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# Iodipamide Kinetics: Capacity-Limited Biliary Excretion with Simultaneous Pseudo-First-Order Renal Excretion

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**Abstract** □ Iodipamide was infused into three dogs with bile fistulas to achieve various steady-state blood levels. When using ultracentrifugation techniques, iodipamide was found to be highly bound to plasma protein. The total blood clearance was low relative to hepatic blood flow. For either the whole blood concentration or the unbound concentration of iodipamide, the biliary excretion was shown to be capacity limited with a transport maximum, $T_m$, of approximately 1.0 μmole/kg/min. The steady-state renal excretion rate, plotted against the whole blood concentration of iodipamide, resulted in a concave ascending curve, which could lead to the false conclusion that iodipamide was undergoing active renal tubular reabsorption. However, when corrected for plasma protein binding, a linear relationship was obtained, suggesting that the renal excretion of iodipamide is a pseudo-first-order process. The Michaelis–Menten parameters for the extrarenal elimination, when calculated using the whole blood concentration of iodipamide, led to a similar discrepancy compared to the parameter estimates obtained from biliary excretion rate data. This discrepancy can be eliminated when one uses the unbound concentration of iodipamide in the parameter estimates.

**Keyphrases** □ Iodipamide—capacity-limited excretion kinetics, dogs □ Excretion kinetics, capacity limited—iodipamide in dogs □ Pharmacokinetics—excretion of iodipamide in dogs □ Radiopaque media—iodipamide, capacity-limited excretion kinetics, dogs

Iodipamide, 3,3′-(adipoyldiimino)bis[2,4,6-triiodobenzoic acid], is the most commonly used intravenous cholangiographic agent in the United States. Clinically, a dose of 166 or 233 mg/kg is recommended for intravenous administration over 3–10 min or the same dose is administered by a slow infusion over 2 hr (1). Nausea, vomiting, hypotension, and occasional kidney damage have been reported with these administration methods. Conflicting opinions exist concerning the appropriate dose and administration route of iodipamide to produce maximal radiological opacification of the biliary tree (1–3) with negligible side effects.

Following intravenous administration, iodipamide is taken up by the liver and excreted unchanged into the bile. Biliary excretion was demonstrated to be capacity limited with a transport maximum, $T_m$ (4, 5). Therefore, plasma levels in excess of those necessary to saturate the biliary excretion offer little or no advantages in opacification of the biliary tree. Increased doses lead to increased drug concentrations in other body organs and add stress on the kidney excretory process. Iodipamide exists in the blood as the unchanged drug and is excreted unchanged in the urine. The percentage of the dose excreted in the urine increases with an increasing dose (6). Therefore, iodipamide offers a good opportunity to investigate the capacity-limited hepatic uptake or biliary excretion in the presence of renal excretion.

A steady-state approach was utilized in the pharmacokinetic studies of iodipamide in dogs to gain a better understanding of the capacity-limited hepatic elimination with simultaneous renal excretion. It is hoped that through this understanding, an optimal dosage and route of administration can be developed to provide maximal visualization of the biliary tree and the least toxic effects.

## THEORETICAL

When a drug is infused into the animal for a sufficiently long time to establish steady-state blood concentration, the elimination rate by all routes should equal the infusion rate. For a drug such as iodipamide, which is eliminated by the kidney and other organs, the elimination rate from the blood is the sum of renal excretion and extrarenal elimination. Therefore, if the renal excretion rate at steady state is determined, the difference between the infusion rate and the steady-state renal excretion should equal the extrarenal elimination rate; *i.e.*:

$$R' = R^0 - \frac{dAu}{dt} \qquad \text{(Eq. 1)}$$

where $R^0$ is the zero-order infusion rate, $R'$ is the steady-state extrarenal elimination rate, and $dAu/dt$ is the steady-state renal excretion rate.

