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COMPARATIVE EFFECTS OF SALICYLIC ACID, PHENYLBUTAZONE, PROBENECID AND OTHER ANIONS ON THE METABOLISM, DISTRIBUTION AND EXCRETION OF INDOMETHACIN BY RATS*

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Abstract—This report describes the effects of salicylate, phenylbutazone, probenecid and other anions on the metabolism, distribution and excretion of indomethacin by the rat. Salicylic acid (100 mg/kg) given intravenously or orally 1 or 3 hr after indomethacin administration (10 mg/kg) significantly decreased (30–60 per cent) concentrations of indomethacin in plasma. Concomitantly, urinary excretion of ^{14}C-indomethacin equivalents was decreased, biliary and fecal excretions were increased, and concentrations in tissues were modified. These changes after salicylic acid treatment were reflected primarily in indomethacin and secondarily in its metabolites. Other agents, such as phenylbutazone, chlorogenic acid and acetic acid, had no effect on the radioactivity in plasma. Probenecid increased the concentrations of indomethacin in plasma by about 20 per cent. The specificity of salicylic acid in decreasing concentrations of indomethacin in plasma of rats and of probenecid in increasing indomethacin concentrations in plasma of both rat and man may arise from the similarity in structure of the benzoyl group of the three compounds. Such a specificity has been discussed with respect to the controversy about the intake of salicylates during the clinical evaluation of indomethacin.

THE CONCURRENT use of several drugs is well established in the treatment of many diseases; however, this practice has resulted in drug interactions or antagonisms. For instance, phenylbutazone administration to man does not change the half-time of acetohexamide but does increase the half-life of its pharmacologically active metabolite, hydroxyhexamide, in plasma;[1] sulfinpyrazone displaces plasma-bound sulfaethylthiadiozole and markedly depresses its renal clearance; probenecid has no effect on plasma-bound sulfaethylthiadiozole[2] *in vitro* or *in vivo*, but decreases the renal clearance of sulfaethylthiadiozole. In a recent publication, Skeith *et al.*[3] reported that probenecid, given concurrently with radioactive indomethacin, decreases the renal excretion of radioactivity in man and increases the radioactivity in serum up to 48 hr.

Salicylates are used concurrently with indomethacin in the therapy of arthritis.[4–7] Boardman and Hart[8] have suggested that the intake of salicylates should be eliminated from comparative clinical trials of nonsteroidal anti-inflammatory agents. Recently, Mielens *et al.*[9] showed that combined administration of aspirin and indomethacin resulted in inhibition of edema in the rat, but that the effects were not significantly different from those obtained with the same doses of either compound alone. However,

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combined administration of aspirin and phenylbutazone in comparative experiments resulted in a slightly greater inhibition of edema. Examples of the effect of a drug on the concentration of naturally occurring substances include the reports of Schmid *et al.*[10] who demonstrated that salicylates lower the serum bilirubin concentrations in a hyperbilirubinemic Gunn rat.

The study in the present report was initiated to determine the effects of several drugs —salicylate, phenylbutazone, probenecid and other anions—on indomethacin metabolism, distribution and excretion in the rat. Sprague–Dawley rats were chosen because they maintain high concentrations of indomethacin in plasma, plasma clearance by liver and kidney is low, metabolism of indomethacin to desmethylindomethacin is fairly extensive, and there is an entero-hepatic circulation of indomethacin.[11, 12] A preliminary report of this study has been presented.[13]

