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EFFECTS OF LABETALOL AND PROPRANOLOL ON HISTAMINE-INDUCED BRONCHOCONSTRICTION IN NORMAL SUBJECTS

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1 The effects of oral propranolol (80 mg), labetalol (400 mg) and placebo on blood pressure, pulse rate and FEV_1 at rest and after inhaled histamine, have been compared in six healthy male volunteers.

2 At 90 and 120 min after ingestion propranolol reduced the pulse rate and labetalol reduced the blood pressure, thus confirming absorption of each drug.

3 At 120 min propranolol reduced resting FEV_1 and enhanced the fall in FEV_1 after histamine, whereas the alterations in FEV_1 after labetalol did not differ from placebo.

4 These findings suggest that labetalol is less likely than propranolol to cause bronchoconstriction in asthmatic patients.

Introduction

β-adrenoceptor blocking agents have been used for a number of years for the treatment of angina pectoris, arterial hypertension and cardiac arrhythmias. One of the complications of this treatment is the development of bronchoconstriction in asthmatic patients (McNeill, 1964). Attempts have been made to avoid precipitating bronchoconstriction by developing compounds which produce blockade of the cardiac β_1-adrenoceptors, but which have less effect upon β_2-receptors of the bronchial smooth muscle (Macdonald & McNeill, 1968). Compounds in this category include practolol, metoprolol (Ablad, Borg, Carlsson, Ek, Johnsson, Malmfors & Regardh, 1975) and possibly acebutalol (Skinner, Palmer & Kerridge, 1975).

Labetalol hydrochloride is a drug which has recently been developed for the treatment of hypertension. It is similar to propranolol in blocking both β_1- and β_2-receptors (Farmer, Kennedy, Levy & Marshall, 1972). In addition, it possesses significant α-adrenoceptor blocking activity in animals (Farmer *et al.*, 1972) and man (Richards, Tuckman & Prichard, 1976). α-adrenoceptors in the human lung may be important in the pathogenesis of bronchoconstriction in some asthmatic patients and α-adrenoceptor blocking drugs have been shown to prevent the bronchoconstriction produced by α-adrenoceptor stimulant drugs (Anthracite, Vachon & Knapp, 1971). It is possible therefore that the additional α-adrenoceptor blocking property of labetalol may cause it to differ from propranolol in its effect on ventilatory function. It has already been shown that intravenous labetalol differs from propranolol in its effects on ventilatory function in asthmatics (Skinner, Gaddie & Palmer, 1975) and it seems reasonable to expect a similar difference after oral administration of the drug. The inhalation of histamine or methacholine is associated with a decrease in ventilatory function in asthmatics (Townley, Dennis & Itkin, 1964) and some normal subjects (Griffin & Turner, 1971). Although normal subjects are less sensitive their responses are more reproducible. The administration of propranolol to asthmatics increases their sensitivity to methacholine (Zaid & Beall, 1966). It seemed possible that a similar increase in sensitivity might occur in normal subjects who are sensitive to histamine and we therefore decided to use this method to compare propranolol and labetalol. The dose of each was chosen on the basis of approximately equivalent myocardial β-adrenoceptor blocking doses (Richards, 1976) and the histamine inhalations were delivered 2 h after drug administration to coincide with anticipated peak pharmacological effects with both drugs (Aellig, 1976; Richards, Woodings, Stephens & Maconochie, 1974).

Methods

Six non-asthmatic male subjects of mean age 28.5 years (range 23-38 years) were included in the study. Subjects were selected on the basis that after inhalation of histamine the subject's FEV_1 was reduced consistently by a mean of at least 0.25 litres. The mean reduction was calculated from the difference between five readings of FEV_1 taken at 1 min intervals immediately before inhalation of histamine and five similar readings immediately afterwards. Four of the subjects (Nos. 2, 3, 4 and 6) had histories of seasonal allergic rhinitis; one (no. 1) had a family history of asthma and the remaining subject (No. 5) had no history of allergic disease. One subject (No. 3) smoked approximately 15 cigarettes daily. The study was conducted during the mid and late autumn in order to avoid seasonal allergic influences in the susceptible subjects.