If one assumes that the extrarenal elimination is capacity limited, it can be described by the Michaelis–Menten equation:

$$R' = \frac{V_m C_{ss}}{K_m + C_{ss}} \qquad \text{(Eq. 2)}$$

where $V_m$ is the maximal rate of extrarenal elimination and $K_m$ is the apparent Michaelis–Menten constant. For a drug that has high blood clearance, $C_{ss}$ will be the whole blood concentration at a steady state; for a drug with low clearance, $C_{ss}$ should be referred to the unbound concentration. If the unbound drug concentration shows a constant proportionality to the whole blood concentration, the use of the steady-state whole blood concentration should theoretically yield the same value of $V_m$ and an apparent value of $K_m$ as when the unbound concentration is used. However, this is not the case with iodipamide, which has a relatively low clearance, probably because the unbound fraction varies with concentration.

The term $V_m$ is used to denote the maximal rate of capacity-limited extrarenal elimination, as defined in Eq. 2, and $T_m$ is used to denote the maximal rate of capacity-limited biliary excretion since it is not known whether these two referred to the same or different capacity-limited

processes. The Michaelis–Menten equation can be linearized in the following manner:

$$\frac{R'}{C_{ss}} = \frac{V_m}{K_m} - \frac{1}{K_m} R' \qquad \text{(Eq. 3)}$$

$$\frac{C_{ss}}{R'} = \frac{K_m}{V_m} + \frac{1}{V_m} C_{ss} \qquad \text{(Eq. 4)}$$

Therefore, from the intercept and the slope of the $R'/C_{ss}$ *versus* $R'$ plot or $C_{ss}/R'$ *versus* $C_{ss}$ plot, initial estimates of $V_m$ and $K_m$ can be obtained and used for the computer fitting of the data.

However, if two capacity-limited processes are involved in the extrarenal elimination, one must fit the extrarenal elimination data to the following equation:

$$R' = \frac{V_{m_1} C_{ss}}{K_{m_1} + C_{ss}} + \frac{V_{m_2} C_{ss}}{K_{m_2} + C_{ss}} \qquad \text{(Eq. 5)}$$

where $V_{m_1}$ and $V_{m_2}$ represent the maximal elimination rates for Processes one and two, respectively, whereas $K_{m_1}$ and $K_{m_2}$ represent the Michaelis–Menten constants for these two elimination processes, respectively. Furthermore, if $R'/C_{ss}$ *versus* $R'$ is plotted, a curvilinear relationship results; it can be resolved into two straight lines with intercepts of $V_{m_1}$ and $V_{m_2}$ on the abscissa and slopes of $1/-K_{m_1}$ and $1/-K_{m_2}$, respectively, for the two processes.

## EXPERIMENTAL

**Materials**—The infusion solution of iodipamide was prepared by diluting commercially available iodipamide meglumine[1,2] with normal saline to concentrations of 21.3 and 55.5 $\mu M$. Sodium taurocholate[3] was prepared as a 1% solution in normal saline. Chronic bile fistulas were implanted in dogs by cholecystectomy, ligation of the accessory pancreatic duct, and insertion of a modified Thomas cannula (7) in the duodenum opposite the opening of the ampulla of Vater.

**Chronic Infusion Studies**—Chronic infusion studies were performed on three unanesthetized, adult labrador dogs (23.4–25.8 kg) with bile fistulas. The dogs were fasted 24 hr prior to each study. The common bile duct was catheterized through the duodenal fistula with a polyethylene tubing (No. 100). Bile was collected by gravity siphoning into graduated cylinders such that the volume could be measured to the nearest 0.1 ml. Superficial leg veins were catheterized with polyethylene tubings for the infusion of iodipamide and sodium taurocholate and for the collection of blood samples.

Sodium taurocholate was infused at rates varying from 7.4 to 10.0 $\mu$moles/min to maintain, insofar as possible, a constant bile flow rate and to replace the loss of the bile salts during the experiment (8). The bladders were catheterized with polyethylene tubing (No. 240) for urine collection.

Throughout each experiment, blood samples were taken at 20-min intervals; bile and urine samples were taken at 30-min intervals. The iodipamide concentration in each sample was determined according to its iodine content by fluorescent excitation analysis (9). Fluorescent excitation analysis assays the iodine concentration in the biological samples in the range of 0.002–40.0 mg of iodine/ml with a ±2% error.

Following appropriate loading doses, iodipamide was infused at rates varying from 0.35 to 4.20 $\mu$moles/kg/min for a minimum of 2 hr at each rate to achieve various steady-state blood concentrations. At least three steady-state blood concentrations were achieved in one experiment.

