

Protective activity of inhaled nonsteroidal antiinflammatory drugs on bronchial responsiveness to ultrasonically nebulized water

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Relatively high doses of oral aspirin are needed to afford a significant protective effect against the bronchial obstructive reaction to ultrasonically nebulized distilled water (UNDW) in asthmatic patients. Sodium salicylate at similar doses and indomethacin at normal dose afford no protection. The present study was undertaken to assess the protective activity of these drugs taken by inhalation. Thirteen asthmatic patients performed two UNDW challenges 20 minutes and 24 hours after inhalation of 900 mg lysine acetylsalicylate (L-ASA) or placebo. The volume of UNDW causing a 20% fall in FEV₁ (UNDW PD₂₀) was calculated by linear interpolation on the dose-response curve. UNDW response after placebo was not significantly different from the preliminary test (PD₂₀ 4.3 ± 0.7 and 4.1 ± 0.4 ml, respectively, mean ± SE), whereas after L-ASA, UNDW PD₂₀ increased to 17 ± 2.7 ml (p < 0.01 vs placebo) and remained significantly increased after 24 hours. In another group of 12 patients under the same experimental conditions, an equivalent dose of inhaled sodium salicylate caused no effect. Finally, in a third group of asthmatic patients pretreatment with inhaled indomethacin at two dose levels (6 patients, 25 mg; 10 patients, 50 mg) resulted in a significant dose-related protective effect. These findings indicate that inhaled indomethacin and especially L-ASA exert against UNDW-induced bronchoconstriction a potent protective effect, which appears to be mediated by inhibition of local prostaglandin synthesis in the airways. This fact could have therapeutic implications. (J ALLERGY CLIN IMMUNOL 1992;90:833-9.)

Key words: Bronchial asthma, bronchial hyperreactivity, lysine acetylsalicylate, indomethacin

We previously reported that oral aspirin (acetylsalicylic acid[ASA]) prevents the bronchial response to ultrasonically nebulized distilled water (UNDW) in a dose-dependent fashion in asthmatic patients.^{1,2} Under the same experimental conditions, sodium salicylate was ineffective,³ suggesting that the protective effect of ASA is related to inhibition of the prostaglandin system. Unfortunately, when given orally, rather high doses of ASA are needed to afford a clinically significant degree of protection. Such doses can

Abbreviations used

ASA:	Acetylsalicylic acid
L-ASA:	Lysine acetylsalicylate
NSAID:	Nonsteroidal antiinflammatory drug
SA:	Salicylic acid
UNDW:	Ultrasonically nebulized distilled water
FEV ₁ :	Forced expiratory volume in 1 second
PD ₂₀ :	Volume causing a 20% fall in FEV ₁

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cause serious side effects in many patients with asthma if taken regularly over a long time.⁴ Inhalation is currently the preferred route of administration of bronchoactive drugs, like β_2 -stimulants and corticosteroids, because it allows maximum effect to be achieved with smaller doses of drug and causes fewer side effects. The aim of the present study was to ascertain whether the inhaled route was also applicable to nonsteroidal antiinflammatory drugs (NSAIDs)

TABLE I. Anthropometric details, baseline FEV₁, atopic status, and therapy of the subjects participating in part 1 of the study (lysine acetylsalicylate)

Subject	Sex	Age (yr)	FEV ₁ * %pred	Allergy	Therapy
1	M	34	94	DP	β ₂ + CS
2	M	24	78	—	β ₂
3	F	39	98	—	β ₂ + CS
4	F	19	100	GR	β ₂
5	F	35	75	—	β ₂ + CS
6	F	40	90	GR	β ₂
7	M	18	81	—	β ₂
9	M	20	106	GR	β ₂ + CS
10	M	47	80	—	β ₂ + CS
11	F	55	92	—	β ₂ + CS
12	F	18	89	DP	β ₂ + CS
13	F	28	100	—	β ₂

DP, *Dermatophagoides*; GR, grass pollen; β₂, inhaled β₂-agonist; CS, inhaled steroids.

*Percentage of predicted value at baseline.

