Effect of Nonsteroidal Anti-Inflammatory and Other Pharmacological Agents on Tuberculin Reaction

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Abstract □ Nonsteroidal anti-inflammatory and other pharmacological agents were tested in the efferent arc of the tuberculin skin reaction in the guinea pig. A low but significant inhibition was produced by the acidic anti-inflammatory agents, including the arylalkanoic acids, the anthranilic acids, indomethacin, and phenylbutazone. Some nonacidic anti-inflammatory agents also were inhibitory; benzydamine caused a high inhibition. Except for methotrexate, the antineoplastic–antimetabolite agents were not potent inhibitors. Inhibition without toxicity was produced by the coumarin anticoagulants, the diuretics, chloroquine, tilorone, and the following immunoregulators: antithymocyte γ-globulin, cyclophosphamide, and penicillamine. Levamisole, colchicine, heparin, and niridazole were inhibitory but produced lethality either at or above the effective dose.

Keyphrases □ Tuberculin reaction—effect of nonsteroidal anti-inflammatory and various other pharmacological agents in guinea pigs □ Anti-inflammatory agents, nonsteroidal—effect on tuberculin reaction in guinea pigs □ Immune systems, cell mediated—tuberculin reaction, effect of nonsteroidal anti-inflammatory and various other pharmacological agents in guinea pigs

The pathogenesis of rheumatoid arthritis involves various immunological aspects. The participation of cellular immunity is suggested by studies of rheumatoid joints (1–5), synovitis (6), and the response of circulating lymphocytes to products of rheumatoid joint tissues and fluids (7–10).

Many nonsteroidal anti-inflammatory agents now in use for rheumatoid arthritis were identified principally with a model of acute inflammation, carrageenan-induced edema (11), and a model with both immunological and inflammatory components, adjuvant-induced arthritis (12).

In view of the suggested role of cellular immunity in rheumatoid arthritis, it was of interest to determine if nonsteroidal anti-inflammatory agents could affect a cell-mediated immune system, particularly at a stage apart from sensitization. These agents were tested in the efferent arc (13) of the tuberculin reaction in the guinea pig. This immunologically specific system has been characterized by its infiltration of mononuclear cells and its presumptive mediation by lymphokines (14, 15).

This study was extended to other pharmacologically active agents, some previously tested and others not tested in the tuberculin reaction. These data could identify new agents that might affect cell-mediated immune reactions and thus form the basis for a new chemical design of therapeutic agents for rheumatoid arthritis.

EXPERIMENTAL

Tuberculin System—The tuberculin reaction in the guinea pig was produced essentially as described previously (16). Briefly, male albino guinea pigs were sensitized to *Mycobacterium tuberculosis*[1] in Freund's incomplete adjuvant[1] as described or by injection intradermally into the right hind footpad and subcutaneously into two sites in the nape of the neck. Three to four weeks later, the animals were challenged with 0.6 μg of tuberculin[2], and the diameters and thicknesses of the lesions were measured after 24 hr.

Table I—Effect of Anti-Inflammatory-Antirheumatic Agents on the Tuberculin Reaction

