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The effects of the combined administration of β-adrenoceptor antagonists and non-steroidal anti-inflammatory drugs on ligation-induced arrhythmias in rats

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1 Pretreatment of anaesthetized rats with intravenously administered β-adrenoceptor antagonists or non-steroidal anti-inflammatory drugs (NSAIDs) reduced the incidence and severity of ventricular arrhythmia which resulted from acute coronary artery ligation.

2 The β-adrenoceptor antagonists preferentially suppressed the immediate (Phase 1A) arrhythmia while the NSAIDs suppressed the delayed (Phase 1B) arrhythmias.

3 Combined administration of β-adrenoceptor antagonists and the NSAIDs produced a more pronounced antiarrhythmic effect than either of the drugs alone.

Introduction

β-Adrenoceptor blockade has been shown to reduce the severity of arrhythmia caused by myocardial ischaemia (Grayson *et al.*, 1968; Khan *et al.*, 1972; Klomer *et al.*, 1977). Similarly, the non-steroidal anti-inflammatory drug (NSAID), aspirin, has been shown to decrease ventricular arrhythmia following acute myocardial ischaemia in dogs and rats (Coker *et al.*, 1981; Fagbemi, 1984). While the β-adrenoceptor blocking drugs suppress the immediate (Phase 1A) arrhythmia (Parratt *et al.*, 1981), the salicylates are more effective in suppressing the delayed (Phase 1B) arrhythmia.

This investigation examines the influence of simultaneous administration of these two classes of drugs on arrhythmias in coronary artery ligated rats.

Methods

The experiments were performed on male Sprague-Dawley rats (250–300 g). Anaesthesia was induced with pentobarbitone (60 mg kg^{-1}). The trachea, right femoral vein and left common carotid artery were cannulated for artificial respiration, drug administration and measurement of blood pressure, respectively. Carotid artery pressure and a standard lead II electrocardiogram (ECG) were recorded using a Devices F-132 physiopolygraph. The method of inducing coronary artery occlusion and evaluation of the subsequent arrhythmia has already been described in detail (Clark *et al.*, 1980; Fagbemi & Parratt, 1981).

Statistics

All values are expressed as mean values ± standard error of the mean (s.e.mean) and the number of animals (n) used in each group was as stated in the Tables. The unpaired Student's t test was used for comparisons between separate groups of data. A P value of less than 0.05 was the criterion for statistical significance. The χ^2 test was used for evaluating the difference between the incidence of events (ventricular fibrillation or mortality).

Drugs

The drugs utilized in this study were propranolol (ICI), practolol (ICI), (±)-oxprenolol (Ciba), aspirin (BDH), sodium meclofenamate (BDH) and indomethacin (BDH). All drugs were dissolved in saline (0.9% w/v NaCl) except the NSAIDs which were dissolved in 2% sodium bicarbonate. Control (drug solvent) studies were performed alongside each drug study. All drugs were administered as intravenous bolus injections 15 min before ligation.

Table 1 Haemodynamic changes induced by β-adrenoceptor antagonists and prostaglandin synthesis inhibitors in anaesthetized rats