TABLE II. Anthropometric details, baseline FEV₁, atopic status, and therapy of the subjects participating in part 2 of the study (sodium salicylate)

Subject	Sex	Age (yr)	FEV ₁ * %pred	Allergy	Therapy
1	F	28	106	GR	β ₂
2	F	61	102	—	β ₂ + CS
3	M	20	102	GR	β ₂
4	M	17	95	—	β ₂ + CS
5	M	41	100	—	β ₂
6	F	18	98	GR	β ₂ + CS
7	F	47	99	—	β ₂
8	F	34	101	GR	β ₂ + CS
9	M	21	83	GR	β ₂ + CS
10	M	18	85	—	β ₂
11	M	34	94	DP	β ₂
12	M	24	78.7	—	β ₂

*Percentage of predicted value at baseline.

such as ASA and indomethacin. The results presented here show that inhaled NSAIDs, and in particular lysine acetylsalicylate (L-ASA), the soluble form of ASA, attenuate the bronchial responses to UNDW.

PATIENTS AND METHODS

Patients

Forty-one nonsmoking subjects with allergic or non-allergic mild asthma, clinically and functionally stable, and with a positive response to a preliminary UNDW challenge (PD₂₀ ≤ 7.5 ml) gave informed consent to participate in the study. All had a baseline forced expiratory volume in 1 second (FEV₁) greater than 70% of the predicted value and had been free of viral and bacterial respiratory infection for

at least 6 weeks.⁵ None of the patients had a history of aspirin asthma, and they had all performed an inhaled aspirin challenge within the previous 3 months with negative results.⁶ All the patients were treated with inhaled β₂-stimulants on demand, and most were taking inhaled beclomethasone on a regular basis (Tables I through IV) in a dose range of 200 to 1000 μg per day. None of the patients was being treated with theophylline or other antiasthmatic drugs. All treatments were withheld at least 10 hours before the challenge test.⁷ Patients allergic to pollen were studied outside the pollen season.

Bronchial challenge with UNDW

Reactivity to UNDW was measured as previously described.^{8,9} In brief, UNDW was generated with a De Vilbiss

TABLE III. Anthropometric details, baseline FEV₁, atopic status, and therapy of the subjects participating in part 3 of the study (25 mg indomethacin)

No.	Sex	Age	FEV ₁ %pred	Allergy	Therapy
1	F	60	87	—	β ₂ + CS
2	M	20	101	DP	β ₂
3	F	40	84	—	β ₂
4	M	25	85	—	β ₂ + CS
5	M	20	98	—	β ₂ + CS
6	F	18	88	GR	β ₂ + CS

Ultraneb 99 nebulizer (De Vilbiss Co., Somerset, Pa.) to which the patients were connected via a cylindrical plastic mouthpiece while wearing a nose clip. Subjects were instructed to breathe normally at tidal volume. By combining output rate (2 to 4 ml/min) with time of exposure (0.25, 0.5, 1, 2, 4, and 8 minutes), increasing doses of H₂O in doubling increments were delivered to the mouthpiece at 2-minute intervals until a fall in 20% of FEV₁ occurred or the cumulative dose of 63 ml was reached. FEV₁ was measured before challenge and immediately after each exposure with use of a dry wedge spirometer (Vitalograph, Buckingham, U.K.) and the highest of the first two satisfactory recordings was taken for analysis. Dose-response curves were constructed by plotting the percentage change in FEV₁ from baseline value against the cumulative volume of UNDW expressed in milliliters. The volume of UNDW required to decrease FEV₁ by 20% was then calculated by linear interpolation.

Study design

The study was divided into three parts, and each part was performed in a double-blind, placebo-controlled manner. The study was approved by the ethical committee of our Institution.

Part 1: inhaled L-ASA versus UNDW challenge. Thirteen adult patients (Table I) were challenged at the same time of the day on two occasions, 2 to 7 days apart, 20 minutes and 24 hours after inhaling 900 mg L-ASA in 5 ml of saline solution, corresponding to 500 mg of ASA (Flectadol, Maggioni Winthrop, Milano, Italy), or placebo (saline), with use of a jet nebulizer run to dryness in approximately 30 minutes. The treatments were administered in random order according to a double-blind protocol. Baseline FEV₁ was recorded immediately before and after treatment.

