Eur Respir J
1990, 3, 872–879

Effects of nonsteroidal anti-inflammatory drugs on the bronchial hyperresponsiveness of middle-aged male smokers

T.K. Lim, N.C. Turner, A. Watson, H. Joyce, R.W. Fuller, N.B. Pride

Effects of nonsteroidal anti-inflammatory drugs on the bronchial hyperresponsiveness of middle-aged male smokers. T.K. Lim, N.C. Turner, A. Watson, H. Joyce, R.W. Fuller, N.B. Pride.

ABSTRACT: Bronchial hyperresponsiveness (BHR) in smokers is believed to be a consequence of airway wall inflammation. We have examined the effects of treatment with nonsteroidal anti-inflammatory drugs (NSAID) on BHR to inhaled histamine, measured as the provocative concentration reducing forced expiratory volume in one second (FEV_1) by 20% (PC_{20}), in middle-aged male cigarette smokers in two separate double-blind, placebo-controlled, cross-over trials. Baseline FEV_1 in these smokers ranged from 41–117% predicted values. In the first study 15 men (mean age 58 yrs, FEV_1 2.20 *l*) were examined before and one hour after a single dose of 1.2 g aspirin. There was no significant change in PC_{20} (geometric mean 1.88 $mg \cdot ml^{-1}$ pre-aspirin, 1.89 $mg \cdot ml^{-1}$ post-aspirin) or baseline FEV_1 and we observed no tachyphylaxis to the effects of inhaled histamine at one hour after placebo. In the second study 10 men (mean age 60 yrs, FEV_1 2.53 *l*) were examined before and after three days' treatment with the NSAID flurbiprofen 50 mg *t.d.s.* Baseline PC_{20} was higher in this group than in the first study. There was no relationship between the excretion of urinary thromboxane metabolites and the intensity of BHR under baseline conditions; flurbiprofen greatly reduced the urinary excretion of thromboxane metabolites, but baseline FEV_1 was not altered. Analysis of change in PC_{20} was complicated by a difference in baseline PC_{20} before the two treatments, but treatment with flurbiprofen did not significantly attenuate BHR. The results suggest that thromboxane or other cyclo-oxygenase products of arachidonic acid metabolism do not play an important role in the short-term maintenance of BHR to histamine in middle-aged male cigarette smokers.

Eur Respir J., 1990, 3, 872–879.

Depts of Medicine and Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK.

Correspondence: N.B. Pride, Dept of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, W12 ONN, UK.

Keywords: Bronchial responsiveness; histamine; nonsteroidal anti-inflammatory drugs; smokers; thromboxane.

Received: October 1989; accepted after revision June 26, 1990.

Supported by grants from the British Medical Research Council and Chest, Heart and Stroke Association. T.K. Lim was the recipient of a Commonwealth Medical Fellowship.

The dominant current hypothesis of the origins of bronchial hyperresponsiveness (BHR) in both subjects with asthma and smokers is that it is a consequence of airway wall inflammation [1]. In support of this hypothesis inhaled corticosteroids, which have anti-inflammatory actions on the bronchi, consistently reduce BHR in asthmatic subjects [2]. Nonsteroidal anti-inflammatory drugs (NSAID) which inhibit cyclo-oxygenase production also alter BHR in certain circumstances in asthmatic subjects, although their effects are generally smaller and less consistent than that of corticosteroids.

The mechanism by which NSAID interfere with bronchial responsiveness has been studied in several animal models. In dogs, thromboxane synthase inhibitors have been reported to inhibit the increase in airway hyperreactivity after antigen challenge [3] or ozone [4]. Furthermore, stable thromboxane mimetics have been shown to induce increased airways responsiveness in both dogs [4] and primates [5]. These results may be relevant to humans, as in normal subjects in whom BHR to methacholine has been induced by breathing ozone, alveolar lavage shows an increase in cyclo-oxygenase products such as prostaglandins E_2 and F_2 alpha and thromboxane B_2 [6].

Airway wall inflammation in smokers is characterized by neutrophil infiltration without the eosinophil infiltration characteristically found in asthma [7] and in this respect resembles the changes produced in animals by exposure to ozone [8, 9]. Furthermore, urinary levels of the major thromboxane metabolites are elevated in the urine of chronic tobacco smokers [10]. These observations suggest that NSAID might attenuate BHR in smokers even though they have not been very effective in asthmatic subjects. No studies of the effects of NSAID on BHR in smokers appear to

