Agents and Actions
vol. 6/5 (1976)
Birkhäuser Verlag, Basel

Anti-Inflammatory and Related Properties of 2-(2,4-Dichlorophenoxy)phenylacetic Acid (Fenclofenac)

by DAVID C. ATKINSON and ELIZABETH C. LEACH
Department of Pharmacology, Reckitt & Colman Pharmaceutical Division, Hull HU8 7DS, England

Abstract

Fenclofenac was shown to possess anti-inflammatory, antinociceptive and antipyretic properties as measured by tests in rats that detect clinically active compounds. In a chronic test for assessing anti-inflammatory activity (established adjuvant arthritis), it was approximately equipotent to alclofenac, fenoprofen calcium and phenylbutazone, more potent than acetylsalicylic acid and ibuprofen, but was less potent than diclofenac sodium, indomethacin, ketoprofen and naproxen. In contrast, the potency of fenclofenac in acute tests for anti-inflammatory, antinociceptive and antipyretic activity was generally lower, the drug being approximately equipotent to acetylsalicylic acid in such tests. The anti-inflammatory activity of fenclofenac was not mediated via the pituitary-adrenal axis or a counter-irritant action. Fenclofenac was shown to have remarkably low gastric ulcerogenic potential, both acutely and chronically.

Introduction

The pharmacological evaluation of a series of 2-aryloxyarylacetic acids [1] has revealed an interesting spectrum of properties in 2-(2,4-dichlorophenoxy)phenylacetic acid (fenclofenac, RX 67408), a novel anti-inflammatory agent which is currently on clinical trial. A preliminary account of its anti-inflammatory and related properties has been published elsewhere [2]; the present paper updates and expands the findings presented.

Fenclofenac (Fig. 1) is a white crystalline powder which is sparingly soluble in water and has a molecular weight of 297.1 and a melting point of 135–137 °C.

Methods

Animals

Albino Sprague-Dawley rats were used throughout. In acute studies, animals were deprived of food overnight but, in other tests, they were allowed food and water ad libitum, unless otherwise stated.

When required, bilateral adrenalectomy was performed under ether anaesthesia through a dorsal midline skin incision on male rats weighing 130–175 g. The skin wound was then closed with Michel suture clips. The rats were maintained on Spillers' Laboratory Small Animal (Autoclaved) diet and 0.9% w/v saline solution until they were required for further experimentation on the fourth day after the operation. Sham-operated animals were subjected to the same surgical procedure as adrenalectomized animals except for removal of the adrenal glands.

Drugs

Unless otherwise stated, the compounds under investigation were administered orally as a suspension in 5% gum acacia. Control animals received the same dose volume (10 ml/kg) of the vehicle alone.

The following reference drugs were used: acetylsalicylic acid, hydrocortisone, indomethacin (Merck, Sharp & Dohme Ltd) and phenylbutazone (Chelsea Drug Chemical Co. Ltd) (acquired unformulated); alclofenac (Berk Pharmaceuticals Ltd), diclofenac sodium (Ciba-Geigy Ltd), ibuprofen (The Boots Co. Ltd), ketoprofen (May & Baker Ltd) and naproxen (Syntex Pharmaceuticals Ltd) (extracted from tablets or capsules); and fenoprofen calcium (synthesized in the Medicinal Chemistry Laboratory of Reckitt & Colman Pharmaceutical Division). The identity and purity of extracted and synthesized material were established by physical tests including n.m.r. spectroscopy and t.l.c. Fenoprofen was examined as the sodium salt prior to conversion to fenoprofen calcium.

