COMPARISON OF THE EFFECTS OF PROPRANOLOL, PINDOLOL, OXPRENOLOL AND ACEBUTOLOL ON ATRIOVENTRICULAR CONDUCTION IN UNANAESTHETIZED DOGS

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1 Atrio-ventricular conduction (AVC) in the unanaesthetized dog (17 animals) was studied using atrial pacing at progressively increasing frequencies applied via electrodes implanted in the right atrium. In animals habituated to the experimental conditions, β -adrenoceptor blocking drugs devoid of intrinsic sympathomimetic activity (ISA) modified neither heart-rate (HR) nor AVC, though 4 mg/kg i.v. propranolol transiently raised HR and facilitated AVC. Due to their ISA, pindolol and oxprenolol raised HR and facilitated AVC at high doses.

2 Thus, when not under anaesthesia, the resting dog, in contrast to man, possesses no tonic adrenergic influence which might be suppressed by β -adrenoceptor blocking drugs.

3 After atropine or pentobarbitone, which considerably increased HR, β -adrenoceptor blocking effects became clearly visible, and the hitherto reported depressant effects on HR and AVC were observed. However, the ISA of oxprenolol, and especially of pindolol, can partly or completely mask their β -adrenoceptor blocking action at high doses under these experimental conditions.

Introduction

Much work has already been published on the effects of β -adrenoceptor blocking drugs on atrio-ventricular (AV) conduction in anaesthetized dogs.

In the anaesthetized dog, the negative dromotropic effect of ($\pm$)-propranolol (Duchène-Marullaz *et al.*, 1967; Fitzgerald & Wale, 1971; Priola, 1973; Giudicelli *et al.*, 1975; Jaillon *et al.*, 1978, 1980); of ($\pm$)-oxprenolol (Fitzgerald & Wale, 1971) and ($\pm$)-pindolol (Giudicelli *et al.*, 1975; Jaillon *et al.*, 1978) was found to be always pronounced when evaluated either in terms of AV interval or refractory period.

However the observed data may result from spurious effects arising out of the special conditions of experimentation in the animal, and particularly from the effects of pentobarbitone, the anaesthetic most often used. The present work set out to investigate this possibility by measuring conduction parameters in dogs under conditions somewhat closer to those likely to be encountered in clinical practice in man. Accordingly, methods of experimentation were chosen which involved the least physiological disturbance and anaesthetics were avoided.

The technique of atrial pacing at progressively increasing frequency was employed. We have made a comparison between the effects of ($\pm$)-propranolol, devoid of intrinsic sympathomimetic activity (ISA), and the effects of ($\pm$)-pindolol, ($\pm$)-oxprenolol and ($\pm$)-acebutolol, drugs which possess ISA.

Methods

Seventeen adult mongrel dogs of either sex were used, weighing between 12 and 18 kg (mean 17 kg). They were anaesthetized with chloralose (0.08 g/kg i.v.), the thorax was opened at the fourth right intercostal space, and a temporary pericardial cradle was used in order to make access to the right atrium easier. Two surgical electrodes (Bruneau) set in stainless steel were stitched, one near the upper edge of the SA node, and the other at a distance of 1 cm away in the atrial wall. The free ends were exteriorized at the back of the animal's neck. The lungs were inflated to expel air from the pleural cavity, and the thorax closed. In addition, a silastic catheter (Dow Corning 0.40 in i.d.) was introduced into the iliac artery in some animals, and exteriorized via an Ealing arterial valve near the electrodes at the back of the animal's neck to allow easy monitoring of blood pressure. Antibiotics were administered systematically during the 3 days following instrumentation. The blood-pressure catheter was regularly rinsed with heparin in saline at least once a week. The animals were habituated to receiving programmed electrical stimulation. ECG were recorded in DI, DII and DIII or in DI and DII when the third track was used to monitor blood-pressure, on a Philips Cardiopan 3 instrument. Blood-pressure was measured via a Statham P23DB unit. Pulses (1 ms) from a Jansen pulse generator were applied to the electrodes

at an intensity twice the threshold value. Initial frequency was slightly above the spontaneous HR. The ventricles responded regularly to the atrial rhythm. As the pacing frequency was progressively increased, AV block appeared in 1 or 2 complexes at a characteristic frequency (Wenckebach Point (WP)), always at the end of expiration when the phasic effect of the cholinergic innervation was maximal. At a certain higher frequency (maximum atrioventricular frequency, MAVF), the ventricles no longer responded to the rhythm set by the atria. The effects of the β -adrenoceptor blocking drugs on HR, WP and MAVF were examined under basal conditions and after atropine or pentobarbitone.

