The effect of β-adrenoceptor blocking agents, with differing ancillary properties, on the arrhythmias resulting from acute coronary artery ligation in anaesthetized rats

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1 The effects of several β-adrenoceptor blocking agents, ((+), (−) and (±)-oxprenolol, *p*-oxprenolol, practolol, propranolol and timolol) were investigated on the ventricular arrhythmias occurring within the first 30 min of acutely ligating the main left coronary artery in anaesthetized rats. The degree of cardiac and vascular β-adrenoceptor blockade was also assessed.

2 All the compounds exhibited antiarrhythmic activity under these conditions. The degree of cardiac β-adrenoceptor blockade required for this protection was less for the cardioselective agents, *p*-oxprenolol and practolol, than for the non-selective β-adrenoceptor blocking agents.

3 A comparison of the two isomers of oxprenolol demonstrated that the (−)-isomer markedly suppressed ischaemic arrhythmias (ventricular ectopic beats, incidence and duration of ventricular tachycardia and duration of ventricular fibrillation) more effectively than the (+)-isomer.

4 Compounds possessing intrinsic sympathomimetic activity (ISA) caused less marked haemodynamic changes (in equivalent β-blocking doses) than those that did not possess this ancillary property.

5 The membrane stabilizing activity of oxprenolol and *p*-oxprenolol did not appear to contribute to the antiarrhythmic activity of these agents; however, the membrane stabilizing activity of propranolol may contribute to its effectiveness.

6 In all the drugs studied, the main pharmacological property required to suppress early postischaemic arrhythmias is blockade of cardiac β-adrenoceptors.

Introduction

Sudden cardiac death due to acute myocardial ischaemia is associated with marked rhythm disturbances and more than 50% of deaths occurring in the first few hours after the onset of symptoms result from ventricular fibrillation (Pantridge, Adgey, Geddes & Webb, 1975; Julian, 1976). There is increasing experimental and clinical evidence that overactivity of the autonomic nervous system is implicated in the genesis of the early arrhythmias that occur as a result of acute myocardial ischaemia (Corr & Gillis, 1978). Although the evidence is not conclusive, some experimental studies show that, following coronary artery ligation, there is enhanced activity in both afferent and efferent cardiac sympathetic nerves (Gillis, 1971; Thoren, 1972; Karlsberg, Penkoske, Cryer,

Corr & Roberts, 1979; Bosnjak, Zuperku, Coon & Kampine, 1979; Malliani, 1982). There is also evidence from surgical and pharmacological denervation experiments that the sympathetic nervous system is involved in the genesis of these arrhythmias (Sethi, Haider, Ahmed, Oldewurtel & Regan, 1973; Fomliss, Sang, Lundy, Ahuja & Colhoun, 1974).

Findings such as these have led to the extensive experimental use of β-adrenoceptor blocking agents to elucidate the processes associated with arrhythmogenesis during myocardial ischaemia (reviewed by Fitzgerald, 1982) and to reduce the ultimate severity of myocardial ischaemic damage. However, some β-adrenoceptor blocking agents are 'cardioselective', some may possess intrinsic sympathomimetic activity (ISA; or partial agonist activity) and others also inhibit the fast sodium current in cardiac fibres ('membrane stabilizing activity'). The aim of this

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study was to investigate the effects of various β-adrenoceptor blocking agents against the serious, early arrhythmias occurring following myocardial ischaemia in an attempt to elucidate whether these ancillary properties contribute to the antiarrhythmic activity of β-adrenoceptor blocking agents in this particular situation. An account of some of the preliminary results has been given to the British Pharmacological Society (Campbell & Parratt, 1981).