Histamine administration

Histamine was administered through a semi-open system (Kingsley, personal communication). Oxygen was delivered at 10 litres/min through 6 ml of histamine acid phosphate solution in a standard 28 ml BOC bottle and nebulizer. Subjects inhaled for 3 s, held their breath for 3 s and exhaled for 3 s guided by a 60 s clock timer marked off in 3 s intervals. This 9 s cycle was repeated for 2 min whilst the subject wore a nose clip. The solution (0.6 ml) was nebulized over the 2 min period so that each subject inhaled approximately 0.2 ml. The concentration of histamine solution varied between individuals but was constant for any subject throughout the experiment. The estimated total dose of histamine inhaled ranged from 600 μg to 2000 μg (mean 1433 μg). All subjects were trained in the procedure before entering the trial.

Study

Each subject attended on three mornings having had only light breakfasts. They rested in the 45° semi-recumbent position except when recording FEV_1 or inhaling histamine. During the latter procedures they sat upright on the side of the couch. Arterial blood pressure was measured by the same investigator throughout the experiment using a Hawksley Random Zero sphygmomanometer. Radial pulse rate was taken by palpation and forced expiratory volume in 1 s (FEV_1) was recorded using a Vitalograph spirometer.

Pulse rate and blood pressure were recorded until they were steady and then five readings of FEV_1 were taken at minute intervals. The subjects then received a single oral dose of either propranolol (80 mg), labetalol (400 mg) or placebo. The order in which each subject took the drugs was randomized, and double-blind conditions were maintained by packing the tablets in rice paper cachets. After drug administration pulse and blood pressure were recorded for 2 h at 30 min intervals. At 2 h five FEV_1 readings were taken at minute intervals before and after inhalation of histamine.

All data from this study were subjected to statistical analysis using Student's *t*-test for paired values.

Results

Effect upon FEV_1

Pretreatment, pre-histamine and post-histamine mean FEV_1 values for each subject and the group

Table 1 The effects of placebo, labetalol (400 mg) and propranolol (80 mg) on resting FEV_1 and FEV_1 after histamine in six subjects

	FEV_1 (litres)								
Subject number	Placebo			Labetalol (400 mg)			Propranolol (80 mg)		
	Pr.T.	P.H.	Po.H.	Pr.T.	P.H.	Po.H.	Pr.T.	P.H.	Po.H.
1	4.28	4.09	3.97	4.29	4.16	3.99	4.24	4.08	3.94
2	2.86	2.88	2.43	2.80	2.79	2.36	2.86	2.69	2.01
3	3.62	3.65	2.43	3.60	3.58	2.63	3.81	3.65	2.53
4	4.34	4.45	4.26	4.42	4.50	4.15	4.46	4.31	3.88
5	4.14	4.04	3.84	4.19	4.14	4.23	4.21	4.10	3.84
6	4.52	4.50	4.26	4.38	4.48	3.99	4.38	4.24	3.34
Mean	3.96	3.93	3.53	3.95	3.94	3.56	3.99	3.84	3.26
s.e. mean	0.24	0.26	0.35	0.28	0.27	0.33	0.25	0.26	0.32

Pr.T. pretreatment; P.H. pre-histamine; Po.H. post-histamine.

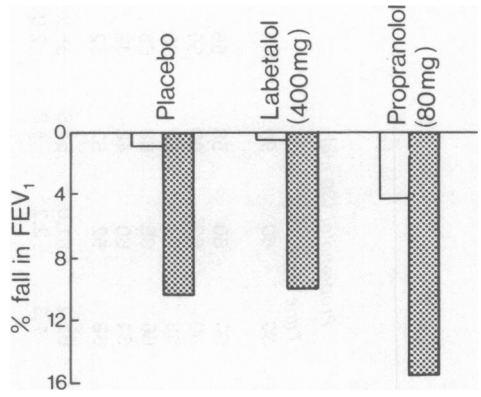

Figure 1 The effects of labetalol (400 mg), propranolol (80 mg) and placebo on the FEV_1 before (□) and after (▣) inhaled histamine.

mean values were compared (Table 1). There was little variation in the individual or group mean values for pretreatment FEV_1; group mean FEV_1 ranging from 3.95-3.99 litres.

The group mean pre-histamine FEV_1 values were lower than the pretreatment values, the reduction after placebo being 30 ml, after labetalol 10 ml and after propranolol 150 ml. This decrease after propranolol was significantly different from placebo and labetalol ($P < 0.01$).

After inhalation of histamine the group mean FEV_1 values were reduced from the pre-histamine values by 400 ml after placebo, 380 ml after labetalol and 580 ml after propranolol. This fall after propranolol was significantly different from labetalol ($P < 0.05$) but not from placebo.