Agent	Percent Inhibition, D/T[a] 50-mg/kg Dose[b]	100-mg/kg Dose[b]
Arylalkanoic acids		
Alclofenac	7 ± 2/32 ± 5 (13)	10 ± 3/30 ± 6 (12)
Aspirin	7 ± 3/19 ± 7 (11)	7 ± 1/25 ± 4 (18)
Cicloprofen	7 ± 2/28 ± 4 (14)	
Ibufenac	9 ± 2/29 ± 4 (35)	
Ibuprofen	17 ± 1/43 ± 4 (29)	
Naproxen	8 ± 2/27 ± 9 (15)	
Sodium salicylate		[c] −2 ± 2/4 ± 7 (12)
Tolmetin sodium	6 ± 1/17 ± 6 (11)	10 ± 2/22 ± 4 (18)
Anthranilic acids		
Diclofenac sodium	5 ± 2/14 ± 8[c] (18)	10 ± 4/41 ± 15 (7)[d]
Flufenamic acid	10 ± 2/30 ± 4 (28)	
Meclofenamic acid	6 ± 3/31 ± 8 (11)	
Mefenamic acid	7 ± 4/18 ± 9 (15)	
Niflumic acid	[c] 3 ± 2/8 ± 6[c] (27)	[c] −2 ± 7/28 ± 9 (9)
Other agents		
Aurothioglucose	18 ± 2/36 ± 6 (17)	13 ± 3/24 ± 8 (6)
Benzydamine hydrochloride	13 ± 3/60 ± 5 (18)	
Flazalone hydrochloride	19 ± 3/41 ± 6 (8)	12 ± 5/39 ± 10 (7)
Indomethacin	[c] 4 ± 4/10 ± 7[c] (17)	12 ± 2/19 ± 6 (14)
Phenylbutazone	[c] 1 ± 3/−3 ± 7[c] (22)	[c] 2 ± 2/−2 ± 7[c] (11)

[a] In this and subsequent tables, percent inhibition diameter/thickness ± *SE* (number of animals). [b] In this and subsequent tables, compounds were administered each time at the listed dose. Unless otherwise indicated, the compounds were administered twice, subcutaneously, as in *Experimental*. [c] Not significant. All other values in this and subsequent tables were significant at $p < 0.05$, unless indicated as not significant. [d] Delayed death of three out of seven animals.

Tuberculin, Turpentine, and Histamine System—The reactions for all three agents were produced on the same animal. Animals were sensitized and challenged with tuberculin, as described. Reactions to turpentine[3] were produced as described previously (16) or, as in later experiments, by intradermal injection of 0.05 ml of turpentine–buffer[4] (1:9 v/v) emulsified by repeated passage through a syringe needle. Turpentine was administered 5 hr after challenge with tuberculin, just after the second administration of the test compound. Evaluation was performed in a manner similar to, and at the same time as, the tuberculin reaction. After evaluation of the reactions to tuberculin and turpentine, reactions to histamine were produced and measured as described previously (16).

Administration of Test Compounds—The test compounds in sesame oil were administered twice, at 30 min before and again at 5 hr after tuberculin, either subcutaneously at ventral sites or orally by gavage, unless otherwise stated. Compounds were tested in groups of four to seven animals. The average inhibition ± *SE* was calculated for the test compound-treated groups in comparison to the control sesame oil-treated groups. Variability within and among the groups of animals was taken into account.

For the control animals, the average diameter, D, and thickness, T, ± *SD* of the lesions from tuberculin were 18.3 ± 1.3 and 0.79 ± 0.13 mm (75 groups), respectively. From turpentine, these values were 18.5 ± 1.7 and 0.87 ± 0.12 mm (six groups), respectively. From histamine, the av-

[1] *M. tuberculosis* H37 RA and adjuvant, Difco Laboratories, Detroit, Mich.

[2] Tuberculin purified protein derivative (I) as lyophilized material, lot 974562C, Parke, Davis and Co., Detroit, Mich. Each milligram of I was equivalent in potency to 50,000 tuberculin units.

[3] Rectified turpentine, Winsor and Newton, Secaucus, N.J.

[4] Hemagglutination buffer, Difco Laboratories, Detroit, Mich.

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Table II—Effect of Anti-Inflammatory-Antirheumatic Agents on the Tuberculin Reaction

Agent	Dose, mg/kg	Percent Inhibition, D/T
Benzydamine	25	7 ± 3/30 ± 8 (16)
	150[a,b]	18 ± 5/55 ± 9 (5)
Indomethacin	100[c]	12 ± 2/36 ± 10 (14)
	150[a]	19 ± 4/50 ± 6 (11)[d]
Niflumic acid	100[c]	10 ± 2/32 ± 9 (14)
	150[a]	14 ± 6/57 ± 14 (8)[d]
Phenylbutazone	100[c]	19 ± 3/59 ± 7 (13)[d]
	150[a]	7 ± 2/28 ± 6 (11)

[a] Oral administration. [b] In saline. [c] Administered once daily at 2 and 1 days before challenge and twice on the day of challenge. [d] Death of animals: with indomethacin, 1/11; with niflumic acid, 2/10; and with phenylbutazone, 2/14.

erage diameter and intensity, I, were 13.6 ± 1.0 mm and 2.9 ± 0.7 (six groups), respectively.