Methods

Coronary artery ligation in anaesthetized rats

Anaesthesia was induced in male Sprague-Dawley rats, weighing between 200 and 350 g, with pentobarbitone sodium (Sagatal) $60 \, mg \, kg^{-1}$ intraperitoneally. Anaesthesia was maintained throughout the experimental period by further (3 mg) intravenous injections of pentobarbitone sodium as required. Following anaesthesia, a cannula was inserted into the aorta via the right carotid artery for arterial blood pressure recording using a capacitance transducer (Elema-Schönander, type EMT 35). A second cannula was inserted into the inferior vena cava via the right femoral vein for drug administration. The trachea was intubated and a thermocouple inserted into the rectum for the measurement of body temperature. The electrocardiogram was recorded using standard limb leads. Arterial blood pressure and the ECG were monitored continuously on an oscilloscope (Racal Instruments Ltd) and recorded using a Mingograph 81 ink-jet recorder (Elema-Schönander, Stockholm). Heart rate was calculated from the electrocardiogram.

The method used for coronary artery ligation has been described by Clark, Foreman, Kane, McDonald & Parratt (1980). A left thoracotomy was performed at the fourth or fifth intercostal space and the animal artificially respired by means of a Palmer small animal respiration pump. The stroke volume was $2 \, ml \, 100 \, g^{-1}$ body wt. and the rate $54 \, strokes \, min^{-1}$. The pericardium was opened to allow access to the heart, which was exteriorized by gentle, downward pressure on the sternum. A6/0 (metric 0.7) braided silk suture attached to a 10 mm reverse cutting needle (Ethicon 812) was passed through the myocardium and under the left main coronary artery at a point close to its origin. The heart was repositioned within the thorax and the animal allowed to stabilize for 15 min. Any animal that showed a sustained fall in mean arterial blood pressure to less than 70 mmHg, or that developed arrhythmias during this period, was discarded at this point. After the stabilization period the ligature was tied and the arterial blood pressure and electrocardiogram recorded for at least 30 min.

Assessment of post-ligation arrhythmias

Rats subjected to the above procedure exhibit two distinct periods of arrhythmic activity; an early phase lasting for up to 30 min and a second, delayed phase beginning approximately 90 min post-ligation. In this study only those ventricular arrhythmias occurring within the first 30 min of the onset of ischaemia were assessed. The total number of ventricular ectopic beats over this 30 min observation period were counted; the incidence (%) and duration (s) of ventricular tachycardia (VT; defined as 7 or more consecutive ventricular ectopic beats) and of ventricular fibrillation (VF; which usually reverts to sinus rhythm spontaneously in this species) were also measured.

Assessment of β-adrenoceptor blockade using isoprenaline hydrochloride

Rats were prepared for the measurement of heart rate and arterial blood pressure, as above, and allowed to stabilize for 15 min. At the end of the stabilization period single doses of isoprenaline hydrochloride (0.01 to $1 \, \mu g \, kg^{-1}$) were injected intravenously every 10 min and the resulting increases in heart rate and decreases in diastolic blood pressure recorded. Subsequently, the β-adrenoceptor blocking drug was injected intravenously and further doses of isoprenaline hydrochloride (up to $1 \, mg \, kg^{-1}$) were injected to obtain similar changes in heart rate and diastolic blood pressure to those observed prior to administration of the drug. Four rats were used for each dose of the β-adrenoceptor blocking drug investigated. The results were analysed graphically and the dose-ratios for increases in heart rate and for decreases in diastolic blood pressure were calculated. Shifts in the dose-response curves of heart rate and diastolic blood pressure were taken as indices of the degree of cardiac (β_1) and vascular (β_2)-adrenoceptor blockade respectively. Stock solutions of isoprenaline hydrochloride ($1 \, mg \, ml^{-1}$) were made by dissolving the drug in 0.9%w/v NaCl solution containing $10^{-5} \, M$ ascorbic acid.

Statistical analysis

Data are expressed as mean ± standard error of the mean (s.e.mean). Statistical significance of differences between mean values was calculated using Student's t test and a level of $P < 0.05$ was considered significant. For evaluating the differences between the incidence of ventricular tachycardia, ventricular fibrillation and mortality a Chi-squared test was used.

