Mode of Action of Bronchodilating Drugs on Histamine-Induced Bronchoconstriction in Asthmatic Children

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Summary

The bronchodilatory response of three β_2 -agonists (fenoterol, salbutamol, and terbutaline), administered by a metered aerosol inhaler, was assessed in 19 asthmatic children after histamine-induced bronchoconstriction. At 1-min intervals, the changes in total pulmonary flow resistance (R_t) and dynamic lung compliance (C dyn) were measured. After rank-ordering according to the base line value of C dyn (62 to 200% predicted), the patients were divided into two groups according to lung compliance: (1) patients with greater compliance (C dyn, 129 to 200% predicted) and (2) patients with lesser compliance (C dyn, 69 to 116% predicted). The effect of the three bronchodilators on the mean decrease of R_t and on the increase of C dyn was studied and analyzed for each drug separately. In all patients, salbutamol was the most efficient bronchodilator of small airways ($P < 0.02$). The most striking feature of this β_2 -mimetic was observed in patients whose lungs were initially overinflated (functional residual capacity over 120% predicted) but not obstructed before the histamine challenge ($P < 0.005$). In these subjects C dyn and R_t are normalized after inhalation of salbutamol.

After fenoterol and terbutaline inhalation, obstruction of the large airways was not fully alleviated. In addition, these two drugs seemed not to affect the ventilatory asynchronism (C dyn alterations) in patients whose lungs had been overinflated before drug inhalation (C dyn again around 150% predicted).

Speculation

On the basis of a distinction between patients with more or less compliant lungs, as defined by measurements of base line values of dynamic lung compliance, the search for optimal individual quantitative and qualitative response to one of the various bronchodilator drugs seems to be possible and of important therapeutic value. From the functional approach of asthmatic children during a symptom-free period and from the values of their lung volumes, total pulmonary flow resistance and dynamic lung compliance it would be possible to choose the most efficient bronchodilator.

The mainstay for bronchial asthma treatment is the use of drugs to alleviate airway obstruction or to prevent its development. The fundamental framework for diagnosis, grading of severity and pharmacologic management, was recently outlined by Ekwo and Weinberger (8). Other reviews on the effects of different bronchodilators and their mode of administration in asthmatic children have been published recently (4, 24, 32-34). Administration of bronchodilator aerosols is a well-established treatment for airway obstruction in children with bronchial asthma (1-8, 14, 22, 27-30, 39). Drugs which may be administered include atropine-like agents (5, 6, 22) and, in order to minimize cardiac side-effects, selective β_2 -sympathomimetics. Recent studies have demonstrated considerable differences in the preferential efficiency of these drugs on peripheral airways (42). It has been suggested (5, 6, 18,

23, 25, 35) that in adult asthmatic patients, atropine-like substances predominantly dilate larger upstream airways and that β_2 -sympathomimetics predominantly dilate smaller upstream airways.

The relative contribution made by large and small airways to flow limitation is of major interest to several research groups. This determination is important from the therapeutical point of view, since it is preferable to use a bronchodilating substance that specifically affects the area of broncho-obstruction in the particular patient.

There have been numerous studies on the effect of β_2 -agonists in children. Little is known about their specific action on the small and/or large airways, especially the site of their action, since most of the published studies conducted lung function tests in the form of "forced breathing manoeuvres" (FEV_1 = forced expiratory volume 1 sec, FVC = forced vital capacity, PF = peak flow, FEF = forced expiratory flow at different percent of the vital capacity). These tests fail to detect changes in small airway caliber. Moreover they are effort and cooperation-dependent.

The present study was, therefore, designed to ascertain whether the immediate bronchodilatory response of three β_2 -sympathomimetic aerosols (fenoterol, salbutamol, and terbutaline) is similar in asthmatic children after histamine respiratory challenge and whether the preferential sites of action of these three drugs can be detected within the bronchial tree.

