Medical Journal of the
Islamic Republic of Iran

Volume 11
Number 2
Summer 1376
August 1997

Basic Science In Medicine

ENHANCED HISTAMINE H_1 RECEPTOR BLOCKADE WITH CHLORPHENIRAMINE IN THE ASTHMATIC TRACHEO-BRONCHIAL TREE: FURTHER EVIDENCE FOR INCREASED DRUG DELIVERY IN ASTHMA

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ABSTRACT

We have measured the competitive antagonistic effect of chlorpheniramine in bronchi of 8 normal and 12 asthmatic subjects. Classical pharmacological theory states that the degree of competitive antagonism depends only upon 1) antagonist concentration at the receptor, and 2) receptor affinity. Delivery and affinity also influence agonist responsiveness, but measurement of bronchial antagonism allows study of these factors in isolation. Bronchial responsiveness to histamine was measured as the dose required to produce a 35% fall in specific conductance (sGaw), called PD_{35}. On different days, 2 measurements of control PD_{35} were made on each subject. Measurements of PD_{35} were also repeated after inhalation of 1.45 mg chlorpheniramine and intravenous injection of 0.17 mg/kg chlorpheniramine. Antagonist effect of chlorpheniramine was measured as Dose Ratio-1 (DR-1), where DR= PD_{35} after chlorpheniramine/control PD_{35}. Geometric mean of DR-1 with inhaled chlorpheniramine in asthmatic subjects (5.8) was 6.8 times that of normal subjects (0.86) (p=0.002), and DR-1 with intravenous chlorpheniramine in asthmatic subjects (4.4) was 2.75 times that of normal subjects (1.6) (p=0.005). There were significant negative correlations between PD_{35} and DR-1, whether chlorpheniramine was administered by inhalation (r= -0.87, p<0.001) or intravenously (r= -0.62, p<0.005). There was also a significant correlation between DR-1 obtained by two routes of administration (r= 0.77, p<0.001). Taken with our previous study showing enhanced antagonism with atropine at bronchial muscarinic receptors in asthma,[1] these results suggest that drug delivery by inhaled and parenteral routes may be increased in asthmatic bronchi.

Keywords: histamine H_1 receptors, asthma, chlorpheniramine, histamine

MJIRI, Vol. 11, No. 2, 115-122, 1997.

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INTRODUCTION

In previous studies we demonstrated that competitive antagonism by atropine and propranolol at the bronchial muscarinic and adrenergic receptors was greater in asthmatic patients than in normal subjects.[1,2] The highest level of blockade was seen in asthmatic patients who were most sensitive to inhaled methacholine and isoprenaline and the lowest level in the least sensitive normal subjects. Classical pharmacological theory[3] states that the degree of competitive antagonism produced by atropine is determined only by: 1), its concentration at the receptor (determined by dose and drug delivery), and 2) receptor affinity for atropine. Thus, we concluded that in asthma either drug delivery or receptor affinity, or both are increased. With regard to drug delivery, we found that enhanced blockade in asthma was seen whether antagonist drugs were administered by inhalation or intravenous injection, as would be expected if the abnormality in asthma was increased receptor affinity, but alternatively this observation would be compatible with an abnormality of drug delivery in the immediate vicinity of the receptor. Significant correlations between the degree of antagonist blockade and agonist responsiveness suggested that these abnormalities of delivery and/or affinity underlie hyperresponsiveness to methacholine in asthma.

In the present study we have widened the application of this analysis to another agonist/antagonist combination, histamine/chlorpheniramine. Chlorpheniramine is a competitive antagonist at the bronchial H_1 histaminergic receptor.[4] We wished to determine whether "antagonist hyperresponsiveness" in asthma was specific to muscarinic and beta-adrenergic receptor-mediated responses, or was a more general phenomenon. If enhanced blockade results from deficiency of a physical barrier to drug diffusion, then all drugs of similar size and charge may be similarly affected; if it is due to a change in receptor structure it may be specific to a single receptor, or class of receptor. We have therefore measured antagonism produced by inhaled and parenteral chlorpheniramine on bronchial responsiveness to inhaled histamine in normal and asthmatic subjects.

