EFFECTS OF ANTIARRHYTHMIC DRUGS (VERAPAMIL, PROPRANOLOL AND LIGNOCAINE) ON THE ELECTROCARDIOGRAM AND HAEMATOLOGY IN ADRENALINE-INDUCED ARRHYTHMIAS IN DOGS ANAESTHETIZED WITH HALOTHANE

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SUMMARY

Twenty adult (1–3 year old) mongrel dogs of either sex were used to study the effects of antiarrhythmic drugs in adrenaline-induced arrhythmias. The dogs were divided randomly into four groups of five dogs each (n=5), anaesthetized with halothane and pretreated intravenously (i.v.) with verapamil 0.1 mg kg^{-1}, propranolol 0.06 mg kg^{-1}, or lignocaine 4 mg kg^{-1} while the controls received sterile physiological saline. Adrenaline (4 $\mu g\ kg^{-1}$) was administered i.v. 10 min after drug pretreatments. Lead II of the ECG was recorded and blood collected for haematology.

Ventricular fibrillations preceded by ventricular tachycardia occurred in the control dogs and three died within one minute of adrenaline administration. The predominant arrhythmias were ventricular premature beats, ventricular tachycardia, and second degree heart block. A significant increase (P<0.05) in T wave amplitude was observed in the control group from 0.16±0.05 mV to 0.43±0.09 mV while only minimal increases were noted in the drug pretreated groups and there were no deaths.

Data obtained from this study suggest that verapamil when administered early compares well with propranolol in the control of adrenaline-induced ventricular arrhythmias in the dog. Lignocaine when administered early prior to the induction of the arrhythmias protected against death but not arrhythmias. Drug pretreatments did not have any clinically significant effects on electrocardiographic parameters.

KEYWORDS: Antiarrhythmic drugs; ECG; haematology; arrhythmias.

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INTRODUCTION

Conditions such as coronary heart disease or hypoxia in dogs in which impulse formation is enhanced, or impulse conduction impaired, or a combination of these factors may precipitate cardiac arrhythmias. Enhancement of automaticity of latent pacemaker cells by increased sympathetic discharge is a common cause of supraventricular and ventricular arrhythmias and a rational use of drugs with accurate diagnosis is required if aggravation of these arrhythmias and death are to be avoided.

Various drugs have been used for the management of cardiac arrhythmias including verapamil, a calcium channel blocker (Kaumann & Aramendia, 1968; Antman *et al.*, 1980; Novotny & Adams, 1986); lignocaine, a local anaesthetic (Gerstenblith *et al.*, 1972; Novotny & Adams, 1986) and propranolol, a beta adrenergic blocker (Gibson & Sowton, 1969; Singh & Jewitt, 1974; Shand, 1975; Gang *et al.*, 1984). Verapamil acts by blocking the calcium channels in the heart (Roy *et al.*, 1974); lignocaine acts directly on the myocardium by blocking the fast sodium channels (Harrison *et al.*, 1981) and propranolol exerts its antiarrhythmic action by blocking the beta adrenergic receptors (Shand, 1975; Adams, 1986). Some electrocardiographic effects have been reported for verapamil (Gang *et al.*, 1984). Rebeiro *et al.* (1982) reported decreased platelet aggregation in rats following verapamil administration and Urthaler (1986) reported an inhibition of platelet aggregation in human platelet-rich plasma. Haematologic changes have not however been studied following administration of the calcium channel blockers.

Although verapamil has been used in clinical trials in man against cardiomyopathies, its clinical usage in veterinary medicine has not been thoroughly investigated. Goad (1982) suggested that calcium channel blockers maybe useful in cats with hypertrophic cardiomyopathy and recommended further studies for potential therapeutic applications of the drugs in veterinary medicine. The present study was conducted to evaluate and compare antiarrhythmic and haematological effects of verapamil, propranolol and lignocaine in adrenaline-induced arrhythmias in halothane anaesthetized dogs.

