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Interactions in Rats Between the Nonsteroidal Antiinflammatory Drugs, Aspirin and Fenoprofen (38397)

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(Introduced by C. M. Gruber)

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We recently observed a pharmacodynamic interaction in healthy volunteers between two antiinflammatory agents, aspirin and fenoprofen. When subjects received both drugs the concentrations of fenoprofen in plasma were lowered significantly, compared to those attained after fenoprofen alone (1). This lowering occurred after both oral and intravenous administration of fenoprofen. The lower plasma concentrations of fenoprofen were associated with a reduction in area under the plasma concentration *versus* time curve, a reduction in peak concentration and a shorter fenoprofen half-life. The magnitude of the reduction of fenoprofen concentrations depended upon the aspirin dosage. In contrast to these findings, fenoprofen did not affect plasma salicylate concentrations when both drugs were co-administered. The reduced fenoprofen plasma concentrations were not totally explainable by effects of aspirin upon protein binding, metabolism or excretion of fenoprofen. In this present paper we describe studies in rats designed to elucidate the mechanism of this drug–drug interaction, including an extension of our earlier experimental designs to permit study of the tissue distribution of fenoprofen, when administered alone and with aspirin.

Similar to our earlier results in man, the fenoprofen concentrations in plasma were lowered by aspirin in the rat. Although our findings still do not provide a complete explanation of the mechanism of this aspirin/fenoprofen interaction, they do suggest that the mechanisms differ in rat and man.

Materials and Methods. Animals. Sprague–Dawley male rats (Harlan Industries in Cumberland, IN), weighing 50–55 g, were kept for 4 days in our animal facilities before use. They were housed in washed plastic cages with pine shavings. Pesticides were not applied in the animal quarters or to the cages during the experiments. Temperature and humidity were controlled in the ranges of 20–25° and 28–34%, respectively. The room lights were off from 6 PM to 6 AM. Purina Laboratory Chow was withdrawn about 12 hr before administration of fenoprofen and was not available during time of plasma sampling or urine collection. Water was always available. No overt evidence of toxic effects from any of the treatments was exhibited (based upon weight loss, hair loss or discoloration, altered grooming behavior or locomotion).

Dosage and dosage forms. Aspirin was dissolved in a minimal amount of 1 *N* NaOH. The solution (prepared fresh daily) was diluted immediately to the desired concentration (12–36 mg/ml) with 0.9% saline, and then adjusted to pH 7.4, if necessary. The aspirin dosage was 62.5 mg/kg twice daily (7:30 AM and 3:30 PM) for 3 days, except when otherwise indicated. On the third night the rats were fasted until the morning of day 4, at which time fenoprofen was given simultaneously with aspirin or its vehicle.

Control animals received the aspirin vehicle, *i.e.*, 0.9% saline adjusted with a small amount of 0.1 *N* NaOH to pH 7.4.

Fenoprofen calcium was suspended by manual homogenization in a solution of saline-Tween 20 (Technicon Corp.) at a ratio of 2 drops Tween 20/10 ml saline. A Duall tissue grinder (Kontes Glass Co., Vineland, NJ) with a clearance of 0.004–0.006 in. was used for the homogenization. The final concentration of fenoprofen in the suspension was 10 mg/ml.

In some experiments, ^{14}COOH-fenoprofen calcium was mixed with the unlabeled fenopro-

fen to a specific activity between 0.1 and 0.25 μCi/mg. The radioactive compound was 99% pure and the position of the label was reported to be metabolically stable in rats (2).

Volumes administered to the rats, in each case, were 0.2 ml or less. The drugs were injected ip for the first experiment, but thereafter were given orally by stomach tube.

Plasma collections. At selected time periods, approximately 2 ml of blood were collected in heparinized capillary tubes by puncturing the orbital sinus. Six animals in each treatment group were bled at each time period; no rat was bled more than once. The blood was centrifuged and the separated plasma was frozen until analyzed. After bleeding, animals were killed by a blow to the head. When additional studies were planned, the cadavers were quick-frozen in liquid N_2 and were stored at $-20°$ until analyzed.