PATIENTS AND METHODS

Subjects

8 normal subjects and 12 well-controlled asthmatic adults were studied (Table I). The normal subjects were all members of staff of this department and were all free of current respiratory complaints and had normal respiratory function: they had no past history of respiratory disease. Five of the asthmatic subjects were also members of staff; at the time of study they had been asymptomatic for several months or years without treatment but had a past history of mild intermittent wheeziness and chest tightness requiring inhaled bronchodilator therapy. The remaining asthmatic subjects were recruited from the Asthma Clinic, Charing Cross Hospital and were all on active treatment for their condition. No subject had suffered from an upper respiratory tract infection in the previous months. All the subjects were volunteers who agreed to take part after having the nature of the experiments and their purpose explained to them. The experiments were approved by the Ethical Committee of Charing Cross Hospital.

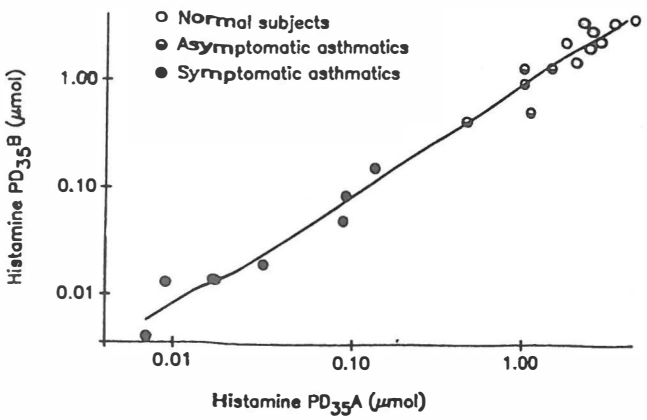

Fig. 1. Comparison of two measurements of histamine responsiveness (PD_{35}). n= 20, Regression equation y= 0.0046+1.04X, r= 0.99.

Techniques and protocol

Each subject attended the laboratory on two occasions with at least 48 hours between attendances over a period exceeding two weeks. Challenge was performed at approximately the same time of day on each occasion.[5] Subjects were requested to refrain from caffeinated drinks for two hours before challenge and from using bronchodilator inhalers for at least 8 hours. On each occasion we performed two histamine challenges, the first without premedication and the second after chlorpheniramine. In random order on the two days the following experimental procedures were performed:

1) Histamine challenge (control A) followed after a 20 min interval by administration of 33 breaths of 0.5% chlorpheniramine maleate (MW 391) (1.45 mg; 3.71 μmol). Histamine challenge was then repeated after a further 20 min interval (post-inhaled chlorpheniramine).

2) Histamine challenge (control B) followed after a 20 min rest by premedication with 0.17 mg/kg chlorpheniramine administered intravenously, 10 min before a further histamine challenge (post-IV chlorpheniramine).

Histamine challenge was performed in the following manner: Histamine acid phosphate (molecular weight= 308), dissolved in 0.9% NaCl solution was delivered intermittently as an aerosol from a Hudson nebulizer (driven by compressed air at 20 psi) which was attached to a breath-activated dosimeter.[6] The dosimeter and nebulizer were triggered by

Table I. Characteristics of normal and asthmatic subjects.

Subjects	Sex & Age	Weight (kg)	Height (cm)	FEV_1 L/sec	sGaw $s^{-1}kPa^{-1}$	Smoking	Atopy	Treatment
Normal								
1	M-27	66	175	3.94	1.32	-	-	-
2	M-34	58	162	3.55	1.41	-	-	-
3	F-33	52	154	2.75	1.48	-	-	-
4	F-29	58	151	2.35	1.96	-	-	-
5	F-27	65	168	3.94	1.88	-	-	-
6	M-31	65	170	3.37	1.56	-	-	-
7	M-36	70	173	3.98	2.09	-	-	-
8	M-30	80	175	3.40	1.30	-	-	-
Asymptomatic asthmatic								
1	F-26	58	161	3.55	1.34	-	+	-
2	M-28	69	172	4.11	1.44	-	+	-
3	M-28	70	175	3.78	1.83	-	+	-
4	F-26	58	164	3.71	1.63	S	+	-
5	M-29	70	180	4.23	1.91	-	+	-
Symptomatic asthmatic								
1	M-49	86	181	3.30	0.36	-	+	Te-Ip-Bf-Theo
2	F-42	77	158	1.05	0.28	-	+	Sal-Ip-Bf-Ned
3	F-62	61	168	0.55	0.21	-	+	Sal-Bud
4	F-68	66	162	2.10	0.48	-	-	Sal-Bf
5	F-47	67	162	2.05	0.26	S	+	Te-Bud-Pred
6	M-44	66	172	1.20	0.24	S	-	Sal-Ip-Bf
7	F-51	56	161	2.35	1.04	-	+	Sal-Bf