MATERIALS AND METHODS

Dogs and anaesthesia induction

Twenty clinically healthy mongrel dogs of either sex, weighing between 10 and 24 kg were obtained for the studies. The dogs were fed a commercial diet once daily with drinking water *ad libitum*. They were dewormed, washed with acaricide solution and acclimatized for 2 weeks. The dogs were randomly divided into four groups of five dogs. Anaesthesia was induced intravenously (i.v.) using thiopentone sodium (Intraval, May and Baker Ltd.) at a dose rate of 10 mg kg^{-1}. The dogs were intubated and maintained under anaesthesia using a semiclosed circuit mixture of halothane (Fluothane, ICI) and oxygen (East African Oxygen Ltd., Nairobi). Group 1 received i.v. physiological saline, group 2 i.v. verapamil (0.1 mg kg^{-1}), group 3 i.v. propranolol (0.06 mg kg^{-1}), and group 4 i.v. lignocaine (4 mg kg^{-1}). Adrenaline was administered i.v. at a dose rate of 4 mg kg^{-1} 10 min after the various pretreatments. The dosage of adrenaline used was within the established arrhythmogenic dose for adrenaline in halothane anaesthetized dogs (Munson & Tucker, 1975).

After recovery from anaesthesia, the dogs were clinically monitored for 72 h during which time temperature, pulse, respiration and appetite were recorded. Any unusual clinical signs were observed.

Electrocardiography

Each dog was placed in right lateral recumbency (Ettinger & Suter, 1970), and a ECG recording taken with lead II using heat sensitive paper at a recording speed of 50 min^{-1} and sensitivity of 10 mm mV^{-1} on a Kenz-ECG-103 (Suzuken Co., Ltd., Japan). The recording was run for 5 min on every dog before drug pretreatment, immediately after drug treatment, following adrenaline administration and, finally, 30 min later as the animal was recovering from anaesthesia. The following parameters were assessed: heart rhythm; arrhythmias min^{-1}; heart rate; P wave height (mV); P wave width (s); P–R interval (s); QRS complex width (s); R wave height (mV); S–T intervals (s) and depression or elevation (mV); T wave height (mV) and Q–T interval (s). Data after adrenaline administration were taken from normal sinus beats that were closely related to the arrhythmias whenever they occurred.

Haematologic parameters

Using a 10 ml syringe, 2 ml blood were collected from the jugular vein before, during, and after the ECG measurements at the following time intervals: 0; 15 min; 30 min; 1; 2; 4; 8; 12; 24; 48 and 72 h. The blood was stored in bijou bottles containing EDTA for haematology. White blood cells, red blood cells, packed cell volume, haemoglobin, and mean cell volume were determined using routine clinical laboratory procedures (Schalm *et al.*, 1975a) employing a Coulter Counter model ZM (Coulter Electronic, Inc.). Absolute differential counts were performed on a smear stained using the May–Grunwald giemsa method. The microhaematocrit method described by Dacie and Lewis (1968) using a Haemofuge, (Heraeus Christ GmBH), was used and PCV was determined from the Hawksley microhaematocrit reader. Total protein was determined using a refractometer (Atago, SPR-T2, Japan).

Data analysis

Data were subjected to analysis of variance (ANOVA) (Daniel, 1983) using an IBM computer with a Panacea statistical programme. Tukey's highest significant difference (HSD) test (Daniel, 1983) was used to determine if there was a significant difference in the group means at 5% level of significance.

RESULTS

Clinical observations

All except one of the dogs had a good appetite throughout the 3 days of the experimental period. One dog displayed muscle tremours on recovery from anaesthesia. Rectal temperatures remained between 37.9° and 39.0°C.

Cardiac parameters

The predominant arrhythmia was a ventricular premature complex (Fig. 1) which preceded ventricular fibrillation in three control dogs that died within one minute of adrenaline administration. The other arrhythmia was second degree heart block (Fig. 2). The number of dogs showing arrhythmias on administration of adrenaline in the various groups is indicated in Table I. These arrhythmias were more severe in the control dogs and lignocaine pretreated dogs though the lignocaine pretreated dogs did not develop second degree heart block (Table I). In the control group, the first arrhythmias occurred after 24±5.2 s (SD) (range 20–33 s); for lignocaine 37.6±25.2 s (13–72 s); propranolol 25±7.4 s (18–34 s) and

