neum), in series with the viable tissues of the epidermis and connective tissue of the dermis. On the basis of this evidence, the hairless mouse might prove generally useful in sorting out membrane contributions to the relative activities of topical drugs and in evaluating the influence of formulation on the activity of a given topical therapeutic compound.

REFERENCES

(1) R. B. Stronghton, in "Animal Models in Dermatology," H. I. Maibach, Ed., Churchill Livingstone, New York, N.Y., 1975, p. 121.

(2) R. J. Scheuplein, *J. Invest. Dermatol.*, **45**, 334 (1965).

(3) *Ibid.*, **48**, 79 (1967).

(4) I. H. Blank, R. J. Scheuplein, and D. J. MacFarlane, *J. Invest. Dermatol.*, **49**, 582 (1967).

(5) R. J. Scheuplein and I. H. Blank, *ibid.*, **60**, 286 (1973).

(6) I. H. Blank, *ibid.*, **43**, 415 (1964).

(7) R. J. Tregear, "Physical Functions of Skin," Academic, London, England, 1966.

(8) M. Katz and B. J. Poulson, *Handbook Exp. Pharmacol.*, **28**, 103 (1971).

(9) R. J. Scheuplein and I. H. Blank, *Physiol. Rev.*, **51**, 702 (1971).

(10) W. Montagna, *Arch. Dermatol.*, **104**, 577 (1971).

(11) S. S. Davis, T. Higuchi, and J. M. Rytting, *Adv. Pharm. Sci.*, **4**, 73 (1974).

(12) G. L. Flynn and S. H. Yalkowsky, *J. Pharm. Sci.*, **61**, 838 (1972).

(13) G. L. Flynn, S. H. Yalkowsky, and T. J. Roseman, *ibid.*, **63**, 479 (1974).

Pharmacokinetic Studies of Propoxyphene I: Effect of Portacaval Shunt on Systemic Availability in Dogs

KATHLEEN M. GIACOMINI *, SHAHEEN M. NAKEEB ‡, and GERHARD LEVY *x

Received August 20, 1979, from the **Department of Pharmaceutics and the* ‡*Department of Laboratory Animal Science, State University of New York at Buffalo, Amherst, NY 14260.* Accepted for publication February 6, 1980.

Abstract □ The elimination kinetics and systemic availability of *d*-propoxyphene were determined in dogs before and after construction of a portacaval shunt. For this purpose, the drug was administered intravenously and orally, in aqueous solution, according to a balanced experimental design. The total plasma clearance of propoxyphene ranged from 14.4 to 31.8 ml/min/kg before the shunt and decreased appreciably in two of four dogs after shunting. There was no significant change in the serum protein binding of the drug. The systemic availability increased from an average of 25% before to an average of 54% after shunting ($p < 0.05$). The ratio of areas under the plasma concentration–time curve of norpropoxyphene to propoxyphene was not significantly affected by the shunt when propoxyphene was administered intravenously; it decreased substantially after shunting when the drug was administered orally. Pharmacokinetic analysis indicates that orally administered propoxyphene is subject to prehepatic as well as hepatic first-pass elimination in dogs. The magnitude of the first-pass effect is similar to that in humans. These results suggest that the dosage of orally administered propoxyphene should be reduced in patients with portacaval shunt or with cirrhosis of the liver.

Keyphrases □ Pharmacokinetics—propoxyphene, effect of portacaval shunt on systemic availability, dogs □ Propoxyphene—pharmacokinetics, effect of portacaval shunt on systemic availability, dogs □ Systemic availability—propoxyphene, effect of portacaval shunt, dogs

The analgesic propoxyphene (*d*-propoxyphene) is one of the most frequently prescribed drugs in the United States. About 31 million prescriptions for it were issued in 1978 (1). Large doses can be fatal and often have been used to commit suicide. Propoxyphene also has been implicated in accidental deaths. A number of these deaths apparently occurred as a result of the consumption of propoxyphene in quantities only slightly larger than the upper limit of the recommended dosage, usually together with alcohol and/or other central nervous system (CNS) depressants (1).

BACKGROUND

Propoxyphene is subject to a pronounced first-pass effect in that only a small fraction of the absorbed dose enters the general circulation in unmetabolized form (2–4). Moreover, there are very large and apparently relatively consistent interindividual differences in the systemic availability of propoxyphene in humans (2–6). This fact suggests that certain accidental (as opposed to suicidal) poisonings due to propoxyphene may result from an unfortunate coincidence of a large (probably larger than prescribed) dose, an unusually small first-pass effect relative to the population average, and ingestion of one or more CNS depressants. For this and other obvious reasons, it is important to determine the factors responsible for interindividual differences in the first-pass effect on propoxyphene.

