Br. J. Pharmac. (1969), **35**, 487–497.

The pharmacology of fenclozic acid (2-(4-chlorophenyl)-thiazol-4-ylacetic acid; I.C.I. 54,450; 'Myalex'); a new compound with anti-inflammatory, analgesic and antipyretic activity

B. B. NEWBOULD

Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire.

1. Fenclozic acid (2-(4-chlorophenyl)thiazol-4-ylacetic acid; I.C.I. 54,450; "Myalex") is one representative of a new class of compounds with anti-inflammatory, analgesic and antipyretic properties as evidenced by its activity in a variety of tests in rats, mice and guinea-pigs.

2. In tests of short duration the potency of fenclozic acid is similar to that of phenylbutazone.

3. In tests of longer duration fenclozic acid is more potent than phenylbutazone.

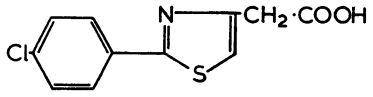
4. The activity of fenclozic acid is not mediated by stimulation of the adrenals and the compound is devoid of corticosteroid-like activity.

During the past seven years we have been using an experimental syndrome known as adjuvant-induced arthritis in rats for the detection and evaluation of compounds which may be of value in the treatment of rheumatoid arthritis in man (Newbould, 1963). This syndrome, produced by an injection of a fine suspension of dead tubercle bacilli in liquid paraffin (adjuvant) into one hind foot pad, is characterized by the development of an inflamed "primary" lesion at the site of injection, a secondary swelling of the injected foot which starts about day 8 after injection and reaches its maximum size on day 14 and the appearance, approximately 10 days after injection, of inflamed "secondary" lesions in areas of the body remote from the injection site (Stoerk, Bielinski & Budzilovich, 1954; Pearson, 1956, 1959; Houssay & Frangione, 1961; Ward & Jones, 1962).

Recently, two compounds with different types of activity have been detected in our laboratories using this experimental model and reported in the literature. The first compound 2-butoxycarbonyl-methylene-4-oxothiazolidine, I.C.I. 43,823 (Clarkson, Hull & Newbould, 1962), was devoid of anti-inflammatory and cytotoxic activity, but prevented completely the development of "secondary" inflamed lesions in areas of the body remote from the injection site (Newbould, 1965). The mode of action of this compound is not yet understood. The second compound 3-acetyl-5-

(4-fluorobenzylidene)-4-hydroxy-2-oxo-2: 5-dihydrothiophen, I.C.I. 47,776 (O'Mant, 1964), exhibited a similar pattern of activity to I.C.I. 43,823 on adjuvant-induced arthritis in rats, but in contrast to the latter compound, I.C.I. 47,776 was shown to have cytotoxic and immunosuppressive activity (Franklin, Newbould, O'Mant, Scott, Stacey & Davies, 1966; Davies 1968).

The object of this report is to describe the biological properties of fenclozic acid (2-(4-chlorophenyl)thiazol-4-ylacetic acid (I), I.C.I. 54,450; "Myalex"*) (Hepworth, Newbould, Platt & Stacey, 1969; Hepworth & Stacey, 1966; Foulkes, 1968, 1969) which is one representative of a third class of compounds which has been detected in the adjuvant-induced arthritis test in rats and evaluated on this and other experimental models.



(I)

In contrast to the two compounds mentioned previously, fenclozic acid has been shown to possess anti-inflammatory, analgesic and antipyretic activity as shown by its effects on a variety of tests in rats, mice and guinea-pigs.

Methods

Animals

Rats. Male specific pathogen-free albino rats, Alderley Park strain I, were used. They belonged to a colony-bred strain of rats of Wistar origin, and weighed approximately 200 g. In experiments involving adrenalectomized rats, the animals were anaesthetized with ether and the adrenals removed through a single dorsal midline skin incision, at the level of the kidneys.

Mice. Male and female specific pathogen-free mice of the Alderley Park strain I were used.

Guinea-pigs. Male and female specific pathogen-free albino animals of the Alderley Park strain I were used.

Compounds

These were administered by stomach tube as ball-milled suspensions in a dispersing agent containing (per 1.): Lissapol NX 1 ml., Lissapol C 1g and Dispersol O.G. 30% 3.3 ml. (each from I.C.I.) adjusted to pH 7.

