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Review of Respira-

Diappi G. The effect
occurring after the
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578-683, 1987
to aspirin: a role for

in BA. Long-term
-dependent asthma.
1, 1990

methacin on exercise-
ness after exercise.
134: 69-72, 1986

Tothul P. et al. Cor-
parison with rheu-
tica. British Medical

Respiration 54 (Suppl.

gretto G, Petrigni G.
ale all'aspirina. Lotta
ali 59: 81-85, 1989

er M, Greif J. et al.
olchicine in asthma.
gy 85: 578-584, 1980
Qingqing LI. et al.
n bronchial asthma.

G, Refini RM, et al.
Olivieri D, Bianco S
on. Progress in Res-
urger, 1990

s DM. Randomized,
methotrexate in ster-
40, 1990

us KL, Block FJ, et
boxane A₂ and leu-
v of Respiratory Dis-

Berstein PR. Mech-
oconstriction in nor-
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P, Berni F, et al. L'a-
o protegge dal bron-
na di Medicina Res-
18-23 ottobre, 1990
Thorax 45: 161-163.

oved protocol for the
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Drug Investigation 3 (Suppl. 2): 39-47, 1991
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Nimesulide, a Nonsteroidal Anti-Inflammatory Drug, Displays Antianaphylactic and Antihistaminic Activity in Guinea-Pigs

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Summary

The nonsteroidal anti-inflammatory compound nimesulide (4-nitro-2-phenoxy methane sulfonanilide) antagonises the effect of histamine and inhibits the release of this autacoid during immunological reaction in guinea-pigs. The antihistaminic activity of nimesulide, studied in isolated guinea-pig trachea, is specific for the H₁-receptor and is of a noncompetitive type. At a concentration of 1×10^{-5} mol/L, the potency of nimesulide is nearly half that of mepyramine (pyrilamine) at 1×10^{-6} mol/L. Furthermore, unlike indomethacin, nimesulide dose-dependently antagonises the effect of histamine on airway resistance of anaesthetised guinea-pigs. In actively ovalbumin-sensitised anaesthetised guinea-pigs, both nimesulide and indomethacin significantly protected the animals from the fatal systemic anaphylactic crisis. However, in perfused sensitised guinea-pig lungs, nimesulide reduced the anaphylactic release of histamine in a concentration-dependent way, whereas indomethacin, in spite of its inhibitory potency on thromboxane A₂ formation, potentiated the immune release of histamine. The bronchoconstriction induced by acetaldehyde, administered by aerosol (2.5% in saline) in sensitised anaesthetised guinea-pigs, was substantially reduced by both nimesulide and mepyramine administered by inhalation and by intravenous injection. These data further support the antihistaminic property of nimesulide and also suggest a possible interference of the compound with the degranulation process of sensitised mast cells in response to acetaldehyde. In conclusion, the capacity of nimesulide to control the immunological release of histamine and to attenuate its effect at the receptor level of the airway smooth muscles of the guinea-pig, may have some therapeutic relevance in patients with inflammation of the respiratory tract aggravated by intolerance to aspirin-like drugs.

Nimesulide (4-nitro-2-phenoxy methane sulfonanilide) has been selected from a number of methane sulfonanilide compounds for its remarkable anti-inflammatory, antipyretic and analgesic properties in a variety of pharmacological studies (Grant et al. 1975; Swingle et al. 1976). The chemical structure of this molecule contains a sulfonanilidic function that has been reported to be a determinant for both the efficacy and safety of nimesulide in the control of the inflammatory response (Rufer

et al. 1982; Vigdhal & Tukey 1977). The mechanism(s) of action of nimesulide is far from fully elucidated in man, but is thought to involve a tissue prostaglandin synthesis inhibition (Vigdhal & Tukey 1977) and a reduction of superoxide-anion generation by activated inflammatory cells (Bevilacqua et al. 1988; Capsoni et al. 1987). The therapeutic activity of nimesulide has been proven in a large number of patients with rheumatic diseases (Milvio 1984; Reiner 1982; Weissenbach 1981), and

satisfactory results have been obtained with this drug in the treatment of inflammatory disorders of the respiratory tract, including chronic bronchopulmonary obstructions (Biscarini et al. 1988; Finiguerra 1986; Reiner 1983).

Chemical mediators, derived from different cellular sources, are known to be responsible for inflammatory hyperreactivity of the airways (Chung 1986; Raphael & Metcalf 1986) and, therefore, the use of anti-inflammatory drugs, when possible, represents an obligatory intervention in this lung pathology (Cadeddu et al. 1988; Mantovani & Dal Prà 1987). These pharmacological and clinical observations, particularly preliminary results obtained in guinea-pigs whom nimesulide protected from histamine-induced bronchoconstriction, prompted an investigation into the capacity of this drug to interfere with both the release and the effects of histamine in normally and actively sensitised guinea-pigs.

1. Materials and Methods

1.1 Anaesthetised Guinea-Pigs

Male Hartley guinea-pigs (350 ± 40 g body-weight) were used for these experiments; they were anaesthetised (ethylurethane 1.3 to 1.5 g/kg intraperitoneally) and intratracheal pressure (ITP) and systemic BP were recorded (Konzett & Rössler 1940), using Hewlett-Packard instrumentation.

