Eur Respir J
1988, 1, 453–457

Effects of terbutaline and atenolol on large and small airways in asthmatic patients

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ABSTRACT: In order to localize the main site of action of the β_2-adrenoceptor selective agonist terbutaline and the β_1-adrenoceptor selective antagonist atenolol in the airways of asthmatic patients, we compared the effects of these drugs on maximal expiratory flow-volume (MEFV) curves when breathing air and when breathing a helium-oxygen (HeO_2) mixture. To investigate whether a shift in localization of the bronchodilator effect occurs when terbutaline is inhaled repeatedly, dose-response curves with terbutaline were performed for parameters derived from MEFV curves when breathing air and for density dependence of expiratory airflow. By measurement of MEFV curves when the patients were breathing air alone, it was not possible to determine whether there is a difference in the bronchoconstrictor effect of atenolol between large and small airways. Inhalation of terbutaline to a cumulative dose of 2.0 mg induced a stepwise improvement in expiratory airflow parameters for large and small airways function when breathing air. Doubling the dose of inhaled terbutaline to 4 mg did not result in any further improvement of lung function. Neither atenolol nor terbutaline induced significant mean changes in density dependence of expiratory airflow. This was partly due to large inter- and intra-individual variations of this parameter. Another possibility is that atenolol and terbutaline effect large and small airways function equally.

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Keywords: β-adrenoceptor blockade; β-adrenoceptor stimulation; density dependence; maximum expiratory flow.

Accepted for publication January 11, 1988.

Ventilatory effects of β-adrenoceptor agonists and antagonists are usually assessed by routine lung function tests, such as measurement of total airway resistance, peak expiratory flow rate (PEFR), and the forced expiratory volume in one second (FEV_1). Although these methods give insight into changes in overall lung function, they do not distinguish between the effects of these drugs on large and small airways. It has been postulated that by measurement of airflow at high and low lung volumes, which can be performed with flow-volume curves, a distinction can be made between the effects of drugs on large and small airways [1–3]. Recently however, LAMBERT [4] concluded from results obtained by analysing maximal expiratory flow-volume (MEFV) curves with a computational model, that during constriction of peripheral airways expiratory flows are reduced at all lung volumes, but proportionately more at the lower lung volumes. Hence, a better distinction between the influences of drugs on large and small airways can probably be made by comparison of flow-volume curves, when the patient is breathing air and when he is breathing a low-density gas mixture like HeO_2 [4, 5].

The assessment of density dependence has been used to determine the site of bronchodilatation by β-adrenoceptor agonists and/or muscarinic antagonists [6–10]. These studies concerned the effect of a single oral or inhaled dose of a bronchodilator. PIERCE *et al.* [3] could not find a difference in site of activity of cumulative doses of terbutaline given either intravenously or by inhalation from a nebulizer. However, these authors investigated asthmatic patients, following recovery from a severe attack of asthma, who were receiving treatment with oral corticosteroids. The present study was therefore initiated to examine whether repeated inhalation of a β_2-adrenoceptor agonist induces a shift in the localization of the bronchodilator effect in mild asthmatic patients, who were not receiving oral corticosteroids.

Moreover, as there is little information on the localization of the bronchoconstriction induced by β-adrenoceptor antagonists in asthmatics, we also investigated the effect of atenolol, a β_1-adrenoceptor selective antagonist, on forced expiratory airflow parameters and density dependence in the same group of asthmatic patients.

Methods

Eleven male patients aged 22–60 yrs, were studied. All suffered from asthma as defined by the American Thoracic Society [11]. Their mean height was 176.9 cm (range 161–188 cm) and their mean weight 73.7 kg (range 54–94 kg). Five patients were smokers and

seven were allergic to one or more pneumallergens. Their lung function was mildly to moderately disturbed: the FEV_1 ranged from 40–74% of the predicted normal value [12]. All patients had shown an increase in their FEV_1 of at least 15% after inhalation of a β_2-adrenoceptor agonist before they entered the study. They were in a stable phase of their disease and none of them required oral corticosteroids or theophylline derivatives. Eight patients used salbutamol by inhalation as bronchodilator medication; this was not used for at least twelve hours prior to the first measurement. Two patients regularly inhaled beclomethasone dipropionate and one cromoglycate; these drugs were not inhaled on the days of investigation. The study was approved by the local Ethics Committee and written informed consent was obtained from each patient before entry into the study.

