Nonlinear Bioavailability of Metoclopramide in the Rat: Evidence for Saturable First-Pass Metabolism

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Received October 12, 1982, from the *Faculty of Pharmaceutical Sciences and Medicine, University of British Columbia, Vancouver, BC V6T 1W5, Canada.* Accepted for publication January 11, 1983.

Abstract □ *In vivo* and *in vitro* experiments were conducted in rats to examine the possibility of either extrahepatic metabolism or saturable first-pass effect as an explanation for the unusual presystemic clearance of metoclopramide (I) previously reported. *In vivo* studies involved two-thirds hepatectomized rats and animals pretreated with carbon tetrachloride to induce hepatic necrosis, whereas *in vitro* studies involved incubation of equal amounts of I (5.0 μmol/mL) with various tissue homogenates (*viz.*, liver, kidney, and lung) or their 9000×*g* supernatant fractions. Results suggest that the metabolism of I principally occurs in the rat liver, and there was no evidence suggesting the involvement of kidney or lung tissue in the metabolism of I. Forty-eight-hour cumulative urinary excretion studies following oral and intravenous administration of ≤5.0 mg/kg of metoclopramide hydrochloride were conducted. The bioavailability (F) values of I at dosage levels 0.1, 0.5, 1.0, and 5.0 mg/kg were 0.49, 0.75, 0.77, and 0.83, respectively. It is concluded that the liver is the primary organ for the metabolism of I in the rat and that the drug exhibits dose-dependent hepatic first-pass metabolism.

Keyphrases □ Bioavailability—nonlinear, metoclopramide in the rat, saturable first-pass metabolism □ Metoclopramide—nonlinear bioavailability, saturable first-pass metabolism, rat □ Metabolism—saturable, first-pass, nonlinear bioavailability, metoclopramide in the rat

Metoclopramide (I), a procainamide analogue, is a potent antiemetic and gastric motility modifier. Recent development of a sensitive and specific analysis for the quantitation of I in biological fluids has considerably facilitated the ability to study the pharmacokinetics of this drug in small animals (1, 2).

Tam *et al.* (1) have shown that after a dose of <15 mg/kg iv, the normal nonrenal clearance of I in the rat (CL_{NR} = 40 mL/min/kg) approaches the liver plasma flow, suggesting that the elimination of the drug may be perfusion limited and that the drug should be expected to undergo extensive hepatic first-pass metabolism in this species. However, after oral and intraperitoneal administration, I does not appear to undergo significant hepatic first-pass metabolism in the rat (1) over the dosage range studied (1–35 mg/kg). Hypotheses of extrahepatic metabolism of I and/or temporary saturation of the binding and metabolic sites in the liver during the absorption phase have been proposed. Recent work on the pharmacokinetics of I in rats with experimental hepatic dysfunction (2) has indicated that the liver is one of the major metabolic organs for I, but the monodeethylated metabolite of I may be formed extrahepatically.

Bateman and his coworkers (3, 4) have reported a fourfold increase in the terminal biological half-life ($t_{1/2}$) of I and a corresponding reduction in the total body clearance (CL_{TB}) of I in patients with chronic renal failure. A similar observation was made by Tam *et al.* (2) in rats with experimentally induced renal dysfunction. Both observations were somewhat unexpected since only ~20–25% of the dose is excreted as intact drug in both rat (2) and human urine (5–7), suggesting that the renal elimination pathway is relatively unimportant. In rats, Tam *et al.* (2) have also shown that a positive correlation (r^2 = 0.997) exists between the total body clearance of I and creatinine clearance, implying that the elimination of I is related to renal function. Based on the renal dysfunction studies in rats (2) and humans (3, 4), it has been proposed that a reduction of hepatic function secondary to renal injury takes place and/or there is loss of extrahepatic (*i.e.*, kidney) metabolic capabilities due to kidney malfunction.

We report the results of various *in vivo* and *in vitro* studies used to test the hypotheses proposed by previous workers in an attempt to explain the underlying mechanism(s) of the elimination of I. Results of bioavailability experiments using 48-h cumulative urinary excretion data are also reported following low-dose (≤5 mg/kg) experiments with I.