Adjuvant-induced arthritis (developing)

The arthritic syndrome was induced by an intradermal injection of 0.05 ml. of a fine suspension of dead tubercle bacilli in liquid paraffin B.P. (concentration 5 mg/ml.) through a No. 20 needle into the plantar surface of the right hind-foot. The tubercle bacilli were derived from human strains PN, DT and C which were grown for 8 weeks, killed by steam and dried in a vacuum oven. In routine tests for chemotherapeutic activity, groups of three rats were weighed and dosed by stomach tube with the compounds to be investigated, one untreated control group being included for every five groups treated. One day later, the thickness of the

* Trade Mark. The property of Imperial Chemical Industries Limited.

right hind-foot was measured with a micrometer and injected with adjuvant. Daily treatment was continued until day 13 after injection, when the weight of each rat was again recorded, the severity of secondary lesions assessed as nil, mild, moderate, moderately severe or severe and the thickness of the injected foot measured, to enable the percentage inhibition of the increase in thickness of the injected foot to be calculated. For more detailed evaluation the swellings in the hind-feet were measured with a micrometer at frequent intervals.

Adjuvant-induced arthritis (established)

Rats were injected with a fine suspension of dead tubercle bacilli in liquid paraffin B.P. as described in the preceding section. They were left untreated until day 14 after injection when secondary lesions were well developed. The thickness of both hind feet was then measured with a micrometer and treatment by stomach tube commenced. The effects of treatment were assessed by measurements of the thickness of both hind feet at frequent intervals and by recording the change in body weight. The experiments were terminated on day 28 after injection—that is, after 14 days of treatment.

Carrageenin oedema in rats

The method used was that described by Winter, Risley & Nuss (1962). Groups of four rats were dosed by stomach tube with the compounds under test. Three hours later, their right hind foot-pads were injected with a solution of carrageenin; 0.1 ml. of a 1% solution in saline, batch R.E.X. 5311 obtained from Marine Colloids Inc. and the thickness of the injected foot was measured with a micrometer. Three hours after injection the thickness of the injected foot was again measured and the percentage inhibition of the increase in thickness of the injected foot calculated.

Adjuvant-induced inflammation in mice

Groups of ten mice were injected into the right hind foot-pad with 0.05 ml. of a fine suspension of dead tubercle bacilli in liquid paraffin (concentration 5 mg/ml.). Treatment by stomach tube, with compounds under test, was commenced the day before injection and continued daily until day 14. On day 14 the thickness of the injected foot was measured with a micrometer, the mice killed with chloroform and the injected feet amputated and weighed. The percentage inhibition of the increase in thickness of the injected foot and the increase in weight of the injected foot was calculated.

Ultraviolet light erythema in guinea-pigs

The method used was similar to that described by Winder, Wax, Burr, Been & Rosiere (1958). The flanks of guinea-pigs were shaved and depilated the day before the skin was exposed to ultraviolet irradiation. To irradiate the animals a special adapter was fitted to a " Hanovia " Kromayer lamp, model 10, so that three circles of skin each 11 mm in diameter could be irradiated at the same time. The skin was irradiated for 1 min. The order of exposure and subsequent assessment was determined randomly. Two hours after exposure, the degree of erythema for each of the three sites was assessed according to the following scoring system: 0=no erythema; 0.5=incomplete circle of erythema; 1.0=complete circle of erythema. Thus

the maximum score for each animal was 3.0. Animals with a total score of 1.5 or less were considered to be protected. For a given dose of compound half the total amount was given by stomach tube 1 hr before exposure and the remainder immediately after exposure. Each group contained four guinea-pigs.

Mouse squirm test

The method used was that described by Whittle (1964). Briefly, mice weighing approximately 20 g were given test compounds by mouth. One hour later 1 mg of acetic acid was injected intraperitoneally as 0.4 ml. of a 0.25% (v/v) solution. Each group consisted of twelve mice which were placed in a twelve-compartment acrylic observation box and the number of squirms for each animal was recorded on a twelve unit tally counter during a period of 15 min. Results were expressed as the percentage reduction in the number of squirms.

Antipyretic activity

Male rats weighing approximately 200 g were kept in a constant temperature room at 25°C for 24 hr before and for 6 hr during the test. The rats were dosed by stomach tube with a suspension of the compound under test and immediately after dosing they were injected intravenously with 0.2 ml. of a 1:10 dilution of Pertussis vaccine, B.P. (Burroughs Wellcome & Co. Ltd.). The temperature of the rats was measured before and at intervals after injection with an oral probe connected to an electrical thermometer.