Established adjuvant-induced arthritis

The method used was based on procedures described previously [3–5]. On day 0 of the test, 0.05 ml of liquid

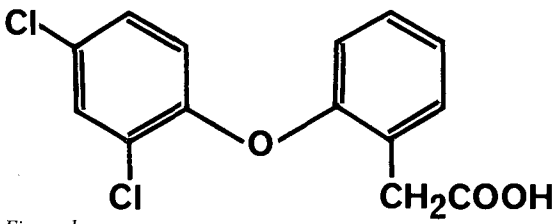

Figure 1
Structure of fenclofenac.

paraffin containing 5 mg/ml of dead *Mycobacterium tuberculosis* (derived from human strains PN, DT and C, grown for 8 weeks, steam killed and dried) was injected into the plantar surface of the left hind paws of male rats (approx. 160–220 g). On day 21, the animals were weighed, and the arthritis was assessed by measurement of the volume of the injected paw with an electronic volume differential meter (the paw volumes measured were linearly related, but not directly proportional, to absolute values). Those animals in which the arthritis was least developed were rejected; in the present investigations, animals with an estimated absolute paw volume of <4 ml were not included. The remaining animals were divided into experimental groups (unless otherwise stated, the drug-treated groups consisted of a maximum of 7 rats, the control group 21) such that the mean left hind paw volume reading for each group was approximately equal. The rats were then dosed orally once daily with the drugs on test on days 21 to 27 inclusive. The left hind paw volumes and body weights were re-determined either daily on days 22 to 28 inclusive, or, as in some experiments (relative potency determinations), only on day 28 (approx. 24 hours after the final dose). Changes in paw volume and body weight were expressed as a percentage of their respective measured initial values, those occurring in drug-treated groups being considered in relation to similar changes occurring in control animals.

Carrageenin-induced paw oedema

Acute anti-inflammatory activity was assessed using a method based on those described previously [6, 7]. Male rats (150–190 g) were used and the drugs on test were administered orally 1 hour prior to the subplantar carrageenin injection.

Local anti-inflammatory activity was determined in male rats (120–150 g) using the method of SHANAHAN [8].

Antinociceptive activity

Antinociceptive activity was determined in male rats using the yeast-induced motor impairment method of ATKINSON and COWAN [9].

Antipyretic activity

Antipyretic activity was assessed by the ability of drugs to inhibit yeast-induced hyperthermia. The oesophageal temperature of female rats (90–140 g) was first measured using an electrical thermometer (Light Laboratories, Brighton, model 3GID). The rats were then injected subcutaneously with 10 ml/kg of a 30% w/v suspension of brewer's yeast (D.C.L.) in 0.9% w/v saline solution. Food was then withheld from the animals. Approximately 17 hours after the yeast injection, the temperature of each rat was re-measured and animals showing a rise in temperature following the yeast injection (yeast-induced temperature change) of less than 0.8 °C were discarded. The remaining rats were then divided into groups and dosed with the drugs under investigation. At hourly intervals starting 2 hours after dosing and continuing until 6 hours after, the oesophageal temperature of each rat was measured and expressed as the change from the pre-drug value. Results from a number of experiments were pooled to give a minimum total of 10 animals at each dose level. The mean change from the pre-drug value over the 2–6-hour period was then calculated for each animal and expressed as a percentage of the pre-drug yeast-induced temperature change recorded for the same animal. Finally, the mean percentage was calculated for the group.

Glucocorticoid activity

Glucocorticoid activity was assessed in rats by measuring the effect of both the acute and chronic administration of drugs on liver glycogen deposition. In the single dose study, male rats (150–200 g) were used. They were killed by neck dislocation 4 hours after drug administration. In the repeated-dose study, larger male rats (200–235 g) were used and these were killed 4 hours after the last of 7 once-daily drug doses. The livers were removed and their glycogen content estimated using the method described by CARROLL et al. [10].

Gastric ulcerogenic activity

The gastric ulcerogenic activity following both the acute and chronic administration of drugs was assessed using a modification of the method described by MARTINDALE et al. [11]. In acute studies, groups of 10 female rats (80–120 g) were dosed with the drugs on test over a suitable range of doses. Either 3 or 24 hours after dosing, the rats were killed by neck dislocation and the stomachs were removed, washed out with 0.9% w/v saline and inflated with 70% v/v alcohol. The stomachs were then numbered randomly and stored in 70% v/v alcohol. An operator working 'blind' then scored the glandular region of the stomachs for damage using transmitted light for examination. Scoring was on a 0–4 scale of increasing severity. The mean score for each group was calculated and the level of significance of the difference between the control and treatment groups was determined using the Wilcoxon rank sum test for non-parametric data [12]. The ulcerogenic potential of each drug was expressed as the minimum ulcerogenic dose (MUD), i.e. the range of doses within which falls the lowest dose producing a statistically significant ($p<0.05$) degree of gastric damage when compared with the controls.