Sal= Salbutamol
Te= Terbutaline
Ip= Ipratropium bromide
Theo= Theophylline
Ned= Nedocromil sodium
Bud= Budesonide
Bf= Beclomethasone dipropionate
Pred= Prednisolone

the fall in mouth pressure at the onset of inspiration. Nebulisation continued for 1.8 sec. Subjects were instructed to inspire deeply from FRC to near TLC during 5 sec. We attached a small spirometer (Coach spirometer, Intersurgical, London) to the mouth piece which was used to display airflow and inspiratory volume to the subject during inspiration. The subject was given a target inspiratory volume and flow rate, calculated to produce full inspiration in approximately 5 sec.[7] The volume of solution delivered per activation was 8.8 μL. The aerosol had a mass median aerodynamic diameter (MMAD) of 3.0 μm as determined by laser light scattering (Malvern Instruments 2600 HSD analyser, Malvern U.K.). The same nebulizer was used throughout the experiment.

At the beginning of each challenge baseline specific conductance (sGaw) was measured using a constant volume body plethysmograph (Fenyves & Gut, Basel, Switzerland). The subject panted at a frequency of 1-2 Hz in order to measure airway resistance (Raw)[8] and thoracic gas volume (Vtg). The output loops from the plethysmograph were displayed on an X-Y plotter and their slopes were measured manually. To minimize bias the loops were read in batches, without reference to the experimental circumstances. sGaw was expressed as s-1 kPa-1, where sGaw= $(Raw. Vtg)^{-1}$. Each determination of sGaw was obtained from the arithmetic mean of five measurements which were performed over a period of 30 sec. The subject then took five inhalations of 0.9% NaCl aerosol (control diluent). Two minutes later sGaw was again measured. The subject then took five breaths of histamine solution, followed by further sGaw measurement after two minutes. The inhaled concentration of histamine solution was then doubled every three minutes with serial measurement of sGaw 2 min after each concentration of aerosol. The challenge was terminated when sGaw had fallen by more then 35% at which point the subject was aware of moderate chest tightness and wheeziness. For normal subjects the starting concentration of histamine was 2g/L (6.5 mmol) and the maximum concentration used was 64 g/L (207.8 mmol) (giving inhaled doses of 0.286 and 9.14 μmol respectively). After

Table II. Individual values of bronchial responsiveness to histamine on two occasions ($PD_{35}A$ and $PD_{35}B$) and chlorpheniramine blockade (DR-1) by inhalation (INH) and injection (IV).

Subjects	$PD_{35}A$ (µmol)	DR-1 INH	$PD_{35}B$ (µmol)	DR-1 IV	Mean PD_{35}
Normal					
1	1.800	2.57	2.400	1.80	2.100
2	2.500	1.82	3.150	2.42	2.830
3	2.430	0.89	2.190	1.29	2.310
4	2.750	0.35	2.520	1.35	2.640
5	4.310	0.50	3.970	1.34	4.140
6	3.240	0.34	3.710	1.43	3.480
7	2.240	1.02	3.780	1.17	3.010
8	2.060	1.14	1.600	2.60	1.830
Arithmetic X	2.670	1.08	2.920	1.68	2.790
SD	0.790	0.78	0.860	0.55	0.760
Geometric X	2.580	0.86	2.790	1.61	2.700
Asymptomatic asthmatic					
1	0.990	1.52	1.360	3.23	1.180
2	1.480	1.56	1.380	0.93	1.430
3	0.450	3.52	0.440	5.45	0.440
4	1.000	3.36	0.980	4.07	0.990
5	1.100	1.76	0.530	4.35	0.820
Symptomatic asthmatic					
1	0.009	7.71	0.013	2.67	0.011
2	0.007	17.34	0.004	13.44	0.006
3	0.016	7.47	0.014	1.69	0.015
4	0.086	9.55	0.052	8.85	0.069
5	0.132	12.13	0.160	8.28	0.146
6	0.029	28.10	0.020	16.40	0.025
7	0.089	10.33	0.089	2.55	0.089
Arithmetic X	0.450	8.70	0.420	6.00	0.430
SD	0.540	7.85	0.530	4.85	0.530
Geometric X	0.130	5.84	0.110	4.41	0.120

premedication with chlorpheniramine some subjects received a maximum dose of 10 inhalations of 64 g/L (inhaled dose =18.28 µmol). For asymptomatic asthmatic subjects the starting concentration was 0.5 g/L (1.62 mmol) and for the symptomatic asthmatic subjects 0.0312 g/L (0.10 mmol) (inhaled dose=0.071, 0.004 µmol, respectively). In all cases the nebulizer was filled with 5 mL of solution. Subjects were asked to avoid coughing or taking deep breaths, particularly during the phase of bronchoconstriction. Duration of each histamine challenge was approximately 20-25 min.