EXPERIMENTAL

Materials—Metoclopramide hydrochloride[1] (mol. wt. 336.31) (I) and deethyl metoclopramide[2] (II) were used. All chemicals were either official or reagent grade.

Animal Handling—Adult male Wistar rats, 225–275 g, were used in all experiments. All animals were maintained in metal cages, 6–8 per cage, in a controlled environment (22°C, 30% relative humidity, 14 h of light/d) for at least 3 d prior to experimentation. Food[3] and tap water were available *ad libitum*.

Urine Sample Collection—Rats were individually housed in stainless steel metabolism cages for the 48-h urine collection. The floors and sides of the cages were rinsed with deionized distilled water to maximize the drug recovery. The diluted urine samples were kept at −20°C until analyzed.

***In Vivo* Experiments**—*Two-Thirds Hepatectomy*—The animals were fasted overnight prior to the surgical removal of two-thirds of the liver using a method similar to that of Higgins and Anderson (8). Following ether anesthesia, a midline incision was made reaching 3–4 cm posteriorly from the xiphoid process of the sternum. Large portions of the median lobe together with the left lobe of the liver were securely ligated and then carefully excised. In this way, portions of the parenchyma ranging from 65 to 75% of the total liver were removed, leaving within the peritoneum, the right lateral, and small caudate lobes. The peritoneum and the abdominal muscles were sutured and the skin was closed; there was no special postoperative care.

For control rats, sham operations were carried out by making a similar midline incision. The peritoneal organs were gently disturbed with a cotton swab and the wound closed as previously described. One day following surgery, intraperitoneal administration of an isotonic solution (0.5 mL/250-g rat) of I, containing the equivalent to 15 mg/kg of base, was carried out in two-thirds hepatectomized as well as sham-operated rats. Urine was collected for 48 h after dosing and kept at −20°C until analyzed.

Carbon Tetrachloride Pretreatment—The animals were randomly selected and separated into two groups. The control and experimental group received an oral dose of 0.5 mL of normal saline or 1.0 mL/kg of carbon tetrachloride (9), respectively, followed by an overnight fast. On the following day, an intraperitoneal dose of the monohydrate hydrochloride salt of I equivalent to 1.0 mg/kg of base was administered to both

[1] Analysis No. 9207; A. H. Robins, Montreal, Can.
[2] AHR-3137; Robins Research Laboratories, Richmond, Va.
[3] Purina Laboratory Chow.

0022-3549/84/0200-0215$01.00/0

Table I—Cumulative Urinary Excretion of I and II [a] in Two-Thirds Hepatectomized and Carbon Tetrachloride-Pretreated Rats

	Recovery, %[b]	
	Test	Control[c]
	Two-Thirds Hepatectomy	
I	32.20 ± 7.61 (5)[d]	14.01 ± 6.13 (5)
II	3.97 ± 1.90 (5)	3.65 ± 1.27 (5)
	Carbon Tetrachloride Pretreatment	
I	72.18 ± 13.43 (5)[d]	21.67 ± 7.14 (6)
II	9.79 ± 1.30 (5)[d]	3.44 ± 0.73 (6)

[a] Expressed as percent of dose of I after correction for the molecular weight difference. [b] Mean ± *SD*; number of animals in parentheses. [c] Sham-operated rats for hepatectomy and saline-pretreated for carbon tetrachloride pretreatment. [d] Statistically significantly different from the controls, $p = 0.05$.

groups. Food was limited to 2–3 pellets[3] per day and water was allowed *ad libitum*. Cumulative urine samples were collected up to 48 h postdose and stored at −20°C until analyzed.

***In Vitro* Metabolism Study**—A method similar to that used by Cowan *et al.* (10) was utilized to study the *in vitro* metabolism of I in the rat. The rats were stunned and sacrificed by decapitation, and their organs (liver, kidney, and lung) immediately were removed and placed in a fresh, ice-cold, isotonic (1.15% w/v) aqueous solution of potassium chloride. All subsequent operations were carried out at 0–4°C. The excised tissues were blotted dry, weighed, and minced with scissors. The liver tissue was homogenized in four volumes of fresh, ice-cold, isotonic potassium chloride using 4–5 passes with an homogenizer[4]. The lung and kidney tissues were homogenized separately in a similar manner. For lung and kidney tissues, a tissue–KCl solution ratio of 1:4 was also used. The homogenates were transferred to plastic tubes and centrifuged at 9000×*g* for 20 min to remove nuclei, mitochondria, and cell debris. Aliquots (0.5, 1.0, 1.5, and 2.0 mL) of supernatants as well as whole tissue homogenates were used for the incubation reactions.