METHODS

Male Sprague–Dawley rats were obtained from the Blue Spruce Farm, Inc., Altamount, N. Y. Most of the rats weighed from 140 to 170 g but the rats for bile duct cannulation weighed 300–350 g. The rats were given single intravenous (caudal vein) or oral (intubation) doses of ^{14}C-indomethacin at 10 mg/kg. The specific activity was about 10,000 dpm/μg and the concentration was 2 or 4 mg/ml in 5% ethanolic 0·05 M phosphate buffer at pH 8·0. Indomethacin and 2-^{14}C-indomethacin were obtained through the courtesy of Merck, Sharp & Dohme Research Laboratory, West Point, Pa. The second, unlabeled drug was injected intravenously or orally at approximately 1 and/or 3 hr after the administration of ^{14}C-indomethacin. Salicylic acid (Aldrich Chemical Co. Inc., Milwaukee, Wisc.) was neutralized to pH 7·4 with NaOH and diluted to a final concentration of 25 mg/ml. ^{14}C-salicylic acid (New England Nuclear Corp., Boston, Mass.) was added to the above solution to give a specific activity of about 1000 dpm per μg. Chlorogenic acid (Sigma Chemical Co., St. Louis, Mo.) was neutralized to pH 7·4 with NaOH and diluted to a concentration of 5 or 50 mg/ml. Phenylbutazone (J. R. Geigy, S. A., Basel, Switzerland) was dissolved in 0·5 ml of absolute ethanol and mixed with 5 ml of 0·1 N NaOH; this basic solution was adjusted to pH 9·0 with 0·1 N HCl and diluted to a final concentration of 5 or 10 mg/ml. Probenecid (Merck, Sharp & Dohme Research Laboratory, Rahway, N. J.) was neutralized to pH 7·3 with NaOH and diluted to a final concentration of 40 mg/ml. Glacial acetic acid (analytical grade) was diluted to a concentration of 0·145 M (8·7 mg/ml). Prior to final dilution, the solution was adjusted to pH 7·4 with NaOH.

The animals selected for bile duct cannulation were anesthetized with chloral hydrate, U. S. P. (Fisher Scientific Co., Fairlawn, N. J.) at a dose of 360 mg/kg and the bile duct was cannulated with Adams polyethylene tubing, P. E. 10 (E. F. Mahady Division, Will Scientific, Inc., Cambridge, Mass.). These surgically prepared rats were restrained but had access to food and water at all times. Radioactive indomethacin was injected intravenously (caudal vein) or administered by oral intubation to restrained rats 3 hr after surgery. These rats were studied continually for 24 hr.

Blood was collected in heparinized capillary tubes from the optic vein or obtained by heart puncture from rats that were lightly anesthetized with ether. After blood collection by heart puncture, tissues were taken immediately from the exsanguinated animals and frozen in liquid nitrogen.

Rats were housed in individual No. 110 metabolism chambers (Maryland Plastic,

Inc., New York, N. Y.) to collect urine during the drug studies. The technique for preventing coprophagy and collecting feces has been described.[11, 14] All animals had access to food and water. The quantitative method for determining indomethacin and its major metabolites from biological tissues has been described.[15] Briefly, tissues were extracted with chloroform and anhydrous, acidic methanol and the extract was made biphasic with aqueous acid. Conjugated indomethacin and its metabolites were partitioned to the aqueous, acid phase while protonated and esterified drug species were partitioned to the organic phase. The ionizable drugs and metabolites (indomethacin, deschlorobenzoylindomethacin and desmethylindomethacin) in this phase were partitioned to an aqueous, basic phase and separated by anion-exchange chromatography (Whatman DEAE-23) and the presumably esterified drug (component-X) remained in the basic aqueous phase. This method also separates salicylic acid and phenylbutazone from indomethacin and its metabolites. Total radioactivity was determined directly with aliquots of urine, plasma and bile, whereas the total radioactivity reported for solid tissues represents the radioactivity extracted from the chloroform:acidic:methanol phase. In these studies, there was a small solid phase which was not assayed for radioactivity; however, recovery of added ^{14}C-indomethacin from biological samples was excellent (>99 per cent) and the amount of radioactivity associated with the solids was negligible.

RESULTS

Indomethacin concentrations in the plasma of nonfasted rats decreased rapidly until about 3 hr when the decrease was slower (Fig. 1). At approximately 1 or 3 hr after an intravenous dose of indomethacin at 10 mg/kg, salicylic acid was given intravenously at a dose of 100 mg/kg. In each case, there was a marked drop in the concentration of indomethacin in plasma. The slope of this initial decrease in the salicylic acid-treated animals approximated the initial decrease in drug concentration in plasma of control animals.