Table 1. – Details of smokers in study of acute effects of aspirin

Subject	Age	Height	Current smoking	Pack years	FEV_1		PC_{20} histamine	Positive skin tests	Treatment
	yrs	m	cigs/day		*l*	%pred	$mg \cdot ml^{-1}$		
A.C.G.	62	1.63	20	45	2.24	87	0.6	o	Atenolol
P.J.E.	56	1.73	40	76	1.74	55	1.5	o	-
W.B.	64	1.75	25	60	1.11	41	0.3	o	-
A.C.B.	57	1.79	20	39	2.88	85	6.7	o	-
J.R.R.	57	1.64	14	29	1.45	52	1.1	o	-
R.G.M.	59	1.76	5	11	2.07	65	4.6	grass	-
A.A.R.	64	1.72	20	50	1.44	50	1.3	o	Atenolol
K.N.O.	53	1.80	40	72	2.56	72	12.3	grass	-
D.G.D.	54	1.73	18	36	2.62	81	0.7	o	-
C.I.B.	60	1.83	10	22	2.32	67	3.3	o	-
N.M.M.	58	1.72	40	86	2.13	69	0.8	o	Atenolol
H.B.	53	1.85	20	31	3.27	88	2.9	house dust mite	-
W.G.C.	54	1.74	35	68	1.88	57	2.9	o	-
H.I.J.	65	1.67	20	46	2.93	111	2.3	feathers	
G.J.D	56	1.85	40	74	2.36	65	1.2	grass house dust mite *Cladosporium* cat fur	
Mean	58	1.75	24.5	49.7	2.20	70	1.81*		
(SEM)	(1.1)	(0.18)	(3.02)	(5.74)	(0.16)	(4.7)	-		

*: geometric mean ($mg \cdot ml^{-1}$); FEV_1: forced expiratory volume in one second; PC_{20}: provocative concentration producing 20% fall in FEV_1 from baseline.

Table 2. – Details of smokers in study of flurbiprofen

Subject	Age	Height	Current smoking	Pack years	FEV_1		PC_{20} histamine	Positive skin tests	Treatment
	yrs	m	cigs/day		*l*	%pred	$mg \cdot ml^{-1}$		
R.G.M.+	61	1.76	13	13	1.71	55	3.2	grass	-
H.I.J.+	67	1.67	20	48	3.01	117	10.9	feathers	-
E.M.A.	59	1.75	20	38	2.44	77	10.0	grass	-
A.C.B.+	59	1.79	15	41	3.18	96	16.1	o	-
A.B.	66	1.71	14	30	3.00	108	33.0	o	-
A.J.B.	52	1.73	24	42	2.79	84	23.4	o	-
P.J.E.+	58	1.72	40	78	1.63	53	5.3	o	-
T.J.K.	56	1.65	40	70	2.72	96	14.0	o	Verapamil
K.N.O.+	56	1.80	45	76	2.38	69	16.5	grass	-
H.S.B.	64	1.74	15	36	2.45	82	5.4	o	-
Mean	60	1.73	24.6	47.2	2.53	84	11.12*		
(SEM)	(1.9)	(0.02)	(3.89)	(6.7)	(0.17)	(6.7)	-		

*: geometric mean ($mg \cdot ml^{-1}$); +: also participated in the aspirin study. For abbreviations see legend to table 1.

have been published. We have, therefore, examined the effects of NSAID on baseline lung function and BHR in middle-aged smokers in two separate experiments. In the first study we examined BHR before and one hour after a single dose of 1.2 g aspirin. *Ex vivo* generation of thromboxane by platelets is maximally depressed to 6% of control levels in blood samples taken one hour after a single large dose of aspirin [11]. In the second study we examined the effects of 3 days' treatment with the potent NSAID, flurbiprofen, and also measured levels of urinary metabolites of thromboxane.

Subjects

The men studied were originally recruited to a prospective study of lung function in 1974 [12]; at recruitment (and at subsequent interviews) any who gave a history of asthma were excluded. In 1982 their bronchial response to inhaled histamine was assessed for the first time [13]. Twenty men who were known to have bronchial hyperresponsiveness (provocative concentration of histamine that reduced forced expiratory volume in one second (FEV_1) by 20% (PC_{20})

Table 3. – Details of the 8 additional smokers in whom thromboxane metabolites were measured

Subject	Age	Height	Current smoking	Pack years	FEV_1		PC_{20} histamine	Positive skin tests	Treatment
	yrs	m	cigs/day		*l*	%pred	$mg \cdot ml^{-1}$		
W.J.B.	67	1.78	14	31	3.95	121	>32.0	o	-
R.F.	63	1.64	7	16	2.65	102	18.4	o	-
C.F.	67	1.75	35	88	2.30	78	6.0	house dust mite	-
J.S.R.	68	1.81	18	48	2.62	84	23.4	o	-
J.M.D.	58	1.76	25	51	2.72	83	>32.0	o	-
R.H.V.	55	1.80	7	14	2.95	85	>32.0	o	-
J.T.W.	54	1.86	10	17	3.65	97	>32.0	o	-
J.W.S.	54	1.70	35	65	2.99	94	13.2	o	-
Mean	61	1.76	18.9	41.2	2.98	93	20.9*		
(SEM)	(2.19)	(0.02)	(4.10)	(9.41)	(0.20)	(4.9)			

*: geometric mean ($mg \cdot ml^{-1}$), assigning values of 32.0 $mg \cdot ml^{-1}$ to 4 subjects. For abbreviations see legend to table 1.

