evidence of the importance of noradrenaline as a modulator of audiogenic seizures.

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Ulcerogenic potential of indomethacin in arthritic and non-arthritic rats

Gastrointestinal disturbance is a well-known effect following excessive doses of steroidal and non-steroidal anti-inflammatory agents (Somogyi, Kovacs & Selye, 1969). Single or multiple doses of indomethacin induce intestinal ulcers in a dose-related manner (Anderson, 1965). Food restriction or bile duct ligation inhibited or significantly reduced the incidence of intestinal ulcers induced with indomethacin or the fenamates (Wax, Clinger & others, 1970; Brodie, Cook & others, 1970). Similarly, catatoxic steroids have also been reported to inhibit indomethacin-induced intestinal ulcers (Selye, 1969).

For several months we have been concerned with studies comparing new non-steroidal anti-inflammatory agents with known standards in several anti-inflammatory and ulcerogenic assays. Since these agents are primarily used only after inflammatory symptomology is evident, it is reasonable to evaluate the ulcerogenic potential of indomethacin at various time-intervals during the development of an adjuvant-induced polyarthritis.

150 male rats (Charles River, Lewis Strain), 170 $\pm$ 10 g were arranged in groups of 5, as summarized in Table 1. Sixty-five rats received an injection of *Mycobacterium butyricum*[1] (250 μg in 0·1 ml sesame oil) in the plantar area of the left hind paw on day 1. The remaining rats served as non-arthritic animals. The arthritic and non-arthritic rats were further arranged into subgroups and indomethacin was administered subcutaneously, (once only) at doses ranging 3·75–30 mg kg^{-1} on day 1, 14 or 28. The animals were killed 24 h later and the small intestine was removed from duodenum to caecum and the inner surface was graded for ulcer incidence and severity (graded 0 to + 3).

Indomethacin at all doses significantly inhibited the *Mycobacterium butyricum*-induced rat paw oedema at 24 h. In the arthritic and non-arthritic rats, the administration of indomethacin at 7·5, 15 and 30 mg kg^{-1}, s.c. on day 1 or 14 induced intestinal ulcers in a dose-related manner. Comparable intestinal ulcers were obtained in both the arthritic and non-arthritic rats at these time intervals. However, a higher incidence

[1] Difco Laboratories, Detroit, Michigan.

Table 1. *Evaluation of indomethacin-induced intestinal ulcers in arthritic and non-arthritic rats*

Autopsy day	Treatment	Dose mg kg^{-1}	Arthritic rats: Body wt. change (g ± s.e.)	Arthritic rats: Ulcer index	Arthritic rats: Ulcer incidence (%)	Non-arthritic rats: Body wt. change (g ± s.e.)	Non-arthritic rats: Ulcer index	Non-arthritic rats: Ulcer incidence (%)
2	(Treated) Control	—	−11 ± 2·2	0	0	1·2 ± 2·1	0	0
	Indomethacin	3·75	−1·2 ± 1·6	0	0	2·4 ± 1·3	0	0
	,,	7·5	−2·4 ± 0·9	0·8 ± 0·58	40	2·8 ± 1·4	0·6 ± 0·39	40
	,,	15·0	0	2·4 ± 0·24*	100	1·2 ± 2·6	2·8 ± 0·19*	100
	,,	30·0	−4·0 ± 1·1	2·8 ± 0·19*	100	−5·2 ± 1·0	3·0 ± 0*	100
15	(Treated) Control	—	43·6 ± 12·5	0	0	76·5 ± 12·5	0	0
	Indomethacin	3·75	42·6 ± 3·9	0	0	70·8 ± 11·8	0	0
	,,	7·5	34·0 ± 7·8	0·8 ± 0·19	80	84·4 ± 2·4	0·2 ± 0·19	20
	,,	15·0	30·8 ± 3·7	2·8 ± 0·19*	100	66·8 ± 3·6	1·4 ± 0·51*§	80
	,,	30·0	42·8 ± 9·4	3·0 ± 0*	100	81·2 ± 2·9	3·0 ± 0*	100
29	(Treated) Control	—	27·8 ± 3·4	0	0	127 ± 10·9	0	0
	Indomethacin	3·75	58·8 ± 20·8	0·4 ± 0·39	20	145 ± 9·4	0	0
	,,	7·5	51·2 ± 17·4	2·0 ± 0·44*†¶	100	135 ± 21·6	1·0 ± 0*†	80
	,,	15·0	36·4 ± 7·3	3·0 ± 0*¶	100	135 ± 4·7	2·4 ± 0·24*	100
	,,	30·0	28·0 ± 6·4	3·0 ± 0*	100	104 ± 12·6	2·8 ± 0·25*	100

(Treated) control received *M. butyricum* into the plantar area of the left hind paw whereas untreated animals were used as controls for non-arthritic rats.
* Significantly different from the treated controls.
† Significantly greater than the group receiving the same dose of indomethacin on day 14.
§ Significantly less than the group receiving the same dose of indomethacin on day 1.
¶ Significantly greater response than the non-arthritic rats receiving the same dose of indomethacin at the same time interval.

of ulcers was evident in arthritic rats which received indomethacin at 7·5 mg kg^{-1}, s.c. on day 14 than on day 1. Similarly, indomethacin at 7·5 mg kg^{-1} induced a greater incidence in the arthritic rats on day 14 than in the non-arthritic rats.

On day 14, the migratory components of the developing polyarthritis are evident. On day 28, significant swelling occurs in all four paws and skin lesions, thymolysis and adrenal gland hypertrophy are also observed (Pearson Waksman & Sharp, 1961; Pearson & Wood, 1963; Newbould, 1963). At this latter time interval, intestinal ulcers are also induced in arthritic rats with indomethacin at 3·75 mg kg^{-1}. Similarly, animals receiving 7·5 and 15 mg kg^{-1} exhibited a greater ulcerogenic index than non-arthritic rats receiving the same dose of indomethacin. It appears that arthritic rats during the later stages are more sensitive to the ulcerogenic potential of indomethacin.

Presently, it is not known if the increased ulcerogenic sensitivity is related to indomethacin alone or results from the combined effects of indomethacin and the increased plasma corticosterone levels (Persellin, Kittenger & Kendall, 1972) and/or other factors.

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