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THE SELECTIVITY OF THE β-ADRENOCEPTOR FOR VENTILATION IN MAN

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1 Minute ventilation, alveolar P_{CO_2}, CO_2 production and heart rate were measured in eight normal subjects before and during infusions of noradrenaline 0.2, 1.0 and 5.0 μg min^{-1} and isoprenaline 0.04, 0.2 and 1.0 μg min^{-1}.

2 These measurements were repeated after propranolol 3.5 mg, atenolol 8 mg or metoprolol 7 mg by intravenous injection.

3 Noradrenaline 5.0 μg min^{-1} and isoprenaline 1.0 μg min^{-1} significantly increased ventilation and CO_2 production and decreased alveolar P_{CO_2}. These changes were attenuated by propranolol, atenolol and metoprolol. There was no significant difference between the blocking effects of the three β-adrenoceptor blockers for these three variables but propranolol was more effective than atenolol or metoprolol in blocking isoprenaline induced tachycardia ($P < 0.001$).

4 The hyperventilatory response to catecholamines is predominantly a β_1-effect.

Introduction

Isoprenaline, noradrenaline and adrenaline stimulate ventilation in man (Whelan & Young, 1953; Eckstein & Hamilton, 1959; Barcroft *et al.*, 1957) and these ventilatory responses can be blocked by the non-selective β-adrenergic receptor blocking drug, propranolol (Heistad *et al.*, 1972). This study compares the effect of propranolol with the selective β_1-adrenoceptor blocking drugs, atenolol and metoprolol, in reducing catecholamine induced hyperventilation in man.

Methods

Seven healthy men and one woman were studied, of age range 26–38 years. They had normal lung function and were not currently taking drugs. A minimum of a 2 h fast was enforced before the studies. All subjects obtained experience with the apparatus and drugs before entering the trial. The subjects were studied while sitting in a comfortable chair in a quiet room and relaxed by stereophonic music via headphones which excluded extraneous sounds. A venous catheter was inserted into a forearm vein and connected to a concealed syringe pump (Sage 355) for infusion of drugs. A comfortable close fitting face mask (P.Q. oronasal) was connected via the expiratory line to a heated pneumotachograph (Fleisch) from which minute ventilation was determined using a pressure transducer (Elema-Schonander EMT 32C) and integrator. Volumes were corrected to standard temperature and pressure. Expired gases passed from the pneumotachograph to a mixing chamber, from which mixed expired P_{CO_2} was measured by an infra-red capnograph (Godart). A line inside the face mask enabled continuous sampling of expired gas by an infra-red capnograph and thus determination of end-tidal P_{CO_2}. The volume of expired gas removed by the capnograph was constant throughout each study and the expiratory minute volume was corrected to include this volume. Changes in end-tidal P_{CO_2} have been shown to accurately reflect changes in arterial P_{CO_2}, although simultaneous values may not be the same (Clark, 1968). This was confirmed in one subject by comparing arterial P_{CO_2} in samples from an indwelling radial catheter with end-tidal P_{CO_2}, over a range of P_{CO_2} from 4 to 6 kPa. Heart rate was counted from an electro-cardiogram. CO_2 production was determined from mixed expired CO_2 concentration and minute ventilation.

The subjects breathed room air and were allowed a minimum of 10 min to reach a steady state before measurements were made. Noradrenaline was infused at doses of 0.2, 1.0 and 5.0 μg min^{-1}, each for 3 min and in ascending order of magnitude. Isoprenaline was infused at doses of 0.04, 0.2 and 1.0 μg min^{-1},

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each for 3 min and in ascending order. Three minutes were allowed between the dose levels of each catecholamine and 5 min between the different catecholamines in order to allow the variables to return to control levels. Measurements were made for the 2 min prior to each infusion and during the second and third minutes of infusion at each dose level.

The infusions and measurements were repeated after an intravenous injection of either propranolol 3.5 mg (Inderal, ICI), atenolol 8 mg (Tenormin, ICI) or metoprolol 7 mg (Lopresor, Ciba-Geigy). The three β-adrenoceptor blocking drugs were tested in each subject at the same time of day but on separate days. The order of infusion of the two catecholamines prior to the β-adrenoceptor blocking drug was randomised and this order repeated after β-adrenoceptor blockade. The order of the β-adrenoceptor blocking drugs was also randomised. The subjects were unaware of the experimental design and of when infusions commenced.