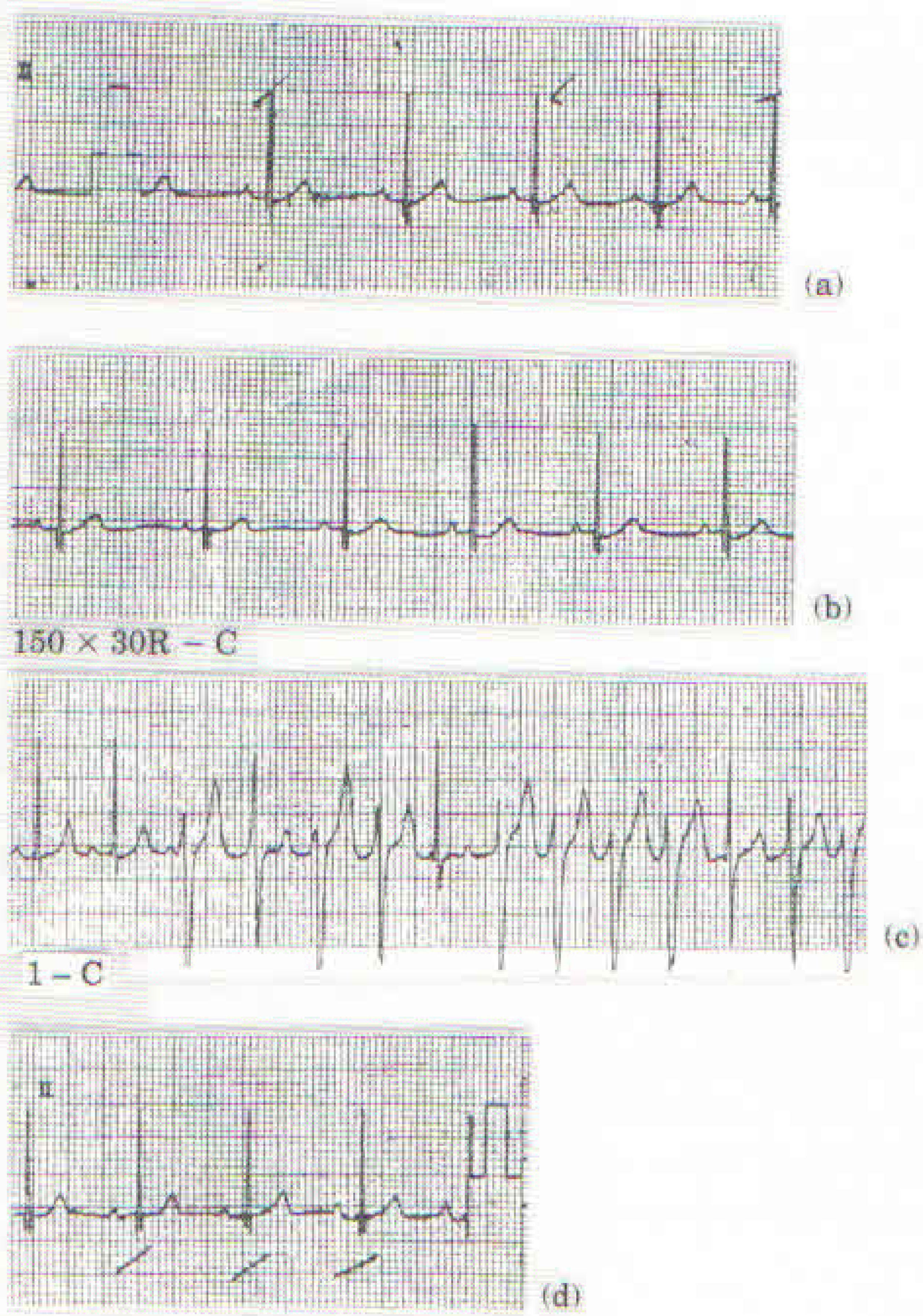

Fig. 1. ECG scan showing the electrocardiographic complexes (a) before drug administration; (b) after administration of physiological saline; (c) ventricular tachycardia; (d) normal sinus rhythm on recovery from anaesthesia (recording lead II, paper speed 50 mm s^{-1} and sensitivity 1 mm=0.1 mV).

