Pharmacokinetic and Metabolic Disposition of *p*-Chloro-*m*-xylenol (PCMX) in Dogs

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The pharmacokinetic and metabolic profile of *p*-chloro-*m*-xylenol (PCMX) was studied in healthy mongrel dogs after intravenous and oral administration of single doses of 200 and 2000 mg of PCMX, respectively. Calculation of pharmacokinetic parameters was based on compartmental and noncompartmental methods. The mean pharmacokinetic parameters of elimination half-life and mean residence time were 1.84 and 1.69 hr, respectively. The apparent volume of distribution at steady state was estimated to be 22.4 liters, and the plasma clearance was 14.6 liters/hr. The bioavailability of PCMX was 21%, indicating low absorption for this drug. PCMX's metabolite data show that a presystemic elimination process (first-pass effect) is also occurring. PCMX plasma concentrations after intravenous administration of 500-, 200-, and 100-mg doses were found to be proportional to the dose given, demonstrating that the pharmacokinetic profile of PCMX is linear over the dose range studied. Biotransformation studies showed that urinary excretion was not the major route for rapid elimination of unchanged PCMX and almost all material excreted in urine was associated with the conjugated species (glucuronides and sulfates). Statistical significant differences were not found ($P > 0.05$) between the percentages excreted in urine of PCMX and its conjugated metabolites after intravenous and oral administration. The percentages excreted in urine after iv and oral doses of unchanged PCMX were, respectively, 0.45 and 0.37; total conjugates, 46.3 and 43.3; sulfates, 38.1 and 33.2; and glucuronides, 8.2 and 10.2.

KEY WORDS: *p*-chloro-*m*-xylenol (PCMX); metabolism; pharmacokinetics; conjugated metabolites.

INTRODUCTION

PCMX is a phenolic compound widely used as an effective disinfectant, antiseptic, and fungicide agent in pharmaceutical, industrial, and cosmetological products. An increasing tendency to exploit the use of PCMX as an effective germicide in products designed to be used several times a day for an indefinite period of time has been observed. Thus, the risk involved in multiple exposure to PCMX needs to be evaluated in order to determine if any organ is affected because of the potential accumulation of this drug in the body of persons utilizing PCMX products. Pharmacodynamic studies on this drug are scarce, and pharmacokinetic and metabolic data are not readily available (1–10). Excretion and metabolic studies by Reckitt and Coleman (2,5) and Havler and co-workers (3,4) in both rats and dogs, after oral dosing of carbon-14 PCMX, showed that PCMX was well absorbed and almost totally excreted in the urine within 24 hr. A percutaneous study in shaved rats showed that about one-half of the PCMX dose was absorbed from an occluded patch in 6 hr. By this route, excretion via the urine was essentially complete in 24 hr. Plasma levels of labeled material reached a peak concentration of 7.8 ± 0.9 μg/ml in 2 hr following percutaneous administration in the rat. The same dose given orally peaked at 38.8 μg/ml plasma within 30 min of dosing. In dogs given only one-quarter the dose in rats, peak plasma levels of 39.4–48.0 μg/ml were reached at 45–60 min. The half-life for total radioactivity in the plasma was calculated to be 60 min in the rat and 50 min in the dog. Essentially the plasma radioactivity in the brain and spinal cord was lower than in other tissues. High levels of radioactivity were found in the kidney and liver shortly after administration, but the levels declined rapidly over the 24-hr observation period (10). All tissues examined showed essentially no radioactivity at the end of 24 hr and most radioactivity disappeared by the sixth hour. Examination of the urine collected during the first 24 hr showed that metabolism occurred by similar paths in both the rat and dog. In both species, PCMX was excreted in a conjugated form with very low levels of free drug. Hydrolysis of the conjugate showed that 85–90% was PCMX, while mass spectrometry showed the minor metabolite (10–15%) to be a hydroxylated derivative of PCMX. These results are in agreement with some excretion studies in humans (6–9) in which elimination was found to be rapid and complete after both topical and oral administrations.

The overall objective of this work is to study the absorption, distribution, and disposition characteristics of PCMX in dogs with the purpose of establishing its pharmacokinetic profile after single intravenous and oral administration and, also, to provide information on the metabolic pathway of PCMX and amount of conjugated metabolites excreted in urine.

