Journal of Pharmacokinetics and Biopharmaceutics, Vol. 3, No. 4, 1975

Computer Simulation of Sulfobromophthalein Kinetics in the Rat Using Flow-Limited Models with Extrapolation to Man

B. Montandon,[1] R. J. Roberts,[1] and L. J. Fischer[1]

Received Nov. 6, 1974—Final June 3, 1975

A linear, flow-limited mathematical model of drug kinetics was used to simulate total sulfobromophthalein (BSP) kinetics in normal anesthetized rats during intravenous infusions and following rapid intravenous injections. Four parameters were used to characterize the distribution and biliary and urinary excretion of BSP: liver-to-plasma concentration ratio, extrahepatic tissue-to-plasma concentration ratio, liver clearance rate constant, and renal plasma clearance rate constant. The same parameters appear to characterize the kinetics of BSP in man through the successful application of "scale-up" techniques utilizing data from experiments in rats. Plasma levels of BSP corresponding to intravenous infusions and rapid intravenous injections in man are approximated by computer simulation.

KEY WORDS: sulfobromophthalein (BSP); kinetics; BSP disposition; mathematical model; flow-limited.

INTRODUCTION

Attempts have been made through the use of mathematical models to gain a better understanding of sulfobromophthalein (BSP) kinetics in man to enhance its use as an index of hepatic function (1–4). Although the results of mathematical modeling showed some qualitative similarities to plasma BSP levels in man, they were relatively unsuccessful in that accurate values of certain critical parameters were not determined and hence no direct comparisons between simulations and experimental data could be made. On the other hand, flow-limited models employ readily measurable physiological and BSP-related parameters and hence may be more applicable to the study of BSP kinetics.

[1]The Toxicology Center, Department of Pharmacology and Department of Pediatrics, University of Iowa, School of Medicine, Iowa City, Iowa 52242.

Flow-limited models of drug disposition in the body have demonstrated promise in helping to explain, both quantitatively and qualitatively, the phenomena observed in various clinical situations. For example, Dedrick and Bischoff (5) have used flow-limited models to predict plasma levels of pentobarbital in patients receiving hemodialysis and have correlated the results with some clinical observations. Dedrick *et al.* (6,7) have used similar models to simulate the distribution of some anticancer agents to tissues, and initial attempts have been made to correlate this information with models of chemotherapeutic effects (8). Anesthesiologists have used these models to help predict the uptake and elimination of anesthetics in order to estimate the rate of onset, degree, and duration of their effect (9,10).

The following investigation was undertaken to see if the kinetics of total BSP (unchanged plus conjugated), after subsaturation doses in rats, could be simulated to a close approximation using a flow-limited model and, further, to see if such simulations could be extrapolated to predict total BSP kinetics in man. The results show that the use of flow-limited models provides a promising approach for defining the kinetics of a dye used to assess hepatic function.

MATERIALS AND METHODS

Male Thorp Sprague-Dawley rats weighing 160–180 g were prepared with bile duct and external jugular catheters (PE-10 and -50) under sodium pentobarbital anesthesia. ^{35}S-BSP (Amersham-Searle, Amersham, England) was dissolved in distilled water with unlabeled BSP (Hynson, Westcott, and Dunning, Inc., Baltimore) (1:2 w/w) to make a stock solution. Corrections of specific activity due to isotopic decay were calculated daily from an isotopic decay table. Radioactivity was determined in all samples using a Cabosil (Packard Instruments Co., Downers Grove, Illinois) containing liquid scintillation medium. Counting efficiency was determined by the channels ratio method using a liquid scintillation system (Beckman, CS-230, Beckman Instruments, Fullerton, California). Body temperature was maintained at 37°C with a heat lamp controlled through a rectal probe and a Thermistemp temperature controller (Yellow Springs Instrument Co., Yellow Springs, Ohio). After collection of a 20-min preinfusion bile sample, dye infusion (200 nmoles/min/kg) was begun without a priming dose. The infusion pump delivered 0.053 ml/min of infusate, and timed bile collections were begun into tared disposable beakers. Preliminary studies showed that a plateau of biliary dye output was reached in 30–40 min. Rats were infused with BSP for 50 min and bile was collected at 3, 6, 9, 12, 15, and 20 min and every 10 min thereafter until completion of the experiment. Each bile sample was immediately weighed, sealed against evaporation, and stored at 4°C. Immediately

