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Effects of clonidine on bronchial responses to histamine in normal and asthmatic subjects

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ABSTRACT: Our aim was to examine the effects of clonidine (C), an agonist of central and peripheral alpha-2 adrenoceptors, on bronchomotor responsiveness to histamine (H). In a double-blind study, we compared on two different days the effects of pretreatment with placebo (P) and with 200 μg or 150 μg of C given orally, in ten normal (NS) and eight asymptomatic asthmatic subjects (AS) respectively, the response to inhalation of serially increasing doses of H. On each day, five doubling doses of H (first dose = 3.5 and 1.1 μmol in NS and AS, respectively) were administered every 5 min; forced expiratory volume in one second (FEV_1) was measured after each dose. The dose-response curves were compared by an analysis of variance. Clonidine caused hypotension with bradycardia in all subjects. Baseline values and pre-challenge values of FEV_1 after P and C were identical on the two study days. Compared to P, C did not modify the response to H in NS but significantly increased it in AS ($p < 0.01$). Our results suggest that the neural control of the airways differs in AS compared to NS and could be explained either by a decrease in sympathetic inhibitory activity or a greater responsiveness of the airways to parasympathetic stimulation and/or a higher parasympathetic tone in AS.

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There are theoretical grounds for hypothesizing that alpha-2 adrenergic agonists may increase bronchial tone or bronchial responses to bronchoconstrictor agents through an enhanced parasympathetic activity or reduced sympathetic tone [1]. However, *in vivo* and *in vitro* effects of clonidine on the airways are controversial. In guinea pigs, intravenous clonidine aggravates, in a dose-dependent manner, the bronchial obstruction caused by histamine, serotonin and acetylcholine [2]. Conversely, aerosolized clonidine reduces in the same species both the acute ovalbumin-induced bronchial obstruction and the bronchospasm caused by vagal stimulation [3]. *In vitro*, clonidine contracts airways smooth muscle of dogs [4] and guinea pigs [5] but not man [6, 7] and mediates inhibition of both the excitatory noncholinergic neurotransmission in guinea pig [8] and the cholinergic neurotransmission in guinea pig [9] and human [10] airways. Clonidine may also have an anti-inflammatory role through inhibition of release of neuropeptides by afferent C fibres [8] and of mediators by inflammatory cells [11].

There are few available data on the effects of clonidine on human bronchi *in vivo*. In asthmatic subjects, aerosolized clonidine (75 μg) caused a slight decrease in resting airways obstruction and a marked reduction in the magnitude of the early bronchial response to inhaled antigen [12]. Conversely, a single case of acute asthma possibly related to the oral intake of clonidine has been reported in a child [13]. We hypothesized that oral clonidine should reinforce the bronchial response to histamine because it reinforces parasympathetic and reduces sympathetic tone [1] and we found in the present study that the bronchial response to histamine was indeed, enhanced by clonidine in asymptomatic asthmatic subjects but not in normal subjects.

Subjects

We studied ten healthy male volunteers and eight asthmatic subjects (four males, four females) whose anthropometric data and lung function tests are listed in table 1. None of the ten healthy subjects had a history of bronchial disease. The eight patients suffered from mild asthma and did not take any anti-asthma medication on a regular basis. All of them were atopic, the diagnosis of atopy being based upon personal and familial history and confirmed by prick tests with common pneumallergens. None of the subjects had suffered from an acute respiratory tract

Table 1. - Anthropometric and lung function data

Subjects	Height m	Sex	age yr	Slow VC %pred	TLC %pred	FEV_1 %pred
			Normal subjects n=10			
1	1.84	M	36	119	110	122
2	1.85	M	55	118	117	106
3	1.76	M	27	108	109	105
4	1.66	M	22	88	86	92
5	1.77	M	30	80	81	83
6	1.83	M	25	106	109	103
7	1.78	M	23	86	89	100
8	1.68	M	22	83	88	93
9	1.73	M	26	88	88	93
10	1.78	M	27	101	89	98
			Asthmatic subjects n=8			
11	1.58	F	22	113	109	100
12	1.63	F	22	109	105	93
13	1.75	M	24	96	91	97
14	1.80	M	23	98	95	94
15	1.70	F	23	119	111	110
16	1.83	M	26	102	105	108
17	1.80	M	21	94	97	100
18	1.70	F	21	90	91	91

Predicted values are those of the European Steel and Coal Community [Quanjer Ph H, ed. Standardized Lung Function Testing. Bull Eur Physiopathol Respir, 1983: 19 (Suppl. 5)]. Lung function data obtained on the first study day. Baseline lung function on the 3 other study days did not differ from those on the first day (two way analysis of variance). Slow VC: slow vital capacity; TLC: total lung capacity;

infection during the six weeks preceding the study. All the subjects were non-smokers. The study was approved by the ethical committee of our medical school and all subjects gave an informed consent.