Urine collections. Groups of four rats were placed in metabolism cages immediately after fenoprofen administration. Glass wool plugs were placed in the funnels of the metabolism cages to avoid contaminating the urine with feces. No food was available during urine collection. Pooled urine specimens were collected, without a preservative, at intervals for 24 hr. After each collection period, the funnels were rinsed with approximately 5 ml distilled water, which was added to the urine. The volume of urine plus rinse water was measured and used for subsequent calculations.

Fenoprofen assays. Plasma fenoprofen concentrations were measured by gas liquid chromatography (3). Plasma and urinary metabolites of fenoprofen were also assayed by GLC by modifying the extraction procedures described earlier (4). The modification, using methylene chloride as the organic solvent, permitted extracting both fenoprofen and 4′-hydroxyfenoprofen simultaneously. This extract was then evaporated to dryness, derivitized with Tri–Sil TBT (Pierce Chemical Co., Rockford, IL) and injected into the chromatographic column.

Radiochemical assays. As detailed in our earlier publication, samples were counted using a Beckman Model LS-100 liquid scintillation spectrometer and were corrected for background and quenching (5). Counting efficiencies exceeded 80%.

Plasma aliquots (0.1 or 0.2 ml) were counted in 10 ml Scintisol-Complete (Isolab Inc., Akron, OH). Urine aliquots (0.1 ml) were counted in 10 ml of a phosphor solution containing 0.5% 2,5 diphenyloxazole (PPO) in 1:1 toluene:Methyl Cellosolve.

Erythrocytes were washed three times with saline, dried at room temperature and combusted in an O_2 atmosphere for counting.

Liver, lung, kidney, stomach and intestinal tract were excised and homogenized in less than 1 ml distilled water in the Duall tissue grinder. The remaining carcasses were homogenized intact in 50 ml of distilled water in a Waring blender operated at high speed for 10 min; the homogenates were then strained through cheese cloth, and aliquots were digested overnight in 1 ml of Soluene (Packard Instrument, Downers Grove, IL). The resultant solution was neutralized with 50 μl of glacial acetic acid, and was counted in 10 ml of 0.5% PPO in toluene.

Zoxazolamine "sleeping times." Zoxazolamine, dissolved in 0.2 *N* HCl, was administered ip to rats at a dosage of 75 mg/kg. "Sleeping time" was considered as the length of time from loss to recovery of the righting reflex (6). A decrease in "sleeping time" was considered as an enzyme inductive effect.

Results and Discussion. 1. *Aspirin and fenoprofen, intraperitoneal.* Our first intention was to determine whether aspirin pretreatment would lower plasma fenoprofen concentrations in rats as it does in man. The dose of aspirin, 62.5 mg/kg bid was selected because it reduces inflammation in rats (7) and is comparable to doses taken by patients with severe and active rheumatoid arthritis. The aspirin solution (or its vehicle for control animals) was injected ip for 3 days, and on the fourth day the rats were challenged with 25 mg/kg fenoprofen intraperitoneally.

In rats as in man, fenoprofen plasma concentrations were lowered significantly by aspirin treatment (Fig. 1). Based upon mean areas under the plasma disposition curves, the aspirin group was reduced 70% compared to the vehicle-treated group. The mean peak concentration of fenoprofen was reduced 78% in the aspirin group.

During the first 9 hr after fenoprofen administration, we did not observe a linear relationship between the logarithm of the fenoprofen plasma concentration and time; therefore, we could not confidently estimate the fenoprofen plasma half-life.

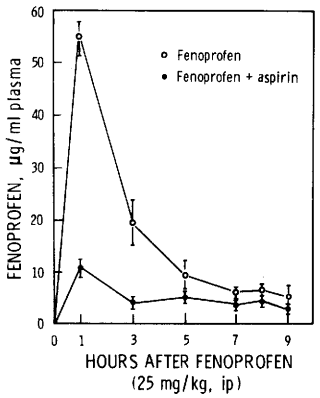

FIG. 1. Plasma fenoprofen concentrations in rats pretreated intraperitoneally for 3 days with aspirin (62.5 mg/kg bid) or vehicle before administration of fenoprofen. Each point represents the mean of six rats ± SE.