after the last bile collection, the urinary bladder was evacuated with needle and syringe, and 2.5 ml of blood was collected from the inferior vena cava in a heparinized syringe. The liver was perfused with 3.0 ml ice-cold saline via the hepatic portal vein to remove residual blood. The liver was then rapidly excised, blotted dry, weighed, and homogenized with 3 vol of 0.25 M sucrose–0.02 M combined phosphate buffer, *p*H 7.4. The following aliquots of the various tissue samples were analyzed for radioactivity: 1.0 ml plasma, all of the collected urine, 0.5 ml homogenate, and 0.005-ml aliquots of each bile sample. Corrections for residual bile in the liver are based on an estimate of 0.005 ml/g tissue (11).

The CSMP (Continuous System Modeling Program) programming language and an IBM 360/65 digital computer were used to perform the simulations.

RESULTS

Experimental Results

The data obtained concerning biliary and urinary excretion and distribution of ^{35}S-BSP in rats during an infusion of ^{35}S-BSP for 50 min at 200 nmoles/min/kg are summarized in Table I. It was found that steady-state conditions (plasma concentration remaining at a constant level) were achieved during the infusion period. Mean (±range) output of BSP in bile was 76% (±6%) of the amount infused. A total of only 0.1% (±0.03%) of BSP was found in urine. Renal plasma clearance was calculated to be 0.004 ml/min, while hepatic plasma clearance was 3.6 ml/min. These figures indicate that the liver clears BSP from plasma at approximately 900 times the rate of the kidney. The mean concentration of BSP observed in the bile at the end of the infusion was 2600 nmoles/ml, while the mean plasma concentration observed was 9.1 nmoles/ml, yielding a bile-to-plasma ratio of 280. At sacrifice, approximately 24% of the amount infused was not accounted for in bile or urine. Of this amount, 15% was in plasma, 41% in liver, and 44% apparently in other tissues.

Bile flow during the infusions was 0.013 (±0.002) ml/min and liver weight of the animals was 6.3 (±1.0)g. The amount of BSP found in the whole livers at the end of the infusions was 230 nmoles or approximately 35 nmoles/g. When corrected for residual bile, the whole livers contained 165 nmoles BSP, approximately 25 nmoles/g. The observed liver-to-plasma ratio at the end of the infusion was 2.7.

Results at other infusion rates (50–2400 nmoles/min/kg) indicate that there is no apparent saturation of the excretion of total BSP at these infusion rates (Gibson and Roberts, submitted for publication). This is probably

Table I. Recovery of Total ^{35}S-BSP (Expressed in BSP Equivalents) in Male Rats

Compartment	Total BSP[a] (nmoles)	Final BSP concentration[a] (nmoles/ml or g)	R^b
Bile	1300 (±100)	2600 (±300)	280
Liver[c]	165 (±25)	25 (±4)	2.7
Plasma	53[d]	9.1 (±0.6)	—
Urine	2	—	—
Extrahepatic tissue	180[e]	1.2[f]	0.13
Total BSP infused	1700		

[a]Values shown are means ± range obtained from eight rats (mean body weight 170 g) at the end of a 50-min infusion at 200 nmoles/min/kg (34 nmoles/min).
[b]Bile- or tissue-to-plasma ratios.
[c]Corrected for residual bile.
[d]Estimated on basis of 5.7 ml of plasma.
[e]Estimated: sum of the amounts found in the other compartments subtracted from the total infused.
[f]Estimated on basis of 145 g of extrahepatic tissue.

due to the fact that biliary excretion of conjugated BSP is essentially unsaturable in male rats at these infusion rates, as was indicated by the results of Philp *et al.* (12). These results are encouraging because they indicate that good simulations of total BSP kinetics in the rat throughout a wide dose range can be obtained using linear models in which the excretion is considered to proceed as a first-order process.

