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Nabumetone (BRL 14777, 4-[6-methoxy-2-naphthyl]-butan-2-one): a new anti-inflammatory agent

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Nabumetone is a compound of novel structure which displays acute anti-inflammatory activity in the carrageenan-induced oedema model in rats and the ultraviolet-induced erythema model in guinea-pigs. Its activity in these tests is greater than that of aspirin but less than that of naproxen and indomethacin. In the cotton pellet-induced granuloma model in the rat, the compound is active and produces no signs of toxicity at doses much greater than the lowest effective dose, unlike aspirin, naproxen or indomethacin. Nabumetone is also active in the adjuvant-induced arthritis test in rats. In contrast to aspirin, indomethacin and naproxen, the compound is well tolerated by the stomach of fasted rats at doses in excess of those with anti-inflammatory activity. These findings could be linked to the relatively poor ability of nabumetone to inhibit the synthesis of prostaglandins in vitro and to its non-acidic structure. The compound has greater mild analgesic activity than paracetamol, is equi-active with phenylbutazone, but less active than aspirin, naproxen and indomethacin. Nabumetone also has antipyretic activity in the rabbit. No interactions with the hypothalamic–pituitary–adrenal axis have been found.

The aryl acetic and aryl propionic acid derivatives introduced in the past few years for the treatment of inflammatory conditions, although undoubtedly useful clinically are not free from undesirable side effects, principally the production of gastrointestinal disturbances (Hart 1976). It has been said (Cuthbert 1974) that the link between activity and irritancy in that group of compounds is so strong that none will be found to be effective and free from gastrointestinal tract toxicity. This unfortunate situation could be related to the physicochemical properties of the drugs and particularly to the presence of a carboxylic acid moiety (Rainsford 1978). The literature suggests a strong correlation between the potency of a non-steroidal anti-inflammatory drug as an inhibitor of prostaglandin synthesis and as an irritant of the gastrointestinal tract (Robert 1974; Gaut et al 1975; Boyle et al 1976; Cashin et al 1977).

Pharmacological evaluation of a series of non-acidic naphthalene derivatives synthesized in these laboratories has shown them to have an interesting spectrum of anti-inflammatory, analgesic and antipyretic properties, and it was suggested that such compounds would be absorbed without causing gastric damage (Goudie et al 1978).

The compound of choice from this series is 4-(6-methoxy-2-naphthyl)-butan-2-one, nabumetone. This paper describes its anti-inflammatory analgesic and antipyretic properties in animals and presents evidence for it being well tolerated by the stomach of rats in contrast to three well-established drugs.

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MATERIALS AND METHODS

Materials

Indomethacin and (+)-naproxen were generous gifts from Merck, Sharp and Dohme Ltd, Hoddesdon, England and Syntex Laboratories Inc., Palo Alto, California, U.S.A. respectively. Aspirin (acetyl salicylic acid BDH Chemicals Ltd, U.K.) phenyl-*p*-quinone (Eastman Kodak Ltd) fentanyl plus fluanisone (Hypnorm, Janssen Pharmaceutica, Belgium) pentobarbitone (Expiral, Abbott Laboratories Ltd, U.K.), diazepam (Valium, Roche Products Ltd, U.K.) and ACTH (ACTHAR, Armour Pharmaceuticals, U.K.) were used. Dental roll was purchased from Claudius Ash, Sons and Co. Ltd, London. [5,6,8,9,11,12,14,15-^{3}H]. Arachidonic acid (specific activity 72 Ci mmol^{-1} New England Nuclear, Boston, U.S.A.) was stored in hexane at −20 °C under nitrogen. All drugs were suspended in 0·7% methyl cellulose (lower substitution) BDH Chemicals U.K. λ-Carrageenan was prepared from a sample of Marine Colloids carrageenan by Mr Verrall, Beecham Pharmaceuticals Research Division,

Brockham Park, U.K. *Mycobacterium butyricum* was from Difco Laboratories, Belmont, U.S.A. and Shigella endotoxin was supplied by the Central Veterinary Laboratories, Weybridge, U.K. Bovine seminal vesicles frozen by Pel-Freez Biological Inc., Rogers, Arkansas, U.S.A. were stored at −20 °C. The silica gel plates were Merck F254, 0·25 mm thickness. Fluorescence measurements were done using a Hitachi Fluorimeter MPF 2A. Scintillation fluid NE260 was from Nuclear Enterprises, Edinburgh, U.K. The plethysmometer used to measure paw volumes was constructed by Mr G. Francis of these laboratories. The light source was a Hanovia Model II lamp, Hanovia Ltd, U.K.

