precise, accurate, specific, and sensitive for the assay of dextromethorphan and its urinary metabolites and have been used to quantitate these compounds in urine from humans who received a therapeutic dose of dextromethorphan hydrobromide.

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Effect of Renal Failure and Bis(2-ethylhexyl) Phthalate Pretreatment on the Disposition and Metabolism of Antipyrine in the Rat

GARY M. POLLACK and DANNY D. SHEN [x]

Received June 16, 1982, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Amherst, NY 14260.* Accepted for publication October 15, 1982.

Abstract ☐ Renal failure patients undergoing hemodialysis are regularly exposed to phthalate plasticizers leached from dialysis tubings. Previous studies have shown that antipyrine is eliminated more rapidly in chronic renal failure patients compared with normal individuals. Therefore, the effect of bis(2-ethylhexyl) phthalate on the metabolism of antipyrine was investigated in normal and renal failure rats. In normal animals, the elimination kinetics of an intravenous dose of antipyrine (20 mg/kg) was determined before and after 14 days of peroral treatment with 2 mL/kg/d of bis(2-ethylhexyl) phthalate. The plasma clearance of antipyrine increased markedly after bis(2-ethylhexyl) phthalate treatment. There was a corresponding decrease in the elimination half-life of antipyrine, whereas the apparent volume of distribution was not affected. Both liver weight and hepatic cytochrome P_{450} content increased following exposure to bis(2-ethylhexyl) phthalate, indicating the induction of hepatic microsomal enzymes. The fractional urinary recovery of the *N*-demethyl, 4-hydroxy, and 3-hydroxymethyl metabolites of antipyrine was not altered, suggesting that all three oxidative pathways were induced to the same extent. Renal failure alone did not affect the elimination kinetics of antipyrine. However, antipyrine clearance was induced to a greater extent by bis(2-ethylhexyl) phthalate treatment in the renal failure rats as compared with the control animals. The potential for phthalate plasticizers to alter hepatic drug metabolism in hemodialysis patients should be considered.

Keyphrases ☐ Antipyrine—disposition, pharmacokinetics, effect of bis(2-ethylhexyl) phthalate pretreatment and renal failure, rats ☐ Bis(2-ethylhexyl) phthalate—pretreatment, effect on antipyrine disposition and pharmacokinetics, renal failure, rats ☐ Renal failure—effect on antipyrine disposition and pharmacokinetics, rats, bis(2-ethylhexyl) phthalate pretreatment

There is increasing evidence suggesting that the metabolism of some drugs may be altered in renal failure (1). In general, an inhibition of drug metabolism is observed; *e.g.*, the oxidative metabolism of propranolol (2) and propoxyphene (3) and the acetylation of drugs such as sulfisoxazole (4) and aminosalicylic acid (5) are apparently inhibited in uremia. Phenytoin (6, 7) and antipyrine (8–10) are apparent exceptions to this rule, as the metabolic clearance of these compounds has been reported to be increased in patients with renal insufficiency.

The increased metabolic clearance of phenytoin in patients with renal failure is attributed to reduced protein binding of this drug in uremic serum (11). Antipyrine, however, is only slightly bound to serum and tissue proteins (12), and a decrease in serum protein binding would not be expected to significantly alter the metabolic clearance of this drug. Alternative explanations for this phenomenon, therefore, should be considered.

It is known that plasticizers can be leached from plastic medical devices such as blood transfusion bags and hemodialysis tubing into blood and certain intravenous fluids. The most common plasticizer used in the production of medical-grade plastics, bis(2-ethylhexyl) phthalate (I), has been identified as a contaminant in blood that was stored in transfusion bags (13, 14) or passed through plastic tubing (15). Clinical studies have shown that patients undergoing maintenance hemodialysis are regularly exposed to I (16, 17). Serum concentrations of I in the microgram/milliliter range were observed in renal failure patients during hemodialysis. It is possible that impaired renal function and repeated dialysis may lead to significant accumulation of I and its metabolites in hemodialysis patients (18).