of less than 32 $mg \cdot ml^{-1}$) and who had continued to smoke cigarettes participated in the two studies of NSAID, 15 in the first study and 10 in the second study; five men participated in both studies. None had a history of peptic ulceration or unfavourable response to aspirin or NSAID. None were taking NSAID or developed symptoms after a trial dose. None of the men were taking any bronchodilator drugs before or during these studies. Any other treatment was taken in an unchanged dose throughout the study periods. Further details of age, baseline FEV_1, PC_{20}, atopic status and drug treatment are shown in tables 1 and 2. To expand the relationship between smoking, bronchial responsiveness and urinary excretion of thromboxane metabolites, an additional group of eight asymptomatic current smokers, four of whom had PC_{20} to histamine >32 $mg \cdot ml^{-1}$, were examined on one occasion. These men were of similar mean age and height to the men studied in the drugs trials and had a similar smoking history (table 3). As expected they had less impairment of FEV_1.

Methods

Bronchial responsiveness

FEV_1 was measured in the standing position with a dry bellows spirometer [14] which was calibrated daily. The highest FEV_1 from three technically satisfactory forced expirations expressed at BTPS was taken as the baseline and compared to reference values [15]. Provocation concentration of histamine was then determined using the same equipment and technique as described previously [13]. Subjects wore a noseclip and inhaled a solution of 0.9% saline followed by doubling concentrations of histamine diphosphate (0.5 to 32 $mg \cdot ml^{-1}$) generated by a compressed air driven Wright nebulizer at a flow rate of 7.5 $l \cdot min^{-1}$ through a mouthpiece during tidal breathing for 2 min. The output of the nebulizer was 0.14 $ml \cdot min^{-1}$ and was checked regularly. FEV_1 was recorded at 30 s, 90 s and 3 min and then at 2 min intervals to determine the lowest value after each inhalation. The challenge was terminated when FEV_1 fell below 20% of the lowest post-saline value or the 32 $mg \cdot ml^{-1}$ concentration of histamine was reached. The concentration of inhaled histamine which provoked a 20% fall in FEV_1 (PC_{20}) was obtained by linear interpolation from a log dose-response curve.

Atopic status

Skin reactivity to extracts from nine common aeroallergens (grass pollen, cat and dog dander, mixed feathers, *Alternaria, Cladosporium, Aspergillus fumigatus*, house dust and *Dermatophagoides pteronyssinus*) was assessed by prick tests in forearm skin. The response to the test was recorded as positive when mean weal diameter was >2 mm.

Measurements of thromboxane B_2 and 2,3 dinor thromboxane B_2 in urine

A 24 h urine collection was made on day 3 of placebo or flurbiprofen treatment. Thromboxane B_2 (TXB_2) and its 2,3 dinor metabolite were analysed in 10 ml aliquots of urine that had been spiked with 5 mg $^2H_4$ TXB_2 and 2,3 dinor TXB_2 internal standards. These urine samples were purified by extraction onto immunoaffinity columns labelled with an antibody to TXB_2, with a high (>60%) cross-reactivity for 2,3 dinor TXB_2 [16]. The thromboxane metabolites were eluted with 95% acetone and the eluate evaporated to dryness under N_2. The residue was subsequently derivatized to the d-trifluoro methyl benzyl - trimethylsilyl derivative and analysed by gas-chromatography, negative ion chemical ionization mass spectrometry on a Finnegan 4500, monitoring M/Z - 585 and -589 for TXB_2 and M/Z - 557 and -561 for its 2,3 dinor metabolite and deuterated standards, respectively. The limit of detection was approximately 1 $ng \cdot mmol^{-1}$ creatinine. In the additional

group of 8 smokers a 24 h urine collection was made before attending the laboratory for histamine challenge.

Protocols

Acute effects of 1.2 g aspirin. Fifteen men who were current cigarette smokers were studied in a double-blind, cross-over trial on two separate mornings one week apart. Details of age, smoking history, baseline FEV_1, PC_{20}, skin prick tests and drug treatment are shown in table 1. The study was made in the winter. After measuring spirometry and PC_{20} to histamine, each subject was given either 1.2 g aspirin tablets or matched placebo tablets. One hour after treatment spirometry and PC_{20} to histamine was repeated. One week later the same protocol was repeated with the alternate treatment.

Effects of 3 days' treatment with flurbiprofen 50 mg t.d.s. Ten men, all current cigarette smokers, were studied in a double-blind, cross-over trial. Details of age, smoking history, baseline FEV_1, PC_{20}, skin prick tests and drug treatment are shown in table 2. The study was made in the winter. After baseline measurements of spirometry and PC_{20} to inhaled histamine, subjects were then instructed to take flurbiprofen 50 mg *t.d.s.*, a potent NSAID with a plasma half-life of 4 h or matched placebo tablets. After 48 h all subjects started a 24 h urine collection, returning to the laboratory 72 h after the initial baseline measurements, for repeat measurement of spirometry and PC_{20} to inhaled histamine. After an interval of 11–24 days without any treatment, the second limb was repeated with an identical protocol, subjects being given the alternative treatment.