Development of the Model Equations and Determinations of Parameter Values

The development of a suitable model for BSP kinetics requires consideration of the fact that the dye is conjugated in the liver of man and laboratory animals (13). In spite of certain differences in the kinetics of unchanged and conjugated BSP (12), the excretion patterns and rates of excretion of conjugated BSP and total BSP (unchanged plus conjugated) are similar, both being rapidly excreted almost entirely in bile (12). Such similarities in the kinetics of total and conjugated BSP indicate that the total dye might behave sufficiently like a single compound to allow good approximations of its kinetics using simple models which do not involve a metabolism step.

The model used in developing the equations is based on the scheme pictured in Fig. 1. The body of the rat is conceived of as being divided into three compartments (plasma, liver, and extrahepatic tissue) with an additional three compartments for the biliary tree. Since all BSP in blood resides in the plasma fraction (13), a plasma-flow model was employed. Allowing a special compartment(s) for the biliary tract enables one to simulate bile concentrations and the lag time involved in movement of the dye from the

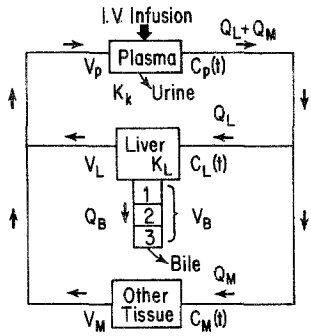

Fig. 1. Schematic diagram of a model for BSP disposition.

origins of the biliary tree to the end of the common duct. Allowing only one compartment for the biliary tree actually results in negligible alterations in the results, but three compartments are used here to coincide with the compartmentalization used by Dedrick *et al.* (6).

As was assumed by Dedrick *et al.* (5–7), the dose is conceived to be infused into the plasma, in which it rapidly mixes and from which it is quickly distributed to the liver and extrahepatic tissue compartments according to the plasma flow to those compartments. Because of the extensive capillary vasculature of almost all tissue, equilibration between the tissue and plasma bathing the tissue is established within a few seconds for substances with diffusion coefficients of the same magnitude as the coefficients for inert gases, sugar, and urea (14). On the basis of this observation and in order to avoid the introduction of parameters which would be difficult to measure, the process of equilibration between tissue and plasma is assumed to occur instantaneously. Thus the model serves to describe an entirely flow-rate-limited uptake process, and hence the name "flow-limited" model.

The work of others (6,7,9) indicates that the concentration of a drug in venous plasma (C_{out}) coming from a tissue compartment may be assumed to be in equilibrium with that tissue concentration ($C_{out} = C_i/R_i$, where R_i is the equilibrium tissue-to-venous plasma concentration ratio and C_i is the tissue concentration). These concepts enable one to write differential (rate) equations quantitatively relating the BSP concentrations in the various compartments. The derivation of these equations is based on the mass balance principle:

Rate of change of amount of BSP in compartment	=	rate of input of BSP into the compartment	−	rate of output of BSP from the compartment

Hence a set of differential equations describing BSP concentrations in the compartments of the model shown in Fig. 1 can be derived (see Appendix).

The equations can be used to describe a unique set of concentration functions if one ascribes initial conditions to the unknown concentration functions. In the case of an infusion with no priming dose, all concentrations are zero at $t = 0$, the start of the infusion. One can numerically integrate this system of linear differential equations and initial conditions to calculate the concentrations of BSP in each compartment at specified times.

The pertinent parameters needed to characterize the kinetics of BSP according to the linear, flow-limited model presented here are a liver-to-plasma concentration ratio, R_l; an extrahepatic tissue-to-plasma concentration ratio, R_m; a hepatic tissue elimination rate constant, k_1; a renal plasma elimination rate constant, k_k; plasma flow rates to the liver and extrahepatic tissues, Q_l and Q_m; and the volumes of the various compartments in the model, V_l, V_m, V_p, and V_b.