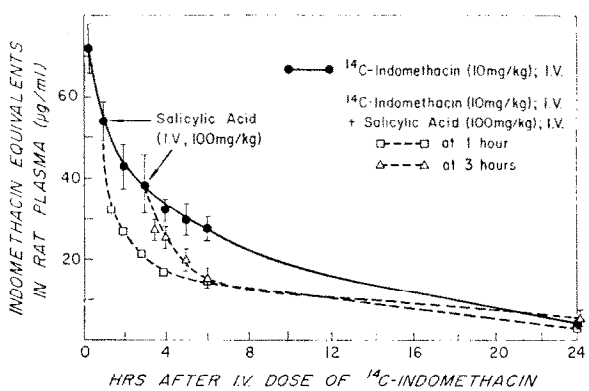

FIG. 1. Effect of intravenous administration of salicylic acid on plasma levels of indomethacin equivalents in rats. Each animal received i.v. 10 mg/kg of ^{14}C-indomethacin (9–10,000 dpm/μg). The data for the control group and salicylic acid-treated group at 3 hr represent the mean ± S.D. of twelve nonfasted animals. The salicylic acid-treated group at 1 hr represent the mean for six animals. Blood was obtained from the optic vein in heparinized capillary tubes and the radioactivity in the plasma was determined directly.

Both indomethacin and salicylic acid were given orally to nonfasted rats (Fig. 2). In the control, indomethacin-treated rats, indomethacin concentrations in plasma plateaued about the fifth hr. The oral intubation of salicylic acid at 1 hr caused an initial decrease of radioactivity in plasma which then increased and plateaued several hours later. Rats given salicylic acid at 3 hr showed a marked decrease in plasma radioactivity. The difference between the two treatment schedules probably indicates that relatively high levels of indomethacin still remained in the intestinal tract at 1 hr.

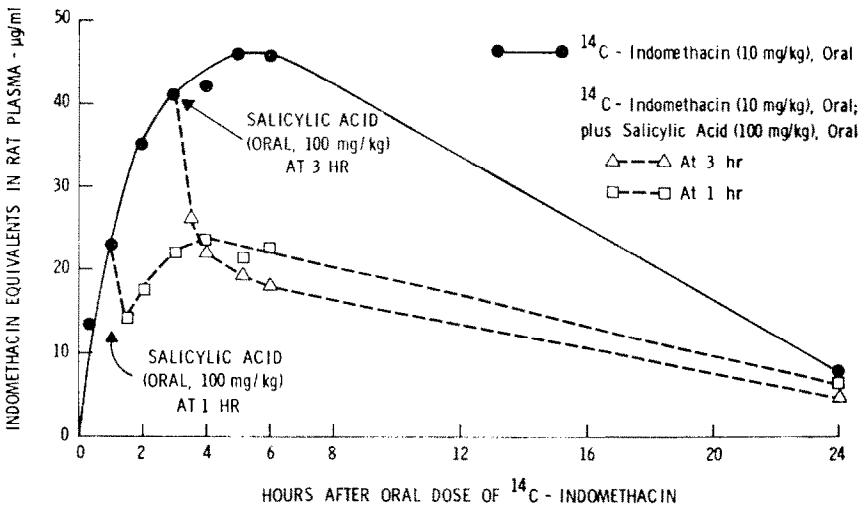

FIG. 2. Effect of oral administration of salicylic acid on plasma levels of indomethacin equivalents in rats. Each animal received p.o. 10 mg/kg of ^{14}C-indomethacin (9–10,000 dpm/µg). The data represent the mean of six nonfasted rats in each group. Blood was obtained from the optic vein in heparinized capillary tubes and the radioactivity in the plasma was assayed directly.

The effects of various doses and various routes of administration of salicylic acid on plasma concentration of indomethacin are summarized in Table 1. As the dose of salicylic acid was decreased from 100 mg/kg to 10 mg/kg, there was a progressively smaller decrease in the concentration of indomethacin because of salicylic acid. Several different combinations of administration of salicylic acid and indomethacin were studied and, in general, a 40–50 per cent decrease in plasma concentration of indomethacin was observed.