As previously described (Rossoni et al. 1980), guinea-pigs were also prepared for extracorporeal circulation in order to detect any circulating thromboxane A_2 -like material (TXA_2 -1m), using the blood-bathed organ technique (Vane 1964). A stream of arterial blood from the left carotid artery superfused a helical strip of rabbit aorta (RbA) treated overnight with a mixture of receptor antagonists and indomethacin ($3 \mu\text{mol/L}$) [Gilmore et al. 1968]. The increase in ITP and blood TXA_2 -1m caused by histamine ($0.05 \mu\text{mol/kg}$ intravenously) was studied in guinea-pigs treated with nimesulide (0.4 , 0.8 and $1.6 \mu\text{mol/kg}$ intravenously) or indomethacin ($1.6 \mu\text{mol/kg}$ intravenously) 3 minutes before challenge with the autacoid.

Guinea-pigs were also actively sensitised to ov-

albumin (100 mg/kg intraperitoneally + 100 mg/kg subcutaneously) [Piper & Vane 1969] and 3 weeks later the animals were anaesthetised and prepared as previously described. Blood pressure, ITP and blood TXA_2 -1m measurements were recorded. The anaphylactic response was elicited with ovalbumin (5 mg/kg intravenously) in control guinea-pigs and in groups of animals treated with nimesulide (1.6 , 3.2 and $6.4 \mu\text{mol/kg}$ intravenously) and indomethacin ($6.4 \mu\text{mol/kg}$ intravenously) 3 minutes before antigen challenge. The severity of ITP changes was expressed as a percentage of maximal bronchoconstriction measured in control animals (Davies & Johnston 1971).

Bronchoconstriction was also induced in actively sensitised guinea-pigs with acetaldehyde dissolved in saline at 2.5%. This solution was administered by aerosol at a flow rate of 0.1 ml/min . The protective activity of nimesulide against acetaldehyde-induced bronchoconstriction was studied. Nimesulide and mepyramine were administered at a dosage of $6.4 \mu\text{mol/kg}$ intravenously and by nebulisation at a concentration of $6.4 \text{ mmol/L} \times 10$ minutes.

1.2 Perfused Sensitised Guinea-Pig Lungs

Ovalbumin-sensitised guinea-pig lungs were perfused through the pulmonary artery with Krebs-Henseleit solution (37°C) at a flow rate of 10 ml/min as previously reported (Berti et al. 1979). Anaphylactic shock was induced by bolus injection of ovalbumin 1 mg in the perfusion system. In order to demonstrate histamine and TXA_2 -1m release caused by the lung immunological response, the pulmonary outflow superfused a terminal segment of guinea-pig ileum (GPI) and RbA disposed in cascade. These bioassay tissues were treated with a mixture of receptor antagonists, as reported above, provided that the GPI-superfusion medium was without the H_1 -receptor antagonist mepyramine. In this experiment, pulmonary perfusion pressure was also monitored.

The total amount of histamine and TXA_2 -1m released was measured in 5-minute perfusates col-

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Guinea-Pig Lungs

Guinea pig lungs were perfused with Krebs- solution at a rate of 10 ml/min (Bert et al. 1979). An intratracheal injection of antigen into the system. In order to measure TXA₂-1m release in response, the terminal segment of the trachea was disposed in an organ bath and treated with antigen as reported above, and the medium was collected. Mepyramine, 10⁻⁶ mol/L, perfusion pressure