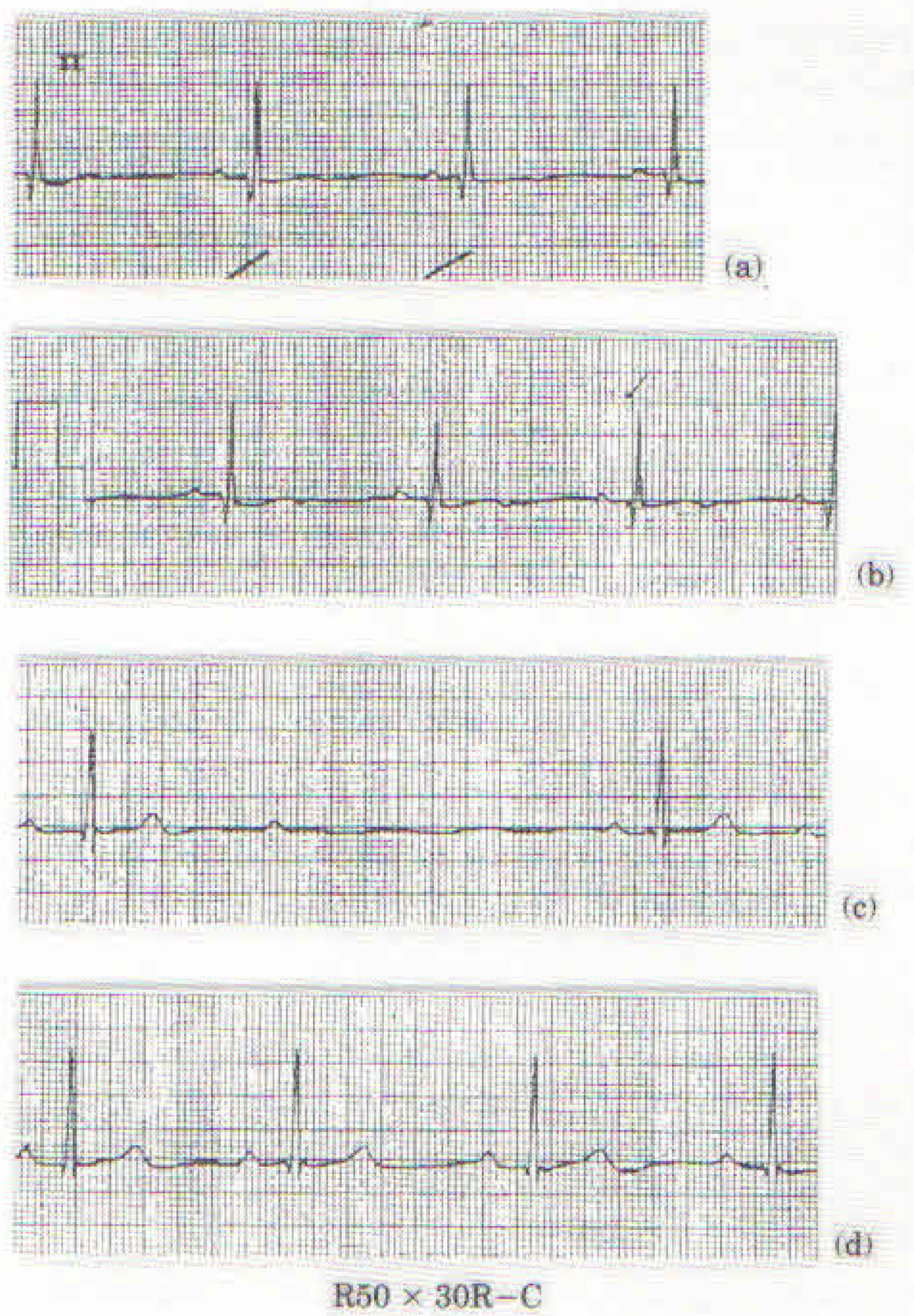

Fig. 2. ECG scan showing normal sinus rhythm (a) before any drug treatment; (b) after physiological saline; (c) second degree heart block after adrenaline administration; (d) normal sinus rhythm on recovery from anaesthesia (recording lead II, paper speed 50 mm s^{-1} and sensitivity 1 mm=0.1 mV).

