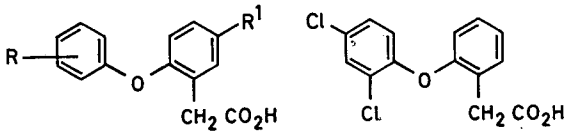
2-(2,4-Dichlorophenoxy) phenylacetic acid (fenclofenac): one of a novel series of anti-inflammatory compounds with low ulcerogenic potential

In a continuing search for anti-inflammatory compounds in these laboratories, we have discovered an interesting spectrum of properties in members of the 2-aryloxy-arylacetic acid series (Godfrey, 1971). The compounds (I) were prepared by the Ullmann reaction between the appropriate 2-chloroacetophenone and phenoxide to give a 2-phenoxyacetophenone, conversion of this into the related acetothiomorpholide by the Willgerodt-Kindler process, and finally hydrolysis to the phenylacetic acid(I).



(I) (II)

In general, using the established rat adjuvant arthritis test, in which dead Mycobacterium 5 mg ml^{-1} in 0·05 ml liquid paraffin was used as adjuvant (Atkinson, 1971), for determining oral activity, the most interesting compounds were those in which R = 2,4-dichloro (optionally with further methyl substitution) or 2-chloro-4-alkyl, and R^1 = hydrogen or methyl. The parent compound, 2-phenoxyphenylacetic acid, was inactive in this test at doses up to 75 mg kg^{-1}. From a large number of compounds in this series, 2-(2,4-dichlorophenoxy) phenylacetic acid, RX67408, fenclofenac(II), was selected for study in depth.

Fenclofenac has substantial activity in the established adjuvant arthritis test in rats, statistically significant effects being generally associated with single daily oral doses in the range 3–10 mg kg^{-1}. It is about 8 times as potent as ibuprofen [2-(4-isobutylphenyl) propionic acid] in this test (see Table 1 which gives data obtained in a single test for fenclofenac and 3 standard drugs). However, fenclofenac is much less active in acute tests for anti-inflammatory activity. For instance, in the carrageenan rat paw oedema test (Winter, Risley & Nuss, 1962), it has only about one-twentieth the potency of ibuprofen, significant activity being associated with oral doses of 25–60 mg kg^{-1}. The anti-inflammatory activity of fenclofenac is not mediated via the pituitary-adrenal axis, since its activity in the rat paw oedema test was not affected by adrenalectomy, and absence of glucocorticoid effects was demonstrated by its inability to increase liver glycogen deposition in both mice and rats.

Fenclofenac produces much less gastric ulceration in female rats than the standard anti-inflammatory drugs that we have examined, both on acute and chronic administration. The acute oral minimum ulcerogenic dose (see Table 1) in the rats was in the range 200–800 mg kg^{-1}, which is very high compared with doses that were effective against adjuvant arthritis. In chronic tests, 7 daily oral doses of up to 120 times the minimum effective dose (MED—3 mg kg^{-1}, see Table 1) of fenclofenac failed to produce any statistically significant damage, while phenylbutazone at an equivalent dose produced highly significant ulceration. Indomethacin produced no gastric ulceration at 30 times its MED, but 100% mortality when this dose was doubled. Ibuprofen produced highly significant ulceration at only 10 times its MED.

Fenclofenac is also active in antipyretic tests in rats and in tests for analgesic activity, e.g. the mouse anti-writhing test (Hendershot & Forsaith, 1959). In these tests, as in

acute anti-inflammatory tests, fenclofenac was active only at doses appreciably greater than those found effective against adjuvant arthritis.

Table 1. *Anti-inflammatory and other properties of fenclofenac and standard anti-inflammatory drugs.*

	Fenclofenac	Phenyl-butazone	Ibuprofen	Indo-methacin
Relative potency (Rat adjuvant arthritis)	1	0·62 (0·24–1·6)*	0·12 (0·05–0·29)	25 (12·5–50)
MED** (mg kg^{-1}) (Rat adjuvant arthritis)	3	2·2	24	0·19
Minimum ulcerogenic dose† (mg kg^{-1}) (Rat acute gastric ulceration)	200–800	38–75	6–13	2·5–5·0
Acute 7-day LD50 (mg kg^{-1}) (Rat)	2280 (1716–3029)*	472 (428–522)	856 (697–1051)	19·8 (12·6–31·1)

* 95% confidence limits.

** MED = minimum effective dose, i.e. minimum daily oral dose that produced a paw volume change significantly different ($P < 0.05$) from that of undosed controls.

† Minimum single oral dose that produced a gastric ulceration score significantly different ($P < 0.05$) from that of undosed controls. The method of assessing gastric ulceration was based on that of Martindale, Somers & Wilson (1960).

The acute oral LD50 of fenclofenac in male rats was higher than that of the standard drugs examined (Table 1). When rats were killed and examined 2 days after the oral administration of a single toxic dose of fenclofenac (2·8 g kg^{-1}), there was kidney damage but no evidence of gastrointestinal irritation. In contrast, when single toxic doses of the standard drugs were administered orally and the rats were examined 1, 2 or 3 days later (depending on the drug), intestinal irritation was observed in all cases, leading to severe ulceration with peritonitis in the case of indomethacin and phenylbutazone. Some kidney and liver damage was also found in phenylbutazone-treated animals.