and TXA₂-1m release were measured in perfusates col-

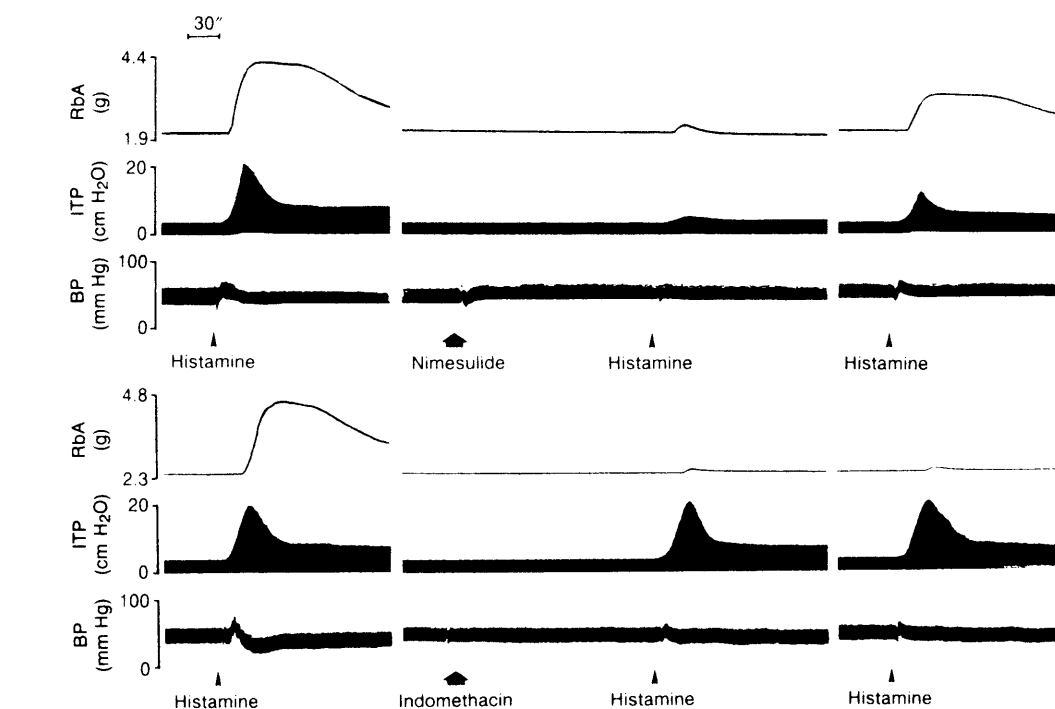


Fig. 1. Effect of intravenous nimesulide and indomethacin (1.6 μ mol/kg) on changes induced by intravenous histamine (0.05 μ mol/kg) in systemic blood pressure (BP), intratracheal pressure (ITP) and tension of blood-bathed rabbit aorta (RbA) in anaesthetised guinea-pigs. Histamine was injected 3 and 20 minutes after nimesulide and indomethacin. In contrast to indomethacin, nimesulide markedly reduced the bronchoconstriction caused by histamine.

collected immediately after challenge of the lungs with the specific antigen.

Histamine was bioassayed in GPI preparations (Berti et al. 1988; Levi 1972), whereas TXA₂ was determined by radioimmunoassay of its stable metabolite thromboxane B₂ (TXB₂) [Simmons et al. 1983]. The anti-anaphylactic activity of nimesulide (1×10^{-6} , 3×10^{-6} , 1×10^{-5} mol/L) was compared with that of indomethacin (3×10^{-7} , 1×10^{-7} , 3×10^{-6} mol/L) in different lung preparations. These treatments were started 15 minutes before antigen and lasted for 10 minutes.

1.3 Isolated Guinea-Pig Trachea

The antihistaminic activity of nimesulide and indomethacin was examined in guinea-pig trachea (GPT) prepared as a helical strip and mounted in

a 10ml organ bath containing the Krebs-Henseleit solution (37°C) gassed with a mixture of 95% oxygen and 5% carbon dioxide. Tissues were allowed to equilibrate for 1 hour under a resting tension of 1g. Changes of smooth muscle tonus were measured with an isometric force-transducer connected to a pen-recorder.

Concentration-response curves to histamine (from 1.5×10^{-6} to 4×10^{-4} mol/L) and acetylcholine (from 3×10^{-8} to 2×10^{-6} mol/L) were constructed in the presence of mepyramine (1×10^{-6} mol/L), nimesulide (1×10^{-5} mol/L) and indomethacin (1×10^{-5} mol/L).

1.4 Drugs Used

The drugs used were as follows: histamine dihydrochloride; acetylcholine bromide; mepyramine maleate; atropine sulfate; acetaldehyde; in-

Table I. Peak effect of nimesulide^a and indomethacin on histamine-induced increases in intratracheal pressure (ITP) and contraction of blood-bathed rabbit aorta (RbA)^a in anaesthetised guinea-pigs. Mean values $\pm$ SEM of 10 animals

Treatment (μ mol/kg IV)	ITP (cm H ₂ O)	% inhibition	RbA (tension in mg) ^b	% inhibition
Control	4.25 $\pm$ 0.02		15 $\pm$ 2	
Histamine 0.05	19.47 $\pm$ 0.82		909 $\pm$ 28	
Nimesulide 0.4 + histamine	16.15 $\pm$ 0.54	21.8	747 $\pm$ 31	18.1
Nimesulide 0.8 + histamine	12.62 $\pm$ 0.77	44.8	435 $\pm$ 29	53.0
Nimesulide 1.6 + histamine	8.96 $\pm$ 0.46	69.0	80 $\pm$ 13	92.7
Indomethacin 1.6 + histamine	18.45 $\pm$ 1.02	6.7	117 $\pm$ 8	88.6

a ED₅₀ = 0.92 (0.88-0.97) μ mol/kg IV for ITP; ED₅₀ = 0.75 (0.73-0.78) μ mol/kg IV for RbA.

b Resting tension of blood superfused RbA was 2.12 $\pm$ 0.17g.

Abbreviations: IV = intravenously; ED₅₀ = effective dose of drug to inhibit 50% of the histamine-induced response.

domethacin and ovalbumin grade V; nimesulide; and [³H] TXB₂.

2. Results

2.1 Anaesthetised Guinea-Pigs

The bolus injection of histamine (0.05 μ mol/kg intravenously) to anaesthetised guinea-pigs (artificially ventilated) brought about a prompt increase in ITP and a fall in BP. This bronchoconstrictive effect lasted 90 seconds and was accompanied by an increase in circulating TXA₂-1m as monitored by a marked contraction of blood superfused RbA (fig. 1).

Nimesulide dose-dependently antagonised the changes induced by histamine on ITP, BP and tension of RbA (fig. 1; table I). In contrast, indomethacin, in spite of its capacity to significantly inhibit the effects of histamine on BP and RbA tension (increased generation of TXA₂-1m), did not modify the bronchoconstrictive effect of this autacoid (fig. 1; table I). In these experiments, nimesulide and indomethacin at a dose of 1.6 μ mol/kg intravenously were both ineffective against bronchoconstriction and fall in BP as a result of acetylcholine (0.1 μ mol/kg intravenously).

