logical fluids such as saliva, cerebrospinal fluid, and dialysate.

(1) A. Calo, C. Cardini, and V. Quercia, *J. Chromatogr.*, **37**, 194 (1968).
(2) B. M. Richard, J. E. Manno, and B. R. Manno, *ibid.*, **89**, 80 (1974).
(3) C. S. Lee and L. Z. Benet, *ibid.*, **128**, 188 (1976).
(4) C. S. Lee and L. Z. Benet, *J. Pharm. Sci.*, **67**, 470 (1978).
(5) R. Kanther, *Antibiot. Chemother.*, **16**, 203 (1970).
(6) C. S. Lee, T. G. Gambertoglis, D. C. Brater, and L. Z. Benet, *Clin. Pharmacol. Ther.*, **22**, 615 (1977).

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Pharmacokinetic Studies of Propoxyphene IV: Effect of Renal Failure on Systemic Clearance in Rats

Keyphrases □ Propoxyphene—pharmacokinetics, effect of renal failure on systemic clearance, rats □ Pharmacokinetics—propoxyphene, effect of renal failure on systemic clearance, rats □ Analgesics—propoxyphene, pharmacokinetics, effect of renal failure on systemic clearance, rats

To the Editor:

There is considerable concern about the safety of the widely used analgesic agent propoxyphene (dextropropoxyphene) (1). Under certain circumstances, death from propoxyphene may occur following ingestion of quantities only slightly larger than the upper limit of the recommended therapeutic dosage (1).

Propoxyphene is subject to pronounced presystemic ("first-pass") biotransformation; only a small fraction of the absorbed dose enters the general circulation in unmetabolized form (2–4). This effect may be due to both hepatic and prehepatic biotransformation of the drug during absorption (5). Plasma concentrations of propoxyphene in patients without functioning kidneys are considerably higher than in normal subjects after oral administration of the drug (6). Indirect evidence suggests that this result is due to decreased presystemic biotransformation in the patients (6). However, since propoxyphene could not be administered by intravenous injection, a decreased systemic clearance or apparent volume of distribution of the drug in anephric patients could not be excluded definitively. For this reason, the systemic clearance and apparent volume of distribution of propoxyphene after intravenous injection have now been determined in normal rats and in rats with renal failure.

Male Sprague–Dawley rats, 260–350 g, received a single 5-mg/kg iv dose of either uranyl nitrate (7) or an equal volume of saline solution. Five days later, when serum urea nitrogen concentrations had increased to 150 ± 37 mg/100 ml (mean ± *SD*) in the uranyl nitrate-treated animals (as compared to 15 ± 8 mg/100 ml in normal rats), all animals received a single dose of tritium-labeled propoxyphene, 8.3 ± 1.9 μg/kg (mean ± *SD*), through an indwelling cannula in the jugular vein (8).