Both studies were approved by the local Medical School Research Ethics Committee.

Calculations

All PC_{20} values were logarithmically transformed before any calculations and are expressed as mean $\log_{10}$ PC_{20} (SEM) and geometric mean in the tables. The double-blind, two period, cross-over trials were analysed for a quantitative response and interactions between treatment and period as set out in the full description of HILLS and ARMITAGE [17].

Results

Study 1

No side-effects of the drugs were encountered.

Reproducibility of PC_{20} after one hour and one week. There was no significant difference in mean baseline FEV_1 or in PC_{20} to inhaled histamine 1 h after placebo (table 4). Paired measurements in individuals lay within one doubling dilution of histamine and there was no tendency for a reduced response to be found for the second test even in those who received the largest dose of histamine (*i.e.* men with highest PC_{20}) (fig. 1 left). When studied at one week apart, two subjects had log PC_{20} which differed by slightly more than one doubling dilution (fig. 1 right).

Table 4. – Effect of 1.2 g aspirin *versus* placebo on FEV_1 and histamine reactivity (PC_{20}) in 15 male smokers (Study 1)

		Aspirin	Placebo
FEV_1 at baseline	*l*	2.16 (0.16)	2.20 (0.16)
FEV_1 after 1 h	*l*	2.10 (0.16)	2.12 (0.15)
PC_{20} at baseline (geometric mean)	$mg \cdot ml^{-1}$	1.88	1.81
	$\log_{10}$	0.2743 (0.1201)	0.2570 (0.1101)
PC_{20} 1 h after treatment (geometric mean)	$mg \cdot ml^{-1}$	1.89	1.81
	$\log_{10}$	0.2772 (0.1523)	0.2568 (0.1218)

Results are expressed as mean and SEM in parenthesis. For abbreviations see legend to table 1.

Effects of a single 1.2 g dose of aspirin on FEV_1 and PC_{20}. There were no significant changes in baseline FEV_1, mean values of PC_{20} (table 4) or individual values of PC_{20} (fig. 2).

Study 2

Effects of 3 days' treatment with flurbiprofen 50 mg t.d.s. This subgroup had on average less impairment of FEV_1 and higher PC_{20} to histamine than the men in Study 1. No side-effects of the drugs were encountered.

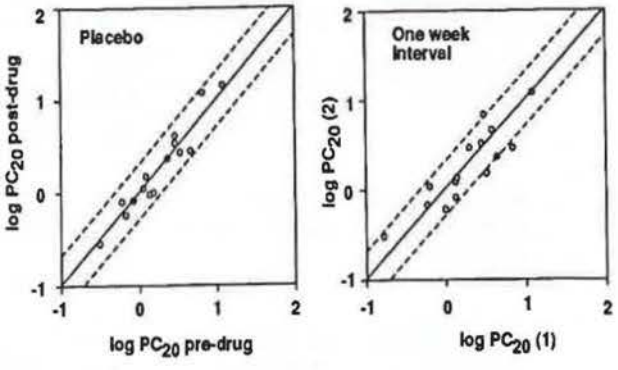

Fig. 1. – (Left panel) Comparison of provocative concentration reducing forced expiratory volume in one second by 20% (log PC_{20}) to inhaled histamine before (horizontal axis) and 1 h after placebo (vertical axis) in 15 smokers. Continuous line is line of identity, interrupted lines indicate limits of one doubling dilution. (Right panel) Comparison of log PC_{20} to inhaled histamine at an interval of 7 days in 15 smokers. First measurement on horizontal axis, second on vertical axis. Continuous line is line of identity, interrupted lines indicate limits of one doubling dilution.

Bronchial response to histamine. There was a significant drug effect for the cross-over study of placebo and flurbiprofen (p=0.009). However, inspection of mean values in table 5 and individual results in figure 3 show that a major factor in this was an unusual distribution of results after placebo; only one subject showed a large increase in PC_{20} after flurbiprofen. In both the placebo and flurbiprofen arms of the study 9 of the 10 pre- and post-drug values of PC_{20} lay within one doubling dilution, indicating repeatibility was comparable to that in Study 1 but in all 10 subjects PC_{20} was slightly reduced (*i.e.* responsiveness increased) after placebo (fig. 3). There was no evidence of a treatment-period interaction (p=0.73).

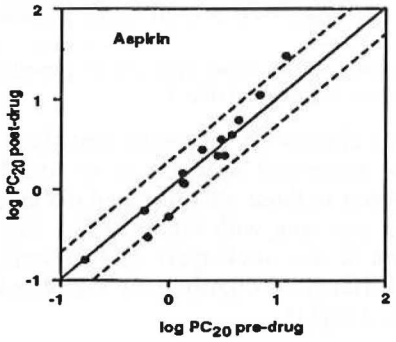

Fig. 2. – Comparison of provocative concentration reducing forced expiratory volume in one second by 20% (log PC_{20}) to inhaled histamine in 15 smokers before (horizontal axis) and 1 h after (vertical axis) a 1.2 g dose of aspirin.