Table I
Means±SD of various arrhythmogenic parameters in the experimental dogs in the 5 min periods after adrenaline administration

Treatment	*n*	*Mortality rate (%)*	*No. of VPC min⁻¹*	*No. of runs ≥ 3 VPC*	*Ectopic foci*	*No. of P waves**
Control	5	60			1	20 (*n*=1)
Verapamil	4	0	14&6 (*n*=2)	3±1.4 (*n*=3)	1	9&1 (*n*=2)
Propranolol	4	0	14.5±3.5 (*n*=3)	4.7±3.1 (*n*=3)	1	6&5 (*n*=2)
Lignocaine	5	0	41.3±31.9	2.7±0.6	1	

VPC=Ventricular premature complex;
n=number of dogs showing arrhythmias per each treatment group.
*, number of P waves without an associated QRS complex in one minute. The AV blocks were mainly 2:1 but one dog in the verapamil group also had one 3:1 block.

Table II
Means±SE of the ECG parameters measured in control and drug treated dogs before drug pretreatments, after drug/saline administration and after adrenaline administration in all the groups of dogs

Parameter	*Treatment*	*Before*	*Saline/Drug*	*Adrenaline*
Heart rate	Control	116±17	112±5	300±155
	Verapamil	139±20	145±18	156±18
	Propranolol	137±17	125±15	104±29
	Lignocaine	148±12	133±13	109±19
T wave (mV)	Control	0.09±0.03	0.16±0.02	0.43±0.05
	Verapamil	0.11±0.03	0.11±0.02	0.24±0.07
	Propranolol	0.12±0.02	0.14±0.04	0.14±0.02
	Lignocaine	0.12±0.03	0.11±0.02	0.22±0.10
R wave (mV)	Control	1.68±0.34	1.67±0.29	1.51±0.2
	Verapamil	2.03±0.32	2.13±0.22	2.19±0.2
	Propranolol	2.08±0.33	2.21±0.33	2.50±0.36
	Lignocaine	2.17±0.31	2.32±0.29	2.49±0.25
P–R (sec.)	Control	0.10±0.01	0.17±0.01	0.13±0.01
	Verapamil	0.10±0.01	0.11±0.01	0.13±0.02
	Propranolol	0.09±0.01	0.11±0.01	0.17±0.04
	Lignocaine	0.10±0.01	0.10±0	0.12±0.01
QRS (sec.)	Control	0.04±0	0.04±0	0.04±0
	Verapamil	0.04±0	0.04±0	0.04±0
	Propranolol	0.04±0	0.04±0	0.04±0
	Lignocaine	0.04±0	0.04±0	0.04±0
Q–T (sec.)	Control	0.26±0.02	0.26±0.01	0.26±0.01
	Verapamil	0.23±0.02	0.23±0.02	0.23±0.02
	Propranolol	0.24±0.01	0.24±0.01	0.26±0.01
	Lignocaine	0.23±0.01	0.22±0.01	0.22±0.01

verapamil 17.3±4.5 s (15–24 s). There was no statistical difference in the time of onset for the first arrhythmia ($P>0.05$).

All dogs in the control group experienced arrhythmias. In animals pretreated with verapamil, one dog had no arrhythmias, another had only one isolated second degree heart block and the remaining three dogs had short premature ventricular complexes. In the propranolol pretreated group, one dog did not develop any arrhythmias on adrenaline administration while the rest developed arrhythmias. Intermittent second degree heart block was seen in one dog, another had second degree heart block that proceeded to ventricular premature complexes while two of the dogs in this group developed only ventricular complexes. On the other hand, all dogs pretreated with lignocaine developed ventricular premature complexes which were paroxysmal in one dog.

The heart rate in the control dogs and propranolol treated dogs decreased whereas in verapamil and lignocaine dogs heart rate increased ($P<0.05$) (Table

