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SHORT TERM VARIATION OF ATROPINE BLOCKADE IN THE TRACHEOBRONCHIAL TREE OF ASTHMATIC SUBJECTS

M.H. BOSKABADY, M.D., Ph.D., AND P.D. SNASHALL*, M.D.

*From the Department of Physiology, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran and the *Dept of Medicine, Charing Cross and Westminster Medical School, Fulham Palace Road, London W6 8RF, U.K.*

ABSTRACT

In asthmatic subjects there is a pronounced diurnal variation in bronchial responsiveness. If this phenomenon is due to variation in factors that control drug delivery, then it should be paralleled by a similar variation in competitive antagonist blockade.

In order to study this possibility, we performed the methacholine challenge test and after 45 minutes, administered atropine by inhalation. Methacholine re-challenge was performed 25 minutes after premedication with atropine. Bronchial responsiveness to methacholine(PB_{35}) and atropine blockade was then measured. Eight normal subjects and 9 asthmatic patients were tested on two separate occasions, one in the morning at 08:00 hours and the other in the evening at 18:00 hours with at least 48 hours gap between them.

In normal subjects there was no significant difference between morning and evening concerning airway caliber, bronchial responsiveness to methacholine and atropine blockade. In asthmatic patients there was a significant difference between morning and evening in bronchial responsiveness to methacholine ($P<0.001$) and atropine blockade ($P<0.001$), although there was no significant difference in airway caliber.

The possible explanation for enhanced atropine blockade as well as methacholine responsiveness in asthmatic subjects in the morning is increased bronchial and tissue permeability due to worsening bronchial inflammation in the early morning leading to increased drug delivery to active sites in the airways.

Keywords: Short term variation, atropine blockade, asthma.

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INTRODUCTION

In normal and asthmatic subjects there is a diurnal variation of airway caliber[1,2] and bronchial responsiveness to histamine.[3] Previous work in this department has demonstrated a morning to evening variation in bronchial responsiveness to methacholine in normal and asthmatic subjects, their responsiveness being approximately 3 times greater in the morning than in the evening.[4] If this diurnal variation is due to a variation of receptor affinity or to variation in

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Table I. Characteristics of normal and asthmatic subjects who participated in the diurnal variation study.

Subjects	Sex & Age	Weight (kg)	Height (cm)	FEV_1 L/sec	Smoking	Atopy	Treatment
Normal							
1	F-27	65	168	3.94	-	-	-
2	M-35	58	162	3.55	-	-	-
3	M-26	60	163	2.40	-	-	-
4	F-39	70	178	3.88	-	-	-
5	M-21	72	179	4.77	-	-	-
6	F-24	58	165	2.85	S	-	-
7	M-31	65	170	3.37	-	-	-
8	M-32	96	182	3.25	-	-	-
Mean	29	68	171	3.50			
SD	6	12	8	0.72			
Asymptomatic asthmatic							
1	F-26	58	164	3.71	S	+	-
2	M-29	70	180	4.25	-	+	-
3	M-48	75	176	4.07	-	+	-
4	M-34	74	179	4.18	-	+	-
5	M-29	70	180	3.78	-	+	-
Symptomatic asthmatic							
1	F-52	56	162	1.56	-	+	Sal-Bf
2	M-30	65	167	ND	-	+	Te-Bud
3	M-50	86	181	3.35	-	+	Te-Theo-Ip-Bf
4	F-16	58	161	2.38	-	+	Sal-Bf
Mean	35	68	172	3.41			
SD	12	10	9	0.96			

Sal= Salbutamol
Te= Terbutaline
Ip= Ipratropium bromide
Theo= Theophylline
Bud= Budesonide
Bf= Beclomethasone dipropionate

factors that control drug delivery, then it should be paralleled by a similar variation in competitive antagonist blockade. Alternatively, if agonist responsiveness changes due to variation in the number of active receptors or to a variation in the intracellular response to receptor binding, antagonist blockade should not change. In previous studies[5-7] we have examined the relationship between agonist response and antagonist blockade. In the present study we will address short-term changes in bronchial responsiveness to agonist and antagonist blockade by measuring bronchial responsiveness to methacholine and atropine blockade at 08:00 and 18:00 hours. Results may demonstrate the different influences on these two types of bronchial responsiveness.