2. *Aspirin and fenoprofen, oral.* Having demonstrated that aspirin could reduce fenoprofen concentrations in rat plasma, we felt that this finding might be more relevant to man if it occurred when the drugs were administered orally. Consequently, in the next experiment the route of administration of aspirin and fenoprofen was changed from intraperitoneal to oral.

^{14}COOH-fenoprofen (25 mg/kg) was administered orally to rats pretreated orally for 3 days with either vehicle or aspirin (62.5 mg/kg bid).

Plasma. In plasma, radioactivity levels due to fenoprofen and its metabolites were notably higher than the corresponding fenoprofen concentrations determined by GLC, particularly during the first 3–4 hr after administration (Figs. 2A and 2B). This finding indicates that considerable amounts of metabolites circulate in rat plasma in contrast to human plasma in which virtually all plasma radioactivity of subjects given ^{14}C-fenoprofen is accounted for as fenoprofen itself (5).

Compared to vehicle-treated controls, the plasma radioactivity after administration of ^{14}C-fenoprofen was lower in the aspirin-treated group at all time periods. Likewise, the area under the plasma radioactivity curve was decreased by about 32% (Fig. 2A). Aspirin decreased the concentrations of fenoprofen itself by 53% (based upon area) (Fig. 2B).

Metabolite concentrations in plasma were significantly increased ($P < 0.05$) in the aspirin-treated rats 3 hr after fenoprofen administration (Fig. 2C). When individual metabolites were assayed in the 1- and 3-hr plasma samples, we observed increased concentrations of conjugated fenoprofen in the plasma of aspirin-treated rats (Fig. 3).

^{14}COOH-fenoprofen was used in this experiment in the hope that it would facilitate estimation of plasma half-life by allowing us to measure the fenoprofen concentrations over an extended time interval. However, as occurred in the first experiment, we had difficulty estimating accurately the fenoprofen half-life because the mean plasma concentrations were not yet log-linear with time even when plasma samples were analyzed 13 hr after fenoprofen administration. Unfortunately, the administration of radioactive fenoprofen did not increase assay sensitivity for fenoprofen in plasma because, as mentioned above, radio-labeled metabolites of fenoprofen, as well as fenoprofen itself, were circulating in rat plasma. Nevertheless, no *gross* differences were detected between the vehicle and aspirin-treated groups with respect to disappearance rates of plasma radioactivity and/or plasma fenoprofen. The half-life of the radioactivity in plasma was 3.5 hr in both treatment groups;

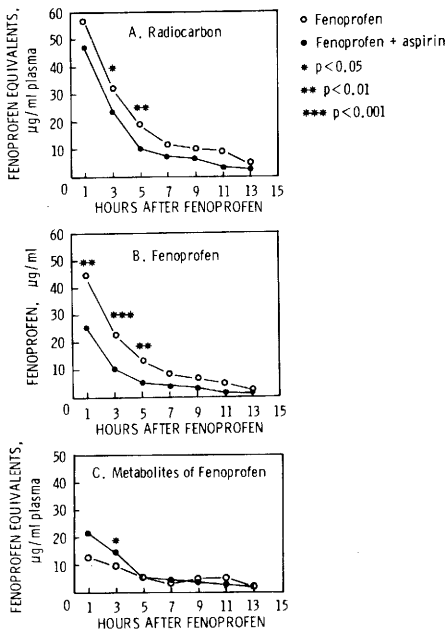

FIG. 2. Plasma concentrations of radiocarbon (a), fenoprofen (b) and fenoprofen metabolites (c) in rats given ^{14}C-fenoprofen (25 mg/kg po) after pretreatment orally with aspirin (62.5 mg/kg bid) or vehicle for 3 days. Each point represents the mean of six rats.