When the post-histamine values were compared with the pretreatment values the reductions in FEV_1 following histamine were 430 ml after placebo, 390 ml after labetalol and 730 ml after propranolol. The fall after propranolol was significantly different from labetalol and placebo ($P < 0.05$).

The differences between the group mean pretreatment and pre-histamine values and between the post-histamine and pre-histamine values are expressed as percentage reductions in FEV_1 in Figure 1.

Effects upon blood pressure and pulse rate

The individual and group mean blood pressure and pulse rate readings are shown in Table 2 and 3. The group mean values for each treatment were compared.

There was little difference between the pretreatment values and similarly between the values at 30 and 60 min after the treatments. However, at 90 and 120 min after labetalol significant reductions ($P < 0.05$) in systolic and diastolic pressure were recorded compared with placebo and propranolol. In respect of pulse rate, at 90 and 120 min after propranolol, significant reductions ($P < 0.01$) were recorded compared with placebo and labetalol. There was no difference between labetalol and placebo.

Discussion

Over the past decade, since McNeill (1964) first described the adverse effects of β-adrenoceptor blocking drugs in asthmatics, the search has gone on for drugs which preserve the valuable therapeutic properties of β-adrenoceptor blocking drugs like propranolol yet avoid those which are undesirable. Macdonald & McNeill (1968) subsequently showed that with practolol there was less bronchoconstriction in asthmatics than with propranolol and that this was probably related to practolol being relatively cardioselective in its β-adrenoceptor antagonism. Practolol enjoyed wide popularity in therapeutics as a result and drugs with similar properties have subsequently been introduced. None of these claim superiority over practolol in respect of cardioselectivity and there remains the concern that when prescribed for asthmatic patients, even these drugs can lead to deterioration in respiratory function (Ablad *et al.*, 1975).

The mechanism of action by which β-adrenoceptor antagonist drugs produce bronchospasm in asthmatics is not completely understood. It has been established that atropine can partially prevent the reduced ventilatory function after propranolol which suggests that at least part of the bronchoconstriction is due to unopposed parasympathetic activity (Gayrard, Orehek & Charpin, 1972). However, the function of α-adrenoceptors in the lung may also be important (Anthracite, Vachon & Knapp, 1971) and it has been shown in asthmatics that α-adrenoceptor blocking drugs can improve ventilatory performance (Bianco, Griffin, Kamburoff & Prime, 1974). It is possible therefore that the combination of α-adrenoceptor antagonism with β-adrenoceptor antagonism could avoid the expected impairment of ventilatory function from β-adrenoceptor blockade alone.

Studying the effects of β-adrenoceptor blocking drugs in asthmatic patients is limited by obvious ethical considerations. Kumana, Marlin, Kaye & Smith (1974) have shown that the cardioselective β-adrenoceptor blocking properties of practolol can be differentiated from the non-selective properties of propranolol by using an exercise procedure in normal healthy subjects. We have

Table 2 The effects of placebo, labetalol (400 mg) and propranolol (80 mg) on arterial blood pressure in six subjects

	Blood pressure (mm Hg)														
	Placebo					*Labetalol (400 mg)*					*Propranolol (80 mg)*				
Subject number	*Time after drug (min)*					*Time after drug (min)*					*Time after drug (min)*				
	Pre-drug	*30*	*60*	*90*	*120*	*Pre-drug*	*30*	*60*	*90*	*120*	*Pre-drug*	*30*	*60*	*90*	*120*
1	116/85	106/86	110/84	112/82	127/70	110/82	108/82	114/74	102/72	104/66	112/87	108/78	108/72	104/76	108/74
2	114/81	106/78	110/78	110/82	104/74	116/76	116/78	108/80	104/72	102/72	121/75	122/78	122/88	118/90	114/92
3	106/62	104/72	106/74	98/64	98/64	113/72	112/72	106/62	100/68	100/66	109/74	102/66	108/70	100/66	96/62
4	123/94	128/96	128/94	122/96	122/96	124/88	117/84	122/96	120/90	110/80	120/84	124/90	118/84	120/84	124/89
5	123/94	118/96	118/96	120/98	128/96	127/96	122/98	118/98	104/84	108/80	117/91	116/82	112/90	116/90	110/84
6	116/81	112/76	114/82	112/80	106/80	118/93	108/84	114/82	106/84	100/78	116/75	108/78	112/82	112/98	106/86
Mean	116/83	113/84	115/84	113/84	111/79	117/84	114/85	113/81	104/77	103/73	116/81	114/79	114/81	112/84	110/82
s.e. mean	2.6/4.2	4.0/4.2	4.5/5.9	4.2/3.8	5.6/3.6	1.5/3.0	4.5/4.1	6.1/5.1	4.0/1.5	1.2/2.0	2.0/3.0	4.2/0.7	5.0/3.4	2.0/4.7	0.5/2.5