Lung function parameters were obtained from maximal expiratory flow-volume (MEFV) curves, which were obtained with flow-volume equipment containing a Fleisch No. 4 pneumotachograph. Before each set of measurements, the flow-volume equipment (Discom, Chest Corporation, Tokyo) was calibrated separately with room air and a mixture of 80% helium and 20% oxygen (HeO_2). Volume history was standardized by maximal inhalation to total lung capacity (TLC) prior to the performance of all MEFV curves. Firstly, three MEFV curves were obtained when breathing room air. Secondly, HeO_2 was washed-in during four minutes when breathing this gas from a Douglas bag and thereafter a second set of three MEFV curves was obtained. The air MEFV curves with the best sum of forced vital capacity (FVC) and FEV_1 [13] were used for calculations of FVC, FEV_1, PEFR and maximal expiratory flow rates when 50 and 25% of the FVC was still to be expired (MEF_{50} and MEF_{25}, respectively). The HeO_2 MEFV curves with the best fitting FVCs compared to the air MEFV curves were used for calculation. We used as parameter for density dependence ΔMEF_{50}:

$$\Delta MEF_{50} = MEF_{50}(HeO_2) - MEF_{50}(air)/ \quad [1, 14]$$
$$MEF_{50}(air) \times 100\%$$

The volume of isoflow ($V_{iso\dot{V}}$) was calculated after superimposing the air and HeO_2 MEFV curves at the level of residual volume [14, 15].

The investigations were performed on two different days. After assessment of baseline lung function at 12.00 am drugs were administered by mouth. On the first day placebo was given single-blind and on the second atenolol 50 mg, both as identical tablets. At 02.00 pm lung function measurements were repeated. Thereafter, a dose-response curve with the β_2-adrenoceptor agonist terbutaline was performed by obtaining air and HeO_2 MEFV curves fifteen minutes after inhalation. Terbutaline was inhaled four times through a 750 ml spacer (Nebuhaler®) from a metered dose inhaler [16] in cumulative doses of 0.5, 1.0, 2.0 and 4.0 mg. The results are presented as means ± SEM.

For statistical analysis the Wilcoxon test for paired observations was used. Comparisons were made between baseline values and the values recorded two hours after drug intake and those recorded after inhalation of terbutaline. The latter values were also compared with the values two hours after intake of placebo and atenolol respectively. Statistical significance was defined as $p < 0.05$.

Results

The baseline values for the different lung function parameters are given in table 1. No significant differences were found between these baseline values measured on the different days of the study. There were no significant changes in lung function parameters two hours after intake of placebo (table 1). Two hours after dosing, however, atenolol 50 mg caused the following decreases in lung function parameters (the changes in percentage of the base-line values are given between parentheses): the FVC fell by 0.35 *l* (8%) and the FEV_1 also by 0.35 *l* (12%); the MEF_{50} decreased by 0.40 $l \cdot s^{-1}$ (19%) and the MEF_{25} by 0.20 $l \cdot s^{-1}$ (23%). The fall in PEFR two hours after intake of atenolol 50 mg was just below significance. Density dependence and $V_{iso\dot{V}}$ were not influenced significantly by atenolol 50 mg (table 1).

Inhalation of terbutaline caused significant improvements in FVC, FEV_1, PEFR, MEF_{50} and MEF_{25} ($p < 0.01$) when compared with the values two hours after drug intake, both during placebo and during atenolol (table 1). In comparison with the baseline values of the same day, the changes induced by terbutaline in all these parameters during placebo reached the same significance level ($p < 0.01$). During atenolol treatment the increases in MEF_{50} and MEF_{25} are presented in figure 1. From two hours after drug intake onwards there was a significant difference in the absolute values of MEF_{50} and MEF_{25} between placebo and atenolol treatment. The shape of the dose-response curve with terbutaline, however, was similar for both placebo and atenolol when compared to the values two hours after drug intake.