Statistical comparisons were made by analysis of variance.

Results

Both isoprenaline 1.0 μg min^{-1} and noradrenaline 5.0 μg min^{-1} significantly increased ventilation with an associated fall in P_{CO_2} and a rise in CO_2 production (Tables 1 and 2). Isoprenaline 0.04 and 0.2 μg min^{-1} and noradrenaline 0.2 and 1.0 μg min^{-1} did not significantly change mean minute ventilation, Pa_{CO_2} or CO_2 production. We will therefore only consider the effect of β-adrenoceptor blockers on changes due to isoprenaline 1.0 μg min^{-1} and noradrenaline 5.0 μg min^{-1}. Propranolol, atenolol and metoprolol attenuated the heart rate response to infused isoprenaline by 96, 47 and 28% respectively.

All catecholamine induced changes in mean minute ventilation, Pa_{CO_2} and CO_2 production were reduced by all three β-adrenoceptor blockers (Table 3). There was no significant difference between the three β-adrenoceptor blockers in reducing catecholamine induced changes in ventilation, Pa_{CO_2} or CO_2 production but propranolol was more effective than atenolol or metoprolol in blocking isoprenaline induced tachycardia ($P < 0.001$, Table 3).

Measurements made prior to catecholamine infusions were compared before and after β-adrenoceptor blockade. β-adrenoceptor blockade reduced the heart rate by 13%. Minute ventilation and CO_2 production were reduced by 4% (Table 4).

Discussion

These studies indicate that the selective β_1-adrenoceptor blocking drugs atenolol and metoprolol are as

Table 1 Analysis of variance of responses to noradrenaline and isoprenaline before and during β-adrenoceptor blockade.

Source of variation	*% sum of squares*	P
Heart rate		
Subjects	29.0	<0.001
β-adrenoceptor blockers	4.6	<0.001
Subject/β-adrenoceptor blocker interaction	12.8	<0.001
Catecholamines	23.6	<0.001
Residual	8.6	
Minute ventilation		
Subjects	14.2	<0.001
β-adrenoceptor blockers	6.6	<0.001
Subject/β-adrenoceptor blocker interaction	38.3	<0.001
Catecholamines	0.9	<0.001
Residual	35.5	
Alveolar P_{CO_2}		
Subjects	41.4	<0.001
β-adrenoceptor blockers	13.1	<0.001
Subject/β-adrenoceptor blocker interaction	29.5	<0.001
Catecholamines	0.1	<0.025
Residual	13.9	
CO_2 production		
Subjects	37.8	<0.001
β-adrenoceptor blockers	13.5	<0.001
Subject/β-adrenoceptor blocker interaction	32.1	<0.001
Catecholamines	0.4	<0.001
Residual	12.1	

Table 2 Effect of noradrenaline and isoprenaline (mean ± s.e. mean, $n = 24$).

	Noradrenaline (μg min^{-1})			*Isoprenaline* (μg min^{-1})		
	0.2	*1.0*	*5.0*	*0.04*	*0.2*	*1.0*
Heart rate (beats min^{-1})	−0.32 ± 0.95	−1.94 ± 0.90*	−6.98 ± 0.97***	=1.75 ± 1.06*	1.37 ± 0.78	7.58 ± 1.14***
Minute ventilation (l min^{-1})	−0.44 ± 0.14	0.33 ± 0.16	1.71 ± 0.30***	−0.12 ± 0.18	0.19 ± 0.18	1.83 ± 0.19***
Alveolar P_{CO_2} (kPa)	0.06 ± 0.04	−0.07 ± 0.05	−0.11 ± 0.07	−0.05 ± 0.03	0.04 ± 0.03	−0.11 ± 0.07
CO_2 production (mmol min^{-1})	−5.0 ± 4.9	2.3 ± 7.4	27.7 ± 7.6***	−6.7 ± 9.1	6.1 ± 7.8	43.4 ± 11.0***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

effective as the non-selective propranolol in attenuating catecholamine induced increases in ventilation. Although there is no general agreement on the relative potency of the three β-adrenoceptor blocking drugs used, in our experiment propranolol was more effective than atenolol and metoprolol in blocking isoprenaline induced tachycardia, a measure of β_1-adrenoceptor blocking activity. Thus our findings that the β-adrenoceptor blockers were equi-effective in reducing catecholamine induced hyperventilation is unlikely to be due to the selection of doses of atenolol and metoprolol with greater β-adrenoceptor blocking activity than the chosen dose of propranolol. Indeed, we may have chosen less effective doses of the selective β-adrenoceptor blockers.