The specificity of salicylic acid in decreasing the concentration of indomethacin in plasma was evaluated. Other carboxylic acids such as acetic and chlorogenic, the major organic acid in coffee, were given at 44 and 250 mg/kg, respectively, which were equimolar to 100 mg/kg of salicylic acid. Neither acid affected the concentration of indomethacin in plasma. Phenylbutazone at 50 mg/kg, like chlorogenic and acetic acids, did not affect the indomethacin concentration when the phenylbutazone was given orally or intravenously. As a result, the plasma curve of indomethacin was identical to the control curves seen in Fig. 1.

TABLE 1. EFFECT OF SALICYLIC ACID ON PLASMA LEVELS OF INDOMETHACIN IN RATS*

Route of administration and dose (mg/kg) Indomethacin	Salicylic acid	Per cent decrease of indomethacin equivalents in plasma after salicylic acid treatment†
I.v., 10	I.v., 100 at 1 hr	40
I.v., 10	I.v., 100 at 3 hr	30
I.v., 10	I.v., 50 at 3 hr	25
I.v., 10	I.v., 25 at 3 hr	15
I.v., 10	I.v., 10 at 3 hr	< 5
I.v., 10	Oral, 100 at 1 hr	35
I.v., 10	Oral, 100 at 3 hr	40
I.v., 10	Oral, 100 at 1 and 3 hr	50
Oral, 10	I.v., 100 at 1 hr	60
Oral, 10	I.v., 100 at 3 hr	55
Oral, 10	Oral, 100 at 1 hr	50
Oral, 10	Oral, 100 at 3 hr	40

* Blood was taken from the optic veins of each animal at all time periods and there were at least six animals per experimental group. The variability of individual data points can be seen in Fig. 1, i.e. the S. D. was approximately ± 5 to 10 per cent.

† The per cent change was calculated using the area under the curves of both the indomethacin and indomethacin–salicylic acid-treated rats and the curves were based on the mean of the individual data points.

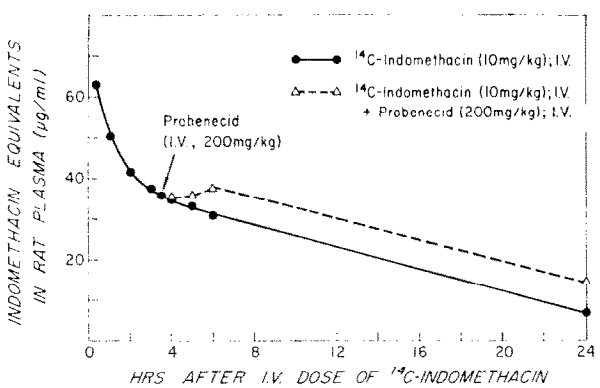

FIG. 3. Effect of intravenously administered probenecid on plasma levels of indomethacin equivalents in rats. Each animal received 10 mg/kg of indomethacin (9000 dpm/μg) i.v. The data represent the mean for six rats in each group. Blood was obtained from the optic vein in heparinized capillary tubes. The radioactivity in the plasma was determined directly.

In contrast to salicylate, which caused a decrease in concentration of indomethacin in plasma, and to acetic acid, chlorogenic acid, and phenylbutazone, which had no effect, a 20 per cent rise in the concentration of indomethacin in rat plasma was seen after probenecid administration at 200 mg/kg (Fig. 3). The concentration of drug in plasma of probenecid-treated animals at 24 hr was significantly ($P < 0.05$) greater than that found in control animals. Skeith *et al.*[3] showed that probenecid increased the radioactivity (^{14}C-indomethacin) in plasma of man and inhibited the urinary excretion of radioactivity. The concentrations of indomethacin and desmethylindomethacin represented about 85 per cent of total radioactivity in the liver and kidneys of control and salicylic acid-treated rats (Fig. 4). The concentrations of indomethacin and