MATERIALS AND METHODS

Animals

Five healthy male mongrel dogs, aged 1.5 to 2.5 years and weighing between 15 to 25 kg, were used in this study. Animal utilization was in compliance with current NIH/PHS and USDA guidelines and regulations. The dogs received intravenously and orally a single dose of 200 and 2000 mg of PCMX, respectively. The dogs were fasted overnight and 4 hr post drug administration, and water was given *ad libitum*. On the day of the experiment, the dogs were catheterized with urinary and intravenous catheters for collection of urine and blood samples, respectively.

Procedure

In the intravenous studies, the saphenous vein in both forelegs of the dog was catheterized using an indwelling 21-gauge butterfly catheter. The drug solution was injected through one saphenous vein and the samples were collected from the other vein. The intravenous solution of PCMX was slowly injected over a period of 1 to 2 min, and the intravenous catheter was thoroughly flushed with saline. Ten-

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milliliter blood samples were withdrawn at 0, 5, 15, 30, and 45 min and 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 7.0, 10.0, and 24.0 hr. For the oral studies, only one saphenous vein was catheterized and 10-ml blood samples were withdrawn at 0, 5, 15, 30, and 45 min and 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 7.0, 10.0, and 24.0 hr. In these studies, the oral solution was deposited directly into the stomach of the dogs using an irrigation catheter connected to an hypodermic syringe. After administering PCMX, the catheter was flushed with 5 ml of the same vehicle (without drug), to be sure that all of the PCMX dose was deposited into the stomach.

After collection of the samples, the blood was transferred from syringes to heparanized tubes. The samples were centrifugated in a Beckman TJ-6 centrifuge at 4°C and plasma was separated and stored at −15°C until assay. The intravenous line was kept open with a continuous slow saline drip for 7 hr.

For urine collection, urinary catheters, 5 French and 22 in. in length, were used. After urinary catheterization and administration of the drug, the dogs were put in restrainers in which they could stand or sit comfortably for the duration of the test. Urine samples were collected by catheterization at 0, 0–0.5, 0.5–1, 1–2, 2–3, 3–4, 4–6, and 6–8 hr. After this period of time, the dogs were transferred to metabolic cages, where the last sample (8–24 hr) was collected by placing a metal tray under the animal cages. A metal screen in the metabolic cage separated feces from urine. The volume of the urine excreted at each collection time was measured and recorded. Duplicate aliquots of approximately 25 ml of each sample were transferred to properly labeled containers and stored in a freezer at −15°C until analysis of PCMX.

Intravenous and Oral Solutions

The iv solution was prepared by dissolving 4 g of PCMX in 20% ethanol, 35% propylene glycol and bringing the volume to 100 ml with water. The resulting preparation (40 mg/ml) was sterilized by filtration, and 5 ml was administered to each dog (200 mg/dog). The vehicle treatment was also included in the study. Each dog received 5 ml of vehicle intravenously the week prior to the initiation of the PCMX trial, with the purpose of observing potential side effects. For the oral study, Dettol (Batch No. E10002) was used as oral solution. This formulation contains 4.8% *p*-chloro-*m*-xylenol, 10% alcohol, and 20% terpineol in a castor-oil soap base. The dogs received orally a single dose of 2000 mg of PCMX. The effect of the oral dose vehicle was also studied.

Drug Analysis

PCMX was analyzed using an HPLC method described previously (11). Briefly, 1 ml of sample was extracted two times with 4 ml of benzene in the presence of internal standard (dichloro-*m*-xylenol; DCMX). The benzene extract was evaporated to dryness and the residue dissolved in mobile phase. The HPLC system consisted of a C_{18} column and a 60:40 methanol:0.05% ammonium carbonate aqueous solution as a mobile phase. An electrochemical detector set at an oxidation potential of 0.9 V versus $Ag^+/AgCl$ 3 *M* NaCl was used to monitor this drug. PCMX-conjugated metabolites were analyzed using an enzymatic high-performance liquid chromatographic method described elsewhere (12). Briefly, aliquots of 1 ml of urine were incubated with 1.3 ml of 0.1 *M* acetate buffer, pH 5.0 (control samples), or 0.1 ml of Glusulase, an enzyme preparation containing β-glucuronidase and arylsulfatase, and 1.2 ml of acetate buffer or with a combination of 0.1 ml of Glusulase and 0.2 ml of 100 m*M* D-saccharic acid-1,4-lactone, an inhibitor of β-glucuronidase, and 1.0 ml of acetate buffer for 24 hr at 37°C. After incubation of the samples, the preparation procedure for the analysis of the metabolic conjugates was continued as PCMX assay.