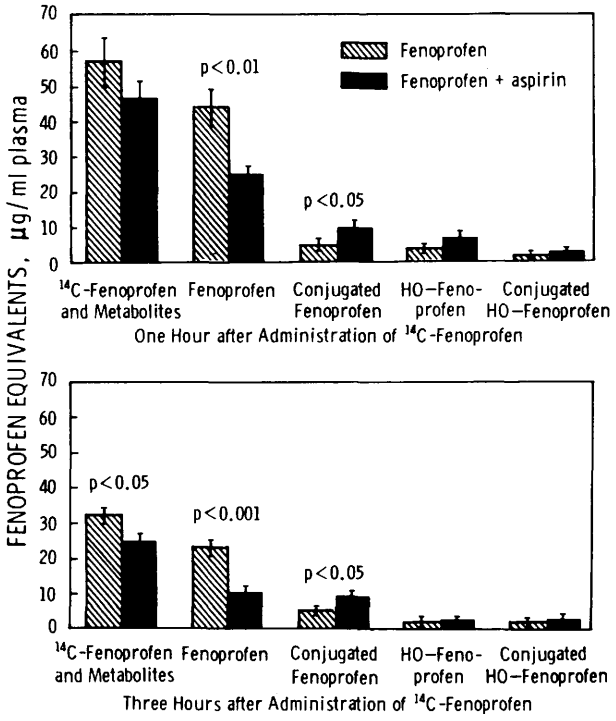

FIG. 3. Plasma concentrations of fenoprofen and its metabolites in rats given ^{14}C-fenoprofen (25 mg/kg po) after pretreatment orally with aspirin (62.5 mg/kg bid) or vehicle for 3 days. Values are means ± SE of six rats.

fenoprofen half-life was approximately 3.5 hr in the control animals and 3.1 hr in the aspirin-treated animals.

^{14}C Distribution in tissues. In an effort to explain the lower radioactivity in plasma of aspirin-treated rats, we measured the radioactivity in several tissues to determine whether aspirin had caused more fenoprofen and/or its metabolites to be taken up from the systemic circulation into tissues.

Only trace amounts of radiocarbon were found in erythrocytes with no statistical differences detectable between the two treatment groups.

The radioactivity levels in liver, kidney, lung, stomach, intestinal tract and the remaining carcass showed no statistically significant differences between the two treatment groups (Fig. 4) at 1 hr after fenoprofen administration. Though not shown on Fig. 4, this was true whether data were expressed as radioactivity per organ or as radioactivity per milligram tissue. However, the mean radioactivity level per mg tissue in the stomach of the aspirin-treated group was twice that of the control animals; but, with a large within-treatment variation, this increase was not statistically significant. Despite this variation in data, we suspected that the aspirin may have decreased the absorption of fenoprofen from the GI tract. When the radioactivity level of the stomach and intestinal tract was studied at the 3-hr time period, again no significant differences

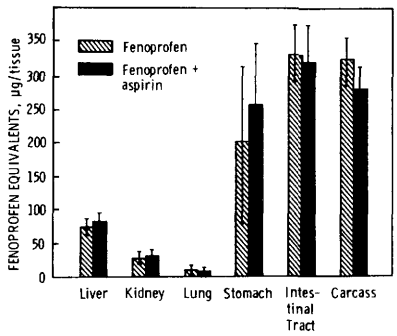

FIG. 4. Radiocarbon distribution in tissues of rats pretreated orally for 3 days with aspirin (62.5 mg/kg bid) or vehicle before administration of ^{14}C-fenoprofen. Values are means ± SE of six rats.

were detected in either tissue between the two treatment groups. Thus, an increased distribution of radiocarbon into the various organs/tissues studied did not appear to explain the lower radioactivity in plasma of aspirin-treated rats. The inability to demonstrate significant differences, if they indeed exist, may be due to the small number of animals used (six per treatment group) and the rather considerable variation within each treatment group. Another possibility is that small quantitative increases in the distribution of radiocarbon into individual tissues did indeed occur; but these increases may have been so minimal and diffuse that they were not detectable on a statistical basis in any given tissue, except in plasma which might reflect the sum of the individual minor effects. Finally, aspirin might have increased the distribution of radiocarbon into those tissues which were not studied individually (*e.g.*, brain, skeletal muscles). Studying the carcass would not necessarily point out these potential increases if the tissue(s) involved were but a minor component of the whole carcass. In any event, our data do not support a contention of an altered distribution of radiocarbon caused by aspirin.

3. *Aspirin dose response study.* Having demonstrated that aspirin at a dosage of 62.5 mg/kg bid reduced plasma fenoprofen concentrations, whether both drugs were administered orally or intraperitoneally, we proceeded to determine the relationship between the magnitude of this aspirin effect and the aspirin dosage. Aspirin doses of 30 mg/kg bid and 90 mg/kg bid were administered orally to rats for 3 days before administration of a challenge dose of 25 mg/kg fenoprofen orally.