**Acute Infusion Studies in Anesthetized Dogs**—Infusion studies were performed in two adult mongrel dogs (21.0 and 27.2 kg) under pentobarbital sodium anesthesia. The visceral organs were exposed through a midline incision, the cystic duct was ligated, and the common bile duct was catheterized with polyethylene tubing (No. 100) for bile collection. Femoral veins were catheterized for the infusion of iodipamide and sodium taurocholate and for the collection of blood samples. The bladder was catheterized, and the total urine output was collected. Timed blood, bile, and urine samples were obtained as in the chronic infusion studies.

After the appropriate loading dose, iodipamide was infused for 3–5 hr at 4.25 and 5.50 $\mu$moles/kg/min, doses that were in excess of the rate reported to saturate the biliary excretory mechanisms (4). The dogs were then sacrificed by anesthetic overdose. The liver, kidneys, heart, and intestines were isolated, drained, weighed, and homogenized. The iodipamide concentration in the blood, bile, urine, and isolated organs was determined by fluorescent excitation analysis (9).

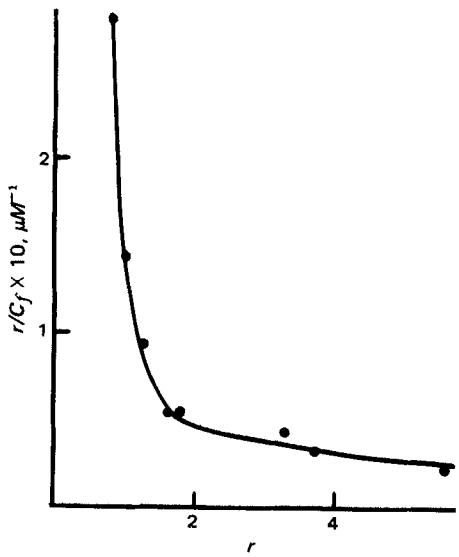


**Figure 1**—*Scatchard plot of iodipamide binding to plasma albumin in Dog C. An attempt to calculate the binding constants was unsuccessful due to insufficient data in the low* r *region.*

**Plasma Protein Binding Studies**—On separate occasions, appropriate amounts of the iodipamide were added to the blood taken from the dogs with bile fistulas used in the chronic infusion experiments to achieve blood iodipamide concentrations varying from 113 to 1295 $\mu M$. These samples were allowed to equilibrate for 2 hr at 37°. The plasma was then separated from blood cells by centrifugation, and the plasma iodipamide concentration was determined by fluorescent excitation analysis. From the hematocrit and the ratio of plasma iodipamide concentration over blood iodipamide concentration, the fraction of iodipamide in the red blood cells was calculated.

The plasma samples were then centrifuged at 60,000 rpm (average force of 369,000×$g$, maximal force of 485,000×$g$) in a preparative ultracentrifuge[4], using a swinging bucket rotor[5], for 18 hr at 37°. The iodipamide concentration in the upper 0.2 fraction of the supernate was determined, and the fraction unbound to plasma protein was calculated.

**Creatinine Clearance Determination**—Endogenous creatinine clearance was determined for two dogs with bile fistulas used in the chronic infusion studies. Twenty-four-hour urine collections were made. A blood sample was taken at the midpoint of the urine collection period. The creatinine concentration in the urine and serum samples was determined by the alkaline picrate method. The creatinine clearance was then calculated by dividing the amount of endogenous creatinine excreted over 24 hr by the serum creatinine concentration at the midpoint time.

In the third dog with a bile fistula used in the chronic infusion studies, the exogenous creatinine clearance was determined by infusing creatinine throughout one infusion experiment along with iodipamide. The creatinine concentration in the timed serum and urine samples was determined. The exogenous creatinine clearance was calculated as already described.

## RESULTS AND DISCUSSION

Iodipamide was highly bound to plasma protein (Fig. 1 and Table I). The percentage unbound varied from 1 to 12% as the blood iodipamide level increased from 113 to 1295 $\mu M$. The iodipamide fraction in the red blood cells varied from less than 1 to 9%; therefore, iodipamide binding to red blood cells should not be a significant factor in iodipamide elimination. Lang and Lasser (10) showed that iodipamide binds to plasma albumin but not to γ-globulin. The plasma level of albumin was determined to be 2.4%, and a molecular weight of 69,000 was used for albumin in the calculation of $r$ in the Scatchard plot (Fig. 1).