The compounds tested are grouped in Tables I–V according to their listed therapeutic use (17).

RESULTS AND DISCUSSION

The temporal difference between the afferent and efferent arcs in the tuberculin reaction (13) allows for evaluation of compounds in the separate stages. Compounds were tested on the events following the interaction of sensitized cells and antigen, the efferent arc, thereby focusing on their potential therapeutic activity.

Anti-Inflammatory-Antirheumatic Agents (Tables I and II)—Statistically significant, but low, inhibitions of the tuberculin reaction were produced by the acidic anti-inflammatory agents, including the arylalkanoic acids, the anthranilic acids, indomethacin, and phenylbutazone, except sodium salicylate. For the arylalkanoic acids, the extent of inhibition appeared to plateau generally at 10% for diameter and 30% for thickness. These values were attained by the other active acidic agents even after administration for multiple days. In instances where this level of inhibition was exceeded, lethality was noted, as shown with indomethacin, niflumic acid, and phenylbutazone (Table II). This greater inhibition might have been due to this lethality.

The similar inhibition shared by these acidic anti-inflammatory agents suggests that they inhibit a common path in the tuberculin reaction. The inhibition of prostaglandin synthesis by these agents (18–21) and the correlation of anti-inflammatory effects and this mechanism (19) suggest that their inhibition of the tuberculin reaction could have occurred through inhibition of prostaglandin synthesis.

Some support for this view comes from the proposal that prostaglandins serve as potentiators of inflammation in the guinea pig, as shown with the tuberculin reaction (22). Furthermore, prostaglandins have been associated with cutaneous inflammation (23), including allergic contact dermatitis, a delayed hypersensitivity reaction. The prostaglandin pathway also has been altered in skin, including that of the guinea pig (24), by indomethacin and aspirin (23).

Phenylbutazone, the least potent acidic anti-inflammatory agent, previously had a slight (25) or no (26) effect in the tuberculin reaction. Sodium salicylate in this and previous (25) studies was inactive. In an assessment of delayed hypersensitivity in the human, aspirin at therapeutic doses had no effect (27). The low activity of aspirin in the present studies may not be demonstrable in humans.

Among the effective nonacidic anti-inflammatory agents, benzydamine inhibited the tuberculin reaction greater than the plateau level achieved by the acidic agents. This result suggests that benzydamine was active by a mechanism separate from or in addition to that for the acidic agents. Benzydamine, as well as flazalone, modulate the prostaglandin pathway (20) but at a site different from that of some acidic agents (28).

In nonimmunologically induced reactions, benzydamine moderately inhibited the turpentine-induced reaction and only slightly inhibited the histamine-induced reaction (Table VI). Some similarity could be noted

Table III—Effect of Antineoplastic-Antimetabolite Agents on the Tuberculin Reaction

Agent	Dose, mg/kg	Percent Inhibition, D/T
Azathioprine	100	[a]10 ± 5/12 ± 12[a] (5)
	150	[a]4 ± 5/6 ± 12[a] (6)
	200[b]	[a]5 ± 4/11 ± 8[a] (5)
	300[b]	13 ± 2/50 ± 4 (10)
Hydroxyurea	50	13 ± 4/13 ± 14[a] (9)
	100	15 ± 5/12 ± 12[a] (11)
Mercaptopurine	100	[a]10 ± 5/25 ± 10[a] (6)
	150	[a]7 ± 5/14 ± 13[a] (6)
	200[b]	20 ± 3/31 ± 8 (5)
	300[b]	13 ± 2/24 ± 4 (10)
Methotrexate	25	[a]12 ± 6/28 ± 20[a] (4)
	50	15 ± 5/37 ± 11 (8)
Oxisuran	50	[a]1 ± 4/11 ± 7[a] (10)
	100	[a]7 ± 4/14 ± 9[a] (5)
	150[c]	[a]3 ± 5/17 ± 10[a] (6)

[a] Not significant. [b] Oral administration. [c] Intraperitoneal administration in saline once daily for 3 days with challenge on the 3rd day.

