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ANTI-INFLAMMATORY AND PHARMACOKINETIC PROPERTIES OF SUDOXICAM N-(2-THIAZOLYL)-4-HYDROXY-2-METHYL-2H-1,2-BENZOTHIAZINE-3-CARBOXAMIDE 1,1-DIOXIDE

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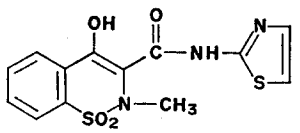
Abstract—Sudoxicam has demonstrated potent anti-inflammatory and antipyretic activity in several laboratory animal models of inflammation, in the range of 0·5–3 times that of indomethacin. The plasma half-life ranged between 8 hr (monkey), 13 hr (rat), 60 hr (dog) and 24–96 hr (man). Sudoxicam, combining the high potency of indomethacin with the extended plasma half-life of phenylbutazone, has been well tolerated by animals and man, and evaluation in human inflammatory diseases is proceeding.

IN THE conservative management of rheumatoid disease, the salicylates are the pre-eminent non-steroidal anti-inflammatory agents. Two further non-steroidal agents, phenylbutazone (Butazolidin) and indomethacin (Indocin), are presently approved for use in human inflammatory diseases in the U.S., and the pharmacology of many novel agents has been described recently.

In our laboratories, the search for novel non-steroidal anti-inflammatory agents has led to the description of the properties of series of 2-arylindandiones,[1] 2-arylbenzothiophenones,[2] dioxoisoquinoline-4-carboxanilides,[3,4] 1,2-benzothiazine-4-carboxamides[5] and 1,2-benzothiazine-3-carboxamides.[6–8] The purpose of this report is to describe the properties of one member of the latter series, *N*-(2-thiazolyl)-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (sudoxicam), which in animal models possesses anti-inflammatory activity comparable to that of indomethacin, coupled with an extended plasma half-life, in animals and man, similar to that of phenylbutazone.



Sudoxicam

MATERIALS AND METHODS

Rats (male) were of the Charles River CD strain; guinea pigs (male) were of the Hartley strain; mongrel dogs and Rhesus monkeys were of both sexes. Adrenalectomy, in the rat, was performed through a retroperitoneal incision, while the animals were anesthetized with ether. The adrenalectomized rats were maintained on 0·9% saline in place of drinking water and were used 5–7 days post-operatively.

Inhibitory activity toward the formation of edema in response to the sub-plantar injection of carrageenan in the hind-paw of the rat (170–180 g) was assessed using the technique of Winter *et al.*[9] Carrageenan (0·05 ml of 1% suspension) was injected 1 hr after drug administration (p.o.), and inhibition of edema formation was assessed after a further 3 hr. Analogous studies were performed in bilaterally adrenalectomized rats.

Inhibitory activity toward ultraviolet-irradiation-induced erythema, was measured in the guinea pig according to the method of Winder *et al.*[10] Drugs were administered orally in divided doses, 1 hr prior and just subsequent to irradiation. Erythema inhibition was assessed 2 hr after irradiation. Groups of five animals were used and erythema was "scored" as follows: no erythema, 0; full circle of erythema 1·0; intermediate responses, 0·5. Erythema was assessed at three irradiation sites on each animal (total possible "score" = 3·0).

Inhibitory activity toward the formation of granuloma tissue around an implanted irritant was measured by a procedure developed in our laboratories.[4] Rats (140–160 g) were shaved, and a 3-in. length of sterile linen string was inserted subcutaneously at the dorsal mid-line (performed under ether anesthesia). Drugs were administered orally 4, 24 and 48 hr after implantation. At 72 hr, the animals were sacrificed with ether, weighed, and the string together with the granulation tissue was removed and weighed.

Adjuvant arthritis was induced in the rat by the injection of *Mycobacterium butyricum* into the distal third of the tail.[11,12] Drugs were orally administered daily, commencing either the day prior to adjuvant injection or on day 21 after adjuvant injection. Blood samples were drawn from the aorta, and plasma "inflammation units" measured by the published procedure using a Coleman model 9 nephelometer.[13]

Antipyretic activity was measured in the rat. Rats (100–120 g), housed in groups of four in large open-topped plastic containers, were kept in the test room for 24 hr prior to use. Pyrexia was induced by the intraperitoneal administration of typhoid/paratyphoid vaccine (Lederle; 1·0 ml). Rectal temperatures were measured with a thermo-couple probe, attached to a Tele-Thermometer (Yellow Springs Instrument Company). Drugs were administered intraperitoneally 2 hr after pyrogen. Temperatures were recorded over a 7-hr period.