The total blood clearance, calculated by dividing the infusion rates by

[1] E. R. Squibb & Sons, Princeton, NJ 08540.
[2] Cholografin meglumine.
[3] ICN Pharmaceuticals, Cleveland, OH 44128.
[4] Beckman model L2-65B.
[5] Beckman SW60 Ti rotor.

**Table I—Plasma Protein Binding of Iodipamide in the Dog**

| Dog | Concentration | | | | Fraction Unbound | Hematocrit | Fraction[b] in Red Blood Cells |
|---|---|---|---|---|---|---|---|
| | Blood[a] | Plasma[a] | Blood / Plasma | Unbound[a] | | | |
| A | 113 | —[c] | —[c] | 2 | —[c] | —[c] | —[c] |
| | 294 | 610 | 0.48 | 38 | 0.062 | 0.50 | 0.00 |
| | 546 | 920 | 0.59 | 66 | 0.071 | 0.42 | 0.02 |
| | 886 | 1492 | 0.59 | 111 | 0.074 | 0.46 | 0.09 |
| B | 133 | 228 | 0.58 | 3 | 0.014 | 0.41 | 0.01 |
| | 491 | 839 | 0.59 | 55 | 0.066 | 0.41 | 0.01 |
| | 942 | 1495 | 0.63 | 157 | 0.105 | 0.42 | 0.08 |
| C | 168 | 302 | 0.57 | 3 | 0.010 | 0.41 | 0.00 |
| | 215 | 361 | 0.60 | 7 | 0.020 | 0.45 | 0.08 |
| | 264 | 458 | 0.58 | 14 | 0.030 | 0.45 | 0.05 |
| | 336 | 602 | 0.59 | 31 | 0.051 | 0.45 | 0.02 |
| | 394 | 665 | 0.59 | 33 | 0.050 | 0.41 | 0.06 |
| | 693 | 1231 | 0.56 | 77 | 0.063 | 0.41 | 0.00 |
| | 864 | 1409 | 0.61 | 115 | 0.081 | 0.43 | 0.07 |
| | 1295 | 2228 | 0.58 | 255 | 0.116 | 0.42 | 0.01 |

[a] Expressed in units of micromolarity of iodipamide. [b] Calculated from the equation $F = 1 - (1/\lambda)(1 - H)$, where $F$ is the fraction in the red blood cells, $\lambda$ is the ratio of the blood concentration divided by the plasma concentration, and $H$ is hematocrit. [c] Not determined.

**Table II[a]—Relationships among the Rate of Infusion ($R^0$), the Steady-State Blood Concentration ($C_b$), the Total Blood Clearance[b] ($Cl_b$), the Renal Clearance Based on Blood Concentration[b] ($Cl_r$), and the Renal Clearance Based on the Unbound Concentration[b] of Iodipamide ($Cl_{rf}$)**

| Dog | $R^0$, μmoles/kg/min | $C_b$, μM | $Cl_b$, ml/kg/min | $Cl_r$, ml/kg/min | $Cl_{rf}$, ml/kg/min |
|---|---|---|---|---|---|
| A | 0.40 | 129 ± 0.0 | 3.1 ± 0.000 | 0.2 ± 0.012 | 6.8 ± 0.42 |
| | 1.40 | 399 ± 8.3 | 3.5 ± 0.076 | 0.8 ± 0.015 | 9.4 ± 1.20 |
| | 2.51 | 690 ± 11.4 | 3.6 ± 0.059 | 1.3 ± 0.022 | 9.3 ± 0.06 |
| | 4.20 | 1089 ± 1.9 | 3.9 ± 0.006 | 1.9 ± 0.003 | 8.4 ± 0.35 |
| B | 0.35 | 122 ± 1.5 | 2.8 ± 0.035 | 0.1 ± 0.002 | 6.5 ± 0.12 |
| | 0.69 | 193 ± 1.5 | 3.6 ± 0.074 | 0.4 ± 0.009 | 12.2 ± 0.50 |
| | 2.08 | 562 ± 7.7 | 3.7 ± 0.051 | 1.4 ± 0.019 | 12.9 ± 0.45 |
| | 3.50 | 945 ± 7.1 | 3.7 ± 0.028 | 2.1 ± 0.015 | 11.4 ± 0.14 |
| C | 0.73 | 267 ± 5.5 | 2.7 ± 0.057 | 0.5 ± 0.010 | 10.2 ± 1.08 |
| | 1.60 | 539 ± 8.0 | 3.0 ± 0.045 | 1.1 ± 0.017 | 12.1 ± 1.36 |
| | 2.00 | 752 ± 3.7 | 2.7 ± 0.014 | 1.5 ± 0.005 | 12.0 ± 0.07 |
| | 3.33 | 1079 ± 0.9 | 3.1 ± 0.003 | 1.6 ± 0.003 | 8.6 ± 1.20 |