Results

Adjuvant-induced arthritis in rats (developing)

The type of activity exhibited by fenclozic acid in the adjuvant-induced arthritis test was similar to that produced by the non-steroidal anti-inflammatory compound phenylbutazone (Fig. 1). The anti-inflammatory activity of both compounds was apparent as early as 1 day after injection and by day 3, phenylbutazone (80 mg/kg) and fenclozic acid (20 mg/kg) had produced respectively 45 and 41% inhibition of the increase in thickness of the injected foot. Thereafter, the inhibitory effect was maintained until the experiment was terminated on day 14. At the day 14 assessment phenylbutazone and fenclozic acid gave respectively 45 and 53% inhibition of

Group	Dose (mg/kg)	Assessment: % Inhibition Day 3	Assessment: % Inhibition Day 14	Wt change (g) 0–14 days
Control				+9
Phenylbutazone	80	45	45	+24
Fenclozic acid	20	41	53	+16

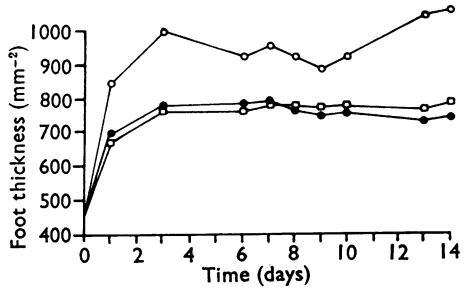


FIG. 1. Effects of fenclozic acid (20 mg/kg by mouth daily) and phenylbutazone (80 mg/kg by mouth daily), on adjuvant-induced arthritis in rats. Each point represents the mean obtained from five rats. Adjuvant injected day 0. ○——○, Controls; ●——●, phenylbutazone; □——□, fenclozic acid.

the increase in thickness of the injected foot. The beneficial effects of treatment with phenylbutazone and fenclozic acid were associated with a gain in body weight which was greater than that noted in control animals. The effects of graded doses of fenclozic acid and phenylbutazone on adjuvant-induced arthritis are shown in Fig. 2 Fenclozic acid was more potent than phenylbutazone at all dose levels. The anti-inflammatory activity of fenclozic acid was not influenced by adrenalectomy or sham-adrenalectomy (Table 1).

Adjuvant-induced arthritis in rats (established)

The injected and non-injected feet of arthritic rats treated with fenclozic acid showed a dose-dependent decrease in foot thickness (Figs. 3a and b). In contrast, the hind foot of untreated control rats increased in size from day 14 after injection

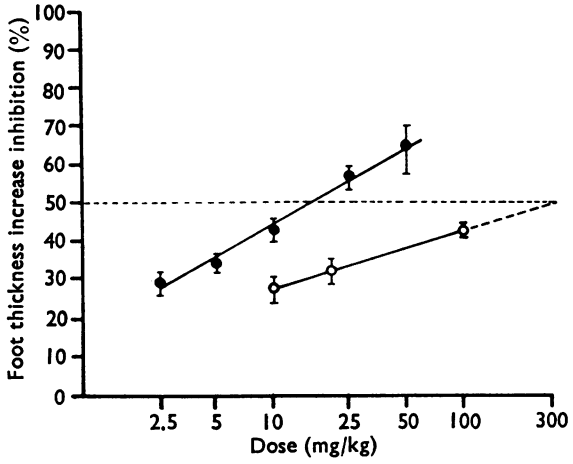


FIG. 2. Effects of graded doses of fenclozic acid and phenylbutazone on the increase in thickness of the injected foot of rats with adjuvant-induced arthritis. Assessment, day 13 after injection. Compounds dosed daily by mouth starting 1 day before the injection of adjuvant into the foot pad. ●——●, Fenclozic acid; ○——○, phenylbutazone. Means ± S.E.

TABLE 1. *The activity of fenclozic acid in adrenalectomized rats with adjuvant-induced arthritis*

Group	Mean % inhibition of the increase in thickness of the injected foot		Mean change in body weight (g)	
	Day 3	Day 14	Day 3	Day 14
Adrenalectomy+DOCA	0	0	0	−5
Adrenalectomy+DOCA+I.C.I. 54,450 20 mg/kg by mouth daily	34	42	+1	+6
Sham adrenalectomy+DOCA	0	0	−1	−4
Sham adrenalectomy+DOCA+I.C.I. 54,450 20 mg/kg by mouth daily	39	48	0	+4
Normal+DOCA	0	0	0	−5
Normal+DOCA+I.C.I. 54,450 20 mg/kg by mouth daily	31	50	+2	+4
Normal	0	0	−1	−6
I.C.I. 54,450 20 mg/kg by mouth daily	34	51	+5	+7

Adrenalectomized rats were maintained on deoxycorticosterone acetate (DOCA) 1 mg/kg daily by subcutaneous injection. Sham adrenalectomized rats were subjected to the same operative procedure as that used to remove the adrenals but the adrenals were left intact. Each group contained six rats.