The area under the fenoprofen plasma disposition curve was decreased 31% by the 30 mg/kg aspirin pretreatment, and 64% by the 90 mg/kg aspirin pretreatment (Fig. 5). These area decreases coupled with the aforementioned area decrease of 53% at the aspirin dosage of 62.5 mg/kg provided a positive correlation between the dose of aspirin and the magnitude of its lowering effect on plasma levels of fenoprofen. A similar dose-response relationship was shown in man (1). In contrast, however, the half-life of fenoprofen in plasma is inversely related to the dose of aspirin administered to human subjects, whereas in rats the half-life does not appear to be grossly altered by aspirin administration. Hence, in this respect (*i.e.*, shortened half-life) the mechanism of the aspirin effect appears to differ in rat and man.

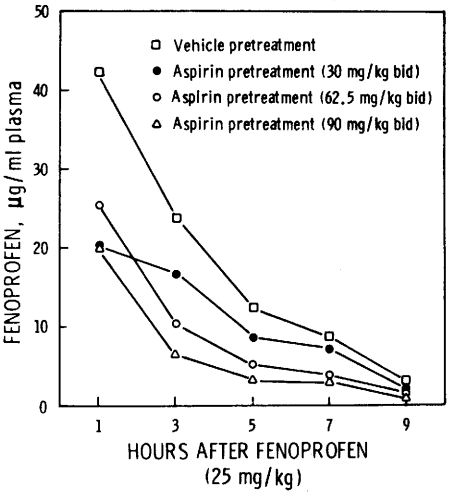

FIG. 5. Plasma fenoprofen concentrations in rats pretreated orally for 3 days with vehicle or increasing doses of aspirin before administration of fenoprofen (25 mg/kg). Each point represents the mean of six rats.

4. *Urinary disposition of fenoprofen in aspirin-treated rats.* Having found no explanation in the aforementioned studies for the decreased plasma fenoprofen concentrations following aspirin pretreatment, we turned our attention to possible effects of aspirin on the urinary excretion of fenoprofen and its metabolites. If the decreased plasma concentrations of fenoprofen when aspirin was given were due to lesser absorption of fenoprofen from the gastrointestinal tract, lower radioactivity and/or fenoprofen recoveries in urine would be expected. Of course, we already had evidence that the aspirin effect was *not* mediated by an interference with gastrointestinal absorption of fenoprofen: In rats the aspirin effect was demonstrable when both drugs were given intraperitoneally; and in man the effect occurred when fenoprofen was administered intravenously and aspirin was given orally (1).

Rats were pretreated orally for 3 days with vehicle or aspirin (62.5 mg/kg bid) before a challenge dose of ^{14}C-fenoprofen (25 mg/kg). Urine was collected at 0–2, 2–4, 4–8, 8–12 and 12–24 hr after administration. The level of total (24 hr) radioactivity in the urine of the aspirin-treated rats (Fig. 6) was significantly *greater* than control ($P < 0.02$; 88% of the administered dose of radioactivity was in the urine of the

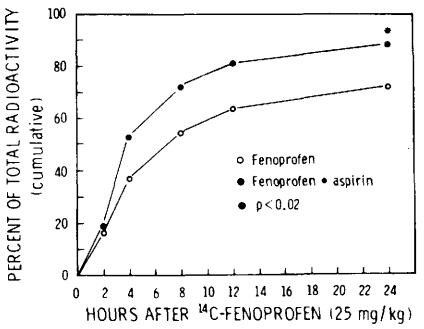

FIG. 6. Urinary excretion of radiocarbon (fenoprofen plus metabolites) in rats given ^{14}C-fenoprofen (25 mg/kg po) after pretreatment orally for 3 days with aspirin (62.5 mg/kg bid) or vehicle.

aspirin-treated group *versus* 72% in the control urine). This finding further indicates that the decreased plasma levels of radioactivity are not due to an overall decrease in the amount of radiocarbon absorbed from the GI tract after aspirin pretreatment.