Data Analysis

Plasma Data. Pharmacokinetic analysis of the data was performed using the nonlinear regression analysis program NONLIN-84 (13). A two-compartment model was used to fit the experimental data. The bicompartmental model was selected applying the *F* test (14). Nonlinear least-squares regression was performed using uniform weights. Pharmacokinetic microconstants were derived from the data using a compartment model which described first-order rates into and out of a peripheral compartment (k_{12} and k_{21}, respectively). In addition, the elimination rate constant from the central compartment was described by k_{10}. The apparent volume of distribution (V_d), volume of the central compartment (V_c), volume of the peripheral compartment (V_p), microconstants k_{12}, k_{21}, and k_{10}, and half-lives $t_{1/2k_{10}}$, $t_{1/2\alpha}$, and $t_{1/2\beta}$ were calculated according to previously published pharmacokinetic equations (15,16) using the NONLIN-84 best-fit equations. Total-body clearance (Cl) and volume of distribution in the steady state (V_{ss}) were calculated according to model-independent equations. The trapezoidal rule was used for calculation of the areas due to its simplicity and the fact that ordinate spaces need not be equal. The area under the curve (AUC), area under the moment curve (AUMC), and mean residence time (MRT) were determined by standard methods (15,16).

Urine Data. The renal clearance of the drug, Cl_R, was estimated by division of the total amount of drug excreted unchanged in the urine, A_{ex}^{∞}, by the area under the plasma concentration curve, AUC_o^{∞}, obtained from the intravenous dose, $Cl_R = A_{ex}^{\infty}/AUC_o^{\infty}$. This equation usually provides a more accurate estimate of Cl_R than the slope of the dA_{ex}/dt vs C_{mid} plot, when urine data is available to account for all the drug excreted unchanged in the urine for at least four to five half-lives. The nonrenal clearance was calculated by subtraction of the renal clearance from the total clearance (of intravenous plasma data) $Cl_{NR} = Cl - Cl_R$. In addition, the fraction of the dose that was excreted unchanged in the urine, f_e, was estimated by division of the total amount of drug excreted unchanged in the urine (A_{ex}^{∞}) by the dose, $f_e = A_{ex}^{\infty}/\text{dose}$. However, for the oral data, *FD* (bioavailability time dose) was used instead of dose (15,16).

The bioavailability of PCMX was estimated using the total amount of unchanged PCMX excreted in urine (A_{ex}^{∞}) after intravenous and oral doses. Because PCMX is rapidly metabolized, the estimate of bioavailability may not reflect the extent of intestinal absorption of PCMX.

Dose Proportionality Studies

In order to determine if PCMX was following linear or nonlinear kinetics, a dose proportionality study was con-

ducted in five mongrel dogs. PCMX total areas under the plasma concentration–time curves were estimated after intravenous administration of 100, 200, and 500 mg of PCMX, respectively.

RESULTS AND DISCUSSION

Plasma Data

Pharmacokinetic parameters were calculated based on the fit of a biexponential model to the plasma concentration versus time curves from five mongrel dogs after intravenous and oral administration of 200 and 2000 mg of PCMX, respectively. The initial estimates of the macroconstants α and β, as well as A and B, were estimated using graphical methods, and nonlinear least-squares regressions were performed with the aid of the computer program NONLIN-84. Individual PCMX plasma concentrations in five dogs as a function of time after intravenous administration of a single dose of 200 mg are illustrated in Fig. 1. Table I presents the mean pharmacokinetic parameters for the 200-mg dose using the compartmental model. The results indicate large variability in the pharmacokinetic parameters among the dogs. The geometric mean of the individual elimination constants (β), distribution constants (α), and elimination half-lives ($t_{1/2\beta}$) were 0.407 ± 1.55 hr^{-1}, 5.74 ± 1.31 hr^{-1}, and 1.70 ± 1.55 hr, respectively.

