Comparative effects of diltiazem and atenolol on lung function and airway response to methacholine in hypertensive subjects

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1 In this double-blind randomized study, after a 4-weeks placebo period, 18 patients with mild to moderate primary hypertension were assigned to treatment with either diltiazem ($n = 9$) daily or atenolol ($n = 9$) over a period of 3 months.

2 Expiratory flows, lung volumes and airway responsiveness (AR) to methacholine were assessed at the end of the placebo period and after an active treatment of 12 weeks. Blood pressure (BP), heart rate (HR) and ECG were monitored during the methacholine challenges. Twice daily peak expiratory flow rates and respiratory symptoms were recorded on a diary card.

3 No significant effects on ECG, HR and BP were observed after methacholine inhalation. In all but one subjects there was no significant change in expiratory flows, lung volumes or AR throughout the study. Mean FEV₁, FVC, PEFR, FRC and PC₂₀ methacholine were unchanged after 3 months of treatment, and not statistically different between patients on diltiazem or atenolol.

4 One subject, without previous history of asthma, developed transient airflow obstruction 8 weeks after beginning diltiazem.

5 Diltiazem and atenolol have no significant effects on pulmonary function and AR in most subjects with no baseline airflow limitation.

6 Airflow obstruction may develop in normal subjects on diltiazem. Methacholine challenges are safe in subjects with uncomplicated hypertension.

Keywords Diltiazem atenolol β -adrenoceptor blocking agents non allergic airway responsiveness

Introduction

β -adrenoceptor antagonists are used extensively in the treatment of cardiovascular diseases. Unfortunately, this category of medication, even the so-called cardioselective agents, may induce or increase airflow obstruction in asthmatic subjects (Benson *et al.*, 1978; Decalmer *et al.*, 1978; Falliers *et al.*, 1986; Ruffin *et al.*, 1982; Skinner *et al.*, 1976).

Studies of non-asthmatic subjects have shown that β -adrenoceptor antagonists are generally

well tolerated and do not significantly change forced expiratory volume in one second (FEV₁) or specific conductance (SGaw). However, reports have shown slight reductions in expiratory flows and increases in airway resistance in patients with chronic bronchitis (Maconochie *et al.*, 1977; Singh *et al.*, 1976; Tattersfield *et al.*, 1973, 1983).

Airway response to methacholine is markedly increased after infusion of propranolol in asth-

matic subjects (Ryo *et al.*, 1976). Even in asthmatic subjects without bronchoconstrictive effects from propranolol, it has been shown that it could increase airway responsiveness (Carpentiere *et al.*, 1988). In keeping with those observations, non-allergic airway responsiveness is a more sensitive index of the effects of β -adrenoceptor antagonists on airway than expiratory flow measurements, especially in mild asthmatics (Ruffin *et al.*, 1979).

The development of asthma symptoms with β -adrenoceptor antagonists in previously asymptomatic subjects suggests underlying airway hyperresponsiveness. There is however little data on the effects of these drugs on airway responsiveness (AR) to non-specific stimuli in the non-asthmatic range of responsiveness and it is still not possible to predict who will develop airway obstruction on these drugs.

Cardioselective agents are not β_1 specific and so can affect β_2 -adrenoceptors, especially if these are sensitised as they may be in asthmatic patients. Dilevalol is a new antagonist of β_1 -adrenoceptors with β_2 -adrenoceptor-agonist properties in bronchi and in vascular resistance vessels. Its β_2 -adrenoceptor agonist properties may then be potentially useful in subjects with asthma or chronic airflow limitation. Dilevalol has been considered a safe and effective drug in the treatment of hypertension (Soberman *et al.*, 1987; Wallin *et al.*, 1988).

This study was set up to look at the comparative effects of chronic use of dilevalol and atenolol, a selective β_1 -adrenoceptor antagonist without β_2 -adrenoceptor agonist properties, on pulmonary function and AR to methacholine in patients with mild to moderate primary hypertension. We wanted to determine if airway response to methacholine could change following dilevalol or atenolol in subjects without respiratory symptoms and if the β_2 -adrenoceptor agonist properties of dilevalol could influence this response. Finally, the cardiovascular effects of high-dose inhaled methacholine were assessed in these hypertensive patients.

Methods

Subjects

Eighteen patients, nine male and nine female aged 38 to 69 years (mean: 55) volunteered to this study. Five were smokers (two in group A and three in group D), six were ex-smokers (five in group A and one in group D). All had mild to moderate uncomplicated primary hypertension

(seated diastolic pressure 95–110 mm Hg after 4 weeks on placebo). None had clinical evidence of heart failure. Five had a past history of asthma (two in group A and three in group D) but were asymptomatic, on no regular medication, and showed no baseline airflow obstruction at the time of the study. None had used β -adrenoceptor antagonists before. Three were considered atopic (one in group A and two in group D) as shown by at least one positive wheal and flare reaction after testing with a battery of 26 common aeroallergens. Four had a familial history of asthma and four of atopy (Table 1). The study was approved by the local Ethics Committee and all subjects signed an informed consent form before starting the study.