Methods

Acute anti-inflammatory activity

Female Wistar rats (OLAC 150–200 g) were dosed orally before (1 h or longer as indicated) injection of 0·1 ml of 1·5% carrageenan solution subcutaneously into the subplantar tissue of the right hind paw, and 0·1 ml of 0·9% NaCl (saline) into the left hind paw (Winter et al 1962). Inflammation was assessed 3 h after injection as the difference in volume between left and right feet. Values for each group were used to calculate the percentage inhibition caused by each compound as described by Boyle et al (1976).

Bilaterally adrenalectomized rats maintained on a normal diet with 1% glucose/saline for 2 days then saline for a further 5 days before test, were similarly treated. Lack of adrenal function was ascertained by a depression of body weight on replacing saline with water for 24 h, one day before testing (Winter et al 1968).

The backs of female guinea-pigs (Porcellus 200–250 g) were shaved, depilated (Nair) washed and dried. Test compounds were given by stomach tube, and 1 h later four areas on the back of each animal were exposed to u.v. light for 30 s and erythema at each site was assessed 2 and 24 h later by an observer unaware of treatment schedules who scored 0 for no visible reaction, 3 for maximum erythema, with 1 and 2 for intermediate reactions. A check that all sites gave scores of 2 or 3 after 24 h ensured sensitivity to the exposures.

Gastric damage in the rat

Fasted rat. The method was essentially as described by Boyle et al (1976) compounds being administered orally or subcutaneously to 18 h fasted female Wistar (OLAC) rats. At least three dose levels per compound were used with a minimum of 10 rats per dose. The percentage of rats showing gastric erosions at each dose level was noted and the dose producing damage in half of the animals (ED50) calculated by the method of Litchfield & Wilcoxon (1949).

Pyloric ligated rat. The method was essentially that of Shay et al (1945). Groups of 5–7 male Wistar rats (OLAC) 150–250 g after 18–20 h starvation were anaesthetized with halothane/O_2/N_2O, and the pylorus ligated. Compounds suspended in 0·5% w/v methyl cellulose were dosed intraduodenally and 3 ml saline placed in the peritoneal cavity and the rats allowed to recover. After 4 h the animals were killed, the volume of gastric juice measured and the stomachs scored for microscopic erosions, a score ranging from 1 for an erosion of 5 mm to 4 for an erosion of greater than 15 mm being given.

Chronic anti-inflammatory activity

Rat cotton pellet granuloma test. Female Wistar rats (OLAC) 130–150 g were anaesthetized using Hypnorm (0·1 ml i.m.) and diazepam 0·1 ml (5 mg ml^{-1} i.p.), then two pre-weighed sterile cotton wool pellets were implanted as described by Freeman et al (1979). Drugs were given orally starting on the day of implantation. On day 6 the rats were killed by an injection of pentobarbitone and the pellets plus granuloma were removed, dried overnight at 80 °C and weighed. Comparison of control and test groups were made using Student's group *t*-test and percentage inhibitions calculated.

Adjuvant induced arthritis in the rat. Male Wistar rats (OLAC 180–250 g) were injected with 0·05 ml liquid paraffin suspension of *M. butyricium* (5 mg ml^{-1}) subcutaneously into the subplantar region of the right hind paw (Newbould 1963). Test compounds were given orally from day 0 until day 13. Arthritis was assessed throughout a 28 day period by measurements of oedema in the injected paw, by a subjective scoring system to assess the extent and severity of the polyarthritis and by changes in body weight.

Analgesic and antipyretic activity. Analgesic activity was assessed in mice (male T/O Banting and Kingman 14–26 g 10 per group) using the phenyl-*p*-quinone-induced writhing test. ED50 values were calculated by the method of Litchfield & Wilcoxon (1949).