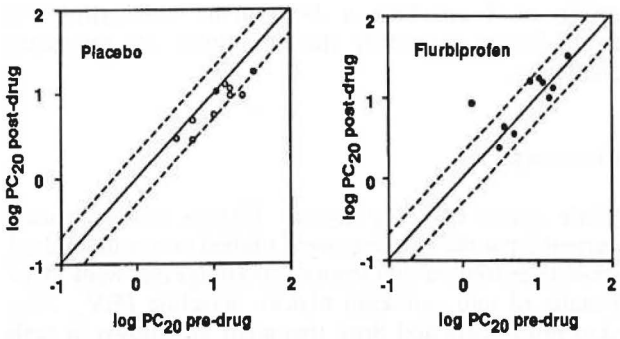

Fig. 3. – Comparison of provocative concentration reducing forced expiratory volume in one second by 20% (logPC_{20}) to inhaled histamine in 10 smokers before (horizontal axis) and after (vertical axis) 3 days' treatment with placebo (left panel), flurbiprofen 50 mg *t.d.s.* (right panel).

Urinary thromboxane metabolites (TXB$_2$: 2,3 dinor TXB$_2$). Individual values of 2,3 dinor TXB_2 in the 10 smokers in the flurbiprofen trial and in the 8 additional control smokers are shown in figure 4. Under baseline conditions there was no significant correlation between PC_{20} histamine and 2,3 dinor TXB_2 excretion in the 18 smokers; mean levels of 2,3 dinor TXB_2 in the 10 men during the placebo arm of the drug study were similar to those in the 8 control smokers, although the control smokers had a significantly higher PC_{20} histamine (p=0.009 Mann-Whitney U) (table 5).

Table 5. – Effect of flurbiprofen on FEV_1, histamine responsiveness and urinary thromboxane B_2 and metabolites

		Flurbiprofen (n=10)	Placebo (n=10)	Control* (n=8)
FEV_1 at baseline	*l*	2.58 (0.16)	2.53 (0.17)	2.98 (0.20)
FEV_1 after 3 days	*l*	2.50 (0.16)	2.52 (0.16)	-
PC_{20} of histamine at baseline	$mg \cdot ml^{-1}$	7.14	11.12	20.9
	log_{10}	0.8541 (0.1250)	0.461 (0.0992)	1.3202 (0.0932)
		p=0.012	p=0.009	
PC_{20} of histamine after 3 days' treatment	$mg \cdot ml^{-1}$	9.37	7.55	-
	log_{10}	0.9724 (0.1114)	0.8781 (0.0873)	-
		p=0.375		
Urinary thromboxane B_2	$ng \cdot mmol^{-1}$ creatinine	0.6 (0.2)	5.1 (1.1)	3.7 (0.7)
		p<0.001		
2,3 dinor thromboxane B_2	$ng \cdot mmol^{-1}$ creatinine	3.8 (1.3)	33.0 (6.5)	35.8 (12.0)
		p<0.001		

Values are arithmetic mean (SEM), except for PC_{20} where geometric mean is shown. The cross-over trial of 3 days' treatment with flurbiprofen 50 mg *t.d.s* and placebo was carried out in 10 male smokers. *: control group comprised an additional 8 male smokers (see table 3 for further details). Appropriate parametric or non-parametric t-tests were used to compare paired measurements on flurbiprofen and placebo. For abbreviations see legend to table 1.