Drug	*Dose* (mg kg^{-1})	n	*Heart rate* (beats min^{-1}) *Pre-drug*	*Post-drug*	*Mean arterial blood pressure* (mmHg) *Pre-drug*	*Post-drug*
Propranolol	0.5	10	484 ± 12	466 ± 11	104.0 ± 4.0	111.4 ± 5.6
	1.0	10	486 ± 8	422 ± 8*	102.7 ± 4.1	88.4 ± 5.0
	5.0	10	464 ± 15	382 ± 14*	99.2 ± 5.0	78.3 ± 3.6*
Oxprenolol	0.5	10	488 ± 12	476 ± 12	97.4 ± 5.0	95.6 ± 5.0
	1.0	10	468 ± 11	440 ± 14	96.0 ± 6.2	98.0 ± 4.0
	5.0	10	497 ± 15	423 ± 18*	100.0 ± 4.3	81.2 ± 3.0*
Practolol	1.0	8	466 ± 11	452 ± 11	94.0 ± 7.2	92.2 ± 5.6
	5.0	9	459 ± 9	400 ± 10*	103.2 ± 4.7	108.6 ± 4.7
Aspirin	1.0	8	488 ± 12	469 ± 12	102.0 ± 6.0	100.7 ± 5.3
	3.0	8	439 ± 18	455 ± 16	95.0 ± 4.0	103.4 ± 4.4
Sodium meclofenamate	1.0	8	456 ± 8	462 ± 14	92.0 ± 7.1	95.6 ± 6.6
	3.0	9	448 ± 16	428 ± 18	98.0 ± 5.0	118.2 ± 4.2*
Aspirin + oxprenolol	1.0 + 0.5	10	460 ± 12	432 ± 11	107.9 ± 6.1	98.1 ± 6.0
Aspirin + oxprenolol	1.0 + 1.0	10	476 ± 16	426 ± 12*	102.5 ± 3.6	109.3 ± 4.2
Sodium meclofenamate + practolol	1.0 + 0.5	10	470 ± 9	481 + 10	108.6 ± 5.6	114.4 ± 5.8
Sodium meclofenamate + practolol	1.0 + 1.0	10	426 ± 18	444 ± 12	111.4 ± 4.2	94.7 ± 5.0*

* $P < 0.05$, significantly different from pre-drug (control) value.

Table 2 The effect of β-adrenoceptor antagonists and prostaglandin synthesis inhibitors on distribution of arrhythmias resulting from acute ischaemia in the anaesthetized rat

Drug	*Dose* (mg kg^{-1})	*Ventricular ectopic beats after ligation* *0–15 min (Phase 1A)*	*16–30 min (Phase 1B)*	*Total*	n
Control	-	907 ± 195	430 ± 74	1337 ± 269	30
Propranolol	0.5	667 ± 148	332 ± 54	989 ± 202	10
	1.0	200 ± 41*	266 ± 56	466 ± 97*	10
	5.0	92 ± 34*	212 ± 67*	304 ± 101*	10
Practolol	0.5	714 ± 127	300 ± 159	1014 ± 286	10
	1.0	444 ± 93*	340 ± 91	784 ± 184*	8
	5.0	120 ± 68*	286 ± 156	406 ± 224	9
Oxprenolol	0.5	635 ± 242	311 ± 62	946 ± 304	10
	1.0	319 ± 152*	369 ± 88*	688 ± 240	10
	5.0	146 ± 117*	160 ± 55*	306 ± 172*	10
Aspirin	1.0	487 ± 205	126 ± 60*	613 ± 265	8
	3.0	316 ± 162*	104 ± 22*	420 ± 184*	8
Sodium meclofenamate	1.0	546 ± 178	208 ± 94*	754 ± 272	8
	3.0	388 ± 83*	99 ± 29*	487 ± 112*	9

* $P < 0.05$, significantly different from control value.

Results

Haemodynamic changes

In the control group (animals which received isotonic saline or solvent), the mean systemic arterial blood pressure was 106 ± 5.0 mmHg (range 82 to 121) and the heart rate 488 ± 14 beats min^{-1} (range 420 to 524). The haemodynamic effects of preligation administration of β-adrenoceptor antagonists or prostaglandin synthesis inhibitors or a combination of these two classes of drug are summarized in Table 1. All the β-adrenoceptor blockers used in this study significantly reduced the heart rate and mean arterial blood pressure. The intravenous administration of aspirin (1 mg kg^{-1}) or sodium meclofenamate (1 mg kg^{-1}) had no significant effect on the blood pressure or heart rate. However, sodium meclofenamate (3 mg kg^{-1}) caused an initial rise in blood pressure which returned to the pretreatment level before ligation. The combination of β-adrenoceptor blockers with any of the prostaglandin synthesis inhibitors did not significantly alter the haemodynamic response to individual drugs.

Effects of β-adrenoceptor antagonists or prostaglandin synthesis inhibitors on early arrhythmias resulting from acute myocardial ischaemia in rats

In the control group of rats, occlusion of the main left coronary artery resulted in marked arrhythmias most of which occurred within 5–20 min. These arrhythmias included ventricular tachycardia (VT) and ventricular fibrillation (VF). All the control animals developed VT within Phase 1A while 60% developed VF during this period (Table 3). Pretreatment with propranolol, practolol and oxprenolol produced a dose-related decrease in ventricular ectopic arrhythmias (Table 2). These results are in agreement with previous studies (Parratt *et al.*, 1981; Campbell & Parratt, 1983). The reduction in ventricular arrhythmias is particularly evident on comparing the duration of ventricular fibrillation (VF) as well as the degree of mortality with the control (Table 3).

