Pretreatment with an inhaled α_1-adrenergic agonist, methoxamine, reduces exercise-induced asthma

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ABSTRACT: In order to assess the role of the bronchial circulation in the pathogenesis of exercise-induced asthma (EIA), we conducted a double-blind, randomized study of the effects of pretreatment with an inhaled α_1-adrenergic agonist, methoxamine (Mx), in nine asthmatic teenagers with known EIA. Exercise consisted of 5 min cycle ergometry at a submaximal, constant work-load, while the subjects breathed dry air at ambient temperature. Forced expiratory volume in one second (FEV_1) was measured at baseline, 15 min after pretreatment of either Mx or saline, and serially after exercise. Mx significantly reduced the exercise-induced fall of FEV_1 without modifying baseline FEV_1 in five of the eight subjects, had little or no effect in three and caused an acute asthmatic attack in the remaining subject. Mx has potent constrictor effects on both bronchial and vascular smooth muscles through stimulation of postjunctional α_1-adrenoceptors. Therefore, the protective effect of Mx on EIA may be attributed to vasoconstriction of tracheobronchial vessels opposing the hyperaemia and mucosal airway oedema that may cause, at least in part, the exercise-induced acute bronchial obstruction in EIA. Alternatively, Mx stimulates mucus, water and electrolyte secretion by airway epithelium and may, therefore, oppose the dehydration of airway surface that could be a causative factor of EIA.
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The mechanisms that cause airway narrowing in exercise-induced asthma (EIA) are still debated. During physical exercise, both heat [1] and water [2] losses increase over resting values but the intermediate mechanisms linking the ensuing increase in energy losses by the airways to post-exertional asthma are poorly understood, although cooling and dehydration of the airway surface may be the primary events [3]. There is circumstantial evidence in favour of a role for the tracheal and bronchial circulation in production of exercise-induced asthma [4, 5]. Rewarming of the tracheobronchial tree during the recovery period that follows exercise is more rapid in subjects suffering from post-exertional asthma than in control subjects. This may stimulate mediator release by mast cells and is suggestive of an exaggerated reactive hyperaemia [4, 5] which may, in turn, result in luminal narrowing due to vascular engorgement and oedema in the airway mucosa and submucosa.

Alpha₁-adrenergic agonists are potent vasoconstrictor agents of the bronchial circulation in experimental animals [6]. We have previously shown that inhaled methoxamine, an α_1-adrenergic agonist, prevented methacholine-induced bronchial obstruction in patients with impaired left ventricular function [7], an effect which we explained by constriction of bronchial vessels, since methoxamine is a contractile agent for bronchial smooth muscle and stimulates submucosal glands, both effects that should, if anything, aggravate airways narrowing. We wondered, therefore, if a potent vasoconstrictor agent such as methoxamine might prevent EIA, which would indirectly confirm the role of vasodilatation of the tracheobronchial circulation [4, 5] in this condition.

Subjects

Nine asthmatic teenagers with sporadic and moderate asthma responding to the definition of the American Thoracic Society [8] were studied (table 1). All subjects had a history of EIA which was documented by a fall in forced expiratory volume in one second (FEV_1) $\geq 20\%$ of baseline FEV_1 after 5 min of outdoor free running. All of them were in a stable phase of their disease; only three of the nine patients made regular use of bronchodilators to control their symptoms and none had been treated with corticosteroids for a month before the study. All other medications were withheld according to standard recommendations [9]. After approval by the Ethical Committee of our Medical School, the design of the study was thoroughly explained to the subjects and their parents before obtaining their informed consent.

Methods

Outline of the study

Eight subjects carried out two standardized exercise tests after inhalation of either methoxamine or saline solution according to a double-blind, randomized design. Fifteen min after pretreatment, the subject carried out a submaximal exercise for 5 min on a cycle ergometer. FEV_1 was measured at baseline, 15 min after dosing, every min for the first 5 min following the end of exercise, and then every 10 min until return to baseline. Blood pressure and heart rate were measured at baseline and 15 min after inhalation of methoxamine or placebo. The study was discontinued in the remaining subject (No. 9) who had an acute asthmatic attack following pretreatment of methoxamine and recovered after administration of salbutamol (2×100 µg) from a metered dose inhaler.