Animal studies have shown that chronic exposure to I can induce changes in the *in vitro* activities of a number of hepatic drug-metabolizing enzymes (19–23). Both inhibition and induction of hepatic enzymatic activities have been observed. The reason for these conflicting results between studies may be due to variations in the selection of drug substrate, treatment schedule, and route of ad-

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Table I—Pharmacokinetic Parameters for Antipyrine Disposition in Normal Rats Receiving Corn Oil or Phthalate Treatment [a]

Parameter	Corn Oil		Phthalate	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
CL_p, mL/min/kg	3.30 (0.44)	4.18 (0.49)	3.86 (0.51)	7.81 (0.53) [b]
Vd_β (area), mL/kg	726 (98)	755 (79)	859 (58)	755 (56)
$t_{1/2\beta}$, min	153 (13)	128 (9)	165 (22)	67.2 (3.1) [b]

[a] Results are expressed as mean ($\pm SE$) of n determinations; $n = 9$ for corn oil and $n = 7$ for phthalate. [b] Significantly different from pretreatment, $p < 0.005$.

ministration of the phthalate. Moreover, appropriate *in vivo* metabolic studies are seldom available for *in vitro–in vivo* correlations.

The primary purpose of the present study was to determine whether chronic treatment with I can induce the *in vivo* metabolism of antipyrine in rats, which may provide a plausible explanation for the apparent increase in the metabolic clearance of this drug in chronic renal failure patients. Secondly, studies were performed in rats with experimentally induced renal failure to assess the effect of uremia on antipyrine metabolism. In addition, possible modulation of the metabolic effect of I in the presence of renal failure was investigated.

EXPERIMENTAL

Chemicals—Antipyrine, *N*-demethylantipyrine, 4-hydroxyantipyrine, and 3-hydroxymethylantipyrine were supplied[1]. Bis(2-ethylhexyl) phthalate[2], and β-glucuronidase–aryl sulfatase[3], in the form of limpet

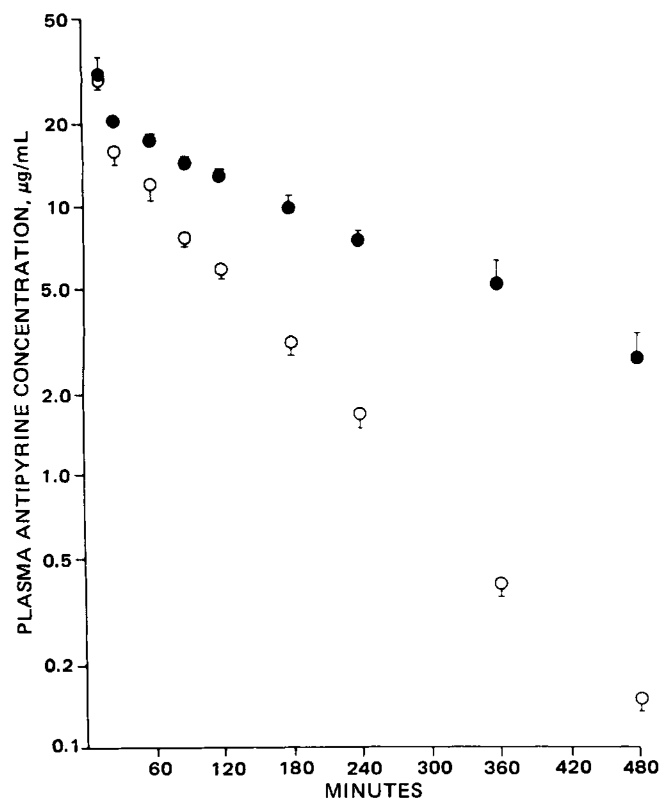

Figure 1—*Mean antipyrine plasma concentration–time profile in rats before (●) and after (○) a 14-d treatment with I. Bars represent* SE.

[1] Supplied by Dr. Charles Hignite, Veterans Administration Medical Center, Kansas City, Mo. and Professor Gerhard Levy, State University of New York at Buffalo.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] Sigma Chemical Co., St. Louis, Mo.

Table II—Liver Weights and Antipyrine Clearance Normalized for Liver Weight in Corn Oil- and Phthalate-Treated Rats [a]

	Corn Oil	Phthalate
Wet liver weight, g/kg	30.7 (1.6)	48.2 (0.9) [b]
CL_p, mL/min/g of liver	0.139 (0.017)	0.162 (0.012)

[a] Results are expressed as mean ($\pm SE$) of n determinations; $n = 9$ for corn oil and $n = 7$ for phthalate. [b] Significantly different from corn oil, $p < 0.005$.