Chlorpheniramine inhalation was performed using the same dosimeter/nebulizer system and the same technique of inhalation as was used for histamine.

At the end of each test the subject took two puffs of salbutamol to relieve chest tightness.

Measurements

For each challenge a non-cumulative log dose-response curve was constructed by plotting sGaw against the logarithm to base 10 of histamine delivered to the subject. For each curve we determined control sGaw measured after inhalation of diluent and the dose of histamine which produced a 35% fall in sGaw= PD_{35}. PD_{35} in control (unpremedicated)

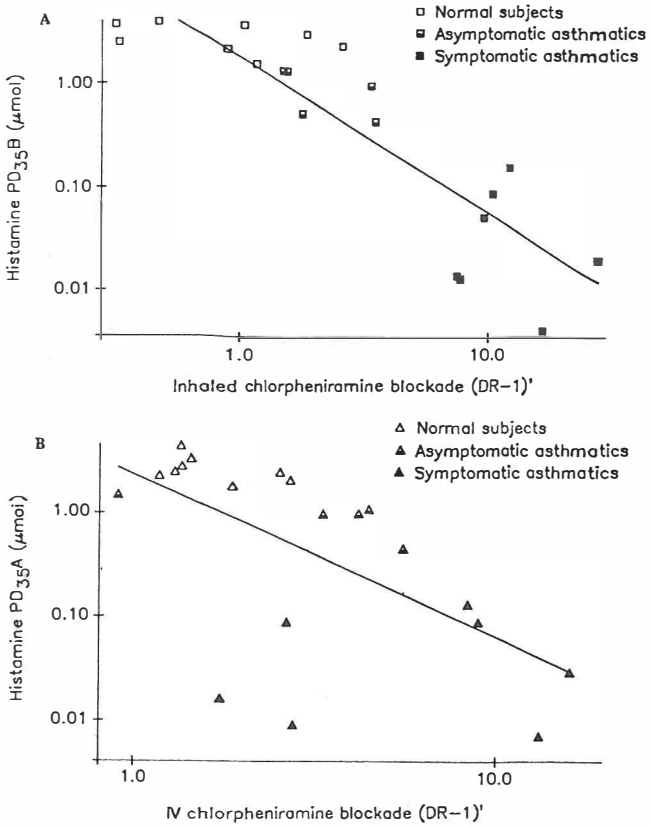

Fig. 2. A) Comparison of bronchial responsiveness to histamine (PD_{35}) and inhaled chlorpheniramine blockade (DR-1). n= 20, Regression equation y= 0.26-1.503X, r= -0.87, $p<0.001$.
B) Comparison of bronchial responsiveness to histamine (PD_{35}) and parenteral chlorpheniramine blockade (DR-1). n= 20, Regression equation y= 0.366-1.58X, r= -0.62, $p<0.005$.

challenges indicates bronchial responsiveness to histamine. The antagonistic effect of chlorpheniramine was indicated by Dose Ratio (DR)= PD_{35} after chlorpheniramine/control PD_{35}, but more accurately, it is quantified as DR-1 because when DR= 1 there is no blockade. Since PD_{35} varies from day to day we believe the most accurate estimate of DR-1 is made by performing both control and premedicated challenges on the same day. We have previously compared this with the conventional approach of performing control and post-medication challenges on separate days.[1]

We also obtained two values for DR-1: 1) by relating obtained post-inhaled chlorpheniramine challenge to control A= $(DR\text{-}1)_{INHALED}$, and 2) by relating PD_{35} from post-intravenous chlorpheniramine to control B= $(DR\text{-}1)_{IV}$.

Statistics

Mean values for DR-1 and PD_{35} quoted are geometric means, since these values are non-normally distributed in the study population. In a previous study we have shown that geometric mean and median values are similar but appreciably lower than arithmetic means for these types of

