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EFFECTS OF TIPRENOLOL, PRACTOLOL AND PROPRANOLOL ON EXPERIMENTAL VENTRICULAR TACHYARRHYTHMIAS

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1 Low doses of tiprenolol (0.01-0.02 mg/kg) and propranolol (0.05 mg/kg) abolished the ventricular arrhythmias produced by the intravenous injection of adrenaline in anaesthetized dogs respired with halothane.

2 Larger doses of tiprenolol (2.0-4.0 mg/kg) restored sinus rhythm in four of five dogs with ventricular tachycardia produced by toxic doses of ouabain. Propranolol (2.0-4.0 mg/kg) had the same effect in each of four dogs.

3 Both tiprenolol (4.0-8.0 mg/kg) and propranolol (4.0 mg/kg) increased the frequency of sinus beats and reduced the ventricular rate in dogs with ventricular tachycardia 20-44 h after ligation of a coronary artery.

4 Practolol (0.5-16.0 mg/kg) did not reduce the ventricular rate or increase the frequency of sinus beats in dogs with ventricular tachycardia after ligation of a coronary artery.

5 In dogs with ouabain-induced ventricular tachycardia mean arterial pressure was reduced after the administration of tiprenolol (0.5-8.0 mg/kg) or propranolol (4.0-8.0 mg/kg). Depression of sinus and atrioventricular nodal function, and of intraventricular conduction developed in some of the dogs given tiprenolol (4-8 mg/kg) or propranolol (8.0 mg/kg).

6 The administration of tiprenolol (1.0-8.0 mg/kg) or propranolol (4.0-8.0 mg/kg) depressed the arterial pressure and caused the deaths of some dogs in which a coronary artery had been ligated. Such deaths did not occur in the group which had been given toxic doses of ouabain.

Introduction

The clinical value of β-adrenoceptor blockade with propranolol has been reported in the management of patients with many conditions, including cardiac arrhythmias (Gibson & Sowton, 1969), angina (Gianelly, Goldman, Treister & Harrison, 1967), hypertension (Prichard & Gillam, 1969), and thyrotoxicosis (Shanks, Hadden, Lowe, McDevitt & Montgomery, 1969). Recently practolol and other compounds have been introduced, and similar beneficial effects noted.

Serious complications have been reported after the administration of each of the currently available compounds to some patients. The most serious of these complications has been the development of hypotension in patients with acute myocardial infarction after treatment with propranolol (Stephen, 1966), alprenolol (Kreus, Salokannel, Isomäki & Waris, 1970), or oxprenolol (Sandler & Pistevos, 1971). Similar adverse effects have attended the use of practolol (Allen, Pantridge & Shanks, 1971a), although it may be the least toxic β-adrenoceptor blocking drug at present available.

Tiprenolol (Fig. 1), a recently described β-adrenoceptor blocking compound (Du-21445; Philips-Duphar), appears to be three to four times more potent than propranolol in reducing the increase in heart rate during exercise or the intravenous infusion of isoprenaline (Kesteloot, Sluyts, Floor-Wieringa & Van Strik, 1970, 1973).

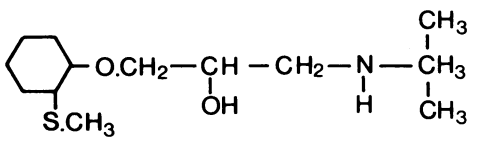

Fig. 1 Structure of tiprenolol.

Clinically, it has been used to slow conduction through the atrio-ventricular node and accessory pathways in patients with Wolff-Parkinson-White syndrome (Roelandt, Schamroth & Hugenholtz,

1972). As it may be of further clinical use, it was of interest to compare its effects on three experimental cardiac arrhythmias with those of propranolol.

Although practolol is of clinical value in the control of lignocaine-resistant ventricular arrhythmias after acute myocardial infarction (Jewitt, Mercer & Shillingford, 1969; Allen *et al.*, 1971a), its mode of action in such patients is not clear. It is known that low doses of practolol abolish or reduce the ventricular ectopic response to intravenous injections of adrenaline given to dogs respired with halothane in room air, and to dogs 2-4 days after ligation of a coronary artery. Infusions of the drug do not abolish ouabain-induced arrhythmias (Dunlop & Shanks, 1968; Laddu & Somani, 1969). However, there are no reports as yet of the effects of practolol on the arrhythmias which are present 20-44 h after ligation of a coronary artery.