Table IV—Effect of Anticoagulants on the Tuberculin Reaction

Agent	Dose, mg/kg	Percent Inhibition, D/T
Acenocoumarol	50	[a]−2 ± 5/18 ± 10[a] (4)
Anisindione	50	[a]1 ± 2/16 ± 8[a] (4)
Dicumarol	50	[a]3 ± 2/15 ± 7[a] (6)
	10[b]	15 ± 2/61 ± 5 (7)
	50[b]	28 ± 2/77 ± 4 (7)
Heparin sodium	10[c]	18 ± 4/27 ± 8 (11)[d]
	50	34 ± 2/44 ± 3 (10)[d]
	10[b]	18 ± 2/35 ± 4 (5)[d]
Warfarin	10[b]	19 ± 2/59 ± 5 (7)
	50[b]	22 ± 2/50 ± 6 (7)

[a] Not significant. [b] Administered once daily at 2 and 1 days before challenge and twice on the day of challenge. [c] Heparin, 10 mg = 1600 units. [d] Deaths of animals at 10 and 50 mg/kg, given for 1 day, were 1/12 and 9/16, respectively; at 10 mg/kg, given for multiple days, death of animals was 2/7.

Table V—Effect of Various Pharmacological Agents on the Tuberculin Reaction

Agent	Dose, mg/kg	Percent Inhibition, D/T
Antigout		
Colchicine	0.1	10 ± 3/24 ± 8 (11)
	0.2	20 ± 2/65 ± 4 (12)
	0.4	26 ± 2/59 ± 8 (5)[a]
	0.8	—[a]
Antihistamine		
Chlorpheniramine maleate	50	15 ± 1/38 ± 7 (13)
	100	29 ± 6/93 ± 1 (2)[a]
Pyribenzamine hydrochloride	25	20 ± 2/61 ± 6 (10)
	50	36 ± 14/76 ± 24 (2)[a]
Antiparasitic		
Chloroquine phosphate	50	15 ± 3/52 ± 8 (12)
	100	21 ± 3/70 ± 7 (6)
Levamisole hydrochloride	50	7 ± 2/17 ± 9[b] (20)
	100	19 ± 1/57 ± 4 (19)[a]
	150	—[a]
Niridazole	50	10 ± 3/16 ± 9[b] (20)
	100	23 ± 2/64 ± 4 (6)
	100[c,d]	13 ± 2/46 ± 5 (5)
	100[c]	—[a]
Antiviral		
Tilorone hydrochloride	50	12 ± 3/29 ± 8 (11)
	100	24 ± 1/63 ± 5 (17)
	100[c]	18 ± 3/51 ± 6 (6)
Chelating agent		
Penicillamine	100	6 ± 3/22 ± 11[b] (13)
	150	[b]0 ± 4/13 ± 15[b] (6)
	50[c,e]	[b]7 ± 3/39 ± 5 (7)
Diuretic		
Chlorothiazide	50	11 ± 1/41 ± 6 (12)
	100	12 ± 2/56 ± 6 (6)
Furosemide	50	29 ± 2/75 ± 6 (8)
Immunoregulator		
Cyclophosphamide	50	[b]3 ± 5/18 ± 8[b] (4)
	100	15 ± 2/32 ± 7 (12)
	150	19 ± 2/53 ± 7 (12)

[a] Death of animals; with colchicine, 7/12 at 0.4 and 6/6 at 0.8 mg/kg; with chlorpheniramine maleate, 4/6; with pyribenzamine hydrochloride, 2/4; with levamisole hydrochloride, 13/32 at 100 and 6/6 at 150 mg/kg; and with niridazole, 6/6. [b] Not significant. [c] Oral administration. [d] Administered only 30 min before challenge. [e] Administered once daily at 2 and 1 days before challenge and twice on the day of challenge.