desmethylindomethacin in the liver of salicylic acid-treated animals were slightly higher. In contrast to the liver, the concentration of drug and metabolite in the kidneys from salicylic acid-treated animals was initially higher than control values and decreases; whereas, in the control kidney, the concentration of both drug species increased 4 and 6 hr after an intravenous dose of indomethacin. Little difference was apparent in the concentration of deschlorobenzoylindomethacin in liver and kidney of the salicylic acid-treated animals and the concentration of all three drug species in liver and kidney of control animals were equivalent to those in liver and kidney of salicylic acid-treated animals at 24 hr.

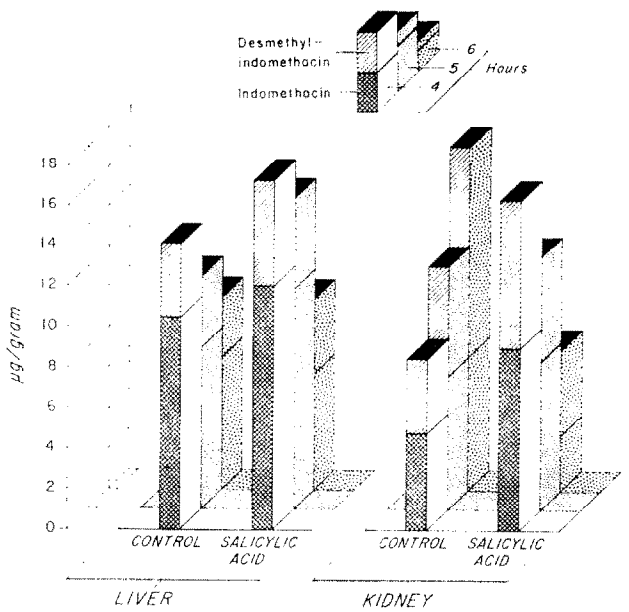

FIG. 4. Effects of salicylic acid on tissue concentrations of indomethacin and desmethylindomethacin in rats. ^{14}C-indomethacin (9000 dpm/μg) was injected i.v. into rats at a dose of 10 mg/kg (control group). Salicylic acid was injected i.v. 3 hr after indomethacin at a dose of 100 mg/kg (salicylic acid group). Two animals were sacrificed each hr; drug and metabolites in individual livers and kidneys were extracted, partitioned and chromatographed on Whatman DEAE-23. The data represent the average concentrations of duplicate determinations.

Although the total excretion of radioactivity by rats that received ^{14}C-indomethacin intravenously was not significantly affected by salicylic acid (Table 2), the salicylic acid treatment increased the amount of radioactivity in the feces by 66 per cent and decreased it in the urine. This increase in the fecal excretion of radioactivity was apparent in the 6- to 12-hr collection period and was noticably increased in the 12- to 24-hr collection period. Although the timing of the increase varied somewhat from animal to animal it was generally over by 24 hr. The decrease in urinary radioactivity was apparent in the 12- to 24-hr collection period and continued through the second day. During these collection periods the volumes and the pH value of the urine from salicylic acid-treated animals were statistically equivalent to those from control animals.

The distribution of the radioactive compounds in the acidic, $CHCl_3$–MeOH

TABLE 2. EFFECT OF SALICYLIC ACID ON THE URINARY AND FECAL EXCRETION OF RADIOACTIVITY BY RATS THAT RECEIVED ^{14}C-INDOMETHACIN INTRAVENOUSLY*

Collection periods (hr after i.v. dose)	Total radioactivity excreted (10^6 dpm) Urine	Feces
	^{14}C-Indomethacin	
0– 3	0·71 ± 0·17†	
3– 6	0·49 ± 0·28	
6–12	0·89 ± 0·25	0·38 ± 0·25
12–24	2·24 ± 1·14	2·22 ± 0·90
24–48	0·99 ± 0·21	2·02 ± 0·37
Total	5·26 ± 0·86	4·67 ± 1·44
	^{14}C-indomethacin plus salicylic acid at 3 hr	
0– 3	0·43 ± 0·18	
3– 6	0·56 ± 0·22	< 0·1
6–12	0·74 ± 0·23	0·97 ± 0·47
12–24	1·21 ± 0·34	4·42 ± 1·41
24–48	0·48 ± 0·09	2·72 ± 1·73
Total	3·46 ± 0·34	7·66 ± 0·41