Antipyretic activity was measured in rabbits (male Dutch Ranch 1·5–2·5 kg) using an intravenous injection of 0·5 μg Shigella endotoxin (0 Somatic antigen) in sterile saline. Changes in body temperature were recorded automatically at 20 min intervals for up to 5 h after endotoxin injection using rectal thermocouples.

Possible interactions with the adrenal-pituitary axis

Acute study. Four groups of 6 rats (Wistar OLAC 150–200 g) were acclimatized for 1 week and housed individually overnight with free access to food and water. The next morning each group received one of the following treatments 45 min before death: 0·7% methylcellulose orally, 5 International Units of ACTH subcutaneously, 140 mg kg^{-1} of nabumetone orally or 15 μg kg^{-1} dexamethasone orally. Blood was withdrawn from the abdominal aorta under ether anaesthesia, the animals were then killed and the adrenals stored at −20 °C. Blood was centrifuged within 2 h of collection and plasma stored at −20 °C.

Chronic study. Nine groups of 5 or 6 rats (Wistar OLAC 150–200 g) were dosed orally for five days with 0·7% methylcellulose, 15 μg kg^{-1} dexamethasone or 140 mg kg^{-1} nabumetone. The animals were housed singly overnight with free access to food and water and on day six a control group from each dosing schedule was anaesthetized and blood withdrawn as above. A further 3 groups were given ACTH (5 International Units) subcutaneously 45 min before blood was withdrawn, and another 3 groups were subjected to 1 min ether stress 30 min before blood was withdrawn. Adrenals were weighed and stored at −20 °C. Plasma and adrenal corticosterone levels were measured by the method of Zenker & Bernstein (1958).

Inhibition of prostaglandin synthesis. Bovine seminal vesicle microsomal (BSVM) pellets were prepared as described by Yoshitomo et al (1970) washed and lyophilized before storage at −20 °C. The powder was reconstituted in 0·2 M Tris-HCl buffer pH 8·0 containing 4% Triton X100 (v/v) to give a protein concentration of approximately 10 mg ml^{-1}. The ability of compounds to inhibit the conversion of [^{3}H]arachidonic acid to PGE_2 by this preparation was determined as described (Boyle et al 1976).

RESULTS

Acute anti-inflammatory activity

Carrageenan-induced oedema in the rat paw. Dose related inhibition of oedema formation was found with nabumetone and the three non-steroidal anti-inflammatory drugs (NSAID's) (Fig. 1). Nabumetone was much more active than aspirin, but less active than naproxen and indomethacin. ID25 values are shown in Table 1. The activity of nabumetone was maintained when adrenalectomized rats were used (Table 2). The duration of action of nabumetone given orally before carrageenan was maintained at up to 6 h with a 70 mg kg^{-1} dose but was less marked at this time with 35 mg kg^{-1}. There was no significant activity at 12 h.

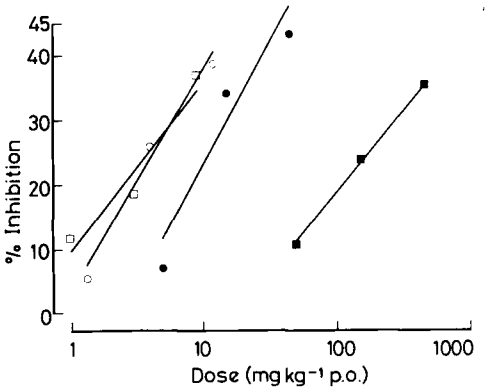

FIG. 1. Inhibition of carrageenan-induced rat paw oedema □ Naproxen. ○ Indomethacin. ● Nabumetone. ■ Aspirin. Each point represents the mean from 8 or more rats. Lines drawn by the method of least squares analysis.

Ultraviolet-induced erythema in the guinea-pig. Dose related inhibition of erythema formation by nabumetone and the three NSAID's was found in this model (Fig. 2). Nabumetone is much more active than aspirin but less active than either naproxen or indomethacin. Table 3 gives ID50 values. Since aspirin-like drugs produce steep dose-response lines with maximum inhibitions of 100% in this test (Adams & Cobb 1963), additive or antagonistic

Table 1. Oral activity of nabumetone, naproxen, indomethacin and aspirin in inhibiting carrageenan-induced oedema in the rat.

