ANTI-INFLAMMATORY DERIVATIVES OF INDAN-1-ACETIC ACIDS WITH LOW GASTRIC IRRITANCY

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Summary : In an attempt to minimize the gastric ulcerogenicity of 6-methoxyindan-1-acetic acid and 5,6-dimethoxyindan-1-acetic acid exhibiting high anti-inflammatory activity, we synthesized their esters, amides and nitrile derivatives. It was found that the anti-inflammatory activity of ethyl esters were almost equal to those of parent acids and phenylbutazone while other derivatives were less potent. Those ethyl esters were also found to be much less ulcerogenic than phenylbutazone.

Key words : anti-inflammatory activity, ulcerogenicity, derivatives of indan-1-acetic acids, phenylbutazone

INTRODUCTION

A major drawback of most non-steroidal anti-inflammatory agents is their acute gastrointestinal ulcerogenicity. Although, there is much controversy over the mechanism of this principal side-effect, it is generally agreed that gastric irritation is associated, directly or indirectly, with the acidic nature of these drugs and their metabolites (1,3,7).

Recently, we reported (8,10) occurrence of significant anti-inflammatory activity in a series of indan-1-acetic acids. Two of them (6-methoxyindan-1-acetic acid and 5, 6-dimethoxyindan-1-acetic acid) possessed activity comparable to that of phyenylbutazone with possibily less acute toxicity and ulcerogenicity. This prompted us to synthesize and screen a series of esters, amides and nitrile derivatives of those two potent indan-1-acetic acids with the hope that the chemical modification may further reduce the gastric ulcerogenic potential while still maintain their anti-inflammatory activity.

Table I shows the structure of derivatives we synthesized and studied in present work.

MATERIAL AND METHODS

Male albino rats of Wistar strain weighing 120 to 160 g were used after acclimatization for 8 days to the laboratory environment.

Carrageenin-oedema test : Following the method of Winter *et al.* (12), the rats were divided at random in groups of 6 animals each and the groups were fed orally (100 *mg/kg*) either the test agents, or phenylbutazone (B.P.) dissolving them in propylene glycol (B.P.). The control group received the vehicle (propylene glycol) only. After 1 hr, 0.1 *ml* of 1.0% carrageenin (Marine Colloids, Inc., U.S.A.) solution in 0.9% saline was injected intradermally into the plantar surface of right hind paw of each rat. The paw volumes upto a fixed mark at the level of lateral malleous were measured before and after selected intervals of carrageenin administration according to the procedure as described earlier (9).

Adjuvant-induced arthritis test : The method followed was essentially that of Newbould (5). Here, the rats were divided at random into groups of 6 animals each. The groups received orally either the test agents, phenylbutazone or vehicle daily for 14 days starting from the day before the intradermal administration of 0.05 *ml* of Freund's complete adjuvant (Difco, U.S.A.) into the plantar surface of right hind paw of each rat. Drugs were administered at 25, 50 and 100 *mg/kg/day*. Both hind paw volumes upto a fixed mark at the level of lateral malleoulus were measured before and after 13 days of adjuvant administration using a simple device as described earlier (9). The average percent change in body weight for each groups were calculated from the body weights of the animals taken before and at the end of the experiment.

In both the tests, percent inhibition of oedema in each drug-treated group was calculated using the formula below.

$$\% \text{ Inhibition} = \frac{C - T}{C} \times 100$$

where, C and T represent the average percent increase in paw volumes of the control and drug-treated groups respectively.

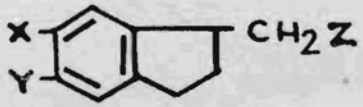
Ulcerogenicity test : The method was essentially that of Wax *et al.* (11). Here, the rats were starved for 24 hr water being given *ad libitum*. Then they were divided at random into groups of 6 animals each. The groups received orally either the test agents, phenylbutazone, or vehicle (Propylene glycol). Drugs were administered at 37.5, 75, 150, 300 and 600 *mg/kg* doses. After 24 hr the rats were sacrificed and the stomachs were dissected out, cut along the greater curvature, washed with saline and observed for any lesions (pin-point ulcer) that developed in the mucous layer by person unaware of the drug treatments.

The results of chronic adjuvant-induced arthritis tests and acute gastric ulcerogenicity tests were statistically analysed following the method of Litchfield and Wilcoxon (4).

RESULTS AND DISCUSSION

The results of acute carrageenin-oedema tests (Table I) show that the peak activity as well as the residual activity at 24 hr after single oral dose are maximum in case of ethyl esters of the indan-1-acetic acids followed by those of amides and nitriles. The peak activity of esters was lower than that of phenylbutazone but their residual activity at 24 hr exceeded or was as good as that of the latter.

TABLE I : Structure and acute anti-inflammatory activity of indan-1-acetic acid derivatives.