Table 3 The effects of placebo, labetalol (400 mg) and propranolol (80 mg) on pulse rate in six subjects

	Pulse rate (beats/min)														
	Placebo					*Labetalol (400 mg)*					*Propranolol (80 mg)*				
Subject number	*Time after drug (min)*					*Time after drug (min)*					*Time after drug (min)*				
	Pre-drug	*30*	*60*	*90*	*120*	*Pre-drug*	*30*	*60*	*90*	*120*	*Pre-drug*	*30*	*60*	*90*	*120*
1	68	66	68	62	62	68	66	64	66	68	65	60	60	58	56
2	70	60	60	60	60	60	60	58	56	54	60	60	62	60	50
3	68	64	64	60	62	74	70	72	72	70	74	68	64	60	60
4	72	72	70	68	72	73	68	64	66	68	70	66	68	68	66
5	70	64	68	68	62	64	60	58	60	58	72	64	60	48	48
6	64	60	64	60	60	60	60	62	62	62	61	58	52	52	52
Mean	68.7	64.3	65.7	63.0	63.0	66.5	64.0	63.0	63.7	63.3	67.0	62.7	61.0	57.6	55.3
s.e. mean	0.57	2.0	3.9	1.6	1.8	2.5	1.9	2.1	2.1	2.8	2.4	1.3	2.2	4.8	2.9

confirmed that rigorous exercise after oral propranolol can lead to deterioration in ventilatory function in normal healthy males whereas neither labetalol nor placebo produce such effects (Richards *et al.*, 1974; Richards, Woodings & Maconochie, 1976).

In this study, in non-asthmatic subjects inhalation of histamine caused a reduction in ventilatory function as measured by FEV_1. In addition, after a single dose of propranolol (80 mg) there was a significant reduction in FEV_1 at rest and an enhancement of the fall in FEV_1 following inhaled histamine. In relation to the therapeutic doses of propranolol, especially those used in the treatment of hypertension, the dose we used in this study was modest. This suggests that even in a non-asthmatic population propranolol may lead to deterioration in ventilatory function. On the other hand, oral labetalol 400 mg, had no effect on the resting FEV_1 nor on the fall in FEV_1 after histamine, the values being similar to those after placebo. This absence of effect on ventilatory function is in keeping with the results of Skinner *et al.* (1975) who found that whereas intravenously administered propranolol induced significant reductions in FEV_1 and FVC in asthmatic patients, intravenous labetalol did not. Their dose difference between intravenous labetalol and propranolol was four-fold. In our study the dose difference was five-fold. These differences may indicate a bias in favour of propranolol since it has been shown that in the treatment of hypertension the dose difference between labetalol and propranolol to produce similar antihypertensive effect is approximately two-fold (Beilin, personal communication). The significant reduction in pulse rate induced by propranolol and the reduction in blood pressure induced by labetalol serve to confirm that both drugs were readily absorbed and exerted their expected pharmacological influences on these parameters.

It is clear that labetalol and propranolol differ in their effects in histamine responsive subjects. However, there is no evidence to suggest that labetalol is cardioselective; on the contrary it has been shown that in man the β-adrenoceptor antagonism of infused isoprenaline is non-selective (Richards *et al.*, 1976). This would suggest therefore that differences between propranolol and labetalol are related to labetalol possessing α-adrenoceptor antagonist properties, in addition to those of β-adrenoceptor antagonism. It has been shown, by comparing the antagonism of isoprenaline and phenylephrine induced changes after an oral dose of labetalol (400 mg), that the relative potency $\alpha : \beta$ antagonism is approximately 1 : 3 (Richards *et al.*, 1976). It is possible that the α-adrenoceptor blocking activity of labetalol is sufficient to prevent the bronchoconstriction which would develop from non-selective β-adrenoceptor blockade. The precise mechanisms involved require further study. However, the results of this study suggest that labetalol is less likely than propranolol to cause bronchoconstriction in asthmatic patients.

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