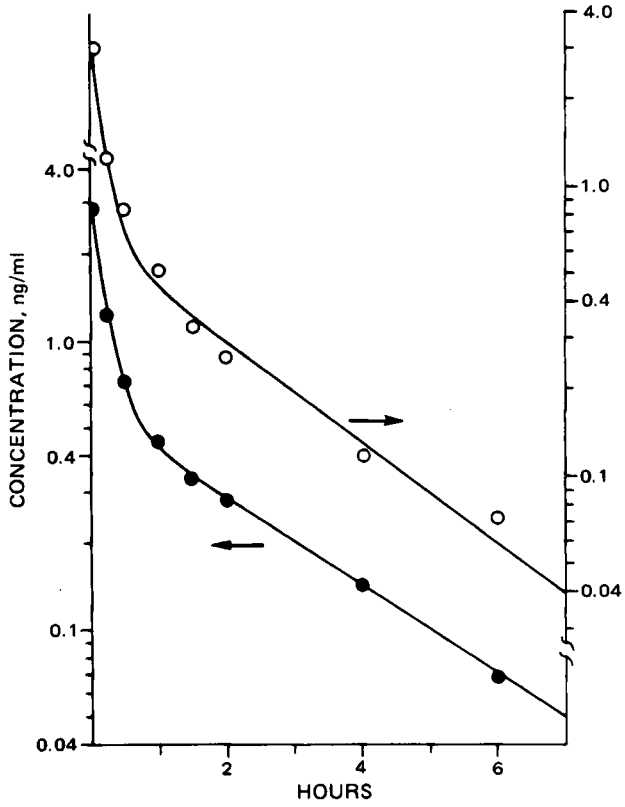

Figure 1—*Serum concentrations of propoxyphene as a function of time after intravenous injection of ^{3}H-propoxyphene at ~8 μg/kg. Key: ●, normal rat; and ○, rat with experimental renal failure. The curves were fitted to the data by nonlinear least-squares regression analysis. (The two vertical axes are displaced relative to one another.)*

Blood samples (0.25–1 ml) were obtained serially for 6–8 hr after injection. Serum was separated, adjusted to pH 9.8, and extracted with butyl chloride; the unmetabolized drug was isolated by TLC (9) and quantified by scintillation spectrometry. An aliquot of the injected solution was assayed similarly. The concentration–time curve was fitted to a biexponential equation by a digital computer (10), with the concentrations weighted as their reciprocals (Fig. 1). The systemic clearance was calculated from the injected dose and the area under the concentration–time curve. The apparent volume of distribution was calculated by dividing the systemic clearance by β.

Compared to surgical methods, injection of uranyl nitrate produces a more reproducible (as determined by serum creatinine and urea nitrogen concentrations) renal failure model. The animals appear to be in better health than after surgery. There was no evidence of hepatocellular damage after a single injection of uranyl nitrate in that glutamic–pyruvic transaminase concentrations in serum were normal[1]. Concomitant injection of tritium-labeled and unlabeled propoxyphene and assay of serum samples by scintillation spectrometry (after TLC) and by GLC

[1] K. M. Giacomini, S. M. Roberts, and G. Levy, unpublished data.

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Table I—Effect of Renal Failure on Pharmacokinetics of Propoxyphene in Rats

Pharmacokinetic Constant	Normal Rats	Renal Failure Rats
Systemic clearance, ml/min/kg	61.4 ± 11.7[a] (47.8–75.1)	59.1 ± 13.2 (38.5–78.0)
Apparent volume of distribution, liters/kg	10.4 ± 3.2 (6.24–13.4)	8.3 ± 2.1 (6.22–11.9)

[a] Mean ± SD, $n = 6$; the range is given in parentheses.

yielded essentially identical results, showing that the tritium exchange was negligible.

The propoxyphene clearance and apparent volume of distribution values for normal rats and rats with experimental renal failure are listed in Table I. Clearance was high and comparable in magnitude to the hepatic plasma flow rate (11). The apparent volume of distribution was very large and comparable to that reported for humans (4). There were no significant differences in the kinetic constants between rats with normal and impaired renal function.

Rats, like humans, eliminate propoxyphene almost exclusively by biotransformation (12). Systemic clearance of propoxyphene in humans is somewhat higher than the hepatic plasma flow rate (4); the two values are similar in the rat. Therefore, the systemic clearance of propoxyphene is primarily a function of the hepatic blood flow rate and should be relatively insensitive to changes in the activity of hepatic drug metabolizing enzyme systems. Hepatic blood flow is not reduced, and the blood plasma flow rate may actually increase in renal failure (13). The results of this study are consistent with these considerations in that the systemic clearance of propoxyphene was not affected by experimental renal dysfunction. This finding and the apparent lack of effect of renal dysfunction on the volume of distribution of propoxyphene support the conclusion that higher plasma propoxyphene concentrations in anephric patients following oral administration are probably due to decreased presystemic biotransformation of the drug (6).

(1) *Fed. Reg.*, **44**, 11837 (1979).

(2) R. L. Wolen, C. M. Gruber, Jr., G. F. Kiplinger, and N. E. Scholz, *Toxicol. Appl. Pharmacol.*, **19**, 480 (1971).

(3) D. Perrier and M. Gibaldi, *J. Clin. Pharmacol.*, **12**, 449 (1972).

(4) L. F. Gram, J. Schou, W. L. Way, J. Heltberg, and N. O. Bodin, *Clin. Pharmacol. Ther.*, **26**, 473 (1979).