Five to seven dogs were used for each series. The same dogs were often used for different series at intervals of at least a week. Individual experiments took 1–2 h. Injection was always preceded by a 20 min observation period during which time control values of HR, WP and MAVF were recorded (see Tables). In order to obviate injection shock effects, the drugs were administered through an 'epicath' catheter placed in a cephalic vein before the start of the experiment. HR (over 1 min), WP and MAVF were determined at regular intervals (see Tables). The β -adrenoceptor blocking drugs were injected under basal conditions, and 20 min after atropine or pentobarbitone.

The doses of the β -adrenoceptor blocking drugs were expressed in terms of salt weight. They were administered as a 'bolus', ($\pm$)-propranolol hydrochloride in distilled water at 0.5, 1 and 4 mg/kg, ($\pm$)-pindolol hydrochloride in citrate solution (citric acid 0.35 g; trisodium citrate 1.96 g; NaCl 1.25 g; distilled water to 250 ml) at 0.0125, 0.025, 0.050, 0.100 and 0.200 mg/kg ($\pm$)-oxprenolol hydrochloride in distilled water at 0.5, 1, 2, 4 mg/kg and ($\pm$)-acebutolol hydrochloride in distilled water at 5 mg/kg. Pentobarbitone (Abbott) was administered at 25 mg/kg and atropine sulphate at 0.15 mg/kg. Controls received 5 ml of sterile saline solution (NaCl 0.9%).

Statistical analysis

The results are expressed in terms of mean $\pm$ s.e. mean. The statistical significance of the effect of the drugs as a function of time upon HR, WP and MAVF was evaluated by two factor analysis of variance followed by the Student-Fischer's *t*-test. The same test was applied in unpaired series after comparison of variances by the Snedecor F test to evaluate the dose-relatedness of the effects of each β -adrenoceptor blocking drug and to compare them with each other.

Results

Control

HR, WP and MAVF were not modified by injection of 5 ml of sterile saline solution (NaCl 0.9%) throughout a 2 h observation period in six dogs. Values before and after injection always remained unchanged; 90 ± 2 , 138 ± 2 and 319 ± 7 beats/min respectively.

Effect of β -adrenoceptor blocking drugs on HR

Basal conditions. The data are summarized in Table 1. Propranolol (0.5 and 1 mg/kg) affected HR only slightly and inconsistently. However, 4 mg/kg propranolol unexpectedly caused a significant cardioacceleration lasting at least 5 min. HR fell to the spontaneous rate only after 35 and 45 min. Propranolol never produced a dose-related effect on HR, pindolol always produced a dose-related cardioacceleration appearing immediately at high doses and later at low doses, and becoming more intense during the experiment. Oxprenolol caused an immediate cardioacceleration at all doses, which fell off within 1 h. Acebutolol (5 mg/kg) produced only a transient cardioacceleration.

After atropine. The data are summarized in Table 2. Injection of 0.15 mg atropine raised HR to between 184 ± 13 and 218 ± 11 beats/min at 20 min according to the series. Propranolol lowered HR significantly. The decrease in the cardioacceleration due to atropine was somewhat less marked with pindolol. Oxprenolol and acebutolol lowered HR in the atropinized dogs similar to propranolol.

Effect of propranolol after pentobarbitone. In five dogs, injection of pentobarbitone raised HR from 98 ± 10 to 177 ± 15 beats/min. Propranolol (1 mg/kg) injected 15 min afterwards lowered this value significantly ($P < 0.001$) to 140 ± 13 beats/min at 5 min and 135 ± 13 beats/min at 15 min (Figure 1).