* Six animals were used in each group. All animals received ^{14}C-indomethacin (9000 dpm/μg) i.v. at a dose of 10 mg/kg. Salicylic acid was injected i.v. 3 hr after indomethacin treatment at a dose of 100 mg/kg. Rats had access to food and water, but coprophagy was prevented.

† Mean ± S. D.

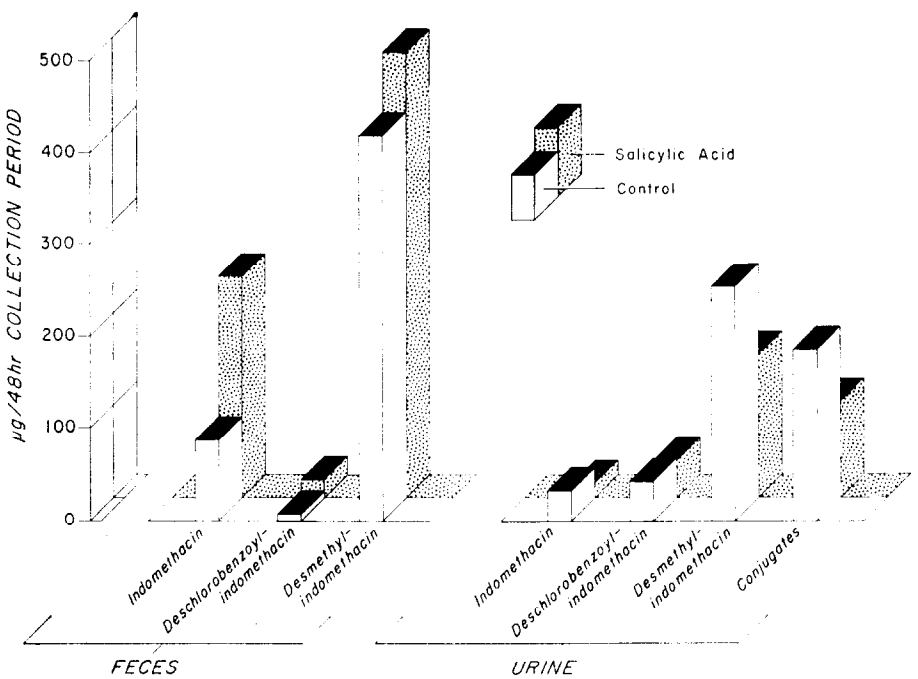

FIG. 5. Effects of salicylic acid on excretion of indomethacin and its metabolites in rats. Two of the six rats from each of the control (^{14}C-indomethacin) and treated (^{14}C-indomethacin plus salicylic acid at 3 hr) groups (Table 3) were selected randomly. Drug and metabolites in individual urine (0–3, 3–6, 6–12, 12–24 and 24–48 hr) and feces (6–12, 12–24 and 24–48 hr) samples were extracted, partitioned, and chromatographed on Whatman DEAE-23. The data for each compound were combined for each animal and these data for the groups represent the averages of duplicate determinations.

extracts of feces and urine are seen in Fig. 5. The urinary excretion of indomethacin by salicylic acid-treated animals was decreased. Apparently, there was no effect on the excretion of deschlorobenzoylindomethacin, but the excretion of both desmethylindomethacin and total conjugates was lower in the urine from the salicylic acid-indomethacin animals. The decrease in total urinary radioactivity in these animals of about 10 per cent (Table 2) was accounted for by these components. In the feces from salicylic acid-treated rats, there was an increase in the total amount of indomethacin, deschlorobenzoylindomethacin and desmethylindomethacin.