Pharmacokinetic studies were carried out in healthy male volunteers during and subsequent to termination of chronic drug administration. Blood samples were drawn by venipuncture into heparinized tubes. In the pharmacokinetic studies conducted in animals, blood samples for analysis of drug concentrations were drawn from the abdominal aorta of rats maintained under pentobarbital anesthesia, or from the jugular vein of dogs and monkeys. Plasma and urine samples were stored at 4° until assayed. Drug plasma half-life in laboratory animals was determined after intravenous administration of drug solution (10 mg/kg). In the rat, the drug was injected into the tail vein; groups of three animals were sacrificed at each time interval. The drug was injected into the cephalic vein of dogs and monkeys, and serial blood samples were withdrawn at intervals. In man, plasma half-life was determined by analysis of the drug plasma concentrations in the period 24 hr after the termination of chronic drug administration (i.e. when absorption was complete), and also following a single 50-mg oral dose.

Lipid water partition ratios were determined by equilibrating at 25° solutions of

drug in pH 7·4 phosphate buffer with an equal volume of organic solvent. The extent of binding to human plasma proteins was determined by equilibrium dialysis at 25° through Visking membranes against pH 7·4 phosphate buffer for 24 hr, followed by filtration and assay of the solution. The pK_a was measured by potentiometric titration in 50% aqueous dioxane solution.

Two modifications of the assay procedure for sudoxicam in biological fluids or other aqueous solutions were developed. In studies where drug concentrations could be anticipated as being in the range 10–100 μg/ml, the procedure was as follows: samples (2 ml) were acidified with 1 N HCl (0·5 ml) and extracted by shaking with *n*-heptane (5 ml) containing 1·5% isoamyl alcohol. The layers were separated by centrifugation, and an aliquot (4 ml) of the organic layer was extracted with pH 7·0 potassium phosphate buffer (5 ml). The optical density of the aqueous phase was determined at 270 and 360 nm in a Beckman model DU spectrophotometer. In studies where drug concentrations were anticipated to be in the range 0·5–10 μg/ml, the sample was acidified and extracted as above. An aliquot (4 ml) of the organic layer was extracted with buffer (1 ml) and the optical density of the aqueous phase was determined at 270 and 360 nm using a Beckman model DU spectrophotometer, equipped to use micro-cells. Each modification of the assay was calibrated by carrying samples of known concentration through the entire assay. Phenylbutazone was assayed by the methods of Burns *et al.*[14]

RESULTS

Anti-edema activity. In the intact rat, sudoxicam significantly inhibited edema formation at doses as low as 0·1 mg/kg, p.o. In a comparative study with indomethacin, the $\log_{10}$ dose (x)–response (y) regression lines, given by least-squares analysis, were: sudoxicam, $y = 16{\cdot}9x + 42{\cdot}6$, and indomethacin, $y = 18{\cdot}8x + 33{\cdot}3$ Fig. 1; solid points). The slopes of these lines were not significantly different, and

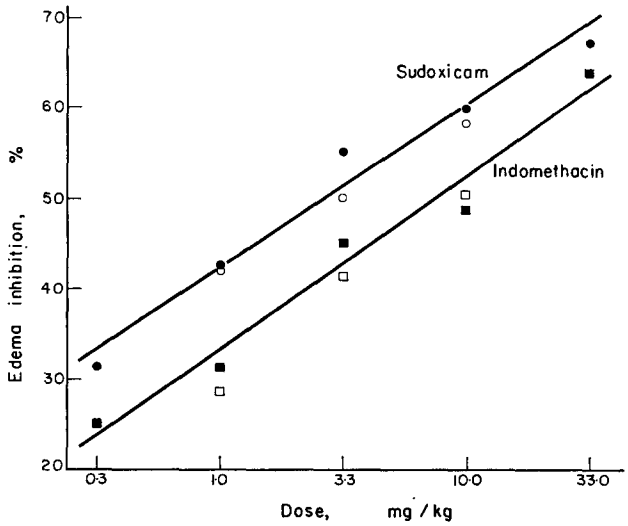


FIG. 1. Anti-edema effects of sudoxicam (○) and indomethacin (□) in normal (solid points) and adrenalectomized (open points) rats. Six animals at each observation.

indicated the 95 per cent confidence limits for the relative potency calculation of sudoxicam as 2·9 (1·5–5·9) times as effective as indomethacin. In adrenalectomized rats, the edema inhibition by both sudoxicam and indomethacin was not significantly different from that seen at corresponding doses in intact rats (Fig. 1; open points). The data for indomethacin are essentially in agreement with that previously reported.[15]

Anti-granuloma activity. In this test, sudoxicam possessed 0·3 (0·2–0·5) times the potency of indomethacin (Fig. 2). Neither drug significantly affected body weight gain during the 3-day test period. The duration of the test procedures employed (3 days) is less than that employed in previous studies with indomethacin. However, in agreement with other workers,[16] rats were found not to tolerate repeated doses of indomethacin above 3–4 mg/kg/day. We were therefore unable to assess the effectiveness of indomethacin at doses which, by extrapolation, should have allowed the high inhibition of granuloma formation seen with sudoxicam (18 mg/kg/day).