PATIENTS AND METHODS

Nineteen asthmatic children (10 boys and nine girls, aged between 5 and 17 yr) were studied after obtaining informed consent. All patients had a long history of moderate or mild asthma and all had positive skin tests for various pneumoallergens. No upper respiratory tract infection was observed in the 4 wk before the study. No asthmatic attack had been noted in the preceding 14 days and the clinical examination was free of symptoms. No patient had been receiving oral or inhaled corticosteroids or antihistaminics for at least 10 days. Sodium cromoglycate was discontinued for at least 7 days and bronchodilators for at least 2 days. All patients had undergone pulmonary function tests before the assays and were thus familiar with the method applied. The lung function investigations included measurement of the functional residual capacity (FRC) using the closed helium dilution method, the lung volumes and capacities (residual volume, expiratory reserve volume, inspiratory capacity, and total lung capacity) (10). Dynamic lung compliance (C dyn) and total pulmonary flow resistance (R_t) were measured by the usual methods (12).

C dyn during normal frequency breathing was calculated from simultaneous volume and intraesophageal pressure changes at zero flow points between the start and the end of the inspiration. The pressure changes were measured with a differential pressure transducer (Elema-Schonander EMT 34) connected to an esophageal catheter the tip of which was covered by a balloon. The balloon (length, 8 cm; circumference, 3 cm; wall thickness, 0.05 cm) was sealed over multiple perforations at the distal end of a

polyethylene catheter (internal diameter 0.14 cm) 100 cm long. It exerted zero pressure at a gas volume in the balloon of 0.3 ml—the volume used for all measurements. The balloon was positioned through the nose in the midesophagus, in a position free from pressure artifacts (12). The volume displacement coefficient of the catheter-manometer system was about 0.002 ml/cm H₂O, and the 90% response time 0.02 sec. Gas flow rate at the mouth was measured with a heated Fleisch pneumotachometer (no. 2) connected to a differential transducer. The intraesophageal pressure and the flow changes as well as the integrated volume values (Fenyves and Gut) were calibrated before each measurement and the response was linear over the range used. R_i was calculated between inspiratory and expiratory mid-tidal-iso-volume points from the intraesophageal pressure and the simultaneously recorded flow curves.

Controlled bronchial inhalation tests were performed by the technique of Geubelle (9, 13, 14, 28, 36, 37) with histamine aerosols in order to appreciate bronchial hyperreactivity. During the inhalation of histamine aerosol and the subsequent 6 min after administration of the bronchodilator, the intraesophageal pressure and the flow and the volume changes of the lung were continuously recorded. An increase of +100% in the intraesophageal recordings assessed by eye was considered an indication of a ventilatory obstruction and the inhalation of histamine was immediately discontinued. For ethical reasons only one histamine

provocation test was performed on each patient. Consequently one bronchodilator had been randomly chosen for each patient assay and given from a metered aerosol inhaler (2 × 0.20 mg; 1.318 μmole fenoterol, 2 × 0.10 mg; 0.835 μmole salbutamol, 2 × 0.25 mg; 1.648 μmole terbutaline, respectively). All inhalations were performed during two deep inspirations followed by a few seconds of breathholding. All the lung function tests were performed between 9 AM and 12 o'clock during the winter months.

The statistical evaluation has been performed by Wilcoxon-Mann-Whitney rank analysis.

RESULTS

CLINICAL MATERIAL

Before the Inhalation of the Histamine Aerosol. The anthropometric data of the patients, the values of their lung volumes and capacities expressed in percentage of the predicted values (11, 12) as well as the threshold doses of histamine determined by the provocation test (9) are collected in Table 1. The patients are rank ordered due to the base line value of the C dyn and divided into two groups.

All cases in group A fulfilled the following criteria: (1) the FRC is near the predicted value, (2) the C dyn is normal or decreased, and (3) the R_i by the mean slightly increased.

