Influence of Cholestasis on Drug Elimination: Pharmacokinetics

LESTER I. HARRISON and MILO GIBALDI ˣ

Abstract □ A two-compartment model representing the body and the GI tract, with elimination occurring in each compartment, was used to study, in theory, the influence of impaired biliary excretion on drug disposition. The results suggest that cholestasis can either increase or decrease a drug's half-life, depending upon the relative values of the two elimination rate constants. In all cases, however, impaired biliary excretion reduced the initial elimination of drug from the body and increased the half-life of the α-phase of drug disposition.

Keyphrases □ Pharmacokinetics—effect of cholestasis on drug half-life and elimination, two-compartment model studied □ Biliary excretion, impaired—effect on drug half-life and elimination, two-compartment pharmacokinetic model studied □ Elimination, drug—effect of cholestasis, two-compartment pharmacokinetic model studied

A rigorous description of the time course of elimination from the body of drugs subject to biliary excretion and enterohepatic cycling is among the most formidable challenges in pharmacokinetics. A general solution to the problem remains elusive, because of the discontinuous nature of bile flow in animals with a gallbladder. Failure of the liver to secrete bile into the duodenum can be due to a multiplicity of causes and can be of intrahepatic or extrahepatic origin (1). The syndrome can be developed experimentally in various laboratory animals by ligation of the common bile duct.

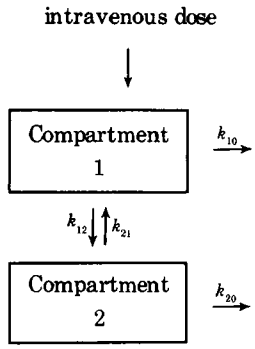
The results of several investigations suggest that cholestasis, like renal failure, can reduce the elimination of certain drugs. The disappearance of diethylstilbestrol from the plasma was markedly faster in control rats than in bile duct-ligated rats (2). The half-lives of ^{131}I-rose bengal were about 20 hr in a normal child, 41 and 61 hr in two children with partial biliary excretory defects, and 118–156 hr in four children with complete cholestasis (3). The average half-life of rifampin was 5.7 hr in five patients with obstructive jaundice (4). This value is about twice as long as in patients without biliary obstruction.

On the other hand, plasma clearance studies in the dog, 1 week after ligation of the common bile duct, revealed an increased clearance of colloidal gold Au 198 (5). Another example of the presumably anomalous effects of cholestasis was observed in this laboratory recently. After intravenous injection of ^{3}H-digoxin, the apparent half-life of elimination of total tritium from the plasma was shorter in bile duct-ligated rats than in control rats (Fig. 1).

The apparently unpredictable effects of cholestasis on drug half-life stimulated the development and examination of hypothetical pharmacokinetic models for enterohepatic cycling to rationalize the phenomenon. One such model is the subject of this report.

THEORETICAL

The model shown in Scheme I is probably the simplest schematic representation of the elimination of a drug subject to enterohepatic circulation. The tacit assumption that bile flow may be described by a continuous function is reasonable in the rat but oversimplifies the situation in most other species.



Scheme I—Pharmacokinetic model used to describe biliary excretion and enterohepatic circulation. Compartment 1 represents the body while Compartment 2 represents the GI tract.

The drug is administered as a bolus by intravenous injection, and the body is envisioned as a one-compartment system (Compartment 1). The GI tract is represented by the additional compartment (Compartment 2). The rate constant k_{10} represents the sum of all rate constants associated with nonbiliary elimination, *i.e.*, renal excretion and biotransformation. The rate constant k_{20} is associated with the removal of drug from the "reabsorption site" due to biotransformation by the intestine or intestinal bacteria and/or eventual fecal excretion.

At the simplest level, k_{12} and k_{21} are the rate constants describing biliary excretion and reabsorption of the drug, respectively. Functionally, k_{12} also may be an apparent rate constant describing the consecutive process of hepatic conjugation and biliary excretion of the metabolite where one step is rate limiting. In this case, k_{21} would be an apparent rate constant describing the consecutive processes of deconjugation and subsequent absorption of parent drug, provided that one step is rate limiting. Cholestasis is simulated by decreasing k_{12}.