Effect of β -adrenoceptor blocking drugs on WP. The data are summarized in Table 3. Propranolol (0.5 mg/kg) lowered WP inconsistently. At 1 mg/kg no significant effect was observed. At 4 mg/kg a significant unexpected facilitation of AV conduction was observed for 20 min. Pindolol at all doses significantly raised WP. At the lowest dose, 0.0125 mg/kg, the effect only became significant at 35 min. At other doses, significance occurred sooner and more markedly with increasing dose. Oxprenolol also facilitated AV conduction dose-relatedly but unlike pindolol, the effect fell off progressively though it remained significant throughout the 55 min

Table 1 Effects of propranolol, pindolol, oxprenolol and acebutolol on heart rate in unanaesthetized dogs (mean ± s.e.mean effects)

	n	Control	+ 1	+ 3	+ 5	+ 15	Time (min)					+ 55	+ 60
Propranolol	0.5 mg/kg	6	78 ± 6	79 ± 5	73 ± 4	71 ± 5	64 ± 4 ^c	70 ± 4 ^a	73 ± 5	68 ± 4 ^b	69 ± 4 ^b		
	1 mg/kg	6	92 ± 10	99 ± 6	94 ± 8	91 ± 9	83 ± 8 ^a	85 ± 9	83 ± 9 ^a	83 ± 10 ^a	86 ± 10		
	4 mg/kg	7	90 ± 3	135 ± 13 ^c	130 ± 12 ^c	120 ± 11 ^c	97 ± 8	94 ± 5	89 ± 7	80 ± 5	78 ± 5 ^b	76 ± 6 ^b	
Pindolol	0.0125 mg/kg	6	78 ± 9	92 ± 8 ^c	84 ± 5	81 ± 3	83 ± 5	84 ± 6	89 ± 5 ^b	94 ± 5 ^c	93 ± 5 ^c		
	0.025 mg/kg	6	89 ± 8	93 ± 7	90 ± 7	92 ± 6	95 ± 6	98 ± 10 ^a	103 ± 7 ^c	109 ± 9 ^c	108 ± 9 ^c		
	0.05 mg/kg	6	92 ± 7	116 ± 7 ^c	100 ± 2	100 ± 5	107 ± 5	112 ± 8 ^b	122 ± 7 ^c	113 ± 8 ^b	120 ± 6 ^c		
	0.1 mg/kg	7	93 ± 9	111 ± 8 ^c	109 ± 7 ^b	111 ± 10 ^c	123 ± 7 ^c	132 ± 4 ^c	145 ± 8 ^c	131 ± 6 ^c	126 ± 5 ^c	133 ± 6 ^c	
	0.2 mg/kg	6	106 ± 2	135 ± 8 ^c	135 ± 9 ^c	135 ± 5 ^c	146 ± 7 ^c	143 ± 4 ^c	148 ± 9 ^c	149 ± 8 ^c	148 ± 6 ^c	146 ± 6 ^c	
Oxprenolol	0.5 mg/kg	7	95 ± 5	108 ± 9 ^a	105 ± 4	103 ± 5	109 ± 7 ^a	106 ± 8	102 ± 7	105 ± 7	97 ± 8		
	1 mg/kg	7	91 ± 9	118 ± 6 ^c	116 ± 5 ^c	118 ± 6 ^c	118 ± 4 ^c	110 ± 5 ^c	107 ± 6 ^b	102 ± 7	100 ± 5	98 ± 6	
	2 mg/kg	6	92 ± 5	132 ± 11 ^c	135 ± 8 ^c	136 ± 8 ^c	133 ± 9 ^c	125 ± 11 ^c	120 ± 11 ^c	117 ± 11 ^c	112 ± 12 ^c	111 ± 11 ^b	
	4 mg/kg	6	86 ± 6	138 ± 9 ^c	146 ± 8 ^c	137 ± 9 ^c	134 ± 10 ^c	121 ± 9 ^c	114 ± 10 ^c	106 ± 6 ^b	100 ± 5	101 ± 7	
Acebutolol	5 mg/kg	6	68 ± 5	88 ± 5 ^c	93 ± 13 ^c	87 ± 9 ^b	71 ± 7	73 ± 8	71 ± 6	72 ± 10	69 ± 6	71 ± 7	

The significant difference from the control group is denoted by: ^a: 0.01 < P < 0.05; ^b: 0.001 < P < 0.01; ^c: P < 0.001