In addition to determination of radioactivity, the urines were also analyzed by GLC for fenoprofen and its metabolites (conjugated fenoprofen, 4′-hydroxyfenoprofen and conjugated 4′-hydroxyfenoprofen). The aspirin-treated rats excreted more conjugated fenoprofen than vehicle treated rats ($P < 0.05$) over the total 24-hr interval (Fig. 7A).

The 2–4 hr urine specimens of the aspirin-treated rats contained more conjugated fenoprofen ($P < 0.02$) and more 4′-hydroxyfenoprofen ($P < 0.02$) compared to urines of vehicle-treated rats (Fig. 7B).

The excretion rates of fenoprofen and its metabolites were determined by linear regression analyses of the urine concentrations at the midpoints of each collection period. The excretion rates of conjugated fenoprofen and of 4′-hydroxyfenoprofen were increased (Table I). Overall, there was an increased excretion rate of the total fenoprofen plus its metabolites.

5. *Zoxazolamine "sleeping times."* The increased excretion rates mentioned above may reflect direct effects of aspirin on mechanisms of renal excretion of fenoprofen and/or may be secondary to increases in metabolism of fenoprofen to more readily excretable metabolites. The latter possibility was supported by our observation (Fig. 2C) that fenoprofen metabolites circulating in plasma were increased after aspirin pretreatment. These changes led us to suspect the possibility of an enzyme inductive effect by aspirin. Of course, had enzyme induction been involved in the aspirin effect, we would have expected to see a significant shortening of the fenoprofen half-life. As mentioned above, that was not our experience. Nevertheless, to study the possibility of an enzyme inductive effect by aspirin, zoxazolamine "sleeping times" were measured in rats pretreated with aspirin or its vehicle. A shorter zoxazolamine sleeping time in aspirin-treated rats might indicate an enzyme inductive effect by aspirin. In dogs, aspirin did not stimulate its own rate of metabolism after repeated administration (8); and in rats aspirin did not affect the metabolism of a variety of drugs after a single dose (9).

We injected rats ip with vehicle or aspirin, 125 mg/kg bid, for 2 days and 62.5 mg/kg bid for 2 additional days. On the day following the last aspirin dose, the rats were challenged ip with a paralyzing dose of 75 mg/kg of zoxazolamine. The mean "sleeping times" of the aspirin-treated animals were not statistically different from the vehicle-treated control animals (Table II). Therefore, based upon these results, it does not appear that aspirin induces the hepatic drug metabolizing enzyme systems responsible for zoxazolamine hydroxylation. By inference, the

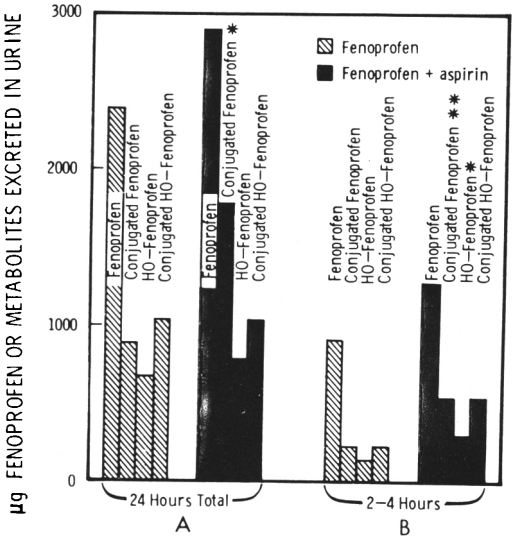

FIG. 7. Urinary excretion of fenoprofen and its metabolites in rats given ^{14}C-fenoprofen (25 mg/kg po) after pretreatment orally with aspirin (62.5 mg/kg bid) or vehicle for 3 days.