Part 2: inhaled sodium salicylate versus UNDW challenge. Twelve patients with characteristics comparable to the first group (Table II) were examined according to the protocol of part 1, except that the

TABLE IV. Anthropometric details, baseline FEV₁, atopic status, and therapy of the subjects participating in part 3 of the study (50 mg indomethacin)

No.	Sex	Age	FEV ₁ %pred	Allergy	Therapy
1	M	18	111	GR	β ₂ + CS
2	M	47	85	—	β ₂ + CS
3	M	24	78	—	β ₂ + CS
4	M	32	102	—	β ₂
5	F	28	103	—	β ₂
6	F	23	87	—	β ₂ + CS
7	F	55	92	GR	β ₂ + CS
8	F	40	85	DP	β ₂ + CS
9	M	18	85	GR + DP	
10	M	28	91	GR + DP	β ₂ + CS

test was not repeated at 24 hours, and 800 mg sodium salicylate was administered instead of L-ASA.

Part 3: inhaled indomethacin at two dose levels versus UNDW challenge. The protocol was the same as for the previous group, except that the UNDW challenge was delayed until 1 hour after the end of treatment, because in preliminary experiments most of the patients complained of irritation of the upper respiratory tract after inhaling indomethacin, sometimes resulting in a transient obstructive response. Six patients (Table III) inhaled 38.6 mg of indomethacin meglumine (Liometacen, Chiesi Farmaceutici, Parma, Italy), corresponding to 25 mg of indomethacin in 5 ml of saline solution or placebo. In the other 10 patients (Table IV) the dose of indomethacin was doubled. The pH of indomethacin solutions was between 7.7 and 7.8.

Statistical analysis

The paired and unpaired *t* tests were used to compare different treatments, and two-way analysis of variance (ANOVA) was used to compare multiple groups. A value of *p* < 0.05 was considered significant.¹⁰ Unless stated otherwise, the data are presented as mean ± SE. All the calculations of PD₂₀ were computed by an operator unaware of the treatment.

RESULTS

Inhaled L-ASA versus UNDW challenge

Inhalation of L-ASA was well tolerated. Baseline FEV₁ did not differ significantly (two-way ANOVA) on the different study days. No significant difference occurred between preliminary test and placebo PD₂₀ (mean ± SE 4.1 ± 0.4 and 4.3 ± 0.7 ml, respec-

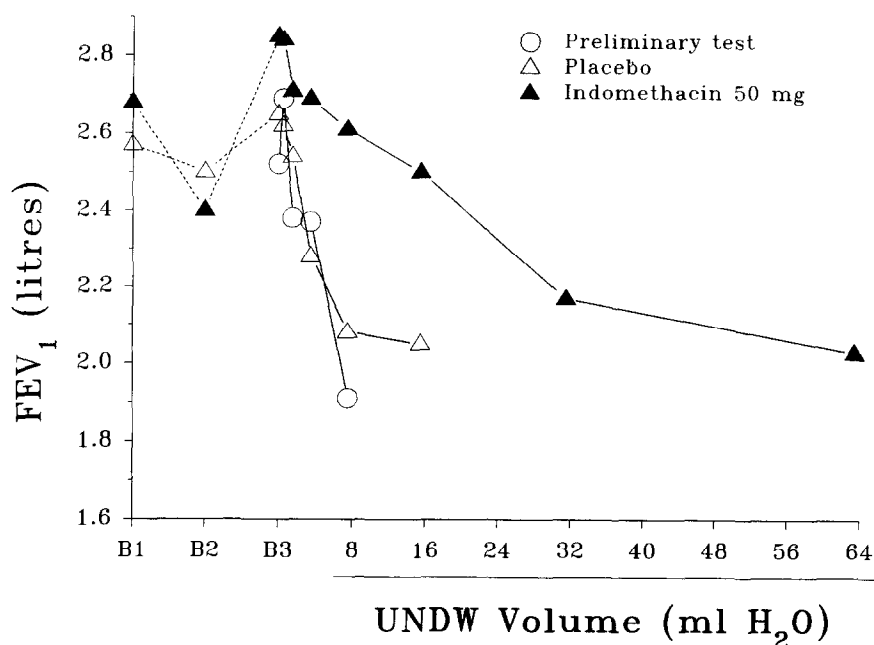


FIG. 1. Effect of inhaled L-ASA (100 mg/ml) on bronchial reactivity to UNDW, 20 minutes and 24 hours after treatment. Data expressed as $M \pm SE$ of UNDW PD₂₀. $p < 0.001$ versus placebo at the corresponding time point. Clinical characteristics of the study group reported in Table I.