The monohydrate hydrochloride salt of I (5 μmol/mL in deionized distilled water) was incubated in uncapped glass tubes at 37°C for 30 min with whole tissue homogenates (liver, kidney, and lung) as well with 9000×*g* tissue supernatant preparations. Each incubation tube contained 1.0 mL of substrate solution, one of the four volumes (0.5, 1.0, 1.5, and 2.0 mL) of whole tissue homogenate or 0.1 mL of 9000×*g* tissue supernatant, one of the corresponding volumes (3.5, 3.0, 2.5, and 2.0 mL) of 0.02 M pH 7.4 phosphate buffer, and 1 mL of cofactor solution (6 mg of glucose-6-phosphate, 3.4 mg of the monosodium salt of NADP, 0.2 mg of 0.1 M $MgCl_2 \cdot 6H_2O$, and 0.8 mL of deionized distilled water).

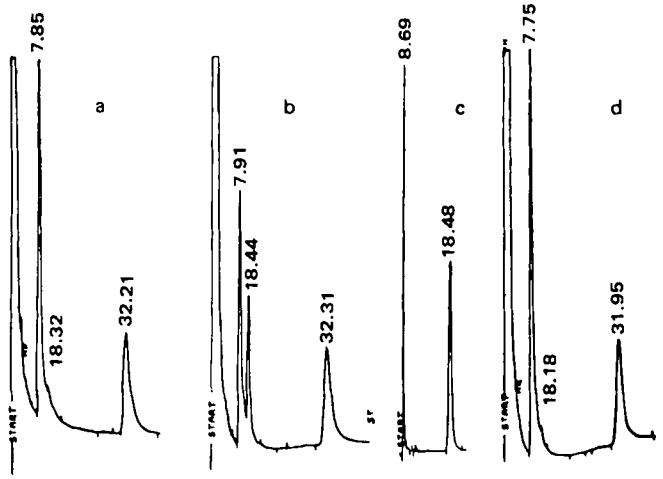

Figure 1—*Representative chromatograms showing the relative amounts of I obtained from various incubation mixtures at the end of each incubation reaction (initially, each incubation mixture contained an equal amount of I). Peaks with retention times of 7.85, 10.44, and 32.21 min represent heptafluorobutyryl derivatives of I, II, and diazepam (internal standard), respectively. Key: (A) in the absence of any tissue homogenate; (B) in the presence of 9000×g supernatant of liver homogenate (note the presence of peak for II); (C) representative chromatogram of II; (D) in the presence of 9000×g supernatant of kidney homogenate.*

[4] Polytron; International Equip. Co. (I.E.C.), Needham Hts., Mass.

Table II—*In Vitro* Metabolism of I in the Absence and Presence of 9000×*g* Supernatants from Liver, Kidney, and Lung Homogenates

Treatment	Area Ratios[a]	
	I	II
Control	1.65 ± 0.12(10)	ND[b]
Liver	0.90 ± 0.06(7)	0.49 ± 0.05(7)
Kidney	1.74 ± 0.20(7)	ND
Lung	1.62 ± 0.06(7)	ND

[a] Heptafluorobutyryl derivative of I or II/diazepam (internal standard) expressed as mean ± *SD*; number of incubation mixtures in parenthesis. [b] ND = not detected.

One milliliter of the substrate solution was replaced with 1 mL of 1.15% KCl in the control experiments, which were carried out concurrently. The incubation reactions were terminated by the addition of 0.5 mL of 3% trichloroacetic acid in all tubes. The tubes were then vortexed for 10 s and centrifuged (5 min at 2000 rpm) at room temperature. A similar experiment was also carried out with II (2.5 μmol/mL of deionized distilled water) using 0.5 mL of liver tissue homogenate only.

Bioavailability Experiments—Urinary excretion studies were carried out following intravenous and oral administrations of a range of doses of the monohydrate hydrochloride salt of I (equivalent to 0.1, 0.5, 1.0, and 5.0 mg of base/kg). Urine samples were collected as described previously.