Table 2 Effects of (mean ± s.e.mean) of propranolol, pindolol and oxprenolol after atropine on heart rate in unanaesthetized dogs

	n	Control	+ 1	+ 3	+ 5	+ 15	+ 25	+ 35	+ 45	+ 55	+ 60
Propranolol	0.5 mg/kg	6	194 ± 11	177 ± 10 ^a	175 ± 14 ^c	171 ± 13 ^c	165 ± 11 ^c	154 ± 9 ^c	149 ± 9 ^c	145 ± 8 ^c	142 ± 6 ^c
	1 mg/kg	6	204 ± 8	176 ± 8 ^c	168 ± 10 ^c	160 ± 9 ^c	153 ± 8 ^c	146 ± 9 ^c	137 ± 10 ^c	133 ± 10 ^c	127 ± 9 ^c
	4 mg/kg	6	198 ± 11	165 ± 7 ^b	156 ± 7 ^b	155 ± 8 ^b	143 ± 7 ^c	137 ± 5 ^c	135 ± 7 ^c	132 ± 6 ^c	131 ± 4 ^c
	0.025 mg/kg	6	203 ± 8	189 ± 10 ^a	180 ± 11 ^c	176 ± 10 ^c	168 ± 10 ^c	165 ± 10 ^c	162 ± 9 ^c	155 ± 9 ^c	159 ± 10 ^c
Pindolol	0.05 mg/kg	6	184 ± 13	188 ± 13	188 ± 11	183 ± 11	181 ± 9 ^c	180 ± 7	171 ± 8	178 ± 8	180 ± 8
	0.1 mg/kg	6	204 ± 15	187 ± 14 ^c	187 ± 15 ^c	184 ± 14 ^c	181 ± 14 ^c	178 ± 15 ^c	179 ± 17 ^c	181 ± 16 ^c	180 ± 17 ^c
	0.5 mg/kg	6	207 ± 15	200 ± 16	195 ± 14	191 ± 13 ^a	174 ± 14 ^c	178 ± 15 ^c	172 ± 18 ^c	161 ± 15 ^c	157 ± 13 ^c
Oxprenolol	1 mg/kg	6	207 ± 12	190 ± 13 ^b	188 ± 12 ^c	184 ± 12 ^c	177 ± 11 ^c	177 ± 13 ^c	169 ± 14 ^c	159 ± 14 ^c	151 ± 14 ^c
	2 mg/kg	6	191 ± 13	175 ± 11 ^c	173 ± 11 ^c	171 ± 11 ^c	169 ± 13 ^c	165 ± 11 ^c	163 ± 12 ^c	157 ± 12 ^c	154 ± 12 ^c
	4 mg/kg	6	218 ± 11	168 ± 10 ^c	176 ± 9 ^c	173 ± 9 ^c	174 ± 10 ^c	171 ± 11 ^c	167 ± 11 ^c	164 ± 12 ^c	153 ± 15 ^c

Atropine (0.150 mg/kg i.v.) was injected 20 min before the β-adrenoceptor blocking drugs. Four control times were observed during this period. Control time value reported in the Table is the last of these four control times. At this time, the β-adrenoceptor blocking drugs were injected i.v. Then nine experimental times were observed from + 1 min to + 60 min

The significant difference from the control group is denoted by: ^a: 0.01 < P < 0.05; ^b: 0.001 < P < 0.01; ^c: P < 0.001

Figure 1 Effects of propranolol (1 mg/kg i.v.) 5 min after injection of 25 mg/kg i.v. of pentobarbitone (control). Results are expressed as means $\pm$ s.e. mean. The number of dogs was 5. Heart rate and maximal auriculo-ventricular frequency (MAVF) decrease significantly. The significant difference from the control groups is in each case denoted by *** ($P < 0.001$). $\square$ control, $\square$ 1 mg/kg propranolol.

observation period. At 5 mg/kg, acebutolol very significantly raised WP ($P < 0.001$) 5 min after injection, but the effect wore off before the end of the experiment. Atropine and pentobarbitone both eliminated the WP. Under these drugs WP and MAVF were coincident.

Effects of β -adrenoceptor blocking drugs on MAVF

Basal conditions. The data are summarized in Table 4. MAVF values were much more dispersed than values of WP.

Control values in the 4 mg/kg propranolol series

were in particular much lower than in the other series. However, propranolol appreciably lowered MAVF at all doses. After pindolol, MAVF was not modified at 0.0125 mg/kg but was raised at 0.025 mg/kg and above, the effect being observed progressively sooner with higher doses. Oxprenolol also raised MAVF.