In addition, noncompartmental methods based on statistical moments were used to calculate some pharmacokinetic parameters, such as total clearance (14.6 ± 2.87 L/hr), steady-state volume of distribution (22.4 ± 7.94 L), area under the curve (15.0 ± 3.14 μg hr/ml), area under the moment curve (26.8 ± 18.2 μg hr^2/ml), and mean residence time (1.69 ± 0.76 hr). Mean pharmacokinetic parameters using noncompartmental methods are presented in Table I. There were no significant differences in the systemic clearance at high and low doses of PCMX, indicating that saturation kinetics do not operate over this dose range.

The proportionality study shows that the PCMX plasma profile after the intravenous administration of 500-, 200-, and 100-mg doses was proportional to the dose given, demonstrating that the pharmacokinetic profile of PCMX is linear over the dose range studied. Figure 2 presents the dose proportionality plot of areas under the plasma curve until time infinity versus PCMX doses. The average areas under the plasma concentration–time curve until infinity in the dogs were 37.9 ± 10.9, 15.0 ± 3.1, and 6.53 ± 1.7 μg hr/ml for the 500-, 200-, and 100-mg doses of PCMX, respectively.

The individual plasma concentrations as a function of time after oral administration of 2000 mg of PCMX are illustrated in Fig. 3. This figure shows that the absorption of PCMX is relatively low and erratic. Plasma levels for dog

Table I. Pharmacokinetic Parameters Obtained After Intravenous and Oral Administration of 200 and 200 mg of PCMX, Respectively[a]

Pharmacokinetic parameter	Units	Mean	SD
	Intravenous		
A	μg/ml	33.69	4.6
B	μg/ml	3.55	1.5
α^b	hr^{-1}	5.74	1.31
β^b	hr^{-1}	0.407	1.55
V_c	L	5.47	0.83
V_p	L	16.54	8.63
V_d	L	38.06	16.8
$K_{10}{}^b$	hr^{-1}	2.66	1.36
$K_{12}{}^b$	hr^{-1}	2.58	1.27
$K_{21}{}^b$	hr^{-1}	0.879	1.55
$t_{1/2k_{10}}{}^b$	hr	0.176	1.28
$t_{1/2\alpha}{}^b$	hr	0.121	1.31
$t_{1/2\beta}{}^b$	hr	1.70	1.55
	Intravenous noncompartmental parameters		
v_{ss}	L	22.45	7.92
Cl	L/hr	13.76	2.74
AUC(0,24)	μg hr/ml	14.14	3.04
AUC(0,∞)	μg hr/ml	15.02	3.14
AUMC(0,∞)	μg hr^2/ml	26.75	18.2
MRT	hr	1.69	0.76
	Oral		
AUC(0,24)	ng hr/ml	375.4	89.6
AUC(0,∞)	ng hr/ml	434.9	81.5
AUMC(0,∞)	ng hr^2/ml	2258	525
MRT	hr	5.16	0.43

[a] AUC(0,∞) oral and AUMC(0,∞) oral were calculated using λ_z from 200 mg.
[b] Geometric mean.

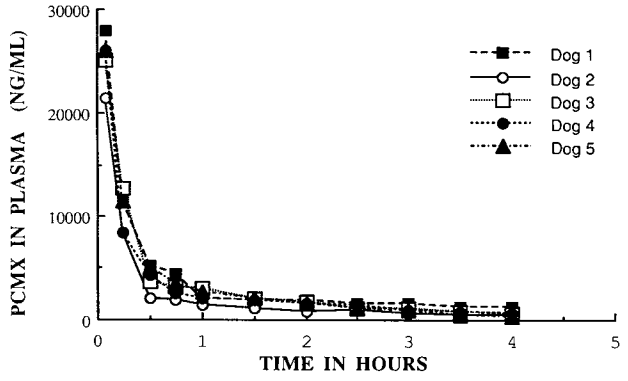

Fig. 1. Individual plasma concentrations of PCMX after intravenous administration of a 200-mg dose of PCMX to five mongrel dogs.