These results have been presented in part to the British Pharmacological Society (Allen, Shanks & Zaidi, 1971b).

Methods

Ventricular arrhythmias were produced in dogs of either sex (weighing 17-35 kg) by methods which have been described in detail (Allen, Shanks & Zaidi, 1971c; Allen, Ekue, Shanks & Zaidi, 1972). When the dogs were anaesthetized, positive pressure respiration was maintained through an endotracheal tube, with a Palmer Ideal pump at a rate of 18 per min, and a tidal volume of 13 ml/kg room air; a catheter was inserted into a foreleg vein.

Halothane-adrenaline arrhythmias

Anaesthesia was induced by the intravenous administration of sodium pentobarbitone (20 mg/kg), 1 h after premedication with morphine sulphate (0.5 mg/kg s.c.). The animals were respired with halothane (1% v/v in room air) during the period from 10 min before the first dose of adrenaline until the end of the experiment. Arterial pressure was measured in mmHg (1 mmHg $\equiv$ 1.333 mbar) through a cannula or catheter inserted into a carotid or femoral artery and attached to a pressure transducer (Consolidated Electrodynamics). Electrocardiograms were obtained from subcutaneous needle electrodes, and recorded with instantaneous heart rate and the arterial pressure (phasic and electronic mean) on a Devices M4 or M8 recorder. The intravenous challenge dose of adrenaline required to produce a consistent ventricular arrhythmia was determined in three dogs. Tiprenolol (0.01 and 0.02 mg/kg) was given intravenously, and the previously determined challenge dose of adrenaline administered 5 min after each dose of the drug.

Ouabain-induced arrhythmias

The dogs were anaesthetized with the same doses of morphine and pentobarbitone as in the preceding group, and the arterial pressure and ECG recorded as before. Successive intravenous injections of ouabain were given until ventricular tachycardia was produced (40 μg/kg, followed 30 min later by 20 μg/kg, and if necessary by 10 μg/kg doses at 15 min intervals). The independence of the arrhythmia from supraventricular influences was shown by the lack of response to stimulation of the caudal end of the divided right cervical vagus nerve. Increasing doses (0.5-8.0 mg/kg) of tiprenolol or propranolol were given as single intravenous injections at 5 min intervals. In five dogs given no drug it has been shown that this arrhythmia persisted for 139 $\pm$ 18 min (mean and s.e.; Allen *et al.*, 1971c).

Arrhythmias after ligation of a coronary artery

Anaesthesia was induced by the intravenous injection of methohexitone (10 mg/kg) or thialbarbitone (50 mg/kg), and after endotracheal intubation the dogs were respired with halothane (0.5-1.5%) in room air. The anterior descending branch of the left coronary artery was ligated in two stages under aseptic conditions in 18 dogs. Twenty to forty-four hours later the effects of the intravenous injection at 5 min intervals of increasing doses of tiprenolol (0.5-8.0 mg/kg), propranolol (0.5-8.0 mg/kg) or practolol (0.5-16.0 mg/kg) were studied in the conscious dogs. In some experiments, arterial blood pressure was recorded through a Cournand needle or a polythene cannula inserted into a femoral artery, under local analgesia.

Drugs used

(±)-Tiprenolol hydrochloride (Philips-Duphar); (±)-propranolol hydrochloride, (±)-practolol hydrochloride, thialbarbitone sodium, halothane (I.C.I. Pharmaceuticals Division); pentobarbitone sodium (Abbott Laboratories); (−)-adrenaline bitartrate (C. Zimmerman); ouabain (British Drug Houses). Powdered drugs were dissolved in 0.9% w/v NaCl solution at the required concentration. Doses are expressed in terms of the salt.

Results

Halothane-adrenaline arrhythmias

Effects of tiprenolol. In three dogs respired with halothane 1% in room air, the intravenous injection of adrenaline 1.5 ± 0.7 μg/kg (mean and s.e.) produced multifocal ventricular ectopic beats and ventricular tachycardia. The administration of tiprenolol (0.01 mg/kg) abolished the arrhythmia in two dogs, and reduced the number of ectopic beats in the third dog; a further dose of tiprenolol (0.02 mg/kg) abolished the arrhythmia in this dog. Although the effect of the test dose of adrenaline was prevented by these doses of tiprenolol, the administration of twice the test dose of adrenaline produced ventricular ectopic beats in each case.