PATIENTS AND METHODS

Subjects (Table I)

Eight normal subjects and nine well controlled asthmatic adults were studied. The normal subjects 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 asymptomatic at the time of study but had a past history of mild intermittent wheezing and chest tightness requiring bronchodilator treatment. The remaining asthmatic subjects were all on active treatment for their condition (Table I). 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.

Techniques and protocol

Each subject attended the laboratory on 2 occasions with at least a 48 hour gap between attendances over a period not

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Table II. Individual values of bronchial responsiveness to methacholine in the morning (PD_{35M}), atropine blockade in the morning $(DR\text{-}1)_M$ and in the evening $(DR\text{-}1)_E$.

Subjects	$sGaw_M$	$sGaw_E$	PD_{35M}	PD_{35E}	$(DR\text{-}1)_M$	$(DR\text{-}1)_E$
Normal						
1	2.24	2.35	27.10	35.80	0.9	1.3
2	1.12	1.90	3.10	2.90	3.5	4.6
3	3.98	3.16	11.60	16.60	0.9	0.9
4	2.04	1.73	12.40	10.00	0.8	2.3
5	1.43	1.46	2.75	2.90	4.9	3.1
6	1.12	1.39	1.21	1.74	19.5	5.3
7	1.53	1.51	27.11	18.83	2.4	1.7
8	0.92	1.27	2.00	3.65	1.6	1.0
Arithmetic X	1.80	1.85	-	-	-	-
SD	0.99	0.63	-	-	-	-
Geometric X	-	-	6.16	7.08	2.3	2.1
Stat. Signif.	-	NS	-	NS	-	NS
Asymptomatic asthmatic						
1	1.22	1.43	1.05	1.86	10.7	7.0
2	1.22	1.43	0.58	0.96	53.5	12.3
3	1.73	1.80	0.13	0.39	49.6	16.9
4	1.02	1.12	0.21	0.37	41.6	17.5
5	1.73	2.24	0.17	0.54	27.6	12.9
Symptomatic asthmatic						
1	1.02	0.86	0.07	0.17	49.6	13.4
2	0.51	0.55	0.03	0.06	24.4	7.7
3	0.31	0.31	0.04	0.14	39.2	9.0
4	0.82	0.9	0.10	0.15	30.7	17.8
Arithmetic X	1.07	1.18	-	-	-	-
SD	0.49	0.61	-	-	-	-
Geometric X	-	-	0.14	0.30	33.1	12.0
Stat. Signif.	*	*	**	**	**	**
	-	NS	-	@	-	@

Significance of differences from normal subjects- *P<0.05, **P<0.001.
Significance of differences from morning values- NS = nonsignificant difference, @P<0.001

exceeding 2 weeks. One challenge was performed in the morning at 08:00 hours and another in the evening at 18:00 hours in random order. Subjects were requested to refrain from caffeinated beverages for 2 hours prior to challenge. Asthmatic subjects were also requested not to use bronchodilator inhalers for at least 8 hours before each challenge. On each occasion we performed two methacholine challenges, with and without premedication with atropine. On both occasions, methacholine challenge test was performed without premedication (control challenge), followed, after a 45 min rest,[8] by atropine inhalation (3.2 mg/mL, 11.0 mmol, 5 inhalations= 0.14 mg, 0.48 µmol). Methacholine challenge was also performed 25 min after premedication with atropine (post-atropine challenge).