Table VI—Effect of Agents on Immunological *versus* Nonimmunological Reactions

Agent	Dose and Route, mg/kg	Percent Inhibition		
		Tuberculin *D/T*	Turpentine *D/T*	Histamine *D/I*
Benzydamine hydrochloride	50 sc	15 ± 2/60 ± 6 (9)	16 ± 3/49 ± 7	[a]6 ± 4/18 ± 9
Chlorpheniramine maleate	25 po	[a]1 ± 4/−4 ± 12[a] (7)	[a]5 ± 2/−2 ± 7[a]	26 ± 2/47 ± 7
	50 po	7 ± 3/45 ± 7 (7)	16 ± 2/26 ± 6	61 ± 10/88 ± 3
	100 po	9 ± 3/77 ± 3 (7)	18 ± 2/61 ± 7	100 ± 0/100 ± 0
Antithymocyte γ-globulin	50 ip[b]	36 ± 3/94 ± 3 (5)	16 ± 4/10 ± 13[a]	[a]−8 ± 6/3 ± 13[a]

[a] Not significant. [b] Intraperitoneal administration in 0.3 *M* glycine buffer, pH 7.4, at 50 mg of IgG/kg twice daily on the day before and on the day of challenge.

between benzydamine and the 9-benzyladenines (16) in their inhibitory activities against immunological and nonimmunological reactions and in their spatial atomic arrangements as constructed with Corey–Pauling–Koltun models.

Antineoplastic–Antimetabolite Agents (Table III)—Except for methotrexate, these agents generally were not effective or potent inhibitors of the efferent arc of the tuberculin reaction, at least after acute administration. Significant inhibition did occur with mercaptopurine or its analog, azathioprine, but only after oral administration of large doses. In other studies, inhibition of expression was observed with mercaptopurine[5] (29) and azathioprine (30) after administration for multiple but not single (25) days; however, multiple administration of mercaptopurine was near the time of sensitization (29) or was associated with lethality[5]. Methotrexate, inhibitory in the present studies, had variable effects (25, 31). Oxisuran did not inhibit the tuberculin reaction, unlike its inhibitory activity in ovalbumin-induced hypersensitivity in the guinea pig (32).

Anticoagulants (Table IV)—The anticoagulants were effective inhibitors of the tuberculin reaction, confirming previous reports (33, 34). The coumarin derivatives were effective only after administration for days before challenge, consistent with their proposed mode of action (35). Heparin sodium was inhibitory whether administered before or only at the time of challenge; lethality accompanied all levels of inhibition. The relationship of the clotting process and direct evidence of its activation in the course of the delayed hypersensitivity reaction were described (34, 36, 37). The induration of the tuberculin reaction may be due to the retention of extravascular fluid by the fibrin meshwork (36, 38). Consistent with this hypothesis was the marked inhibition of this reaction by the tested diuretic agents (Table V).

Various Pharmacological Agents (Table V)—Colchicine, an antigout agent, significantly inhibited the tuberculin reaction, as shown in this study and a previous report (39). Its dose–response range was very narrow, with noted lethality at about four times its minimally effective dose. Its mechanism of action in the tuberculin reaction is suggested by the indication that microtubular disruptive agents promote macrophage migration and counteract the influence of the macrophage migration inhibitory factor (39) without influencing the production of this factor (40, 41). Nonetheless, colchicine, although effective in gout (42), is not clinically effective in rheumatoid arthritis. Its narrow therapeutic index, as shown with the tuberculin reaction, may preclude its activity against cell-mediated immune aspects in rheumatoid arthritis.