Table 1. Anthropometric data, lung function base line value and histamine provocation threshold of the 16 asthmatic children, rank ordered according to the base line value of C dyn

Patient	Sex	Age	FRC ¹	RV ¹	TLC ¹	FRC/ TLC	Cdyn	Cdyn/FRC	R _i ¹ -(lung) ¹	sG _L ¹	Histamine provo- cation threshold (10 ⁻⁶ mg/ml)	Randomized choice of the drug
Group A												
B. Ch.	F	8	92	109	93	45	82	47	96	113	1000	Terbutaline
A. M.	F	9	103	126	100	47	67	44	104	93	500	Salbutamol
B. J.	F	8	97	113	84	52	69	47	145	71	2500	Terbutaline
L. M.	F	10	96	112	100	45	79	58	109	95	500	Salbutamol
B. A.	M	14	96	93	100	43	87	47	84	124	2500	Fenoterol
P. M.	M	9	108	132	94	45	87	56	120	77	1000	Fenoterol
L. I.	F	9	105	119	105	46	97	49	131	72	500	Terbutaline
D. S.	M	15	122	140	98	48	107	51	103	79	1000	Salbutamol
G. F.	F	11	112	107	103	50	105	58	104	85	2500	Fenoterol
Mean			103.4	116.7	97.4	46.7		50.6	110.6	81.2		
S.D.			9.5	14.2	6.3	2.8		5.5	18.6	33.4		
S.E.			3.2	4.7	2.1	0.9		1.8	6.7	11.2		
Group B												
D. P.	F	8	130	146	106	56	116	63	84	91	1000	Terbutaline
G. Ph.	M	8	149	158	126	50	129	55	105	63	1000	Salbutamol
D. M.	F	12	126	143	109	50	131	78	100	79	250	Fenoterol
M. M.	F	14	117	110	107	49	135	76	84	101	1000	Fenoterol
B. R.	M	6	134	171	120	49	144	74	101	73	500	Salbutamol
H. S.	M	7	149	151	130	50	145	64	89	75	250	Terbutaline
R. M.	F	11	122	125	110	51	154	82	86	95	1000	Salbutamol
D. M.	M	8	140	167	112	52	180	79	81	88	2500	Terbutaline
S. JM.	M	12	110	135	105	46	189	94	84	197	250	Terbutaline
B. R.	M	5	171	188	112	58	200	94	82	71	500	Fenoterol
Mean			134.8	149.4	113.7	51.1		75.8	89.6	84.9		
S.D.			18.1	22.9	8.7	3.5		12.6	8.8	14.4		
S.E.			5.7	7.2	2.7	1.1		3.9	2.8	4.5		
Significance P (Wilcoxon-Mann- Whitney)			<0.001	<0.005	<0.001	<0.005		<0.001	0.05	NS		

¹RV, residual volume; TLC, total lung capacity; Cdyn and R_i all parameters expressed in percentage of predicted values (11, 12). Significance level calculated according to the Wilcoxon-Mann-Whitney test; NS, not significant.

Because gas is trapped in nonventilated lung units, the thoracic gas volume was not measured. It may be assumed that the lungs of this group were not significantly overinflated.

The ventilatory obstruction is demonstrated by the R_i increase and a ventilatory asynchronism is indicated by the C_{dyn} decrease. Both, large and peripheral airways are obstructed.

All cases of group B present the three following criteria: The FRC and the C_{dyn} are increased and R_i is normal or decreased. A similar assumption concerning the possible trapped gas has to be considered. The ventilated lung units are hyperinflated and consequently the lung elastic recoil is increased. The pulling forces applied to the walls of the peripheral airways might explain the increase of the C_{dyn} : there is no obstruction of the peripheral airways and the specific compliance per litre of FRC is near the normal value in all cases.

Moreover, the distending forces are applied to the whole bronchial tree—the large as well as the more peripheral airways—and the resistance to the air flow is normal or, in most cases, below the predicted values.