Methacholine challenge was performed in the following manner: methacholine hydrochloride (molecular weight= 196), 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.[9] The dosimeter and nebulizer were triggered by 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 mouthpiece 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.[10,11] The volume of solution delivered per activation was 8.8 µL. The aerosol had a mass

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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)[11] 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 5 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 methacholine solution, followed by further sGaw measurement after two minutes. The inhaled concentration of methacholine solution was then doubled every 3 minutes with serial measurement of sGaw 2 min after each concentration of aerosol. The challenge was terminated when sGaw had fallen by more than 35% at which point the subject was aware of moderate chest tightness and wheezing. For normal subjects the starting concentration of methacholine was 1.56g/L (7.8 mmol) and the maximum concentration used was 200 g/L (1.02 Mol) (giving inhaled doses of 0.35 and 45 μmol respectively). After premedication with atropine some subjects received a maximum dose of 10 inhalations of 200 g/L (inhaled dose= 90 μmol). For asymptomatic asthmatic subjects the starting concentration was 0.39 g/L (1.95 mmol) and for the symptomatic asthmatic subjects starting concentration ranged from 0.0122 g/L (6.1 μmol) to 0.39 g/L (1.95 mmol) (inhaled dose= 0.085, 0.003 and 0.085 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 methacholine challenge was approximately 30 min.

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

At the end of each test the subject took 2 puffs of salbutamol to relieve chest tightness.

Measurements

For each challenge a cumulative log dose-response curve was constructed by plotting sGaw against the logarithm to base 10 of cumulative doses of methacholine delivered to the subject. For each curve we determined control sGaw measured after inhalation of diluent and the cumulative dose of methacholine which produced a 35%

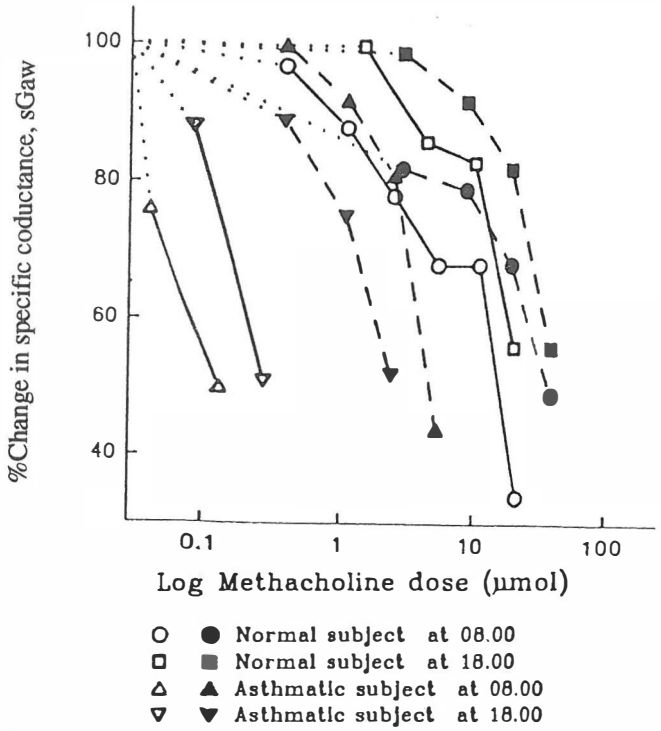

Fig. 1. Normalized methacholine cumulative dose-response curve in one normal and one asthmatic subject before (open symbols) and after (filled symbols) inhaled atropine at 08:00 and 18:00 hours.