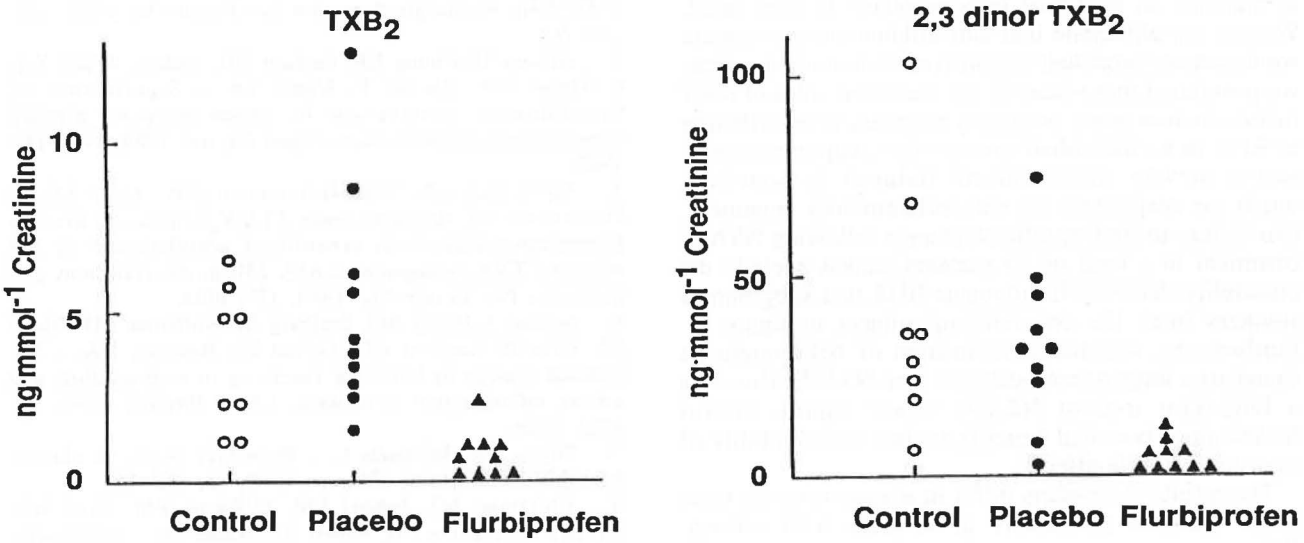

Fig. 4. – 24 h urinary excretion of thromboxane B_2 (TXB_2) and 2,3 dinor TXB_2 in 8 control smokers studied on one occasion and in 10 smokers studied on two occasions - the third day of placebo treatment and the third day of flurbiprofen treatment.

Administration of flurbiprofen produced nearly tenfold reductions in urinary excretion of both TXB_2 and 2,3 dinor TXB_2 (fig 4, table 5).

Discussion

Despite the considerable experimental evidence in animals [3–5] and the more limited evidence in humans [6], for involvement of thromboxane and prostaglandins in BHR we found no relationship between urinary excretion of 2, 3 dinor TXB_2 and PC_{20} histamine under baseline conditions and were unable to demonstrate any attenuation of BHR to histamine in middle-aged smokers with NSAID treatment. The levels of urinary 2, 3 dinor TXB_2 found in smokers under baseline conditions were similar to those reported in current smokers by Nowak *et al.* [10] who also found mean levels in control nonsmoking subjects to be about 50% (16±2 ng·mmol^{-1} creatinine) of those in smokers. Treatment with flurbiprofen greatly reduced 2, 3 dinor TXB_2 excretion. Considerable reductions in urinary 2, 3 dinor TXB_2 have been found in the first collection period after a single dose of aspirin [18] and probably also occurred in our first study.

The failure of a single dose of aspirin to attenuate BHR in the first study was clear cut. Interpretation of the second study of three days' treatment with flurbiprofen is less satisfactory because of the finding of a significant drug effect. We believe this result was due to an unusual distribution of results before placebo. We have no explanation except chance for this finding. The studies on placebo were interspersed with those in the flurbiprofen arm so that a temporary technical error cannot be implicated and there were no significant differences between post-placebo and post-flurbiprofen, or pre- and post-flurbiprofen values. We examined whether pre-placebo PC_{20} could have been increased by a longer lasting effect of prior treatment with flurbiprofen. Four of the 10 men had flurbiprofen before placebo; only two of these men showed a possible small sustained effect of flurbiprofen. In these two men pre-placebo PC_{20} was measured 11 days after the last dose of flurbiprofen and values of PC_{20} were slightly lower three days later. However, the effects of NSAID (other than aspirin) on thromboxane production only last a few hours after the last dose, with a time course similar to the plasma concentration; furthermore, each of the six men who received placebo first, who included the one subject with a large reduction in PC_{20} after flurbiprofen (fig. 3), also showed lower PC_{20} after placebo treatment. Formal statistical tests [17] confirmed the absence of a treatment-period interaction. Hence, we interpret the results of the second study as showing no significant effect of flurbiprofen on PC_{20} to histamine, supporting the more conclusive results of the first study with aspirin.

Studies in recent years have highlighted differences between BHR in smokers and in asthma [19], although atopy, which is very common in the general population, will inevitably be present in a proportion of smokers. The present group of smokers all denied asthmatic symptoms but, as expected, some had evidence of atopy. In previous studies we found most smokers had PC_{20} >32 mg·ml^{-1} [13]; in general, the prevalence of BHR in smokers increases with the severity of airways obstruction but the present group of smokers included several without significant obstruction. Although abnormal airway geometry plays an important role in the BHR of smokers, treatment with salbutamol can considerably increase PC_{20} without producing much bronchodilation [19]. Concurrent drug treatment was unchanged during the trials and the effect of cardioselective beta-adrenoceptor blocking agents such

as atenolol on bronchial responsiveness is very small. We did not anticipate that anti-inflammatory treatment would restore bronchial responsiveness to normal; rather, we postulated that whatever the particular roles of other factors such as atopy or altered geometry in contributing to BHR in an individual smoker, the component due to active airway inflammation induced by smoking might be responsive to anti-inflammatory treatment. Our failure to find significant change following NSAID treatment in a total of 20 smokers cannot exclude the possibility that NSAID attenuate BHR in a subgroup of smokers (note the one outlying subject in figure 3). Furthermore, significant attenuation of BHR might be found after longer-term treatment with NSAID. However a long-term trial of NSAID would require careful balancing of potential benefits against the possibility of troublesome side-effects.