The values of R_i show a wide variation within the two groups, not inversely related to the values of C_{dyn} . Nevertheless, if the resistance is related to the concomitant lung volume and the specific conductance (sG_L) is calculated it can be observed that the degree of impairment of the bronchial conductivity is about 20% in each group (sG_L % pred.: group A: 74.2 ± 9.8 and group B: 87.2 ± 13.7 , not significantly different). Also the sG_L in the randomly selected drug subgroups is nearly equal (sG_L % pred.: salbutamol 83.0 ± 13.4 ; terbutaline 88.3 ± 17.1 ; fenoterol 89.5 ± 19.7).

The scattering of the base line values of R_i and C_{dyn} demonstrates clearly, that even the so called "symptom-free interval" lung function abnormalities can be present, which are not detected clinically.

The difference between the values in groups A and B is statistically significant for FRC ($P > 0.001$), for residual volume ($P > 0.005$), for total lung capacity ($P > 0.001$), for C_{dyn} /FRC ($P > 0.001$), and for R_i ($P > 0.05$) (C_{dyn} was taken as selection criterion).

After Inhalation of the Histamine Aerosol. The threshold doses of response to histamine is not significantly different in both groups A and B.

Histamine induces a ventilatory obstruction of the large as well as of the small peripheral airways in both groups A and B. Indeed R_i increases and C_{dyn} decreases. The R_i increase, in percentage of the predicted value, is actually larger in group B than in group A. But the R_i values are similar in both groups after the respiratory challenge even if these values were in most cases lower than those predicted before the inhalation of histamine in group B.

Similarly, the drop of C_{dyn} is larger in group B. But before the inhalation, C_{dyn} was lower in most cases of group A: in those patients whose small airway calibre was normal or subnormal, histamine induced an obstruction of the large as well as of the small airways.

The bronchoconstricting effect of histamine is short. It is thus impossible to determine the lung volumes and capacities on the top of a provocation, for such measurements require at least 10 min.

Response of the β_2 -Mimetics. Table 2 and Figures 1 and 2 illustrate the R_i and the C_{dyn} changes, respectively, after the inhalation of the β -mimetics.

Concerning the values of R_i (indicating mostly the effect of the drugs on the large airways) the efficiency of the β -mimetics may be graded in the following way for both groups A and B: fenoterol, terbutaline and, the most efficient, salbutamol. In group A these differences are smaller than in group B.

Concerning the values of C_{dyn} (indicating mostly the effect of the drugs on the small airways) the "obstructed" patients of group A have to be separated from the "overinflated" subjects of group B.

In patients of group A, terbutaline and fenoterol have little effect on C_{dyn} . Salbutamol inhalations induce an increase of C_{dyn} up to normal values. However, R_i is still moderately increased

R_i % pred. $\pm$ SEM

Fig. 1. Total resistance changes to the air flow in percentage predicted to the standard height (12) in the groups A (circles; initially normal inflated) and B (triangles; initially overinflated), before and after provocation, as well as in the next 6 min after administration of the β_2 -agonists (F, fenoterol; T, terbutaline, and S, salbutamol). Open symbols represent the changes of the three treatment subgroups, closed symbols represent the mean values of groups A and B.

C_{dyn} % pred. $\pm$ SEM

Fig. 2. C_{dyn} changes in percentage predicted to the standard heights (12) in the group A (circles; initially normal ventilated) and B (triangles; initially overinflated), before and after provocation, as well as in the next 6 min after administration of the three β_2 -agonists (F, fenoterol; T, terbutaline; S, salbutamol). Open symbols represent the changes of the three treatment subgroups, closed symbols the mean values of groups A and B.