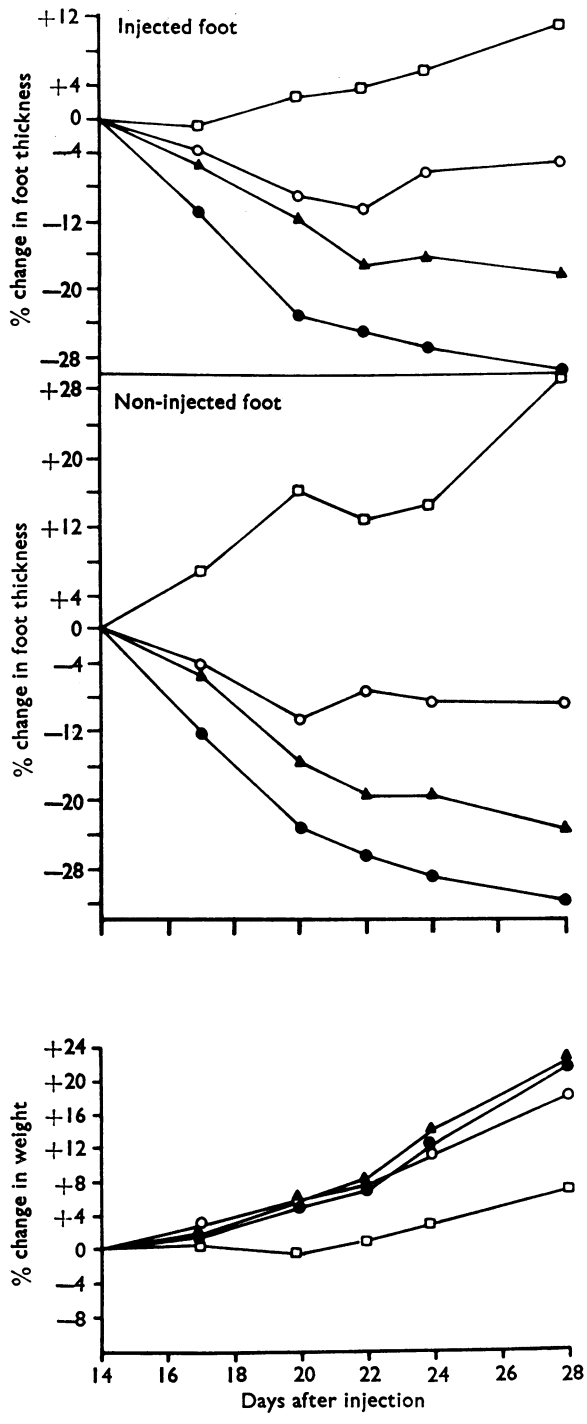


FIG. 3. Changes in the foot-thickness and weight of rats with established adjuvant-induced arthritis during treatment with fenclozic acid (5, 15 and 45 mg/kg by mouth daily). □—□, Controls; ○—○, 5 mg/kg; ▲—▲, 15 mg/kg; ●—●, 45 mg/kg.

to day 28. The beneficial effects of treatment with fenclozic acid were reflected in an improved weight gain compared with that observed in the untreated control group (Fig. 3c). Phenylbutazone (15 mg/kg or higher) was also an effective treatment.

Carrageenin oedema in rats

Fenclozic acid and phenylbutazone gave a dose-dependent reduction in the swelling produced by the injection of carrageenin into the foot pad of rats (Fig. 4). There was no difference in the potencies of the two compounds.