The effects of consecutive inhalations of terbutaline on ΔMEF_{50} are shown in figures 2 and 3. There was a tendency towards an increase in ΔMEF_{50} after inhalation of 0.5 mg terbutaline during placebo (fig. 2). This difference was, however, not significant. As can be seen in figure 3, where the effects of terbutaline on ΔMEF_{50} during placebo treatment have been separated between smokers and non-smokers, this small change in ΔMEF_{50} mainly occurred in the smoking patients. Further inhalation of terbutaline up to a cumulative dose of 4.0 mg did not influence ΔMEF_{50}, either during placebo or during atenolol 50 mg. There was also no change in $V_{iso\dot{V}}$ after inhalation of terbutaline (table 1).

Discussion

The effects of atenolol and terbutaline on the FEV_1, FVC and PEFR in this group of asthmatic patients have been described in detail previously [4].

Table 1. - Ventilatory parameters before and 2 h after intake of placebo and atenolol and after inhalation of 4 mg terbutaline

		Placebo				Atenolol			
		baseline values	2 h after drug intake	p*	after 4 mg terbutaline	p+	baseline values	2 h after drug intake	p*	after 4 mg terbutaline	p+
FVC	l	4.58±0.31	4.56±0.28	NS	5.11±0.30	<0.01	4.58±0.29	4.24±0.30	<0.02	5.00±0.28	<0.01
PEFR	$l \cdot s^{-1}$	6.95±0.64	7.13±0.72	NS	9.37±0.91	<0.01	7.36±0.72	6.84±0.75	NS	9.14±0.90	<0.01
FEV_1	l	2.89±0.27	2.88±0.28	NS	3.74±0.31	<0.01	2.84±0.30	2.49±0.28	<0.01	3.37±0.34	<0.01
MEF_{50}	$l \cdot s^{-1}$	2.11±0.33	2.11±0.35	NS	3.39±0.55	<0.01	2.10±0.35	1.70±0.29	<0.01	2.75±0.53	<0.01
MEF_{25}	$l \cdot s^{-1}$	0.85±0.14	0.86±0.15	NS	1.34±0.23	<0.01	0.86±0.16	0.66±0.12	<0.01	1.11±0.22	<0.01
ΔMEF_{50}	%	38.70±5.0	31.10±8.20	NS	38.30±5.50	NS	30.60±6.80	36.80±7.30	NS	48.20±4.00	NS
$V_{iso}\dot{V}$	%FVC	81.20±5.1	79.60±5.00	NS	79.60±4.40	NS	81.10±5.20	76.00±4.30	NS	81.60±2.90	NS

Values are means±SEM; p*: baseline values *versus* values 2 h after drug intake; p+: values 2 h after drug intake *versus* values after terbutaline; NS: not significant.

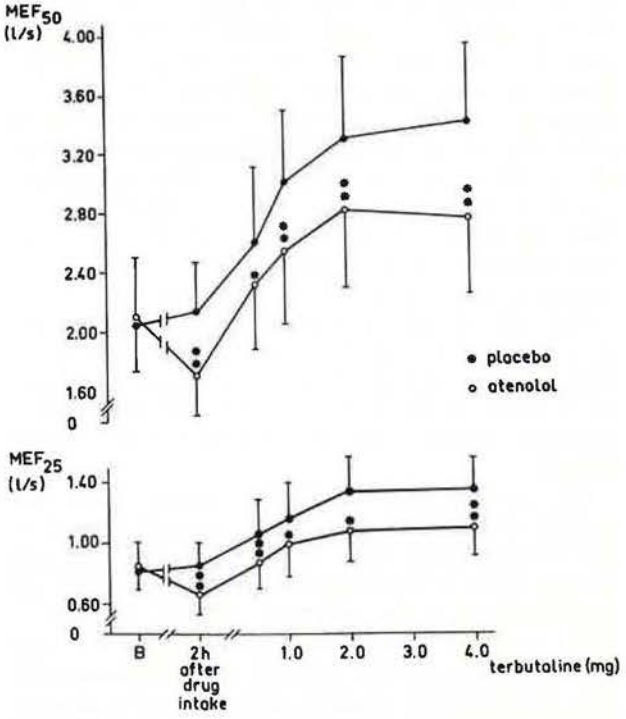

Fig. 1. Effects of terbutaline in cumulative doses on MEF_{50} and MEF_{25} during placebo (●) and atenolol 50 mg (○) (mean ± SEM). Asterisks indicate significant difference between values after placebo and those during atenolol. *$p < 0.05$, **$p < 0.01$.