The results in smokers differ in several respects from those reported previously in subjects with asthma. Whereas some attenuation of bronchial responsiveness to inhaled histamine has been noted by some authors after treatment with indomethacin [20] or flurbiprofen [21] in asthmatic subjects, we found no attenuation in either study in smokers. In addition we found no evidence of a reduced response to inhaled histamine when a second test of responsiveness was applied after an interval of one hour. The dose of histamine given and the time interval was similar to that associated with tachyphylaxis in asthmatic subjects in the study of MANNING *et al.* [22]; these authors further showed that tachyphylaxis was abolished by treatment with indomethacin. Although others [23] have noted tachyphylaxis to the effects of inhaled histamine in asthmatic subjects, this effect is not consistently present (see discussions in [22, 23]). There appear to be no other studies of tachyphylaxis in smokers with increased responsiveness.

In summary, we were unable to show any relationship between the excretion of urinary thromboxane metabolites and the intensity of BHR in middle-aged smokers under baseline conditions. A single dose of aspirin failed to attenuate BHR. Three days' treatment with flurbiprofen greatly reduced urinary thromboxane metabolites but, although there were some problems with the analysis, probably did not significantly attenuate the bronchial response to histamine. Thus, we found no evidence that cyclo-oxygenase products contribute to short-term maintenance of BHR to histamine in smokers.

References

1. Chung F. – Role of inflammation in the hyperreactivity of the airways in asthma. *Thorax*, 1986, 41, 657–662.
2. Kraan J, Koëter GH, Van der Mark ThW, Boorsma M, Kukler J, Sluiter HJ, de Vries K. – Dosage and time effects of inhaled budesonide on bronchial hyperreactivity. *Am Rev Respir Dis*, 1988, 137, 44–48.
3. Chung KF, Aizawa H, Becker AB, Frick O, Gold WM, Nadel JA. – Inhibition of antigen-induced airway hyperresponsiveness by a thromboxane synthetase inhibitor (OKY 046) in allergic dogs. *Am Rev Respir Dis*, 1986, 134, 258–261.
4. Aizawa H, Chung KF, Leikauf GD, Ueki I, Bethel RA, O'Byrne PM, Hirose T, Nadel JA. – Significance of thromboxane generation in ozone-induced airway hyperresponsiveness in dogs. *J Appl Physiol*, 1985, 59, 1918–1923.
5. McFarlane CS, Ford-Hutchinson AW, Letts LG. – Inhibition of thromboxane (TXA_2)-induced airway hyperresponsiveness to aerosolized acetylcholine by the selective TXA_2 antagonist L-655, 240 in the conscious primate. *Am Rev Respir Dis*, 1988, 137, 100A.
6. Seltzer J, Bigby BG, Stulbarg M, Holtzman MJ, Nadel JA, Ueki IF, Leikauf GD, Goetzl EJ, Boushey HA. – O_3-induced change in bronchial reactivity to methacholine and airway inflammation in humans. *J Appl Physiol*, 1986, 60, 1321–1326.
7. Glynn AA, Michaels L. – Bronchial biopsy in chronic bronchitis and asthma. *Thorax*, 1960, 15, 142–153.
8. Holtzman MJ, Fabbri LM, O'Byrne PM, Gold BD, Aizawa H, Walters EH, Alpert SE, Nadel JA. – Importance of airway inflammation for hyperresponsiveness induced by ozone in dogs. *Am Rev Respir Dis*, 1983, 127, 686–690.
9. Fabbri LM, Aizawa H, Alpert SE, Walters EH, O'Byrne PM, Gold BD, Nadel JA, Holtzman MJ. – Airway hyperresponsiveness and changes in cell counts in bronchoalveolar lavage after ozone exposure in dogs. *Am Rev Respir Dis*, 1984, 129, 288–291.
10. Nowak J, Murray JJ, Oates JA, Fitzgerald GA. – Biochemical evidence of a chronic abnormality in platelet and vascular function in healthy individuals who smoke cigarettes. *Circulation*, 1987, 76, 6–14.
11. Reilly IAG, Fitzgerald GA. – Inhibition of thromboxane formation *in vivo* and *ex vivo*: implications for therapy with platelet inhibitory drugs. *Blood*, 1987, 69, 180–186.
12. Tattersall SF, Benson MK, Hunter D, Mansell A, Pride NB, Fletcher CM, Peto R, Gray R, Humphreys PRR. – The use of tests of peripheral lung function for predicting future disability from airflow obstruction in middle-aged smokers. *Am Rev Respir Dis*, 1978, 118, 1035–1050.
13. Taylor RG, Joyce H, Gross E, Holland F, Pride NB. – Bronchial reactivity to inhaled histamine and annual rate of decline in FEV_1 in male smokers and ex-smokers. *Thorax*, 1985, 40, 9–16.
14. McDermott M, McDermott TJ, Collins MM. – A portable bellows spirometer and timing unit for the measurement of respiratory function. *Med Biol Engineering*, 1968, 6, 291–293.
15. Quanjer PH, ed. – Standardized lung function testing. *Bull Eur Physiopathol Respir*, 1983, 19 (Suppl. 5), 7–10.
16. Krause W, Jacobs U, Schultz PE, Nieuwehoer B, Hümpel M. – Development of antibody-mediated extraction followed by GC/MS (antibody/GC/MS) and its application to iloprost determination in plasma. *Prostaglandins Leukotrienes and Medicine*, 1985, 17, 167–182.
17. Hills M, Armitage P. – The two-period cross-over clinical trial. *Br J Clin Pharmacol*, 1979, 8, 7–20.
18. Vesterqvist O, Green E. – Urinary excretion of 2, 3 dinor thromboxane B_2 in man under normal conditions, following drugs and during some pathological conditions. *Prostaglandins*, 1984, 27, 627–644.
19. Pride NB, Taylor RG, Lim TK, Joyce H, Watson A. – Bronchial hyperresponsiveness as a risk factor for progressive airflow obstruction in smokers. *Bull Eur Physiopathol Respir*, 1987, 23, 369–375.