After atropine. The data are summarized in Table 5. Atropine eliminated the WP in all series and appreciably raised MAVF (from 265 ± 18 to 351 ± 15 beats/min). Propranolol at all doses reduced the effect of atropine, but not dose-relatedly, the effect at 0.5 mg/kg not being significantly different from that at 4 mg/kg. Pindolol also reduced MAVF but only significantly at 0.025 and 0.1 mg/kg. Oxprenolol was active at all doses but not dose-relatedly. Acebutolol produced a significant effect 25 min after injection (Figure 2). Comparison of the effects of each drug showed that 0.025 mg/kg pindolol had the same effect as propranolol at 0.5, 1 and 4 mg/kg, but 0.05 and 0.1 mg/kg pindolol reduced MAVF less after atropine than did propranolol ($P < 0.01$). Oxprenolol (4 mg/kg) reduced MAVF more after atropine than did 0.05 or 0.1 mg/kg pindolol ($P < 0.05$).

After pentobarbitone. Pentobarbitone raised MAVF from 277 ± 27 to 287 ± 10 beats/min. After pentobarbitone, propranolol 1 mg/kg lowered MAVF ($P < 0.01$) (Figure 1).

Effects on blood-pressure

Only propranolol and oxprenolol both at 4 mg/kg i.v.

Table 3 Effects (mean $\pm$ s.e. mean) of propranolol, pindolol, oxprenolol and acebutolol on Wenckebach point in unanaesthetized dogs

			Time (min)							
			n	Control	+ 5	+ 15	+ 25	+ 35	+ 45	+ 55
Propranolol	0.5 mg/kg	6	120 ± 13	109 ± 11 ^a	108 ± 11 ^b	112 ± 12	108 ± 9 ^b	111 ± 6	109 ± 11 ^a	
	1 mg/kg	6	124 ± 13	119 ± 11	119 ± 13	121 ± 13	129 ± 15	133 ± 20	131 ± 18	
	4 mg/kg	7	110 ± 9	172 ± 31 ^c	160 ± 35 ^b	134 ± 28	120 ± 21	108 ± 7	104 ± 15	
Pindolol	0.0125 mg/kg	6	106 ± 9	113 ± 9	119 ± 10	116 ± 7	123 ± 14 ^a	125 ± 10 ^b	122 ± 8 ^a	
	0.025 mg/kg	6	121 ± 14	148 ± 13	159 ± 13	204 ± 41 ^b	217 ± 39 ^c	256 ± 43 ^c	199 ± 33 ^b	
	0.05 mg/kg	6	131 ± 10	158 ± 18	166 ± 20 ^a	156 ± 17 ^c	161 ± 15 ^c	158 ± 6 ^c	194 ± 21 ^c	
	0.1 mg/kg	7	130 ± 15	150 ± 16 ^a	182 ± 18 ^c	191 ± 14 ^c	234 ± 24 ^c	200 ± 13 ^c	191 ± 13 ^c	
	0.2 mg/kg	6	138 ± 7	340 ± 4 ^c	333 ± 5 ^c	337 ± 6 ^c	337 ± 8 ^c	340 ± 8 ^c	340 ± 8 ^c	
Oxprenolol	0.5 mg/kg	7	137 ± 12	197 ± 27 ^c	219 ± 33 ^c	231 ± 28 ^c	224 ± 28 ^c	244 ± 31 ^c	225 ± 30 ^c	
	1 mg/kg	7	133 ± 13	217 ± 22 ^c	219 ± 23 ^c	185 ± 20 ^c	196 ± 26 ^c	190 ± 29 ^b	186 ± 30 ^b	
	2 mg/kg	6	126 ± 8	265 ± 21 ^c	260 ± 26 ^c	236 ± 29 ^c	267 ± 27 ^c	232 ± 33 ^c	235 ± 31 ^c	
	4 mg/kg	6	137 ± 9	278 ± 24 ^c	277 ± 19 ^c	282 ± 21 ^c	287 ± 22 ^c	285 ± 25 ^c	267 ± 29 ^c	
Acebutolol	5 mg/kg	6	93 ± 6	143 ± 21 ^c	123 ± 18 ^b	118 ± 17 ^a	112 ± 12	115 ± 11 ^a	108 ± 10	

The significant difference from the control is denoted by: ^a: $0.01 < P < 0.05$; ^b: $0.001 < P < 0.01$; ^c: $P < 0.001$

Table 4 Effects (mean $\pm$ s.e.mean) of propranolol, pindolol, oxprenolol and acebutolol on maximal auriculo-ventricular frequency in unanaesthetized dogs