In repeated-dose studies, female rats were divided into groups of 10–11. They had access to water at all times and to food for the first 6 days of the test. The rats were dosed once daily, and, 4 hours after the final (7th) dose, they were killed and the degree of gastric damage assessed as described above.

Acute toxicity

Acute toxicity following oral drug administration was assessed in male rats (160–200 g), the dose volume used being 20 ml/kg. The animals were allowed food 1 hour after dosing and were kept at a mean ambient temperature of 23 °C and observed for at least 7 days. The LD_{50} was calculated from the number of deaths recorded at 7 days, using a logit analysis method [13].

Statistical methods

Unless otherwise stated, the statistical significance of difference between experimental groups was calculated us-

ing the two-tailed Student's t-test. Differences were considered significant if $p \leqslant 0.05$. In cases where the control and test variances were not homogeneous, the procedure described by WELCH [14, 15] was employed. Potency ratios were determined using a standard parallel-line assay method [16].

Results

Established adjuvant-induced arthritis

The dose-related effect of fenclofenac on the injected paw volume and body weight gain of rats with established adjuvant arthritis is shown in Figure 2. The mean percentage paw volume change occurring in each drug-treated group was statistically significantly different from that occurring in the control group on all days. The inhibitory effect of fenclofenac on the arthritis was accompanied by a beneficial effect on body weight gain which was significantly greater than that observed in the control group on days 22–28 at 75 mg/kg, days 23–28 at 15 mg/kg, but only on days 22, 23 and 25 at 3 mg/kg.

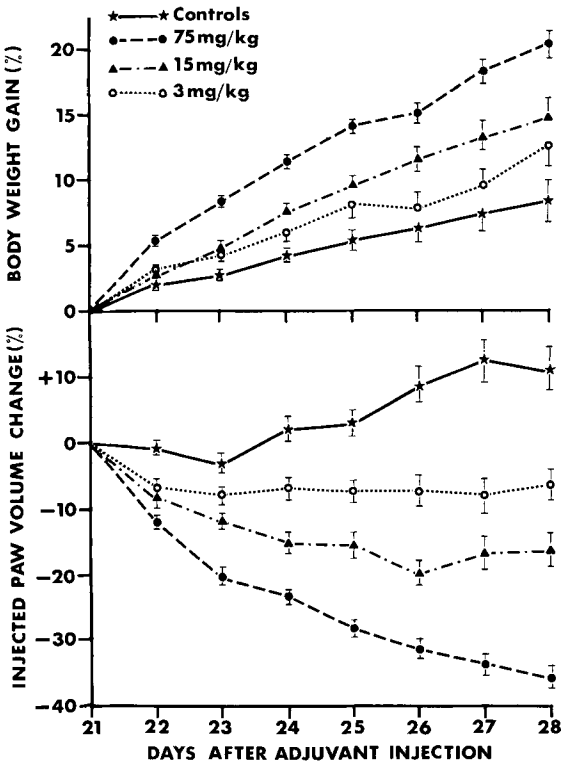

Figure 2
The effect of fenclofenac on the body weight gain and injected paw volume of rats with established adjuvant arthritis. The drug was administered orally once daily on days 21–27 inclusive at the doses indicated. Results represent the mean ± standard error of 20 observations.

The anti-arthritic potency of fenclofenac relative to four reference drugs was determined in a single test and the following potency ratios, together with their 95% confidence limits, were obtained (fenclofenac = 1): acetylsalicylic acid, 0.06 (0.04–0.12); ibuprofen, 0.12 (0.05–0.29); indomethacin, 24 (13–44) and phenylbutazone, 0.85 (0.44–1.6). Significant differences between preparations ($p < 0.01$) were obtained in all assays except that of phenylbutazone, but the other criteria for validity of comparison (regression, parallelism and linearity) were satisfied in all cases. In this particular test, the minimum effective dose (MED), i.e. the lowest daily dose required to produce a statistically significant anti-arthritic effect, was also calculated and was found to be 3 mg/kg for fenclofenac. Corresponding values for acetylsalicylic acid, ibuprofen, indomethacin and phenylbutazone were 71.7, 24.4, 0.19 and 2.2 mg/kg, respectively.