Technical details

The two exercise tests were performed on the same day. There was at least a 6 h interval between the first and the second challenges which took place, respectively, before 9 am and after 3 pm. This interval was chosen in order to avoid the confounding effect of the refractory period that may occur after a first attack of EIA [10]. The exercise consisted of 5 min of pedalling on a cycle ergometer (Gauthier MSR, France) while the subject, wearing a nose-clip, breathed compressed dry air (0% humidity) at room temperature through a mouthpiece. The work-load used for each subject was chosen to obtain 90% of predicted maximal heart rate (HRmax) determined from the usual formula: HRmax=220-age (yrs). Heart rate was monitored (Gould IM 1000, USA) and recorded every 30 s. Individual tailoring of the work-load was chosen to account for differences in height and weight between subjects (table 1). Immediately after the exercise, the subjects began to respire room air and continued to do so throughout the entire recovery period, as recommended by GILBERT *et al.* [5].

Methoxamine was diluted in saline at a concentration (w/v) of 40 mg·ml⁻¹. Osmolarity and pH of the solution were 300 mosm·*l*⁻¹ and 7, respectively. Aerosols were generated by a DeVilbiss model 646 nebulizer operated by compressed air at 1.50 kPa and an inhalation triggered dosimeter (FDC 87, Mediprom S.A., Paris), set to deliver an aerosol of 1 s duration, that provided 0.8 mg of methoxamine for each inspiration. Volume history was standardized by having each participant inhale from functional residual capacity to total lung capacity. The total number of inhalations was predetermined as a function of body weight to achieve a target dose of inhaled methoxamine of about 0.15 mg·kg⁻¹ of body weight (table 1). FEV_1 was measured in triplicate at each time point and the highest value was retained for analysis.

Statistical analysis

The entire set of values of FEV_1, blood pressure and heart rate was submitted to a two way analysis of variance (treatment, time) for repeated measurements (subjects). Intra-individual comparisons of the effects of methoxamine and placebo on FEV_1 were made by a paired Wilcoxon signed rank test.

Results

The eight subjects, whose airways patency was not affected after pretreatment of methoxamine as shown by an unchanged FEV_1, carried out the two exercise challenges and results from these subjects form the basis of this report.

Individual time-response curves for FEV_1 are presented in figure 1. As a result of the randomized design of the study, pretreatment before the 9 am exercise was methoxamine in four subjects and placebo in the remaining four subjects and pretreatments were crossed-over for the afternoon exercise. Since there was no order effect, results of both subgroups were analysed together.

Group-average (±SD) values for pre- and post-exercise

Table1. – Anthropometric, baseline lung function and exercise data

Subjects	Sex	Age	Height cm	Weight kg	FEV₁ *l*	FEV₁ %pred	HR (mean±SD) P	HR (mean±SD) Mx	Inhaled Mx mg
1	M	13	166	58	3.0	101	171±6	174±6	8.8
2	F	12	146	38	1.8	94	163±8	163±9	5.6
3	M	13	161	51	2.8	101	176±4	177±6	7.2
4	F	10	149	39	2.3	114	178±3	179±4	5.6
5	M	16	163	47	2.8	100	176±6	174±6	7.2
6	M	12	142	36	2.2	114	174±6	174±8	5.6
7	F	16	154	65	2.2	99	177±4	177±4	9.6
8	F	17	160	46	2.4	97	176±5	177±7	7.2
9	M	18	177	63	3.2	90	-	-	9.6