The challenge with the specific antigen (ovalbumin 5 mg/kg intravenously) in anaesthetised sen-

Table II. Peak effect of nimesulide^a and indomethacin on bronchoconstriction and generation of thromboxane A₂-like material induced by ovalbumin (5 mg/kg intravenously) in actively sensitised anaesthetised guinea-pigs. Drugs were injected 3 minutes before ovalbumin. Mean values $\pm$ SEM of 8 animals

Treatment (μ mol/kg IV)	ITP (% max. overflow)	% inhibition	RbA (tension in mg) ^b	% inhibition
Control	0		25 $\pm$ 3	
Ovalbumin	100		2585 $\pm$ 83	
Nimesulide 1.6 + ovalbumin	76 $\pm$ 1.9	24	1720 $\pm$ 49	33.8
Nimesulide 3.2 + ovalbumin	44 $\pm$ 1.7	56	995 $\pm$ 37	62.1
Nimesulide 6.4 + ovalbumin	20 $\pm$ 1.4	80	185 $\pm$ 17	93.7
Indomethacin 6.4 + ovalbumin	37 $\pm$ 3.0	63	360 $\pm$ 29	86.9

a ED₅₀ = 2.95 (2.65-3.27) μ mol/kg IV for ITP; ED₅₀ = 2.36 (2.14-2.60) μ mol/kg IV for RbA.

b Resting tension of blood superfused RbA was 2.16 $\pm$ 0.15g.

Abbreviations: ITP = intratracheal pressure; RbA = rabbit aorta; IV = intravenously; ED₅₀ = effective dose of drug to inhibit 50% of the ovalbumin-induced response.

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sitised guinea-pigs caused a severe and irreversible bronchoconstriction associated with a progressive fall in BP. This pronounced immunological reaction was also marked by a sustained contraction of blood-bathed RbA, indicating that TXA₂-1m was strongly contributing to the anaphylactic crisis (table II). In fact, the control animals died within 8 to 10 minutes.

Nimesulide administered intravenously 3 minutes before antigen induced a clear cut protection against the anaphylactic response of the guinea-pigs (table II). The protective effect of nimesulide was dose-dependent and, at a dose of 6.4 µmol/kg intravenously, was approximately 20% more potent than indomethacin (6.4 µmol/kg intravenously) in preventing the increase in ITP (table II). Animals treated with both nimesulide and indomethacin were still alive 50 minutes after ovalbumin administration.

Administration of acetaldehyde by inhalation (2.5% solution for 2 minutes) to anaesthetised sensitised guinea-pigs resulted in a prompt and well maintained increase in ITP without any significant changes in BP (fig. 2). This effect of acetaldehyde on airway resistance was only minimally affected by atropine (1.5 µmol/kg intravenously) but was very sensitive to the H₁-receptor antagonist mepyramine, which, when administered by aerosol (6.4 mmol/L × 10 minutes) and intravenously (6.4 µmol/kg), reduced the bronchoconstrictive effect induced by acetaldehyde by 68% and 58%, respectively. Similar results were obtained with nimesulide administered by aerosol at a concentration of 6.4 mmol/L × 10 minutes (54% inhibition) and by intravenous injection at a dose of 6.4 µmol/kg (39% inhibition) [fig. 2].

2.2 Perfused Sensitised Guinea-Pig Lungs

When ovalbumin (1mg) was injected through the sensitised lungs, a significant increase in perfusion pressure and a concomitant release in the pulmonary effluent of histamine and TXA₂-1m were observed. This phenomenon was indicated by a notable increase in both GPI and RbA tension set up in cascade under the lungs.

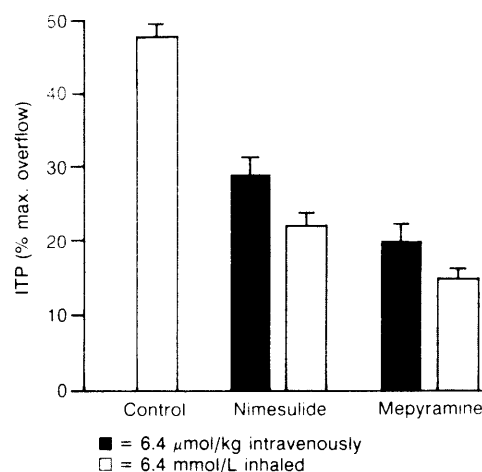


Fig. 2. Protective activity of nimesulide and mepyramine against bronchoconstriction induced by inhalation of acetaldehyde in anaesthetised ovalbumin-sensitised guinea-pigs. Columns represent mean values at the peak effect ($\pm$ SEM) of 6 experiments. ITP = intratracheal pressure. For comparisons, a paired Student's t-test was used. Differences vs control were highly significant ($p < 0.01$).

The results obtained with this series of experiments, reported in figure 3, clearly indicate that the immunological release of histamine is diminished by nimesulide and increased by indomethacin. However, in order to avoid the effects of relaxant substances on GPI, the total amount of histamine and TXB₂ released in the pulmonary outflow (5-minute collection) was determined in groups of lungs perfused with various concentrations of both nimesulide and indomethacin. As reported in table III, whereas nimesulide caused a concentration-dependent reduction in histamine release, indomethacin was shown to potentiate the secretion of this autacoid.