Table 1   A summary of the main and relevant ancillary properties of the drugs used in the present study

	Potency[†]	Cardio selectivity	Intrinsic sympathomimetic action	'Membrane stabilizing activity'
(±)-Oxprenolol	2	—	+	+
(−)-Oxprenolol	4	—	+	− (?)
(+)-Oxprenolol	0	—	−	+ +
p-Oxprenolol	2	+	+ +	+ +
Practolol	0.3	+	+	—
Propranolol	1	—	—	+ +
Timolol	2	—	—	+

[†]Relative to propranolol and on myocardial β_1-adrenoceptors; this of course depends on the species, tissue and conditions. These approximate potencies were largely derived from the present studies in anaesthetized rats. *A negative value (−) for 'membrane stabilizing activity' is not meant to imply that a higher doses there is no effect whatsoever on the fast sodium channel.

Drugs used

(±)-Oxprenolol and its isomers and p-oxprenolol (Vaughan Williams, Bagwell & Singh, 1973) were gifts from Ciba Laboratories, Horsham. Propranolol and practolol were gifts from I.C.I. and timolol was kindly provided by Dr Warren Cooper of Merck, Sharp & Dohme. Table 1 summarizes the various ancillary properties of these drugs. All were dissolved in (0.9% w/v NaCl solution) saline and given 15 min before coronary artery ligation by way of a femoral vein.

Results

Effect of β-adrenoceptor blocking agents on the arrhythmias resulting from acute coronary artery ligation

The effects of (±)-oxprenolol, its optical isomers and its substituted derivative on the arrhythmias resulting from acute coronary artery ligation are given in Table 2. (+)-Oxprenolol (1 mg kg^{-1}), the isomer which is virtually devoid of β-adrenoceptor blocking activity, significantly reduced the incidence of ventricular fibrillation from 69 to 23% ($P < 0.05$) but had no effect on VT or on the ventricular ectopic activity. In contrast (−)-oxprenolol at the same dose significantly reduced the number of ventricular ectopic beats (from 1081 ± 147 to 324 ± 124; $P < 0.05$), the incidence of ventricular tachycardia from 100 to 28% ($P < 0.01$) and the incidence of ventricular fibrillation from 69 to 28% ($P < 0.05$). Racemic oxprenolol caused dose-related decreases in all of these arrhythmic parameters with (in doses of 2 mg kg^{-1} and above) a significant reduction in the number of ventricular ectopic beats, the duration of VT and the incidence of VF. Further increasing the dose to

5 mg kg^{-1} oxprenolol resulted in an even greater antiarrhythmic effect (Table 2).

In a dose of 0.5 mg kg^{-1} the cardioselective p-oxprenolol reduced VT, the number of VEB's and totally prevented ventricular fibrillation. Increasing the dose to 1 mg kg^{-1} resulted in even more pronounced activity (e.g. a reduction in the number of ventricular ectopic beats and in the duration of VT; $P < 0.01$). Practolol (1.0 mg kg^{-1}) did not influence ischaemic arrhythmias whereas increasing the dose to 5 mg kg^{-1} significantly reduced ($P < 0.01$) the number of VEB's and the incidence of VF (Table 3). Table 3 also presents the results with two β-adrenoceptor blocking agents, propranolol and timolol which do not possess cardioselectivity. Propranolol, in doses of 2 or 5 mg kg^{-1}, significantly reduced the number of VEBs ($P < 0.01$), the incidence of VT ($P < 0.001$) and totally prevented VF. Timolol reduced all the arrhythmic parameters although only the reduction in the number of VEBs with the higher dose achieved statistical significance.