Predicted values of forced expiratory volume in one second (FEV_1) are those of BOUHUYS [40]. Heart rate (HR) was recorded every 30 s during the two exercises that followed pretreatment of placebo (P) or methoxamine (Mx) and the maximal HR on exercise is listed in the table. Doses of inhaled Mx are given as a function of corporeal weight (0.15 mg·kg⁻¹).
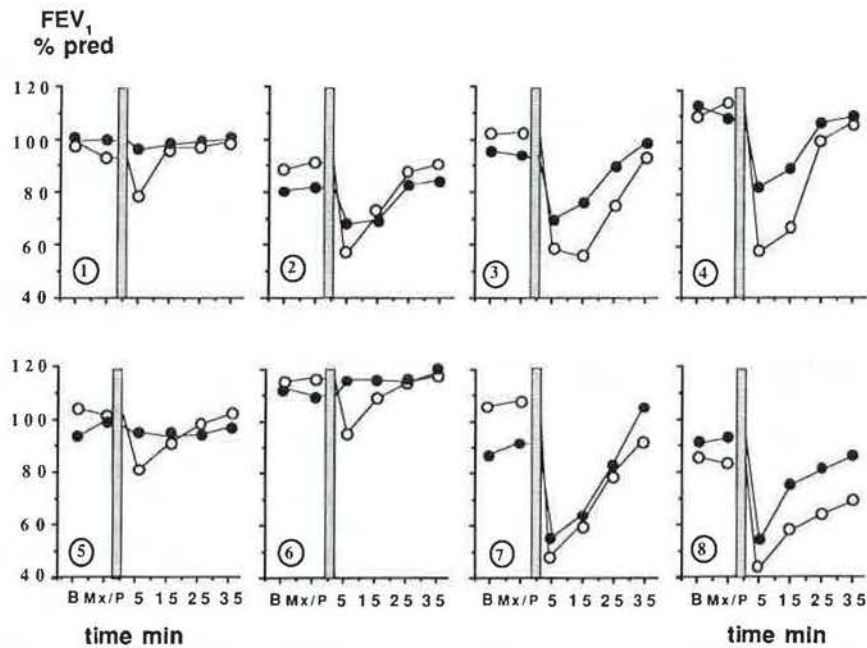
Fig. 1. – Changes in forced expiratory volume in one second (FEV₁) caused by exercise after pretreatment of methoxamine and placebo. FEV₁ was recorded at baseline (B), after pretreatment of methoxamine (Mx: closed circles) or placebo (P: open circles) and serially after the exercise challenge (column).
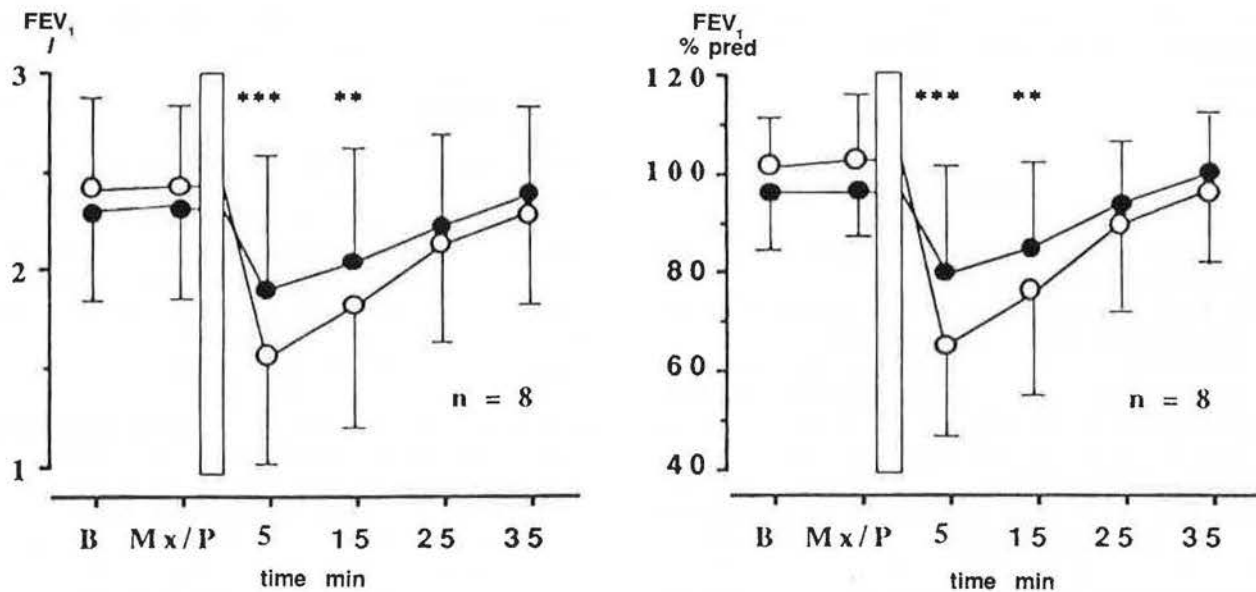