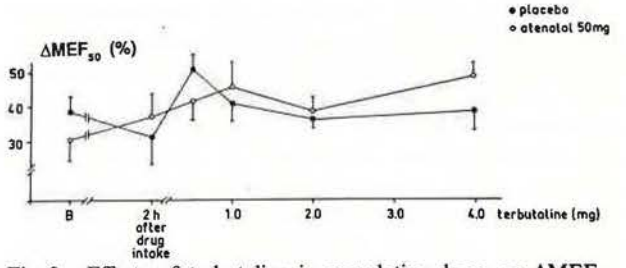

Fig. 2. Effects of terbutaline in cumulative doses on ΔMEF_{50} during placebo (●) and atenolol 50 mg (○) (mean ± SEM; n = 11).

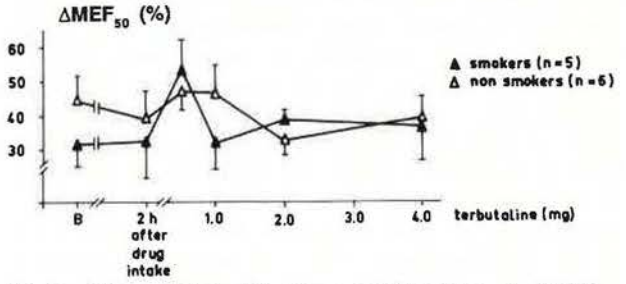

Fig. 3. Effects of terbutaline in cumulative doses on ΔMEF_{50} during placebo in smokers (▲) and non-smokers (△) (mean ± SEM).

Two hours after intake, atenolol 50 mg caused significant decreases in all parameters derived from the MEFV curves when the patients were breathing air, except for the PEFR. Therefore atenolol probably induced constriction of both large and small airways [1, 4, 17].

Inhalation of terbutaline up to a cumulative dose of

2.0 mg resulted in regular increases in FVC, FEV_1, MEF_{50} and MEF_{25} (table 1 and fig. 1). An additional dose of 2 mg terbutaline did not induce a further change in these expiratory airflow parameters. The increases in MEF_{50} and MEF_{25} caused by inhaled terbutaline remained significantly lower during atenolol treatment than the changes in these parameters caused by terbutaline after intake of placebo (fig. 1). This inhibitory effect of atenolol on the terbutaline dose-response curve is probably due to the fact that atenolol, even in a low dose of 50 mg, is not completely β_1-adrenoceptor selective and blocks airway β_2-adrenoceptors to a certain extent [18]. A higher dose of the β_2-adrenoceptor agonist terbutaline is therefore necessary to achieve a bronchodilator response during atenolol treatment than during placebo.

By measurement of MEFV curves when the subjects were breathing air alone, we were not able to determine whether there were differences between the sites of action of atenolol and terbutaline on large and small airways in the asthmatic subjects. Changes in both large and small airways will affect FEV_1 and PEFR. It appears that changes in these parameters only reflect calibre changes of large central airways, when the FVC and the terminal portion of the MEFV curves are unchanged [19]. However, this was not the case in our subjects, either for atenolol, or for terbutaline.