The potency of some recently introduced anti-inflammatory agents was also examined relative to that of fenclofenac in a further series of tests and the following potency ratios were obtained (fenclofenac = 1): alclofenac, 0.87 (0.43–1.7); diclofenac sodium, 61 (30–126); fenoprofen calcium, 0.88 (0.31–2.5); ketoprofen, 38 (17–83) and naproxen, 4.4 (1.8–11).

In an additional experiment, the effect of drug treatment on the arthritic swelling of the non-injected (right) hind paw was studied. A similar protocol to that described under *Methods* for the injected paw was employed, except that the selected animals had an estimated absolute paw volume $\geqslant 3.75$ ml. As an additional measure of anti-inflammatory activity in these animals, plasma fibrinogen levels were determined, the rats being bled by cardiac puncture within 2 hours of the final paw volume measurement on day 28 of the test. Plasma fibrinogen was estimated using a heat precipitation micromethod [17].

Fenclofenac significantly reduced the severity of the remote arthritic lesions, an action which was again accompanied by a favourable effect on body weight gain (Table 1). Furthermore, fenclofenac significantly lowered the elevated plasma fibrinogen levels occurring in the arthritic rats.

Table 1
The effect of fenclofenac on the non-injected hind paw volume, body weight gain and plasma fibrinogen levels of rats with established adjuvant arthritis.

Drug	Daily dose (mg/kg, p.o.)	% change in non-injected paw volume ± S.E.M.	% body weight gain ± S.E.M.	Plasma fibrinogen concentration ± S.E.M. (g/100 ml)[1])
5% gum acacia[2]) (controls)	10 ml/kg	+20.9 ± 5,9	6.0 ± 1.4	0.836 ± 0.030
Fenclofenac	75	−25.2 ± 2.4[3])	19.2 ± 1.8[3])	0.547 ± 0.054[3])
	15	− 8.9 ± 6.2[5])	14.6 ± 2.4[4])	0.674 ± 0.031[4])

[1]) Mean plasma fibrinogen concentration obtained for 9 non-arthritic rats = 0.302 g/100 ml.
[2]) 21 rats in this group; 7 rats in each of the other groups.
Levels of significance: [3]) $p < 0.001$; [4]) $p < 0.01$; [5]) $p < 0.05$ compared with controls.
S.E.M. = standard error of the mean.

Carrageenin-induced paw oedema

The inhibitory effect of fenclofenac and selected reference drugs on carrageenin-induced oedema is shown in Table 2. In this test situation, fenclofenac was equipotent to acetylsalicylic acid but considerably less potent than ibuprofen and indomethacin. The MED of fenclofenac in this test was 23.8 mg/kg p.o. Corresponding values for acetylsalicylic acid, indomethacin and phenylbutazone were 39.4, 1 and 7.2 mg/kg, respectively. The MED of ibuprofen fell outside the dose range investigated but was estimated by extrapolation to be approximately 0.6 mg/kg p.o.

Table 2
The effect of drugs on carrageenin-induced paw oedema in rats.