An orally administered drug may be subject to hepatic as well as prehepatic (intestinal) first-pass effects. The relative contribution of these two sites of biotransformation is important in assessing the reasons for interindividual differences in the systemic availability and for predicting the possible effect of surgically induced or endogenous portacaval shunts (*i.e.*, shunts due to hepatic cirrhosis). There are indirect indications, based on pharmacokinetic analysis of systemic availability relative to total clearance, that propoxyphene may be subject to some prehepatic biotransformation in humans (3, 4).

It is not possible to determine the magnitude of the prehepatic biotransformation of a drug such as propoxyphene by comparing its systemic availability in normal subjects and in patients with surgically constructed portacaval shunts. Such shunts are used to relieve variceal bleeding secondary to portal hypertension caused by hepatic cirrhosis and other pathological conditions associated with obstruction of portal blood flow. Liver disease and the drugs taken by the recipients of a portacaval shunt may modify the metabolic clearance of propoxyphene and thereby introduce an additional variable that cannot be controlled or defined readily because propoxyphene is not available for intravenous injection. Moreover, patients with portacaval shunts can develop various degrees of collateral circulation. Therefore, it is necessary to conduct studies on a suitable animal model.

Some published evidence suggested that the dog, like humans, exhibits a pronounced first-pass effect on orally administered propoxyphene (7). Demethylation to norpropoxyphene is a major elimination pathway of propoxyphene in both species (8). The dog is large enough for the convenient surgical construction of a portacaval shunt. Other investigators successfully used dogs to study the first-pass effect on orally administered drugs before and after a portacaval shunt (9).

In the present investigation, propoxyphene was administered both orally and intravenously to dogs before and after a portacaval shunt, according to a balanced experimental design. Propoxyphene was administered intravenously before and after surgery because the shunt may affect the plasma clearance of a drug (9). There is conflicting evidence concerning the dose dependence of the first-pass effect on propoxyphene in humans (2–4, 10, 11). The intravenous dose in this study was lower than the oral dose so that the areas under the concentration–time curve produced by both routes of drug administration would be similar.

0022-3549/80/0700-0786$01.00/0

Table I—Experimental Design Indicating the Order of Intravenous and Oral Propoxyphene Administration [a]

Dog	Before Shunt		After Shunt	
	Intravenous	Oral	Intravenous	Oral
1	1	2	3	4
2	1	2	4	3
3	2	1	3	4
4	2	1	4	3

[a] Intravenous and oral doses of *d*-propoxyphene hydrochloride were 2.0 and 7.5 mg/kg, respectively.

Norpropoxyphene, a major metabolite of propoxyphene, is eliminated from the body much more slowly than its precursor and appears prominently in the circulation following propoxyphene administration (12, 13). The formation and elimination kinetics of norpropoxyphene are of clinical interest because this metabolite, like propoxyphene, can depress cardiac conduction and may contribute to the cardiac toxicity produced by ingestion of large amounts of propoxyphene (14–16). Therefore, norpropoxyphene concentrations also were determined in this investigation.

EXPERIMENTAL

Four male mongrel dogs, 14–27 kg, received *d*-propoxyphene hydrochloride intravenously (cephalic vein of the foreleg) in saline solution (0.5 ml/kg) at a dose of 2 mg/kg and orally in 100 ml of water *via* a stomach tube at a dose of 7.5 mg/kg. The dogs were fasted overnight and during the study. The doses were administered according to a crossover design (Table I) at 1-week intervals. Prior to each dose, a heparin trap was placed in a cephalic vein and 10 ml of blood was withdrawn. After drug administration, 10-ml blood samples were withdrawn serially for 8 hr.

One week after administration of the second dose, a modified side-to-side portacaval shunt was constructed under pentobarbital sodium anesthesia (30 mg/kg). The technique employed was that of a straight Eck fistula (17). Basically, this technique involved anastomosing the side of the portal vein to the side of the vena cava and then tying off the portal vein just proximal to the liver. Thus, a complete shunt of blood from the portal vein to the vena cava was produced.