As previously reported (Menken *et al.*, 1979; Parratt, 1981), these β-adrenoceptor blockers preferentially suppressed the immediate (Phase 1A) arrhythmias (those occurring between 0–15 min).

Aspirin and sodium meclofenamate significantly reduced the total number of ventricular ectopic beats as well as the duration and incidence of VT and VF (Table 3). Unlike the β-adrenoceptor blockers, the prostaglandin synthesis inhibitors were more effective in suppressing the delayed (15–30 min) arrhythmias. A similar finding has been observed previously (Fagbemi, 1984).

Effect of combined administration of β-adrenoceptor blockers and prostaglandin synthesis inhibitors on ventricular ectopic beats

The simultaneous administration of NSAIDs and β-adrenoceptor blockers produced a significant reduction in the total number of ventricular extrasystoles and an almost complete abolition of VF (Table 4). This antiarrhythmic effect was noticeable at doses (0.5 mg kg^{-1}) of each drug which had no effect when used alone.

Table 3 The effect of β-adrenoceptor antagonists or prostaglandin synthesis inhibitors on early post-infarction arrhythmias in anaesthetized rats

Drug	*Dose* (mg kg^{-1})	n	*Duration of VT* (s)	*VF* (s)	*% incidence of VT during* Phase 1A	Phase 1B	*% incidence of VF during* Phase 1A	Phase 1B	*% mortality*
Control	-	30	83.6 ± 6.4	55.7 ± 5.3	100	20	60	10	30
Propranolol	0.5	10	77.1 ± 9.1	40.0 ± 6.7	90	20	40**	10	20
	1.0	10	36.2 ± 6.4	0	40***	10	0***	0*	0***
	5.0	10	54.4 ± 9.6*	0	30***	0*	0***	0*	0***
Practolol	0.5	10	73.8 ± 5.0	49.4 ± 6.2	100	30	50	20	30
	1.0	8	56.0 ± 11.6*	23.6 ± 5.3*	88	20	38**	13	30
	5.0	9	28.3 ± 6.4*	14.3 ± 7.1*	67**	33	22***	0*	10***
Oxprenolol	0.5	10	51.4 ± 11.2*	38.1 ± 6.6*	100	40	40**	20	30
	1.0	10	68.2 ± 12.0	33.4 ± 6.8*	80	20	30***	20	0***
	5.0	10	22.6 ± 7.1*	12.1 ± 4.3*	40***	10	20***	0*	0***
Aspirin	1.0	8	34.3 ± 4.1*	26.1 ± 5.2*	63**	10	38**	0*	0***
	3.0	8	28.6 ± 6.7*	9.0 ± 3.6*	50**	0*	13***	0*	0***
Sodium meclofenamate	1.0	8	45.3 ± 6.6*	40.0 ± 5.1	88	38	50	0*	0***
	3.0	9	32.0 ± 5.8*	19.0 ± 3.0*	56**	11	22***	0*	0***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; significantly different from control value.
VT: ventricular tachycardia, VF: ventricular fibrillation

Table 4 Effect of combined prostaglandin synthesis inhibitors and β-adrenoceptor antagonists on early arrhythmias resulting from acute myocardial ischaemia in anaesthetized rats

Drug	*Dose* ($mg\,kg^{-1}$)	*Total number of ectopic beats*	*Duration of VT (s)*	*Duration of VF (s)*	*% incidence of VT*	*% incidence of VF*	*% mortality*	n
Control	–	1337 ± 269	83.6 ± 6.4	55.7 ± 5.3	100	60	30	30
Practolol + sodium meclofenamate	0.5 + 0.5	430 ± 144*	48.8 ± 5.3*	27.0 ± 4.1*	60***	30***	10***	10
Practolol + sodium meclofenamate	1.0 + 1.0	353 ± 204*	17.5 ± 4.5*	0*	50***	0***	0***	10
Aspirin + oxprenolol	1.0 + 0.5	408 ± 147*	21.7 ± 3.7*	8.4 ± 3.7*	50***	30***	0***	10
Aspirin + oxprenolol	1.0 + 1.0	332 ± 196*	18.7 ± 2.6*	0*	60***	0***	0***	10

* $P<0.05$, ** $P<0.01$, *** $P<0.001$; significantly different from control value.
VT: ventricular tachycardia, VF: ventricular fibrillation.