The amount of drug in the body, A, as a function of time after administration of the dose, D, is given by:

$$A = \frac{(\alpha - k_{21} - k_{20})D}{(\alpha - \beta)} \exp(-\alpha t) + \frac{(k_{21} + k_{20} - \beta)D}{(\alpha - \beta)} \exp(-\beta t) \quad \text{(Eq. 1)}$$

where:

$$\alpha = \tfrac{1}{2}[k_{21} + k_{20} + k_{12} + k_{10} + \sqrt{(k_{21} + k_{20} + k_{12} + k_{10})^2 - 4(k_{12}k_{20} + k_{10}k_{21} + k_{10}k_{20})}] \quad \text{(Eq. 2)}$$

and:

$$\beta = \tfrac{1}{2}[k_{21} + k_{20} + k_{12} + k_{10} - \sqrt{(k_{21} + k_{20} + k_{12} + k_{10})^2 - 4(k_{12}k_{20} + k_{10}k_{21} + k_{10}k_{20})}] \quad \text{(Eq. 3)}$$

If enterohepatic cycling is maximally efficient, *i.e.*, $k_{20} \to 0$, then Eq. 3 reduces to:

$$\beta = \tfrac{1}{2}[k_{21} + k_{12} + k_{10} - \sqrt{(k_{21} + k_{12} + k_{10})^2 - 4k_{10}k_{21}}] \quad \text{(Eq. 4)}$$

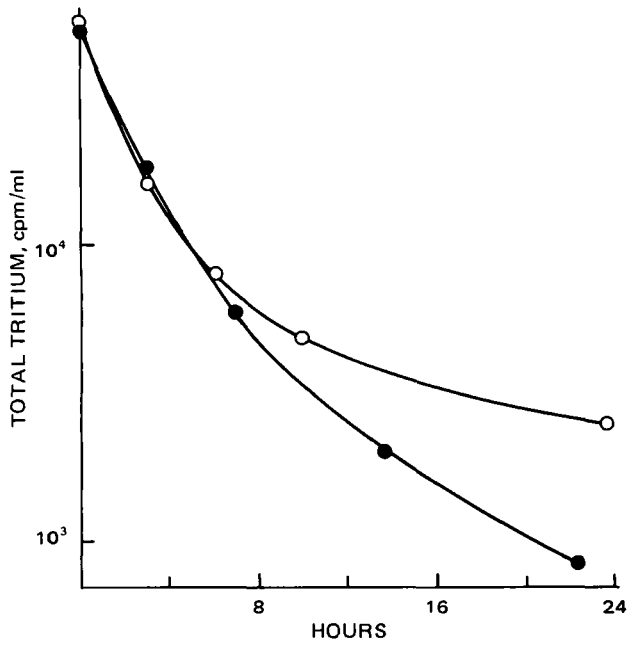


Figure 1—*Time course of total radioactivity in the plasma after intravenous administration of 1 mg of ^{3}H-digoxin/kg to a control rat (○) and a bile duct-ligated rat (●). Experimental details are given in Ref. 9.*

The half-life of the drug is given by:

$$t_{1/2} = 0.693/\beta \qquad \text{(Eq. 5)}$$

The half-life of the drug in complete cholestasis is given by:

$$t^*_{1/2} = 0.693/k_{10} \qquad \text{(Eq. 6)}$$

since the system then reduces to a one-compartment model.

EXPERIMENTAL

Numerical analyses were carried out with Eqs. 2 and 3, using values of k_{10}/k_{20} from 0.1 to 10 while k_{12}/k_{21} varied from 0.01 to 100 and k_{12}/k_{10} varied from 0.1 to 10. Simulated drug levels in the body were obtained by using the appropriate differential equations to describe the model in Scheme I, a unit dose, and various sets of rate constants as input data for the MIMED digital computer analog simulation program (6).

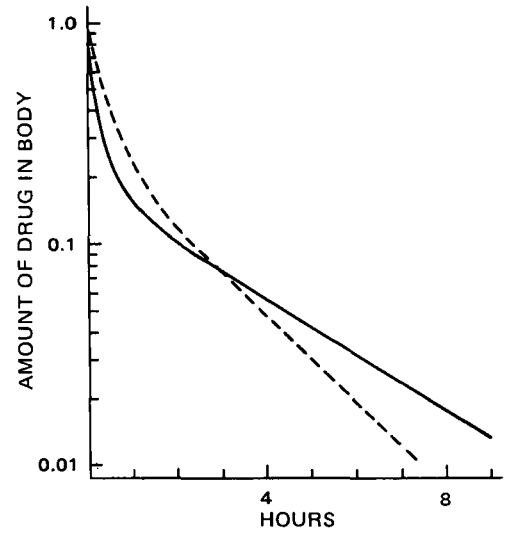


Figure 3—*Effect of reduced biliary excretion on biological half-life when $k_{10}/k_{20} > 1$. Key: —, control, $k_{12} = 3.0$, $k_{21} = 1.0$, $k_{10} = 1.0$, and $k_{20} = 0.1\ hr^{-1}$; and - - -, partial cholestasis, $k_{12} = 1.0$, $k_{21} = 1.0$, $k_{10} = 1.0$, and $k_{20} = 0.1\ hr^{-1}$.*