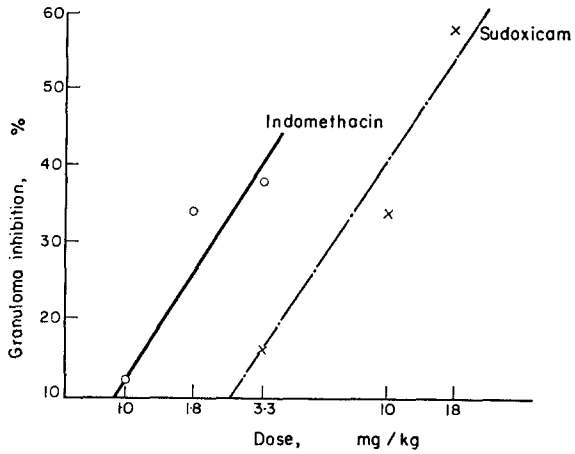


FIG. 2. Anti-granuloma effects of sudoxicam (○) and indomethacin (×) in rats. Five animals at each observation.

Nevertheless, the results are essentially in agreement with those previously reported.[15]

Anti-erythema activity. Sudoxicam, phenylbutazone and indomethacin each inhibited the erythema caused by ultraviolet irradiation in the guinea pig (Fig. 3). Because of the subjective nature of the end-point of this test (degree of erythema), rigorous potency estimates were not made. However, approximate potencies of sudoxicam, indomethacin and phenylbutazone in this test are 3 : 1·5 : 1.

Effects on adjuvant arthritis

Prophylactic treatment. Rats were dosed with test drug daily. One day after commencing treatment, the animals were injected with *M. butyricum* in Primol suspension, in the tail. The arthritic state which developed was evaluated through 21 days after injection (Table 1), using as indices the progression of body weight and the involvement of the hind-paws. Sudoxicam (1·0 and 0·3 mg/kg/day) and indomethacin (1 mg/kg/day) both ameliorated these parameters of the arthritic state.

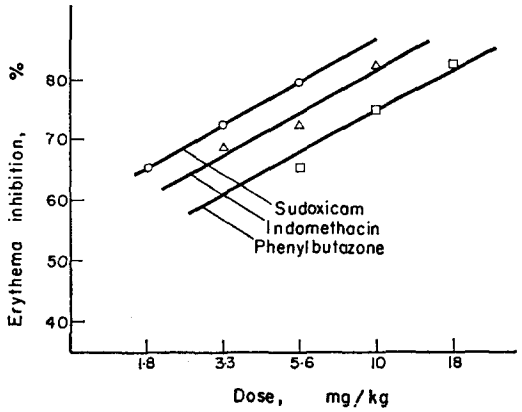


FIG. 3. Inhibition of ultraviolet-induced erythema in the guinea pig by sudoxicam (○), indomethacin (△) and phenylbutazone (□). Six animals at each observation.

TABLE 1. EFFECTS OF SUDOXICAM AND INDOMETHACIN IN DEVELOPING ADJUVANT-ARTHRITIS

Drug	Dose (mg/kg/day)	No. of rats	Average body wt. gain (g) from initial day of observation			Foot volume (% increase from initial day of observation)					
			7	14	21	7(R)	7(L)	14(R)	14(L)	21(R)	21(L)
Uninjected control		10	41	68	107	11	10	23	21	27	29
Adjuvant control		10	19	23	42	5	5	41	52	46	53
Sudoxicam	1·0	10	28	48	84	9	5	21*	19*	23*	25*
	0·3	10	26	34	55	9	5	38	27*	36	29*
	0·1	10	23	23	45	5	2	50	37	39	36
Indomethacin	1·0	10	30	50	79	9	5	21*	20*	14*	16*

* Significantly different from adjuvant control ($P < 0·05$).

Therapeutic treatment. Rats were injected with *M. butyricum* in Primol suspension, in the tail. The arthritic state which developed was evaluated 28 days after injection. Drugs were administered daily, commencing at day 21. Sudoxicam and indomethacin, at doses above 1 mg/kg/day, were both effective in reducing plasma inflammation units, in reducing the swelling of inflamed hind-paws and restoring toward normal the daily gain in body weight (Table 2).

Anti-pyretic activity. After pyrogen administration, there was an initial fall in body temperature, rising rapidly to elevated levels which were maintained for a further 4 hr (Fig. 4). Sudoxicam (3·3 mg/kg, i.p.) and aspirin (33 mg/kg, i.p.) were both capable of counteracting the pyrexia induced by the intraperitoneal injection of typhoid/paratyphoid vaccine in rats, maintaining body temperature about that of uninjected control rats.