Haemodynamic effects of β-adrenoceptor blocking agents

The effects of the β-adrenoceptor blocking agents (in the doses studied against ischaemia-induced arrhythmias) on heart rate and mean arterial blood pressure are presented in Tables 4 and 5. (+)-Oxprenolol (1 mg kg^{-1}) had no effect on either heart rate or mean arterial blood pressure. In contrast, (−)-oxprenolol (1 mg kg^{-1}) caused a significant and sustained reduction in heart rate and a transient decrease in mean arterial blood pressure; pressure had returned to pre-treatment levels by 15 min i.e. at the time when ischaemia was induced. With the exception of those drugs with partial agonist activity, all the β-blockers significantly reduced heart rate in a dose-related manner (e.g. oxprenolol, Table 4); only oxprenolol

Table 2 The effect of (±)-oxprenolol, its two optical isomers and its para-substituted derivative, on the severity and incidence of the arrhythmias resulting from acute coronary artery ligation in anaesthetized rats

	n	Ventricular ectopic beats†	Ventricular tachycardia duration (s);	incidence (%)	Ventricular fibrillation duration (s);	incidence (%)	Mortality (%)
Control	32	1081 ± 147	72 ± 13	100	75 ± 26	69	16
(+)-Oxprenolol (1 mg kg⁻¹)	9	986 ± 178	61 ± 17	100	58 ± 43	23*	0
(−)-Oxprenolol (1 mg kg⁻¹)	9	324 ± 124*	35 ± 2	28**	0	28*	28
(±)-Oxprenolol (1 mg kg⁻¹)	11	964 ± 278	65 ± 27	91	37 ± 16	45	0
(±)-Oxprenolol (2 mg kg⁻¹)	10	374 ± 100**	15 ± 7*	90	14 ± 13	27*	0
(±)-Oxprenolol (5 mg kg⁻¹)	8	278 ± 71**	12 ± 5**	38	7	13**	0
p-Oxprenolol (0.5 mg kg⁻¹)	8	623 ± 293	59 ± 40	63	0	0***	0
p-Oxprenolol (1 mg kg⁻¹)	9	238 ± 115**	15 ± 9*	88	0	11**	11

The drugs were given 15 min before the onset of ischaemia. The values for ectopic beats, and the durations of ventricular tachycardia and fibrillation, refer to those rats that survived the 30 min period.
Values are expressed as mean ± s.e.mean. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ in comparison with control (saline-treated) group.
†Total number of ventricular ectopic beats occurring within the first 30 min of the onset of ischaemia i.e. 'early arrhythmia'.

Table 3 The effect of practolol, propranolol and timolol on the severity and incidence of ventricular arrhythmias resulting from acute coronary artery ligation in anaesthetized rats.

	n	Ventricular ectopic beats	Ventricular tachycardia duration (s);	incidence (%)	Ventricular fibrillation duration (s);	incidence (%)	Mortality (%)
Control	32	1081 ± 147	72 ± 13	100	75 ± 26	69	16
Practolol (1 mg kg⁻¹)	13	1153 ± 272	82 ± 23	100	65 ± 30	46	23
Practolol (5 mg kg⁻¹)	9	270 ± 120**	22 ± 13*	71	86	22**	22
Propranolol (2 mg kg⁻¹)	7	182 ± 62**	13 ± 6**	43***	0	0**	0
Propranolol (5 mg kg⁻¹)	9	337 ± 67**	72 ± 54	33***	0	0***	0
Timolol (1 mg kg⁻¹)	10	832 ± 312	70 ± 29	80	8 ± 3	30	0
Timolol (2 mg kg⁻¹)	10	483 ± 168*	24 ± 13	89	74 ± 71	30	10

The drugs were given 15 min before the onset of ischaemia. The values for ectopic beats, and the durations of ventricular tachycardia and fibrillation, refer to those rats that survived the 30 min period.
Values are expressed as mean ± s.e.mean. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ compared to control (saline-treated) group.

and propranolol lowered arterial pressure. *p*-Oxprenolol (which has pronounced ISA) did not reduce either heart rate or blood pressure in doses that caused a 5–33-fold shift in the cardiac responses to isoprenaline.