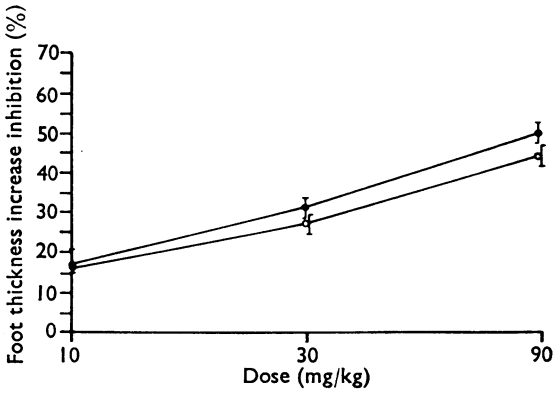


FIG. 4. Effects of graded doses of fenclozic acid and phenylbutazone on carrageenin oedema in rats. ●——●, Fenclozic acid; ○——○, phenylbutazone. Means ± S.E.

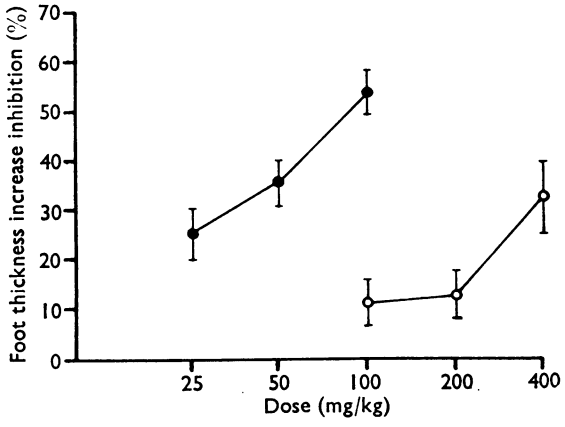


FIG. 5. Inhibition by fenclozic acid and phenylbutazone of the increase in foot-thickness of mice with adjuvant-induced inflammation. Assessment day 14 after injection. Compounds dosed daily by mouth starting 1 day before the injection of adjuvant into the foot-pad. ●——●, Fenclozic acid; ○——○, phenylbutazone. Means ± S.E.

TABLE 2. *Inhibition of ultraviolet light erythema in guinea-pigs with fenclozic acid*

Dose mg/kg by mouth	Number protected / Number tested	% protection
1·0	7/20	35
2·5	14/32	44
5·0	25/43	58
7·5	11/16	69
10·0	17/19	89
20·0	4/4	100
Untreated control	12/62	19

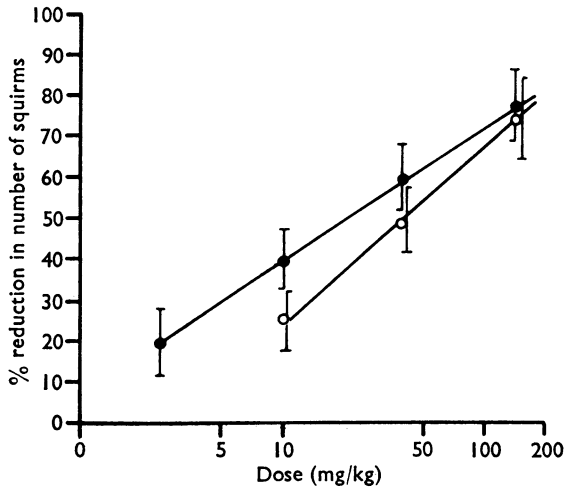


FIG. 6. Effects of graded doses of fenclozic acid and phenylbutazone on the mouse squirming syndrome. ●——●, Fenclozic acid ; ○——○, phenylbutazone. Means ± S.E.