Drug	Dose (mg/kg, p.o.)	Mean increase in paw volume ± S.E.M. (ml)	% inhibition of control oedema	*p* vs. controls	Potency ratio (with 95% confidence limits)
5% gum acacia (controls)	10 ml/kg	0.68 ± 0.05	-	-	-
Fenclofenac	180	0.35 ± 0.03	49	< 0.001	
	60	0.51 ± 0.05	25	< 0.05	1.0
	20	0.52 ± 0.05	24	< 0.05	
Acetylsalicylic acid	300	0.25 ± 0.03	63	< 0.001	0.92
	100	0.45 ± 0.04	34	< 0.005	(0.45-1.9)
	33.3	0.54 ± 0.05	21	N.S.	
Ibuprofen	27	0.31 ± 0.03	55	< 0.001	20
	9	0.41 ± 0.04	39	< 0.001	(6.1-66)
	3	0.43 ± 0.04	36	< 0.005	
Indomethacin	9	0.22 ± 0.03	67	< 0.001	41
	3	0.43 ± 0.05	37	< 0.005	(18-92)
	1	0.50 ± 0.06	26	< 0.05	
Phenylbutazone	90	0.33 ± 0.04	52	< 0.001	3.8
	30	0.35 ± 0.03	48	< 0.001	(1.6-9.1)
	10	0.53 ± 0.05	22	N.S.	

9 rats per group.
S.E.M. = standard error of the mean.
N.S. = not significant ($p > 0.05$).

The results presented in Table 3 indicate that the anti-carrageenin oedema activity of fenclofenac was not significantly modified in bilaterally-adrenalectomized rats. Fenclofenac was also capable, albeit at a high concentration, of producing a significant anti-inflammatory effect when injected at the site of inflammation (Table 4).

Table 3
The effect of adrenalectomy on the anti-carrageenin paw oedema activity of fenclofenac in rats.

Treatment	Dose (mg/kg, p.o.)	Mean increase in paw volume ± S.E.M. (ml)	% inhibition of respective control oedema (S.E. limits)
Sham-operated			
5% gum acacia (controls)	10 ml/kg	0.56 ± 0.03	-
Fenclofenac	100	0.37 ± 0.03	34 (25-43)
Adrenalectomized			
5% gum acacia (controls)	10 ml/kg	0.54 ± 0.07	-
Fenclofenac	100	0.26 ± 0.03	52 (37-67)

10 rats per group.
S.E.M. = standard error of the mean.

Table 4
The effect of the local administration of fenclofenac on carrageenin-induced paw oedema in rats.

Treatment (injection volume 0.05 ml)	Mean increase in paw volume ± S.E.M. (ml)	*p* vs. carrageenin
Carrageenin (10 mg/ml)	0.58 ± 0.03	-
Carrageenin (10 mg/ml) + fenclofenac (100 mg/ml)	0.43 ± 0.03	< 0.001

20 rats per group.
S.E.M. = standard error of the mean.

Antinociceptive activity

Fenclofenac demonstrated antinociceptive activity as judged by its ability to reverse yeast-induced motor impairment in rats. Its ED_{50} (with 95% confidence limits) was found to be 54.3 (14.3-206) mg/kg p.o. Corresponding ED_{50} values obtained in these laboratories for reference drugs were: acetylsalicylic acid, 78.3 (30.6-200); ibuprofen, 5.53 (0.32-94.6); indomethacin, 1.21 (0.41-3.53) and phenylbutazone, 12.4 (5.63-27.4) mg/kg p.o. [9]. Thus, based on the calculated ED_{50} values, fenclofenac is approximately equipotent to acetylsalicylic acid as an inhibitor of inflammatory pain.

Antipyretic activity

The results obtained for fenclofenac and the reference drugs examined simultaneously are given in Table 5. Estimations of relative potency gave the following (fenclofenac = 1): acetylsalicylic acid, 0.62 (0.34-1.1); indomethacin, 20 (9.0-46) and phenylbutazone, 1.2 (0.72-2.0). The potency ratio for ibuprofen cannot be reliably quoted owing to significant deviations from both linearity and parallelism, but the results indicated that it was considerably more potent than fenclofenac.

An additional experiment designed to investigate whether fenclofenac was capable of exerting a hypothermic action in normothermic rats was undertaken. The results obtained showed that fenclofenac produced no significant hypothermia at oral doses of 50 and 150 mg/kg when compared with vehicle-treated controls over the same period of observation (2-6 hours after drug administration).

Glucocorticoid activity

The results (Table 6) show that fenclofenac, following either acute or chronic administration, produced no increase in liver glycogen levels. Instead, a significant decrease was observed at the intermediate and high doses examined. In marked contrast, hydrocortisone, after only a single dose, significantly increased liver glycogen levels.