Table III—Comparison of Cumulative Urinary Recovery of Antipyrine and Metabolites Between Corn Oil and Phthalate Treatments [a]

Compound	Corn Oil	Phthalate
Antipyrine	2.11 (0.38)	3.26 (0.65)
N-Demethylantipyrine	2.97 (0.61)	2.08 (0.32)
4-Hydroxyantipyrine	17.8 (4.7)	13.0 (2.8)
3-Hydroxymethylantipyrine	26.1 (2.3)	24.9 (2.8)
Total	48.9 (5.5)	43.2 (3.4)

[a] Results are expressed as mean percent of dose ($\pm SE$) of six determinations.

acetone powder (type I) were purchased and used without further purification.

Studies in Normal Rats—*Antipyrine Clearance Kinetics*—Male Sprague–Dawley rats[4] weighing 300–350 g were used. A silicone rubber cannula was implanted in the right jugular vein under ether anesthesia 48 h before the first experiment. Antipyrine (20 mg/kg) dissolved in physiological saline (10 mg/mL) was administered through the cannula. Serial venous blood samples (0.2–0.3 mL) were drawn through the cannula over an 8-h period and collected in heparinized tubes. The plasma was separated and stored at −20°C until assayed. Food was restricted only during the blood collection period, and water was available *ad libitum* throughout the entire experiment. The plasma concentration of antipyrine was determined by the high-performance liquid chromatographic (HPLC) procedure of Danhof *et al.* (24).

Following the blood sampling, I dissolved in corn oil (2:3 v/v) or corn oil alone was administered once daily for 14 days *via* gastric intubation. The total volume administered was 5 mL/kg/d, yielding a dosage of I of 2 mL/kg/d or 1.96 g/kg/d, which is comparable to dosages employed in previous studies of the effect of I on *in vitro* hepatic drug-metabolizing enzyme activities.

On the final treatment day, a silicone rubber cannula was implanted in the left jugular vein under ether anesthesia, and the posttreatment time course of antipyrine was determined 48 h later. The 48-h washout period was included to avoid the possibility of direct effects of the plasticizer on the disposition of antipyrine. It has been shown that a single dose of radiolabeled I is completely eliminated in the rat within this time period (25). Following blood sampling the animals were sacrificed and the livers were excised and weighed.

The pretreatment and posttreatment antipyrine plasma concentration time course data were fit to a biexponential equation using a nonlinear least-squares regression computer program (26). The apparent volume of distribution (Vd_β), plasma clearance (CL_p), and terminal disposition half-life ($t_{1/2\beta}$) were calculated.

Urinary Recovery of Antipyrine Metabolites—Rats weighing 300–350 g were treated with I or corn oil for 14 d as in the previous experiment. Antipyrine (20 mg/kg) was administered intravenously *via* the dorsal tail vein under light ether anesthesia 48 h following the final day of treatment. The rats were placed in plastic metabolism cages, and urine was collected for 24 h. Urinary excretion of antipyrine and its metabolites has been reported to be essentially complete within 8 h (27). Food and water were available *ad libitum* during the urine collection period. The urine samples were incubated with β-glucuronidase–aryl sulfatase (limpet acetone powder) at 37°C for 3 h, and the total (free plus conjugated) amounts of 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, *N*-demethylantipyrine, and the parent drug were then assayed by the HPLC method of Danhof *et al.* (24).

Hepatic Hemoprotein Content—Rats weighing 265–315 g were treated for 14 d with I or corn oil as in the previous experiment. Twenty-four hours following the final treatment, the animals were anesthetized lightly with ether and exsanguinated by cutting the renal blood vessels. The livers were quickly excised, washed in ice-cold 0.25 M sucrose, blotted dry, and weighed. Following homogenization in ice-cold 0.25 M sucrose (1:4 w/v) the hepatic microsomes were isolated by the calcium precipi-

[4] Blue Spruce Farms, Altamont, N.Y.