Analyses—The urine samples and the various fractions of tissue homogenates were assayed for I and the metabolite (II) using a minor modification of a GC assay method of Tam and Axelson (11). The method involved an extraction procedure and the conversion of the drug and metabolite to their respective heptafluorobutyryl derivatives before analysis by electron-capture GC. A 1.8-m × 2-mm i.d. glass column packed with 3% Silar-9CP on Chromosorb-W (High Performance), 100–120 mesh, was used.

The bioavailability of I at different dose levels was calculated by comparing the percent of dose recovered as I in 48-h cumulative rat urine samples after equal oral and intravenous doses:

$$F = \frac{\left(\sum_0^{48} X_u\right)_{po}}{\left(\sum_0^{48} X_u\right)_{iv}}$$

where F is the systemic bioavailability, $(\Sigma_0^{48} X_u)_{po}$ and $(\Sigma_0^{48} X_u)_{iv}$ are the 48-h cumulative amounts of intact I excreted in the urine following administration of equal doses of I *via* oral and intravenous routes, respectively. The unpaired, two-tailed Student's t test was employed to statistically test the difference between groups of data; the level of significance was $p = 0.05$ for all analyses.

RESULTS

***In Vivo* Studies**—*Two-Thirds Hepatectomy*—The total percentages of I and II recovered in 48-h cumulative urine samples from two-third hepatectomized and sham-operated rats after intraperitoneal administration of the monohydrate hydrochloride salt of I (equivalent to 15 mg of base/kg) is shown in Table I. The levels of intact I recovered in the 48-h cumulative urine samples from two-thirds hepatectomized rats were significantly higher than those of sham-operated rats. There was no significant difference in the percentage of II recovered in the urine of two-third hepatectomized rats compared with that of sham-operated rats.

Carbon Tetrachloride Pretreatment—The results of carbon tetrachloride pretreatment study with respect to the percentage of intact I recovered from the 48-h cumulative urine samples were similar to that of the two-thirds hepatectomy study (Table II). The total amount of II recovered in the urine of carbon tetrachloride-pretreated rats was also significantly higher when compared with that of saline-pretreated rats.

***In Vitro* Studies**—*9000×g Liver, Kidney, and Lung Homogenate*—Figure 1 represents a series of chromatograms obtained from the extraction of various incubation mixtures, followed by heptafluorobutyric anhydride derivatization in the presence of the internal standard, diazepam (with retention time, $t_R = 32.2$ min). All mixtures contained an equal amount of I prior to initiating the incubation reaction. The first

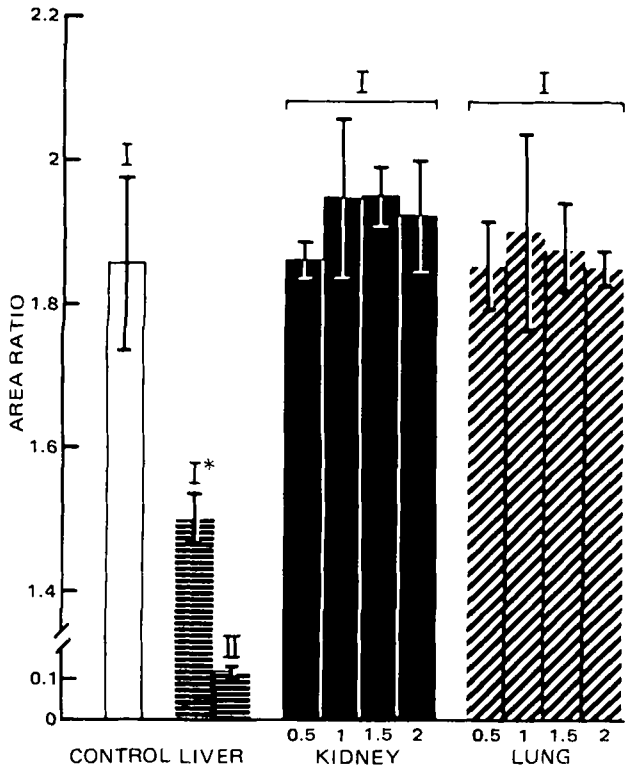

Figure 2—*Histograms representing the area ratios (heptafluorobutyryl derivative of I or II/diazepam) obtained from the* in vitro *metabolism of I in the absence and presence of different volumes of whole tissue homogenates of liver (2.0 mL), kidney (0.5, 1.0, 1.5, and 2.0 mL), and lung (0.5, 1.0, 1.5, and 2.0 mL). The asterisk signifies statistical significance,* $p < 0.05$.