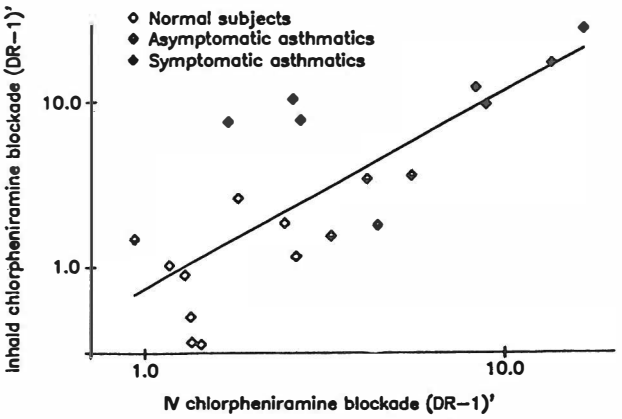

Fig. 3. Comparison of chlorpheniramine blockade by two different routes of administration. n= 20, Regression equation y= 0.252+0.501X, r= 0.77, $p<0.001$.

data.[9] We have related log PD_{35} to log DR-1 using least squares regression and also using Spearman rank correlation to avoid any assumption of normal distribution of the log data. To avoid the same value of control PD_{35} being used on both axes of this relationship, DR-1 was calculated as above and plotted against the PD_{35} measured on the other challenge day. In comparing values of sGaw, PD_{35} and DR-1 between normal and asthmatic subjects we have employed the non-parametric Mann-Whitney 'U' test.

RESULTS

sGaw

The mean baseline sGaw for all challenges in normal subjects was 1.63±0.3 $s^{-1}kPa^{-1}$ and in asthmatic subjects was 0.93±0.68 $s^{-1}kPa^{-1}$ (p=0.1). After inhalation of chlorpheniramine, mean sGaw in normal subjects was 1.71±0.4 and in asthmatic subjects was 1.00±0.7. Neither of the changes was statistically different from baseline. After intravenous chlorpheniramine, sGaw increased significantly in normal subjects to 1.9±0.3 (p= 0.039) and in asthmatics to 1.1±0.8 (p= 0.046).

Control PD_{35}

Values for control PD_{35} on two occasions are shown in Table II. The geometric mean control PD_{35} in normal subjects (2.7 µmol; range 1.83-4.0) was 22.5 times greater than in asthmatic subjects (0.12 µmol; 0.006-1. 43, $p<0.001$). The most sensitive asthmatic subject was 700 times more sensitive to histamine than the least sensitive normal subject.

DR-1

Values for different measurements of DR-1 are shown in Table II. Geometric mean $DR\text{-}1_{INHALED}$ in asthmatic subjects (5.84) was 6.8 times greater than for normal subjects (0.86) (p=0.002). The range of $DR\text{-}1_{INHALED}$ between the least sensitive normal subject and the most sensitive asthmatic subject was 82.5 fold. Geometric mean $DR\text{-}1_{IV}$ in asthmatic subjects (4.4) was 2.75 times greater than in normal subjects (1.6) (p=0.005). The range of $DR\text{-}1_{IV}$ between the least sensitive normal subject and the most sensitive asthmatic subject was 14 fold.

Table III. Reproducibility and correlations of PD_{35} and DR-1.

Stat. tests	$PD_{35}A$ vs $PD_{35}B$	$DR\text{-}1_{INHALED}$ vs $PD_{35}B$	$DR\text{-}1_{IV}$ vs $PD_{35}A$	$DR\text{-}1_{INHALED}$ vs $DR\text{-}1_{IV}$
Least squares regression (r)	0.99	-0.87	-0.62	0.77
p–value	<0.001	<0.001	<0.005	<0.001
Coefficient of determination (r^2)	0.98	0.76	0.38	0.59
Spearman-Rank correlation(r_s)	0.88	-0.83	-0.69	0.77
p–value	<0.001	<0.001	<0.001	<0.001

Reproducibility

(a) Baseline sGaw

The mean coefficient of variation for baseline sGaw (between days) in all challenges for normal subjects was 10.4±7.2% and for asthmatic subjects was 16.3±14%.

(b) Control PD_{35}

There was close correlation between log PD_{35} values measured on different occasions (Fig. 1, Table III). For PD_{35} control A vs PD_{35} control B, r= 0.99, $p<0.001$. The mean coefficient of variation in all two measurements for normal subjects was 14.8±10.2 and for asthmatic subjects was 18.96±16.07.

Relationship between PD_{35} and DR-1

There was a significant negative correlation between PD_{35} and $DR\text{-}1_{INHALED}$ (r= -0.87, $p<0.001$, r^2= 0.76, Fig. 2a, Table III). There was also a significant negative correlation between $PD_{35}A$ and $DR\text{-}1_{IV}$ (r= -0.62, $p<0.005$, r^2= 0.38, Fig. 2b, Table III). Significant correlations were similarly given by the non-parametric Spearman-Rank correlation (Table III).