The concentration of fenclofenac in body fluids was estimated by gas-liquid chromatography of the methyl ester using a suitable internal standard and electron capture detection. Peak whole blood levels of fenclofenac after a single oral dose of 10 mg kg^{-1} were usually in the range 10–15 μg g^{-1} for dogs and baboons and 5–10 μg g^{-1} for rats. The MED (adjuvant arthritis) in rats was therefore associated with whole blood levels in the range 1·5–10 μg g^{-1}. Half-lives, estimated from intravenous studies, were about 6, 13 and 8 h for dogs, baboons and rats, respectively. Whole blood levels in healthy volunteers were similar to those found in animals given a much higher dose so that single oral doses of 100 mg (approx. 1·3 mg kg^{-1}) gave peak whole blood levels of about 5 μg g^{-1}, the half-life being about 12 h. As expected, higher blood levels occurred with 3 × 100 mg doses given at intervals of 12 h; peak levels were about 10 μg g^{-1}, values that approached those found after a single oral dose of 200 mg (approx. 12 μg g^{-1}).

Fenclofenac therefore has an unusual spectrum of properties in animal tests. The combination of much greater activity in the adjuvant arthritis test than in acute anti-inflammatory tests, a low level of gastrointestinal irritancy and a long half-life in man suggests that fenclofenac may be an improvement on existing drugs for treating human rheumatic diseases. Clinical trials are now in progress.

Pharmaceutical Research Laboratories,
Reckitt & Colman Pharmaceutical Division,
Dansom Lane, Hull HU8 7DS, U.K.

D. C. ATKINSON
K. E. GODFREY
B. J. JORDAN
E. C. LEACH
B. MEEK
J. D. NICHOLS
J. F. SAVILLE

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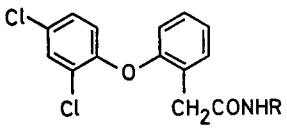
Taurine conjugation of fenclofenac in the dog

Taurine conjugation of bile acids has long been known but it is only recently that conjugation of drugs with this amino-acid has been reported. Quinaldic acid has been shown to be excreted as quinaldylglycyltaurine in the cat (Kaihara & Price, 1961) and James, Smith & Williams (1972a) showed that phenacetyltaurine was present in the urine of a variety of species after dosing with phenylacetic acid, though usually as a minor metabolite in the presence of larger quantities of glycine or glutamine conjugates. James, Smith & others (1972b) suggested that unidentified metabolites found in the urine of several species when dosed with 4-chloro- or 4-nitrophenylacetic acids might be taurine conjugates. Osiyemi & Smith (1972) found a similar pattern of metabolism for indolylacetic acid and suggested that taurine conjugation might be an important metabolic reaction of arylacetic acids in certain species. Case (1973) presented nmr evidence for the conjugation of a substituted propionic acid with taurine though details of the species and structure of the drug were not disclosed. The interest in this route of metabolism prompted us to report our findings on the metabolism, in dog, of fenclofenac, a novel anti-inflammatory agent (Atkinson, Godfrey & others, 1974)*.

Fenclofenac [2-(2,4-dichlorophenoxy)phenylacetic acid] was labelled with tritium in the methylene group of the acetic acid side-chain. Male beagle dogs (4 animals; 10–16 kg) were dosed orally with fenclofenac (10 mg kg^{-1}). Urine and faeces were collected for 3 or 7 days. Analysis for radioactivity showed that the drug was excreted almost equally in urine and faeces. Metabolite identification was performed on samples excreted in the first 24 h after dosing. The taurine, glycine and glutamine conjugates of fenclofenac, which were synthesized by reaction of the arylacetic acid chloride with the sodium salts of the amino-acids, were used as standards for chromatography.



I

Spectral and analytical properties

Fenclofenac taurine conjugate (I; R = $CH_2CH_2SO_3Na$). Found: C, 44·8; H, 3·3; N, 3·0%. $C_{16}H_{14}Cl_2NNaO_5S$ requires C, 45·1; H, 3·3; N, 3·3%. M.p. sodium salt 190–195°; methyl ester 116°. Ultraviolet (sodium salt in ethanol) $\lambda_{max.}$ (nm) 271, 278, 283 sh, 292 sh. ϵ, 1730, 1720, 1470, 910 respectively. Infrared Nujol mull (sodium salt) (cm^{-1}) 3400 broad, 3325 sharp:— bonded and non-bonded –NH. 1635:— > C=O. 1210, 1060, 1050:— $-SO_3$ Na. No absorbtion in the 1650–1800 cm^{-1} region. Nmr (in D_2O, sodium salt) δ 2·81 complex t ($J \approx 6$) 2H $-CH_2SO_3^{\ominus}$,

* Full details of the metabolic studies carried out on fenclofenac will be reported elsewhere.