Table 2. $R_{1\text{p}}^{\text{-(lung)}}$ and C_{dyn} provocation ($R_{1\text{p}}^{\text{-(lung)}}$, C_{dyn} resp.) and in the 6 min after administration of a β -mimetic¹

	R ₁ after stimulation						with:	C dyn _o	C dyn _p	C dyn after stimulation				
	R _{1o}	R _{1p}	30"	1'	2'	4'				6'	30'	1'	2'	4'
Group A														
96	181	124	89	65	72	67	Terbutaline	62	42	70	85	75	78	85
104	195	125	96	94	92	80	Salbutamol	67	37	47	57	87	83	103
145	256	218	184	174	177	174	Terbutaline	69	49	53	51	61	74	79
109	262	162	140	143	133	133	Salbutamol	79	56	64	85	100	89	94
84	250	150	126	102	102	86	Fenoterol	87	45	72	72	72	73	89
120	197	165	151	129	137	87	Fenoterol	87	40	54	57	64	65	67
131	296	164	149	109	112	109	Terbutaline	97	47	67	72	79	96	100
103	222	101	116	103	106	108	Salbutamol	107	79	107	103	100	102	109
104	193	189	164	130	148	144	Fenoterol	105	41	55	54	66	69	79
Group B														
84	177	147	106	87	91	94	Terbutaline	116	55	72	81	99	108	122
105	228	150	118	104	89	102	Salbutamol	129	76	80	80	102	106	120
100	214	184	178	159	149	143	Fenoterol	131	67	125	137	143	148	140
84	274	234	168	149	138	142	Fenoterol	135	66	102	115	144	178	186
101	229	153	120	124	107	101	Salbutamol	144	86	94	86	102	122	128
89	199	131	124	126	115	96	Terbutaline	145	81	163	171	163	179	190
86	184	151	116	114	106	105	Salbutamol	154	55	94	103	101	109	112
81	215	156	160	158	164	100	Terbutaline	180	89	118	131	128	136	136
84	250	158	130	125	113	102	Terbutaline	189	77	138	151	129	136	141
82	214	184	161	139	127	140	Fenoterol	200	76	88	117	135	145	159

¹ All values expressed as percentage of predicted values (12).

Table 3. Comparison between I and II according to the nonparametric test of the rank-sum-analysis of Wilcoxon-Mann-Whitney

Statistical evaluation

Histamine-provocation test

Comparison between group A and B	Mann-Whitney statistics		
	n^A/n^B		P
R_1 increase in % pred.	9/10	1.143	NS ¹
C_{dyn} decrease in % pred.	9/10	3.429	<0.001

Drug response

measured by $R_{1\text{p}}^{\text{-(lung)}}$ -changes

group A:

Salbutamol/terbutaline/fenoterol

NS

group B:

Salbutamol/terbutaline

15/20

0.833

NS

Salbutamol/fenoterol

15/15

3.671

<0.0001

Terbutaline/fenoterol

20/15

3.300

<0.0004

measured by C_{dyn} -changes

group A:

Salbutamol/terbutaline

15/15

2.011

<0.022

Salbutamol/fenoterol

15/15

2.883

<0.002

Terbutaline/fenoterol

15/15

NS

group B:

Terbutaline/salbutamol

20/15

2.600

<0.005

Terbutaline/fenoterol

20/15

NS

Fenoterol/Salbutamol

15/15

3.587

<0.0001

inhalation, are observed after the administration of these two β -mimetics. One may assume that these patients are once again overinflated as before the assay: even if the large airways are still moderately obstructed (R_1 being around 120% of the predicted values), the small bronchi are dilated (C_{dyn} being around 15% of the normal values).

At a first approach, salbutamol is less efficient than the two other β -mimetics: C_{dyn} does not increase up to the values observed before the histamine inhalation. But in this subgroup R_1 is decreased up to the predicted value. One may assume that the obstruction of the large bronchi is fully alleviated, and in addition these patients are no longer overinflated.

Table 3 gives a summary of the different statistical analyses. It becomes clear that the different response to salbutamol, namely in respect of C_{dyn} changes, is the most pronounced.