TABLE I. Effect of Aspirin Pretreatment on Urinary Excretion Rates of Fenoprofen and Its Metabolites in Rats.[a]

Treatment	Excretion rate constants, hr^{-1}			
	Fenoprofen	Conjugated fenoprofen	4′-hydroxy fenoprofen	Conjugated 4-hydroxy fenoprofen
Fenoprofen + vehicle	0.25	0.25	0.12	0.11
Fenoprofen + aspirin	0.26	0.36	0.15	0.13
P value (one-tailed *t* test)	ns	0.05	0.02	ns

[a] Rats were pretreated orally for 3 days with vehicle or aspirin (62.5 mg/kg bid) before administering a challenge dose of fenoprofen (25 mg/kg po).

lowering effect of aspirin on fenoprofen plasma concentrations does not appear to be due to an inductive action on this enzyme system. This study does not exclude the possibility, however, of an induction by aspirin of enzymes involved in fenoprofen metabolism, but *not* involved in zoxazolamine metabolism.

6. *Acetaminophen pretreatment.* Acetaminophen, a widely used analgesic drug, might also be administered to patients receiving fenoprofen. Van Arman and associates (7) found that acetaminophen antagonized the antiinflammatory effect of indomethacin in rats. These facts, coupled with our observation of an aspirin-fenoprofen interaction, stimulated our interest in whether acetaminophen, like aspirin, might lower plasma fenoprofen concentrations in rats.

When rats were administered acetaminophen orally, 25 mg/kg bid, for 3 days prior to oral fenoprofen (25 mg/kg), the plasma concentrations of fenoprofen at each time period were lower than corresponding concentrations for control rats (Fig. 8A). The decreases were not statistically different, however. Compared to control, the mean peak concentration of fenoprofen was 12% less after acetaminophen pretreatment; the area under the plasma disposition curve was 17% less.

When we administered 50 mg/kg bid of acetaminophen, the mean peak concentration of fenoprofen in plasma was again 12% less than the control (Fig. 8B) and the area was 20% less. Only at 5 hr was the mean plasma concentration significantly lower in the acetaminophen group. These results suggest that acetaminophen may lower plasma fenoprofen concentrations, but not as dramatically as aspirin. Also, an obvious relationship was not observed between the magnitude of the effect and the dose of actaminophen, in the dose range studied.

General discussion. We have previously reported that fenoprofen is extensively and firmly bound to human plasma albumin; however, this binding is unaffected by aspirin or salicylic acid *in vitro* at concentrations comparable to those observed *in vivo* (1, 5). Also, we observed no aspirin-induced reduction in plasma albumin or total protein which might reduce fenoprofen binding and accelerate its clearance from plasma.

In the rat, further studies of fenoprofen binding to plasma proteins *in vitro* revealed that at concentrations up to 50 μg/ml aspirin or 200

TABLE II. Effect of Aspirin Pretreatment on Zoxazolamine Sleeping Times in Rats[a]

Treatment ip	No. rats	Sleeping time, mean (range) (min)
Fenoprofen + vehicle	12	112 (76–164)
Fenoprofen + aspirin	12	106 (48–169)[b]

[a] Rats were injected ip with either vehicle or aspirin (125 mg/kg bid for 2 days and 62.5 mg/kg bid for 2 additional days). On the day following the last dose, the rats were challenged with zoxazolamine (75 mg/kg ip).
[b] NSD.

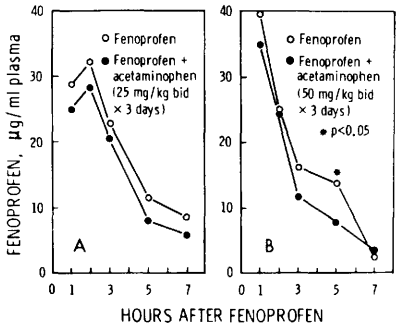

FIG. 8. Plasma fenoprofen concentrations in rats pretreated orally for 3 days with acetaminophen or vehicle before administration of fenoprofen (25 mg/kg). Each point represents the mean of six rats.

μg/ml salicylic acid, protein binding of fenoprofen (25 μg/ml) was unaffected. These results indicate that salicylates do not displace fenoprofen from protein binding sites in the rat; consequently, such a mechanism does not appear to play a significant role in the aspirin-induced reduction of plasma concentrations of fenoprofen in either species.