Relationship between $DR\text{-}1_{INHALED}$ and $DR\text{-}1_{IV}$

In the same individual, there was a significant positive correlation between DR-1 values obtained by the two routes of administration (r= 0.77, $p<0.001$ and r^2= 0.59, Fig. 3, Table III).

All values for least squares regression coefficient of determination and for Spearman-Rank correlation are shown in Table III.

DISCUSSION

This study has demonstrated that the H_1-blocking effect of inhaled and parenteral chlorpheniramine is enhanced in asthmatic subjects, confirming previous work from this laboratory.[10] This is also entirely in line with our previous findings with atropine and methacholine,[1] and also propranolol and isoprenaline. We have therefore shown enhanced blockade in asthma with two separate competitive antagonists acting at different receptors.

Based on *in vitro* experiments,[3] the degree of rightward shift of the agonist dose-response curve measured as dose ratio is determined by concentration of antagonist at the receptor ([I]) and receptor affinity (ka):

$$DR = [I]\,ka + 1$$
$$(DR-1) = [I]\,ka$$

To apply this principle to the more complex situation *in vivo* involves assumptions about the mode of action of chlorpheniramine in the intact, *in situ* bronchus. We have previously demonstrated that chlorpheniramine is an antagonist at the H_1 receptor in the bronchial tree,[4] that causes a parallel, righward shift in the log dose-response curve, as is seen with competitive antagonists *in vitro*.[10] The fact that three receptor systems show enhanced competitive blockade in asthma suggests that the abnormality lies with [I] rather than ka. This conclusion is also supported by *in vitro* experiments which suggest that receptor affinity for a given antagonist shows little variation between species and tissues.[11]

If, in fact, receptor affinity is constant we have to explain how apparently wide intersubject differences in drug concentration could be generated in the environment of the receptor. Even with intravenous chlorpheniramine there was an 18-fold range of DR-1 values. By this route, chlorpheniramine is delivered by the bronchial muscle microcirculation and, if due to asthmatic inflammation blood flow is increased, more drug may be delivered. However, the same asthmatic subjects also showed enhanced blockade when chlorpheniramine was inhaled and this cannot be due to increased perfusion. In fact, increased perfusion would probably decrease the effectiveness of an inhaled drug by increasing clearance. Alternatively if chlorpheniramine was more slowly metabolized in asthmatic bronchi this would increase [I] with both routes of administration. Equally, a physical barrier of some kind, close to the receptor, could impede chlorpheniramine diffusion however administered. If the permeability of this barrier was variable, and increased in asthma, it would explain the variation in DR-1 produced by both routes of administration, and the correlation between individual degrees of blockade achieved by both routes (Fig. 3). A physical barrier, depending on its precise nature would tend to be non-specific in impeding the diffusion of drugs, whereas a metabolic defect would be specific to certain drugs. Chlorpheniramine (MW 275), histamine (MW 115), atropine (MW 579), methacholine (MW 160), propranolol (MW 296) amd isoprenaline (MW 248), while being chemically distinct, are all small cationic molecules with water and lipid solubility that may be handled similarly by a charged molecular barrier. A deficiency of the barrier in asthma could therefore also explain bronchial hyperresponsiveness to the agonists as well as increased blockade with the antagonists. It would also explain the correlations seen in individuals between agonist and antagonist effects (Figs. 2a & 2b), regardless of the route of administration of the latter.

A wider intersubject range of values for DR-1 was seen when chlorpheniramine was administered by inhalation (83 fold). The total intersubject variation of $DR\text{-}1_{INHALED}$ results from the sum of variation due to quantity of deposition and variation in delivery from epithelium to muscle, plus any variation that exists in receptor affinity, and these factors must also partly determine responsiveness to histamine. It is therefore not surprising that the negative correlation between chlorpheniramine $DR\text{-}1_{INHALED}$ and PD_{35} is closer ($r = -0.87$) than that between $DR\text{-}1_{IV}$ and PD_{35} ($r = -0.62$), where routes of administration differ.