			<i>Time (min)</i>							
			n	<i>Control</i>	+ 5	+ 15	+ 25	+ 35	+ 45	+ 55
Propranolol	0.5 mg/kg	6	261 ± 18	226 ± 17 ^c	232 ± 14 ^c	229 ± 13 ^c	224 ± 11	231 ± 14 ^c	225 ± 12 ^c	
	1 mg/kg	6	263 ± 30	227 ± 21 ^c	232 ± 27 ^b	234 ± 24 ^b	235 ± 23	232 ± 23 ^b	232 ± 21 ^b	
	4 mg/kg	7	207 ± 17	204 ± 20	198 ± 23	190 ± 18 ^b	185 ± 18	187 ± 18 ^b	189 ± 20 ^a	
Pindolol	0.0125 mg/kg	6	303 ± 43	297 ± 26	309 ± 34	327 ± 31	319 ± 33	348 ± 34	325 ± 26	
	0.025 mg/kg	6	287 ± 37	301 ± 14	315 ± 10	311 ± 16	330 ± 13 ^a	345 ± 12 ^c	349 ± 13 ^c	
	0.05 mg/kg	6	279 ± 24	271 ± 18	312 ± 16	321 ± 20 ^a	329 ± 21 ^b	331 ± 19 ^b	332 ± 23 ^b	
	0.1 mg/kg	7	255 ± 30	309 ± 11 ^b	331 ± 11 ^c	344 ± 7 ^c	343 ± 13 ^c	341 ± 13 ^c	343 ± 15 ^c	
	0.2 mg/kg	6	361 ± 14	340 ± 4	333 ± 5	337 ± 6	337 ± 8	340 ± 8	340 ± 8	
Oxprenolol	0.5 mg/kg	7	264 ± 16	266 ± 16	266 ± 17	283 ± 13	273 ± 17	282 ± 14	286 ± 14	
	1 mg/kg	7	260 ± 23	287 ± 8	283 ± 7	298 ± 16	298 ± 8 ^a	294 ± 14	286 ± 13	
	2 mg/kg	6	270 ± 31	309 ± 9 ^a	309 ± 8 ^a	308 ± 7 ^a	311 ± 8	312 ± 9 ^a	312 ± 9 ^a	
	4 mg/kg	6	298 ± 28	292 ± 17	288 ± 14	298 ± 11	305 ± 11	306 ± 10	302 ± 12	
Acebutolol	5 mg/kg	6	249 ± 42	267 ± 30	234 ± 34	233 ± 34	231 ± 34	227 ± 30 ^a	233 ± 27	

The significant difference from the control group is denoted by: ^a: 0.01 < P < 0.05; ^b: 0.001 < P < 0.01; ^c: P < 0.001

were found to modify blood-pressure in the unanaesthetized dog. Propranolol (Figure 3) brought about a reduction in systolic pressure from 122 $\pm$ 2 to 105 $\pm$ 8 mmHg (P < 0.001), significantly for 3 min, the effect then wearing off. The observed cardioacceleration is in all likelihood due to this hypotension which lowers the vagal tone. At the same dose, propranolol significantly raised diastolic pressure from the third min onwards.

Oxprenolol lowered systolic pressure from 128 $\pm$ 6 to 113 $\pm$ 1 mmHg (P < 0.001), the effect persisting throughout the experiment. Diastolic pressure also tended to fall, but not significantly.

Discussion

All four β -adrenoceptor blocking drugs used in this study exert membrane stabilizing effects (MSE), propranolol being particularly active in this respect (Singh, 1973). All of them except propranolol also exhibit intrinsic sympathomimetic activity (ISA). In spinalized rats the activities of pindolol and oxprenolol are about 56%, and 29% that of isoprenaline respectively. The extent to which MSE and ISA modify AV conduction could thus be examined.

The relative β -adrenoceptor blocking potencies of the four drugs are propranolol: 1; oxprenolol: 1

Table 5 MAVF effects (mean $\pm$ s.e.mean) of propranolol, pindolol and oxprenolol after atropine on maximal auriculoventricular frequency in unanaesthetized dogs