The generation of TXB₂ during the immunological response of the lungs was significantly affected by the 2 compounds. Nevertheless, indomethacin was more potent than nimesulide in reducing the immune TXB₂ release, and this result reflects the different potencies of the 2 anti-inflammatory compounds in affecting arachidonic acid cyclo-oxygenase enzymes. Moreover, the pro-

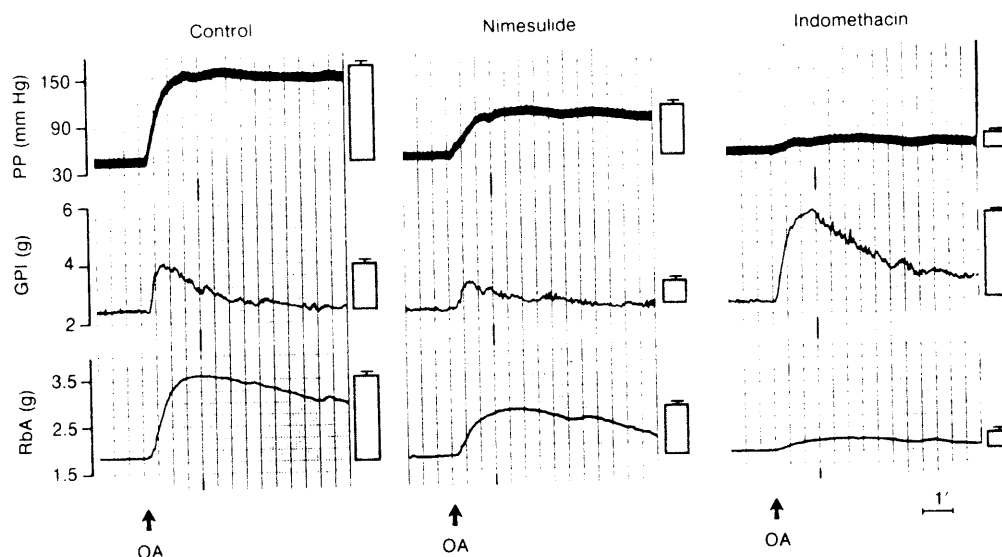


Fig. 3. Changes in perfusion pressure (PP), resting tension of guinea-pig ileum (GPI) and rabbit aorta (RbA) during anaphylactic response in sensitised perfused guinea-pig lungs in control, nimesulide- ($3 \mu\text{mol/L}$) and indomethacin- ($3 \mu\text{mol/L}$) treated preparations. OA = injection of ovalbumin 1mg through the perfused lungs. Columns represent mean values at the peak effect ($\pm \text{SEM}$) of 8 experiments. Differences between control, nimesulide- and indomethacin-treated preparations were statistically highly significant ($p < 0.01$).

nounced increase in perfusion pressure obtained during the lung anaphylactic response was linked to arachidonic acid metabolites formed via pros-

taglandin G/H synthetase, since the phenomenon correlated well with the vasoactive TXA_2 -lm generation.

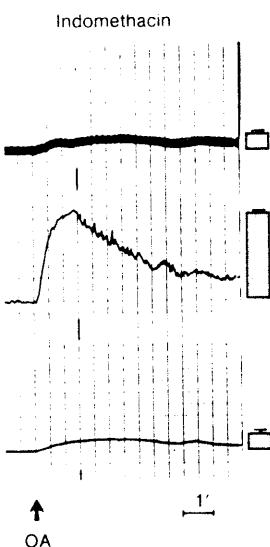
Table III. Effect of nimesulide (NIM)^a and indomethacin (INDO)^b on histamine and thromboxane B_2 (TXB_2) release during the anaphylactic response in 10 ovalbumin-sensitised perfused guinea-pig lungs. Perfusion with NIM and INDO started 15 minutes before ovalbumin (bolus of 1mg) and lasted for 10 minutes after antigen challenge. Values are means $\pm \text{SEM}$

Treatment ($\mu\text{mol/L}$)	Histamine ($\mu\text{g/5 min}$)	% inhibition	TXB_2 (ng/5 min)	% inhibition
Control	ND		ND	
Ovalbumin	25.0 ± 1.3		2691 ± 99	
Nimesulide 1 + ovalbumin	19.1 ± 1.1	23.6	2094 ± 65	22.6
Nimesulide 3 + ovalbumin	12.8 ± 1.7	48.6	1441 ± 89	46.5
Nimesulide 10 + ovalbumin	5.3 ± 0.4	78.9	654 ± 61	75.7
Indomethacin 0.3 + ovalbumin	30.5 ± 1.5	+21.9	1811 ± 101	32.7
Indomethacin 1 + ovalbumin	38.4 ± 0.8	+53.4	973 ± 57	63.8
Indomethacin 3 + ovalbumin	45.3 ± 2.3	+81.1	452 ± 23	83.2

a $\text{EC}_{50} = 3.06$ (2.59 - 3.62) $\mu\text{mol/L}$ for histamine. $\text{EC}_{50} = 3.35$ (2.90 - 3.88) $\mu\text{mol/L}$ for TXB_2 .

b $\text{EC}_{50} = 0.89$ (0.67 - 1.17) $\mu\text{mol/L}$ for histamine. $\text{EC}_{50} = 0.62$ (0.51 - 0.74) $\mu\text{mol/L}$ for TXB_2 .