Study design

After inclusion in the study, patients entered a 4 week single-blind placebo period. They were then randomized to a double-blind treatment with a single daily dose of either dilevalol 200 mg ($n = 9$) or atenolol 50 mg ($n = 9$). Active treatment and placebo tablets were identical and patients were not aware of when the treatment was begun. After 4 weeks, the patients who had normalized their seated diastolic blood pressure continued their medication at the same dosage for an additional 10 weeks.

In those who remained hypertensive, dilevalol was increased to 400 mg ($n = 3$) and atenolol to 100 mg ($n = 1$) daily and then continued at this dosage for another 10 weeks. Upon enrolment in the study, patients were seen once every 2 weeks during the placebo period and then monthly.

All subjects came to the laboratory at the end of the placebo period and after 3 months of medication. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), were measured using a Vitalograph spirometer (S-model Cat. no 20–60). Lung volumes were determined by body plethysmography (Dubois *et al.*). All values are given in BTPS. Two baseline methacholine inhalation tests up to a dose of 64 mg ml^{-1} , were performed on the first visit, to verify the repeatability of this measure.

Patients were asked to write daily on a diary card the best of three consecutive peak expiratory flow (PEF) measurements, using a Mini-Wright peak flow meter, on arousal and at bedtime, for the whole duration of the study. During the last week of the placebo period and the 12 weeks on treatment, daily respiratory symptoms of cough and dyspnea were rated on a scale from 0 = nothing to 10 = maximum.

Table 1 Subjects' characteristics

Subject	Sex	Age (years)	Atopic status*	FEV ₁ (l)#		FVC (l)#		FRC (l)#		RV (l)#	
				Baseline	3 months	Baseline	3 months	Baseline	3 months	Baseline	3 months
Dilevalol											
1	M	64	0	2.66	2.37	3.56	3.25	2.84	2.71	2.22	1.66
2	F	56	0	1.57	1.72	2.20	2.55	2.53	2.78	1.48	2.56
3	F	56	0	2.17	2.14	2.63	2.68	ND		ND	
4	M	53	1	3.49	3.58	3.99	4.30	2.65	2.68	2.11	2.06
5	M	66	0	2.01	1.88	2.61	2.36	2.64	3.11	1.84	2.61
6	M	47	0	3.00	2.77	3.38	3.19	2.36	2.00	2.04	1.08
8	F	38	0	2.47	2.74	3.06	3.37	ND		ND	
9	M	66	0	2.45	1.32	3.26	2.17	3.22	3.90	2.56	3.13
Atenolol											
10	F	42	2	2.50	2.71	3.69	3.58	3.30	3.29	1.49	1.85
11	F	52	0	2.48	2.54	3.24	3.37	3.17	3.03	2.55	2.11
12	F	51	0	2.04	2.07	2.48	2.64	ND	ND	ND	ND
13	M	44	0	3.10	3.14	3.87	4.05	2.34	2.07	1.57	1.50
14	F	64	0	1.90	1.87	2.41	2.37	2.25	2.05	1.98	1.84
15	M	62	0	1.43	1.20	2.01	1.75	3.29	3.64	2.99	3.12
16	M	38	ND	3.71	3.55	5.05	4.69	2.76	3.11	1.72	2.34
17	M	69	ND	3.31	3.11	4.49	4.55	4.48	4.53	2.31	2.70
18	M	53	ND	2.55	1.89	3.07	2.36	2.56	2.57	2.21	1.90

* Number of positive (> 2 mm) reactions on skin prick tests,

ND: not determined

FEV₁: forced expiratory volume in one second

FVC: forced vital capacity

FRC: functional residual capacity

RV: residual volume

Methacholine inhalation tests

Determination of airway responsiveness to methacholine (MIT) was performed according to the method described by Cockcroft *et al.* (1977). Placebo, dilevalol or atenolol were taken on the morning of the visits, 2 h before starting the tests.

After a phosphate buffered saline control inhalation, doubling concentrations of methacholine aerosols were administered by a Wright nebulizer for periods of 2 min every 5 min at an output of 0.13 ml min^{-1} . FEV₁ was measured 30, 90 and 180 s after the last inhalation or every 2 min until it starts to increase. The bronchial response was expressed by the PC₂₀, the provocative concentration of methacholine causing a 20% fall in FEV₁.