Fig. 2. – Group-average values of forced expiratory volume in one second (FEV₁) (mean±SD). Difference between pretreatment of methoxamine (Mx: closed circles) and placebo (P: open circles) are signficant at the p<0.001 (***) and p<0.01 (**) threshold at 5 and 15 min post-exercise, respectively. B: baseline.

FEV₁ and changes of FEV₁ from baseline on pretreatment of methoxamine and placebo are shown in figures 2 and 3, respectively. On average, inhaled methoxamine did not change resting FEV₁ (FEV₁=2.4±0.5 *l* (mean±SD) and 2.4±0.4 *l* at baseline and after pretreatment of saline; FEV₁=2.3±0.5 *l* and 2.3±0.5 *l* at baseline and after pretreatment with methoxamine). Methoxamine reduced the exercise-induced fall in FEV₁, an effect which was maximal and significant at 5 min (ΔFEV₁=0.9±0.3 *l* and 0.4±0.4 *l* on placebo and methoxamine, respectively

p<0.001) and 15 min post-challenge (ΔFEV₁=0.6±0.5 *l* and 0.3±0.2 *l* on placebo and methoxamine, p<0.01 and p<0.001, respectively).

As shown in figure 1, methoxamine had a full protective effect against EIA in three subjects (Nos 1, 5 and 6) and a partial protective effect in two (Nos 3 and 4). Conversely, in the remaining subjects (Nos 2, 7 and 8) FEV₁ fell to similar values on both placebo and methoxamine, the latter having had no protective effect. Inspection of individual dose response curves in figure 1 conveyed the

impression that methoxamine had a full protective effect only in subjects having a mild degree of exercise-induced bronchial obstruction. Indeed, by use of a Spearman rank correlation test, we found that patients with the largest bronchial responses to exercise placebo also had the largest responses on methoxamine, whereas subjects with the lesser falls on placebo were also the most likely to be partially or fully protected by methoxamine ($r_s=0.83$, $p<0.05$).
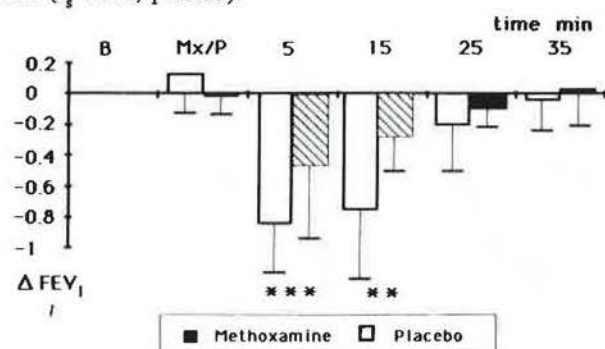

Fig. 3. – Group-average values (±SD) of fall in forced expiratory volume in one second (FEV$_1$) from baseline. Post-exercise fall in FEV$_1$ on methoxamine (Mx: closed areas) is significantly less than on placebo (P: open areas). ** $p<0.01$; *** $p<0.001$; B: baseline.

Blood pressure and heart rate were not modified by inhalation of methoxamine. Monitoring of heart rate during the two exercises did not show any difference between the two challenges (table 1).

Discussion

The main result of this study is that pretreatment with inhaled methoxamine, on average partially and in some individual cases totally, inhibits EIA without modifying resting bronchial tone in young asthmatic subjects.