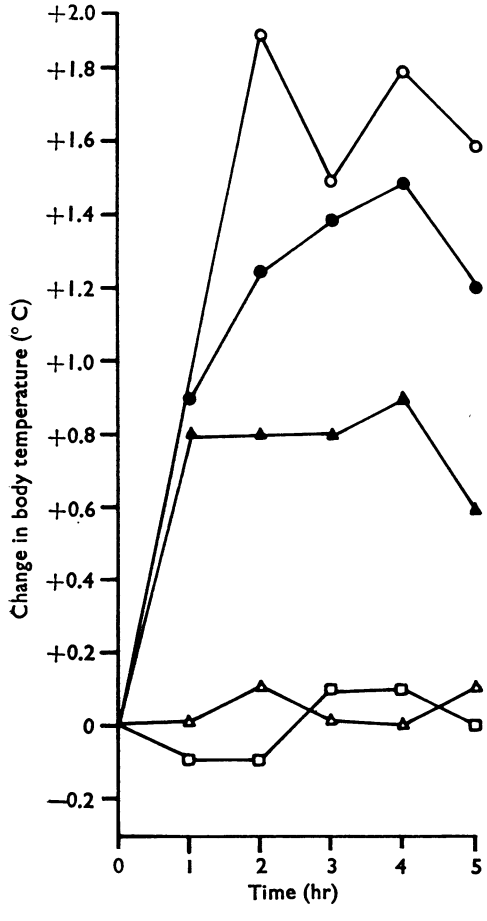


FIG. 7. Inhibition by fenclozic acid of the pyresis induced in rats by the intravenous injection of Pertussis vaccine B.P. ○——○, Pyrogen-injected controls ; ●——●, fenclozic acid 25 mg/kg ; ▲——▲, fenclozic acid 50 mg/kg ; △——△ fenclozic acid 100 mg/kg ; □——□, normal rats.

Adjuvant-induced inflammation in mice

Daily treatment for 14 days with fenclozic acid (25 to 100 mg/kg) gave a dose-dependent decrease in foot thickness (Fig. 5). Phenylbutazone showed an effect only at the highest dose (400 mg/kg daily).

Ultraviolet light erythema in guinea-pigs

A dose of fenclozic acid 10 mg/kg prevented the development of erythema in seventeen of nineteen guinea-pigs irradiated with ultraviolet light (Table 2). The dose required to protect 50% of guinea-pigs was within the range 2.5–5.0 mg/kg. Phenylbutazone has an ED50 of about 7 mg/kg on this test (Winder *et al.*, 1958).

Mouse squirm test

Fenclozic acid and phenylbutazone reduced the number of squirms exhibited by mice injected with acetic acid into the peritoneal cavity (Fig. 6). The inhibitory effects were dose-dependent and the ED50 of each compound was approximately 25 mg/kg.

Antipyretic activity

A single dose of fenclozic acid 100 mg/kg administered immediately before the injection of pyrogen prevented completely the increase in body temperature. Lower doses of 50 and 25 mg/kg partially suppressed the temperature rise (Fig. 7).

TABLE 3. *Effect of fenclozic acid and cortisone on the survival time of adrenalectomized rats*

Group	Dose	No. of rats per group	No. of rats dead on days 0	4	6	8	12	14
I.C.I. 54,450	20 mg/kg per day by mouth	12	0	3	3	6	9	9*
Cortisone	5 mg/kg per day s.c.	5	0	0	0	0	0	0
Cortisone	1 mg/kg per day s.c.	6	0	1	1	1	1	1
Distilled water	3 ml./kg per day	12	0	0	0	5	8	9*
Normal rats	—	12	0	0	0	0	0	0

* Two of the three survivors in each of these two groups had remnants of adrenal tissue present at post-mortem.

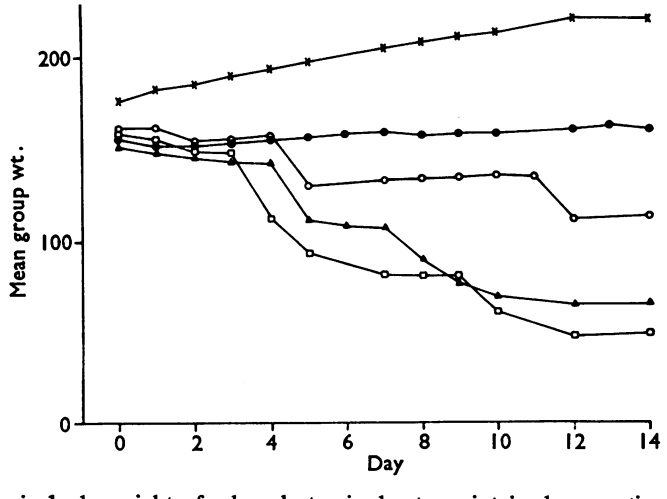


FIG. 8. Change in body weight of adrenalectomized rats maintained on cortisone or fenclozic acid. ×——×, Normal; ○——○, cortisone 1 mg/kg per day subcutaneously; ●——●, cortisone 5 mg/kg per day subcutaneously; ▲——▲, distilled water 5 ml./kg per day by mouth; ■——■, fenclozic acid 20 mg/kg per day by mouth.

Studies in adrenalectomized rats

Daily treatment with fenclozic acid did not prolong the survival time of adrenalectomized rats (Table 3), nor did the compound influence favourably the rate of change of body weight (Fig. 8). In contrast, treatment with cortisone 5 mg/kg per day subcutaneously enabled all the animals to survive.