One to 2 weeks after construction of the shunt, the dogs again received propoxyphene orally and intravenously (same dose per kilogram as before the shunt). As before, 1 week elapsed between administration of the two doses. Blood samples were collected as described.

Plasma was assayed simultaneously for propoxyphene and norpropoxyphene by the GLC method of Verebely and Inturrisi (18) with the following minor modifications. The gas chromatograph[1] had a 182.9-cm long × 2-mm i.d. glass spiral column. The column, detector, and injector port temperatures were 220, 240, and 230°, respectively. The carrier gas flow was 40 ml/min. The internal standard was trifluperazine. Under these conditions, the retention times for propoxyphene, norpropoxyphene, and trifluperazine were 2.5, 7.0, and 10 min, respectively. The assay is sensitive to 50 ng of propoxyphene and 100 ng of norpropoxyphene. The volume of plasma used for the assay was adjusted to yield amounts of the drug and the metabolite in the 500–3500-ng range. The coefficient of variation of the assay in this range was 6.3% for propoxyphene and 7.0% for norpropoxyphene.

The plasma protein binding of propoxyphene in each dog before and after portacaval anastamosis was determined by equilibrium dialysis. Two 1.5-ml predose plasma samples from each dog were dialyzed at 37° against an equal volume of pH 7.4 Sorensen phosphate buffer (0.13 *M*) containing *d*-propoxyphene hydrochloride (1.2 μg/ml), using Plexiglas cells separated by a cellophane membrane[2]. The dialysis time was 12 hr.

The total protein concentrations in the plasma of each dog before and after portacaval shunt were determined by the method of Gornall *et al.* (19) with crystalline dog albumin as the standard. The albumin fractions were determined by electrophoresis[3], and albumin concentrations were obtained by multiplying the total protein concentration by the fraction of albumin.

The area under the plasma concentration–time curve (*AUC*) after oral drug administration was calculated by the trapezoidal method for the first 8 hr and then extrapolated to infinity according to $AUC_{t-\infty} = C_t/\beta$, where $AUC_{t-\infty}$ is the area under the plasma concentration–time curve from the last observed plasma concentration (obtained at 8 hr) to infinity, C_t is the plasma concentration at 8 hr, and β is the terminal disposition rate constant (determined after intravenous injection). The $AUC_{t-\infty}$ was ~20% of $AUC_{0-\infty}$ before the shunt and ~28% after the bypass.

The plasma propoxyphene concentrations obtained after intravenous injection were fitted to the equation $C = Ae^{-\alpha t} + Be^{-\beta t}$ by a nonlinear least-squares regression procedure (20). The data were weighted by use of their reciprocal. The $AUC_{0-\infty}$ value was determined as the sum of A/α and B/β.

The total clearance, *Cl*, was calculated according to $Cl = D_{iv}/AUC_{iv}$, where D_{iv} is the intravenous dose of the free base and AUC_{iv} is the area under the intravenous plasma concentration–time curve from time zero to infinity.

The systemic availability, *F*, was calculated from $F = (100 \times D_{iv} \times AUC_{po})/(D_{po} \times AUC_{iv})$, where D_{iv} and D_{po} are the respective intravenous and oral doses and AUC_{po} and AUC_{iv} are the respective total areas under the plasma concentration–time curves following the oral and intravenous doses.

Table II—Pharmacokinetics of Propoxyphene in Dogs before and after Portacaval Shunt

Parameter[a]	Before	After
A, ng/ml	1360 ± 390[b]	1530 ± 435
B, ng/ml	237 ± 70	425 ± 30
α, hr^{-1}	4.13 ± 1.22	5.48 ± 1.30
β, hr^{-1}	0.202 ± 0.033	0.223 ± 0.032
Free fraction in plasma[c]	0.129 ± 0.037	0.159 ± 0.031

[a] Based on the relationship $C = Ae^{-\alpha t} + Be^{-\beta t}$, where *C* is the drug concentration in plasma at time *t* after intravenous injection of 1.81 mg (expressed as the base)/kg of body weight. [b] Mean ± *SEM*, $n = 4$. [c] At a total drug concentration at equilibrium of ~1000 ng/ml.