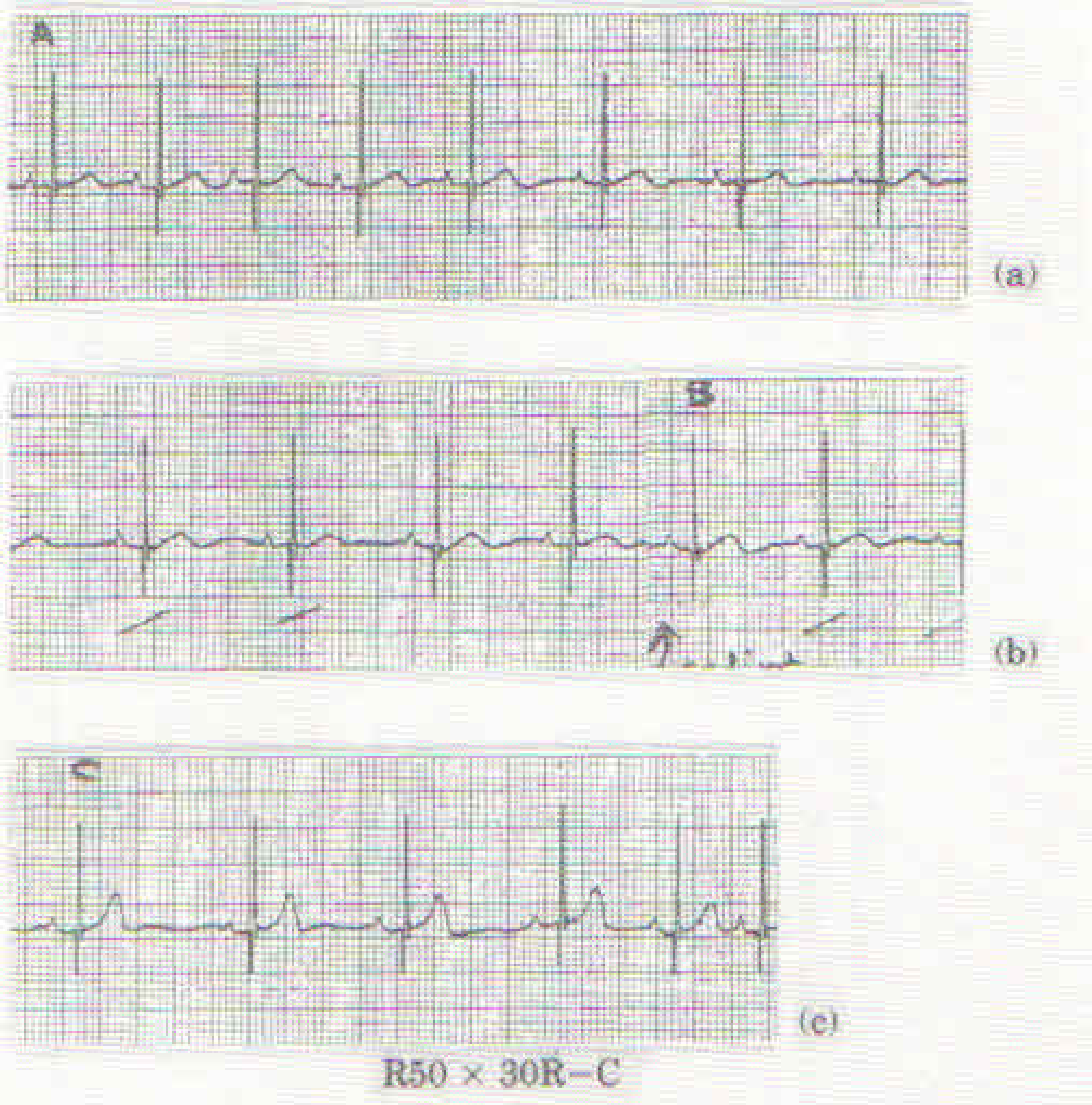

Fig. 3. ECG scan showing T wave (a) before any drug administration; (b) after physiological saline; (c) increased T wave amplitude after adrenaline (recording lead II, paper speed 50 mm s^{-1} and sensitivity 1 mm=0.1 mV).

II). There was no statistical difference in the P–R, QRS and Q–T intervals among the various groups of dogs. The T wave amplitude increased in all the groups just before the arrhythmia occurred (Fig. 3). There was a significant increase ($P<0.05$) in the T wave amplitude after adrenaline in the control dogs from 0.16±0.05 mV to 0.43±0.09 mV (Table II).

Heamatological parameters

There was an apparent increase in red blood cells and total neutrophils in all groups of dogs in the first 2 and 8 h respectively (Table III). There were no significant changes in the white blood cell counts in dogs receiving the various drugs. Propranolol pretreated dogs had a significantly lower total neutrophil count compared with the control dogs ($P<0.05$) (Table III), although all these changes were within the normal species range.