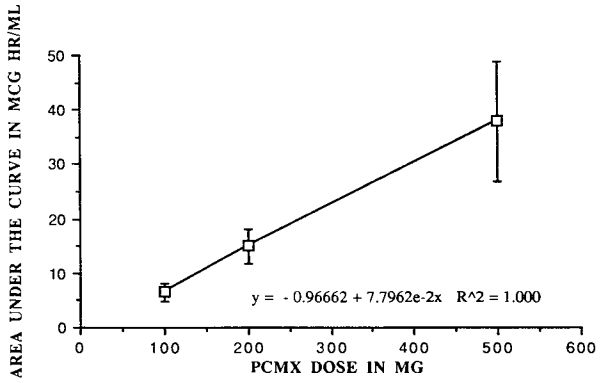

Fig. 2. Plot of the PCMX area under the plasma concentration–time curve (time 0–∞) after intravenous administration versus the PCMX dose.

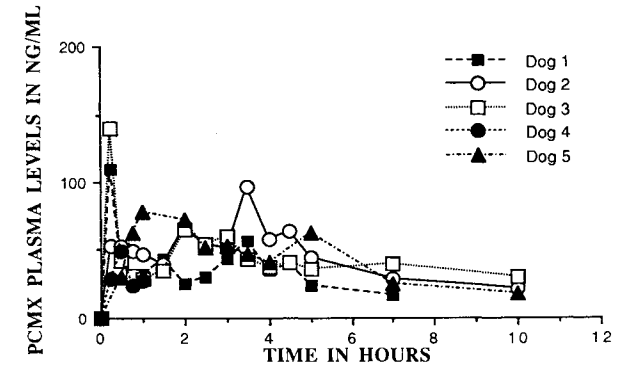

Fig. 3. Individual plasma concentrations of PCMX as a function of time after oral administration of a 2000-mg dose of PCMX.

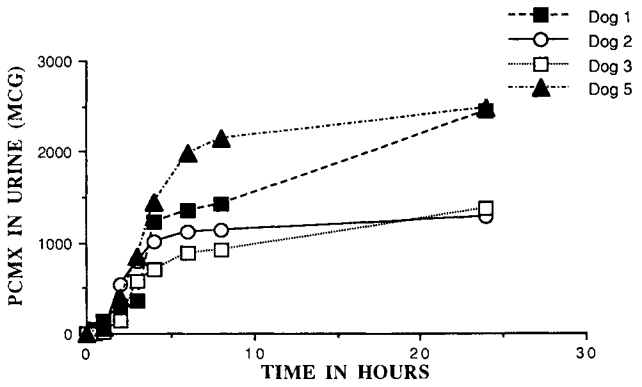

Fig. 5. Cumulative levels of PCMX in urine after oral administration of 2000 mg of PCMX.

No. 4 are incomplete, because this dog vomited approximately 1 hr after oral administration of PCMX, and the collection of blood and urine samples was stopped. Because PCMX absorption after the oral administration was low and erratic, there were not enough data to estimate accurately the area under the moment curve until time infinity. This value was estimated using λ_z (terminal slope) from the 200-mg iv bolus, therefore, bioavailability values were calculated using urine data. Table I shows the mean standard values of AUC_{0-24}, $AUC_{0-\infty}$, $AUMC_{0-\infty}$, and MRT. The mean $AUC_{0-\infty}$ and mean $AUMC_{0-\infty}$ values were 434.9 ± 81.5 ng hr/ml and 2258.4 ± 52.5 ng hr^2/ml.

Urine Data

The individual cumulative amounts of PCMX excreted in urine as a function of time in five dogs after intravenous and oral administration of single doses of 200 and 2000 mg are illustrated in Figs. 4 and 5. Figure 4 shows that dog No. 1 presented unusually high concentrations of PCMX after the intravenous dose. Based on the amount of PCMX excreted in urine for 24 hr after the intravenous administration of 200 mg of PCMX, the following parameters were calculated: renal clearance, nonrenal clearance, and fraction of drug excreted in urine. The mean values of these parameters were 0.048 L/hr, 14.58 L/hr, and 0.446%, respectively. The amount of unchanged PCMX excreted in urine is 892.6 mg after intravenous and 1896 mg after oral administration of 200 and 2000 mg of PCMX, giving a mean bioavailability value of 21.2%. Therefore, urinary excretion is not the major route for rapid elimination of unchanged PCMX. Urinary pharmacokinetic parameters after intravenous and oral administration of PCMX are presented in Table II.

