15–20 min		20–25 min		25–30 min		30–35 min		35–40 min	
Dose (mg/kg)	Control		0·5		1·0		2·0		4·0		8·0		16·0		32·0	
	SB	TVR	SB	TVR	SB	TVR	SB	TVR	SB	TVR	SB	TVR	SB	TVR	SB	TVR
No drug (n=4)	57·7 ±30·8	820·2 ±80·5	75·5 ±37·5	814·7 ±35·2	72·7 ±35·6	871·0 ±59·7	83·0 ±20·5	828·2 ±64·9	109·2 ±36·6	770·0 ±72·3	97·0 ±35·1	803·0 ±37·8	—	—	—	—
Kö 1173 (n=5)	83·6 ±30·2	821·6 ±62·9	116·8 ±29·3	805·6 ±74·2	101·4 ±21·1	819·8 ±45·3	186·8 ±32·3	764·6 ±46·2	412·4 ±60·4	674·6 ±27·8	613·8 ±37·8	695·4 ±25·9	—	—	—	—
Phenytoin (n=4)	77·7 ±44·9	759·0 ±88·0	156·2 ±62·6	785·5 ±82·0	171·1 ±64·1	761·7 ±82·9	238·7 ±55·6	766·0 ±59·0	439·0 ±24·0	707·0 ±31·4	632·5 ±73·9	737·5 ±46·9	—	—	—	—
Procainamide (n=3)	57·0 ±29·6	932·0 ±68·2	32·6 ±21·4	975·0 ±99·0	44·6 ±29·2	968·6 ±90·1	78·6 ±20·3	901·1 ±82·3	80·3 ±51·0	927·3 ±100·1	62·0 ±14·0	871·0 ±78·0	236·6 ±144·1	846·3 ±66·0	363·3 ±241·6	796·0 ±50·3

The ventricular rate (TVR) and the number of sinus beats (SB) are given for consecutive 5 min periods (beats/5 min) in four 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 shown.

Discussion

In the present experiments all three drugs were effective in preventing the ventricular arrhythmia produced by the intravenous injection of adrenaline in dogs respired with halothane. Kö 1173 was more active than phenytoin which was more active than procainamide. Previous studies (White, Megirian & Swiss, 1955) have shown that phenytoin, 10 mg/kg, increased the duration of ectopic rhythm produced by adrenaline in dogs respired with cyclopropane while a larger dose, 30 mg/kg, suppressed the arrhythmia in 7 out of 12 dogs. Phenytoin did not potentiate the adrenaline-induced arrhythmia in the present experiments and a much smaller dose ($1{\cdot}1 \pm 0{\cdot}3$ mg/kg) was effective in abolishing it. Procainamide has been shown to give protection against adrenaline-induced arrhythmias in dogs anaesthetized with cyclopropane (White *et al.*, 1955).

The effects of Kö 1173 on the ouabain-induced ventricular tachycardia were assessed in the present experiments by using two end-points, a return to sinus rhythm and the absence of ectopic beats during vagal induced slowing of this sinus rhythm. Kö 1173 abolished the ventricular tachycardia with a return to sinus rhythm in 8 out of the 9 dogs studied. Vagal slowing of this sinus rhythm occurred in 4 out of the 5 dogs in which it was performed. Phenytoin restored sinus rhythm in the 3 dogs tested but ectopic beats recurred on vagal stimulation in 2 of these. Previous studies have shown that phenytoin is effective in abolishing ouabain-induced ventricular tachycardia in unanaesthetized dogs (Mosey & Tyler, 1954). Comparison of the effects of Kö 1173 and phenytoin on the ouabain-induced ventricular tachycardia would suggest that the former is more effective in abolishing this arrhythmia.

Procainamide was less effective than the other two drugs in abolishing the ouabain-induced ventricular tachycardia. When it was infused at 0·2 (mg/kg)/min, a large dose ($16{\cdot}6 \pm 1{\cdot}3$ mg/kg) was required to restore sinus rhythm in the 3 dogs studied and in only 2 of these did a larger dose prevent the appearance of ectopics on vagal stimulation. The effectiveness of procainamide was not improved by increasing the rate of infusion to 1 (mg/kg)/min, as sinus rhythm was only restored in 1 of 3 dogs. The present results are similar to those of Goldberg & Cotten (1951) who reported that procainamide was effective in restoring sinus rhythm in 8 out of 14 unanaesthetized dogs with an ouabain-induced ventricular tachycardia. The mean effective dose of procainamide given as bolus injections of 10 mg/kg was 13·7 mg/kg.