RESULTS AND DISCUSSION

If one considers the limiting case of maximal enterohepatic cycling (*i.e.*, $k_{20} \to 0$), the model shown in Scheme I reduces to a form identical to the customary two-compartment open model. It has been shown (7) that:

$$\beta = f_c^* k_{10} \qquad \text{(Eq. 7)}$$

where f_c^* is the fraction of drug in the system in Compartment 1 in the postdistributive phase. At any given values of k_{21} and k_{10}, a decrease in k_{12} results in an increase in f_c^*; in fact, as $k_{12} \to 0$, $f_c^* \to 1$. It follows that a decrease in k_{12} produces an increase in β. The model, therefore, predicts that cholestasis will actually decrease the biological half-life for drugs simply subject to biliary secretion and enterohepatic circulation but not to "gut elimination." A simulated example is shown in Fig. 2.

In cases where k_{20} was finite, an unambiguous relationship between β and k_{10} was not apparent and it was necessary to evaluate Eq. 3 by

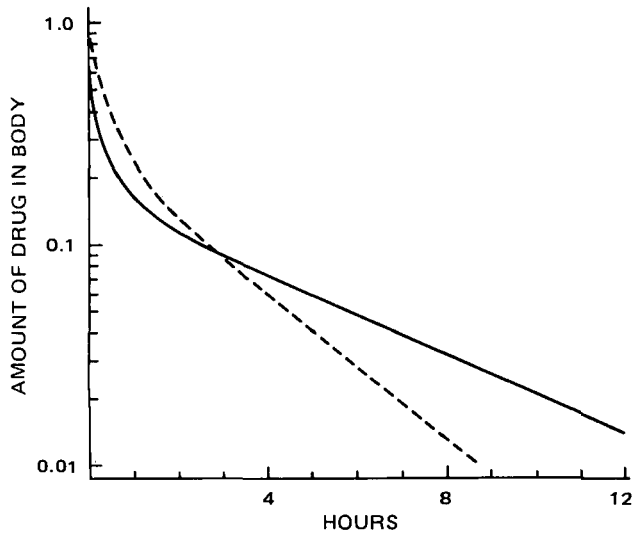


Figure 2—*Effect of reduced biliary excretion on biological half-life when $k_{20} = 0$. Key: —, control, $k_{12} = 3.0$, $k_{21} = 1.0$, and $k_{10} = 1.0\ hr^{-1}$; and - - -, partial cholestasis, $k_{12} = 1.0$, $k_{21} = 1.0$, and $k_{10} = 1.0\ hr^{-1}$.*

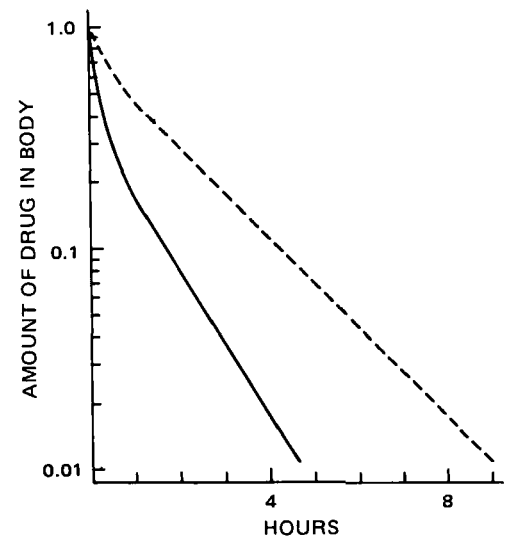


Figure 4—*Effect of reduced biliary excretion on biological half-life when $k_{10}/k_{20} < 1$. Key: —, control, $k_{12} = 3.0$, $k_{21} = 1.0$, $k_{10} = 0.1$, and $k_{20} = 1.0\ hr^{-1}$; and - - -, partial cholestasis, $k_{12} = 1.0$, $k_{21} = 1.0$, $k_{10} = 0.1$, and $k_{20} = 1.0\ hr^{-1}$.*