The effective dose of tiprenolol reduced the resting heart rate (201 ± 13 to 163 ± 3 per minute). Resting mean arterial pressure was unaltered by the doses of tiprenolol used (154 ± 7 to 146 ± 9 mmHg). The maximum mean arterial pressure produced during continued sinus rhythm in the protected response (175 ± 21) was greater than the mean arterial pressure at the onset of the arrhythmia before tiprenolol administration (157 ± 3 mmHg).

Effects of propranolol. In an earlier study (Allen *et al.*, 1971b), propranolol in the only dose tested (0.05 mg/kg) abolished the ventricular ectopic response to a mean test dose of 3.6 ± 1.0 μg/kg adrenaline in four dogs, reduced resting heart rate (131 ± 19 to 113 ± 14 per min) and did not alter resting arterial pressure (107 ± 24 to 106 ± 26 mmHg).

Ouabain-induced arrhythmias

Effects of tiprenolol. In five dogs the administration of ouabain (mean dose: 62 ± 4 μg/kg) produced ventricular tachycardia. Tiprenolol was given intravenously in increasing doses at 5 min intervals. The mean results are given in Table 1. A dose of 0.5 mg/kg reduced the ventricular rate in all dogs. Sinus rhythm was restored in four of the five dogs after 2 mg/kg had been given. Depression of cardiac conduction pathways developed in these four dogs after tiprenolol (4 mg/kg), and especially after 8 mg/kg, when first degree atrioventricular block with left axis deviation (one dog), sinus arrest with ventricular asystole for 20-70 s before the onset of nodal rhythm (two dogs), and left axis deviation alone (one dog) were recorded. In the fifth dog Wenckebach atrioventricular block developed 7 min after the highest dose of tiprenolol. This depression of sinus and atrioventricular nodal function reduced the number of sinus beats seen in the 5 min period after the administration of tiprenolol (8 mg/kg) to the group of five dogs (Table 1).

Table 1 The effects of tiprenolol and propranolol on ouabain-induced ventricular tachycardia

Dose of drug (mg/kg)	*0*	*0.5*	*1.0*	*2.0*	*4.0*	*8.0*	*S.e. of varietal mean*
Tiprenolol (n = 5)							
V.R. per 5 min	975	881	786**	729**	631**	440**	27.0
S.B. per 5 min	19	7	140	427**	442**	240	80.0
M.A.P. mmHg							
Before drug	212	214	165**	151**	129**	123**	4.3
+ 4 min	210	171**	149**	139**	122**	85**	3.9
Propranolol (n = 4)							
V.R. per 5 min	964	894	728**	586**	533**	420**	34.4
S.B. per 5 min	25	16	202**	467**	524**	419**	47.7
M.A.P. mmHg							
Before drug	177	178	175	186	185	168	6.8
+ 4 min	189	176	183	179	163*	73**	6.3

* $P < 0.05$; ** $P < 0.01$ compared with corresponding values at 0 mg/kg.

Ventricular tachycardia was produced by the administration of ouabain. After the arrhythmia had been present for 10 min increasing doses of tiprenolol or propranolol were injected intravenously. The effects of the drugs on the ventricular rate (V.R.) and number of sinus beats (S.B.) occurring in the 5 min period after the administration of each dose are shown (mean, and s.e. of varietal mean), with the mean arterial blood pressure 4 min after each dose.

There were significant reductions in V.R. after tiprenolol (1.0-8.0 mg/kg) and propranolol (1.0-8.0 mg/kg), and increases in the frequency of sinus beats after the administration of propranolol (1.0-8.0 mg/kg; $P < 0.01$ in each case). Arterial blood pressure was reduced by tiprenolol (0.5-8.0 mg/kg) and propranolol (4.0-8.0 mg/kg).

Arterial pressure was reduced progressively by each dose of tiprenolol (Table 1).

Effects of propranolol. In four dogs the effects of increasing doses of propranolol were studied after ventricular tachycardia had been produced by the intravenous injection of ouabain (64 ± 4 μg/kg). The administration of propranolol (1.0 mg/kg) reduced the ventricular rate and increased the number of sinus beats (Table 1). Sinus rhythm was restored in three dogs after the administration of propranolol (2 mg/kg), and in the fourth by 4 mg/kg. Propranolol (8 mg/kg) greatly reduced the ventricular rate in the four dogs, and this effect was associated with the development of second degree atrioventricular block (two dogs), and transient complete atrioventricular block with ventricular asystole, followed by second degree block (one dog).