Compound	Oral ID25 value mg kg^{-1}	Dose range used to determine ID25 values mg kg^{-1}
Nabumetone	11	5–45
Naproxen	4	1–9
Indomethacin	4	1·33–12
Aspirin	180	50–450

ID25 is the dose calculated to produce a 25% reduction in oedema volume.

Table 2. The effects of nabumetone on carrageenan-induced oedema in adrenalectomized and sham-operated rats.

Treatment	Oral dose mg kg^{-1}	n.	Mean oedema ± s.e.m.	inhibition
Sham operated	—	10	98·5 ± 11·1	
Nabumetone	70	10	***31·0 ± 5·8	69
Nabumetone	35	9	**58·9 ± 5·8	40
Adrenalectomized	—	10	120·7 ± 6·4	
Nabumetone	70	9	***50·2 ± 6·5	58
Nabumetone	35	10	***56·2 ± 6·0	53

*** $P < 0.001$.
** $0.001 < P < 0.01$.
Significances determined by Student's *t*-test.

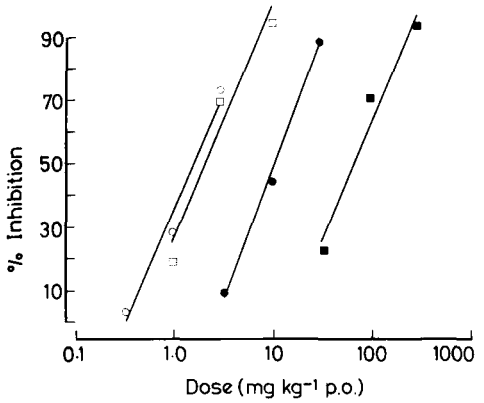

FIG. 2. Inhibition of erythema induced by ultraviolet irradiation of guinea-pig skin. □ Naproxen. ○ Indomethacin. ● Nabumetone. ■ Aspirin. Each point represents the mean of 6 animals. Lines drawn by the method of least squares analysis.

effects were sought using combinations of nabumetone and aspirin. The effects of the two drugs were additive.

Gastric irritation. Aspirin, naproxen and indomethacin produced a dose-related incidence of gastric erosions and from these data ED50 values (Litchfield & Wilcoxon 1949) were calculated for erosion production at the time of peak effects (Table 4).

Doses of nabumetone (oral and s.c.) as much as 40 times greater than those of naproxen and indomethacin were used (up to 200 mg kg^{-1}) but it was still not possible to calculate an ED50 value. These doses are compared in Table 4 with the effective doses found in the carrageenan oedema model and ultraviolet erythema model and show that nabumetone has a much greater therapeutic ratio than the other three drugs based on these values.

This lack of irritation was further demonstrated with pyloric ligated rats. Systemically mediated damage was found after indomethacin at 12 mg kg^{-1} whereas doses of up to 200 mg kg^{-1} of nabumetone were without effect (Table 5).

Table 3. Oral activity of nabumetone, naproxen, indomethacin and aspirin in ultraviolet light-induced erythema in the guinea-pig.

Compound	Oral ID50 value mg kg^{-1}	Dose range used to determine ID50 values mg kg^{-1}
Nabumetone	11·0	3·3–30
Naproxen	2·1	1–9
Indomethacin	1·7	0·33–3·0
Aspirin	68·0	33·3–300

ID50 is the dose calculated to produce a 50% reduction in ultraviolet light induced erythema.

Table 4. Comparison of nabumetone with indomethacin, naproxen and aspirin in a starved rat model and their effective anti-inflammatory doses in the carrageenan oedema and ultraviolet erythema models.

Drug	Time of peak effect (h)	ED50 mg kg^{-1} + 5% fiducial limits	ED50 Irritancy / ID25 oedema test	ED50 Irritancy / ID50 erythema test
Nabumetone	4	>200	>18	>18
Indomethacin	4	2·7 (1·5–4·9)	0·68	1·59
Naproxen	4	7·0 (4·5–10·9)	1·75	3·33
Aspirin	1	68·6 (50·8–92·6)	0·38	0·99

ED50 irritancy is the dose calculated to cause damage in 50% of the dosed rats.