A determination of the hepatic tissue-to-hepatic venous plasma ratio, R_l (hereafter called the "actual" liver-to-plasma ratio), can be based on the observation that, at steady state, plasma and tissue levels will be constant. Thus the differential equation for liver concentration (see Appendix) becomes

$$0 = V_l \frac{dC_l}{dt} = Q_l(C_p - C_l/R_l) - V_l k_l C_l$$

One can solve this relationship for R_l, yielding

$$R_l = Q_l C_l/(Q_l C_p - V_l k_l C_l) \tag{1}$$

When $V_l k_l C_l = 0$ (hypothetically assuming no excretion from the liver compartment), equation 1 reduces to $R_l = C_l/C_p$. Thus, when there is no excretion from the compartment, the "actual" tissue-to-plasma ratio, R_l, can be expected to be the same as the tissue-to-peripheral plasma ratio, "peripheral plasma" meaning the well-mixed plasma peripheral to the liver (in the large veins, heart, and arteries).

In fact, the rapid clearance of BSP by the liver will cause the concentration of BSP in the plasma draining the liver to be lower than the concentration of dye in peripheral plasma. The observed liver-to-peripheral plasma ratio according to the data in Table I is 2.7. The actual liver-to-plasma ratio, R_l, calculated using equation 1 is 7.6. This reflects the hepatic arterial–venous difference in dye concentration and is in accordance with observations of arterial BSP concentrations which were 2–3 times greater than hepatic venous concentrations (3). The observed extrahepatic tissue-to-peripheral plasma ratio according to the data in Table I is 0.13 (assuming no extrahepatic or extrarenal excretion). In the following simulation, therefore, we let $R_m = 0.13$ and $R_l = 7.6$.

In the model presented here, we have let

$$\begin{pmatrix}\text{Net rate of excretion of BSP from liver}\\ \text{tissue into bile (nmoles/min)}\end{pmatrix} = k_l V_l C_l$$

where V_l is liver volume (g), k_l is the elimination rate constant of BSP from liver into bile (min^{-1}), and C_l is the concentration of BSP in liver tissue (nmoles/g). The value of k_l can be calculated by finding the values of the other quantities in this equation at some given time, e.g., at the end of an intravenous infusion. In the experiments described, V_l was measured in each rat and the mean was found to be 6.5 g. The measured C_l was 25 nmoles/g at the end of the infusion (Table I). The net rate of biliary excretion of BSP at the end of the infusion is given by Q_bC_b, where Q_b is the bile flow rate (0.013 ml/min) and C_b is the concentration of BSP in bile at the end of the infusion (2600 nmoles/ml). Thus $Q_bC_b = 33$ nmoles/min. Hence k_l = (excretion rate)$/V_lC_l = (Q_bC_b)/(V_lC_l) = 33$ nmoles/min/(6.5 g $\times$ 25 nmoles/g) = 0.20 min^{-1}. This is the value of k_l used in the following simulations. (The hepatic plasma clearance may similarly be computed as $Q_bC_b/C_p = 33$ nmoles/min/9.1 nmoles/ml = 3.6 ml/min.)

The renal plasma clearance rate was computed by dividing the total urinary excretion of BSP during the infusion by the estimated area under the plasma concentration curve, giving 1.7 nmoles/400 nmoles $\times$ min/ml = 0.004 ml/min. The values for plasma volume, V_p, volume of extrahepatic tissue, V_m, volume of hepatic bile, V_b, plasma flow to liver Q_l, and plasma flow to extrahepatic tissues, Q_m, were not measured in this study but collected from many literature sources.

Simulation Results

The simulated plasma, bile, and liver levels and cumulative biliary excretion corresponding to a 200 nmoles/min/kg infusion of BSP in a 170-g rat are shown in Fig. 2. The graphs of the simulated variables fall well within the ranges of data values observed. The simulated liver-to-plasma ratio (2.7) and the simulated extrahepatic tissue-to-plasma ratio (0.13) at 50 min matched the average values determined from the data (Table I).