Table IV—Hepatic Microsomal Protein and Hemoprotein Content in Rats Treated with Corn Oil or Phthalate [a]

	Corn Oil	Phthalate
Wet liver weight, g/kg	24.9 (2.1)	44.6 (3.1)[c]
Total microsomal protein, mg/g of liver	23.8 (4.0)	24.7 (9.4)
Cytochrome p_{450},		
nmol/mg of protein	0.544 (0.004)	0.860 (0.112)[b]
nmol/g of liver	13.0 (1.1)	19.5 (1.6)[c]
Cytochrome b_5		
nmol/mg of protein	0.310 (0.037)	0.338 (0.051)
nmol/g of liver	7.53 (1.24)	8.96 (2.57)

[a] Values are mean ($\pm SE$) of five determinations. [b] Significantly different from corn oil, $p < 0.05$. [c] Significantly different from corn oil, $p < 0.001$.

tation method of Kamath and Rubin (28). The microsomal content of cytochrome P_{450} and cytochrome b_5 was determined spectrophotometrically as described by Omura and Sato (29). Microsomal protein content was determined by the method of Lowry *et al.* (30).

Studies in Renal Failure Animals—Renal failure was induced by a two-step subtotal nephrectomy (31). Two-thirds of the right kidney was removed in the first step, followed by removal of the entire left kidney 1 week later. The sham procedure consisted of removal of the connective tissue surrounding the appropriate kidney on each of the 2 surgical days. Care was taken at all times to avoid damaging the adrenal glands. Penicillin-G (20,000 U/kg) and streptomycin (10 mg/kg) were administered intramuscularly following each surgical procedure to prevent infection and reduce mortality (31). Preliminary studies with this renal failure model showed that the procedure significantly elevated the serum creatinine level without affecting the serum glutamic pyruvic transaminase activity, indicating that subtotal nephrectomy does not produce hepatic damage.

Renal failure and sham-operated animals received the following treatments: (1) sham-operated rat dosed with corn oil; (2) renal failure rat dosed with corn oil; (3) sham-operated rat dosed with 0.5 mL/kg/d of I; (4) renal failure rat dosed with 0.5 mL/kg/d of I; (5) sham-operated rat dosed with 2 mL/kg/d of I; and (6) renal failure rat dosed with 2 mL/kg/d of I. The treatment scheme was designed to ascertain the effect of renal failure on antipyrine elimination. In addition, the combined effect of renal failure and phthalate pretreatment was assessed at low (0.5 mL/kg/d) and high (2 mL/kg/d) dosages of I.

Phthalate treatment began 48 h after the completion of the nephrectomy procedure (*i.e.*, after the second surgical day). The renal function of nephrectomized rats remains depressed for 10 d after surgery. Thereafter, a gradual recovery in renal function is observed in some animals. Therefore, the length of phthalate treatment was reduced to 7 d as compared with the 2-week period in the studies with normal animals. At 48 h after the final dose of I, the elimination kinetics of antipyrine was determined as previously described.

Statistical Analysis—The paired Student's t test was used to test the significance of differences between means of the pretreatment and posttreatment antipyrine pharmacokinetic parameters. Differences between the phthalate and corn oil treatment in normal animals were analyzed using the unpaired Student's t test. The Wilcoxon summed ranks test was used to test the significance of differences between the uremic and sham-operated animals receiving I or corn oil. A probability level of $p < 0.05$ was considered statistically significant.

RESULTS

Studies in Normal Rats—*Antipyrine Disposition*—The mean antipyrine pharmacokinetic parameters for the corn oil- and phthalate-treated animals are presented in Table I. The disposition of antipyrine was not significantly affected by corn oil administration, although there was a trend towards an increased CL_p and decreased $t_{1/2}$. In contrast, treatment with I resulted in a significant increase in plasma clearance and a decrease in the terminal disposition half-life of antipyrine. No alteration in the volume of distribution was observed. The mean pre- and posttreatment antipyrine concentration–time profiles for the phthalate-treated animals are presented in Fig. 1.

Liver weight data are presented in Table II. A significant increase in wet liver weight was observed following treatment with I. When the posttreatment plasma clearance of antipyrine was normalized for wet liver weight, the difference between the two groups was no longer statistically significant.