DISCUSSION

Several recent studies concerning the mechanical factors involved in flow-limitation have demonstrated that conventional methods of detecting a ventilatory obstruction, such as measurement of pulmonary airway resistance to airflow, may fail to detect peripheral airway obstruction (18, 19, 23, 25, 31, 41). Moreover, forced breathing manoeuvres, such as forced vital capacities, forced expiratory volumes in 1 sec, and maximal flow volume curves require full cooperation from the subject, so the data obtained from children are less reproducible than those from trained adults (10, 15, 16, 40). In addition, attempts have been made to ascertain the decrease of C_{dyn} by increasing the respiratory frequency, assuming that this is a more sensitive method of detecting ventilatory obstruction of the small and peripheral airways (19, 26, 41). This estimation of the frequency dependence of dynamic compliance also requires full cooperation from the patient and is therefore only of limited validity when performed on children. Moreover, the expiratory level (*i.e.*, FRC) has to be known during this procedure (10, 26).

It is generally accepted that R_1 changes reflect mainly alterations in the dimensions of large airways (17), so that a decrease of R_1 after drug inhalation implies a dilation of these more central airways (*e.g.*, the first 5 to 7 airway generations). In contrast, changes in C_{dyn} are thought to be due to modifications in the

in this salbutamol-subgroup. One may assume that at the end of the assay these patients are not overinflated and that the obstruction of the small airways are alleviated even if a moderate obstruction of the large bronchi is still observed.

In patients of group B, terbutaline and fenoterol are immediately and significantly more efficient than salbutamol. Indeed the abnormally high values of C_{dyn} preexisting before the histamine

more peripheral, small airways, leading to a ventilatory asynchronism (31).

Concerning these ventilatory abnormalities the inhalation of three bronchodilators is followed by a decrease in R_i and an increase in C_{dyn} (Figs. 1 and 2).

In patients of group A, the pathologic mechanism involved may be considered as an usual and classical pattern in asthmatic children during symptom-free period: little or no overinflation (the gas trapped in the lung not being considered in this appreciation), an increase of R_i and a decrease of C_{dyn} , both large and small airways being moderately obstructed (20).

In patients of group B, these mechanisms have to be discussed. The ventilated units are overinflated, R_i is decreased and C_{dyn} is increased: the higher the expiratory level, the higher the elastic forces are on the lung (C_{dyn} increase) and the pulling on the outer walls of the bronchi (R_i decrease) (21). But the primary cause of this overinflation is still disputed. It might be a sustained reflex response in some patients or a moderate bronchoconstriction, similar to the leveling on expiratory level at the start of a dyspnoeic attack. The effects of salbutamol in the patients of group B support this hypothesis. But in some overinflated patients the lung compliance seems to be abnormally high for the volume of the ventilated units. If the values of dynamic compliance might be confirmed by abnormally high values of the so-called static compliance and abnormally low intra-thoracic pressure for the expiratory level, one might assume that in a too compliant lung, the small and peripheral airways are almost collapsed at a normal lung volume: the leveling on expiratory level would be a reflex from these collapsed peripheral airways.

From the practical point of view the following conclusions may be suggested:

(1) From the values of the lung volumes, total pulmonary flow resistance, and C_{dyn} , a distinction between patients with more or less compliant lungs can be made and consequently the different mode of action of the bronchodilating drugs individually estimated.

(2) If during a symptom-free period the patient is not usually overinflated and if large (R_i increase) and small (C_{dyn} decrease) airways are obstructed, salbutamol is efficient on both types of bronchi, at least after an histamine provoked ventilatory obstruction. Salbutamol is a little more efficient than the two other β stimulants, fenoterol and terbutaline, on the large bronchi but it is significantly more active on the small airways.

(3) In overinflated patients without obstruction of the airways, the small bronchi being distended by the increased lung elastic forces, fenoterol and terbutaline seem to fail efficacy on the provoked ventilatory obstruction with respect to small bronchi. One may assume that in a majority of such cases the lungs remain overinflated. However, in some cases, one may suspect a too compliant lung with concomitant ventilatory asynchronism.

In view of these considerations, the search for an individual optimal quantitative and qualitative response to a bronchodilator aerosol appears to be justified.

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