Mean arterial pressure was reduced by both of the higher doses of propranolol (4 and 8 mg/kg; Table 1).

Arrhythmias after ligation of a coronary artery

Control studies. Seven dogs were given no drug, and the electrocardiogram was recorded continuously for 35 minutes. The frequency of sinus beats was low, and ventricular tachycardia persisted throughout this period (Table 2). There were no significant differences between the results in any of the 5 min periods.

Effects of tiprenolol. The effects of a series of doses of tiprenolol were studied in ten dogs. Some of the records from one experiment are shown in Figure 2. In this dog, 23.5 h after ligation of the anterior descending branch of the left coronary artery, there was a ventricular tachycardia, with sinus beats (12-20% of the total). Although a reduction in total ventricular rate occurred at lower doses, only 8 mg/kg increased the number of sinus beats. Mean arterial pressure fell transiently after the injection of both 4 and 8 mg/kg.

Similar results were observed in 5 other experiments, where tiprenolol (8 mg/kg) increased the number of sinus beats in the 5 min period after administration of the drug (mean results, Table 2), but two of these dogs died 5 min after this dose (8 mg/kg). In the 4 remaining experiments, there was no increase in the frequency of sinus beats;

Table 2 Effects of no drug, tiprenolol, propranolol or practolol on the ventricular arrhythmia after ligation of a coronary artery in a dog

Time (min)	*0-5*	*5-10*	*10-15*	*15-20*	*25-30*	*30-35*		*S.e. of varietal mean*
No drug								
No. of experiments	7	7	7	7	7	7		
V.R. per 5 min	887	855	866	851	848	864		31.1
S.B. per 5 min	55	74	86	98	98	79		13.1
Dose of drug (mg/kg)	*0*	*0.5*	*1.0*	*2.0*	*4.0*	*8.0*	*16.0*	
Tiprenolol								
No. of experiments	10	10	9	9	9	7	–	
V.R. per 5 min	955	952	937	875**	808**	722†	–	13.8
S.B. per 5 min	55	60	60	107	177*	416†	–	27.7
Propranolol								
No. of experiments	10	10	10	10	10	4	–	
V.R. per 5 min	852	818	776*	708**	627**	524	–	20.8
S.B. per 5 min	106	81	89	144	280**	160	–	28.2
Practolol								
No. of experiments	4	4	4	4	4	3	3	
V.R. per 5 min	974	947	899	885	935	951	930	24.0
S.B. per 5 min	32	58	69	54	19	13	24	19.6

* $P < 0.05$; ** $P < 0.01$ compared with corresponding value at 0 mg/kg.
† Differs from values in same animals at 4.0 mg/kg, at $P < 0.01$.
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 successive 5 min periods before and after the intravenous injection of the test drugs. Mean values and s.e. of varietal mean are indicated. There was a significant increase in the number of sinus beats after tiprenolol (4-8 mg/kg) or propranolol (4 mg/kg), and a significant reduction in the ventricular rate after tiprenolol (2-8 mg/kg) or propranolol (1-4 mg/kg). There was no significant difference in V.R. or S.B. between different groups before any drug was given.