DISCUSSION

Three dogs died in the control group whereas none died in the drug pretreated groups. The deaths were due to ventricular fibrillations preceded by premature ventricular beats. The results indicate that verapamil pretreatment prevented ventricular fibrillation and are in agreement with the findings of Kaumann and Aramendia (1968) who found that dogs pretreated with i.v. verapamil before

Table III

Red blood cell (RBC) ($\times 10^6$), total white cell count (WBC) ($\times 10^3$) and total neutrophil (TN) percent (means±SD) from the dogs during the experimental period

Treatment	*Parameter*	*Time (hours)*										
		0	*1/4*	*1/2*	*1*	*2*	*4*	*8*	*12*	*24*	*48*	*72*
Control	RBC ($\times 10^6$)	6.43±1.0	6.42±0.74	6.98±1.7	7.20±1.21	7.67±0.69	6.88±0.34	7.56±1.03	7.28±0.28	7.10±0.21	7.20±0.79	7.17±1.39
	WBC ($\times 10^3$)	9.05±4.17	8.80±3.39	10.85±7.28	10.80±5.94	12.10±6.36	13.15±6.43	16.50±8.34	15.30±6.22	13.15±5.57	11.70±2.83	12.05±5.05
	TN (%)	75±4.24	67±5.66	66.5±2.12	63.5±2.12	66.5±2.12	76.5±2.12	81±0	75±4.24	73±0	71.5±10.61	69.5±4.95
Verapamil	RBC ($\times 10^6$)	5.81±1.14	6.65±1.40	5.58±0.94	6.00±1.09	6.40±1.18	6.25±1.00	6.35±1.18	6.19±1.15	6.21±1.32	6.06±1.43	5.97±1.30
	WBC ($\times 10^3$)	6.98±2.42	8.44±2.65	7.20±2.74	8.82±4.29	10.38±2.90	9.36±3.73	12.56±0.34	13.35±4.64	10.38±2.24	10.12±6.13	11.88±3.75
	TN (%)	67.2±23.12	60.4±13.22	67±17.13	70±14.21	70.2±14.04	68.8±12.03	73.8±6.94	73±10.23	69±11.66	66±15.91	67.25±9.07
Propranolol	RBC ($\times 10^6$)	6.20±0.78	7.09±1.27	6.57±1.19	7.14±1.25	7.07±1.09	6.33±0.78	7.06±1.27	6.89±1.15	7.37±0.87	7.46±1.67	7.02±1.15
	WBC ($\times 10^3$)	7.20±3.40	8.22±4.08	8.25±3.10	9.56±4.43	9.92±3.68	10.24±3.12	12.73±5.54	9.78±3.97	10.42±3.54	10.04±2.72	10.03±2.42
	TN (%)	51.8±6.83	55.6±9.24	55.7±9.71	59±10.56	56.6±12.03	70.2±5.76	65.5±3.87	62.8±6.40	67.2±10.94	60.2±12.90	58±7.70
Lignocaine	RBC ($\times 10^6$)	6.43±1.26	7.73±1.50	6.30±1.03	6.75±1.34	7.10±1.56	7.12±1.74	7.21±1.94	6.59±1.64	7.65±1.34	6.96±1.52	6.92±0.89
	WBC ($\times 10^3$)	6.54±0.87	8.36±1.85	6.40±0.86	7.22±1.57	8.24±1.07	8.16±2.16	8.96±2.92	9.03±2.12	9.55±2.98	7.84±1.43	8.23±0.70
	TN (%)	66±14.97	62.6±10.48	63.4±15.19	64.8±9.12	65±13.78	69.2±6.61	68.8±9.86	63.7±15.53	63.8±11.09	58±14.92	60.7±11.85

coronary artery ligation did not develop ventricular fibrillation. Dogs with dilatative cardiomyopathy frequently have ventricular arrhythmias and the most likely cause of sudden death in these dogs may be ventricular fibrillation (Rush & Keene, 1989).

In a study of human patients with ventricular tachycardia, Harrison and Alderman (1971) found that lignocaine completely abolished ventricular premature beats when the plasma concentration of the drug was 6–7 μg ml^{-1}. Similar results were obtained in dogs by Wilcke *et al.* (1983). In the present study, dogs pretreated with 4 mg kg^{-1} lignocaine IV still have premature ventricular beats following adrenaline administration even though lignocaine has been reported to increase the arrhythmogenic dose of adrenaline both in humans and dogs anaesthetized with halothane (Johnstone *et al.*, 1976; Chapin *et al.*, 1980). This difference could have been due to a decrease in plasma lignocaine concentration by the time of adrenaline administration although in the present study the plasma concentrations of the drug were not measured. Moreover, in practice, bolus administration of lignocaine is generally followed by a constant IV infusion (Muir & Lipowitz, 1978). Although lignocaine did not prevent ventricular arrhythmias, no second degree heart block occurred in these dogs unlike in the other groups. Furthermore, lignocaine did not cause any alteration in the P–R, QRS, and QT intervals in agreement with the findings of Smith *et al.* (1972) although on adrenaline administration the P–R interval did increase but not significantly.