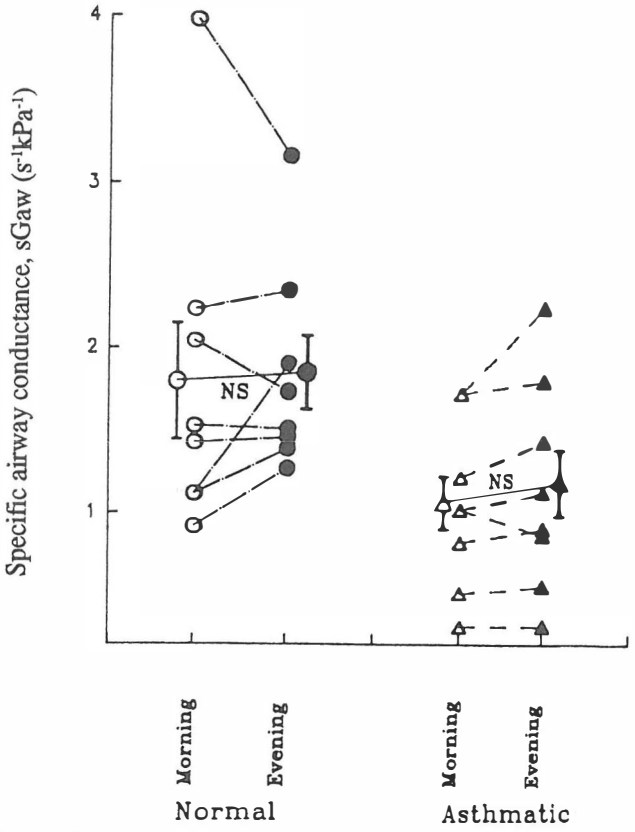

Fig. 2. Specific airway conductance at 08:00 and 18:00 hours in 8 normal and 9 asthmatic subjects.
NS= nonsignificant difference between morning and evening sGaw.

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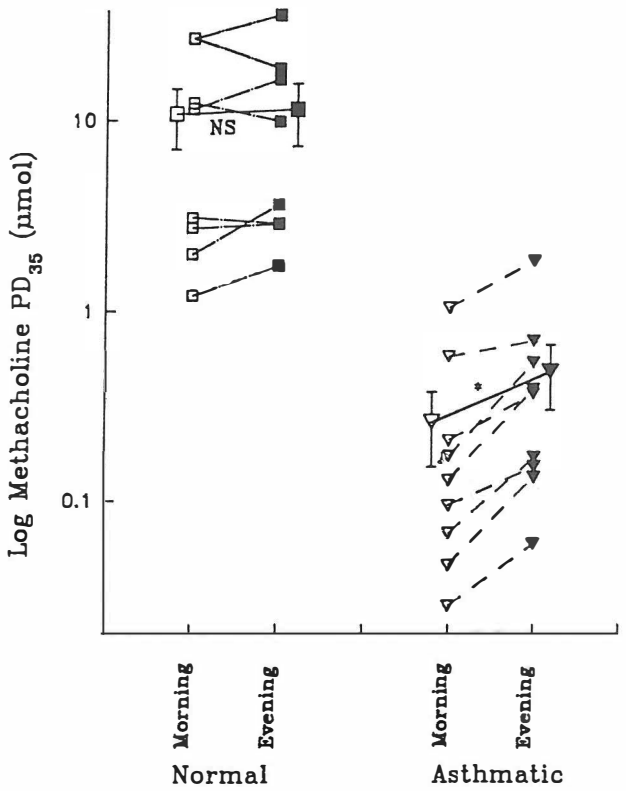

Fig. 3. Bronchial responsiveness to methacholine (PD_{35}) at 08:00 and 18:00 hours in 8 normal and 9 asthmatic subjects.
NS= nonsignificant difference between morning and evening PD_{35}. *= significant difference between morning and evening PD_{35}, P<0.001.

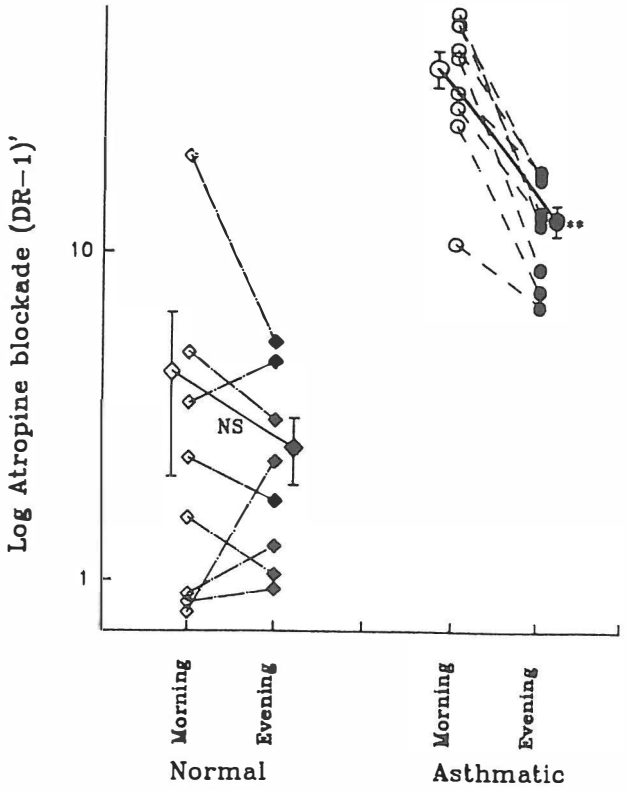

Fig. 4. Atropine blockade (DR-1) of methacholine bronchoconstriction at 08:00 and 18:00 hours in 8 normal and 9 asthmatic subjects.
NS= nonsignificant difference between morning and evening DR-1. **= significant difference between morning and evening DR-1, P<0.001.