Assessment of β-adrenoceptor blockade

Tables 4 and 5 also present values obtained for the shift in the isoprenaline dose-response curves induced by the various β-adrenoceptor blocking agents used. Changes in heart rate (tachycardia) were used to assess β_1 (myocardial) responses and changes in diastolic blood pressure (vasodilatation) to assess changes in β_2-adrenoceptor reactivity. (+)-Oxprenolol shifted both the cardiac and vascular dose-response curves by a factor of 5, whereas (−)-oxprenolol (in the same dose) did so by a factor of 70; thus virtually all of the β-adrenoceptor blocking activity resides in the (−)-isomer. Oxprenolol inhibited cardiac (β_1) and vascular (β_2)-adrenoceptors to the same extent whereas propranolol had a more marked effect on vascular than on myocardial β-adrenoceptors. *p*-Oxprenolol, and the lower dose of practolol, preferentially blocked cardiac β-adrenoceptors.

Discussion

This investigation was designed to examine the effects of various β-adrenoceptor blocking agents on the arrhythmias induced by coronary artery ligation with a view to determining whether the ancillary properties of these drugs (intrinsic sympathomimetic activity, membrane stabilizing activity, cardioselectivity) contribute to their antiarrhythmic activity in acute myocardial ischaemia.

Relevance of β-adrenoceptor blockade

The results presented in this study, using oxprenolol (and its two constituent isomers), *p*-oxprenolol, practolol, propranolol and timolol as examples of β-adrenoceptor blocking agents with differing ancillary properties, indicate that blockade of cardiac β-adrenoceptors is the most important property relevant to the antiarrhythmic effect.

The evidence for this is: (a) the (−)-isomer of oxprenolol markedly suppressed the incidence of ventricular ectopic activity, the incidence and duration of VT and the incidence of fibrillation. In the same dose (+)-oxprenolol had no effect on ventricular ectopic activity or on VT, although it did decrease the incidence of fibrillation to the same extent as the (−)-isomer (Table 2). The effects of (±)-oxprenolol on ectopic activity and VT (Table 2) can therefore be accounted for by β-adrenoceptor blockade.

(b) Increasing the dose of each of the β-blocking drugs usually increased antiarrhythmic activity, whether assessed by a reduction in VEBs, VT or in VF (e.g. oxprenolol in Table 2) and resulted in a more pronounced degree of β-adrenoceptor blockade, as indicated by a greater displacement to the right of isoprenaline dose-response curves (Table 4).

These results should not be taken as implying that 'membrane stabilizing activity' is completely unimportant for antiarrhythmic efficacy in ischaemic conditions; this is discussed further below. However it does suggest that the main property involved is the ability of these drugs to suppress ventricular ectopic activity and that this is related to their capacity for blocking (myocardial) β-adrenoceptors.

Relevance of intrinsic sympathomimetic activity

Three of the drugs used in this study (oxprenolol, *p*-oxprenolol and practolol) had some degree of partial agonist activity. This was particularly evident with *p*-oxprenolol; even in doses that caused more than a 30 fold shift to the right of isoprenaline dose-response curves, there was no effect on resting heart rate (Table 4). This compares with oxprenolol (in a dose of 1 mg kg^{-1}) which caused a similar degree of myocardial (β_1) adrenoceptor blockade (Table 4) yet reduced resting heart rate by more than 50 beats min^{-1} (Table 4) and with propranolol (2 mg kg^{-1}) which resulted in only a slightly greater degree of β-blockade yet which also reduced resting heart rate by more than 50 beats/min (Table 5).

The question has often been raised as to whether or not intrinsic sympathomimetic activity is useful under conditions of myocardial ischaemia. Certainly, it has been argued that this is a useful property rather later in the progression of ischaemia. Thus, Marshall & Parratt (1976; 1977) compared, in anaesthetized greyhounds, the ability of several β-adrenoceptor blocking drugs to maintain myocardial blood flow in developing infarcts and to reverse lactate production in the ischaemic region. They found that it was only those drugs (practolol, H 87/07 and oxprenolol) with some degree of intrinsic sympathomimetic activity that maintained blood flow.