Discussion

These experiments were set up in order to determine whether additional benefit accrues from combining β-adrenoceptor blockers with NSAIDs in the treatment of cardiac arrhythmias. The results with β-adrenoceptor blocking drugs in general support previous studies. Practolol ($5\,mg\,kg^{-1}$) and oxprenolol (1 and $5\,mg\,kg^{-1}$) significantly reduced ($P<.05$) the incidence and duration of ventricular fibrillation. Propranolol (1 and $5\,mg\,kg^{-1}$) prevented ventricular fibrillation. Other β-adrenoceptor blockers have also been shown to be protective in the dog, cat, rat and man (Grayson *et al.*, 1968; Reimer *et al.*, 1973; Jennings & Reimer, 1979; Khan *et al.*, 1972; 1973; Campbell & Parratt, 1983). This protective effect has been shown to be dose-related and due solely to β-adrenoceptor blockade since the L-isomers were more effective than the D-isomers (Parratt *et al.*, 1983).

There are several ways by which β-adrenoceptor blockers could minimize the extent of the ischaemic arrhythmia and cardiac necrosis resulting from coronary occlusion. Some of these are a reduction of myocardial oxygen consumption, improvement in the delivery of oxygen by decreasing the affinity of haemoglobin for oxygen (Pendleton *et al.*, 1972), better distribution of coronary flow and enhanced substrate utilization.

The antiarrhythmic effect of the NSAIDs, aspirin and sodium meclofenamate, observed in this study agrees with earlier findings on the antiarrhythmic efficacy of this class of drugs (Haft *et al.*, 1972; Kraikitpanitch *et al.*, 1976; Coker *et al.*, 1981; Fagbemi, 1984). Their antiarrhythmic action has been shown to be due probably to the preferential blockage of platelet cyclo-oxygenase and hence generation of thromboxane A_2 (Smith & Willis, 1971; Coker & Parratt, 1981). Blockade of thromboxane synthesis and the uninhibited production of prostacyclin may possibly allow the latter to exert its vasodilator, platelet anti-aggregating and therefore antiarrhythmic effect (Coker & Parratt, 1981). In support of this view is the observation of Hanley *et al.* (1982) that 40 mg aspirin taken every 48 h consistently reduces platelet thromboxane A_2 synthesis to a level at which it failed to support platelet aggregation while producing only a short lasting effect on vein wall prostacylin production.

This study demonstrates that the simultaneous administration of β-adrenoceptor blockers and aspirin-like drugs produces a more pronounced antiarrhythmic effect than either of the drugs alone (practolol 1 mg + aspirin $1\,mg\,kg^{-1}$). The combination of both drugs permits a reduced dose of β-adrenoceptor blocker to be used without a reduction in the antiarrhythmic efficacy.

The additional antiarrhythmic effect may be due to a much more pronounced platelet anti-aggregating effect. β-Adrenoceptor blockers have been shown to inhibit the platelet aggregation due to adenosine diphosphate, adrenaline, isoprenaline, fibrinogen, thrombin and arachidonic acid (Haft *et al.*, 1973; Mehta *et al.*, 1978; Keber *et al.*, 1979; Campbell *et al.*, 1981). This decreased platelet aggregation has been

attributed to a direct action of the drugs on the platelet membrane and not to β-adrenoceptor blockade (Thomas, 1967; Weksler *et al.*, 1977). Whatever the mechanism responsible for the pronounced antiarrhythmic effect, the results suggest that beneficial responses can be obtained from the combined use of β-adrenoceptor blockers and aspirin-like drugs in the treatment of the early and frequently fatal ventricular arrhythmia resulting from acute myocardial ischaemia.

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