Urinary Excretion of Antipyrine Metabolites—A comparison of the mean cumulative urinary recovery of antipyrine and three of its oxidative metabolites in the corn oil and phthalate groups is presented in Table III. None of the differences between the two groups were statistically significant, indicating that the three major metabolic pathways of antipyrine, *i.e.*, *N*-demethylation, hydroxylation at the 4 position of the pyrazole ring, and hydroxylation at the 3-methyl side chain, were uniformly induced by I.

Hepatic Hemoproteins—The hepatic hemoprotein data are presented in Table IV. In comparison with control animals, treatment with I significantly increased the hepatic content of cytochrome P_{450} and the weight of the liver. The recovery of microsomal protein per gram of wet liver and the hepatic content of cytochrome b_5 were not significantly altered.

Table V—Mean Serum Creatinine Concentrations (mg/dL) in the Six Treatment Groups

Treatments[a]	Mean ± *SE*
1	0.356 ± 0.046
2	0.490 ± 0.041
3	0.452 ± 0.031
4	2.21 ± 0.51[b]
5	1.37 ± 0.06[b]
6	1.71 ± 0.35[b]

[a] See text for explanation of treatment codes. [b] Significantly different from their respective sham-operated controls ($p < 0.005$).

Studies in Renal Failure Rats—Serum creatinine concentrations at the time of antipyrine studies in the various treatment groups are given in Table V. Subtotal nephrectomy increased serum creatinine three- to fivefold, while phthalate treatment apparently had no effect on creatinine concentrations.

The mean antipyrine plasma clearances and half-lives for the nephrectomized animals and sham-operated controls are given in Tables VI and VII, respectively. Nephrectomy alone did not significantly affect the disposition of antipyrine in the corn oil-treated animals. As in the earlier study in normal rats, administration of I to the sham-operated animals resulted in a significant increase in CL_p and a corresponding decrease in $t_{1/2}$. Treatment with I at a dose of 2 mL/kg/d produced significantly greater changes in the elimination kinetics of antipyrine than a lower dose of 0.5 mL/kg/d, suggesting that the magnitude of the increase in antipyrine clearance is related to the dose of plasticizer administered. The apparent volume of distribution was not affected by nephrectomy, pretreatment with I, or combinations thereof. Equivalent doses of I tended to produce a greater increase in antipyrine clearance in the nephrectomized animals as compared with the sham-operated controls. The differences between the two groups are statistically significant at the low dose of I, but not at the high dose. The lack of a difference at the high dose of I may be due to the large variability in the clearance estimates in the renal failure group. Alternatively, near maximal induction may have been reached with the phthalate dosage of 2 mL/kg/d such that any enhancement in response in the presence of renal failure was not readily discernible.

The effects of nephrectomy and phthalate treatment on wet liver weight per kilogram of body weight are presented in Table VIII. Nephrectomy alone tended to decrease liver weight slightly, although the difference was statistically significant. It is likely that this difference is the result of a decreased food intake in these animals. Phthalate treatment led to a marked increase in liver weight in both renal failure and sham-operated control animals. There was no significant difference in liver weight between the nephrectomized and sham-operated control animals at either phthalate dosage level, possibly because the decrease in liver weight due to uremia was partly offset by an increase response to the plasticizer in the renal failure rats.

DISCUSSION

Chronic exposure to I can induce hepatic drug metabolism in the rat. The magnitude of increase in the plasma clearance and the decrease in terminal disposition half-life of antipyrine following chronic treatment with I is comparable to the reported changes in antipyrine disposition produced by phenobarbital (27), 3-methylcholanthrene (27), and polychlorinated biphenyls (32). Also, the increase in antipyrine clearance was dependent on the pretreatment dosage of I.