[a] All data, except the infusion rate, are expressed as the mean steady-state values following each infusion ± *SD*. [b] Total blood clearance was obtained by dividing the infusion rate by the corresponding blood concentration of iodipamide at steady state. Renal clearance based on blood iodipamide concentration was obtained by dividing the steady-state renal excretion rate by the corresponding blood iodipamide concentration. Renal clearance based on the unbound iodipamide concentration was obtained by dividing the steady-state renal excretion rate by the corresponding unbound iodipamide concentration.

the steady-state blood iodipamide concentrations, was low, varying from 2.7 to 3.9 ml/kg/min (Table II). The low total blood clearance and the high degree of plasma protein binding of iodipamide make it likely that the unbound fraction is the major determinant in iodipamide elimination. The data analysis was made using both the whole blood and the unbound concentration of iodipamide.

Pooled data from a series of chronic infusion experiments in the dogs with bile fistulas are reported here. Different symbols in each figure represent data from each experiment in the same dog. In two dogs, the biliary excretion rate reached a maximal value of 0.9 and 1.0 μmole/kg/min, respectively, with increasing blood levels, indicating a saturation phenomenon with a transport maximum, $T_m$ (Fig. 2).

Transport maxima of 1.07 (%$CV$ = 14%) and 1.10 (%$CV$ = 8%) μmoles/kg/min were obtained when the data of the biliary excretion rate and blood iodipamide levels were fitted to the Michaelis–Menten equation using a nonlinear least-squares computer program[6] and a digital computer[7] (Fig. 2). When the same data were fitted to the unbound iodipamide concentration, transport maxima of 0.88 (%$CV$ = 7%) and 0.94 (%$CV$ = 3%) μmole/kg/min were obtained (Fig. 3). The estimated $T_m$ values were statistically different at the $p = 0.05$ level when compared with $T_m$ values obtained using blood iodipamide levels. Theoretically, the $T_m$ values would not change if the degree of plasma protein binding remained constant. However, the percent iodipamide unbound varied up to 10-fold (Table I) in the concentration range studied.

While the renal excretion rate of iodipamide remained essentially constant once steady-state blood iodipamide concentrations had been achieved, the steady-state renal excretion rate increased disproportionately with an increasing blood iodipamide concentration (Table II). Plotting the relationship between steady-state renal excretion rates and the blood iodipamide levels yielded a concave ascending curve from which one might conclude that active tubular reabsorption was occurring (Fig. 4) with an apparent threshold blood concentration of approximately 130 μM. This conclusion, of course, neglects the effect of plasma protein binding on the renal excretion.

When the steady-state renal excretion rates were plotted against the unbound iodipamide concentrations, the data appeared to fit a linear relationship with a zero intercept (Fig. 5). This result indicates that the renal clearance remains relatively constant and that the renal excretion can be treated as a pseudo-first-order process (in the concentration range studied) when one corrects for the effect of plasma protein binding. The renal clearance of unbound iodipamide estimated from the slope of this plot (Fig. 5) was 10.4 ml/kg/min for Dog A. Creatinine clearance for this dog was 2.4 ml/kg/min. Similar ratios were found in other dogs.

This fourfold difference indicated the existence of an active secretion process of iodipamide occurring in the renal tubule. Usually one presumes active tubular secretion to be saturable. The fact that renal clearance of unbound iodipamide remained constant over the iodipamide concentration range studied might lead to the conclusion that the Michaelis–Menten constant for the active secretion process was significantly greater than the unbound iodipamide concentrations achieved.