Table 5
The effect of drugs on yeast-induced hyperthermia in rats.

Drug	Dose (mg/kg, p.o.)	Mean % reduction of fever ± S.E.M.	*p* vs. controls
5% gum acacia (controls)	10 ml/kg	9.6 ± 8.4	-
Fenclofenac	25	61.3 ± 15.9	< 0.05
	12.5	51.7 ± 12.8	< 0.05
	6.25	2.7 ± 8.0	N.S.
Acetylsalicylic acid	40	57.3 ± 10.0	< 0.01
	20	35.9 ± 10.0	N.S.
	10	18.2 ± 8.3	N.S.
Ibuprofen	2	60.9 ± 9.0	0.001
	1	69.7 ± 9.9	< 0.001
	0.5	48.7 ± 9.4	< 0.01
Indomethacin	2	59.1 ± 9.3	< 0.01
	1	63.2 ± 14.7	< 0.01
	0.5	35.3 ± 6.3	< 0.05
Phenylbutazone	30	88.0 ± 8.5	< 0.001
	15	42.2 ± 8.6	< 0.05
	7.5	34.2 ± 7.2	< 0.05

10–11 rats per group.
S.E.M. = standard error of the mean.
N.S. = not significant ($p > 0.05$).

Table 6
The effect of fenclofenac and hydrocortisone on liver glycogen deposition in rats.

Experiment	Drug	Dose (mg/kg, p.o.)	Mean liver glycogen concentration ± S.E.M. (mg/g wet liver)	*p* vs. respective controls
1 (Acute)	5% gum acacia (controls)	10 ml/kg	44.1 ± 2.4	-
	Fenclofenac	250	30.2 ± 2.7	< 0.005
		50	31.6 ± 2.5	< 0.005
		10	49.3 ± 1.5	N.S.
2 (Acute)	5% gum acacia (controls)	10 ml/kg	38.0 ± 5.1[1])	-
	Hydrocortisone	10	57.4 ± 3.8[1])	< 0.02
3 (Chronic)	5% gum acacia (controls)	10 ml/kg[2])	49.4 ± 4.4.	-
	Fenclofenac	250[2])	24.3 ± 4.3	< 0.001
		50[2])	33.2 ± 5.8	< 0.05
		10[2])	43.1 ± 4.0	N.S.

[1]) 5 rats in these groups; 10 rats in all other groups.
[2]) Dose administered once daily for 7 days.
S.E.M. = standard error of the mean.
N.S. = not significant ($p > 0.05$).

Gastric ulcerogenic activity

Table 7 lists the minimum ulcerogenic doses obtained for fenclofenac and reference drugs as determined 3 and 24 hours after the oral administration of single doses. The results show that the ulcerogenic activity of fenclofenac was, in the majority of cases, markedly less than that of the reference drugs examined when comparisons were made at both assessment times.

Table 7
Acute gastric ulcerogenic activity of anti-inflammatory drugs in rats.

Drug	Minimum ulcerogenic dose (mg/kg, p.o.) 3 hrs	24 hrs
Fenclofenac	400–800	200–800[1])
Acetylsalicylic acid	< 15–30[1])	< 15–60[1])
Alclofenac	30–60	60–120
Diclofenac sodium	4–8	4–8
Fenoprofen calcium	30–60	30–60
Ibuprofen	6–13	6–13
Indomethacin	1.3–2.5	2.5–5.0
Ketoprofen	0.6–1.3	5–10
Naproxen	2–4	2–4
Phenylbutazone	40–80	38–75

[1]) Derived from the results of several tests.

In the chronic test, fenclofenac was compared with four reference drugs. The doses used were multiples of the MED as determined simultaneously in a single rat adjuvant arthritis test (see above), and the results obtained are given in Table 8. These show that fenclofenac was the least ulcerogenic (and toxic) of the drugs examined. In marked contrast to the other drugs, doses of fenclofenac equivalent of up to 120 times the anti-arthritic MED caused no significant gastric ulceration nor any deaths.