Pantuk *et al.* (10) have reported that in rats exposed to cigarette smoke or pretreated with 3,4-benzpyrene, the metabolism of phenacetin *in vivo* is increased by enzymes in the intestinal mucosa which are induced. They postulated that this mechanism may have been operative in their human studies, wherein cigarette smoking lowered plasma concentrations of phenacetin without changing its plasma half-life. In rats given aspirin, we observed higher concentrations of certain fenoprofen metabolites in plasma, lower concentrations of fenoprofen itself, no obvious change in its plasma half-life and no evidence that absorption was impaired; these findings are consistent with a mechanism involving accelerated gastrointestinal metabolism of fenoprofen caused by aspirin. But it should be recalled that the aspirin lowering effect is demonstrable even when fenoprofen is not administered into the gastrointestinal tract. Therefore, induction of enzymes in intestinal tissue which might catalyze the metabolism of fenoprofen does not appear to explain the aspirin effect. Indeed, we have no data to suggest that fenoprofen is metabolized in the gastrointestinal tract to any significant degree at all.

Possibly the decreased plasma concentrations of fenoprofen caused by aspirin reflect several minor effects of aspirin on fenoprofen disposition, *e.g.*, decreased absorption, increased distribution to tissues, increased metabolism and enhanced excretion. Such minor effects might not be obvious individually, and without conducting studies involving inordinate sample sizes, they might not be recognized. These effects might have become manifest when plasma was analyzed because plasma might reflect the sum of these individual minor effects.

Conclusion. 1. Despite the observation that aspirin administration reduced fenoprofen concentrations in both rat and human plasma, the mechanism of the reduction is still largely unexplained. In one respect (*i.e.*, shortening of half-life), one might infer that different mechanisms appear to be operative in the two species.

2. In both man and rat, the aspirin effect could not be explained by a decrease in the amount of fenoprofen absorbed. This conclusion was based upon: (a) equivalent urinary recovery of fenoprofen and its metabolites after treatment with fenoprofen alone or with aspirin; and (b) demonstration of the aspirin effect when both drugs were administered by several different routes.

3. In both species, the magnitude of the aspirin effect depended upon the amount of aspirin administered, within dosage ranges considered to exert pharmacological effects rather than toxicological effects.

4. Results from rat experimentation indicate no significant differences in the distribution of radiocarbon into various tissues after administering ^{14}C-fenoprofen alone or with aspirin. Of course, these results do not preclude an increased distribution into tissues of fenoprefen itself.

5. In man, aspirin produced no marked effects on the excretion rates of fenoprofen and its metabolites. In rats, however, the excretion rates of conjugated fenoprofen and of 4′-hydroxyfenoprofen were increased significantly by aspirin. Paradoxically, aspirin administration shortens the plasma half-life of fenoprofen in human subjects, but no change in plasma half-life was observed in rats.

6. Our findings in rats confirmed earlier reports wherein aspirin did not induce the hepatic microsomal enzymes responsible for drug hydroxylation. The aspirin-induced reduction of fenoprofen plasma concentrations does not, therefore, appear to be related to enhancement by aspirin of the rate of fenoprofen hydroxyla-

tion by this enzyme system. We have not excluded the possibility, however, of an increase in fenoprofen metabolism by other enzyme systems. However, this seems unlikely because one would expect a decreased half life of fenoprofen if enzyme induction had occurred.

7. Studies of human and rat plasma indicate no mutual displacement between aspirin and fenoprofen from common binding sites on plasma proteins.

8. Results in rat suggest that acetaminophen may lower plasma fenoprofen concentrations, but not as dramatically as aspirin.

Summary. We have previously reported that when healthy human volunteers ingested fenoprofen and aspirin, the concentrations of fenoprofen in plasma were reduced significantly compared to those observed after fenoprofen alone (1). In contrast, fenoprofen administration did not alter the plasma concentrations of salicylate.

The present study was designed to reproduce the aspirin effect in rats and to elucidate the mechanism of this drug–drug interaction. We were able to demonstrate the effect of aspirin on fenoprofen plasma levels in rats by two routes of administration (po and ip) and at dosages considered to be in pharmacological and not in toxicological ranges. However, the mechanism of this effect remains largely unexplained. In certain aspects, different mechanisms appear to be involved in rat and man, and in neither species can we account fully for the interaction on the basis of effects of aspirin on the absorption of fenoprofen, its tissue distribution, metabolism, protein binding and/or excretion.

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