TABLE V. Effect of inhaled sodium salicylate and indomethacin on baseline FEV₁ and UNDW PD₂₀*

	No.	Preliminary test		Placebo FEV ₁				Active drug FEV ₁			
		FEV ₁ (1)	PD ₂₀ †	Before	30 min	60 min	PD ₂₀	Before	30 min	60 min	PD ₂₀
Sodium salicylate	12	3.35 (0.22)	3.6 (0.4)	3.33 (0.21)	3.27 (0.20)	—	3.5 (0.3)	3.30 (0.21)	3.26 (0.21)	—	4.9 (0.8)
Indomethacin 25 mg	6	3.21 (0.38)	4.6 (1.3)	3.12 (0.31)	3.02 (0.32)	3.06 (0.31)	3.8 (1.1)	3.28 (0.38)	2.92 (0.33)	3.10 (0.30)	8.6‡ (2.4)
Indomethacin 50 mg	10	3.24 (0.27)	5.6 (0.9)	3.28 (0.30)	3.25 (0.32)	3.30 (0.31)	5.6 (0.7)	3.29 (0.33)	2.87§ (0.30)	3.14 (0.30)	16.8 (2.4)

*Data expressed as the mean $\pm$ SE (in parentheses).

†PD₂₀ to UNDW, expressed in milliliters of H₂O.

‡ $p < 0.02$ versus UNDW PD₂₀ after placebo.

§ $p < 0.01$ versus baseline FEV₁ before treatment.

|| $p < 0.001$ versus UNDW PD₂₀ after placebo.

tively). By contrast, PD₂₀ markedly increased after L-ASA (17.8 ± 7.6 ml, 4.8 ± 0.9 times higher than after placebo) and was still significantly higher 24 hours after premedication (9.1 ± 1.3 ml, 2.3 ± 0.2 times over placebo). UNDW reactivity 24 hours after placebo did not differ significantly from the baseline value (Fig. 1).

Inhaled sodium salicylate versus UNDW challenge

Inhaled SA was also well tolerated, but it had no effect on the response to UNDW. Baseline FEV₁ and

PD₂₀ did not differ significantly on the 3 study days (Table V).

Inhaled indomethacin versus UNDW challenge—lower dose

Inhalation of 25 mg indomethacin was well tolerated, and no significant changes in FEV₁ were observed 30 and 60 minutes after treatment (Table V). The treatment afforded significant protection against UNDW-induced bronchoconstriction: UNDW PD₂₀ after indomethacin was 2.3 ± 0.3 times higher than after placebo. The UNDW dose-response curves in

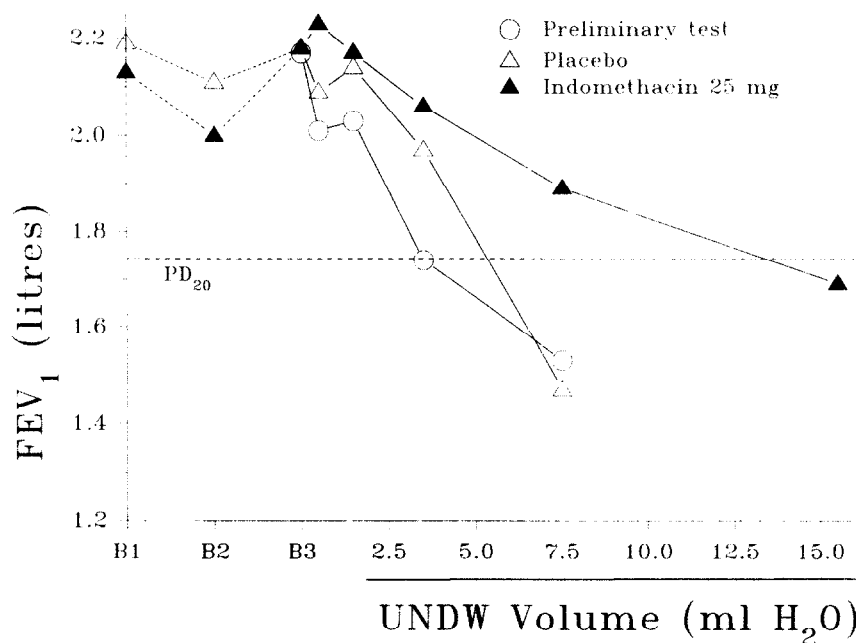


FIG. 2. Effect of 25 mg inhaled indomethacin (*solid triangles*) and placebo (*open triangles*) on baseline FEV₁ and UNDW-induced bronchoconstriction in a typical case (no. 1 of Table III). The response to UNDW in the preliminary challenge, without treatment, is also reported (*open circles*). B1, Baseline FEV₁ before treatment; B2, FEV₁ 30 minutes after treatment; B3, FEV₁ 60 minutes after treatment, baseline for UNDW challenge.