When the extrarenal elimination rate data were plotted against blood iodipamide concentrations according to one linearized Michaelis–Menten equation (Eq. 3), estimated values of 5.67 μmoles/kg/min and 1529 μM were obtained for $V_m$ and $K_m$, respectively, for Dog A (Fig. 6A). These estimates were then used as the initial estimates for the computer fitting[7] of the data to the hyperbolic function of the Michaelis–Menten equation using a nonlinear least-squares program[6]. Values of 3.77 (%$CV$ = 13%) μmoles/kg/min and 833 (%$CV$ = 23%) μM were obtained for $V_m$ and $K_m$, respectively.

Comparison of the $V_m$ value to the biliary excretory $T_m$ reported indicates an approximately fourfold difference. This difference suggests that if the liver is the only eliminating organ besides the kidney, it should

[6] BMDO7RT.
[7] IBM 360-50.

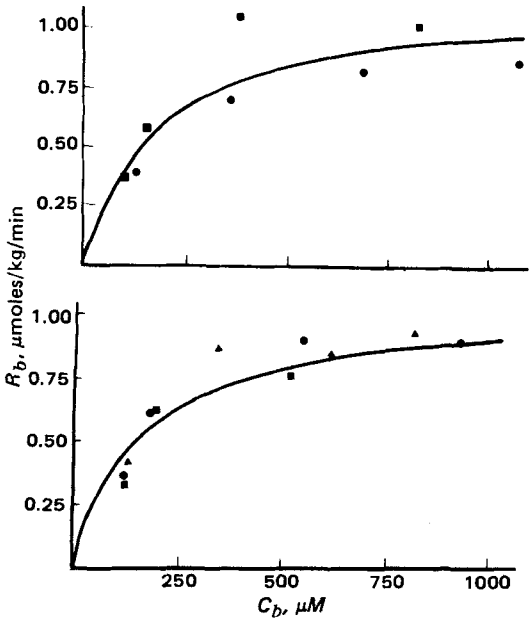


**Figure 2**—*Relationship between the steady-state biliary excretion rate* ($R_b$) *and the steady-state blood concentration* ($C_b$) *of iodipamide in Dogs A (upper curve) and B (lower curve).*

have a larger capacity to take up iodipamide than to excrete it into the bile. Under these conditions, if iodipamide is infused into the dog at the rate greater than that needed to saturate the biliary excretory mechanism, iodipamide must accumulate in the liver.

The $V_m$ value for the hepatic uptake has been reported to be greater than the $T_m$ value for biliary excretion for sulfobromophthalein sodium (11), indocyanine green (12), and taurocholate (13). These results led various investigators to propose that these compounds accumulate within the liver when they are infused at rates greater than those needed to saturate the biliary excretory mechanisms (12, 14). When iodipamide was infused into anethesized dogs at rates greater than those needed to saturate the biliary excretion, the data shown in Table III were obtained. These results clearly showed no accumulation of iodipamide in the liver. This discrepancy can partly be explained when one calculates the Michaelis–Menten parameters using the unbound iodipamide concentration.

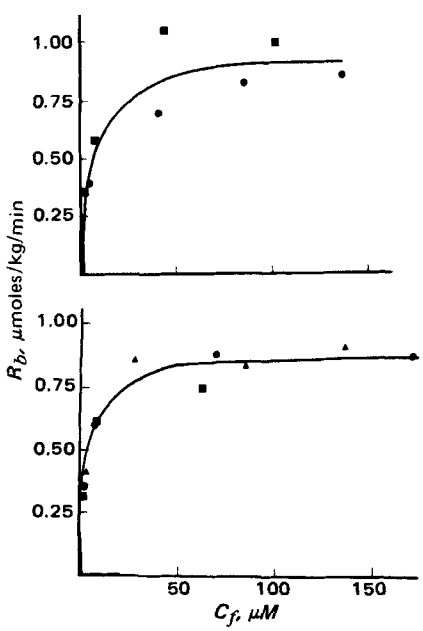


**Figure 3**—*Relationship between the steady-state biliary excretion rate* ($R_b$) *and the steady-state unbound concentration* ($C_f$) *of iodipamide in Dogs A (upper curve) and B (lower curve).*