Propranolol is reported to be effective in controlling ventricular arrhythmias both in humans and dogs (Woosley *et al.*, 1979; Muir, 1986). Gang *et al.* (1984) reported that propranolol abolished ventricular fibrillation in dogs with myocardial infarction. In the present study, propranolol prevented ventricular fibrillation developing in dogs with induced arrhythmias. Our success in preventing death after pretreatment was in agreement with the results of Koppes *et al.* (1980) who observed suppression of premature beats after acute myocardial infarction and hence the prevention of sudden death in human patients. Propranolol prevented development of arrhythmias in one dog whereas in the others second degree heart block and ventricular premature beats were noted although these were not as predominant as those in the control dogs. A reduction in premature ventricular beats has also been reported by Winkle *et al.* (1978).

Although Kaumann and Aramendia (1968) found that verapamil prolonged the P–R interval in dogs with coronary artery ligation, and similar results were obtained by Heng *et al.* (1975) in humans, the present study did not show any significant increase in the P–R interval due to verapamil pretreatment. Drug pretreatments did not cause any significant alteration in the QRS and QT intervals on adrenaline administration suggesting that adrenaline did not cause any alteration in the rate of depolarization or repolarization of the ventricles. Lack of effect on depolarization or repolarization of action potentials by verapamil in patients with sinus rhythm has been reported by Heng *et al.* (1975). Adrenaline acts on adrenergic receptors in the heart to exert both positive inotropic and chronotropic effects resulting in higher demands for oxygen. Hypoxia and myocardial ischaemia cause an increase in the T wave amplitude (Bolton, 1975). In this study, administration of adrenaline significantly ($P<0.05$) increased the T wave amplitude from 0.16±0.05 mV to 0.43±0.09 mV in the controls (Fig. 3) suggesting that the oxygen demand of the myocardium had increased. Furthermore, since the polarity of the T wave changed in some of the animals, the cause for the increased T wave amplitude was most likely due to hypoxia. The T wave amplitude increase occurred just prior to the start of the arrhythmias and suggests that in halothane anaesthetized dogs adrenaline-induced arrhythmias may be precipitated by increased oxygen demands leading to myocardial hypoxia. The hypoxia causes the ventricular myocardium to become irritable and stimulates ventricular arrhythmias which may then lead to ventricular fibrillations—a more serious consequence of ventricular myocardial irritability (Bolton, 1975). Verapamil was apparently superior in prevention of adrenaline induced arrhythmias in these halothane anaesthetized dogs. Pretreatment prevented arrhythmias in one dog and in another only one isolated second degree heart block occurred. Propranolol and lignocaine had little effect, possibly due to low concentrations of the drugs at the myocardium receptor sites at the time of adrenaline administration. This suggestion is supported by another study (Kitaa, 1990) in which propranolol at a higher dose of 0.5 mg kg^{-1} was found to be better than verapamil and lignocaine in the prevention of adrenaline-induced arrhythmias in halothane and anaesthetized dogs.

Haematological parameters remained within the normal species range with only total neutrophil counts for the controls at 8 h being slightly above the normal. The increase in mature neutrophil cells suggests that the effect is mainly one of redistribution of cells already available within the capillary beds (Schalm *et al.*, 1975b). Most of the changes were noted within the first 8 h of the study. The increase in these parameters may have been due to stress and a release of blood reserves from the spleen, bone marrow and shunting of blood from non-essential organs which occurs when adrenaline is released or administered into the blood stream.

The results obtained in this study suggest that verapamil when administered early compares well with propranolol in the control of adrenaline-induced ventricular arrhythmias in the dog. Lignocaine, administered as a bolus early prior to the induction of the arrhythmias, is of little clinical use in preventing adrenaline induced arrhythmias. Drug pretreatments did not have any clinically significant effects on the ECG or haematological parameters.

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