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).

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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

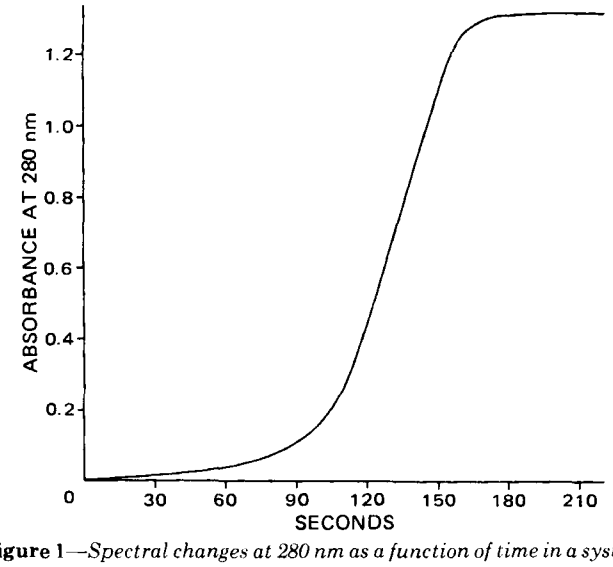

Figure 1—*Spectral changes at 280 nm as a function of time in a system containing 2 × 10^{-4} M cis-platinum and 0.01 M sodium bisulfite at pH 4.2 and 25°.*

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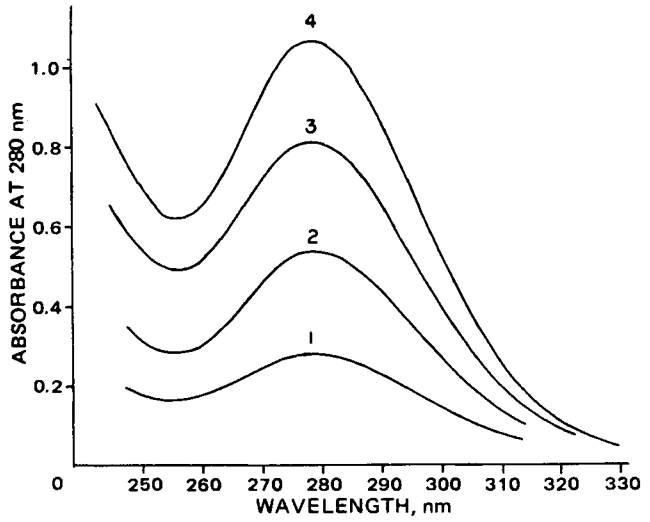

Figure 2—*UV spectra of solutions containing 1 × 10^{-2} M sodium bisulfite and varying amounts of* cis-*platinum. Key: 1, 4 μg/ml; 2, 8 μg/ml; 3, 12 μg/ml; and 4, 16 μg/ml.*

in nonlinear fashion as a function of the bisulfite concentration. Furthermore, in the presence of nitrogen or concentrations of ethanol or methanol as low as 1 × 10^{-3} *M*, no reaction was observed indicating autoxidation.

When 0.5 ml of 1 *M* sodium bisulfite (pH 4.2) was added to different concentrations of *cis*-platinum (0.1–0.5 ml of 1 mg of *cis*-platinum/ml) in water and the reaction mixture was left for 5 min at room temperature and diluted with pH 4.2 acetate buffer to 25 ml, the maximum absorbance at 280 nm varied linearly with the *cis*-platinum concentration (Fig. 2).

The absorbance at 280 nm remained constant for several hours. Although the exact mechanism of this interesting reaction is not known at this time, such a chemical reaction possibly may occur *in vivo* between the antitumor agent and the enzymes containing a sulfhydryl group found in the body.

Furthermore, in view of the enhancement of the UV absorbance of *cis*-platinum in the presence of bisulfite, this reaction can be used for the analysis of the drug in dosage forms. This observation also is important from the pharmaceutical standpoint when the drug is added to intravenous fluids containing antioxidants such as sodium bisulfite. It may be possible that the antioxidant will inactivate the drug in the intravenous fluids prior to administration.

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Percutaneous Absorption of Nitroglycerin

Keyphrases □ Nitroglycerin—percutaneous absorption, rhesus monkeys □ Absorption, percutaneous—nitroglycerin, rhesus monkeys □ Vasodilators—nitroglycerin, percutaneous absorption, rhesus monkeys

To the Editor:

We wish to report the percutaneous absorption of nitroglycerin in the rhesus monkey, an animal model that has been shown to be similar to humans (1, 2).

Sublingual nitroglycerin therapy has been the principal treatment for the symptomatic relief of angina pectoris. Sublingual nitrates are very effective, but their symptomatic improvements are not long lasting. Recently, nitroglycerin administered topically as an ointment was shown to be clinically effective for angina (3), and the slower absorption rate after topical administration results in a longer duration of action than after sublingual administration. Oral administration of nitroglycerin is not effective.

Our objective was to study some parameters of the percutaneous absorption of nitroglycerin. We wanted first to determine if there is an optimal site for absorption because the anatomical site of application affects skin absorption (4, 5). We then wanted to ascertain if the size of the application area affects the absorption of nitroglycerin.

The study was done *in vivo* with the rhesus monkey (*Macaca mulata*). Nitroglycerin (40 mg, 5 μCi) labeled with carbon 14 was applied to a 2-cm^2 area of skin. The areas tested were the chest, arm (upper inside), inner thigh, and postauricular region. After the application, each area was occluded with aluminum foil and adhesive tape for 24 hr. Then the occlusion was removed, and the site was washed with soap and water.

In addition, absorption of an identical dose was determined on the chest using a surface area of 50 cm^2. For this larger surface area, it was necessary to dissolve the dose in 250 μl of absolute ethanol. This solution was applied, and the ethanol was gently evaporated. Alcohol does not significantly alter nitroglycerin absorption (6). Percutaneous absorption was determined by the urinary excretion of carbon 14.

Absorption was quantified on the basis of the percent of radioactivity excreted in urine for 5 days following application of a known amount of the labeled compound to the skin. Daily urinary excretion values were corrected for excretion of radioactivity by other routes and retention of radioactivity in the body by administration of an intravenous dose of [^{14}C]nitroglycerin (1). Urinary radioactivity represents only the apparent nitroglycerin absorption. The potential for skin metabolism of nitroglycerin during absorption is unknown.

After intravenous administration of [^{14}C]nitroglycerin, 59.0 ± 1.9 (*SEM*) % of the dose was excreted in the urine in 5 days. Percent absorptions were 13.4 ± 1.2 (chest), 12.9 ± 1.2 (arm), 8.9 ± 1.4 (postauricular), and 14.8 ± 2.2 (thigh). None of the absorption values for doses applied to the 2-cm^2 areas was statistically different from each other. The majority of the unabsorbed dose in each case was recovered in the wash. Absorption of an identical dose

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