Approximately 65 per cent of the intraveneous dose of indomethacin is secreted in the bile of rats in 24 hr (Table 3).[11] In the same period, salicylic acid increased biliary

TABLE 3. EFFECT OF SALICYLIC ACID ON BILIARY AND URINARY EXCRETION OF ^{14}C-INDOMETHACIN IN BILE-CANNULATED RATS*

Route of administration and dose (mg/kg)		Per cent of i.v. radioactive dose in 24-hr collection†	
^{14}C-indomethacin	Salicylic acid	Urine	Bile
I.v., 10		24·0 ± 7·8‡	65·9 ± 6·3§
I.v., 10	I.v., 100 at 3 hr	8·6 ± 1·7‡	81·3 ± 4·2§
Oral, 10		4·5 ± 1·7	24·7 ± 4·5
Oral, 10	I.v., 100 at 1 hr	1·2 ± 1·0	6·3 ± 3·3
Oral, 10	I.v., 100 at 3 hr	2·8 ± 1·2	17·6 ± 6·4
Oral, 10	Oral, 100 at 3 hr	5·6 ± 1·9	18·9 ± 6·2

* There were three rats with cannulated bile ducts in each group. They were restrained during the experimental period, but had access to food and water.

† Mean ± S. E.

‡ The per cent distribution (mean ± S. E.) of radioactive compounds in urine from the indomethacin plus salicylic acid groups was: conjugates 49 ± 3, 58 ± 5; indomethacin 9 ± 6, 5 ± 1; deschlorobenzoylindomethacin 10 ± 4, 15 ± 3; and desmethylindomethacin 28 ± 3, 19 ± 2 respectively.

§ The per cent distribution (mean ± S. E.) of radioactive compounds in bile from the indomethacin and indomethacin plus salicylic acid groups was: conjugates, 35 ± 7, 34 ± 5; indomethacin, 40 ± 5, 42 ± 5; deschlorobenzoylindomethacin, 13 ± 4, 13 ± 3; and desmethylindomethacin, 6 ± 2, 6 ± 1 respectively.

secretion of drug-derived radioactivity about 10–15 per cent, which is approximately equivalent to the decreased excretion in the urine. The per cent distribution of the radioactivity in bile and in urine from both groups of animals was approximately equivalent. When indomethacin was given orally, about 30 per cent of the dose was secreted in urine and bile. Administration of salicylic acid intravenously at 1 hr greatly reduced the appearance of radioactivity in both the bile and urine.

DISCUSSION

The administration of salicylic acid to rats after an intravenous or oral dose of ^{14}C-indomethacin resulted in a significant decrease in plasma and urinary radioactivity and a significant increase in fecal radioactivity. Acetic acid, chlorogenic acid, or phenylbutazone had no measurable effect on the concentration of indomethacin equivalents in plasma of rats. This observation with probenecid was similar to the findings of Skeith *et al.*[3] in man. Since acids *per se* did not affect the concentration of indomethacin in plasma, whereas probenecid increased the concentrations of indomethacin radioactivity in plasma of rats, the effects of salicylic acid and probenecid on the concentration of indomethacin in plasma may be related to the benzoyl group which is common to all three compounds.

The effects of salicylic acid were restricted primarily to the physiological disposition of indomethacin and desmethylindomethacin. The initial increase in their concentrations in kidneys suggests that salicylic acid inhibits the renal excretion of both compounds. This was further borne out by analysis of the urine, which showed that the urinary excretion of desmethylindomethacin and indomethacin, and presumably, their respective conjugates, were decreased in salicylic acid-treated rats. In rats with bile ducts cannulated, salicylic acid decreased the plasma clearance by kidneys of desmethylindomethacin and indomethacin to about 25–30 per cent of that of control rats which received only indomethacin. The plasma clearance of deschlorobenzoylindomethacin was less affected by salicylic acid. It was about 60–70 per cent of the clearance of control rats. The concentrations of deschlorobenzoylindomethacin in kidney and urine were unaffected by salicylic acid treatment.