Methods

Outline of the study

In all subjects, dose-response curves for the effects on FEV_1 of doubling doses of histamine after pretreatment with either placebo or clonidine were obtained at the same time of day on two different days at least 72 hours apart. In order to assess the reproducibility of the histamine challenge, four of the ten normal subjects were also studied on two different placebo days. The study was double-blind and randomized. All subjects abstained from drinking tea and coffee between the preceding evening and the end of each trial.

Each trial was carried out in the morning and started with the measurement of basal lung function. The subject then ingested tablets of either placebo or clonidine (200 µg in the healthy subjects, 150 µg in the asthmatic subjects) and remained comfortably seated for the rest of the study. Heart rate and arterial blood pressure were measured every 30 min. At 2 hours, functional residual capacity (FRC), slow vital capacity (VC) and FEV_1 as a function of stepwise doubling doses of histamine were obtained. Thus, we established the dose-response curve between 120 and 150 min after placebo or clonidine, when blood concentration of clonidine is near-maximal [1].

Technical details

Lung volumes, including FRC (helium dilution method) were measured with a water-sealed spirometer (Pulmonet 3, Gould Godart). Since it has been shown that there is a carry-over effect of a first FEV_1 manoeuvreon a subsequent one [14], we used duplicate measurements of FEV_1 only in those instances in which the first manoeuvre was not satisfactory. Subsequently, we compared all duplicate values of FEV_1 by a paired t-test. Having found no significant difference between them, we retained the highest value of each pair.

Histamine dichloride (molecular weight=183 g) was administered according to standard recommendations [15] by the reservoir method [16]. Known amounts of the agonist were nebulized with a calibrated nebulizer (Gauthier, France) into a water-sealed spirometer from which the subject slowly inhaled a predetermined volume. The dose of agonist actually inhaled by the patient is not precisely known due to deposition and sedimentation in the connecting tubes and spirometer bell. However, this does not affect intrasubject comparisons of dose-response curves since the manoeuvre is carefully standardized and each subject acts as his own control. Three minutes after administration of

each dose of histamine, FEV_1 and slow VC were measured. In the healthy subjects, the first dose of histamine nebulized into the spirometer was 3.5 µmol and four successive doubling doses were administered thereafter at 5 min intervals. Although a fall in FEV_1 >20 % of initial FEV_1 was not obtained in five of the ten subjects, the study was interrupted after the fifth dose because four subjects developed severe flushing and headache. In the asthmatic subjects, the first dose of histamine was 1.1 µmol. Thereafter one to four successive doubling doses of histamine were administered in order to obtain a fall in FEV_1 >15 % of initial FEV_1 on the first study day and the same doses were used on the second study day.

Individual dose-response curves were plotted by hand. The log dose of histamine causing a 15 or 20% fall (PD_{15} and PD_{20}, respectively) from the post-placebo or post-clonidine FEV_1 was obtained by linear interpolation.

Statistical analysis

Blood pressure and heart rate on the two study days and the two dose-response curves for normal and asthmatic subjects were compared with separate two-way analysis of variance (Triomphe software and Tektronics microcomputer, series 4050).

We also used a paired t-test for comparisons of log PD_{15}, log PD_{20} and maximal fall in FEV_1 on placebo and clonidine in asthmatic subjects. In normal subjects only the fall in FEV_1 could be analysed with a paired t-test since PD_{15} and even more PD_{20} could not be determined in most subjects.

Results

Although the study was double-blind, the subjects were aware that they had taken clonidine because of light headedness, thirst and dryness of the mouth.

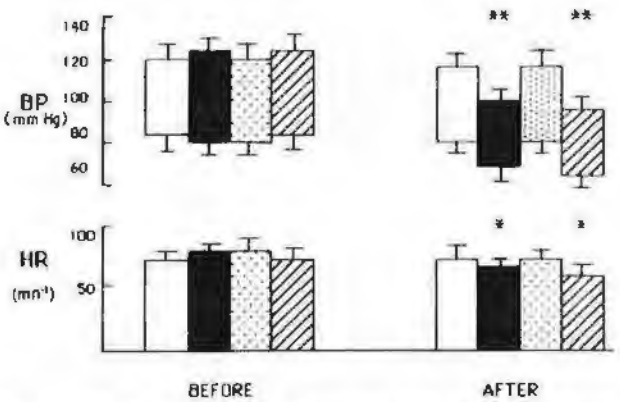

Fig. 1. - Blood pressure (BP) and heart rate (HR) before ingestion of placebo or clonidine and two hours after, at the start of the bronchial challenge with histamine. Open and stipled boxes: placebo in normal and asthmatic subjects, respectively. Black and hatched boxes: clonidine in normal and asthmatic subjects, respectively. (*) p = 0.05; (**) p < 0.01.