fall in sGaw= PD_{35}. PD_{35} in control (unpremedicated) challenges indicate bronchial responsiveness to methacholine. In this study we made two control measurements of PD_{35} in each subject; once in the morning (PD_{35M}) and once in the evening (PD_{35E}). For evaluating atropine blockade, we calculated DR-1 (DR-1= post atropine PD_{35}/control PD_{35}-1). We also obtained two values for DR-1, 1) by relating post-atropine PD_{35} to control PD_{35} in the morning. We refer to this value as $(DR\text{-}1)_M$. 2) By relating post-atropine PD_{35} to control PD_{35} in the evening. We refer to this value as $(DR\text{-}1)_E$. Figure 1 shows dose-response curves in one normal subject and one asthmatic patient in the morning and in the evening before and after atropine premedication.

Stastistics

Mean values for DR-1 and PD_{35} quoted are geometric means, since these values are clearly 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 data.[12] 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. 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

Baseline sGaw

The mean baseline sGaw for all challenges in normal subjects in the morning was 1.8±0.99 and in the evening 1.85±0.63 $s^{-1}kPa^{-1}$. In asthmatic subjects the mean baseline sGaw in the morning was 1.07±0.5 and in the evening, 1.18±0.6 $s^{-1}kPa^{-1}$ (significantly different from normal subjects both in the morning and in the evening, P<0.05), (Fig. 2, Table II).

Control PD_{35}

The geometric mean control PD_{35} in normal subjects in the morning (6-16 μmol; range 1.21-27.1) was 44 times greater than in asthmatic subjects (0.14 μmol; range 0.028-1.05) (P<0.001). In the evening the geometric mean PD_{35} in normal subjects (7.08 μmol, range 1.74-35.8) was 23 times

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greater than in asthmatic subjects (0.3 μmol, range 0.06-1.86) (P<0.001) (Fig. 3, Table II).

DR-1

The geometric mean DR-1 in normal subjects in the morning (2.3, range 0.8-19.5) was 14.4 times greater than in asthmatic subjects (33.1, range 10.7-53.5) (P<0.001). In the evening the geometric mean DR-1 in normal subjects (2.09, range 0.94-5.3) was 5.8 times greater than asthmatic subjects (12.02, range 7.0-17.8) (P<0.001) (Fig. 4, Table II).

Differences in sGaw, PD_{35}, and DR-1 between morning and evening

In normal subjects there were no significant difference in sGaw, PD_{35} and DR-1 between morning and evening. In asthmatic subjects there was a significant difference in PD35 (P<0.001) and DR-1 (P<0.001), although there was no morning-evening change in sGaw (Figs. 2,3,4, Table II).

DISCUSSION

In this study we have demonstrated a significant morning to evening variation in bronchial responsiveness to methacholine in asthmatic subjects which was not present in normal subjects. Compared with measurements at 18.00 hours, those at 08.00 show increased responsiveness to methacholine and a greater degree of muscarinic blockade.

Diurnal variation of asthma symptoms has been recognized for many years[13,14] and is known to be due to diurnal variation in airway caliber.[15] Diurnal variation in bronchial responsiveness has been shown against histamine,[3,16] house dust,[17] acetylcholine[18] and methacholine.[4] The diurnal rhythm of airway caliber is closely entrained to the sleep-wake cycle and rapidly reverses with shift work.[1]