chromatogram (a) reflects the relative amount of I (t_R = 7.85 min) present in the 9000×*g* supernatant after the incubation reaction in the absence of any tissue homogenate. The second chromatogram (b) represents the proportion of I present in the 9000×*g* supernatant of liver homogenate after the incubation reaction. There was an additional peak in this second chromatogram (t_R = 10.44 min) which was subsequently identified as the metabolite, II, as shown in the third chromatogram (c). The relative amount of I present in the mixture after the incubation reaction, in the presence of 9000×*g* supernatant of kidney homogenate only, is shown in the fourth chromatogram (d) in Fig. 1. The results of 9000×*g* supernatant of lung tissue were similar to those of kidney tissue.

Table II illustrates the relative amount of I remaining after various treatment procedures. Area ratios (heptafluorobutyryl derivative of I and II/diazepam as the internal standard in fixed amounts) were used for this purpose. The relative amount of I in the presence of liver tissue preparations was significantly lower than that of controls, as illustrated by the lower area ratio values. In addition, appreciable amounts of II were formed in the incubation mixture containing liver tissue. The relative amounts of I incubated in the presence of kidney and lung tissue preparations did not change significantly from controls, and metabolite II was absent.

Whole Fraction Tissue Homogenate—A study utilizing whole fraction tissue homogenates was conducted to examine the involvement of the lungs and/or kidneys in the metabolism of I. The results of the aforementioned experiment are shown in Fig. 2. There was no significant difference in the area ratios of lung and kidney tissue preparations compared with that of controls. The area ratios of liver homogenate preparations were significantly lower than the controls (Fig. 2).

***In Vitro* Metabolism of II**—The levels of II in the test incubation mixture containing 9000×*g* supernatant of liver tissue homogenate after the incubation reactions were significantly ($p < 0.05$) lower (heptafluorobutyryl derivative of II/diazepam = 1.199 ± 0.21, n = 6) compared with those of controls (without liver tissue) (1.96 ± 0.037, n = 6).

Bioavailability of I as a Function of Dose—The pharmacokinetic behavior of I in the rat was studied as a function of dose and route of administration. Forty-eight-hour cumulative urinary excretion data of intact I and II was utilized to study the effect of route of administration at different dose levels. Table III shows the percent recovery of intact I and II in 48-h cumulative urine samples after administration of equal doses of the monohydrate hydrochloride salt of I (equivalent to 5, 1.0, 0.5, and 0.1 mg of base/kg) *via* oral and intravenous routes in two randomly selected groups of rats. At the 5.0-mg/kg dose level the mean percent recovery of intact I (n = 9) following the oral route was lower than that of the intravenous route suggesting a slight hepatic first-pass effect, provided that complete absorption had occurred. The levels of II recovered were <5% for both routes. Statistically, the levels of both intact I as well as II recovered after oral administration were not significantly different from those of the intravenous route.

Table III—Percent of Dose Recovered as I and II [a] in Urine and Nonlinear Dose-Dependent Bioavailability of I [b]

Dose, mg/kg		Recovery, %[c] Oral	Intravenous	Bioavailability (F)
5.0	I	23.69 ± 7.81(9)	28.71 ± 6.09(8)	0.83
	II	3.43 ± 1.12(9)	4.12 ± 1.13(8)	
1.0	I	19.92 ± 5.27(6)	25.65 ± 6.21(6)	0.78
	II	3.20 ± 0.54(6)	4.40 ± 1.67(6)	
0.5	I	16.22 ± 2.03(6)[d]	21.89 ± 2.83(6)	0.75
	II	3.51 ± 1.21(6)	2.57 ± 1.62(6)	
0.1	I	9.75 ± 4.35(5)[d]	20.44 ± 5.02(5)	0.49
	II	1.14 ± 0.51(5)	1.51 ± 0.40(5)	
15.0				0.91[e]

[a] Expressed as percent of dose of I after correction for the molecular weight difference. [b] Bioavailability of I calculated as the ratio of 48-h cumulative urinary excretion data following oral and intravenous administration of different doses. [c] Mean ± *SD*; number animals in parentheses. [d] Statistically significantly different from the intravenous group, p = 0.05. [e] Calculated by comparing area under plasma concentration *versus* time curve after oral route to that of route of administration. Data taken from Ref. 1.