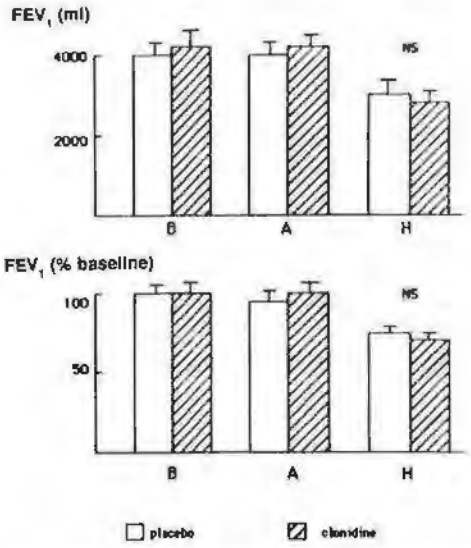

Fig. 2. - Group-average values of FEV_1 expressed in absolute values and as % of baseline in normal subjects (n = 10) before (B), two hours after (A) intake of either placebo or clonidine and at the highest dose of histamine (H).

Table 2. – Fall in forced expiratory volume in one second (FEV_1) as percent of predicted FEV_1 and as percent of badeline FEV_1 with the highest dose of histamine after pretreatment with placebo and clonidine in normal and asthmatic subjects.

Subjects	FEV_1 %pred FEV_1		FEV_1 %baseline FEV_1	
	Histamine		Histamine	
	Placebo	Clonidine	Placebo	Clonidine
	Normal subjects n=10			
1	6	11	5	9
2	13	20	12	19
3	12	21	11	20
4	20	8	23	9
5	2	18	3	23
6	11	1	9	1
7	8	19	8	19
8	20	13	23	14
9	19	29	20	29
10	2	5	3	7
Mean	11.3	14.5	11. 7	15.0
±SD	6.9	8.5	7.8	8.5
p	NS		NS	
	Asthmatic subjects n=8			
11	13	43	13	43
12	21	27	23	29
13	43	52	44	54
14	27	38	28	39
15	43	59	38	54
16	12	25	11	22
17	40	45	40	45
18	42	46	47	51
Mean	30.1	41.9	30.5	42.1
±SD	13.5	11.6	13.9	11.7
p	<0.01		<0.01	

p value was obtained with a paired t-test

The usual cardiovascular effects of clonidine were present as shown by the progressive decrease in blood pressure ($p<0.01$) and a slight, though barely significant, slowing in heart rate ($p=0.05$) over the two hours that followed the intake of clonidine but not that of placebo (fig. 1).

Results in normal subjects

Group average dose-response curves for histamine obtained on two separate days in four of the healthy subjects after placebo treatment did not differ from one another. Group average effects on FEV_1 of histamine after pretreatment with clonidine or placebo are presented in figure 2. FEV_1 was the same at the onset of the study on the two days and was not modified by clonidine or placebo at two hours, so that the initial values of FEV_1 for the two dose-response curves differed by less than 3.5% from one another. The analysis of variance showed that the dose-response curves for histamine after treatment with placebo or clonidine did not differ from one another. Individual changes in FEV_1 caused by the highest dose of histamine were extremely variable (table 2). With the highest dose of histamine used (56 µmol), the fall in FEV_1 was less than 20% of initial FEV_1 in seven of ten subjects. A 15% fall in FEV_1 was obtained in three of ten subjects on placebo and five of ten on clonidine. There was no difference in the fall in FEV_1 caused by the highest dose of histamine used between pretreatment with clonidine or placebo (fig. 2).

Results in asthmatic subjects

On average, clonidine did not modify resting FEV_1 but significantly enhanced the bronchial response to histamine as shown by a greater fall in FEV_1 at the highest dose used (fig. 3). Seven of eight subjects had a shift to the left of the dose-response curve after clonidine compared to placebo (fig. 4). The final change in FEV_1 after the highest dose of histamine was significantly greater ($p<0.01$) after clonidine than placebo and was greater than 20% of initial FEV_1 in all subjects after pretreatment with clonidine and in six of eight subjects after pretreatment with placebo (table 2). After pretreatment with clonidine, log PD_{15} and log PD_{20} (table 3) were on average slightly lower than after pretreatment with placebo ($p<0.01$).