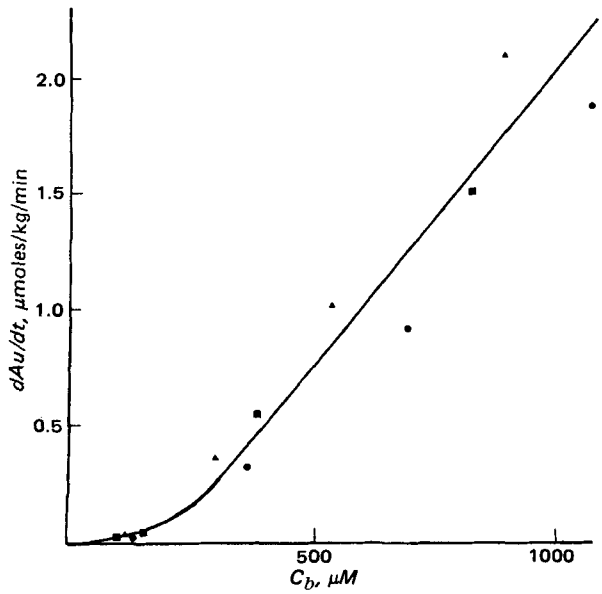


**Figure 4**—*Relationship between the steady-state renal excretion rate* (dAu/dt) *and the steady-state blood concentration* ($C_b$) *of iodipamide in Dog A.*

When the extrarenal elimination rate data were plotted against the unbound iodipamide concentration according to one linearized Michaelis–Menten equation (Eq. 3), a curvilinear relationship was obtained (Fig. 6B); it can be interpreted as indicating the existence of more than one capacity-limited elimination process. By presuming that two capacity-limited processes are occurring, the initial estimates of $V_m$ and $K_m$ for these two processes were obtained from this plot. These initial estimates were then used for the computer fitting[7] of the data using a nonlinear least-squares program[6] according to Eq. 5.

A $V_m$ value of 0.86 (%$CV$ = 45%) μmole/kg/min was obtained, which was comparable to the experimentally determined $T_m$ of 1.01 μmoles/

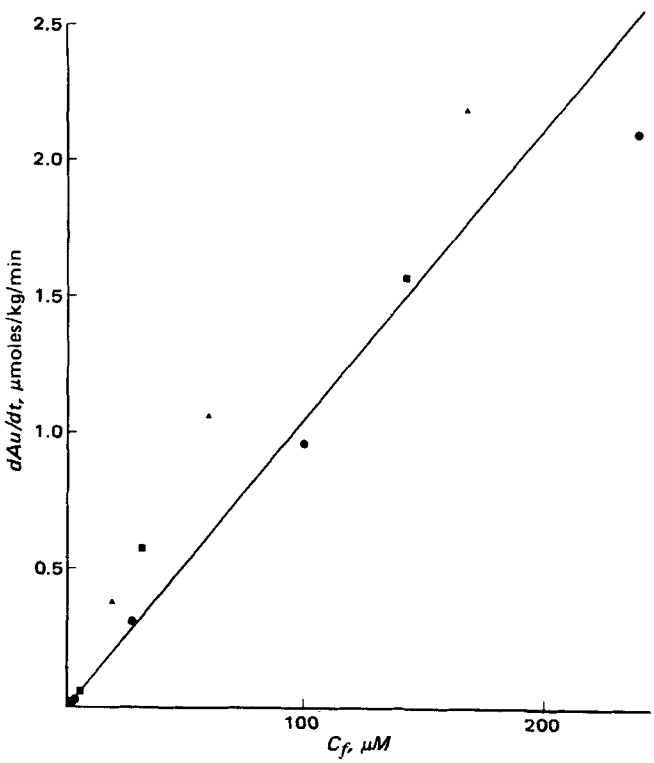


**Figure 5**—*Relationship between the steady-state renal excretion rate* (dAu/dt) *and the steady-state unbound concentration* ($C_f$) *of iodipamide in Dog A.*