RESULTS

The propoxyphene concentrations in plasma declined biexponentially after intravenous injection. The drug was absorbed very rapidly after oral administration (Figs. 1 and 2). The pharmacokinetic constants for the elimination of injected propoxyphene are listed in Table II. The plasma total protein and albumin concentrations were 6.5 ± 0.2 and 3.0 ± 0.1 g/100 ml before the shunt and 6.0 ± 0.6 and 2.6 ± 0.2 g/100 ml after the shunt (mean ± *SEM*, differences not significant), respectively. The free fraction values of propoxyphene in plasma were similar before and after shunting (Table II).

The plasma clearance of injected propoxyphene was high (Table III) and comparable in magnitude to the hepatic plasma flow rate in dogs (21). It decreased appreciably after the portacaval shunt in the two dogs that exhibited the highest clearance values before the shunt (Dogs 2 and 3). The systemic availability of orally administered propoxyphene increased substantially after shunt construction in all of the animals; the average increase was from 25% before to 54% of the dose after the shunt (Table III). The areas under the concentration–time curve, time zero to infinity, following oral administration of propoxyphene increased even more, changing from 1470 ± 450 (ng hr)/ml before to 4390 ± 645 (ng hr)/ml after the bypass (mean ± *SEM*, $p < 0.025$).

Pertinent information concerning the norpropoxyphene concentrations in plasma is summarized in Table IV. The delayed occurrence of maxi-

Table III—Systemic Availability and Total Clearance of Propoxyphene in Dogs before and after Portacaval Shunt

Dog	Before		After	
	Availability[a], %	Clearance[b], ml/min/kg	Availability[a], %	Clearance[b], ml/min/kg
1	24.9	14.4	72.6	15.8
2	16.2	25.8	25.1	11.0
3	20.3	31.8	59.1	12.3
4	39.7	17.9	60.1	15.7
Mean	25.3	22.5	54.2[c]	13.7
SEM	5.1	3.9	10.2	1.2

[a] Systemic availability of an oral dose of 6.79 mg (base)/kg. [b] Total plasma clearance of a 1.81-mg (base)/kg intravenous dose. [c] Significantly different from availability before shunt ($p < 0.05$ by paired *t* test).

[1] Hewlett-Packard model 5830.
[2] Cut from dialysis tubing having an average pore radius of 24 Å, VWR Scientific, Rochester, N.Y.
[3] Serum protein electrophoresis system, Gelman Instrument Co., Ann Arbor, Mich.

Table IV—Concentrations of Norpropoxyphene in Plasma of Dogs following Intravenous and Oral Administration of Propoxyphene before and after Portacaval Shunt

	Intravenous[a]		Oral[b]	
	Before	After	Before	After
Maximum concentration, ng/ml	459 ± 152[c]	462 ± 67	2310 ± 1040	1820 ± 775
Time of maximum concentration, hr	0.8 ± 0.2	3.6 ± 1.0	1.8 ± 0.8	3.5 ± 1.0
Area under 0–8-hr curve, (ng hr)/ml	2440 ± 855	3380 ± 795	12,600 ± 5700	11,000 ± 5300
Ratio of areas[d] of norpropoxyphene to propoxyphene	1.87 ± 0.46	1.90 ± 0.47	10.4 ± 3.1	3.34 ± 1.14[e]

[a] 1.81 mg (base)/kg. [b] 6.79 mg (base)/kg. [c] Mean ± *SEM*, $n = 4$. [d] Areas under 0–8-hr plasma concentration curve. [e] Significantly different from ratio value before shunt ($p < 0.05$ by paired t test).

mum concentrations and apparently increased areas under the 0–8-hr concentration–time curve after intravenous injection of propoxyphene suggest decreased clearance of the metabolite after the shunt, but the differences were not statistically significant. The ratio of areas under the concentration–time curve (*AUC* ratio) of norpropoxyphene to propoxyphene after intravenous injection of propoxyphene was not affected by the portacaval shunt. The *AUC* ratio after oral administration of the drug was much higher than after intravenous injection and decreased appreciably after construction of the portacaval shunt (Table IV).

DISCUSSION

The dogs in this study received oral propoxyphene as an aqueous solution. Consistent with the results of clinical studies (2, 4–6, 8, 11–13), the drug was absorbed rapidly after oral administration. A clinical study showed that there is no apparent difference in the systemic availability of propoxyphene administered in capsules and in solution (11). The urinary recovery of radioactivity following oral and intravenous administration of [^{14}C]propoxyphene is not significantly different (4). On the basis of this information, it is reasonable to conclude that the incomplete systemic availability of propoxyphene observed in this study is due to presystemic biotransformation rather than incomplete absorption.