The model was also used to assess whether variations in certain parameters would markedly influence total BSP kinetics. Variations in R_l between 7.0 and 7.6, R_m between 0.11 and 0.13, and V_p between 5.1 and 8.5 produced simulations that were almost indistinguishable from those presented in Fig. 2. This indicates that total BSP kinetics are not sensitive to variations in these parameter values within the range of reasonable experimental error or normal individual differences.

Winkler and Gram (1–3) have obtained plasma levels of BSP during constant-rate infusions with and without a priming dose in patients having no signs of liver disease or circulatory disturbance. Their data provided the opportunity to compare "scale-up" simulations with pertinent human data corresponding to a variety of dosage regimens.

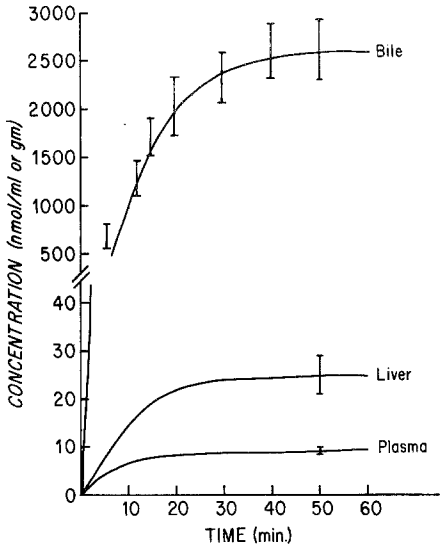

Fig. 2. Disposition of ^{35}S-BSP in male rats (160–180 g) during constant-rate intravenous infusion of 200 nmoles/min/kg. The range of experimental values observed is indicated by a bar. Solid lines denote simulated disposition curves corresponding to a 34 nmoles/min intravenous infusion in a 170-g rat. The following parameter values were used: $R_l = 7.6$, $R_m = 0.13$, $k_l = 0.20$, $k_k = 0.004$, $V_p = 5.7$, $V_l = 6.5$, $V_m = 145$, $V_b = 0.04$, $Q_l = 5.6$, $Q_m = 17$, $Q_b = 0.013$. Units for values are given in text.

The same model conception and equations that were used for rats were used to model total BSP kinetics in man by using values for plasma flow rates (Qs) and tissue and plasma volumes (Vs) corresponding to a 70-kg man. These values were obtained from the literature (15, 16). The tissue-to-plasma ratios (Rs) were assumed to be the same in man and rat. The liver clearance rate term, $k_l V_l C_l$, has been written so as to allow scale-up according to liver weight, V_l, by simply using the value of V_l appropriate to the size of the animal to be modeled. The expression $k_l C_l$ represents the excretion rate per gram of liver tissue. In scaling up, we assumed that the same value of k_l may be used for man and rat; i.e., that given the same liver BSP concentration in man and rat the excretion rate per gram of liver tissue is essentially the same in the two species. This assumption is made reasonable on the basis of the qualitative observation that BSP is excreted by man in the same fashion

as the rat (almost entirely excreted in bile with similar plasma half-lives) (1,17).

The kinetics of BSP in a 70-kg man were simulated corresponding to an 8.5 mg/min infusion of BSP and corresponding to an 8.5 mg/min infusion of BSP following a rapid intravenous injection of 5.5 mg/kg BSP. The data of Winkler and Gram (1–3) indicate that in either situation steady-state plasma levels of BSP are reached usually within an hour and the steady-state level is about the same in any given patient whether a priming dose is given or not.

The plasma levels of the simulations of an infusion without and with a priming dose of 5.5 mg/kg are shown in Figs. 3 and 4. Although there is variation in the steady-state levels achieved in individual patients, the simulated plasma levels correspond to the observed plasma levels. Further, the scale-up simulations, like the actual data of Winkler and Gram (2), show that whether or not a priming dose is used the steady-state plasma levels reached are the same (1.3 mg/100 ml) and the steady-state plasma level is reached in about an hour.