Performing two exercises on the same day may lead to a systematic bias related to diurnal variation of the resting bronchial tone. We believe, however, that such a bias is unlikely. Firstly, previous studies have shown absence of diurnal variation in EIA [11, 12]. Secondly, randomization achieved an identical distribution of pretreatments of methoxamine and placebo in the morning and the afternoon without discernable effects of the order of administration of the pretreatments on the bronchial response to exercise of our subjects. Exercise challenge was only performed once on placebo in this study since a preliminary study of six other comparable asthmatic subjects demonstrated that duplicate exercise challenges without active pretreatment and similar to that used in the present study caused almost identical maximal falls from baseline FEV$_1$ of 31±7% and 30±7% of predicted FEV$_1$.

We used a 15 min interval between pretreatment of inhaled methoxamine and the exercise test since we have shown in a previous work that methoxamine fully prevented the bronchial obstruction caused by a methacholine challenge commencing 15 min after dosing in cardiac patients with impaired left-ventricular function [7].

Methoxamine is a selective α_1-adrenoceptor agonist [13] that has various effects on different effector structures of the airways. Stimulation of postjunctional α_1-adrenoceptor of airway smooth muscle and submucosal glands induces in vitro contraction of the former [14, 15] and secretion of mucus by the latter [16]. These effects account for the aggravation of the bronchial obstruction by alpha-adrenergic agonists observed in a majority of asthmatic subjects [17, 18]. Consistent with the deleterious effects of alpha-agonist agents in asthma is the observation that EIA may be prevented by alpha-adrenergic antagonists [19–22]. The direct effects of alpha-adrenergic agonists on bronchial smooth muscle and glands warrant the contention that such compounds are contra-indicated in asthmatic patients. However, beneficial effects on airways patency of α_1-adrenergic agonists have already been reported in animals [23] and humans [7] and we report in this study that inhaled methoxamine is capable of preventing EIA in patients with mild asthma.

Firstly, the protective effect may be explained by stimulation of bronchial vascular post-junctional α_1-adrenoceptors. Stimulation of α_1-adrenoceptors of vascular smooth muscle causes vasoconstriction [6, 13, 24] and therefore reduces vasodilatation and vascular engorgement. Direct evidence in support of a role for the tracheobronchial vasculature in EIA is not yet available. GILBERT et al. [5] measured the temperature within the respiratory tract of asthmatic subjects during exercise and the subsequent recovery period and found cooling of the airstream during exercise followed by a fast rewarming during the first minutes of recovery [4, 5]. Thus, rewarming takes place at the same time as the exercise-induced increase in resistance to gas flow in the airways: this is strong, though circumstantial evidence, of vasodilatation of the tracheobronchial circulation. The post-exercise vasodilatation may be a rebound phenomenon subsequent to vasoconstriction during exercise and permitted by the rapid fall in sympathetic tone and circulating catecholamines upon cessation of exercise. Tracheobronchial vasoconstriction during exercise may be facilitated by the increase of alpha-adrenoceptor sensitivity of vascular smooth muscle upon cooling [25], although airway temperature does not fall on exercise to the low 20–24°C at which this effect was found in vitro [26]. A rapid rise in bronchial blood flow may lead to increased thickness of the airways wall due to vascular engorgement, plasma exudation, submucosal and mucosal oedema facilitated by the presence of chronic inflammatory changes in the airways of asthmatic subjects. Additional evidence for deleterious effects of local vasodilatation in asthmatic subjects has been provided by a recent study in which it was shown that inhaled prostacyclin may cause airway narrowing which was best explained by mucosal engorgement [27].

It is not possible to explain the protection offered by both alpha-adrenergic agonists and antagonists against EIA by only taking into account their effects on airway smooth muscle. Methoxamine is a potent vasoconstrictor agent [6, 13, 24] and may therefore protect against EIA by preventing the rebound hyperaemia at recovery. In addition, methoxamine may also reduce, through its

vasoconstrictor effect, the rate of water delivery to the airways after exercise [28] that is supposed to modify the airway surface osmolarity which is a possible triggering factor of EIA [2, 29]. Alpha-adrenergic antagonists [19–22] and calcium channel blockers [30] are bronchodilator as well as vasodilator agents and have a protective effect against EIA. In addition to their relaxant effect on bronchial smooth muscle, these drugs may, therefore, limit hyperpnoea-induced vasoconstriction, thus minimizing the post-challenge rebound hyperaemia.