Analysis

The difference between mean ($\pm$ s.d.) FEV₁, FVC, functional residual capacity (FRC), residual volume (RV) and PC₂₀ from baseline to after 3 months of D or A were analysed by paired *t*-test. To allow calculation of mean PC₂₀, a value $> 64 \text{ mg ml}^{-1}$ was considered equal to 64. The difference in the changes in lung function parameters between dilevalol or atenolol was also compared using this test. We accepted a *P* value

of < 0.05 as a significant difference. We considered $\geq 20\%$ as a significant change in PEF_R.

Results

Subjects' characteristics are reported in Table 1. Baseline FEV₁ and FVC (mean in litres $\pm$ s.d., % predicted) were respectively of 2.38 ± 0.63 (93%) and 2.95 ± 0.73 (86%) for group D and 2.56 ± 0.72 (91%) and 3.37 ± 1.00 (89%) for group A. Baseline FRC and RV (mean in litres $\pm$ s.d., % predicted) were respectively of 2.79 ± 0.35 (100%) and 1.97 ± 0.39 (111%) for group D and 3.01 ± 0.72 (109%) and 2.10 ± 0.52 (123%) for group A.

Mean blood pressure (systolic/diastolic mm Hg) at the end of the placebo period and after the 3 months of treatment was 169/101 and 158/91 for dilevalol and 159/100 and 142/83 for atenolol.

Symptoms of dyspnea and cough were absent throughout the study for all subjects but subject 9. Patient 9 developed a cough immediately after he began dilevalol, then symptoms of airflow obstruction, 8 weeks later, with progressive reduction of his peak flow rates. PEF remained unchanged in all other subjects (Table 2). The first study week PEF and last study week PEF (mean in litres $\pm$ s.d.) were respectively of 404

Table 2

	PC ₂₀ (mg ml ⁻¹)			PEFR (mean daily, l min ⁻¹)			
	Baseline	3 months		First study week Lowest	Highest	Last study week Lowest	Highest
<i>Dilevalol</i>							
1	> 64	> 64	> 64	526	583	587	601
2	5.9	ND	3.6	255	331	287	311
3	> 64	> 64	> 64	360	396	380	398
4	> 64	> 64	> 64	445	497	423	473
5	4.2	4.9	8.1	ND	ND	ND	ND
6	> 64	> 64	> 64	576	626	622	646
7	4.2	7.0	3.3	334	364	344	351
8	> 64	> 64	> 64	369	378	361	367
9	20.9	23.2	ND	370	429	322	376
<i>Atenolol</i>							
10	7.1	5.6	20.3	ND	ND	ND	ND
11	> 64	> 64	> 64	341	353	317	331
12	> 64	> 64	> 64	439	450	450	452
13	> 64	> 64	> 64	583	610	603	617
14	5.4	8.9	4.6	340	372	340	357
15	ND	ND	ND	358	373	320	332
16	> 64	> 64	> 64	567	582	570	575
17	> 64	> 64	> 64	482	501	506	518
18	ND	ND	ND	351	374	341	371

ND = not determined

Figure 1 There were no significant changes in expiratory flows and lung volumes in the group of subjects on A or D after the study, compared with the baseline. There were also no significant differences in the pulmonary function parameters between the two medications. Results are expressed as mean $\pm$ s.d. (FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity, FRC = functional residual capacity, RV = residual volume)

± 0.7 and 405 ± 16 for group D and 443 ± 14 and 438 ± 9 for group A.

Overall, there were no significant changes in expiratory flows, lung volumes or airway responsiveness in the group of subjects on D or A at the end of the active treatment, compared to the baseline. The medications compared with baseline were respectively of $-4.7\% \pm 11.5$, $-3.48\% \pm 9.6$, $-0.04\% \pm 8.5$ and $4.81\% \pm 19.1$ for A and $-5.09\% \pm 16.3$, $-4.22\% \pm 15.1$, $4.42\% \pm 12.8$ and $13.31\% \pm 36.4$ for D (all $P > 0.05$) (Figure 1).

There were no significant differences in the % changes in pulmonary function parameters when the two medications were compared. Airway responsiveness to methacholine was unchanged throughout the study, with a mean PC₂₀ methacholine (mg ml⁻¹) before/after atenolol or dilevalol respectively of 33.4/37.3 and 24.7/23.9.

No significant side-effects were reported during the tests, even in subjects who inhaled the highest methacholine concentrations used (64 mg ml^{-1}). Only a mild irritation of the throat was reported, with short-lasting phlegm production. No cardiac arrhythmia was observed. The sitting blood pressure, ECG and heart rate did not change significantly during methacholine challenges.