A 1-min infusion of a 5 mg/kg intravenous dose was also simulated for a 70-kg man and the results were compared with the plasma level data of Winkler (3) (Fig. 5). One can see that the simulated plasma levels compare reasonably well with the data and show the rapid decline of plasma levels to values of 1.0 mg/100 ml at 20 min and 0.2 mg/100 ml at 45 min. However, inspection of Fig. 5 reveals that the simulation is less accurate between 0 and 10 min.

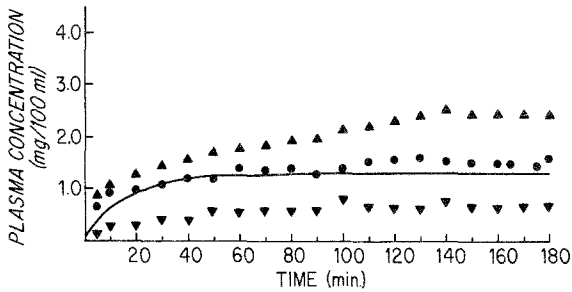

Fig. 3. BSP plasma levels in man during intravenous infusions of 8.3–8.6 mg/min taken from the literature (2). The solid line denotes the simulated plasma level of total BSP corresponding to an 8.5 mg/min intravenous infusion in a 70-kg man. The following parameter values were used: $R_l = 7.6$, $R_m = 0.13$, $k_l = 0.20$, $k_k = 0.9$, $V_p = 3000$, $V_l = 1700$, $V_m = 54{,}500$, $V_b = 40$, $Q_l = 870$, $Q_m = 2600$, $Q_b = 8.0$. Units for values are given in text.

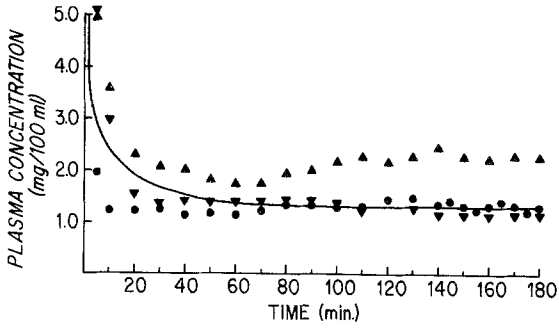

Fig. 4. Plasma levels taken from the literature (2) of BSP in man during intravenous infusions of 8.0–8.5 mg/min with rapid intravenous priming dose. The solid line denotes the simulated plasma level of total BSP corresponding to an 8.5 mg/min intravenous infusion in a 70-kg man with a 5.5 mg/kg intravenous priming dose. The parameter values used were the same as those for the simulation in Fig. 3.

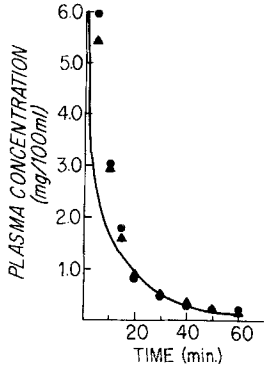

Fig. 5. BSP plasma levels in man following a rapid intravenous injection of 5 mg/kg BSP taken from the literature (3). The solid line denotes the simulated plasma level of total BSP corresponding to a 5 mg/kg rapid intravenous injection in a 70-kg man. The parameter values used were the same as those for the simulations in Figs. 3 and 4.

DISCUSSION

The linear flow-limited model and parameter values presented characterize the total BSP kinetics in normal rats during intravenous infusions and following rapid intravenous injection of BSP. By knowing four measurable "drug-dependent" parameters, i.e., actual liver-to-plasma concentration ratio, extrahepatic tissue-to-plasma ratio, hepatic clearance rate constant, and renal clearance rate constant, along with appropriate physiological parameters, one can describe the kinetics of BSP. The renal clearance rate constant could be eliminated from the calculations since insignificant amounts of BSP are cleared by this pathway. It is important to note that the "drug-dependent" parameters determined in rats also characterize the kinetics of BSP in humans. To our knowledge, a comparison between the rat and human has not been made using modeling techniques, and our results show that there do not appear to be important differences between these species in the factors controlling the elimination of BSP from the body.