Abbreviations and symbols: ND = nondetectable; EC_{50} = effective concentration of drug to inhibit 50% of the ovalbumin-induced response; + = % potentiation of the ovalbumin-induced response.



and rabbit aorta (RbA) during anaphylaxis (OA) in the presence of indomethacin (3 μ mol/L). Columns represent mean values at the time of the peak response. Indomethacin-treated preparations were

anaphylaxis, since the phenomenon was not inhibited by the vasoactive TXA_2 -Ir

oxane B_2 (TXB_2) release during the anaphylaxis. Indomethacin (INDO) started 15 minutes before the anaphylaxis. Means $\pm$ SEM

TXB_2 (ng/5 min)	% inhibition
1 $\pm$ 99	
4 $\pm$ 65	22.6
1 $\pm$ 89	46.5
4 $\pm$ 61	75.7
1 $\pm$ 101	32.7
3 $\pm$ 57	63.8
2 $\pm$ 23	83.2

2. to inhibit 50% of the ovalbumin-induced anaphylaxis. The DR for mepyramine and indomethacin were 0.83 (3.51 to 4.19), and 0.87 (0.80 to 0.95), respectively. The DR for nimesulide was not calculated.

2.3 Isolated Guinea-Pig Trachea

The ability of nimesulide to interfere with histamine H_1 -receptor activation was evaluated in helical strips of guinea-pig trachea. When concentration-response curves for histamine were repeated in the presence of nimesulide (1×10^{-5} mol/L), a significant shift on the right was obtained. At the same concentration, indomethacin did not modify the effect of histamine on tracheal smooth muscle (fig. 4).

The antihistaminic activity of nimesulide is of a noncompetitive type, since maximal response of the tracheal tissue to histamine was not achieved in the presence of this antagonist (fig. 4). Moreover, this effect of nimesulide was rather selective, since concentration-response curves of the tracheal preparations to acetylcholine were not modified by this anti-inflammatory drug.

3. Discussion

The results obtained with these experiments indicate that nimesulide, a well established anti-inflammatory compound (Capsoni et al. 1987; Vighdhal & Tukey 1977), displays both antihistaminic and antiasthmatic activity. The antihistaminic activity, which is significantly (approximately 80 times) less potent than that of mepyramine on isolated guinea-pig trachea, is rather specific for histamine- H_1 receptors and is characterised by a non-competitive mechanism of action. This somewhat unexpected effect of an anti-inflammatory compound has also been confirmed in multiphasic positive inotropic response to histamine mediated by H_1 -receptors in guinea-pig left atria (data not shown). These *in vitro* findings are further substantiated by the antihistaminic activity of nimesulide observed in anaesthetised guinea-pigs. In this series of studies, nimesulide antagonised the increase in airway resistance caused by histamine,

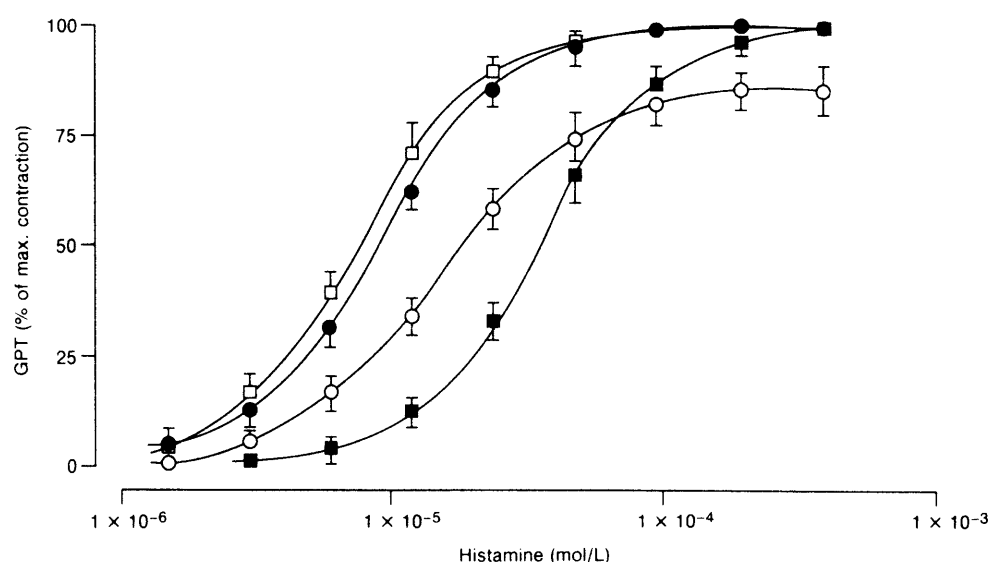


Fig. 4. Concentration-response curves for histamine alone (control; ●) and in the presence of nimesulide (1×10^{-5} mol/L; ○), indomethacin (1×10^{-5} mol/L; □) and mepyramine (1×10^{-5} mol/L; ■) in isolated guinea-pig trachea (GPT). Points are means ($\pm$ SEM) of 5 experiments. Dose ratio (DR) and fiducial limits (95%) for mepyramine and indomethacin were 0.83 (3.51 to 4.19), and 0.87 (0.80 to 0.95), respectively. The DR for nimesulide was not calculated.