Discussion

These results show that fenclozic acid has anti-inflammatory analgesic and antipyretic properties as shown by its activity in a variety of tests in rats, mice and guinea-pigs.

In tests of short duration, such as carrageenin oedema in rats, the potency of fenclozic acid was similar to that of phenylbutazone. In tests of longer duration, however, such as adjuvant-induced arthritis in rats or adjuvant-induced inflammation in mice, fenclozic acid was considerably more potent than phenylbutazone. The superiority of fenclozic acid over phenylbutazone in tests of long duration may be primarily accounted for by the difference in persistence of the two compounds in the serum. Thus fenclozic acid has a half-life in the serum of rats of about 30 hr (Platt, 1968) while phenylbutazone has a half-life of only about 6 hr in this species, (Burns, Rose, Chenkin, Goldman, Schubert & Brodie, 1953).

While these studies were in progress, Grame, Fabry & Sigg (1966) reported that phenylbutazone 200 mg/kg gave 50% inhibition of the increases in thickness of the feet of mice injected with adjuvant. In contrast, oxyphenbutazone had no effect on this experimental model. For reasons not yet known we have been unable to confirm the former observation.

Not only was fenclozic acid of benefit in the treatment of "developing" inflamed lesions in rats, guinea-pigs and mice, it was also of value in reducing the inflammation associated with fully developed lesions as evidenced by its activity in the "established" rat arthritis test. Daily treatment with doses as low as 5 mg/kg resulted in a rapid reduction in the thickness of both hind feet and the general beneficial effects were reflected in an improved weight gain compared with controls.

Many compounds with anti-inflammatory and analgesic properties also have antipyretic activity. Fenclozic acid is no exception, as shown by its ability to reduce the pyrexia produced in rats by the intravenous injection of a bacterial pyrogen.

The mode of action of fenclozic acid is not yet understood. It is clear from the studies in adrenalectomized arthritic rats, however, that activity is not mediated by stimulation of the adrenals. Furthermore, the inability of the compound to maintain life in adrenalectomized rats shows that it is devoid of corticosteroid-like activity.

Toxicity studies showed that rats would tolerate for 3 months a daily oral dose of 50 mg/kg without exhibiting clinical, biochemical or histological signs of toxicity (Alcock, Baker & Platt, unpublished). Some rats dosed with 80 mg/kg daily died from peptic ulceration but, when the dose was reduced to 70 mg/kg no other animals died. At the termination of the experiment none of the surviving animals had ulcers or any other abnormalities. Thus rats were able to tolerate for 3 months daily oral doses in excess of ten times the minimal effective dose in the rat arthritis test.

One feature which has been of value in the development of fenclozic acid is the ease with which the concentration of the compound can be estimated in body fluids.

Correlation of the biological activity of fenclozic acid in laboratory animals with serum levels showed that significant anti-inflammatory activity was associated with a serum level of about 50 μg/ml. (Platt, 1968). We believe that correlation of serum levels with activity may be of more value in the extrapolation of animal data to humans than are calculations of potency ratios of unknown and novel compounds. The latter type of calculation seems to have been of little predictive value, for example, in the development of indomethacin (Winter, Risley & Nuss, 1963; O'Brien 1968).

I wish to thank Mr. G. E. Davies and Mr. P. L. Finney for examining the effects of fenclozic acid on ultraviolet erythema in guinea-pigs and Dr. O. L. Davies for the statistical analysis. I also wish to express my sincere gratitude to Mrs. R. Bradbury, Miss R. van Heteren, Miss S. Warrington and Mr. R. A. Siddall for their expert technical assistance. The phenylbutazone was kindly supplied by Geigy (U.K.) Limited, Pharmaceuticals Division.

REFERENCES

BURNS, J. J., ROSE, R. K., CHENKIN, T., GOLDMAN, A., SCHUBERT, A. & BRODIE, B. B. (1953). The physiological disposition of phenylbutazone (Butazolidin) in man and a method for its estimation in biological material. *J. Pharmac. exp. Ther.*, **109**, 346–357.

CLARKSON, R., HULL, R. & NEWBOULD, B. B. (1962). United Kingdom Patent No. 971,176.

DAVIES, G. E. (1968). Immunosuppressive activity of 3-acetyl-5-(4-fluorobenzylidene)-4-hydroxy-2-oxo-2 : 5-dihydrothiophen (I.C.I. 47,776). *Immunology*, **14**, 393–399.

