Arthritis and Psoriasis: The Effects of Antipsoriatic Agents in the Adjuvant-Induced Arthritic Rat (35138)

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The coexistence of psoriasis and some form of arthritis is statistically much greater than can be ascribed to chance (1, 2). Clinically distinct psoriatic arthritis apart, the two diseases share a number of similarities: joint involvement, probable genetic transmission, and periods of exacerbation and remission (frequently waxing and waning together in patients suffering from both). While neither psoriasis nor rheumatoid arthritis is of known etiology, it may be that both are sustained by autoimmune mechanisms (3, 4).

Historically, anti-inflammatory agents (both steroidal and nonsteroidal) have provided the clinician confronted by psoriasis with his principal therapy (1, 2). This has been extended in more recent times to the use of immunosuppressive agents in the treatment of psoriasis (5) following their demonstrable utility in arthritis (6). Exceptions to this pattern have been the development of anthralin (1, 8, 9-trihydroxyanthracene; Dithranol) and anthralin triacetate (1, 8, 9-triacetoxyanthracene; Exolan) as specific antipsoriatic agents. Anthralin is possibly the most effective single agent for the treatment of chronic psoriasis (7), although anthralin triacetate is believed to hold the potential of replacing it in out-patient use (8).

Despite the fact that antipsoriatic agents like anthralin and its triacetoxy derivative are frequently applied over very large areas of the body for prolonged periods of time (9) (and some absorption is therefore probable), to our knowledge no animal studies have been disclosed which describe the systemic properties of these agents. In this regard, we felt that evaluation of anthralin and its triacetate in the adjuvant-induced arthritic rat, a model characterized by both inflammatory and immunological lesions, would be especially appropriate to shed light on their possible mechanisms of action. It may be noted that an adjuvant-induced psoriatic guinea pig has been described (3).

Materials and Methods. Animals used in these experiments were male Lewis-strain rats (Microbiological Associates) weighing 150–200 g. Adjuvant arthritis was induced by a single intradermal injection of 0.75 mg of *M. butyricum* (Difco) suspended in white paraffin oil into the foot pad of the left hind paw of the rat. Using the hairline as an anatomical reference point, total hind leg volume was measured by the method of Van Arman *et al.* (10). Hemagglutination assays were carried out according to Stavitsky's method (11) with the aid of an Autotiter (Aztec Inc.). Seven-S antibody was determined after treatment with 2-mercaptoethanol according to the method of Deutsch and Morton (12). Skin tests were carried out by intradermal injection of a solution of 50 μg of Purified Protein Derivative (PPD) in 0.1 ml of buffered saline as described by Flax and Waksman (13). Induration was measured 24 hr later.

Experimental Method. Eight animals were used for each test compound and the results were evaluated statistically by the Student *t* test. Compounds studied were the two antipsoriatic agents, anthralin and anthralin triacetate; standard agents were the immunosuppressive, methotrexate, and the anti-inflammatory steroid, prednisolone. Control animals received *M. butyricum* in paraffin oil (Freund's complete adjuvant). Experimental protocol was as follows: agents were administered orally, in tragacanth, on days 0 to 3, 6 to 10, and 13 to 16. Freund's complete adjuvant was injected 3 hr post-drug administration on day 0. Body weights were mea-

TABLE I. Effects of Antipsoriatic, Immunosuppressive, and Anti-inflammatory Agents on Various Parameters of the Adjuvant-Induced Arthritic Rat.

Agent	Dose (mg/kg, po)	Leg vol (ml)			Body wt change (g)		Hemagglutination titers			Skin wheal (mm)
		Left		Right						
		Day 3	Day 16	Day 16	Day 3	Day 16	Total	19S	7S	
Anthralin	100	2.24[c]	3.61[b]	1.86[a]	—27[c]	—16	6.8	3.3	3.5	0[b]
Anthralin triacetate	100	2.75[c]	4.17	3.17	—10	—5	8.6	2.0	6.6	4
Methotrexate	0.25	2.92[c]	2.09[c]	1.32[c]	—9	—9	0.0[c]	0.0[a]	0.0[a]	0[b]
Prednisolone	20	2.25[c]	2.81[c]	1.54[a]	—13	—3	6.5	5.5	1.0	6
Adjuvant controls	—	3.20	4.46	2.82	—7	1	8.2	3.4	4.8	8

[a] $0.05>p>0.01$.
[b] $0.01>p>0.001$.
[c] $p<0.001$.

sured on days 3 and 16. On day 8, the rats were immunized with an intraperitoneal injection of 2.5 ml of a 10% sheep red blood cell (SRBC) suspension. On day 16, the animals were injected with PPD and the response was measured on day 17. The animals were sacrificed on day 17, and titers of the total, 19S and 7S antibody production to SRBC was determined.

Results and Discussion. The results of the four agents studied are summarized in Table I. At an oral dose of 100 mg/kg anthralin suppresses both primary and secondary lesions of the adjuvant-induced arthritic rat; both inflammatory and immunological processes are therefore involved. In contrast to these oral effects, anthralin is said to exert a pro-inflammatory response when applied topically (14).

Since anthralin completely inhibits the PPD-induced skin wheal but does not statistically affect the antibody production to SRBC, it would appear that this agent has a greater effect on cellular mediated (delayed) hypersensitivity than on immediate (humoral) hypersensitivity. This tends to support the view that psoriasis is a cellular mediated disease.

At day 3, anthralin significantly reduces body weight gain of the test animals when compared to the control group; this observation may reflect the general toxicity of the agent (7). Body weight changes at day 16 were not significantly different from the adjuvant-control animals.

While anthralin triacetate shows very significant oral activity at 100 mg/kg suppressing the primary inflammatory response, the acetylated derivative exerts no apparent effect on the secondary lesions, no effect on antibody production to SRBC, no suppression of the PPD-induced skin wheal, and no adverse effects on body weight gain.

By way of comparison, the immunosuppressive agent, methotrexate, at an oral dose of 0.25 mg/kg produces marked suppression of the secondary lesions but exerts only a marginal effect on primary inflammation. Both the antibody response to SRBC and the skin response to PPD were inhibited, and there were no observable effects on body weight gain. At an oral dose of 20 mg/kg the steroid, prednisolone, suppresses both primary and secondary lesions, but exerts no effect on antibody production to SRBC, no alteration in the response to PPD, and no change in body weight gain.

Summary. In summary, we have shown that two topically useful antipsoriatic agents, anthralin and anthralin triacetate, both exert potent anti-inflammatory effects on oral administration. Anthralin further shows antiarthritic activity, inhibiting the cellular mediated immune processes as evidenced by suppression of both secondary lesions and skin wheal in the rat model. These data are pre-

liminary in nature and further studies are in progress to elaborate on the biological profile of these two agents.

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