Both antihistamines greatly inhibited the tuberculin reaction; lethality was noted at the larger dose. In a comparison to nonimmunologically induced reactions, chlorpheniramine maleate at two 25-mg/kg po doses markedly inhibited the histamine-induced reaction without significantly inhibiting the tuberculin and turpentine-induced reactions (Table VI). These two latter reactions were inhibited as the dose was increased to levels that abolished the histamine-induced reaction. Exclusion of a role for histamine in the tuberculin reaction cannot be made from these data, even though half of the reactivity to histamine can be abolished without significantly affecting the tuberculin reaction. An increase of histamine (43–45) as well as the histamine-forming capacity (46) has been found at the site of delayed hypersensitivity reactions; however, its significance in guinea pigs is currently unknown (47, 48).

The antiparasitic agents effectively inhibited the tuberculin reaction. Chloroquine phosphate was inhibitory without any noted toxicity, as in a previous study (25). Its biological effects are numerous (49), and clinically it is of value in rheumatoid arthritis (50–52). Niridazole, orally administered, suppressed delayed hypersensitivity in guinea pigs (53), mice (54), and humans (55). Data in the present study extend this activity of niridazole after both oral and parenteral administrations to the tuberculin reaction in the guinea pig. Activity occurred without overt toxicity, but lethality was noted at larger oral doses. Studies suggest that administration of niridazole prevented production of the macrophage migration inhibitory factor (53).

Another antiparasitic agent, levamisole, enhanced the cell-mediated immune response (56) and was effective in rheumatoid arthritis (57). Penicillamine, a chelating agent, is similar to levamisole in its immunostimulatory properties (58) and its effectiveness in rheumatoid arthritis (59–61). In the present studies, at identical parenteral doses, levamisole suppressed the tuberculin reaction only in association with lethality and penicillamine was inactive. Inhibition by penicillamine was observed after oral administration for multiple days, a regimen similar to that resulting in enhancement of pertussis vaccine pleurisy in the rat (58). Failure to enhance the tuberculin reaction could have resulted because the stimulatory effects were most marked in compromised animals (56) while the animals in the present study were optimally sensitized.

A cell-specific immunoregulator, anti-guinea pig thymocyte γ-globulin[6], essentially abolished the thickness and markedly inhibited the diameter of the tuberculin reaction. Associated with this inhibition was a 50% reduction in the peripheral lymphocytes. Turpentine- and histamine-induced reactions were not inhibited significantly (Table VI). Previously, contact dermatitis was inhibited by antithymocyte serum (62), and the tuberculin reaction was inhibited by antilymphocyte serum (63, 64). Another immunoregulator, cyclophosphamide, administered acutely, did not cause significant inhibition at small test doses in this and a previous (25) study but was active at the larger doses. Inhibition of the tuberculin reaction also occurred after administration of multiple doses after sensitization (30, 65). Thus, apart from its immunosuppressive effect, cyclophosphamide can inhibit the efferent arc of the tuberculin reaction.

Tilorone, an antiviral agent, suppressed tuberculin skin reactivity (66) and adjuvant arthritis (66, 67) in the rat and tuberculin footpad reactivity in the mouse (68). In adjuvant disease, the inhibitory effect occurred when the compound was administered during sensitization (66, 67) but not after sensitization (67). In the present study, tilorone significantly inhibited tuberculin reactivity at the efferent arc without overt toxicity.

Overall, expression of a cell-mediated immune reaction has been inhibited to various extents by different pharmacological agents. In view of the proposed involvement of this type of immunity in rheumatoid arthritis, as well as other disease states, and the possible therapeutic value from inhibition of this immunity, those agents that displayed significant activity apart from lethality warrant continued studies on their mode of action. The low inhibition of the acidic anti-inflammatory agents suggests limitation in this regard, although they may be active on other aspects of the disease state. Significant activity is suggested by such agents as the coumarin anticoagulants, antithymocyte (lymphocyte) γ-globulin, benzydamine, chloroquine, niridazole, and tilorone.

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