Pharmacokinetic studies. The physicochemical properties of sudoxicam are shown in Table 3. In common with other non-steroidal anti-inflammatory agents, sudoxicam

TABLE 2. EFFECTS OF SUDOXICAM AND INDOMETHACIN IN ESTABLISHED ADJUVANT ARTHRITIS

Drug	Dose (mg/kg/day)	No. of rats	Average changes in inflammatory parameters: Body wt. gain between day 21 and 28 (g)	Decrease in inflammation units (%)	Decrease in foot volume (%) day 21–day 28: Right foot	Left foot
Controls		10	22		0	0
Sudoxicam	10·0	10	37	29·9	15	21
	3·3	10	46	28·8	14	10
	1·0	10	42	34·4	10	12
Indomethacin	2·0	10	35	18·9	14	14
	1·0	10	35	27·7	11	11
	0·3	10	35	11·5	13	10
Controls		10	27		5	4
Sudoxicam	1·0	9	40	23·1	10	9
	0·3	10	37	4·8	5*	6*
Indomethacin	1·0	10	46	22·7	13	12

* Not significantly different from controls.

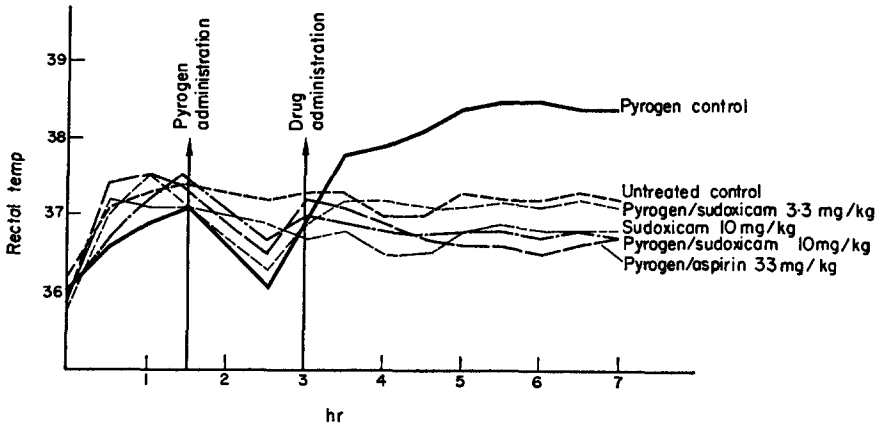


FIG. 4. Antipyretic activity of sudoxicam against the hyperpyrexia induced by typhoid vaccine. Four rats in each group.

TABLE 3. PHYSIOCHEMICAL PROPERTIES OF SUDOXICAM, PHENYLBUTAZONE AND INDOMETHACIN

		Sudoxicam	Phenylbutazone	Indomethacin
Partition coefficient	*n*-Heptane/pH 7·4 buffer	0·0	1·2	0·24
	CH_3CHCl_2/pH 7·4 buffer	1·3	> 100	0·22
	Octanol/pH 7·4 buffer	0·5	4·8	0·31
	pK_a*	5·3	6·4	7·0
Solubility (μg/ml)	0·1 N HCl	14·5	13·2	27·0
	Water	73·2	26·9	73·3
Binding to human plasma proteins (%)		96	95–99	90–98

* Measured in aqueous dioxane (1 : 2).

is a slightly water soluble, lipophilic, moderately strong acid, which is extensively bound to plasma proteins. The oral absorption of sudoxicam was studied in the rat, dog, monkey and man. After an oral dose of sudoxicam (10 mg/kg) in the rat, peak plasma concentrations (*ca.* 50 μg/ml) occurred within 4 hr. In the dog, after an oral dose of 10 mg/kg, plasma concentrations in excess of 40 μg/ml were attained within 4 hr, and were maintained at high levels beyond 36 hr. In the monkey, the same oral dose led to plasma concentrations above 50 μg/ml, attained 4–6 hr after administration. In man, after an oral dose of 50 mg (approx. 0·7 mg/kg), peak plasma concentrations of 4 μg/ml were reached within 3 hr. These data were further analyzed by a mathematical model derived from chemical kinetics[17,18] to permit the construction of smooth curves through experimental points. The curves for sudoxicam in three laboratory animal species and man are shown in Figs. 5–8 (solid lines), together with similar curves for phenylbutazone (dashed lines; determined in this study) and indomethacin (broken lines; adapted from ref. 19).