whereas indomethacin was ineffective in spite of its ability to impair cyclo-oxygenase enzymes together with a marked reduction in TXA_2 -lm generation. It is well known that the bronchoconstrictive effect of histamine in guinea-pigs is due primarily to activation of H_1 -receptors (Douglas et al. 1977) as well as the vagal reflex discharge on the airway smooth muscles (Mills & Widdicombe 1970). TXA_2 -lm generation induced by histamine does not seem to contribute significantly to the increase in lung resistance (Rossoni et al. 1980), but it appears primarily to affect the pulmonary vasculature, since the inhibited biosynthesis of TXA_2 -lm induced by the 2 anti-inflammatory compounds resulted in a reduction in pulmonary perfusion pressure.

Another point of interest emerging from these experiments is the capacity of nimesulide to affect systemic anaphylactic crisis, an irreversible reaction widely occurring because of the release of histamine, together with other lipidic mediators from sensitised mast cells in different organs of guinea-pigs such as lungs and heart (Berti et al. 1988). The protective mechanism(s) of nimesulide differs from that of indomethacin, as evidenced by the opposite effects of the 2 compounds on histamine release during anaphylaxis. In fact, nimesulide decreases the immunological release of histamine in perfused lungs, whereas indomethacin potentiates it. In this regard, it has been reported (Adcock et al. 1978) that the potentiating mechanism of indomethacin on histamine release involves the lack of synthesis of relaxing prostaglandins and the generation of arachidonic acid metabolites, different from leukotrienes, which facilitate histamine release. Similarly, 'in-vitro' preparation of sensitised human bronchus containing cyclo-oxygenase enzyme activity inhibited by indomethacin responded to an increase in smooth muscle contraction and enhancement of histamine release when undergoing specific antigen challenge (Adams & Lichtenstein 1985).

The bronchoconstrictive effect of acetaldehyde in sensitised guinea-pigs deserves comment. This phenomenon, which does not occur in nonsensitised animals, seems to indicate a stimulatory ef-

fect of acetaldehyde (direct or indirect via afferent sensory fibres) on sensitised mast cells lying on the luminal mucosa, with a considerable release of histamine among the other mediators. The protective activity observed in this series of experiments could be 2-fold: firstly, interference of the compound with histamine release, as also observed in sensitised perfused lungs and, secondly, blockade of the airway H_1 -histamine receptors, as observed in isolated trachea. The mechanism(s) whereby nimesulide inhibits histamine release remains unclear and the possibility that this compound or its 4-hydroxymetabolite (Capsoni et al. 1987) may have impaired the early secretory events at the membrane level of the sensitised mast cells should be investigated. Whatever the mode of action, the finding that nimesulide may control immunological secretion of histamine while also attenuating the effect of this mediator at the receptor site provides evidence of an unusual pharmacological profile for a nonsteroidal anti-inflammatory compound. This may be of therapeutic relevance in patients affected by lung inflammation and those with a history of allergic bronchial obstruction.

References

- Adams GK, Lichtenstein LM. Indomethacin enhances response of human bronchus to antigen. *American Review of Respiratory Disease* 131 (Suppl. 1): 8-10, 1985
- Adcock JJ, Garland LG, Moncada S, Salmon GA. The mechanisms of enhancement by fatty acid hydroperoxides of anaphylactic mediator release. *Prostaglandins* 16: 179-187, 1978
- Berti F, Folco GC, Nicosia S, Omini C, Pasargiklian R. The role of histamine H_1 - and H_2 -receptors in the generation of thromboxane A_2 in perfused guinea-pig lungs. *British Journal of Pharmacology* 65: 629-633, 1979
- Berti F, Galli G, Magni F, Puglisi L, Rossoni G, et al. BN-52021, a specific PAF-receptor antagonist, prevents antigen-induced mediator release and myocardial changes in guinea-pig perfused heart. In Braquet P (Ed.) *Ginkgolides, chemistry, biology, pharmacology and clinical perspectives*. Vol. 1, pp. 399-410, J.R. Prous Science Publishers, SA, Barcelona, 1988
- Biscarini L, Pattoia L, Del Favero A. Nimesulide a new non-steroidal anti-inflammatory agent. *Drugs of Today* 24 (Suppl. 1): 23-27, 1988
- Cadeddu L, Piragine F, Puxeddu P, Scornavacche V, Sellari Franceschini S. Comparison of nimesulide and flurbiprofen in the treatment of non-infectious acute inflammation of the upper respiratory tract. *Journal of International Medical Research* 16: 466-473, 1988
- Capsoni F, Venegoni E, Minonzio F, Ongari AM, Maresca V, et al. Inhibition of neutrophil oxidative metabolism by nimesulide. *Agents and Actions* 21: 121-129, 1987
- Chung KF. Role of inflammation in the hyperreactivity of the airways in asthma. *Thorax* 41 (Suppl. 9): 657-662, 1986

(direct or indirect via afferent sensitised mast cells lying on the surface) with a considerable release of histamine and other mediators. The protection in this series of experiments is due to the interference of the compound with the release, as also observed in guinea pigs and, secondly, blockade of histamine receptors, as observed in man. The mechanism(s) whereby nimesulide release remains unknown. It is likely that this compound or its metabolites (Capsoni et al. 1987) may interfere with secretory events at the sensitised mast cells should the mode of action, the compound may control immunological events while also attenuating histamine release at the receptor site possibly through a pharmacological pro-anti-inflammatory component. The therapeutic relevance in the treatment of inflammation and those conditions associated with bronchial obstruction.