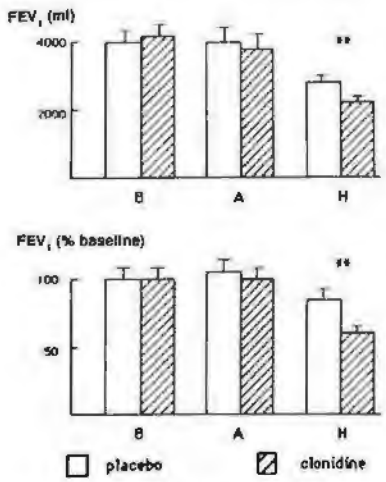

Fig. 3. - Group- average values of FEV_1 expressed in absolute values and as % of baseline in asthmatic subjects (n=8). Same format as figure 2.

Table 3. - Log doses of histamine causing a 15 (PD_{15}) or 20 (PD_{20}) % fall from initial FEV_1 in 8 asthmatic subjects

Subjects	log PD_{15}		log PD_{20}	
	Placebo	Clonidine	Placebo	Clonidine
11	3.6	2.8	3.75	2.92
12	3.7	3.59	3.82	3.72
13	4.04	3.82	4.24	4.12
14	4.14	3.87	4.34	4.06
15	2.82	2.6	2.94	2.74
16	4.64	4.06	4.91	4.37
17	3.45	3.04	3.69	3.31
18	3.55	3.31	3.72	3.44
Mean	3.74	3.39	3.93	3.58
±SD	0.54	0.53	0.58	0.58
p	<0.01		<0.01	

p value was obtained with a paired t-test.

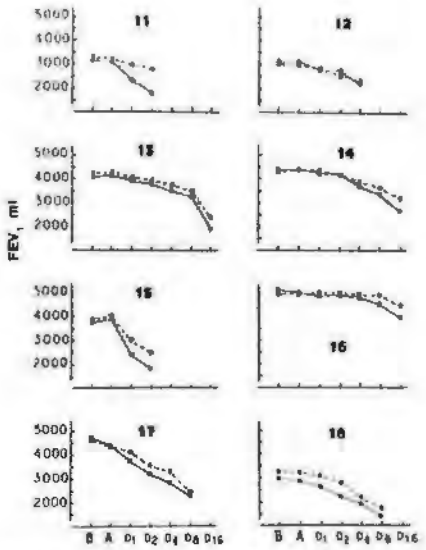

Fig. 4. - Individual dose-response (FEV_1 % of baseline) curves to histamine in asthmatic subjects (identified by a number). Placebo: interrupted line; clonidine: solid line.

Discussion

The main result of the present study is that pretreatment with clonidine had no significant effect on the dose-response curves to histamine of FEV_1 in healthy adult subjects and caused a moderate though significant shift to the left in the dose-response curves to histamine of asymptomatic asthmatic subjects in the absence of changes in resting FEV_1.

The use of FEV_1 to assess the bronchial response may lead to underestimation of the bronchial obstruction caused by histamine [17] but, since the subject acted as his own control, this does not invalidate the conclusion that clonidine enhanced the bronchial response to histamine in asthmatic but not in normal subjects.

Our results suggest that alpha-2 agonists are useful for the study of nervous control of bronchial tone in man. Firstly, clonidine did not modify the basal tone of the airways as suggested by the unchanged FEV_1 in the subjects studied. This is an advantage over other drugs, *e.g.* anticholinergic agents, the bronchodilator effect of which can make the interpretation of subsequent histamine challenge extremely difficult [18]. Secondly, due to its pharmacological properties, clonidine may be a suitable agent to investigate sympathetic moderating activity of vagal tone and vagal reflexes involved in the control of the airways in man. The cardiovascular effects of clonidine reflect an increased parasympathetic tone and a decreased sympathetic tone, presumably through stimulation of central and/or prejunctional alpha adrenoceptors [1]. The reinforcement by clonidine of the bronchial response to histamine that we observed in asthmatic subjects is, therefore, consistent with the participation of a vagal reflex in histamine-induced bronchial obstruction in such subjects [19-21].

There are some possible explanations for an increase in bronchial tone or bronchial reflexes with clonidine. Firstly, clonidine has a well documented antagonistic activity on the release of catecholamines, not only through its main effect on the central nervous system [1] but also through a concomitant peripheral effect [22]. Furthermore, clonidine is capable of contracting isolated tracheal strips through a peripheral action on postjunctional alpha-2 adrenoceptors in the dog [4] or alpha-1 adrenoceptors in the guinea pig [5], an effect which has not been confirmed with human airways [6, 7].