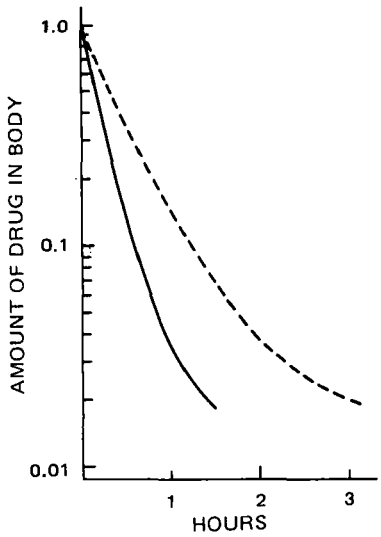


Figure 5—*Effect of reduced biliary excretion on the α-phase when* $k_{10}/k_{20} > 1$. *Key: —, control,* $k_{12} = 3.0$, $k_{21} = 0.1$, $k_{10} = 1.0$, *and* $k_{20} = 0.1\ hr^{-1}$; *and - - -, partial cholestasis,* $k_{12} = 1.0$, $k_{21} = 0.1$, $k_{10} = 1.0$, *and* $k_{20} = 0.1\ hr^{-1}$.

numerical analysis. The results of this analysis were quite clear over a wide range of rate constants. When $k_{10}/k_{20} > 1$, regardless of the value of k_{12}/k_{21}, a decrease in k_{12} produces an increase in β and a decrease in the half-life of the drug (Fig. 3). On the other hand, when $k_{10}/k_{20} < 1$, a decrease in k_{12} results in a decrease in β and an increased biological half-life (Fig. 4). Hence, the model in Scheme I suggests that cholestasis can either increase or decrease the biological half-life; the effect one observes depends on the relationship between the rate constants associated with nonbiliary elimination of the drug from the body and with "elimination" of the drug in the gut.

An interesting finding, made during the simulation and confirmed by numerical analysis of Eq. 2, suggests that an apparent decrease in drug elimination would be the most common observation in cholestasis. Regardless of the value of k_{10}/k_{20}, a decrease in k_{12} produces a decrease in α for any given set of rate constants. In other words, the half-life of the α-phase for a given drug will always be longer in cholestasis than under normal conditions. Limited computer studies suggest that this will also be the case when a multicompartment model is required to represent the body.

If, because of experimental design or assay limitations, the time course of drug concentrations in the plasma is followed for a period shorter than the time required to attain distribution equilibrium, *i.e.*, the time at which the β-phase becomes evident, one would conclude that the reduced biliary excretion increases the half-life of the drug, even if k_{10}/k_{20} were greater than 1 (Fig. 5). Although this conclusion is mathematically incorrect, it is realistic from a clinical and toxicological point of view. For example, it is highly likely that the LD_{50} of any drug subject to biliary excretion in the test species would be decreased in the bile duct-ligated animal compared to that observed in the control animal (8).

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Biliary Secretion of Methotrexate in Rats and Its Inhibition by Probenecid

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Abstract □ The biliary secretion of methotrexate was investigated in rats under steady-state conditions. The transport system involved was saturable and displayed Michaelis–Menten-type kinetics. Values for the maximal rate of transport and a transport constant analogous to the Michaelis constant were 12 mg/hr and 32 mg/liter ($7 \times 10^{-5}\ M$), respectively. The inhibition of this transport mechanism by probenecid also was investigated, and the relationship between the plasma concentration of probenecid and the biliary clearance of methotrexate was elucidated. The value of K_i, the dissociation constant for the transport carrier–inhibitor complex, was 23 μg/ml ($8 \times 10^{-5}\ M$).

Keyphrases □ Methotrexate—biliary secretion, effect of coadministration of probenecid, rats □ Probenecid—effect on biliary secretion of methotrexate, rats □ Biliary secretion—methotrexate, effect of coadministration of probenecid, rats □ Antineoplastic agents—methotrexate, biliary secretion, effect of probenecid, rats □ Uricosuric agents—probenecid, effect on biliary secretion of methotrexate, rats

The effectiveness of methotrexate as an anticancer drug was first reported 25 years ago. Since then, its mechanisms of action have been studied extensively to determine how it can be utilized effectively in treating neoplastic diseases. As with other anticancer drugs, methotrexate is a nonspecific agent which arrests cell