the preliminary test, after treatment with 25 mg indomethacin and placebo in a typical case, are shown in Fig. 2.

Inhaled indomethacin versus UNDW challenge—higher dose

After inhalation of 50 mg indomethacin, all patients complained of laryngotracheal irritation, with a corresponding transient decrease in FEV₁. After 1 hour, however, FEV₁ returned to within 10% of baseline value in all subjects (Table V). In spite of this local side effect, the degree of protection observed in this group was significantly higher than that afforded by the lower dose (Table V). In fact, after treatment UNDW PD₂₀ was found to be 3.1 ± 0.3 times higher than after placebo. The UNDW dose-response curves in the preliminary test, after treatment with 50 mg indomethacin and placebo in a typical case, are shown in Fig. 3.

DISCUSSION

Nonspecific bronchial hyperresponsiveness to a large variety of direct and indirect stimuli is a feature of asthma in the clinically active phase.^{11, 12} Unsuccessful attempts have been made to attenuate the exaggerated response to provoking agents such as exercise and UNDW with use of indomethacin at doses known to cause almost complete inhibition of pros-

taglandin synthesis in the peripheral blood.^{13, 14} At the same doses, however, indomethacin prevented the development of refractoriness of the airways after repeated challenge with both the above stimuli.^{13, 14}

This discrepancy has been attributed to a more selective inhibitory effect of indomethacin on the synthesis of antibronchoconstrictor prostaglandins, like PGI₂, than on bronchoconstrictor prostanoids.¹⁵ The low sensitivity of bronchial cyclooxygenases to pharmacologic inhibition must also be taken into account, as human pulmonary cyclooxygenase has been found to be 59 times more resistant to ASA and 532 times to indomethacin than platelet cyclooxygenase *in vitro*.¹⁶

Using a more specific and potent cyclooxygenase inhibitor, flurbiprofen, Finnerty and Holgate¹⁵ recently obtained a significant attenuation of exercise-induced bronchoconstriction. In a similar manner we observed that oral ASA prevents UNDW-induced bronchoconstriction in a dose-related manner, giving quite good protection at a dose of 4 gm of ASA.^{1, 2}

The present study shows that even better and longer-lasting protection is afforded by inhalation of ASA as an aerosol of L-ASA solution. On the average, such treatment determined a 4.54-fold increase in UNDW PD₂₀ with respect to placebo, whereas the corresponding increase observed in a previous study with 4 gm or oral ASA was only 2.8-fold (placebo 4.0 ± 2.3