Schenker and Combes (18), using Sprague-Dawley rats, found that 30 min after an intravenous injection of BSP (67 mg/kg) the percent of total BSP found unchanged was 85% in plasma, 60% in liver, and 19% in bile. These data indicate that under normal conditions most of the BSP that is conjugated is excreted before it can be regurgitated from the liver into the plasma. The tissue-to-plasma ratios and clearance rate constants used here for modeling total BSP kinetics are "effective" values based on the concentrations of ^{35}S found in plasma, bile, urine, and tissues. The results of Schenker and Combes indicate that the effective extrahepatic tissue-to-plasma ratio used here may reflect the extrahepatic tissue-to-plasma ratio of unchanged BSP, while the hepatic clearance rate constant may represent essentially the clearance of conjugated BSP.

The present model assumes that no saturation of the rate-limiting process concerned with BSP elimination is occurring. This was the case in these experiments in rats in which low infusion rates were used. Considerable variation exists in the T_m for BSP in humans (2,19). The data from human subjects chosen for analysis here were selected because infusion of BSP produced steady-state plasma levels (2). This indicates, by one of the usual criteria, that the BSP elimination system was not saturated in these subjects. We cannot be certain, however, that the rates of infusion of BSP were not approaching the T_m in these subjects. If this were so, it is apparent that the linear model would remain predictive in that situation. The present linear model readily lends itself for adaptation to Michaelis–Menten kinetics should evidence for saturation of elimination processes become evident. A term for the Michaelis constant can be added to equation 1 to produce expressions similar to those used by Dedrick *et al.* (6) for methotrexate kinetics.

The relative inaccuracy with which the model simulates total BSP disappearance in man between 0 and 10 min after a rapid intravenous injection (Fig. 5) may be due to differences in the kinetics of conjugated and unconjugated BSP which are accentuated due to nonequilibrium conditions at early times. Use of a model which accounts for BSP conjugation may produce a better result at these times.

Computer simulations with a more refined model, but similar to that proposed here, may be useful in associating BSP disappearance curves with certain abnormalities in BSP kinetics including abnormalities in hepatic perfusion. Although good results were obtained here in modeling total BSP, the techniques used would have a particularly clear interpretation when used with unmetabolized dyes.

APPENDIX

Differential equations describing concentrations of BSP in compartments of the model shown in Fig. 1:

$$V_p \frac{dC_p}{dt} = Q_l C_l/R_l + Q_m C_m/R_m - (Q_l + Q_m)C_p - k_k C_p + f(t)$$

$$V_l \frac{dC_l}{dt} = Q_l(C_p - C_l/R_l) - V_l k_l C_l$$

$$V_m \frac{dC_m}{dt} = Q_m(C_p - C_m/R_m)$$

$$f_1 V_b \frac{dC_{b1}}{dt} = V_l k_l C_l - Q_b C_{b1}$$

$$f_2 V_b \frac{dC_{b2}}{dt} = Q_b C_{b1} - Q_b C_{b2}$$

$$f_3 V_b \frac{dC_{b3}}{dt} = Q_b C_{b2} - Q_b C_{b3}$$

Cumulative excretion of drug in urine up to time $t = \int_0^t k_k C_p(t)\,dt$

Cumulative excretion of drug in bile up to time $t = \int_0^t Q_b C_{b3}(t)\,dt$

Total infused up to time $t = \int_0^t f(t)\,dt$

The notation used is that of Bischoff *et al.* (2) with a few additions:

C_p = BSP concentration in plasma
C_l = BSP concentration in liver
C_{bi} = BSP concentration in bile compartment i, $i = 1, 2, 3$
C_m = BSP concentration in extrahepatic tissue
V_p = volume of plasma
V_l = volume of liver
V_b = volume of bile
V_m = volume of extrahepatic tissue
Q_l = plasma flow rate through liver
Q_m = plasma flow rate through extrahepatic tissue
Q_b = bile flow rate through biliary tract
R_l = hepatic tissue-to-hepatic venous plasma concentration ratio of BSP
R_m = extrahepatic tissue-to-extrahepatic venous plasma concentration ratio of BSP
k_l = hepatic tissue elimination rate constant for BSP
k_k = renal plasma clearance rate constant for BSP
$f(t)$ = infusion rate function
f_i = volume of bile in the bile duct compartment as a fraction of the total bile volume V_b