This study allows some approximate quantitation of the factors controlling agonist and antagonist responsiveness. The correlation between $DR\text{-}1_{INHALED}$ and $DR\text{-}1_{IV}$ ($r = 0.77$; $r^2 = 0.59$) demonstrates the importance of factors common to both routes (delivery in the immediate vicinity of the receptor and receptor affinity) in determining blockade. Thus approximately 60% of the variance of chlorpheniramine $DR\text{-}1_{INHALED}$ is explained by the variance of $DR\text{-}1_{IV}$. An identical conclusion was reached when we compared DR-1 values obtained by inhaled and intravenous atropine[1] and propranolol.[2] If there is a molecular barrier close to the receptor then this is a measure of its importance in determining DR-1. In another study with inhaled atropine approximately 30% of the variance of $DR\text{-}1_{INHALED}$ was explained by the variance of aerosol deposition in central bronchi.[9] These factors controlling $DR\text{-}1_{INHALED}$ must also influence the response to agonist. The relationship between chlorpheniramine $DR\text{-}1_{INHALED}$ and PD_{35} histamine ($r = -0.87$; $r^2 = 0.76$) suggests that approximately 75% of the variance of PD_{35} is explained by $DR\text{-}1_{INHALED}$ variance. An identical conclusion was reached with atropine/methacholine[1] and a similar conclusion with propranolol/isoprenaline.[2] This means that the variances of aerosol deposition, drug delivery from epithelium to receptor (and possibly receptor affinity) contribute very substantially to the variance of bronchial responsiveness to histamine and methacholine.

However, the variance of histamine PD_{35} is greater than that of $DR\text{-}1_{INHALED}$ demonstrating that there are factors

which influence agonist responsiveness but have no effect on the response to the antagonist. Such factors could be receptor numbers, second messengers or muscle thickness. The relationship between chlorpheniramine $DR\text{-}1_{IV}$ and PD_{35} ($r = -0.62$, $r^2 = 0.38$) suggests that approximately 40% of PD_{35} variance is explained by factors controlling $DR\text{-}1_{IV}$ delivery close to the receptor (and perhaps receptor affinity).

A deficiency of a molecular barrier close to the receptor in asthma would have an equal effect on both inhaled and intravenous chlorpheniramine. Thus in asthma, significantly higher blocking effects are seen with both routes than in normal subjects. However, in symptomatic asthma, the enhancement of blockade due to the inhaled drug is greater. Thus, the ratio $DR\text{-}1_{INHALED}/DR\text{-}1_{IV}$ is significantly higher in the symptomatic asthmatic group than in the other groups despite the fact that all subjects received the same doses of chlorpheniramine. Individual differences in pattern and quantity of aerosol deposition are unlikely to explain all this enhancement[9] and we therefore suggest that it may be caused by increased epithelial permeability. Epithelial damage is a well-recognized feature in asthma,[12,13] which is perhaps due to airway inflammation[14,15] and this appears to increase the permeability to small charged molecules.[16]

Airway inflammation in asthma has been known for a long time, even in mild disease.[17] One of the consequences of this inflammation is airway epithelial damage,[18] and there is association between airway inflammation and epithelial damage,[19] as well as a significant correlation between epithelial damage and bronchial hyperresponsiveness in asthma.[13,20] There is also close association between airway inflammation, epithelial damage and bronchial hyperresponsiveness, both in sensitized animals[21] and in asthmatic patients,[22] and all of these (airway inflammation, epithelial damage and bronchial hyperresponsiveness) are improved after topical corticosteroid treatment in asthma.[22] Thus airway inflammation can cause epithelial damage and this in turn can result in better access of ligand to the active sites in the airway and bronchial hyperresponsiveness in asthma. The increased chlorpheniramine blockade in asthmatic subjects shown in this study as well as increased atropine and isoprenaline blockade in our previous studies[1,2] perhaps is due to higher concentration of antagonists at the receptor sites achieved by the above phenomenon. The close correlation between chlorpheniramine blockade and histamine responsiveness as well as other antagonist blockade and agonist responsiveness,[1,2] indicates that bronchial hyperresponsiveness to different stimuli in asthma at least in part is due to increased bronchial epithelial permeability.

In conclusion, the competitive H_1 antagonistic effect of inhaled chlorpheniramine is enhanced in asthma to a degree that in individuals correlates with bronchial responsiveness to histamine. This enhancement may in part be due to greater aerosol deposition and increased epithelial permeability, but because there is also enhancement of antagonism from parenterally administered chlorpheniramine we suggest that in asthma there is additionally an increase in permeability of tissues close to the receptor, or alternatively, increased receptor affinity. Because receptor affinity to antagonists tends to be constant[11] and because we have shown very similar results with inhaled and parenteral atropine[1] and propranolol[2] we favor the notion of a molecular barrier which is deficient in asthma. Variation in the permeability of this barrier is probably also important in determining bronchial responsiveness to inhaled histamine and methacholine.

This is a novel hypothesis in the study of bronchial hyperresponsiveness in asthma that merits further analysis by pharmacological, histological and histochemical studies.