FOULKES, D. M. (1968). The metabolism of 14C I.C.I. 54,450 (MYALEX^{R}) in various species; an *in vivo* NIH shift. *J. Pharmac. exp. Ther.*, submitted for publication.

FOULKES, D. M. (1969). Metabolism of thiazole acetic acid derivatives and the NIH shift. *Nature, Lond.*, **221**, 582.

FRANKLIN, T. J., NEWBOULD, B. B., O'MANT, D. M., SCOTT, A. I., STACEY, G. J. & DAVIES, G. E. (1966). New type of cytotoxic immunosuppressive agent: 3-acetyl-5-(4-fluorobenzylidene) 4-hydroxy-2-oxo-2 : 5-dihydrothiophen. *Nature, Lond,*, **210**, 638–639.

GRAEME, M. L., FABRY, E. & SIGG, B. B. (1966). Mycobacterial adjuvant periarthritis in rodents and its modification by anti-inflammatory agent. *J. Pharmac. exp. Ther.*, **153**, 373–380.

HEPWORTH, W. & STACEY, G. J. (1966). United Kingdom Patent No. 1,099,389.

HEPWORTH, W., NEWBOULD, B. B., PLATT, D. S. & STACEY, G. J. (1969). 2-(4-chlorophenyl)thiazol-4-ylacetic acid ('Myalex'): A new compound with anti-inflammatory, analgesic and anti-pyretic activity. *Nature, Lond.*, **221**, 582–583.

HOUSSAY, R. H. & FRANGIONE, B. (1961). On the pathogenesis of the arthropathy induced with Freund's adjuvant. In *Atti Del X Congresso della Lega Internazionale Contro il Reumatism*, vol. 2, p. 950. Turin: Tipografia Edizioni Minerva Medica.

NEWBOULD, B. B. (1963). Chemotherapy of arthritis induced in rats by mycobacterial adjuvant. *Br. J. Pharmac. Chemother.*, **21**, 127–136.

NEWBOULD, B. B. (1965). Suppression of adjuvant-induced arthritis in rats with 2-butoxycarbonylmethylene-4-oxo-thiazolidine. *Br. J. Pharmac. Chemother.*, **24**, 632–640.

O'BRIEN, W. M. (1968). Indomethacin: A survey of clinical trials. *Clin. Pharmac. Ther.*, **9**, 94.

O'MANT, D. M. (1964). United Kingdom Patent No. 1,058,243.

PEARSON, C. M. (1956). Development of arthritis, periarthritis and periostitis in rats given adjuvants. *Proc. Soc. exp. Biol., N.Y.*, **91**, 95–101.

PEARSON, C. M. (1959). Development of arthritis in the rat following injection with adjuvant. In *Mechanisms of Hypersensitivity*, ed. Shaffer, J. H., Lo Grippo, G. A. & Chase, M. W., pp. 647–671. Boston: Little, Brown & Co.

PLATT, D. S. (1968). The pharmacokinetics in laboratory animals of I.C.I. 54,450, a new anti-inflammatory agent. *J. Pharmac. exp. Ther.*, submitted for publication.

STOERK, H. C., BIELENSKI, T. C. & BUDZILOVICH, T. (1954). Chronic polyarthritis in rats injected with spleen adjuvant. *Am. J. Path.*, **30**, 616.

WARD, J. R. & JONES, R. S. (1962). The role of adjuvant composition and its route of administration in the production of rat polyarthritis. *Arthritis Rheum.*, **5**, 125–126.

WHITTLE, B. A. (1964). The use of change in capillary permeability in mice to distinguish between narcotic and non-narcotic analgesics. *Br. J. Pharmac. Chemother.*, **22**, 246–253.

WINDER, C. V., WAX, J., BURR, V., BEEN, M. & ROSIERE, C. E. (1958). A study of pharmacological influences on ultra-violet erythema in guinea-pigs. *Archs int. Pharmacodyn. Thér.*, **116**, 261–292.

WINTER, C. A., RISLEY, E. A. & NUSS, G. W. (1962). Carrageenin-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. *Proc. Soc. exp. Biol., N.Y.*, **111**, 544–547.

WINTER, C. A., RISLEY, E. A. & NUSS, G. W. (1963). Anti-inflammatory and anti-pyretic activities of indomethacin, 1-(*p*-chloro-benzoyl)-5-methoxy-2-methylindole-3-acetic acid. *J. Pharmac. exp. Ther.*, **141**, 369–376.

(*Received November* 5, 1968)