Compound No.+	*Structure substituents*	*Percent increase in paw volumes (mean ± SE)*		
		*2 hr**	*4 hr*	*23 hr*
1.	X=OCH_3, Y=H, Z=$COOC_2H_5$	57.94 ± 2.81[b] (31.68)[f]	73.0 ± 3.62[a] (38.42)	54.08 ± 3.20[c] (25.12)
2.	X=Y=OCH_3, Z=$COOC_2H_5$	55.52 ± 3.48[b] (34.54)	69.67 ± 3.25[a] (41.23)	52.47 ± 2.84[b] (27.35)
3.	X=OCH_3, Y=H, Z=$CONH_2$	60.53 ± 3.62[c] (28.62)	85.89 ± 4.33[b] (27.54)	58.78 ± 3.16[e] (18.61)
4.	X=OCH_3, Y=H, Z=$CONHCH_3$	61.48 ± 4.08[c] (27.51)	87.47 ± 3.93[b] (26.21)	59.0 ± 3.25[e] (18.30)
5.	X=OCH_3, Y=H, Z=$CONHC_2H_5$	61.18 ± 3.55[c] (27.86)	87.00 ± 3.84[b] (26.60)	57.95 ± 3.01[d] (19.76)
6.	X=Y=OCH_3, Z=$CONH_2$	57.52 ± 2.86[b] (32.18)	80.06 ± 3.88[b] (32.46)	57.75 ± 2.82[d] (20.04)
7.	X=Y=OCH_3, Z=$CONHCH_3$	58.30 ± 3.81[b] (31.26)	82.10 ± 4.07[b] (30.74)	56.81 ± 2.69[d] (21.34)
8.	X=Y=OCH_3, Z=$CONHC_2H_5$	58.97 ± 3.24[b] (30.47)	81.58 ± 3.45[a] (31.18)	57.88 ± 3.18[d] (19.86)
9.	X=OCH_3, Y=H, Z=CN	68.97 ± 2.92[d] (18.68)	85.27 ± 3.76[b] (28.07)	60.93 ± 2.38[e] (15.63)
10.	X=Y=OCH_3, Z=CN	65.67 ± 3.85[d] (22.57)	81.97 ± 3.22[a] (30.85)	60.98 ± 2.91[e] (15.56)
	Phenylbutazone	44.91 ± 3.97[a] (47.05)	69.70 ± 3.44[a] (41.20)	54.76 ± 3.11[c] (24.18)
	Propylene glycol (Control)	84.81 ± 3.67	118.54 ± 4.10	72.22 ± 2.94

+ All drugs were administered orally (100 *mg/kg* in propylene glycol) 1 hr before carrageenin administration.

* Time after carrageenin administration.

+ All values are means from 6 rats.

[a-e] Probability values (calculated as compared to control using Student's t-test) : a < .001, b < .005, c < .01, d < .025, e < .05.

[f] Figures in parentheses represent the percent inhibition of oedema.

The chronic adjuvant-induced arthritis test and the acute gastric ulcerogenicity test were performed only with the more potent ester derivatives as shown in the results of acute carrageenin-oedema tests (Table I) taking phenylbutazone as standard. The results (Table II) show the ED_{40} doses for inhibiting the development of arthritis in both the injected and uninjected hind paws of rats 13 days after adjuvant administration. It is seen that the ethyl ester of 5,6-dimethoxyindan-1-acetic acid (compound No. 2) is more potent, while the ethyl ester of 6-methoxyindan-1-acetic acid (compound No. 1) is less potent than phenylbutazone. It was also observed that the drug treated groups always gained more weights than the control group (3.4±0.8 p.c.) but these changes were not statistically significant.

The results of acute ulcerogenicity tests (Table II) show that the esters are 5-6 times less ulcerogenic than phenylbutazone when given orally.

TABLE II : Chronic anti-inflammatory activity and acute gastric ulcerogenicity of indan-1-acetic esters compared to that of phenylbutazone.

Compound No.[a]	*Inhibition of oedema ED_{40}, (mg/kg/day)*		*Gastric ulcerogenicity ED_{50} (mg/kg)*
	Injected paw	*Uninjected paw*	
1.	55 (33 to 92)[b]	62 (41 to 94)[b]	315 (207 to 479)[b]
2.	40 (23 to 68)	45 (31 to 66)	355 (228 to 554)
Phenylbutazone	48 (28 to 81)	61 (41 to 91)	61 (42 to 89)

[a] See Table I.

[b] 95% confidence limits.

From these studies it appears that the ethyl esters of 6-methoxyindan-1-acetic acid and 5,6-dimethoxyindan-1-acetic acid significantly retain the anti-inflammatory activity of the parent acids as reported earlier (8,10) while their amide and nitrile derivatives are less potent. It seems possible that the ethyl esters undergo guantitative biotransformation to their parent acids after oral administration while the amide and nitrile derivatives probably follow more complicated biochemical pathways and release lesser amount of the corresponding indan-1-acetic acids in the system, making themselves much less potent than phenylbutazone.

It also appears from this study that the duration of activity rather than the peak activity after single oral dose as shown in the results of acute carrageenin-oedema tests (Table I) plays major role in the chronic adjuvant-induced arthritis tests and thus the ethyl ester of 5,6-dimethoxyindan-1-acetic acid (compound no. 2) becomes more active than phenylbutazone in the chronic arthritis test (Table II).

The lesser ulcerogenic potential of the ethyl esters than phenylbutazone is possibly due to slow release of their active acid metabolites in the system which are probably less irritating to gastric mucosa than phenylbutazone due to their higher pKa values (6.66-6.74, see 2) than that of phenylbutazone itself 4.5, see 6).

The wide separation of the anti-inflammatory activity and gastric ulcerogenicity of the ethyl esters of 6-methoxyindan-1-acetic acid and 5,6-dimethoxyindan-1-acetic acid compared to that of phenylbutazone may have important implications in future studies

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