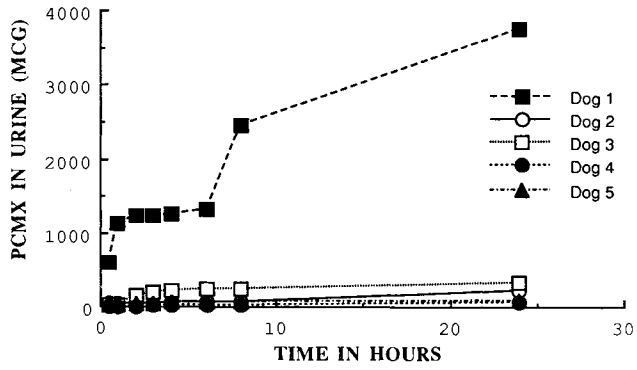

Fig. 4. Cumulative levels of PCMX in urine after intravenous administration of 200 mg of PCMX.

Metabolic Data

Metabolic Pathway. Biotransformation studies in urine samples showed that essentially all the excreted material was in the form of conjugated species (glucuronides and sulfates). Studies involving enzyme hydrolysis indicate that, in addition to conjugation, biotransformation of PCMX by oxidation is also a possibility. According to PCMX's structure, the alkyl side chain (−CH3) might be oxidated to an alcohol and/or the aromatic ring may be hydroxylated. The results of these additional studies showed that both PCMX and monohydroxylated species were present mainly in the form of conjugated species. After hydrolysis a portion of an unknown metabolite present as a material of higher polarity than the parent phenol was detected. Preliminary work after purification of this material by preparative TLC and identification by mass spectroscopy suggests a monohydroxy-PCMX derivative. Methylation with diazomethane yielded a monomethoxy derivative consistent with the metabolite possessing the benzyl alcohol structure rather than the alternative catechol structure. In addition, traces of an unknown

Table II. Urinary Pharmacokinetic Parameters Obtained After iv and Oral Administration of 200 and 2000 mg of PCMX, Respectively

Pharmacokinetic parameter	Units	Mean	SD
	Intravenous		
A_{ex}^{∞}	μg	892.6	1606
Cl_R	L/hr	0.048	0.079
Cl_{NR}	L/hr	14.58	2.93
f_e	%	0.446	0.804
	Oral		
A_{ex}^{∞}	μg	1896	649
f_e	%	0.095	0.032

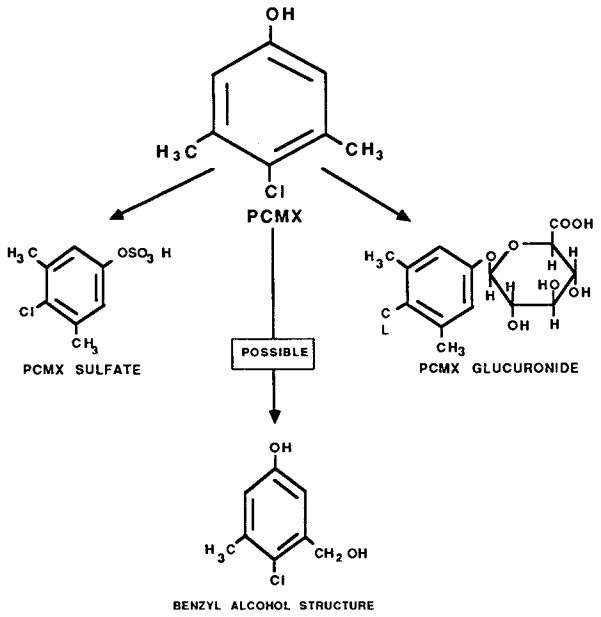

Fig. 6. Proposed metabolic pathway of PCMX.

metabolite more polar than PCMX were also detected. The proposed metabolic pathway for PCMX is shown in Fig. 6.

Metabolite Levels. Figures 7 and 8 present the mean cumulative amounts of PCMX-total conjugates, PCMX-sulfates, and PCMX-glucuronides excreted in urine after single intravenous and oral administration of 200 and 2000 mg of PCMX to five mongrel dogs, respectively. Table III presents a summary of the mean percentages excreted in urine in 24 hr of unchanged PCMX and its conjugated metabolites after intravenous and oral administration of 200 and 2000 mg of PCMX. The percentages of PCMX, PCMX-total conjugates, PCMX-sulfates, and PCMX-glucuronides were 0.45, 46.3, 38.1, and 8.2% after intravenous dose and 0.14, 43.3, 33.2, and 10.2% after oral dose, respectively. These percentages were calculated considering the 200- and 2000-mg dose as 100%. Further, Table III provides the sulfates and glucuronides ratio, when the total conjugates excreted in urine are considered as 100% (sulfates/total conjugates and glucuronides/total conjugates ratio). In addition, a statistical summary of the percentage of PCMX, PCMX-total conjugates, PCMX-sulfates, and PCMX-glucuronides excreted in urine in 24 hr is shown in Table III. Statistical analysis (ANOVA)