Similar results were obtained after a 1-mg/kg dose (Table III). The percent of dose recovered as intact I and II after the oral route was not significantly different from that seen after an intravenous route of administration. These results are consistent with the work done by previous investigators (1).

To test the hypothesis of temporary saturation of liver enzymes during the absorptive stage after relatively high doses (>1 mg/kg), the 48-h cumulative urinary excretion pattern at lower doses (<1 mg/kg) was studied. The results of the 0.5- and 0.1-mg/kg studies are also shown in Table III. In both cases, the total amounts of intact I recovered after oral dosing were significantly lower than those following intravenous administration. The total amount of II recovered was <5% by either route, and there was no significant difference between routes. Table III also represents the compilation of experimentally determined bioavailability data at different dose levels.

DISCUSSION

The two-thirds hepatectomy study assessed the involvement of the liver in the metabolism of I. The study was based on the assumption that surgical removal of two-thirds the liver of the rat would decrease hepatic function. If the liver is involved in metabolism of I, then one would expect increased amounts of intact drug in the cumulative urine of surgically altered rats as compared with normal rats. Surgical removal of two-thirds of the liver is a major operation, and ideally the rat should be allowed to recuperate from the surgically associated stress and trauma for at least 3 d prior to the beginning of an experiment. However, Higgins and Anderson (8) found that the regeneration of liver tissue in rats is very rapid. They reported that it took only 3 d after the surgery to restore the liver mass from 29% to ~70% of normal. Therefore, in the present study the animals were allowed to recuperate for only 1 d following surgery. Sham-operated rats were used for controls.

The intraperitoneal route of drug administration without ether anaesthesia, as stated earlier, was preferred over other routes (*i.e.*, intravenous or oral) which required the use of ether anesthesia. This was done to minimize mortality due to increased ether toxicity in two-third hepatectomized rats.

The total amount of intact I in urine samples at 48-h was significantly higher in two-third hepatectomized rats compared with that found in the urine from sham-operated rats (Table I). This strongly suggests that the liver is involved in the metabolism of I. The percentage of dose excreted as the metabolite (II) was too low (<5%) in both treatments to allow further interpretation of the effect of hepatectomy on the metabolism of I.

Carbon tetrachloride, a well-known hepatotoxin, has been widely used in experimental animals to produce varying degrees of liver impairment including necrosis (12), fatty infiltration (13), and decreased activity of

microsomal enzymes that catalyze the oxidation of drugs (14–16). Carbon tetrachloride impairs oxidative enzymes in liver microsomes by decreasing the amount of cytochrome P_{450} either due to an active metabolite (17) or free radical formation (18, 19).

Hepatotoxicity in rats is evident within 24 h of carbon tetrachloride treatment (1.0 mL/kg) (8). However, the toxic effects of carbon tetrachloride to other organs such as the kidney do not occur until many hours to several days after the exposure to the toxin (20–22). Therefore, rats pretreated with carbon tetrachloride 24 h prior to study were used to ensure minimal damage to other organs. The intraperitioneal route of drug administration, without ether anesthesia, was used as before to avoid ether toxicity.

The percentage of intact I recovered from the 48-h cumulative urine samples of carbon tetrachloride-pretreated rats is almost threefold higher (Table I) than that of saline-pretreated rats. This observation strongly suggests that the liver is a major organ for the metabolism of I in the rat.

A similar pattern of recovery of I was found by Tam *et al.* (2), who found no significant difference in the levels of II in the 48-h cumulative urine samples of carbon tetrachloride-pretreated rats as compared with the saline-pretreated rats. Based on the unchanged levels of II in both of these treatments, these investigators have speculated that extrahepatic metabolism of I is possible in the rat. But, in the present studies the levels of II in the 48-h cumulative urine samples of carbon tetrachloride-pretreated rats were higher than those of saline-pretreated rats. This observed difference may be a function of the dose of I, which was 1 mg/kg in the present study and 15 mg/kg for Tam *et al.* (2).