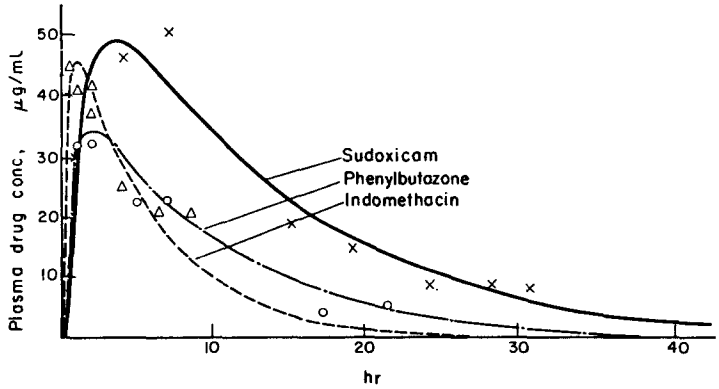


FIG. 5. Plasma drug concentrations obtained after the oral administration of 10 mg/kg of sudoxicam (×), phenylbutazone (○) and indomethacin (△) to the rat. For sudoxicam and phenylbutazone, each point is average of four animals. Indomethacin data from reference 19. Smooth curves for each drug drawn by kinetic analysis as described in refs. 17 and 18.

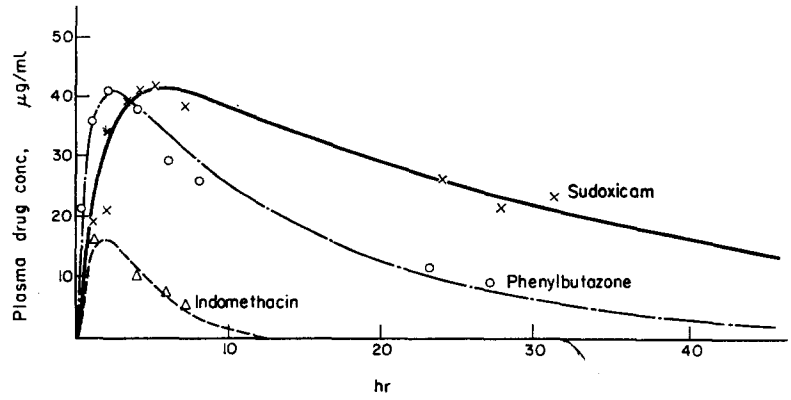


FIG. 6. Plasma drug concentrations obtained after the oral administration of 10 mg/kg of sudoxicam (×), phenylbutazone (○) and indomethacin (△) to the dog. For sudoxicam and phenylbutazone, each point is the average of two animals. Indomethacin data from reference 19. Smooth curves for each drug drawn by kinetic analysis as described in refs. 17 and 18.

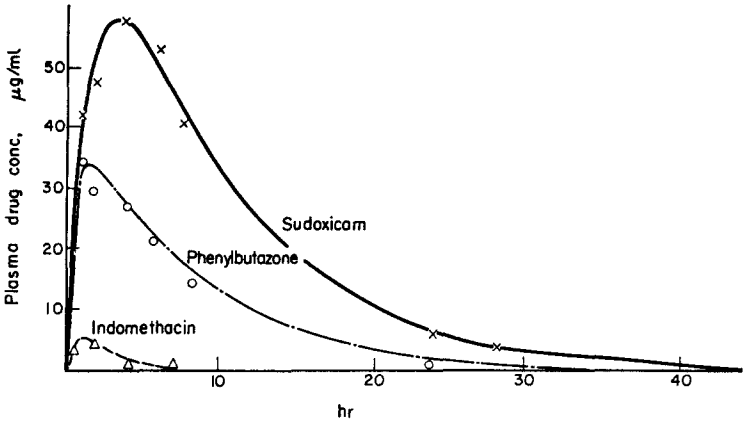


FIG. 7. Plasma drug concentrations obtained after the oral administration of 10 mg/kg of sudoxicam (×), phenylbutazone (○) and indomethacin (△) to the monkey. For sudoxicam and phenylbutazone, each point is the average of two animals. Indomethacin data from ref. 19. Smooth curves for each drug drawn by kinetic analysis as described in refs. 17 and 18.