Chronic anti-inflammatory activity

Rat cotton pellet granuloma test. Nabumetone by mouth was active in reducing granuloma formation at doses down to 16·7 mg kg^{-1} for 6 days. Even at 150 mg kg^{-1} day^{-1} this activity was not accompanied by signs of toxicity apart from a small but statistically significant reduction in thymus weight at the highest dose (Table 6). In contrast, hydrocortisone produced toxic effects on body weight gain and thymus weight even at doses that were ineffective in reducing granuloma formation. We have experienced difficulty in establishing dose-dependent inhibition of granuloma formation with the NSAID's tested. Aspirin was without activity up to an oral dose of 300 mg kg^{-1} even though a large decrease in thymus weight was found. Naproxen, active at oral doses of 20 mg kg^{-1} and above in most tests, was toxic, a reduction in body weight gain, and some deaths occurred with doses of 30 mg kg^{-1} and above. At oral doses lower than 20 mg kg^{-1} no consistent results were obtained. Indomethacin had shown good activity orally at 3 mg kg^{-1} and above but it was usually accompanied by a pattern of toxicity similar to that for naproxen. At 6 mg kg^{-1} all the rats died. Below 3 mg kg^{-1} it was not possible to show activity consistently.

Table 5. Effects of intraduodenally administered nabumetone, naproxen and indomethacin on gastric damage in the 4 h pyloric ligated rat.

Treatment	Dose mg kg^{-1}	Gastric damage mean score ± s.e.m.
Vehicle	—	0 (5)
Nabumetone	50	0 (6)
	100	0 (6)
	200	0 (6)
Vehicle	—	0·4 ± 0·2 (5)
Naproxen	10	11·3 ± 6·4 (4)
Vehicle	—	0 (7)
Indomethacin	12	2·0 ± 1·4 (4)

Numbers in brackets are the group sizes.

Table 6. Mean values for granuloma weight, body weight gain, thymus and spleen weights in control rats and rats treated with hydrocortisone or nabumetone.,

	Mean of:			
Treatment	Granuloma wt mg ± s.e.m.	Body wt gain g ± s.e.m.	Thymus wt mg ± s.e.m.	Spleen wt mg ± s.e.m.
Vehicle dosed controls	45·5 ± 1·8	19 ± 1	420 ± 11	571 ± 11
Hydrocortisone				
10 mg kg^{-1}	***24·7 ± 0·9	***12 ± 1	***222 ± 10	***485 ± 10
3·3 mg kg^{-1}	***30·4 ± 1·0	***12 ± 1	***289 ± 15	***509 ± 13
1·1 mg kg^{-1}	43·2 ± 2·0	***13 ± 1	**356 ± 16	527 ± 12
Nabumetone				
150 mg kg^{-1}	***30·5 ± 1·6	19 ± 1	**374 ± 12	575 ± 13
50 mg kg^{-1}	***33·5 ± 1·4	22 ± 3	400 ± 10	574 ± 11
16·7 mg kg^{-1}	**37·4 ± 1·5	19 ± 1	401 ± 11	580 ± 12

10 rats/group; compounds dosed day 0–5.
Statistically significant from the control values by Student's t-test: ***$P < 0.001$, **$0.001 < P < 0.01$.

Adjuvant-induced arthritis. Dose-related effects of nabumetone and NSAID's on injected paw depth measured on day 13 after adjuvant (Fig. 3a) and arthritis score on day 18 (Fig. 3b) show nabumetone to be less active than either indomethacin or naproxen but probably more active than aspirin. Given at an oral dose of 300 mg kg^{-1} nabumetone was effective in reducing the injected paw depth and arthritis score and also in reversing the reduction in body weight gain induced by the disease (Fig. 4). At post mortem, nabumetone treatment had reversed adjuvant-induced changes in spleen, adrenal and thymus weights (Table 7).