Acute toxicity

The oral LD_{50} (with 95% confidence limits) of fenclofenac in male rats was found to be 2280 (1720–3030) mg/kg. Corresponding values for reference drugs were: acetylsalicylic acid, 1400 (1130–1720); ibuprofen, 856 (697–1050); in-

Table 8
Chronic (7-day) gastric ulcerogenic activity of anti-inflammatory drugs in rats.

Drug	Daily dose (mg/kg, p.o.)	(xM.E.D.)	Mean score	*p* vs. respective controls	Mortality
5% gum acacia (controls)	10 ml/kg	–	0.6	–	0/10
Fenclofenac	180	60	0.8	N.S.	0/10
Acetylsalicylic acid	215	3	2.0	< 0.005	0/10
Ibuprofen	244	10	3.1	< 0.005	2/10
Indomethacin	5.7	30	0.8	N.S.	0/10
Phenylbutazone	132	60	1.1	< 0.025	0/10
5% gum acacia (controls)	10 ml/kg	–	0.7	–	0/11
Fenclofenac	360	120	0.8	N.S.	0/11
Acetylsalicylic acid	430	6	2.5	< 0.005	1/11
Ibuprofen	488	20	–	–	11/11
Indomethacin	11.4	60	–	–	11/11
Phenylbutazone	264	120	2.9	< 0.005	1/11

M.E.D. = minimum effective dose as determined simultaneously for each drug in a single rat adjuvant arthritis test.
N.S. = not significant ($p > 0.05$ as calculated using the Wilcoxon rank sum test for non-parametric data).

domethacin, 19.8 (12.5–31.1) and phenylbutazone, 472 (428–522) mg/kg.

In an additional experiment designed to elucidate the possible cause of death following the administration of single toxic oral doses, post-mortem examination of fenclofenac-treated rats (2800 mg/kg, surviving rats examined 2 days after dosing) revealed the presence of kidney damage (tubular dilatation with P.A.S.-positive casts) but no evidence of gastrointestinal irritation. In contrast, after the administration of single toxic doses of acetylsalicylic acid (2500 mg/kg-examined 1 day post-drug), ibuprofen (1400 mg/kg-2 days post-drug), indomethacin (40 mg/kg-3 days post-drug) and phenylbutazone (500 mg/kg-1 day post-drug), intestinal irritation was observed in all cases, leading to ulceration with peritonitis in the case of the latter two drugs. Kidney and liver damage was also found in phenylbutazone-treated animals.

Discussion

These results show that fenclofenac possesses anti-inflammatory, antinociceptive and antipyretic properties as measured by tests in rats that detect clinically-active compounds.

The results obtained in the established adjuvant arthritis test indicate that fenclofenac decreases the severity of arthritic lesions both at and remote from the adjuvant injection site, an action which is accompanied by a beneficial effect on body weight gain. Additional evidence that fenclofenac exerts an anti-inflammatory action in adjuvant-arthritic rats is its ability to reduce the elevated plasma fibrinogen levels occurring in such rats. GLENN [18] examined the relationship of plasma fibrinogen to experimental inflammation and found that the increase in plasma fibrinogen levels was related to the magnitude of the inflammation. Hence a reduction of elevated levels may be considered as supportive evidence of anti-inflammatory activity. The fibrinogen-lowering action of fenclofenac in arthritic rats is a property shared by other non-steroidal anti-inflammatory agents [18].

Relative potency estimations undertaken in arthritic rats show that fenclofenac is approximately equipotent to alclofenac, fenoprofen calcium and phenylbutazone, more potent than acetylsalicylic acid and ibuprofen, but less potent than diclofenac sodium, indomethacin, ketoprofen and naproxen. In contrast, the potency of fenclofenac in an acute anti-inflammatory test is lower. Thus in the carrageenin-induced paw oedema test, fenclofenac was found to be equipotent to acetylsalicylic acid but significantly less potent than phenylbutazone, ibuprofen or indomethacin. The reason for this reduced level of activity in an acute anti-inflammatory test situation is not known but it may be a reflection of the drug's mechanism of action in that it may have greater specificity against adjuvant-induced lesions. To date, there are no readily apparent pharmacokinetic or metabolic explanations to account for the observed difference in potency [19]. Indomethacin, likewise, is less active in the carrageenin oedema test but this observation is of unknown significance.