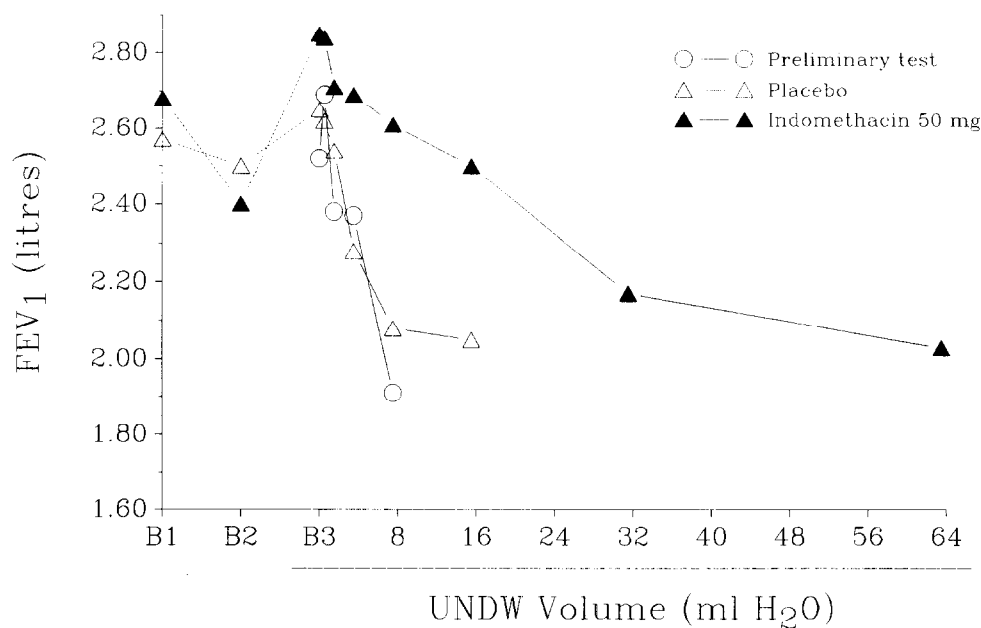


FIG. 3. Effect of 50 mg inhaled indomethacin and placebo on baseline FEV₁ and UNDW-induced bronchoconstriction in a typical case (no. 2 of Table IV). The response to UNDW in the preliminary challenge is also reported. For explanation of symbols, see legend to Fig. 2.

ml, ASA 11.4 ± 4.0).³ This difference is even more impressive in view of the fact that approximately only 10% of the nebulized solution actually reaches the airways.¹⁷ It is very unlikely that the protection observed after inhalation of L-ASA is an artifact caused by spontaneous variability of the test or to the effect of inhaled steroids, since UNDW reactivity after placebo was no different from the preliminary test in all the study groups (Table V). Indeed, all experiments in the same patient were performed in the period of a week, and the response to UNDW is known to be quite reproducible in such a short interval.^{8,9}

The greater efficacy of inhaled L-ASA with respect to the oral form is probably mostly due to the rapid hepatic and renal conversion of the latter into SA after gastrointestinal absorption.¹⁸ The fraction of ingested ASA available for the bronchial tissue is thus too small to exert an effective protective effect, unless rather high doses of ASA are administered. The large fraction of SA does not result in any acute bronchial effect, because oral and inhaled SA are both devoid of protective activity.³ The increased protection afforded by inhalation may also be due to more direct access of the drugs to the cells such as mast cells, macrophages, nerve endings, and epithelial cells responsible for the triggering of asthma.

Unlike ASA, sodium salicylate does not exhibit direct anticyclooxygenase activity.¹⁹ This indicates that the protective effect of ASA against UNDW-

induced bronchoconstriction is due to the inhibition of prostaglandin synthesis. The protective, dose-related effect of inhaled indomethacin points to the same conclusion. When administered at equivalent anti-inflammatory doses, inhaled indomethacin was less effective than L-ASA in preventing UNDW-induced bronchoconstriction. In addition to the relatively low sensitivity of lung cyclooxygenase to this agent,¹⁶ it is possible that the irritative reaction of the upper respiratory tract observed in the present study after inhalation of this drug might reduce its inhibitory activity. We have no explanation for this irritative reaction, or for the transient bronchoconstriction observed after inhalation of indomethacin, especially at the higher dose. It is not likely to be due to the alkaline pH of the solution, since the low dose of indomethacin had a very similar pH but caused very little discomfort. Furthermore, our previous experiences have shown that control solutions of even higher pH have no effect on bronchial reactivity and do not cause irritation or bronchial obstruction even in patients with severe bronchial hyperresponsiveness.^{8,9}

We did not investigate the mechanism of the protective activity of NSAIDs. Since bronchial inflammation appears to play a fundamental role in the pathogenesis of asthma,²⁰ and these drugs have shown potent antiinflammatory activity in a variety of pathologic conditions,²¹ they might directly affect the mechanisms responsible for bronchial hyperreactivity.

If this is the case, inhaled NSAIDs may offer a new approach to the treatment of asthma, in addition to other drugs available for treatment of mucosal inflammation. This article, however, is only concerned with the study of acute bronchoconstriction in asthmatic subjects, not the long-term effect of these drugs on bronchial hyperreactivity.