Cunningham *et al.* (1962) showed that the higher the Pa_{O_2} the smaller is the effect of noradrenaline on ventilation. It therefore appears that catecholamines activate oxygen sensitive chemoreceptors in man. Brain concentrations of lipophilic β-adrenoceptor blockers e.g. propranolol and metoprolol are high and of hydrophilic β-adrenoceptor blockers e.g. atenolol low (brain/plasma ratios of 26, 12 and 0.2 respectively) (Cruickshank *et al.*, 1980). Our studies therefore also suggest that catecholamine induced hyperventilation is a peripheral effect. Heistad *et al.* (1972) showed that propranolol blocks the hyperventilatory response to catecholamines but not to hypoxia and suggested that the activation of chemoreceptors by catecholamines is dependent on a mechanism involving β-adrenergic receptors. Our results suggest that these are predominantly β_1-adrenoceptors.

There was a 4% fall in minute ventilation during β-adrenoceptor blockade in our subjects. β-adrenoceptor blockers might reduce ventilation either indirectly by reducing metabolic rate or directly by an effect on the chemoreceptors. Gibson (1976) reviewed the evidence on metabolic rate and concluded that there is a 3–4% reduction with β-adrenoceptor blockers in conventional dose. The 4% reduction in CO_2 production in our subjects supports his findings. The small rise in alveolar P_{CO_2} (0.06 kPa) suggests that a change in ventilatory drive also occurred.

Dyspnoea due to hyperventilation e.g. in emphysema and anxiety states might be alleviated by β-adrenoceptor blockers. Because of the greater risk of inducing airflow obstruction with propranolol than with atenolol or metoprolol, β_1-adrenoceptor blockers would be more suitable for trials in these conditions.

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Table 3 The effect of atenolol, metoprolol and propranolol on the changes induced by isoprenaline and noradrenaline.

	Isoprenaline[1]		*Noradrenaline*[1]	
	Minute ventilation			
β-adrenoceptor blocker	*Reduction in ventilation (l min^{-1})*	t^2	*Reduction in ventilation (l min^{-1})*	t^2
Atenolol	1.51	0.4	2.45	1.88
Metoprolol	0.73	0.65	1.85	1.06
Propranolol	1.21		1.07	
	Heart rate			
β-adrenoceptor blocker	*Reduction in heart rate (beats min^{-1})*	t^2	*Increase in heart rate (beats min^{-1})*	t^2
Atenolol	2.65	4.52***	2.25	0.74
Metoprolol	1.06	5.66***	1.38	1.37
Propranolol	8.81		3.26	
	Alveolar P_{CO_2}			
β-adrenoceptor blocker	*Increase in Pa_{CO_2} (kPa)*	t^2	*Increase in Pa_{CO_2} (kPa)*	t^2
Atenolol	0.07	0.20	0.19	1.86
Metoprolol	0.02	0.29	0.16	1.67
Propranolol	0.05		0.01	
	CO_2 production			
β-adrenoceptor blocker	*Reduction in CO_2 production (mmol min^{-1})*	t_2	*Reduction in CO_2 production (mmol min^{-1})*	t_2
Atenolol	29.0	0.80	27.2	1.12
Metoprolol	21.3	1.47	39.3	2.18*
Propranolol	38.1		14.5	

[1] This column represents the difference between the changes induced by isoprenaline (1 μg min^{-1}) or noradrenaline (5 μg min^{-1}) before the specified β-adrenoceptor blocker (Table 2) and the catecholamine induced changes in the presence of that β-adrenoceptor blocker.
[2] Values of Student's *t*-test for comparison with propranolol.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$
All other *t*-values are not significant. There was no significant difference between atenolol and metoprolol for all variables.

Table 4 Effect of β-adrenoceptor blockers.

	Heart rate (beats min^{-1})	*Minute ventilation (l min^{-1})*	*Alveolar P_{CO_2} (kPa)*	*CO_2 production (mmol/min)*
Before β-adrenoceptor blockers	74.9	10.40	4.97	219
After β-adrenoceptor blockers	65.1	9.95	5.03	211
Effect of β-adrenoceptor blockers	−9.8***	−0.45*	0.06*	−8**

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