REFERENCES

1. Boskabady MH, Snashall PD: Enhanced muscarinic receptor blockade with atropine in the asthmatic tracheobronchial tree: evidence for increased drug delivery. Am Rev Respir Dis 145: 756-761, 1992.
2. Boskabady MH, Snashall PD: Enhanced drug delivery to bronchial smooth muscle in asthma. Eur Respir J 4(suppl 14): 609s, 1991.
3. Arunlakshana O, Schild HO: Some quantitative uses of drug antagonists. B J Pharm 14: 48-83, 1959.
4. Eiser NM, Mills J, Snashall PD, Guz A: The role of histamine receptors in asthma. Clin Sci 60: 363-370, 1981.
5. Heaton RW, Gillett MK, Snashall PD: Morning-evening changes in airway responsiveness to methacholine in normal and asthmatic subjects; analysis using partial flow volume curves. Thorax 43: 727-728, 1988.
6. Rosenthal RR, Norman PS, Summer WR, Permutt S: Role of parasympathetic system in antigen-induced bronchospasm. J Appl Physiol 42: 600-606, 1977.
7. Pavia D, Thomson ML, Clarke SW, Shanon HS: Effect of lung function and mode of inhalation on penetration of aerosol into the human lung. Thorax 32: 194-197, 1977.
8. Dubois AB, Botelho SY, Comroe JH: A new method for measuring airway resistance in man using a body plethysmograph; values in normal subjects and patients with respiratory disease. J Clin Invest 35: 327-335, 1956.
9. Gillett MK, Briggs BA, Snashall PD: The influence of aerosol retention and pattern of deposition on bronchial responsiveness to atropine and methacholine. Am Rev Resp Dis 140: 1727-1733, 1989.
10. Chung KF, Morgan B, Keyes SJ, Snashall PD: Histamine dose-response relationships in normal and asthmatic subjects. The importance of starting airway calibre. Am Rev Respir Dis 126: 849-854, 1982.
11. Bowman WC, Rand MJ: Textbook of Pharmacology. 2nd ed, Oxford: Blackwell Scientific Publications, p. 3925, 1980.
12. Laitinen LA, Heino M, Laitinen A, Kava T, Haantela T: Damage of airway epithelium and bronchial reactivity in patients with asthma. Am Rev Respir Dis 131: 599-606, 1985.
13. Jeffery PK, Wardlaw AJ, Nelson FC, Collins JV, Kay AB:

Bronchial biopsies in asthma; an ultrastructural quantitative study and correlation with hyperreactivity. Am Rev Respir Dis 140: 1745-1753, 1989.

14. Lundgren R, Soderberg M, Horstedt P, Stenling R: Morphological studies of bronchial mucosal biopsies from asthmatics before and after ten years of treatment with inhaled steroids. Eur Respir J 1: 883-889, 1988.
15. Martin RJ, Cicutto LC, Smith HR, Ballord RD, Szefler SJ: Airway inflammation in nocturnal asthma. Am Rev Respir Dis 143: 351-357, 1991.
16. Ilowite JS, Bennett WD, Sheetz MS, Groth ML, Nierman DM: Permeability of bronchial mucosa to ^{99m}Tc-DTPA in asthma. Am Rev Respir Dis 139: 1139-1143, 1989.
17. Busse W, Banks-Schlegel SP, Larson GL: Childhood- versus adult-onset asthma. Am J Respir Crit Care Med 151: 1635-1639, 1995.
18. Filley WV, Kephart GM, Holley KE, Gleich GJ: Identification by immunofluorescence of eosinophil granule MBP in lung tissue of patients with bronchial asthma. Lancet 3: 11-15, 1982.
19. Jeffery PK: Morphology of airway wall in asthma and in chronic obstructive pulmonary disease. Am Rev Respir Dis 143: 1152-1153, 1991.
20. Beasely R, Roche WR, Roberts JA, Holgate ST: Cellular events in the bronchi in mild asthma and after bronchial provocation. Am Rev Respir Dis 139: 806-817, 1989.
21. Padrid P, Snook S, Finucane T, Shiue P, Cozzi P, Solway J, Leff AR: Persistent airway hyperresponsiveness and histologic alteration after chronic antigen challenge in cats. Am Respir Crit Care 151: 184-193, 1995.
22. Booth H, Richmond I, Ward C, Gardiner PV, Harkawat R, Walters HE: Effect of high-dose inhaled fluticasone propionate on airway inflammation in asthma. Am J Respir Crit Care Med 152: 45-52, 1995.