REFERENCES

1. K. C. Winkler and C. Gram. Model for description of the bromosulphalein elimination curves in man after single intravenous injections. *Acta Med. Scand.* **169**:263–272 (1961).
2. K. Winkler and C. Gram. The kinetics of bromsulphalein elimination during continuous infusion in man. *Acta Med. Scand.* **178**:439–452 (1965).
3. K. Winkler. The kinetics of elimination of bromsulphalein in man after single injections and continuous infusion. In W. Taylor (ed.), *The Biliary System,* Blackwell Publications, Oxford, 1965, pp. 551–565.
4. C. A. Goresky. Initial distribution and rate of uptake of sulfobromophthalein in the liver. *Am. J. Physiol.* **207**:13–26 (1964).
5. R. L. Dedrick and K. B. Bischoff. Pharmacokinetics in applications of the artificial kidney. *Chem. Eng. Progr. Symp.* **64**:32–44 (1968).
6. R. L. Dedrick, D. S. Zaharko, and J. Lutz. Transport and binding of methotrexate *in vivo*. *J. Pharm. Sci.* **62**:882–890 (1973).
7. R. L. Dedrick, D. D. Forrester, J. N. Cannon, S. M. El Dareer, and L. M. Mellett. Pharmacokinetics of 1-β-D-arabinofuranosylcytosine (Ara-C) deamination in several species. *Biochem. Pharmacol.* **22**:2405–2417 (1973).
8. K. J. Himmelstein and K. B. Bischoff. Mathematical representation of cancer chemotherapy effects. *J. Pharmacokin. Biopharm.* **1**:51–68 (1973).
9. W. W. Mapleson. An electric analogue for uptake and exchange of inert gases and other agents. *J. Appl. Physiol.* **18**:197–204 (1963).
10. L. J. Saidman and E. I. Eger. Uptake and distribution of thiopental after oral, rectal, and intramuscular administration: Effect of hepatic metabolism and injection site blood flow. *Clin. Pharmacol. Ther.* **14**:12–20 (1973).

11. G. Barber-Riley. Measurement of capacity of biliary tree in rats. *Am. J. Physiol.* **205:**1122–1126 (1963).
12. J. R. Philp, G. M. Grodsky, and J. V. Carbone. Mercaptide conjugation in the uptake and secretion of sulfobromophthalein. *Am. J. Physiol.* **200:**545–547 (1961).
13. J. S. Krebs and R. W. Brauer. Metabolism of sulfobromophthalein sodium (BSP) in the rat. *Am. J. Physiol.* **194:**37–43 (1958).
14. S. S. Kety. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol. Rev.* **3:**1–41 (1951).
15. A. L. Cowles, H. H. Borgstedt, and A. J. Gillies. Tissue weights and rates of blood flow in man for the prediction of anesthetic uptake and distribution. *Anesthesiology* **35:**523–526 (1971).
16. W. R. Hendee. *Medical Radiation Physics*, Yearbook Medical Publishers, Chicago, 1970, p. 558.
17. C. D. Klaassen and G. L. Plaa. Species variations in metabolism, storage, and excretion of sulfobromophthalein. *Am. J. Physiol.* **213:**1322–1326 (1967).
18. S. Schenker and B. Combes. Role of hepatic adenosine triphosphate in BSP transport and metabolism *in vivo*. *Am. J. Physiol.* **212:**295–300 (1967).
19. H. O. Wheeler, J. I. Metzler, and S. E. Bradley. Biliary transport and hepatic storage of sulfobromophthalein sodium in the unanesthetized dog, in normal man and in patients with hepatic disease. *J. Clin. Invest.* **39:**1131–1144 (1960).