In addition it is possible that the respective role of contraction of airway smooth muscle and reactive hyperaemia differs between subjects. Indeed a high degree of airway smooth muscle reactivity in subjects having a severe exercise-induced fall of FEV_1 is suggested by our finding that the protective effect of methoxamine is very modest or even absent in such patients.

Alternatively, it can be hypothesized that methoxamine prevented EIA through effects on electrolyte secretion and water-mediated movement across airway epithelium. Alpha-adrenergic agonists enhance the transport of Cl^- and Na^+ ions and of accompanying water from submucosa to the airway lumen in cats [31]. However, in vivo transmucosal potential difference of airway epithelium is not modified by phenylephrine in dog, whereas it increases upon application of the secretagogues isoproterenol and epinephrine [36]. Circumstantial evidence that pharmacological manipulation of ion and water transport by airway epithelium [33] may modify the bronchial response to exercise of asthmatic subjects has recently been provided [32]. These authors have shown that inhaled but not intravenous frusemide prevented exercise-induced asthma. Frusemide reduces the secretion of chloride from the serosal but not from the luminal side of dog tracheal epithelium by reducing uptake of chloride ions at the basolateral membrane [35, 37, 38] which results in decrease of intracellular activity of chloride and, presumably, of chloride secretion at the apical membrane. It is difficult to understand how local application of two drugs of which one reduces and the other enhances chloride secretion towards airway lumen share a preventive effect on exercise-induced asthma but it is tempting to speculate that pharmacological manipulation of ion and water movements across airway epithelium may have a potential for management of this condition.

Occurrence of an acute attack of asthma in one of our nine subjects after treatment by inhaled methoxamine confirms earlier reports [17, 18] and can probably be ascribed to stimulation of post-junctional α_1-adrenoceptors located on bronchial smooth muscle [14, 15] and submucosal glands [16]. Alternatively, methoxamine, by causing tracheobronchial vasoconstriction may reduce vascular clearance of paracrine endogenous bronchoconstricting mediators. However, the reason why inhaled α_1-adrenoceptor agonists induce bronchial obstruction in some subjects but not in others is unknown. That only one case of acute asthma was caused by methoxamine in our group of nine asthmatic subjects reflects the general opinion of a weak role for alpha-adrenoceptors on the basal bronchial tone [39].

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Prétraitement par un α_1-agoniste adrénergique inhalé, méthoxamine, réduit l'asthma post-exercise. A.T. Dinh Xuan, M. Chaussain, J. Regnard, A. Lockhart.
RÉSUMÉ: Pour déterminer le rôle de la circulation bronchique dans l'asthme post-exercice (APE), nous avons étudié en double-insu l'effet d'un prétraitement par un alpha-1 agoniste inhalé, la méthoxamine (Mx), chez 9 adolescents asthmatiques ayant un APE connu. L'exercice rectangulaire est effectué sur bicyclette ergométrique pendant 5 min à puissance submaximale, le sujet respirant par la bouche de l'air sec à température ambiante. Le volume expiratoire maximal seconde (VEMS) est mesuré à l'état de base, 15 min après inhalation du produit, et régulièrement après l'exercice. La Mx réduit significativement la chute du VEMS induite par l'exercice sans modifier le VEMS de base chez 5 des 8 sujets, a peu d'effet chez 3 autres sujets mais entraîne une crise d'asthme chez le sujet restant. En stimulant les récepteurs alpha-1 adrénergiques post-jonctionnels, la Mx exerce un effet constricteur sur le muscle lisse, aussi bien bronchique que vasculaire. Son action préventive de l'APE pourrait être expliquée par la vasoconstriction des vaisseaux trachéo-bronchiques qui s'opposerait à l'hyperhémie et à l'œdème muqueux des voix aériennes qui seraient, au moins en partie, responsables de l'obstruction bronchique induite par l'exercice. Une autre possibilité est que, du fait de son effet secrétagogue sur l'épithélium des voies aériennes, la Mx s'oppose à la déshydratation de la surface de celles-ci qui est peut-être un facteur responsable de l'APE.
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