The anti-inflammatory activity of fenclofenac, at least as typified by its anti-carrageenin oedema activity, does not appear to be mediated via the pituitary-adrenal axis, since the drug retains its activity in bilaterally-adrenalectomized animals. The finding that fenclofenac exerts no glucocorticoid effects, as indicated by its inability to increase liver glycogen deposition in rats following both acute and chronic administration, would appear to support this conclusion.

The observation that fenclofenac inhibits carrageenin oedema when injected locally into the hind paw strongly suggests that it does not exert its systemic anti-inflammatory effect via a counter-irritant action. GOLDSTEIN et al. [20], using a carrageenin abscess method in rats, showed that genuine anti-inflammatory agents exert their activity after both systemic and local administration whereas irritants do so only after systemic administration. The differential activity of irritants and anti-inflammatory agents given locally has also been observed using paw oedema models [7, 8, 21]. However, it should be noted that a high local concentration of fenclofenac, unlikely to be achieved following oral administration, was required to produce a local anti-inflammatory effect. This requirement is very probably related to the low water solubility of the drug and its consequently reduced accessibility to the inflamed tissue following local administration.

In common with other acidic non-steroidal anti-inflammatory agents, fenclofenac possesses both antinociceptive and antipyretic properties. However, as in the case of the acute anti-inflammatory activity, the doses required to produce these effects are generally higher than those producing significant anti-arthritic activi-

ty. The failure of fenclofenac to induce hypothermia in normothermic rats at doses higher than those necessary to give an antipyretic effect strongly suggests that the latter effect is not the result of a non-specific hypothermic action.

The most notable feature of the spectrum of activity of fenclofenac is its remarkably low gastric ulcerogenic potential. The acute studies described show that, on a weight-for-weight basis, fenclofenac is clearly the least ulcerogenic of the drugs examined. Even when differences in therapeutic potency are taken into account, fenclofenac is still relatively less ulcerogenic, especially when ulcerogenicity is related to activity in the adjuvant arthritis test. However, this latter comparison is not strictly valid in that an action resulting from chronic administration is being compared with that observed following single doses. Thus the ulcerogenic activity observed following repeated doses of the drugs can be considered to be of greater relevance and it is clear from the results that fenclofenac is less ulcerogenic and toxic than those particular reference drugs examined concurrently. Moreover, gastrointestinal irritation was not detected in rats examined 2 days after receiving a potentially lethal oral dose of fenclofenac, whereas intestinal irritation, in some cases leading to severe ulceration with peritonitis, was detected in rats given potentially lethal doses of all the reference drugs. Whether the low ulcerogenic potential of fenclofenac is related to some intrinsic biological property of the drug or is a reflection of its physico-chemical properties (e.g. low water solubility at gastric pH) is not yet clear, but preliminary investigations in both the rat and guinea-pig would seem to indicate that the latter may be important [22]. The relatively low acute toxicity of fenclofenac observed following oral administration may in part be a reflection of its low gastrointestinal irritant potential.

Acknowledgments

The authors wish to thank Mr D. Green for commenting upon the manuscript; Mrs C. Davies, Miss D. Gregory, Mrs C. Havler and Miss L. Scholey for technical assistance; Mrs G. Shilcock for undertaking the liver glycogen studies; Mr C. Park for measuring the plasma fibrinogen levels; Mr R.L.F. Dawes and Mr J.J. Preece for performing the acute toxicity studies; and Mr R.C. Hoare for statistically evaluating the majority of the results. Gifts of steam-killed tubercle bacilli from the Ministry of Agriculture Veterinary Laboratories, Weybridge, Surrey, and of indomethacin from Merck, Sharp & Dohme Ltd are also gratefully acknowledged.

Received 27 January 1976. Revised 8 March 1976.

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