Our results differ from those of LINDGREN *et al.* [12] who found in ten asthmatic subjects a slight improvement of the resting airways obstruction and a marked reduction in the magnitude of the early bronchial response to inhaled antigen after pretreatment with inhaled clonidine. There is, however, an important difference as regards the mode of administration of clonidine between the two studies. We used 200 and 150 μg of clonidine given orally in the ten healthy subjects and the eight asthmatic subjects, respectively, and observed in all subjects arterial hypotension, bradycardia and other usual side-effects attributable to the central action of the drug [1]. Conversely, it is likely that the dose of 75 μg of inhaled clonidine exerted mainly, or even solely, a local inhibitory effect on bronchial smooth muscle because there were no central side-effects, *e.g.* no fall in blood pressure. Indeed, the bronchial relaxant effects of clonidine were attributed to a local action of the drug resulting from stimulation of peripheral prejunctional alpha-2 adrenoceptors [12]. Clonidine inhibits the acute bronchial obstruction resulting from vagal stimulation in guinea-pigs [3] and cholinergically mediated contraction of isolated airways of guinea-pigs [9] and man [10]. In addition, clonidine inhibits release of neuropeptides from sensory nerves [8] and of inflammatory mediators by mast cells and polymorphonuclear basophils [11]. The latter effect is probably mediated via H_2 receptors since it can be abolished by the H_2 antagonist cimetidine [23].

On the basis of the above-mentioned properties of clonidine, it is possible to reconcile the findings of LINDGREN *et al.* with our data. Our observation that a dose of clonidine given orally increased bronchial responsiveness to histamine is best explained by a predominant central effect of the drug. Conversely, the findings of LINDGREN *et al.* that a smaller dose of clonidine administered by inhalation reduced bronchial tone and allergenic bronchial responsiveness in asthmatic subjects is best explained by a predominant peripheral effect of the drug. However, we cannot exclude the possibility that the difference in the bronchial effects of inhaled and oral clonidine may be related to differences in local tissue concentrations of the drug. Further evidence in favour of a predominantly central effect of clonidine given orally or intravenously is the observation that the new compound, rilmenidine (Laboratoire Servier, France), an agonist of peripheral alpha-2 adrenoceptors with less central effects than clonidine, does not reinforce the acute airways obstruction caused by histamine in guinea pigs [24]. Therefore, our findings provide circumstantial evidence in favour of a greater contribution of excitatory vagal tone or vagally mediated reflexes in the control of airway calibre in asthmatic rather than normal subjects as suggested by studies with anticholinergic agents, *e.g.* in exercise-induced asthma [25]. It is, indeed, unlikely that the difference we found in the bronchial response to histamine of asthmatic and normal subjects is due to a direct effect of clonidine on bronchial smooth muscle since the latter is almost unresponsive to clonidine in man [6, 7].

In conclusion, our observation of a reinforcement of the bronchial response to histamine supports the hypothesis that an enhanced parasympathetic tone or a decreased sympathetic moderating activity may be a factor of bronchial hyperreactivity in asthmatic subjects. However, this conclusion needs to be qualified, since the change in bronchial responsiveness caused by clonidine is small and does not mimic the marked hyperreactivity which is a hallmark of symptomatic asthma.

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RÉSUMÉ: Notre but était de comparer, par une étude en double-insu et contre placebo, chez 10 volontaires sains (Nx) et 8 asthmatiques asymptomatiques (A) l' effet de la clonidine (C) administrée aux doses de 200 µg et de 150 µg respectivement chez les Nx et les A sur les courbes dose-réponse à l' histamine (H). La première dose d' H utilisée a été de 3,5 µmol chez les Nx et 1,1 µmol chez l' A et une dose double de la précédente a été ensuite administrée toutes les cinq minutes. Le VEMS a été mesuré après chaque dose inhalée. Les courbes effet-dose ont été comparées par analyse de variance. Sous C il y a chez tous les sujets une chute de la pression artérielle avec ralentissement de la fréquence cardiaque. La C ne modifie pas le VEMS à l' état basal chez l' ensemble des sujets. Elle ne change pas la réponse bronchique à l' H chez les Nx. Par contre elle aggrave de façon significative ($p < 0,01$) l' obstruction bronchique causée par l' H chez les asthmatiques. Nos résultats suggèrent qu' il existe une différence de la commande nerveuse réglant la perméabilité au courant gazeux des voies aériennes entre les A et les Nx. Cette différence pouvant résulter soit de la diminution du contrôle sympathique soit de l' augmentation du tonus parasympathique et/ou d' une plus grande sensibilité des voies aériennes aux stimulations parasympathiques chez l' As.