Only one subject (9) developed chest symptoms during the study, in association with airflow obstruction. This 66 year old man, non-smoker, had no past history of asthma or atopy. His baseline spirometry, peak flow rates, lung volumes and the initial PC₂₀ (22.1 mg ml^{-1}) were in the normal range. Physical examination was normal and he had never taken other regular medication than diuretics and vasodilators. Immediately after beginning dilevalol, he developed a persistent cough. Although initially mild, at the 8th week of the study this symptom became bothersome and associated with dyspnea and chest tightness. There was no evidence of cardiac failure. His initial mean PEFR which was initially at $400\text{--}450 \text{ l min}^{-1}$ decreased to 300 l min^{-1} . At this time, FEV₁ was at 52% of predicted. FEV₁ (l), FVC (l) and FRC (l) went from a baseline of 2.35, 3.25 and 3.22 to 1.32, 2.17 and 3.90. Because of this significant obstruction, a methacholine test was not done. After stopping dilevalol, symptoms disappeared and pulmonary function returned to normal within a few days. On a control visit, 4 months later, his FEV₁/FVC was 2.58/3.60 and his PC₂₀ was back to the normal range (18.0 mg ml^{-1}). Although we cannot entirely exclude this possibility, airflow obstruction did not seem related to intercurrent infection or contact with a sensitizing agent.

Discussion

This study shows that the β -adrenoceptor antagonists dilevalol and atenolol generally have no significant respiratory effects in normal subjects and in asymptomatic subjects with minimal increase in non specific airway responsiveness. However, dilevalol seems to have the potential to induce airflow obstruction. The fact that dilevalol did produce bronchospasm in one subject (9) despite its β_2 -adrenoceptor agonist properties, suggests that dilevalol has induced β -adrenoceptor blockade, acting as a partial agonist at the β -adrenoceptor rather than just as a β -adrenoceptor agonist. This stresses the fact that such drugs should be avoided or given with extreme care in subjects with asthma or

chronic airflow limitation. Moreover, clinicians should be aware that airflow obstruction may occur while using these drugs even in subjects without past history of asthma.

Although we know that in asthmatics, β -adrenoceptor antagonists may increase AR, this effect remains ill defined in subjects with normal airway responsiveness (Maconochie *et al.*, 1977; Ryo *et al.*, 1976). Fraley *et al.* (1980) have reported cases of propranolol-induced bronchospasm in subjects without history of asthma. As reported with sensitizing agents such as antigens or some occupational substances, β -adrenoceptor antagonists possibly increase AR to non-specific stimuli up to the asthmatic range, and then lead to the appearance of asthma symptoms.

Attention has been focused recently on adverse effects of β -adrenoceptor antagonists in atopic subjects. The possibility that β -adrenoceptor blockade could enhance the effects of mediators in the lung and increase the morbidity associated with immunologic or nonimmunologic triggers has been suggested (Kaliner *et al.*, 1982; Toogood *et al.*, 1988). Atopic subjects could be at greater risk of such problems.

With the development of new β -adrenoceptor antagonists with intrinsic sympathomimetic activity (ISA) it was hoped that the adverse effects of these drugs on airways could be minimized. Studies on pindolol, a drug with ISA, showed that it had less influence on resting airway function than propranolol, a non-selective β -adrenoceptor antagonist, or atenolol, a β_1 -adrenoceptor selective antagonist but without ISA (Ruffin *et al.*, 1982, 1986). However, accord-

ing to the current literature, no drug with β -adrenoceptor blocking properties can be considered safe in patients with airflow obstruction.

In this study, we have shown that in most subjects with no baseline airflow obstruction, there are usually no significant changes in pulmonary function after 3 months of intake of dilevalol or atenolol. However, an increase in responsiveness and airflow obstruction was observed in one subject, 8 weeks after beginning dilevalol. Since he had no evidence of respiratory infection or contact with a sensitizing agent, and that his respiratory symptoms and function returned to baseline after stopping dilevalol, we believe that it is justified to suspect that dilevalol was responsible for his respiratory condition.

While previous reports have suggested that high-dose methacholine is safe in normal subjects (Cockcroft *et al.*, 1985), this remained to be confirmed in hypertensive subjects. In this study, no significant clinical cardiovascular side-effects were observed after doses of inhaled methacholine up to 64 mg ml⁻¹ in some of our patients with moderate primary hypertension.

In conclusion, β -adrenoceptor antagonists such as dilevalol and atenolol have no significant effects on pulmonary function and AR in most subjects without baseline airflow limitation. However, although it shows β_2 -adrenoceptor agonist properties, significant airway obstruction may develop after chronic use of dilevalol. Finally, inhaled methacholine, at doses up to 64 mg ml⁻¹ does not have significant effects on ECG, blood pressure and heart rate in patients with uncomplicated primary hypertension.

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