When β-adrenoceptor blocking drugs are given very early after the onset of ischaemia, as in the recent clinical studies of Sleight, Yusuf, Peto, Rossi, Ramsdale, Bennett, Bray & Furse (1981) and of Hjalmarson (1981), it is conceivable that ISA might be a useful ancillary property since the possibility of inducing myocardial depression should be less with such compounds. The present studies indicate that *p*-oxprenolol, in doses that had no effect on resting heart rate, markedly suppressed early arrhythmic activity (Table 2). There was thus no evidence that possession of ISA attenuated antiarrhythmic activity

Table 4   Changes in heart rate (beats min^{-1}) and in mean systemic arterial blood pressure (mmHg) induced by oxprenolol in anaesthetized rats.

Drug	Dose (mg kg^{-1})	n	Heart rate		Degree of β$_1$-blockade	Mean arterial blood pressure		Degree of β$_2$-blockade
			Pre-	Post-drug		Pre-	Post-drug	
(±)-Oxprenolol	1.0	11	461±20	406±15***	30	99±7	0100±7	30
(±)-Oxprenolol	2.0	10	458±17	394±17**	80	100±6	87±3*	80
(±)-Oxprenolol	5.0	8	439±14	356±21***	800	96±6	76±3*	800
(+)-Oxprenolol	1.0	9	421±17	416±9	5	92±5	99±6	5
(−)-Oxprenolol	1.0	9	413±22	376±18*	70	84±6	82±4	70
p-Oxprenolol	0.5	8	434±12	428±11	5	89±3	98±6	0
p-Oxprenolol	1.0	9	458±16	451±13	33	97±6	94±6	0

Values after drug administration were those recorded 15 min after intravenous injection. Also given (in parentheses) is the mean shift in isoprenaline log-dose response curves for β$_1$-adrenoceptor mediated responses (tachycardia) and β$_2$-adrenoceptor mediated responses (vasodilatation). Values are means ± s.e.mean. *$P < 0.01$; **$P < 0.01$; ***$P < 0.001$

Table 5   Changes in heart rate (beats min^{-1}) and in mean systemic arterial blood (mmHg) induced by β-adrenoceptor blocking drugs in anaesthetized rats.

Drug	Dose (mg kg^{-1})	n	Heart rate		Degree of β$_1$-blockade	Mean arterial blood pressure		Degree of β$_2$-blockade
			Pre-	Post-drug		Pre-	Post-drug	
Practolol	1.0	10	461±11	435±17	14	86±8	82±6	0
Practolol	5.0	9	424±9	404±12*	16	94±7	103±7	12
Propranolol	2.0	7	417±8	364±12***	45	84±4	70±3*	450
Propranolol	5.0	9	434±15	336±14***	400	97±7	71±1***	2000
Timolol	1.0	10	407±11	382±15*	50	94±7	91±6	†
Timolol	2.0	10	399±8	374±16**	55	99±5	90±5*	†

Values after drug administration were those recorded 15 min after intravenous injection. Also given is the mean shift in isoprenaline log-dose response curves for β$_1$-adrenoceptor mediated responses (tachycardia) and β$_2$-adrenoceptor mediated responses (vasodilatation). Values are mean ± s.e.mean. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. †Results not determined; dose-response curves after timolol were not parallel.

early in ischaemia, at least as assessed from the number of ectopic beats and from the duration and incidence of VT and VF. The mortality data are more difficult to evaluate, simply because so few animals died. It is possible that spontaneous reversal of VF is less common after treatment with β-blockers with ISA (e.g. practolol, Table 3).