If the liver were the only metabolic organ for I, then during liver damage (*e.g.*, carbon tetrachloride pretreatment) metabolism would be impaired, the extent of impairment being a function of the hepatic injury. This damage should result in a greater proportion of parent drug being excreted unchanged and a lower fraction of metabolite in the urine of rats with hepatic injury as compared with the saline pretreated rats. The observation that the levels of II in our present study are higher, rather than lower, in the carbon tetrachloride-pretreated rat urine as compared with those of normal rats appears inconsistent. This can be rationalized from the *in vitro* metabolism studies of I and II. It has been found in our present *in vitro* studies that I is metabolized in the rat liver and one of its metabolites is II, which is then further metabolized in the liver. Therefore, during carbon tetrachloride pretreatment, the metabolism of both I and II are probably impaired resulting in higher overall levels of both of these compounds in the urine as compared with those in saline-pretreated rats.

The results of investigations using 9000×*g* homogenates suggest that the liver tissue is involved in the metabolism of I. The evidence of the presence of II in the incubation mixture containing liver homogenate (Fig. 1) suggests that microsomal oxidation of I had occurred. There was no such indication for the metabolism of I in the presence of kidney homogenate. The amount of I remaining in the incubation mixture containing kidney homogenate was similar to that of the control (Fig. 1d), suggesting that the kidney tissue is not involved in the metabolism of I in the rat. The results using lung homogenates are similar to those of the kidney homogenate study, indicating that lung tissue is not involved in significant metabolism of I in the rat (Table II).

Whole fraction tissue homogenate studies were performed because the exact location of I-metabolizing enzymes in the lung and/or kidney was not identified. Also, as the optimum tissue protein concentration for the metabolic reaction was not known, a wide range of whole tissue homogenate volumes (0.5, 1.0, 1.5, and 2.0 mL) was used. An incubation period of 30 min was chosen for the study of the *in vitro* metabolism of I (10). Evidence for the metabolism of I was found only with the whole liver tissue homogenate (Fig. 2). There was no indication of lung or kidney tissue involvement in the metabolism of I.

The results of both *in vivo* and *in vitro* experiments have clearly shown that the liver is the primary organ responsible for the metabolism of I in rats, essentially eliminating the hypothesis of significant extrahepatic metabolism. Based on this hypothesis, bioavailability studies involving urinary excretion patterns following oral and intravenous administration of various doses of I were characterized. These studies were undertaken to explore the possible reason(s) why I does not undergo hepatic first-pass metabolism following oral and intraperitoneal administration over the dose range studied (1) despite the fact that total body clearance of I approaches the hepatic blood flow. One of the hypotheses proposed by Tam *et al.* (1) to explain this phenomenon was that the concentration of I in the hepatoportal vein during the absorption phase is high enough to saturate the enzyme capacity of the liver at the dose range studied (1–35 mg/kg). To test this, the bioavailability (F) of I was determined at lower doses (0.1, 0.5, 1.0, and 5.0 mg/kg). The 48-h cumulative urinary excretion data obtained in our present studies showed significant hepatic first-pass metabolism of I at the 0.1- and 0.5-mg/kg doses, resulting in lower bioavailability values (Table III). A nonlinear, dose-dependent trend in the bioavailability values of I at different doses was evident. The bioavailability of I increased with increasing dose, suggesting that saturation of the liver enzyme capacity occurs at higher doses of I during GI absorption. This may explain why I does not undergo significant hepatic first-pass metabolism at doses >1.0 mg/kg. The phenomenon of dose-dependent bioavailability has also been exhibited by other high liver clearance drugs such as propranolol (23–29) and alprenolol (30, 31).

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ACKNOWLEDGMENTS

This work was supported by the Medical Research Council of Canada (MA-7027), the Kidney Foundation of Canada (65-4461), and the University of British Columbia.

The authors wish to thank Tracy Lakevold for assistance in manuscript preparation and Dr. Milo Gibaldi for advice during the composition of the manuscript.