Analgesic activity

Phenyl-p-quinone-induced writhing in mice. In this test naproxen and indomethacin are clearly very active whilst aspirin and nabumetone are less so (Table 8) but both are more active than paracetamol, nabumetone being comparable to phenylbutazone.

Antipyretic activity

Nabumetone produced a dose-dependent reduction of fever in this test and from previous data its potency would appear similar to aspirin in this system (Fig. 5).

Table 7. The ability of nabumetone to reverse organ weight changes in adjuvant arthritic rats. Nabumetone dosed orally at 300 mg kg^{-1} days 0–13.

	Weights mg ± s.e.m.		
Treatment	Adrenal	Thymus	Spleen
Normal rats	**25·3 ± 1·20	462·0 ± 21·2	**707·6 ± 67·4
Arthritic rats	32·1 ± 1·7	363·4 ± 46·1	1108·9 ± 94·5
Arthritic rats given nabumetone	**24·4 ± 1·4	472·1 ± 15·9	*796·6 ± 56·0

8 rats per group.
Significantly different from arthritic rats as calculated using the Student's t-test.
**$P < 0.05$.
*$P < 0.01$.

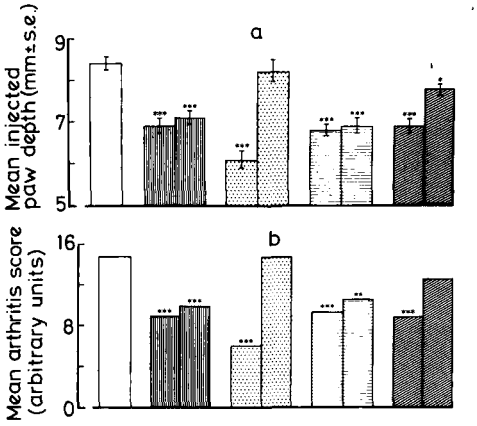

FIG. 3. Inhibition of adjuvant-induced arthritis in the rat (a) Effects on injected paw depth. Treatment and doses in mg kg^{-1} orally. High dose on left. Open columns: Arthritic control; vertically hatched columns: indomethacin at 1·5 and 0·5; dotted columns: aspirin at 270 and 90; horizontally hatched columns: naproxen at 15 and 5; cross hatched columns: nabumetone at 150 and 50. Significantly different from the arthritic control and using the Student's t-test. ***$P < 0.01$, *$P < 0.05$.
(b) Effects on arthritic score. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, significantly different from arthritic control, using the Mann Whitney 'U' test.

Possible interactions with the adrenal-pituitary axis

No increase in plasma or adrenal corticosterone levels were seen after single oral doses of nabumetone 140 mg kg^{-1} or dexamethasone 5 μg kg^{-1}. Both were active doses in the cotton pellet test.

Adrenal glands were still able to respond either to exogenous ACTH or an ether stress after 5 days oral dosing with nabumetone at 140 mg kg^{-1}, the level of corticosterone in plasma in the nabumetone-treated rats being the same as control rats. In contrast, both the level of the response to ACTH and ether stress were significantly reduced in rats given orally dexamethasone 15 μg kg^{-1} for 5 days even though the final weights of the adrenal glands were unaffected.

Inhibition of prostaglandin synthesis. Nabumetone is

Table 8. Analgesic activity of several compounds measured in the phenyl-p-quinone-induced writhing test in mice.

Compound	Analgesic ED50 mg kg^{-1} +5% fiducial limits
Nabumetone	152 (117–198)
Aspirin	62 (41–94)
Naproxen	4·0 (2·2–7·2)
Indomethacin	1·3 (0·7–2·2)
Paracetamol	300 (153–588)
Phenylbutazone	100 (65·8–152·0)

a much weaker inhibitor of this enzyme preparation than naproxen and indomethacin (Table 9).

DISCUSSION

The comparative studies reported here show nabumetone to be an effective anti-inflammatory agent with mild analgesic and antipyretic properties in animals.