One other study, which compared the efficacy of practolol and propranolol in anaesthetized dogs, showed that practolol was much the more effective (Pearle, Williford & Gillis, 1978). Indeed, in this particular study six out of seven of the dogs given propranolol (or saline) died after coronary artery ligation; in the practolol group only one of seven dogs died. Since the drug was given in equivalent (cardiac) β-blocking doses, one suggested explanation for this marked difference was the possession, by practolol, of ISA.

Relevance of 'membrane stabilizing activity'

The ability to inhibit the rapid Na^+ current in cardiac muscle is one major property responsible for antiarrhythmic activity (class 1 in Vaughan Williams classification; Vaughan Williams, 1970) and such drugs are, in general, effective against early ischaemic arrhythmias (reviewed by Marshall & Winslow, 1982). For example, lignocaine and the aminosteroid Org 6001 are effective in the anaesthetized rat model used in the present studies (Kane, McDonald & Parratt, 1979; Clark et al., 1980). A number of β-adrenoceptor blocking drugs have this particular ancillary property (Morales-Aguilera & Vaughan Williams, 1965; Vaughan Williams, 1977) including several of those used in the present study (Table 1). The question is whether this additional property contributes to the undoubted effectiveness of these β-blocking drugs against early ischaemic arrhythmias.

Perhaps the best information from the present experiments comes from the use of the (+) and (−)-isomers of oxprenolol (Table 2). If we assume that, as with propranolol (Barrett & Cullum, 1968), the (+) and (−)-isomers have similar 'membrane stabilizing activity' but that the (−)-isomer is considerably more active as a β-blocker (Table 4 shows that in this species the (−)-isomer is about 14 times more active than the (+)-isomer), then the results with (+)-oxprenolol show that a class 1 action contributes to the efficacy of this compound in reducing the incidence of fibrillation (Table 2). Certainly no animal so treated died in the early stages of infarction. It is also possible that the considerable 'membrane stabilizing activity' of propranolol contributes to the complete abolition of fibrillation observed in these experiments (Table 3). Studies in the same model with compounds solely possessing class 1 activity

(lignocaine, Org 6001) also lends support to the conclusion that this particular property is responsible for anti-fibrillatory activity under ischaemic conditions (Kane et al., 1979; Clark et al., 1980).

Relevance of cardioselectivity

It was, on reflection, rather unfortunate that both of the available drugs with some degree of cardioselectivity (p-oxprenolol, practolol) also had some degree of intrinsic sympathomimetic activity. The paper by Vaughan Williams et al. (1973) was important in drawing attention to the role of para substitution in providing some degree of cardioselectivity. They showed that p-oxprenolol (in contrast to oxprenolol itself) caused no blockade of the vascular ($β_2$) effects of isoprenaline whereas blockade of the myocardial ($β_1$) effects of isoprenaline was comparable with that of oxprenolol. The present results, albeit in a different species, agree precisely with this (Table 4). Thus both (±)-oxprenolol and (±)-p-oxprenolol, in the same dose ($1.0\ mg\ kg^{-1}$) caused a 30 fold shift in the myocardial responses to isoprenaline. However, whereas with oxprenolol the shift in the vascular ($β_2$) responses was similar to this, p-oxprenolol did not modify isoprenaline-induced vasodilatation at all. Since p-oxprenolol was as effective as oxprenolol in suppressing early ischaemic arrhythmias (Table 2) one can reasonably conclude that it is an ability to block myocardial $β_1$-adrenoceptors that is important for this protection; the studies also confirm an important role for endogenous catecholamines in the genesis of these arrhythmias. In the clinical situation cardioselectivity would clearly be of value in those patients where blockade of $β_2$-adrenoceptors (e.g. in the bronchioles and in the coronary circulation) might be detrimental. This might be of some importance in respect to blood flow changes in the ischaemic myocardium where the unmasking of an α-adrenoceptor-mediated localized vasoconstriction would appear to be less likely to occur in the presence of drugs preferentially active in blocking $β_1$-adrenoceptors. This possibility has recently been discussed in detail (Parratt, 1980).

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