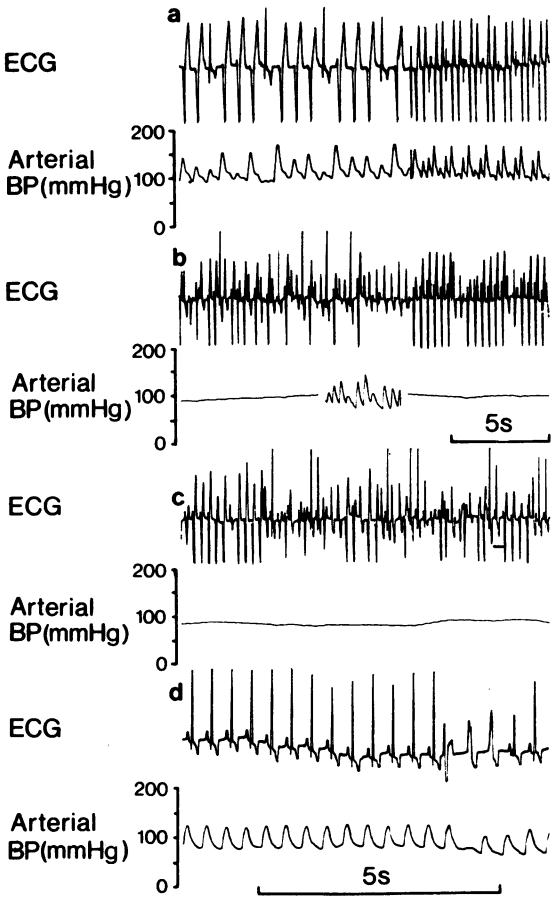

Fig. 2 Some of the records of mean and phasic arterial pressure and the electrocardiogram are shown of a dog with ventricular tachycardia, which received increasing doses of tiprenolol at 5 min intervals, 23.5 h after ligation of a coronary artery. (a) During the control period. (b) 4 min after the intravenous administration of tiprenolol (0.5 mg/kg). (c) 4 min after the administration of 4.0 mg/kg. (d) 7 min after the administration of tiprenolol (8.0 mg/kg), the frequency of sinus beats is greatly increased, although some ectopic beats persist.

three of these dogs died after lower doses of the drug (1.0 mg/kg, one dog; 4 mg/kg, two dogs), and in the last experiment the 8 mg/kg dose of the drug reduced the ventricular rate without any change in the incidence of sinus beats.

In the seven dogs in which arterial pressure was recorded it was reduced by the increasing doses of tiprenolol (Table 3). An acute depressant effect was observed after the injection of 4 and 8 mg/kg. The ECG and arterial pressure changes associated with death were similar to those observed with propranolol (see below). Left axis deviation occurred in two of the seven dogs given tiprenolol (8 mg/kg).

Effects of propranolol. Observations were made in ten dogs after the intravenous injection of propranolol (0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg) at 5 min intervals (Table 2). In eight of the ten dogs, propranolol (0.5-2.0 mg/kg) reduced the ventricular rate with little effect on the number of sinus beats. The frequency of sinus beats was increased in the other two dogs. After the administration of propranolol (4.0 mg/kg) to the ten dogs there was a further reduction in ventricular rate, and a significant increase in the number of sinus beats. However, four of the ten dogs died after this dose of the drug. The largest dose of propranolol (8 mg/kg) produced a further reduction in ventricular rate in the remaining six dogs, but five of the dogs died, three within 5 min of receiving the drug. Left axis deviation developed in four of the six dogs after this dose of the drug.

Propranolol (2-8 mg/kg) reduced the mean arterial pressure in seven dogs in which the pressure changes were recorded (Table 3). Acute cardiac depression appeared to be the cause of death, with cardiac asystole or ventricular fibrillation as the terminal rhythm.

Effects of practolol. Practolol (0.5-16.0 mg/kg) did not increase the number of sinus beats in four dogs with ventricular arrhythmias after coronary artery ligation (Table 2). Furthermore, there was little reduction in the ventricular rate after any of the doses of practolol. One dog died after the injection of practolol (4.0 mg/kg). In one dog, arterial pressure was not reduced by any of the doses of practolol (Table 3).

Dose-response curves for tiprenolol and propranolol

Dose-response curves were calculated to examine the relation between the % reduction in the frequency of ventricular ectopic beats in the three arrhythmias and the dose of tiprenolol or propranolol administered. The halothane-adrenaline arrhythmia was abolished by a low dose of tiprenolol (mean 0.02 mg/kg), but 1.4 mg/kg was required for a 50% reduction in the number of ventricular ectopic beats in the dogs with ouabain-induced ventricular tachycardia, and 6.2 mg/kg for a similar effect in the arrhythmia after coronary artery ligation. The doses of propranolol required for comparable effects were. 0.05 mg/kg (halothane-adrenaline), 1.0 mg/kg (ouabain) and 3.0 mg/kg (after coronary artery

ligation). No conclusion can be drawn as to the relative potencies of tiprenolol and propranolol in abolishing the halothane-adrenaline arrhythmia as the propranolol-treated group received no dose less than 0.05 mg/kg of the drug and twice as much adrenaline was required to produce the arrhythmia in the dogs receiving propranolol as in the tiprenolol group. The administration of practolol (0.5-16.0 mg/kg) produced no reduction in the frequency of ventricular ectopic beats.

Discussion

These results indicate that tiprenolol can abolish the ventricular arrhythmias produced by adrenaline in dogs respired with halothane, and has a variable effect on the arrhythmias produced by ouabain and those after ligation of a coronary artery.