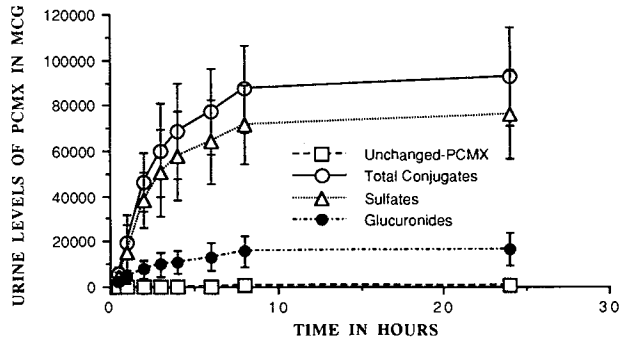

Fig. 7. Mean cumulative urine levels of PCMX and its conjugated metabolites after single intravenous administration of 200 mg of PCMX.

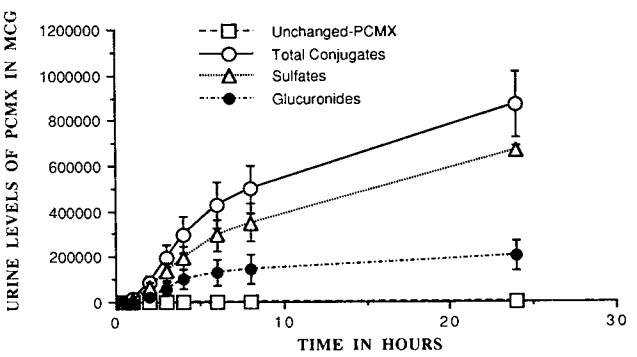

Fig. 8. Mean cumulative urine levels of PCMX and its conjugated metabolites after single oral administration of 2000 mg of PCMX.

shows that there are no statistical differences ($P > 0.05$) between the percentage excreted in urine of PCMX and its conjugated metabolites after intravenous and that after oral administration of PCMX.

Analysis of the previous data shows that 47% of the intravenous dose and 44% of the oral dose were excreted in urine. These results demonstrate incomplete mass balance. Thus, about 50% of the PCMX is still missing. Several possibilities exist to account for the rest of the dose. First, urine samples were collected only for 24 hr. The data suggest that PCMX-conjugated metabolites are being excreted after 24 hr. Second, the PCMX-conjugated metabolites may not be the only metabolites excreted in urine. Third, PCMX-conjugated metabolites were quantitated in urine, but they were not analyzed in feces or other biological materials. Therefore, PCMX metabolites or conjugated metabolites may have other routes of excretion, in addition to the urinary route.

Finally, based on the fact that approximately 44% of the dose administered orally was excreted in urine as PCMX-conjugated metabolites, it is necessary to consider the possibility that PCMX oral doses were relatively well absorbed from the gastrointestinal tract, but presystemic metabolism (first-pass effect) may have prevented sufficiently high levels of unchanged PCMX in blood plasma for analysis.

Table III. Statistical Analysis of Percentage Excreted in Urine in 24 hr of PCMX and Its Conjugated Metabolites After Single Intravenous and Oral Administration of 2000 and 200 mg of PCMX to Mongrel Dogs

	Intravenous		Oral		ANOVA
	Mean	SD	Mean	SD	$\alpha = 0.05$
Parent	0.446	0.804	0.143	0.121	NS
Total conjugates	46.27	10.86	43.31	7.16	NS
Sulfates	38.06	9.78	33.15	10.17	NS
Glucuronides	8.21	3.55	10.15	3.35	NS
Sulfates and glucuronides ratio					
Sulfates/total conjugates	81.89	7.43	75.46	10.49	NS
Glucoronides/total conjugates	18.09	7.46	24.54	10.49	NS

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