The increased fecal excretion of indomethacin, and to a lesser extent of desmethylindomethacin and deschlorobenzoylindomethacin—after the administration of salicylic acid—may have resulted from increased secretion in the bile. Since indomethacin is absorbed from the intestine of normal rats,[12,13] since salicylic acid is absorbed from the intestine,[16] and since salicylic acid inhibits the transport of glucose,[17] water,[17] phenylalanine,[18] and tryptophan[19] from the intestine, it is possible that salicylic acid inhibited the intestinal absorption of indomethacin, and that this inhibition contributes to the increased concentration of indomethacin in the feces. This explanation implies that intravenously administered salicylic acid is also secreted in the bile. In our studies, approximately 5 per cent of an intravenous of p.o. dose (100 mg/kg) of salicylic acid was secreted in the bile. This amount (5 per cent of 100 mg/kg) of salicylic acid is equivalent on a molar basis to 10 mg/kg of indomethacin. Williams *et al.*[20] showed that less salicylic acid (1·5 per cent of an i.p. dose) is secreted in the bile after a smaller dose (50 mg/kg). It is possible that this dose-related secretion of salicylic acid in bile contributes to the dose-related effect of intravenously administered salicylic acid on concentration of indomethacin in plasma of rats.

An alternative explanation is suggested from the data of Schmid *et al.*[10] Schmid showed that salicylic acid decreased the serum bilirubin concentration and that after human albumin was injected, the serum bilirubin concentration returned to normal. Schmid *et al.*[10] proposed that the injected salicylate enhanced the diffusion of the unbound bilirubin into extra-vascular spaces and that albumin shifted this equilibrium process. We have found initially higher levels of both indomethacin and desmethylindomethacin in the liver and kidneys of salicylic acid-treated rats, but the concentration of both drug species in liver and kidney was equivalent to or less than the control values about 3 hr after the dose of salicylic acid. Thus, it seems unlikely that the deposition of indomethacin and metabolites in tissues was the only mechanism.

Salicylic acid is metabolized to glucuronide conjugates,[16] as is indomethacin and its metabolites.[21] Their competition for the glucuronide-synthesizing enzymes and/or for excretion of the conjugates may also be affecting the physiologic distribution of indomethacin.

Salicylic acid has been reported to displace albumin-bound bilirubin[10] and it is possible that salicylic acid has a similar effect on indomethacin. Kucera and Bullock[22,*] have shown that indomethacin and its metabolites are bound extensively to plasma constituents of humans, dogs, rats, guinea pigs, rabbits and monkeys. At a concentra-

* J. Kuchera and F. Bullock, personal communications.

tion of 50 μg of compound per ml of rat plasma *in vitro*, indomethacin and desmethylindomethacin are bound about 90 per cent, whereas deschlorobenzoylindomethacin is bound about 60 per cent. At 50–500 μg/ml, salicylic acid is bound 33 to 47 per cent to plasmas and is bound primarily to the albumin fraction of rat plasma. In displacement studies of indomethacin by salicylic acid, a 130-mole excess of salicylic acid caused a slight (ca. 5–10 per cent) displacement of indomethacin, but a 13-mole excess of salicylic acid had no effect on the 90 per cent binding of indomethacin to rat plasma.

The specificity of salicylic acid in lowering the concentration of indomethacin in plasma of rats is relevant to the controversy regarding the possible effects of salicylate intake during the clinical evaluation of indomethacin.[4–8] Man excretes indomethacin mainly as a glucuronide conjugate in the urine (54 per cent of an intravenous dose in 24 hr) and excretes a significant quantity (25 per cent of an intravenous dose in 72 hr) in feces.[12, 22] Preliminary data of Hucker *et al.*[12] suggest that biliary excretion of indomethacin was about 15 per cent of an intravenous dose in 24 hr in man. The extent to which salicylates affect these normal patterns in man is not known. However, since probenecid increased the radioactivity from ^{14}C-indomethacin in the plasma of man[3] and, as seen above, in rats, the effect of salicylates on indomethacin distribution and excretion in rats should be evaluated in man.

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