In conclusion, inhaled indomethacin and especially ASA exhibit potent protective activity against UNDW-induced bronchoconstriction. Preliminary results in our laboratories suggest that the same is true of other NSAIDs like tenoxicam and ketoprofen and for other stimuli such as exercise and the early and late reaction to allergen challenge. These findings stress the importance of inhalation for exploiting the protective activity of NSAIDs. Whether inhaled NSAIDs might prove useful for the treatment of patients with asthma will require further study.

REFERENCES

1. Bianco S, Robuschi M, Damonte C, Simone P, Vaghi A, Pargiklian M. Bronchial response to nonsteroidal anti-inflammatory drugs in asthmatic patients. *Prog Biochem Pharmacol* 1985;20:132-42.
2. Robuschi M. Control of bronchial tone. *Respiration* 1988;54(suppl 1):100-7.
3. Robuschi M, Vaghi A, Pieroni MG, Sestini P, Bianco S. Aspirin but not sodium salicylate prevents fog-induced bronchoconstriction. *Am Rev Respir Dis* 1991;143:A422.
4. Sweet GM, Stevenson DD, Simon RA, Matlison DA. Long-term effects of aspirin desensitization treatment for aspirin-sensitive rhinosinusitis-asthma. *J ALLERGY CLIN IMMUNOL* 1990;85:59-65.
5. Quanjer PhJ. Standardized lung function testing. *Bull Eur Physiopath Respir* 1983;19(suppl 5):1-92.
6. Bianco S, Robuschi M, Simone P, et al. Aspirin-induced tolerance in aspirin asthma detected by a new challenge test. *IRCS J Med Sci* 1977;129:5.
7. Chai H, Farr RS, Froelich LA, et al. Standardization of bronchial inhalation challenge procedures. *J ALLERGY CLIN IMMUNOL* 1975;56:323-7.
8. Bianco S, Robuschi M, Damonte C. Drug effect on bronchial response to PGF₂α and water inhalation. *Eur J Respir Dis* 1983;64(suppl):213-21.
9. Robuschi M, Gambaro G, Spagnotto S, Vaghi A, Bianco S. Inhaled furosemide (F) is highly effective in preventing ultrasonically nebulized water (UNH₂O) bronchoconstriction. *Pulmon Pharmacol* 1989;1:187-91.
10. Snedecor GW, Cochran WG. *Statistical methods*. 7th ed. Ames: Iowa University Press, 1980.
11. Juniper EF, Frith PA, Hargreave FE. Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. *Thorax* 1981;36:575-9.
12. Cockcroft DW. Nonallergic airway responsiveness. *J ALLERGY CLIN IMMUNOL* 1988;81:111-9.
13. O'Byrne PH, Jones GL. The effect of indomethacin on exercise-induced bronchoconstriction and refractoriness after exercise. *Am Rev Respir Dis* 1986;134:69-72.
14. Mattoli S, Foresi A, Corbo GM, Valente S, Ciappi G. The effect of indomethacin on the refractory period occurring after the inhalation of ultrasonically nebulized water. *J ALLERGY CLIN IMMUNOL* 1987;79:678-83.
15. Finnerty JP, Holgate ST. Evidence for the role of histamine and prostaglandins as mediators of exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. *Eur Respir J* 1990;3:540-7.
16. Toivanen J, Ylikorkala O, Viinikka L. Differential inhibition of platelet thromboxane and lung prostacyclin production by sulphapyrazone, acetyl-salicylic acid and indomethacin by human tissues in vitro. *J Thromb Res* 1985;37:493-502.
17. Newman SP. In: Clarke SW, Pavia D, eds. *Aerosols and the lung*. London: Butterworths, 1984:197-224.
18. Needs CI, Brooks PM. Clinical pharmacokinetics of the salicylates. *Clin Pharmacokin* 1985;10:164-77.
19. Hamberg M. Inhibition of prostaglandin synthesis in man. *Biochem Biophys Res Commun* 1972;49:720-6.
20. Djukanovich R, Roche WR, Wilson JW, et al. Mucosal inflammation in asthma. State of the art. *Am Rev Respir Dis* 1990;142:434-57.
21. Insel PA. Analgesic-antipyretics and antiinflammatory agents: drugs employed in the treatment of rheumatoid arthritis and gout. In: Goodman Gilman A, Rall TW, Nies AS, Taylor P, eds. *Goodman & Gilman's The pharmacological basis of therapeutics*. 8th ed., New York: Pergamon press, 1990:638-73.

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