The urinary recovery of the *N*-demethyl and hydroxyl metabolites of antipyrine remained unchanged after treatment with I. Danhof *et al.* (27) showed that 3-methylcholanthrene preferentially induced the 4-hydroxylation pathway in the metabolism of antipyrine in rats, while phe-

Table VI—Antipyrine Clearance (mL/min/kg) in Renal Failure and Sham-Control Rats after Treatment with Corn Oil or Phthalate

<table>
<tr><th rowspan="2">Statistical Comparisons[a]</th><th colspan="6">Treatments[b]</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th></tr>
<tr><td>Mean (n)</td><td>3.71 (7)</td><td>3.83 (7)</td><td>5.14 (6)</td><td>6.56 (5)</td><td>7.54 (7)</td><td>9.53 (7)</td></tr>
<tr><td>SE</td><td>0.11</td><td>0.24</td><td>0.38</td><td>0.13</td><td>0.58</td><td>1.20</td></tr>
<tr><td rowspan="2">Between renal failure and sham-operated rats treated with corn oil</td><td colspan="2">NS[c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="3">$p < 0.05$</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Between low- and high-dose phthalate in sham-operated rats</td><td></td><td></td><td colspan="3">$p < 0.05$</td><td></td></tr>
<tr><td colspan="5">$p < 0.001$</td><td></td></tr>
<tr><td rowspan="3">Between low- and high-dose phthalate in renal failure rats</td><td></td><td colspan="3">$p < 0.005$</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="3">$p < 0.005$</td></tr>
<tr><td></td><td colspan="5">$p < 0.001$</td></tr>
<tr><td>Between renal failure and sham-operated rats treated with phthalate</td><td></td><td></td><td colspan="2">$p < 0.05$</td><td colspan="2">NS</td></tr>
</table>

[a] Wilcoxon's summed rank test. [b] See text for explanation of treatment codes. [c] No statistically significant difference.

nobarbital treatment resulted in an almost uniform stimulation of all known metabolic pathways. The present urinary metabolite data suggest that induction of antipyrine metabolism by I resembles induction produced by phenobarbital more closely than that produced by 3-methylcholanthrene. However, it should be noted that in our study as well as in others, only ~50% of the antipyrine dose could be accounted for as either intact antipyrine or its known metabolites in urine. A previous study of Aarbakke (33) in rats with radiolabeled antipyrine showed that ~74% of the radioactive dose is recovered in urine while <3% appeared in the feces and expired air. Recently, 4,4′-dihydroxyantipyrine was identified as a metabolite in rat urine (34). Therefore, the effect of I on other metabolic pathways of antipyrine is presently unknown.

The increase in hepatic cytochrome P_{450} content following treatment with I is similar in magnitude to that reported by other investigators (19, 20, 22, 23). It is well recognized that treatment with 3-methylcholanthrene results in a shift in the wavelength maximum of the carbon monoxide difference spectrum of reduced hepatic microsomes from 450 nm to 448 nm, whereas no such shift is observed with liver microsomes from phenobarbital-induced animals. The carbon monoxide difference spectrum of reduced microsomes from both control and phthalate-treated rats in the present study displayed a maximum at 450 nm. This finding would also suggest that the inductive properties of I more closely resemble phenobarbital than 3-methylcholanthrene.

Treatment with I had no apparent effect on the hepatic content of cytochrome b_5. Little data concerning the induction of this cytochrome is available; however, phenobarbital (35) has been reported to increase hepatic cytochrome b_5. This may indicate a subtle difference between the inductive properties of I and phenobarbital. The importance of this difference, however, is not known.

It should be noted that normalizing the plasma clearance of antipyrine by liver weight rather than body weight, eliminates any significant difference between the phthalate and corn oil groups. This would suggest that the clearance of antipyrine is governed primarily by the amount of normally functioning hepatic tissue present in the organism. The lack of a significant difference in mean plasma clearance per gram of liver weight between the phthalate and corn oil groups also suggests that, while I increases the amount of hepatic tissue, it does not change the intrinsic metabolic activity of the newly generated tissue towards antipyrine.

The elimination of antipyrine was not altered by the impairment of renal function. Furthermore, the effect of I on antipyrine clearance was enhanced in the presence of renal failure. The *in vivo* data are consistent with the study by Leber *et al.* (20), who observed that pretreatment with I at a dosage of 0.2 mL/kg/d led to an increase in the *in vitro* drug-metabolizing enzyme activities in subtotally nephrectomized rats, but not in sham-operated controls. The enhanced response to phthalate treatment in uremic rats may be explained by a greater exposure to the inducing agent(s), as a result of accumulation of I and/or its metabolites during renal failure. Alternatively, uremia may promote the intrinsic response of the liver to treatment with the plasticizer.