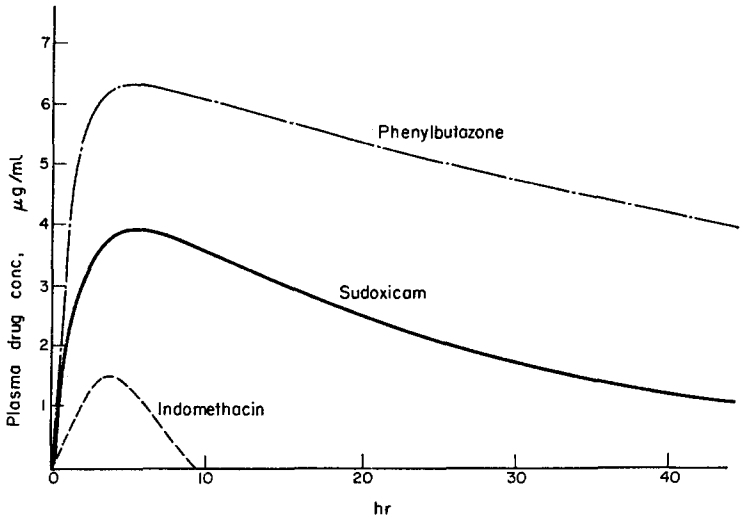


FIG. 8. Plasma drug concentrations obtained after the oral administration of 50 mg of sudoxicam, phenylbutazone, or indomethacin to man. For sudoxicam and phenylbutazone, each point is the average of five subjects. Indomethacin data from reference 19. Smooth curves for each drug drawn by kinetic analysis as described in refs. 17 and 18.

After intravenous administration to laboratory animals, plasma concentrations of sudoxicam decayed exponentially (Table 4). By extrapolation of plasma drug concentrations after intravenous administration to zero time, an approximate volume of distribution can be calculated. In all laboratory animals this fell between 150–250 ml/kg (essentially that of extracellular water) for all drugs studied. This is further confirmation of the physicochemical/pharmacokinetic similarities between sudoxicam, phenylbutazone and indomethacin. The extended half-life of sudoxicam would lead to the expectation that, upon repeated administration, plasma concentrations would

TABLE 4. PLASMA HALF-LIFE OF SUDOXICAM, PHENYLBUTAZONE AND INDOMETHACIN IN VARIOUS SPECIES

Species	Plasma half-life (hr)		
	Sudoxicam	Phenylbutazone	Indomethacin
Rat	13	6*	4†
Dog	60	6*	0·3†
Monkey	8	7‡	0·3†
Man	24–96§	72*	2†

* Ref. 14.
† Ref. 19.
‡ Ref. 20.
§ Dependent upon plasma concentration (see text).

tend to plateau at a level above that seen upon acute administration. Indeed, in chronic administration studies in the dog, plasma drug concentrations 24 hr after a 15 mg/kg oral dose were in the range of 30–40 μg/ml, which upon successive daily doses rose to and stabilized at 50–60 μg/ml. In the monkey, drug concentrations 24 hr after a 10 mg/kg oral dose were 7–10 μg/ml, which upon successive daily dosing rose to and stabilized at 18–25 μg/ml. In man, after an oral dose of 20 mg, plasma concentrations 24 hr after administration of the first dose were below 1 μg/ml, increasing to 3–7 μg/ml, measured 24 hr after the fourteenth successive daily dose. Upon daily administration of 50 mg, human plasma concentrations reached 15–26 μg/ml, measured 24 hr after the eighth dose. After drug withdrawal from these subjects, the rate of disappearance of drug from plasma constantly changed, such that, depending on the initial plasma concentration, the apparent half-life ranged from as much as 12 days to a minimum of 24 hr (Fig. 9).

DISCUSSION

The search for, and evaluation of, new agents useful in the management of arthritic diseases present a unique pharmacologic challenge. Arthritis is a human disease, the etiology and pathogenesis of which are unknown. Many animal models, each mimicking one of the cardinal symptoms of inflammation (heat, redness, swelling, pain and loss of function), have been devised and sudoxicam has demonstrated potent inhibitory activity in many of these. Thus, in these rodent tests, sudoxicam inhibited the erythema formed in response to ultraviolet irradiation; it inhibited carrageenan-induced foot edema; and it reduced the hyperpyretic response to vaccine injection. In models of more chronic inflammation, sudoxicam inhibited the formation of granulation tissue around an implanted irritant (sterile string), and reduced both plasma "inflammation units" and the foot swelling in the adjuvant-arthritic rat. The potency of sudoxicam in these tests varied from 10 to 20 times that of phenylbutazone, and from 0·5 to 3 times that of indomethacin. Sudoxicam retained full anti-edema activity in adrenalectomized rats, demonstrating that its anti-inflammatory activity does not depend upon stimulation of the adrenal gland.