Many possible mechanisms, singly or in combination, have been proposed for diural variation in airway caliber and bronchial responsiveness. These include: (a) altered airway adrenoceptor function at night,[2,19] (b) circadian variation in plasma concentration of cortisol,[20] (c) diurnal variation in catecholamine excretion,[20] and circadian variation in cholinergic reflex mechanisms.[2,21] None of these, however, have been proven. In fact, there is no evidence for reduced adrenoceptor function at night; nocturnal bronchodilator responses to infused or to inhaled adrenaline are unimpaired at night.[22] If diurnal variation was due to variations in plasma cortisol, it would be abolished by supraphysiological doses of corticosteroids, but this does not occur.[23] Nocturnal bronchial narrowing is not due to a fall in plasma adrenaline because intravenous infusion of adrenaline, while reducing the circadian variation of peak expiratory flow rate, does not completely abolish it.[22] Similarly the rise of nocturnal plasma histamine and change in cholinergic tone have been discounted as important mechanisms.[24]

By showing a diurnal variation of DR-1 this study provides evidence for other mechanisms for the diurnal variation of bronchial responsiveness. DR-1 is determined by receptor affinity for the antagonist and antagonist concentration at the receptor. One can only speculate as to why either of these variables should change diurnally. If asthmatic bronchial inflammation is worse early in the morning,[25] then bronchial epithelial and tissue permeability may be increased. Alternatively if bronchial mucosal blood flow was reduced in the morning then clearance of both atropine and methacholine may have been decreased.

In these well-controlled asthmatic subjects the measured diurnal variation of airway caliber was very modest and seems an unlikely explanation for the changes in PD_{35} and DR-1.

Atropine blockade was significantly higher in the morning than the evening in asthmatic subjects but not in normal subjects. Similarly bronchial responsiveness to methacholine in asthmatic subjects was higher in the morning. These results suggest that the diurnal variation in bronchial responsiveness in asthmatic subjects is in part due to variation in factors that control drug delivery to the receptors or receptor affinity. In previous studies[5-7] we examined stable asthma with static values of PD_{35} and DR-1. Here we have examined an acute diurnal variation in PD_{35} and found that DR-1 varies with PD_{35} in the one individual in a similar manner to which it does between different subjects under static circumstances. In both cases DR-1 increases as PD_{35} falls. However the numerical relationship between DR-1 and PD^{35} is somewhat different in this study from those that preceded it.[5-7] The change of PD_{35} (increasing by 2.14 times from 08:00 hours to 18:00 hours) was similar (though of opposite sign) to that of DR-1 (increasing from 18:00 to 08:00 by 2.80 times), and thus it is plausible to suggest that an increase in deposition and delivery may have caused both. Therefore it is possible to account for the whole of the diurnal change in bronchial responsiveness by the change in concentration of drug at the receptor (drug delivery) or change in receptor affinity, whereas in static studies[5-7] variation in bronchial responsiveness could be explained only in part by variation in factors that control antagonist blockade. Thus symptomatic asthmatics were 114, 93, and 41.7 times more sensitive to methacholine, histamine, and isoprenaline respectively compared to normal subjects, but the corresponding increases in DR-1 to inhaled atropine, chlorpheniramine and propranolol were only 7, 15, and 66 times, respectively. Clearly, in asthma, factors in addition to those controlling DR-1 decrease PD_{35} to methacholine and histamine.

The most probable explanation for enhanced atropine blockade as well as bronchial responsivesness to methacholine in asthmatic patients in the morning is increasing bronchial epithelial and tissue permeability due to bronchial inflammation in the early morning leading to

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increased drug delivery to the active sites (receptors) in the airways. These findings support the hypothesis that change in delivery of the drug to the receptors or perhaps receptor affinity are important factors determining bronchial responsiveness in asthma.

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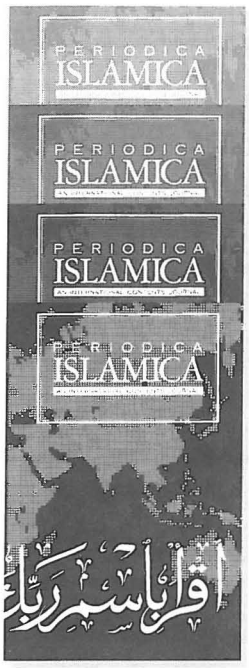

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Consulting Editor ❑ Zafar Abbas Malik
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