DESPAS *et al.* [5] introduced the measurement of density dependence as a method of assessing the main localization of obstruction in the airways of patients with asthma and chronic bronchitis. A density dependence of less than 20% indicates that the major site of obstruction is located in small peripheral airways, whilst a density dependence of more than 20% is compatible with mainly large airways obstruction [5, 14]. Later on, HUTCHEON *et al.* [15] and other authors [4, 14, 20] described the volume of isoflow as another method to discriminate between large and small airways function. A volume of isoflow at which the MEFV curves when breathing air and when breathing HeO_2 coincide by more than 80% is assumed to indicate that the major site of bronchoconstriction is located in larger airways. Measurement of density dependence and volume of isoflow have been used to assess the main site of action of bronchoconstrictor and bronchodilator drugs. Several authors [1, 6–9] mention a different localization of the bronchodilator effects of muscarinic receptor antagonists and β-adrenoceptor agonists. While the former mainly induce dilation of larger airways, the latter would preferentially dilate smaller airways. LAMBERT [4] divided the bronchial tree into three zones and suggested that constriction of each of these zones gives rise to three distinct density dependence responses. In his model, constriction of peripheral airways (those with an internal diameter <2mm) caused a drop in ΔMEF_{50} and an increase in $V_{iso\dot{V}}$. When extraparenchymal, intrathoracic airways were constricted $V_{iso\dot{V}}$ did not change, whilst the effect on MEF_{50} was variable. Constriction of middle airways (those within the parenchyma and >2mm diameter) resulted in a normal ΔMEF_{50} and a reduction of $V_{iso\dot{V}}$.

In our patients, the β_1-adrenoceptor selective antagonist atenolol did not affect mean density dependence or the mean value of the volume of isoflow. By this method, therefore, no distinction could be made between the effects of atenolol on large or small airways. We could not discern the above described pattern of Lambert.

During placebo, there was no significant change in density dependence or the volume of isoflow after inhalation of terbutaline. PIERCE *et al.* [3] could also not demonstrate a significant effect of terbutaline, either given intravenously or after inhalation, on density dependence. In our study, however, there was a tendency towards a mean increase in density dependence after inhalation of 0.5 mg terbutaline in smoking patients (fig. 3). The small rise in ΔMEF_{50} was followed by a decrease after further inhalation of terbutaline. From these results it seemed that bronchodilation by inhaled terbutaline first occurred in the smaller airways of the smoking asthmatics and after a higher dose shifted to larger airways. These changes were, however, not significant and the smaller number of smoking patients ($n=5$) prohibits too many conclusions. Moreover, at every point in the dose-response curves of ΔMEF_{50} for all patients, there were large intra- and inter-individual variations resulting in mean values with high standard errors. Other authors [21–23] also describe a large variability of density dependence and $V_{iso\dot{V}}$. Recently, it has been suggested that sites of flow limitation, airway geometry and patterns of flow may differ with the density of the respired gas [24, 25], and it therefore remains questionable whether this method is reliable enough to localize bronchodilation and bronchconstriction.

On the other hand, it is possible that asthmatic patients do not have a uniform pattern in their reactions to bronchoconstrictor and bronchodilator stimuli.

Another possibility is that atenolol and terbutaline cause proportionately equal constriction and dilatation of large and small airways, leaving density dependence relatively unchanged [3, 8].

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RÉSUMÉ: Nous avons comparé les effets d'un agoniste sélectif pour les adrénorécepteurs bêta 2, et d'un antagoniste sélectif pour les adrénocépteurs bêta 1, sur les courbes débits-volumes expiratoires maximaux, sous air et sous un mélange hélium-oxygène, afin de déterminer le site principal de leur action. Pour investiguer si un déplacement du site de l'effet bronchodilatateur se produit par inhalations répétées de la terbutaline, des courbes dose-réponse à la terbutaline ont été réalisées pour des paramètres dérivés des courbes débits-volumes maximaux expiratoires, et pour la dépendance de débit expiratoire à l'égard de la densité. La mesure des courbes débits-volumes maximaux expiratoires sous air n'a pas permis de déterminer s'il y avait une différence quant à l'effet bronchoconstricteur de l'atenolol sur les voies aériennes de grand ou de petit calibre. L'inhalation de terbutaline jusqu'à des doses cumulatives de 2.0 mg introduit une amélioration progressive des paramètres de débits expiratoires pour les petites et les grandes voies aériennes sous inhalation d'air. Un doublement de la dose de terbutaline inhalée jusqu'à 4 mg n'entraîne pas d'amélioration supplémentaire de la fonction pulmonaire. Ni l'atenolol, ni la terbutaline, n'ont introduit de modifications significatives dans la dépendance du débit expiratoire à l'égard de la densité. Ceci est apparu partiellement attribuable à d'importantes variations inter- et intra-individuelles de ce paramètre. Une autre possibilité est que l'atenolol et la terbutaline affectent de manière égale les voies aériennes de grand et de petit calibre.