(5) K. M. Giacomini, S. M. Nakeeb, and G. Levy, *J. Pharm. Sci.*, in press.

(6) T. P. Gibson, K. M. Giacomini, W. A. Briggs, W. Whitman, and G. Levy, *Clin. Pharmacol. Ther.*, **21**, 103 (1977).

(7) W. Flamenbaum, M. L. Huddleston, J. S. McNeil, and R. J. Hamburger, *Kidney Int.*, **6**, 408 (1974).

(8) J. R. Weeks and J. D. Davis, *J. Appl. Physiol.*, **19**, 540 (1964).

(9) P. J. Murphy, R. C. Nickander, G. M. Bellamy, and W. L. Kurtz, *J. Pharmacol. Exp. Ther.*, **199**, 415 (1976).

(10) C. M. Metzler, "NONLIN, A Computer Program for Parameter Estimation in Nonlinear Situations," The Upjohn Co., Kalamazoo, Mich., 1969.

(11) E. E. Ohnhaus and J. T. Locher, *Eur. J. Pharmacol.*, **31**, 161 (1975).

(12) R. E. McMahon, A. S. Ridolfo, H. W. Culp, R. L. Wolen, and F. J. Marshall, *Toxicol. Appl. Pharmacol.*, **19**, 427 (1971).

(13) P. Corvol, X. Bertagna, and J. Bedrossian, *Acta Endocrinol.*, **75**, 756 (1974).

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Reaction of *cis*-Platinum with Sodium Bisulfite

Keyphrases □ *cis*-Platinum—reaction with sodium bisulfite □ Sodium bisulfite—reaction with *cis*-platinum □ Antitumor agents, potential—*cis*-platinum(II) diaminedichloride, reaction of *cis*-platinum with sodium bisulfite

To the Editor:

cis-Platinum(II) diaminedichloride is a promising antitumor agent for the treatment of testicular cancer. Although the exact mechanism of its action is not fully understood, it is known that the agent reacts with DNA (1) and inhibits DNA synthesis (2). Recent studies showed that the antitumor agent reacts with DNA bases to form complexes of different composition (3).

In our study of the reaction of *cis*-platinum with pharmaceutical additives, we observed a rather unusual reaction between the antitumor agent and sodium bisulfite. When sodium bisulfite solutions (0.005–0.2 *M*) were mixed directly in the spectrophotometric cell with freshly prepared *cis*-platinum solution (10^{-4} *M*) in pH 4.2, 0.5 *M* acetate buffer, the absorbance at 280 nm increased. At this wavelength and concentration, *cis*-platinum has no absorbance; sodium bisulfite was present in both the sample and the blank.

The increase in the absorbance at 280 nm exhibited a lag time, followed by a rapid change, and finally leveled off (Fig. 1). However, the rate of change in absorbance varied

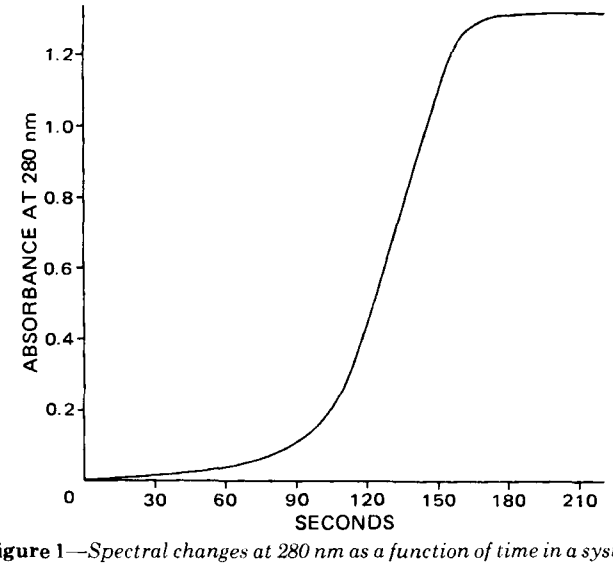

Figure 1—*Spectral changes at 280 nm as a function of time in a system containing 2 × 10^{-4} M cis-platinum and 0.01 M sodium bisulfite at pH 4.2 and 25°.*

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