Low doses of tiprenolol (0.01-0.02 mg/kg) abolished the halothane-adrenaline arrhythmias. This compares with the similar effects of low doses of propranolol (Lucchesi & Iwami, 1968) or practolol (Laddu & Somani, 1969) in abolishing this arrhythmia. These effects are attributed to specific blockade of the cardiac β-adrenoceptors (Barrett & Cullum, 1968).

Ouabain-induced arrhythmias

Tiprenolol and propranolol, in single increasing doses, restored sinus rhythm in dogs with ouabain-induced ventricular tachycardia. Toxic effects on the arterial pressure after the injection of tiprenolol (8 mg/kg) were similar to those seen with the same dose of propranolol. The combined effects of the glycoside and tiprenolol on atrioventricular conduction were similar to those of propranolol in the ouabain-treated dogs.

The effects of propranolol on the ouabain-induced arrhythmias are ascribed to a combination of β-adrenoceptor blockade and local anaesthetic (or membrane) activity (Barrett & Cullum, 1968). The local anaesthetic effect of tiprenolol on the frog sciatic nerve has yet to be determined. Some local anaesthetic activity was observed in the mouse tail, but not on the mouse cornea (Philips-Duphar, personal communication). The toxic effects of tiprenolol on the arterial pressure, and atrio- and intra-ventricular conduction are at least as severe as those of similar doses of propranolol.

Arrhythmias after ligation of a coronary artery

In dogs with ventricular tachycardia after ligation of a coronary artery, the administration of tiprenolol (8 mg/kg) and of propranolol (4 mg/kg) did not restore sinus rhythm in every case, and caused reductions in arterial pressure and the deaths of some animals. These results contrast with the greater efficacy and lower toxicity of drugs such as lignocaine, mexiletine (Kö 1173) and diphenylhydantoin in concurrent studies (Allen *et al.*, 1971c; Allen *et al.*, 1972).

Practolol had no beneficial effect on the arrhythmia which is present 24 h after ligation of a

Table 3 Effects on mean arterial pressure (in mmHg) of the administration of tiprenolol, propranolol or practolol to conscious dogs with ventricular arrhythmia after ligation of a coronary artery

Dose (mg/kg)	*0*	*0.5*	*1.0*	*2.0*	*4.0*	*8.0*	*16.0*	*S.e. of varietal mean*
Tiprenolol								
Before drug	114	109	95**	92**	91**	85	–	3.0
4 min after drug	113	93*	95*	90**	75**	60 (n = 6)	–	3.0
Propranolol								
Before drug	114	112	113	106	103*	94	–	2.9
4 min after drug	112	113	102	99*	84**	55 (n = 5)	–	3.4
Practolol								
Before drug	58	67	90	88	87	105	97	–
4 min after drug	58	79	76	105	108	92	98	–

* $P < 0.05$; ** $P < 0.01$, compared with corresponding values at 0 mg/kg.
Mean arterial pressure was obtained by electronic damping or by planimetry of the phasic arterial pressure recording in dogs given tiprenolol (7 experiments), propranolol (7 experiments) or practolol (1 experiment). Significant reductions in arterial pressure were seen after each dose of tiprenolol, and after propranolol (2.0-8.0 mg/kg).

coronary artery. In contrast to tiprenolol and propranolol, it failed to increase the number of sinus beats and it did not reduce the frequency of ventricular ectopic beats.

The effects of propranolol on the arrhythmia 20-44 h after coronary artery ligation are probably due to non-specific membrane, or local anaesthetic activity, as low doses of propranolol, which block β-adrenoceptors, have no effect in restoring sinus rhythm (Shanks & Dunlop, 1967). The present results are consistent with the absence of local anaesthetic activity with practolol (Dunlop & Shanks, 1968) and with the possession of some non-specific membrane effects by tiprenolol.

The toxic effects of the three drugs in the dogs with the arrhythmias after coronary artery ligation were observed usually at the higher doses of the drug (4-8 mg/kg). Deaths at such doses bear little relation to the left ventricular dysfunction and death which have occurred during clinical use of less than 0.2 mg/kg of the drugs. The toxic effects in these experimental studies appear to be due in part to non-specific membrane activity, whereas clinical problems arise in patients dependent on increased sympathetic activity for maintenance of cardiac function (Epstein & Braunwald, 1969).

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