Gram *et al.* (4) found that the systemic availability of orally administered propoxyphene hydrochloride in humans was independent of the dose in the 65–195-mg dose range. The use of oral to intravenous *AUC* ratios in the present study to determine the systemic availability of orally administered propoxyphene in dogs was based on the assumption that the kinetics were linear under the experimental conditions. Moreover, the oral and intravenous doses were chosen to produce similar *AUC* values to minimize the effect of possible nonlinearity on the systemic availability determinations.

As in humans, the plasma clearance of injected propoxyphene in dogs is high and comparable in magnitude to the hepatic plasma flow rate. Since the renal clearance of propoxyphene is very low (8, 12), the plasma clearance of the drug is due almost entirely to metabolism. Therefore, propoxyphene should be subject to a large first-pass effect, based on theoretical pharmacokinetic considerations (3). Its plasma clearance after intravenous injection should be affected by the activity of drug-metabolizing enzyme systems and by hepatic blood flow (3), both of which may be reduced following the portacaval shunt (9, 22). Indeed, the plasma clearance of propoxyphene was substantially decreased in two of four dogs after the shunt. The two affected animals had the highest propoxyphene clearance before surgery and, therefore, were most sensitive to a reduction of hepatic blood flow. Other investigators reported reduction of lidocaine and antipyrine clearance after portacaval shunting in dogs (9).

The systemic availability of propoxyphene increased, but was not complete, after the portacaval shunt. This result suggests that the drug is subject to a prehepatic first-pass effect, which is consistent with the tentative conclusions of investigators who noted that the observed first-pass effect on propoxyphene in humans is larger than the magnitude of the hepatic first-pass effect predicted on the basis of pharmacokinetic considerations (3, 4).

If a drug is subject to prehepatic as well as hepatic first-pass biotransformation, then the fraction of the dose available systemically, F,

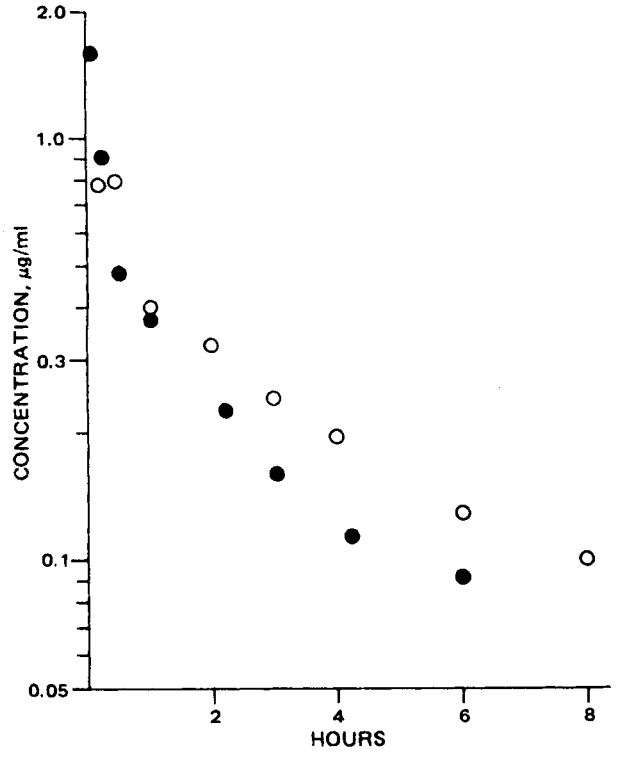

Figure 1—*Concentrations of* d-*propoxyphene in plasma of Dog 4 after oral administration of 7.5 mg/kg* (○) *and intravenous injection of 2.0 mg/kg* (●) *of propoxyphene hydrochloride in separate experiments before portacaval shunt.*