			Time (min)						
n			Control	+ 5	+ 15	+ 25	+ 35	+ 45	+ 55
Propranolol	0.5 mg/kg	6	342 ± 13	289 ± 15 ^c	287 ± 15 ^c	287 ± 15 ^c	286 ± 11 ^c	280 ± 8 ^c	285 ± 9 ^c
	1 mg/kg	6	406 ± 11	318 ± 12 ^c	320 ± 8 ^c	316 ± 6 ^c	314 ± 6 ^c	313 ± 5 ^c	317 ± 8 ^c
	4 mg/kg	6	350 ± 27	273 ± 16 ^c	278 ± 16 ^c	277 ± 13 ^c	283 ± 15 ^c	290 ± 16 ^c	263 ± 26 ^c
Pindolol	0.025 mg/kg	6	315 ± 24	290 ± 27	285 ± 26 ^a	275 ± 28 ^c	270 ± 27 ^c	271 ± 31 ^c	289 ± 29
	0.05 mg/kg	6	331 ± 16	321 ± 13	324 ± 14	324 ± 14	327 ± 14	326 ± 12	330 ± 12
	0.1 mg/kg	6	338 ± 15	316 ± 10 ^c	315 ± 11 ^c	316 ± 12 ^c	320 ± 12 ^c	322 ± 13 ^c	323 ± 11 ^c
Oxprenolol	0.5 mg/kg	6	365 ± 15	333 ± 9 ^c	330 ± 9 ^c	333 ± 8 ^c	335 ± 8 ^b	333 ± 8 ^c	330 ± 7 ^c
	1 mg/kg	6	350 ± 17	307 ± 12 ^c	315 ± 9 ^c	322 ± 10 ^c	318 ± 9 ^c	315 ± 11 ^c	315 ± 11 ^c
	2 mg/kg	6	358 ± 22	320 ± 13 ^c	313 ± 11 ^c	323 ± 13 ^c	315 ± 11 ^c	320 ± 15 ^c	320 ± 16 ^c
	4 mg/kg	6	373 ± 17	302 ± 15 ^c	312 ± 12 ^c	315 ± 13 ^c	310 ± 12 ^c	322 ± 10 ^c	322 ± 9 ^c

Atropine (0.150 mg/kg i.v.) was injected 20 min before the β -adrenoceptor blocking drugs. Four control times were observed during this period. Control time value reported in the Table is the last of these four control times. At this time, β -adrenoceptor blocking drugs were injected i.v. Then six experimental times were observed from + 5 min to + 60 min.

The significant difference from the control group is denoted by: ^a: 0.01 < P < 0.05; ^b: 0.001 < P < 0.01; ^c: P < 0.001

Figure 2 A representative experiment showing the effect of administering of acebutolol to unanaesthetized dogs after atropine. Results are expressed as means $\pm$ s.e. mean. The number of dogs was 6. Atropine (0.150 mg/kg i.v.) was injected at time zero, and acebutolol (5 mg/kg i.v.) was administered 20 min later. After atropine, heart rate (HR) and maximal auriculoventricular frequency (MAVF) increase significantly. After acebutolol, HR and MAVF decrease significantly. The significant difference between the atropine group and acebutolol group is each time denoted by: * ($P < 0.05$); *** ($P < 0.001$).

(Barrett & Carter, 1970); pindolol: 16 (Giudicelli *et al.*, 1969), acebutolol: 0.3 (Cuthbert & Owusu-Ankhomah, 1971).

Under our experimental conditions, 0.5 and 1 mg/kg propranolol modified HR and WP only slightly and inconsistently. This result is consistent with those of Wallace *et al.* (1966) who after injecting 0.2 mg/kg propranolol in three unanaesthetized dogs instrumented 4–12 weeks previously, found that the AH interval remained unchanged.

However, in the unanaesthetized dog using telemetric ECG recording, 2.5 mg/kg propranolol does not significantly alter HR which remains at about

70 beats/min (Duchêne-Marullaz *et al.*, 1967). Bergamaschi *et al.* (1971), with dogs habituated to ECG recording obtained similar results with 0.04, 0.2 and 1 mg/kg propranolol. Thus, when not under anaesthesia, the resting dog in contrast to men, evidently possesses no tonic adrenergic influence which might be suppressed by β -adrenoceptor blocking drugs. Indeed, no difference in telemetrically recorded HR was found between resting dogs after bilateral thoracic, sympathectomy, and control dogs during one nycthemeron (Duchêne-Marullaz *et al.*, 1963). At 4 mg/kg propranolol paradoxically raised HR and WP doubtlessly due to a lowering of blood-pressure induced by the high dose and the resulting fall in vagal tone. After atropine, propranolol lowered HR and MAVF to the same extent at 0.5, 1 and 4 mg/kg.