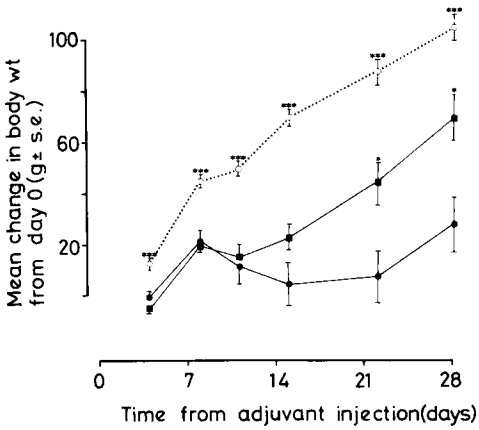

FIG. 4. The effect of nabumetone in reversing adjuvant induced body weight loss. ● Arthritic control. ■ Nabumetone treated animals. ○ Normal animals. ***$P < 0.001$, *$P < 0.05$, significantly different from arthritic control by Student's t-test.

Nabumetone is much more active than aspirin although somewhat less active than naproxen and indomethacin in the carrageenan-induced oedema test and the duration of action was at least 6 h. The results were similar in the ultraviolet-induced erythema test and when given as admixtures with aspirin the activities were additive. In this respect nabumetone may differ from other NSAID's. Fenoprofen plasma levels are reduced in rat and man by the simultaneous administration of aspirin (Warrick & Rubin 1974). Also, in the rat, co-administered aspirin and indomethacin or aspirin and naproxen are not additive in producing anti-oedema effects (Swingle et al 1970; Chaplin 1973).

With the fasted rat model claimed by Hitchens et al (1969) to be predictive of the propensity of a drug to cause gastric irritancy in man, dose-dependent damage was found with aspirin, naproxen and indomethacin. Diamantis et al (1980) report ulcerogenic doses for those drugs which are in close agreement with the findings in this paper. Doses of nabumetone up to 200 mg kg^{-1} (i.e. some 40 times greater than those of naproxen and indomethacin) were used but it was still not possible to calculate an

Table 9. The comparative ability of nabumetone, indomethacin and naproxen in inhibit prostaglandin synthesis in vitro.

Compound	ID50 value μg ml^{-1}	ID50 values M × 10^{-6}
Nabumetone	46·0	201·7
Indomethacin	1·65	4·6
Naproxen	1·5	6·5

ED50 value after oral or subcutaneous administration of the drug. Its lack of gastric irritation was further demonstrated in pyloric ligated rats in which it was given intraduodenally, with no effect being seen up to a dose of 200 mg kg^{-1}. In contrast, considerable systemically-mediated damage was found in this test with indomethacin at 12 mg kg^{-1} and naproxen at 10 mg kg^{-1}.

Nabumetone is non-acidic and it has been shown that it is a relatively weak inhibitor of prostaglandin synthesis. The possibility that potency in inhibiting prostaglandin synthesis may be related to gastric irritation has been commented upon (Boyle et al 1976; Cashin et al 1977) and our results add weight to this theory. Nabumetone is well absorbed and extensively metabolized, in man and laboratory animals the major plasma metabolite being 6-methoxy-2-naphthyl acetic acid (unpublished results). This compound is a more potent inhibitor of prostaglandin synthesis than nabumetone and,

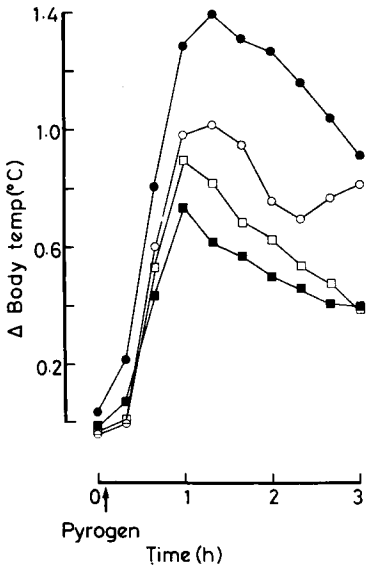

FIG. 5. The effect of nabumetone on endotoxin-induced pyresis in the rabbit. ● Vehicle treated. ○ 50 mg kg^{-1}. □ 100 mg kg^{-1}. ■ 200 mg kg^{-1} nabumetone. 5 animals were used at each dose, and 4 vehicle-treated animals served as controls.

although the mode of action of nabumetone is not known, the available evidence indicates that its activity resides in its metabolites rather than the drug as administered. Nabumetone is therefore a non-steroidal anti-inflammatory drug which because of its metabolic properties can be administered orally to animals and yet not produce the gastric effects associated with such agents.