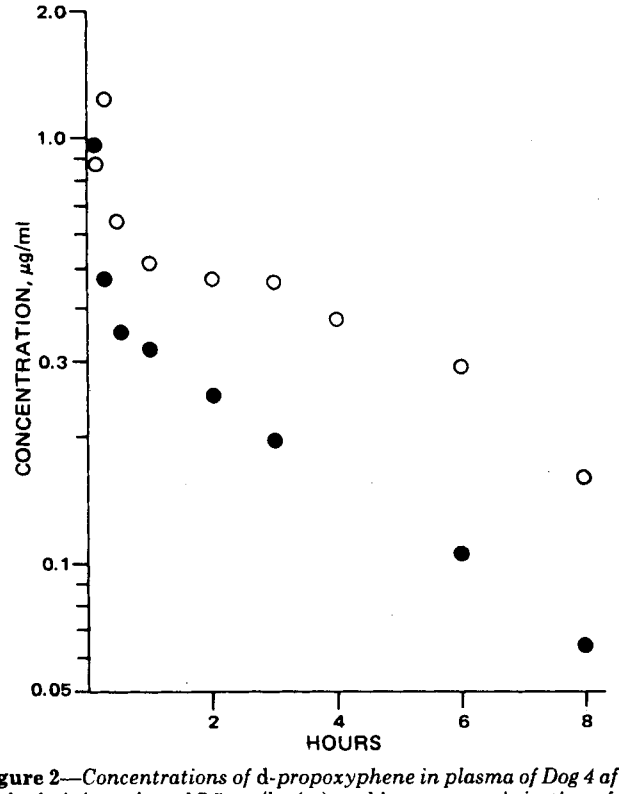

Figure 2—*Concentrations of* d-*propoxyphene in plasma of Dog 4 after oral administration of 7.5 mg/kg* (○) *and intravenous injection of 2.0 mg/kg* (●) *of propoxyphene hydrochloride in separate experiments after portacaval shunt.*

is $F_{PH}F_H$, where F_{PH} is the fraction of the dose reaching the liver as intact drug and F_H is the fraction of the drug reaching the liver intact that enters the systemic circulation in unmetabolized form. If $F_{PH} = F$ after portacaval shunt (assuming that F_{PH} was not affected by the surgery and that there was no significant development of collateral circulation after the surgery), then F_H before surgery was 0.253/0.542 or 0.47 (based on the average systemic availability values from Table III). Thus, the prehepatic and hepatic first-pass effects on propoxyphene appear to be of similar magnitude in the dog.

Hepatic cirrhosis often is associated with the formation of portacaval shunts and reduction of drug-metabolizing enzyme activity (23, 24). These changes should increase the systemic availability of a drug with the pharmacokinetic characteristics of propoxyphene. This increase should be less pronounced if a substantial part of the first-pass effect is due to prehepatic biotransformation, provided that liver disease does not affect the prehepatic metabolism of propoxyphene. Unfortunately, the effect of liver disease on the prehepatic biotransformation of drugs is not known. However, it appears prudent to reduce the dosage of propoxyphene in patients with portacaval shunt or with cirrhosis of the liver.

REFERENCES

(1) *Fed. Regist.*, **44**, 11837 (1979).

(2) R. L. Wolen, C. M. Gruber, Jr., G. F. Kiplinger, and N. E. Scholz, *Toxicol. Appl. Pharmacol.*, **19**, 480 (1971).

(3) D. Perrier and M. Gibaldi, *J. Clin. Pharmacol.*, **12**, 449 (1972).

(4) L. F. Gram, J. Schou, W. L. Way, J. Heltberg, and N. O. Bodin, *Clin. Pharmacol. Ther.*, **26**, 473 (1979).

(5) G. W. A. Slywka, A. P. Melikian, P. L. Whyatt, and M. C. Meyer, *J. Clin. Pharmacol.*, **15**, 598 (1975).

(6) A. Melander, A. Berlin-Wahlen, N. O. Bodin, K. Danielson, G. Gustafsson, L. Lindgren, and D. Westerlund, *Acta Med. Scand.*, **202**, 119 (1977).

(7) R. E. McMahon and H. R. Sullivan, *Res. Commun. Chem. Pathol. Pharmacol.*, **14**, 631 (1976).

(8) R. E. McMahon, A. S. Ridolfo, H. W. Culp, R. L. Wolen, and F. J. Marshall, *Toxicol. Appl. Pharmacol.*, **19**, 427 (1971).

(9) R. Gugler, P. Lain, and D. L. Azarnoff, *J. Pharmacol. Exp. Ther.*, **195**, 416 (1975).

(10) R. L. Wolen, E. A. Ziege, and C. M. Gruber, *Clin. Pharmacol. Ther.*, **17**, 15 (1975).

(11) J. G. Wagner, P. G. Welling, S. B. Roth, E. Sakmar, K. P. Lee, and J. E. Walker, *Int. J. Clin. Phdrmacol.*, **5**, 371 (1972).

(12) K. Verebely and C. E. Inturrisi, *Clin. Pharmacol. Ther.*, **15**, 302 (1973).