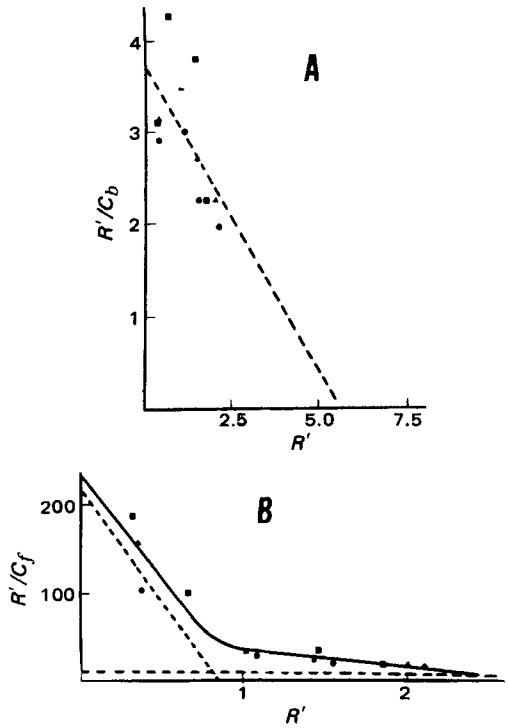


**Figure 6**—*A: Relationship between the steady-state extrarenal elimination rate (R′ in micromoles per kilogram per minute) and the steady-state blood concentration ($C_b$ in micromolar) of iodipamide in Dog A shown as* $R'/C_b$ versus R′. *The broken line is the unweighted linear regression. B: Relationship between the steady-state extrarenal elimination rate (R′ in micromoles per kilogram per minute) and the steady-state unbound concentration ($C_f$ in micromolar) of iodipamide shown as* $R'/C_f$ versus R′. *Key: —, computer-fitted line; and - - -, computer-resolved linear component.*

kg/min for biliary excretion. The $V_{m_2}$ was evaluated to be 10.77 (%$CV$ = 443%) μmoles/kg/min, indicating the presence of another elimination process with a higher capacity to take up iodipamide than the biliary excretion route. However, since it is more difficult to ascertain that steady states were achieved following the higher iodipamide infusion rates, the value of $V_{m_2}$ should be considered only as an approximate estimate.

Present data analysis, therefore, supports the contention that the unbound drug concentration should be used in the calculation of the parameters of elimination for drugs such as iodipamide with a high degree of plasma protein binding and low blood clearance.

Iodipamide, sulfobromophthalein sodium, and indocyanine green share common hepatic uptake binding sites (15, 16). It is particularly important to compare iodipamide and indocyanine green, since both are excreted in the bile unchanged. However, iodipamide is eliminated to a varying degree (depending on the dose) by the kidney, while indocyanine green apparently is only eliminated by the liver. While iodipamide has a low hepatic extraction ratio (<10%), indocyanine green has a high hepatic extraction ratio (>80%) (based on plasma clearance). Klassen and Plaa (17) administered indocyanine green to dogs by both intravenous bolus and infusion and obtained a $T_m$ value of approximately 20 nmoles/kg/min. In contrast, a $T_m$ for iodipamide in dogs of about 1.0 nmole/kg/min was obtained in the present study, about a 50-fold greater value.

Paumgartner (12) showed the $V_m$ for indocyanine green in the rat to be 3200 μmoles/kg/min while the $T_m$ for the biliary excretion was 240 μmoles/kg/min. Paumgartner also measured the liver concentration of indocyanine green in rats and verified that indocyanine green accumulated in the liver at the rate equivalent to the $V_m$ (12). This result is in remarkable contrast to the results obtained in the present study on iodipamide in dogs using the steady-state infusion method wherein no accumulation of iodipamide was found in the liver. It is possible that these two compounds are handled by different mechanisms in the biliary excretion.

**Table III—Distribution of Iodipamide following an Acute Infusion to Anesthetized Dogs**

| Amount of Iodipamide, μmoles | Dog 19018 | Dog 19213 |
|---|---|---|
| Administered | 29,181 | 46,761 |
| Excreted in bile and urine | 11,853 | 12,828 |
| In liver | 639 | 903 |
| In kidneys | —[a] | 812 |
| In heart | —[a] | 118 |
| In intestines | —[a] | 1,988 |
| In blood | 2,887 | 2,556 |
| Not accounted for | 13,802 | 27,555 |

[a] Not determined.

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