20. Walters EH. – Prostaglandins and the control of airways responses to histamine in normal and asthmatic subjects. *Thorax*, 1983, 38, 188–194.
21. Curzen N, Rafferty P, Holgate ST. – Effects of a cyclo-oxygenase inhibitor, flurbiprofen, and an H_1 histamine receptor antagonist, terfenadine, alone and in combination on allergen induced immediate bronchoconstriction in man. *Thorax*, 1987, 42, 946–952.
22. Manning PJ, Jones GL, O'Byrne PM. – Tachyphylaxis to inhaled histamine in asthmatic subjects. *J Appl Physiol*, 1987, 63, 1572–1577.
23. Connolly MJ, Stenton SC, Avery AJ, Walters EH, Hendrick DJ. – Refractory period following bronchoconstriction provoked by histamine in asthmatic subjects. *Thorax*, 1989, 44, 146–150.

Effets de médicaments anti-inflammatoire non stéroïdiens sur l'hyperréactivité bronchique de fumeurs d'âge moyen. T.K. Lim, N.C. Turner, A. Watson, H. Joyce, R.W. Fuller, N.B. Pride.

RÉSUMÉ: On pense que l'hyperréactivité bronchique (BHR) des fumeurs est une conséquence de l'inflammation des parois des voies aériennes. Nous avons examiné les effets des traitements au moyen de médicaments anti-inflammatoires non stéroödiens (NSAID) sur BHR à l'égard de l'inhalation d'histamine (mesurée comme la concentration de provocation qui réduit le VEMS de 20% [PD_{20}]) chez des fumeurs de cigarettes de sexe masculin et d'âge moyen, au cours de deux essais séparés en double anonymat avec contrôle par placebo et permutation croisée. Les valeurs de base du VEMS chez ces fumeurs s'étendaient entre 41 et 117 % des valeurs prédites. Dans la premi ere étude, 15 hommes (aâge moyen 58 ans, VEMS 2.20 *l*) ont été examinés avant et 1 heure après une dose unique de 1.2 g d'aspirine. L'on pas noté de modification significative du PC_{20} (moyenne géométrique 1.88 mg·ml avant l'aspirine, 1.89 mg·ml après l'aspirine) ou du VEMS de base. Nous n'avons pas observé de tachyplylaxie à l'égard des effets de l'histamine inhalée 1 heure après le placebo. Dans la deuxième étude, 10 hommes (âge moyen 60 ans, VEMS 2.53 *l*) ont été examinés avant et après 3 jours de traitement au moyen de 50 mg de flurbiprofen 3 fois par jour (NSAID). Le PC_{20} de base était plus élevé dans ce groupe que dans la première étude. L'on n'a pas observé de relation entre l'excrétion de métabolites urinaires du thromboxane et l'intensité de l'hyperréactivité bronchique dans les conditions basales. Le flurbiprofen a réduit considérablement l'excrétion urinaire des métabolites du thromboxane, mais n'a pas modifié le VEMS de base. L'analyse des modificaitons du PC_{20} a été par une différence dans le PC_{20} de base avant les deux traitements, mais le traitement au flurbiprofen n'a pas atténué significativement BHR. Ces résultats suggèrent que le thromboxane ou d'autres produits de la cyclo-oxygénase provenant du métabolisme de l'acide arachidonique ne jouent pas un rôle important dans l'entretien d'une hyperréactivité bronchique à court terme chez les fumeurs de cigarettes d'âge moyen et de sexe masculin.
Eur Respir J., 1990, 3, 872–879.