However, our results differ in particular from those of Fitzgerald & Wale (1971), Priola *et al.* (1973), Giudicelli *et al.* (1975), and Jaillon *et al.* (1978) who observed HR reduction and increase in junctional effective refractory period of up to 40% in dogs under pentobarbitone anaesthesia. Most of the authors consider that the β -adrenoceptor blocking action of propranolol is on its own sufficient to explain these effects. Thus Fitzgerald & Wale (1971) found no effect in dogs previously given syrosingopine. However, Priola *et al.* (1973) found that even after complete β -adrenoceptor blockade with practolol, propranolol was still able to lengthen AV conduction time, and so inferred that the drug exerts a direct depressant action upon the junctional region.

The differences found between our results and those obtained in the anaesthetized dog are evidently, attributable to the effect of pentobarbitone – the anaesthetic always used in the experiments referred to above. The adrenergic stimulation resulting from acute surgical intervention may in most cases be an additional factor. It is well-known that pentobarbitone produces an immediate tachycardia which falls off partially in about 15 min but remains significant.

Figure 3 Electrocardiogram (lead I and lead II) and arterial pressure (AP) modifications caused by injection of propranolol (4 mg/kg i.v.) in unanaesthetized dogs. Systolic and diastolic pressure decrease from 145 and 95 mmHg to 105 and 85 mmHg at 3 min after the injection ($t = 0$ min). Heart rate increases from 70 beats/min to 95 beats/min after 3 min.

ant for over 2 h after injection (Nash *et al.*, 1956; Barlow & Knott, 1964; Manders & Vatner, 1976). This effect has generally been explained in terms of a certain vagolytic potency (Schafer *et al.*, 1930; Olmstead & Page, 1966) though more recently (Manders & Vatner, 1976) by an adaptation of barosensitive reflexes. Our results are consistent with those generally reported. Nevertheless, our results do not enable an MSE to be detected for propranolol at the doses used. This effect had, however, been reported at much higher doses than those used here (Coltart *et al.*, 1971).

Pindolol, oxprenolol and acebutolol produced significant cardioacceleration at all doses. The effect was somewhat delayed with pindolol, which gave a maximum increase in HR after 35 min. Oxprenolol and acebutolol acted more rapidly and their effect wore off gradually. This difference can be attributed to a metabolite of pindolol, not present in man, which possesses large ISA (Buckingham *et al.*, 1977). Effects on WP were comparable. Pindolol raised WP at all doses, both the intensity and the onset of the effect being dose-related. At 0.2 mg/kg the ISA effect was so marked that the WP point was eliminated. Both oxprenolol and acebutolol also facilitated AV conduction.

In the dog after atropine, β -adrenoceptor blocking activity and ISA compete. β -adrenoceptor blocking activity generally dominated as far as HR was concerned, but for pindolol at high doses, the two activities tended to balance out in their effects on AV conduction.

In experiments in man, involving measurement of HR, WP, AH interval and functional refractory period in the junctional region, lower i.v. doses of

β -adrenoceptor blocking drugs have generally been used than here. 0.1 mg/kg propranolol (Berkowitz *et al.*, 1969; Seides *et al.*, 1974), 0.01 mg/kg pindolol (Di Biase *et al.*, 1977a) 0.1 mg/kg oxprenolol (Di Biase *et al.*, 1977b), 0.5 mg/kg (Touboul *et al.*, 1975) or 1 mg/kg acebutolol (Mason, 1978). Overall results are consistent; variations lie in the ranges; 7–13% for HR, 8–13% for AH, 7–13% for WP and 7–14% for junctional FRP. At the doses used, no difference is detectable between propranolol (devoid of ISA) and pindolol (large ISA).

It is evident that experimental conditions such as anaesthesia under pentobarbitone, and operatory shock heighten the effects of β -adrenoceptor blocking drugs upon both HR and AV conduction. In man, the same may be true of cardiological examinations, which can produce slight anxiety with concomitant adrenergic stimulation. The rather slight effects observed in man may be explained by the suppression by β -adrenoceptor blocking drugs of such factors of adrenergic overactivity. The experimental conditions used in the present work seem to be able to reduce spurious adrenergic effects very considerably.

All dogs showed a marked cholinergic tone and the technique of atrial pacing at progressively increasing frequency allowed finding two stages of AV permeability (WP and MAVF). The level of these two stages in each dog was subordinate to the respiratory-related changes of the cholinergic tone. Individual variations of the MAVF were much greater than those of the WP so some inconsistency appeared in the data between WP and MAVF. So measurement of the WP can be used to study the effect of drugs on AV conduction in unanaesthetized dogs.

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