In many laboratories, the search for novel anti-inflammatory agents has been aided by the discernment of common features in the physicochemical properties of known drugs. Indomethacin, mefenamic and flufenamic acid, salicyclic acid and

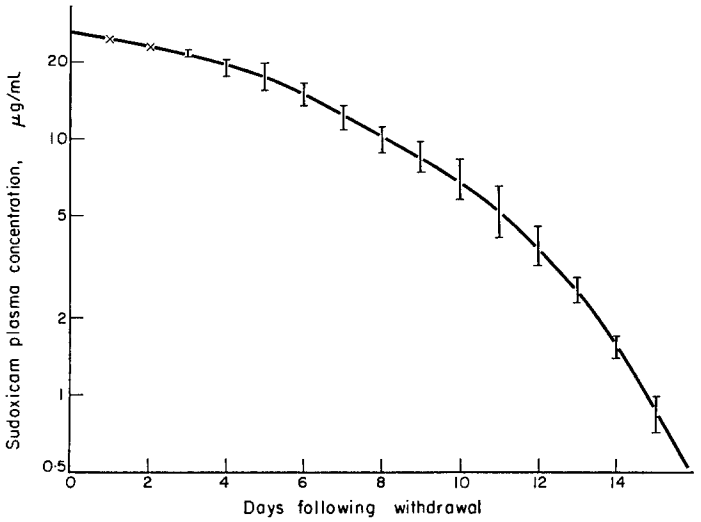


FIG. 9. Decay of sudoxicam plasma concentrations after withdrawal of drug from subjects who received repeated daily oral doses of sudoxicam. Thirteen subjects received, on consecutive days, doses of 10 mg (2 days), 25 mg (2 days), 35 mg (2 days) and 50 mg (6 days); eighteen subjects received, on consecutive days, doses of 50 mg (4 days), 25 mg (11 days) and 20 mg (7 days); seventeen subjects received 50 mg (6 days), 35 mg (9 days) and 25 mg (7 days). Subjects have been grouped according to plasma drug concentrations at day of withdrawal. The plots of average drug concentration vs. time for each group were superimposed on each other (i.e. the time scale was shifted) so that each group was compared at identical plasma concentrations.

phenylbutazone are all lipophilic, moderately strong organic acids, extensively bound to plasma proteins, properties shared by sudoxicam. Extensive pharmacokinetic studies have demonstrated that sudoxicam is swiftly and completely absorbed after oral administration to the rat, dog, monkey and man. The drug half-life in plasma varied between 8 hr (monkey), 13 hr (rat), 60 hr (dog) and 24–96 hr (man). The apparent volume of distribution of the drug is 150–250 ml/kg, indicating that like other acidic anti-inflammatory agents, sudoxicam is largely confined to extracellular. water.

Since, by definition, arthritis is a disease of the joints, rapid transport of a potentially useful drug to the site of inflammation, as well as the attainment and maintenance of effective drug concentrations at that site, is of prime importance. This may be represented as: therapeutic usefulness ∞ intrinsic potency $\times$ duration of effective drug concentrations.

In all animal species investigated, the plasma drug concentrations attained (concn), and the time for which they are maintained (hr), are greater with sudoxicam than with either phenylbutazone or indomethacin, when administered at the same dose. The ratio of the areas (concn. $\times$ hr) under the time vs. drug plasma concentration curves (shown in Figs. 5–8) are summarized in Table 5. The combination of high intrinsic potency and long plasma half-life therefore places sudoxicam in a unique position in comparison with non-steroidal acidic drugs currently employed for the management of arthritis.

The validity of the foregoing analysis is supported by the recent clinical experience with indomethacin in the treatment of inflammatory disorders.[21] Despite a potency

TABLE 5. RATIO OF AREAS (CONCN. HR) UNDER TIME VS. DRUG PLASMA CONCENTRATION CURVES FOR SUDOXICAM, PHENYLBUTAZONE AND INDOMETHACIN IN ANIMALS AND MAN

Species	Dose	Ratio of areas (concn hr)		
		Sudoxicam	Phenylbutazone	Indomethacin
Rat	10 mg/kg	3	1·5	1
Dog	10 mg/kg	16	8	1
Monkey	10 mg/kg	30	13	1
Man	50 mg	13	29	1

advantage of 20- to 85-fold for indomethacin over phenylbutazone in animal anti-inflammatory tests,[15] the presently recommended daily dose of indomethacin is 150–200 mg,[22] while that of phenylbutazone is 400 mg,[23] representing a clinical advantage for indomethacin of only 2- to 3-fold over phenylbutazone. A possible explanation of this anomaly may lie in the low plasma drug concentrations of short duration which follow administration of indomethacin compared with the sustained high plasma drug concentrations seen following the oral administration of the same dose of phenylbutazone to man (Fig. 8). This has the effect of diminishing the advantage of the greater potency of indomethacin as compared with phenylbutazone. In fact, the ratio of the areas (concn × hr) under the time vs. drug plasma concentration curves for indomethacin and phenylbutazone in man (1 : 29, Table 5), taken in conjunction with animal potency ratios (20–85 : 1) would lead to a prediction that clinically useful doses for indomethacin and phenylbutazone should be approximately in the ratio of 1 : 3. This ratio is in line with clinical experience and stands in sharp contrast to that predicted from animal potency data.