The present animal data with I suggest that the increased metabolic clearance of antipyrine in renal failure patients could be a result of chronic exposure to phthalate ester plasticizers through repeated hemodialysis. However, it is important to note that in this study the antipyrine clearance measurements were all performed at 48 h after the last dose of I, by which time much of the administered dose of phthalate should have been eliminated. Hence, the possibility of a direct inhibitory effect on antipyrine metabolism cannot be ruled out. Metabolic inducers such as phenobarbital are known to also exhibit inhibitory activity (36). The potential for induction and inhibition of drug metabolism to occur simultaneously during continuous treatment with I should be recognized. In fact, a recent study by Agarwal *et al.* (23) showed that either induction or inhibition of *in vitro* hepatic microsomal oxidative enzyme activities

Table VII—Antipyrine Elimination Half-life (min) in Renal Failure and Sham-Operated Rats after Treatment with Corn Oil or Phthalate

<table>
<tr><th rowspan="2">Statistical Comparisons[a]</th><th colspan="6">Treatments[b]</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th></tr>
<tr><td>Mean (n)</td><td>157 (7)</td><td>152 (7)</td><td>108 (6)</td><td>70.9 (5)</td><td>76.9 (6)</td><td>70.2 (7)</td></tr>
<tr><td>SE</td><td>5</td><td>14</td><td>6</td><td>7.4</td><td>4.8</td><td>4.0</td></tr>
<tr><td>Between renal failure and sham-operated rats treated with corn oil</td><td colspan="2">NS[c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">Between low- and high-dose phthalate in sham-operated rats</td><td colspan="3">$p < 0.005$</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="3">$p < 0.005$</td><td></td></tr>
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<tr><td rowspan="3">Between low- and high-dose phthalate in renal failure rats</td><td></td><td colspan="3">$p < 0.005$</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="3">NS</td></tr>
<tr><td></td><td colspan="5">$p < 0.001$</td></tr>
<tr><td>Between renal failure and sham-operated rats treated with phthalate</td><td></td><td></td><td colspan="2">$p < 0.005$</td><td colspan="2">NS</td></tr>
</table>

[a] Wilcoxon's summed rank test. [b] See text for explanation of treatment codes. [c] No statistically significant difference.

Table VIII—Liver Weights in Renal Failure and Sham-Operated Rats after Treatment with Corn Oil or Phthalate

<table>
<tr><th rowspan="2">Statistical Comparisons[a]</th><th colspan="6">Treatments[b]</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th></tr>
<tr><td>Mean (*n*)</td><td>35.7 (7)</td><td>31.2 (7)</td><td>43.6 (6)</td><td>46.6 (5)</td><td>54.3 (7)</td><td>52.7 (7)</td></tr>
<tr><td>*SE*</td><td>1.4</td><td>1.2</td><td>1.4</td><td>0.7</td><td>1.4</td><td>2.6</td></tr>
<tr><td>Between renal failure and sham-operated rats treated with corn oil</td><td colspan="2">$p < 0.05$</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">Between low- and high-dose phthalate in sham-operated rats</td><td colspan="3">$p < 0.001$</td><td></td><td></td><td></td></tr>
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<tr><td></td><td></td><td></td><td colspan="3">NS[c]</td></tr>
<tr><td></td><td colspan="5">$p < 0.001$</td></tr>
<tr><td>Between renal failure and sham-operated rats treated with phthalate</td><td></td><td></td><td colspan="2">NS</td><td colspan="2">NS</td></tr>
</table>

[a] Wilcoxon's summed rank test. [b] See text for explanation of treatment codes. [c] No statistically significant difference.

can result depending on the route of administration of I. Induction of metabolism was observed after oral administration of I, whereas inhibition was evident after intraperitoneal administration. Unfortunately, these investigators used very high doses of I (>2 mL/kg/d). Since the degree of metabolic inhibition is usually dependent on the dose or concentration of the inhibitor, the likelihood for metabolic inhibition to occur at phthalate levels that have been observed in human subjects is not known. Studies are currently underway to investigate the effects of phthalate plasticizers on hepatic drug metabolism under more clinically relevant experimental conditions.

In conclusion, the presence of circulating plasticizers in patients undergoing regular hemodialysis should be considered as a complicating factor in the interpretation of clinical data concerning the effect of renal failure on drug metabolism.

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