Domesticacin enhances response to histamine. American Review of Respiratory Diseases 10, 1985

Rossoni G, et al. BN-52021, a new histamine H₁ antagonist, prevents antigen-induced changes in guinea-pig peritoneal leukocytes, chemistry, biology and immunology. Vol. 1, pp. 399-404. S.A. Barcelona, 1988

Domesticacin, a new non-steroidal anti-inflammatory drug. Drugs of Today 24 (Suppl. 2), 1987

Domesticacin, a new non-steroidal anti-inflammatory drug. Drugs of Today 24 (Suppl. 2), 1987

Davies GE, Johnston TP. Quantitative studies on anaphylaxis in guinea pigs passively sensitized with homologous antibodies. International Archives of Allergy and Applied Immunology 41: 648-654, 1971

Douglas JS, Ridgway P, Brink C. Airway responses of the guinea-pig in vivo and in vitro. Journal of Pharmacology and Experimental Therapeutics 202: 116-124, 1977

Figueroa M, Conti P, Galione F, Ferrario F. Un nuovo anti-inflammatorio non steroideo, nimesulide, nel trattamento delle forme infiammatorie di interesse pneumologico. Clinica Terapeutica 117 (Suppl. 3): 199-206, 1986

Gilmore N, Vane JR, Wyllie TH. Prostaglandins released by the spleen. Nature 218: 1135-1140, 1968

Grant TJ, Moore GGI, Swingle KF. Antiinflammatory activity of 4-nitro-2-phenoxyethanesulfonamide (R-805). Federation Proceedings 34: 759, 1975

Konzett H, Rossler R. Versuchsanordnung Zu untersuchungen an der bronchial muskulatur. Archiv Fur Experimentelle Pathologie und Pharmacologie 195: 71-74, 1940

Levi R. Effect of exogenous and immunologically released histamine on the isolated heart: a quantitative comparison. Journal of Pharmacology and Experimental Therapeutics 182: 227-238, 1972

Mantovani M, Dal Prà L. Nuova prospettiva terapeutica nella patologia infiammatoria delle vie aeree. Aulin. Otorinolaringologia 37: 1-7, 1987

Mills JE, Widdicombe JG. Role of the vagus nerves in anaphylaxis and histamine-induced bronchoconstrictions in guinea-pigs. British Journal of Pharmacology 39: 724-731, 1970

Milvio C. Nimesulide for the treatment of painful inflammatory process in the ear, nose and throat areas: a double-blind controlled study with benzydamine. Journal of International Medical Research 12 (Suppl. 6): 327-332, 1984

Piper PJ, Vane JR. Release of additional factors in anaphylaxis and its antagonism by anti-inflammatory drugs. Nature 233: 29-35, 1969

Raphael GD, Metcalf DD. Mediators of airway inflammation. European Journal of Respiratory Diseases 147: 44-56, 1986

Reiner M. Nimesulide in the short-term treatment of osteoarthritis: a pilot study for assessing the minimal effective dose. Journal of International Medical Research 10: 92, 1982

Reiner M. Nimesulide and antibiotics in the treatment of acute infections of the respiratory tract. Current Medical Research and Opinion 8 (Suppl. 7): 487-492, 1983

Rossoni G, Omini C, Viganò T, Mandelli V, Folco GC, et al. Bronchoconstriction by histamine and bradykinin in guinea-pigs: relationship to thromboxane A₂ generation and the effect of aspirin. Prostaglandins 20: 547-557, 1980

Rufer C, Shillinger E, Botcher I, Repenthin W, Herrmann CH. Non-steroidal anti-inflammatories-XII. Mode of action of anti-inflammatory methane sulfonamides. Biochemical Pharmacology 31: 3591-3596, 1982

Simmons PM, Salmon JA, Moncada S. The release of leukotriene B₄ during experimental inflammation. Biochemical Pharmacology 32: 1353-1359, 1983

Swingle KF, Moore GGI, Grant TJ. 4-nitro-2-phenoxyethanesulfonamide (R-805): a chemically novel anti-inflammatory agent. Archives Internationales de Pharmacodynamie et de Thérapie 221: 132-139, 1976

Vane JR. The use of isolated organs for detecting active substances in the circulating blood. British Journal of Pharmacology and Chemotherapy 23: 360-373, 1964

Vigdhall RL, Tukey RH. Mechanisms of action of novel anti-inflammatory drugs diflumidone and R-805. Biochemical Pharmacology 26: 307-311, 1977

Weissenbach R. Clinical trial with nimesulide, a new non-steroidal anti-inflammatory agent in rheumatic pathology. Journal of International Medical Research 9: 349, 1981

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