(13) R. L. Wolen, B. D. Obermeyer, E. A. Ziege, H. R. Black, and C. M. Gruber, in "Stable Isotopes. Applications in Pharmacology, Toxicology, and Clinical Research," T. A. Baille, Ed., University Park Press, Dallas, Tex., 1978, p. 113.

(14) R. Nickander, S. E. Smits, and M. I. Steinberg, *J. Pharmacol. Exp. Ther.*, **200**, 245 (1977).

(15) H. Lund-Jacobsen, *Acta Pharmacol. Toxicol.*, **42**, 171 (1978).

(16) D. R. Holland and M. I. Steinberg, *Toxicol. Appl. Pharmacol.*, **47**, 123 (1979).

(17) J. Markowitz, J. Archibald, and H. G. Downie, "Experimental Surgery," Williams & Wilkins, Baltimore, Md., 1964, p. 542.

(18) K. Verebely and C. E. Inturrisi, *J. Chromatogr.*, **75**, 195 (1973).

(19) A. C. Gornall, C. J. Bardawill, and M. M. David, *J. Biol. Chem.*, **177**, 751 (1949).

(20) C. M. Metzler, "NONLIN, A Computer Program for Parameter Estimation in Nonlinear Situations," Upjohn Co., Kalamazoo, Mich., 1969.

(21) P. L. Altman and D. S. Dittmer, "Biological Data Book," vol. III, 2nd ed., Federation of American Societies for Experimental Biology, Bethesda, Md., 1974, p. 1701.

(22) R. Kato, *Xenobiotica*, **7**, 25 (1977).

(23) E. A. Neal, P. J. Meffin, P. B. Gregory, and T. F. Blaschke, *Gastroenterology*, **77**, 96 (1979).

(24) D. G. Shand, *ibid.*, **77**, 184 (1979).

ACKNOWLEDGMENTS

Supported in part by Grant GM 20852 from the National Institute of General Medical Sciences, National Institutes of Health.

Anti-Inflammatory and Analgesic Profile of Amidines of 3-Amino-1,2,4-benzotriazine and 3-Amino-1,2,4-benzotriazine-1-oxide

B. A. REGAN, J. W. HANIFIN, M. J. LANDES, A. C. OSTERBERG, G. J. PATEL, D. N. RIDGE, A. E. SLOBODA, and S. A. LANG, Jr. ˣ

Received March 19, 1979, from the *Medical Research Division, American Cyanamid Company, Pearl River, NY 10965.* Accepted for publication February 6, 1980.

Abstract □ Several formamidine and acetamidine derivatives prepared from 3-amino-1,2,4-benzotriazine and 3-amino-1,2,4-benzotriazine-1-oxide displayed an aspirin-like anti-inflammatory and analgesic profile. The test systems included adjuvant-induced arthritis in rats, carrageenan-induced edema in rats, UV-induced erythema in guinea pigs, the analgesic gait test, the antipyretic test, and GI ulcer studies.

Keyphrases □ Anti-inflammatory activity—amidine derivatives of 3-amino-1,2,4-benzotriazines and their 1-oxides, synthesis and testing, rats □ Analgesic activity—amidine derivatives of 3-amino-1,2,4-benzotriazines and their 1-oxides, synthesis and testing, rats □ 3-Amino-1,2,4-benzotriazines—amidine derivatives, synthesis and testing for anti-inflammatory and analgesic activity, rats

Various new, nonsteroidal, anti-inflammatory agents such as ibuprofen, tolmetin, fenoprofen, naproxen, and sulindac have been introduced to the medical community in the past several years (1). Although these agents ameliorate the arthritic condition, they are not curative and have adverse effects, largely GI disturbances (1).

The continuing interest and need for more efficacious and safe anti-inflammatory agents prompted the synthesis of various formamidine and acetamidine derivatives of 3-amino-1,2,4-benzotriazine and 3-amino-1,2,4-benzotriazine-1-oxide. These agents were tested for analgesic, anti-inflammatory, and antipyretic properties in a battery of tests including adjuvant-induced arthritis, carrageenan-induced edema, and UV-induced guinea pig erythema (2, 3). Particular emphasis was placed on GI toxicity. The results are presented, and the potential of the active series is discussed.

RESULTS AND DISCUSSION

Chemistry—The amidines were prepared by the reaction of the

0022-3549/80/0700-0789$01.00/0