The studies described and the arguments developed in this report support the contention that animal models of inflammation are of use mainly in predicting relative potencies of comparative drugs—more specifically in determining the minimum plasma drug concentration that is associated with anti-inflammatory activity in that model. Despite differences in plasma half-life, the plasma drug concentrations achieved in the rat by equal doses of sudoxicam, indomethacin and phenylbutazone are not greatly different, especially in the short duration (1–4 hr) of the acute inflammatory tests (carrageenan edema, ultraviolet erythema). This is clearly shown in Fig. 5, and holds at other oral doses of these drugs. The appearance of significant anti-edema activity of sudoxicam is correlated with plasma drug concentrations of 1–2 μg/ml.

Subsequent to extensive safety evaluation studies in animals,* studies have been undertaken in human subjects.† Daily oral doses of 20 mg were well tolerated and plasma drug concentrations were maintained above 7 μg/ml at all times during the day. Thus, in contrast to indomethacin, the extended plasma half-life that sudoxicam exhibits in man leads to much higher "concn hr" values for the latter drug. The evaluation of the utility of sudoxicam in the management of human inflammatory diseases is proceeding.

* The acute oral LD_{50} of sudoxicam in the mouse is 260 mg/kg and in the rat 157 mg/kg; the drug has been well tolerated over several months by rats (5 mg/kg) and monkeys (10 mg/kg). (Dr. E. J. Gralla and Dr. R. B. Stebbins, personal communication.)

† Dr. J. R. Migliardi and Dr. C. R. Taylor, unpublished observations.

REFERENCES

1. J. G. LOMBARDINO and E. H. WISEMAN, *J. med. chem.* **11,** 342 (1968).
2. J. G. LOMBARDINO and E. H. WISEMAN, *J. med. chem.* **13,** 206 (1970).
3. S. B. KADIN and E. H. WISEMAN, *Nature, Lond.* **222,** 275 (1969).
4. E. H. WISEMAN, E. J. GRALLA, J. CHIAINI, J. R. MIGLIARDI and Y.-H. CHANG, *J. Pharmac. exp. Ther.* **172,** 138 (1970).
5. J. G. LOMBARDINO and E. H. WISEMAN, *J. med. chem.* **14,** 973 (1971).
6. J. G. LOMBARDINO, E. H. WISEMAN and W. M. MCLAMORE, *J. med. chem.* **14,** 1171 (1971).
7. J. CHIAINI, E. H. WISEMAN and J. G. LOMBARDINO, *J. med. chem.* **14,** 1175 (1971).
8. J. G. LOMBARDINO and E. H. WISEMAN, *J. med. chem.*, in press.
9. C. A. WINTER, E. A. RISELY and G. W. NUSS, *Proc. Soc. exp. Biol. med.* **111,** 554 (1962).
10. C. V. WINDER, J. WAX, V. BURR, M. BEEN and C. E. ROSIERE, *Archs int. Pharmacodyn. Thér.* **116,** 261 (1958).
11. E. M. GLENN, *Am. J. vet. Res.* **116,** 339 (1966).
12. C. A. WINTER and G. W. NUSS, *Arthritis Rheum.* **9,** 394 (1966).
13. E. M. GLENN and W. M. KOOYERS, *Life Sci.* **5,** 619 (1966).
14. J. J. BURNS, R. K. ROSE, T. CHENKIN, A. GOLDMAN, A. SCHULERT and B. B. BRODIE, *J. Pharmac. exp. Ther.* **109,** 346 (1953).
15. C. A. WINTER, E. A. RISLEY and G. G. NUSS, *J. Pharmac. exp. Ther.* **141,** 369 (1963).
16. J. R. WARD and R. S. CLOUD, *J. Pharmac. exp. Ther.* **152,** 116 (1966).
17. R. G. WEIGAND and J. D. TAYLOR, *Biochem. Pharmac.* **3,** 256 (1960).
18. E. H. WISEMAN, E. C. SCHREIBER and R. PINSON, JR., *Biochem. Pharmac.* **13,** 1421 (1964).
19. H. B. HUCKER, A. G. ZACCHEI, S. V. COX, D. A. BRODIE and N. H. R. CANTWELL, *J. Pharmac. exp. Ther.* **153,** 237 (1966).
20. B. B. BRODIE and W. D. REID, *Fedn Proc.* **26,** 1062 (1967).
21. W. M. O'BRIEN, *Clin. Pharmac. Ther.* **9,** 94 (1968).
22. L. M. LOCKIE and B. M. NORCROSS, in *Arthritis and Allied Conditions* (Ed. J. R. HOLLANDER), p. 333. Lea & Febiger, Philadelphia (1966).
23. C. A. L. STEPHENS, JR., E. E. YEOMAN, W. P. HOLBROOK, D. F. HILL and W. L. GOODIN, *J. Am. med. Ass.* **150,** 1084 (1952).