Of particular interest is the activity shown by nabumetone in reducing the granuloma formed in rats around implanted sterile cotton pellets. The compound is active at oral doses as low as 16·7 mg kg^{-1} and produced no marked toxicity at oral doses up to 150 mg kg^{-1} for 6 days. Roszkowski et al (1971) showed a dose-related effect for naproxen in the reduction in granuloma formation around carrageenan-impregnated cotton pellets up to an oral dose of 20 mg kg^{-1} for 7 days. However, toxicity, including a reduction in body weight gain and death, in a proportion of treated rats occurred above this dose. We, too, have found naproxen active at oral doses of 20 mg kg^{-1} for 6 days with toxicity similar to that reported by Roszkowski et al (1971) at 30 mg kg^{-1} and above. However, in our model the pellets were not impregnated with carrageenan and we have been unable to show consistent activity below an oral dose of 20 mg kg^{-1}. Indomethacin at 3 mg kg^{-1} by mouth for 6 days is active but toxic whereas doses below this did not produce consistent activity; at 6 mg kg^{-1} all the animals died. Aspirin was without effect at oral doses up to 300 mg kg^{-1} for 6 days. Difficulty in obtaining dose responses to NSAID's in similar tests have been reported for example with aspirin (Schiatti et al 1974) and indomethacin (Lassman et al 1977). Nabumetone is also active in a second model of chronic inflammation, adjuvant-induced arthritis. A high oral dose (300 mg kg^{-1}) was well tolerated and reversed adjuvant-induced changes in organ weights and body weights. Aspirin and indomethacin have been reported (Rosenthale et al 1974) as being unable to adequately reverse the adjuvant-induced changes in body weight and organ weights at doses (aspirin 150 mg kg^{-1} and indomethacin 2 mg kg^{-1}) which reduce paw volume. Higher doses, for example 300 and 400 mg kg^{-1} of aspirin and 3 mg kg^{-1} day^{-1} of indomethacin, were reported to result in death of a proportion of the dosed animals.

To be an effective treatment for painful inflammatory conditions, a drug needs to possess an acceptable level of analgesic activity. In a model designed to show peripheral analgesia both nabumetone and aspirin are clearly less active than naproxen and indomethacin. However, both are more active than paracetamol, which along with aspirin, is used extensively for the relief of mild pain. The activity of nabumetone in this model appears to be equivalent to that of phenylbutazone. From limited studies performed in the rabbit the drug also possesses antipyretic activity.

Since nabumetone showed good activity in the cotton pellet test in which glucocorticoids are particularly active we were concerned to show that it did not share any properties with the steroids which would preclude prolonged clinical use. We therefore performed experiments to rule out any interaction of nabumetone with the hypothalamic-pituitary-adrenal axis. The initial experiment showed that its anti-inflammatory activity was maintained in adrenalectomized animals. We also showed that a single dose was unable to elicit the release of corticosterone from rat adrenal glands in vivo. In contrast to dexamethasone, dosing with nabumetone for 5 days did not inhibit the response of the adrenal glands to either an ether stress or an ACTH stimulus. Furthermore, no thymolytic activity was observed with nabumetone in the standard cotton pellet test apart from a small reduction at 150 mg kg^{-1} day^{-1} whereas active doses of hydrocortisone consistently brought about a large reduction in thymus weight.

In summary, four features distinguish nabumetone from most NSAID's currently in therapeutic use. Firstly, the compound is not acidic as presented to the gut. Secondly, in two models designed to indicate the propensity of drugs to cause gastric irritancy in man, nabumetone is very well tolerated at doses well above those showing anti-inflammatory activity, in contrast to the comparative drugs used in this study. Thirdly, nabumetone is active in a chronic model of inflammation, the cottton pellet test, at doses far removed from those which cause toxicity. Fourthly, nabumetone is a relatively weak inhibitor of prostaglandin synthesis in vitro, a feature which may be responsible for the good degree of tolerance to it by the rat stomach.

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