Kö 1173 and phenytoin were equally effective in suppressing the ventricular ectopic beats which occurred in conscious dogs after coronary artery ligation with a resultant increase in the number of sinus beats. After administration of the largest dose (8·0 mg/kg) of both drugs over 80 per cent of all ventricular beats were sinus in origin and long runs of sinus beats interspersed with occasional ectopic beats were seen. The effect of Kö 1173 was still present at the end of the period of observation in each experiment (10–30 min). The effect of phenytoin lasted for at least 10 min in all experiments. The duration of effect of these drugs is in contrast to the brief effect of lignocaine on these arrhythmias (Allen, Shanks & Zaidi, 1971). Using similar experimental methods, these authors showed that 1–2 min after the administration of lignocaine, 8·0 mg/kg, there was almost complete suppression of the ventricular ectopic beats but that this effect had worn off after 5 minutes. Harris & Kokernot (1950) have previously shown that the

intravenous administration of a variety of doses of phenytoin (10–200 mg/kg) by intravenous injection abolished the ectopic beats occurring 24 h after coronary artery ligation in dogs. Comparison of these observations with those in the present experiments cannot be made as Harris & Kokernot did not give details of the protocol for drug administration or values for the number of sinus and ectopic beats before and after drug administration.

There was marked variation between the 3 dogs in the effects of procainamide on the arrhythmia occurring after coronary artery ligation. The ventricular ectopic beats were completely abolished in one dog, reduced in one and unaffected in the third. The reasons for these differences is not clear. Although the observations of Harris, Estandia, Ford, Smith, Olsen & Tillotson (1952) are not directly comparable to the present experiments as they did not give the number of ectopic and sinus beats before and after each of a series of doses of procainamide, they showed that procainamide was effective in reducing the frequency of rapid ectopic ventricular tachycardia after coronary artery ligation. They suggested that it was more effective in dogs with a high ectopic rate but this does not account for the differences in effect of the drug in the present experiments as the control ectopic rates were 162 and 150 per min in the dogs in which complete suppression and no effect were observed respectively.

Comparison of the effects of Kö 1173, phenytoin and procainamide on the arrhythmias occurring after coronary artery ligation with those previously described

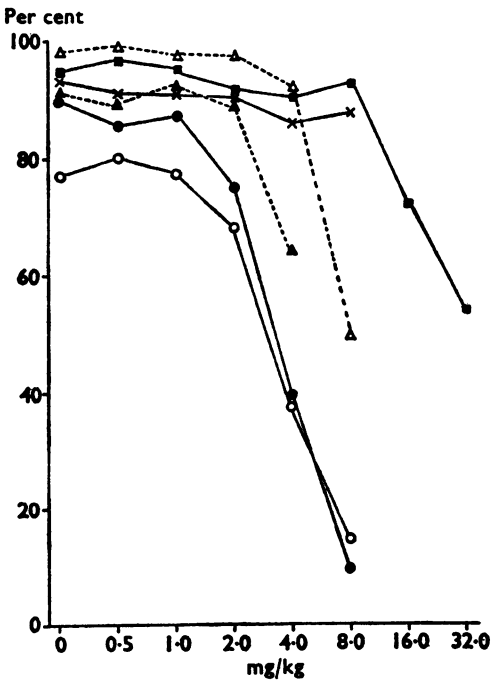


FIG. 6. Dose-response curves for the effects of procainamide, lignocaine, propranolol, phenytoin and Kö 1173 on ventricular ectopic beats occurring in conscious dogs after coronary artery ligation. Abscissae: dose of drug injected intravenously. Ordinates: reduction in ectopic beats/5 min expressed as per cent of number of ectopic beats before administration of each drug. Mean of observations on 3 dogs for procainamide, 4 for lignocaine, propranolol and phenytoin and 5 for Kö 1173.

for lignocaine and propranolol (Allen *et al.*, 1971b) using the same experimental procedure in this laboratory is shown in Fig. 6. The incidence of ectopic beats during a 5 min control period preceding drug administration and during the first 5 min period after each dose of each drug has been expressed as a percentage of the total ventricular rate during that period. The results indicate that Kö 1173 and phenytoin are equally effective in suppressing these ventricular ectopic beats and that both are more active than any of the other drugs.

As phenytoin, procainamide and lignocaine are effective in controlling ventricular arrhythmias in experimental animals and in patients, the present studies indicate that Kö 1173 should be studied for its antiarrhythmic effect in man both on intravenous and oral administration.

Two dogs receiving Kö 1173 for ouabain-induced ventricular tachycardia developed ventricular fibrillation. In one dog ventricular fibrillation occurred 5 min after the start of the infusion of Kö 1173 and before any change in the rhythm had occurred. It seems likely that ouabain was the cause of ventricular fibrillation in this dog. However, in the second dog ventricular fibrillation occurred after sinus rhythm had been restored and the infusion of Kö 1173 was continued to suppress ectopic beats on vagal stimulation. The cause of ventricular fibrillation in this dog is not clear.

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