the *p*-aminobenzoate dissolution rate. The difference between several dissolution rate tests was less than ±5% during the first 3 min of dissolution when the surface areas of the tablets were still nearly identical. The dissolution rate was calculated over the portion of the dissolution profile that followed zero-order kinetics.

The increase in the dissolution rate as compared with that of pure drug tablets was greatest when the drug content was lowest. The dissolution rate of a xylitol dispersion containing 5% butyl *p*-aminobenzoate was about 10 times, per unit area, the pure drug dissolution rate. When the increase in area caused by dispersion of the drug with xylitol (1:20) was considered, the dissolution rate of a 5% dispersion was about 200-fold that of the pure drug. The dissolution rate of the methyl *p*-aminobenzoate dispersion was fivefold per unit area, which corresponds to a 100-fold increase in the dissolution rate of the pure drug when the increase in area is considered. When the dispersion drug content was 20–30%, the changes in the dissolution rate per unit area decreased. In this case, the increase in the dissolution rate was primarily due to an increase in area.

A curve depicting the dissolution rates as a function of the drug content of the dispersion was of nearly the same shape for each compound (Fig. 1). When the *p*-aminobenzoic acid ester alkyl group carbon chain was increased, the xylitol dispersion dissolution rate showed a nearly linear decrease.

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Pharmacokinetics of Drugs Subject to Enterohepatic Circulation

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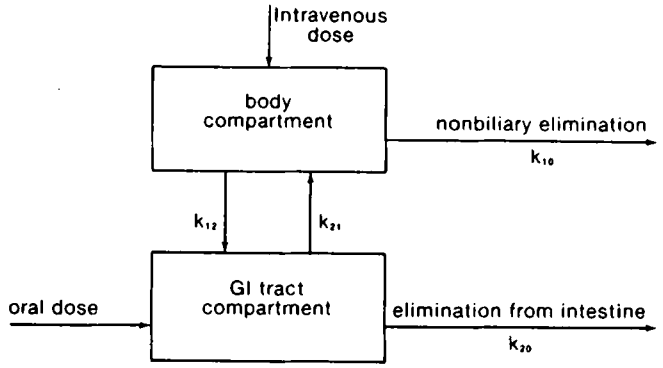
Abstract □ The influence of the changes in biliary excretion and reabsorption rates on the pharmacokinetics of drugs subject to enterohepatic circulation was examined analytically. A recently proposed two-compartment model with drug elimination occurring in each compartment was adapted to represent the body and the GI tract. Enhanced reabsorption was equivalent to biliary excretion rate reduction, except that the latter always decreased α and prolonged the α-phase half-life while the former always increased α and shortened the half-life. However, depending on the relative values of the two elimination rate constants, biliary excretion reduction (or reabsorption enhancement) could either increase or decrease the terminal drug half-life (β-phase). Whether the terminal drug half-life was prolonged or shortened, a biliary excretion reduction always increased the area under the plasma decay curve for intravenous and oral doses and also raised the steady-state drug level in the body for constant-rate intravenous infusion. As a consequence, the lethality, toxicity, or effectiveness of the drug will be increased for patients with impaired bile flow or enhanced drug reabsorption; therefore, the clinical dosage may have to be reduced.

Keyphrases □ Enterohepatic circulation—effect of biliary excretion and reabsorption rates on drug pharmacokinetics, two-compartment model □ Distribution—enterohepatic circulation, effect of biliary excretion and reabsorption rates, pharmacokinetics, two-compartment model □ Pharmacokinetics—enterohepatic circulation, effect of biliary excretion and reabsorption rates, two-compartment model

When a substance is excreted into the bile, passes through the lumen of the intestine, is reabsorbed, and then is carried to the liver *via* blood flow, it undergoes enterohepatic circulation or cycling. Many endogenous and exogenous substances (bile salts, morphine, methadone, methotrexate, digitoxin, *etc.*) can undergo enterohepatic circulation (1). Pharmacokinetic study of drugs subject to enterohepatic circulation has gained importance in recent years.

A two-compartment model representing the body and the GI tract was recently proposed by Harrison and Gibaldi (2) to describe the influence of cholestasis (bile flow reduction or discontinuance) on the elimination of drugs undergoing enterohepatic circulation. Scheme I shows the



Scheme I—Pharmacokinetic model for a drug subject to enterohepatic circulation.

pharmacokinetic model of the biliary excretion (k_{12}) and reabsorption process (k_{21}) of a drug eliminated by both compartments. Cholestasis was simulated numerically by reducing the transfer rate constant k_{12}. Results (2) suggested that cholestasis can either increase or decrease the terminal drug half-life ($T^{\beta}_{1/2}$), depending on the ratio of the two elimination rate constants k_{10}/k_{20}. If the ratio is greater than unity, cholestasis will increase β and reduce the drug half-life. The reverse is true if the ratio is less than unity. In contrast, a biliary excretion reduction will always decrease α and prolong the α-phase half-life.

Although the terminal drug half-life may be decreased, many experiments showed that drug lethality and toxicity are greater in animals with a ligated bile duct than in normal animals (1). Furthermore, since enterohepatic circulation is characterized by biliary excretion and reabsorption, the reabsorption influence on drug disposition should also be studied. In the present work, the effects of both processes on the pharmacokinetics of drugs undergoing enterohepatic circulation were examined analytically. The dependence of the drug half-lives, the area

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under the plasma decay curve, and the steady-state drug level after intravenous infusion on changes in biliary drug excretion and reabsorption rates were studied.

THEORETICAL

The model used by Harrison and Gibaldi (2) was adopted, although it involved the assumption that the bile flow is a continuous process. The drug can be administered either as an intravenous bolus injection into the body compartment or as an oral bolus dose into the GI tract. Drug elimination occurs linearly in both compartments. The rate constant k_{10} represents the sum of all first-order rate constants associated with nonbiliary elimination; the constant k_{20} is the drug disappearance rate from the reabsorption sites (intestine) by biotransformation in the intestine or by fecal elimination.

The biliary excretion and reabsorption rates are represented by the constants k_{12} and k_{21} separately. Disease states like cholestasis that reduce biliary excretion or mechanisms (1) that enhance bile flow can all be simulated by corresponding changes in k_{12}. Similarly, changes in the conjugate hydrolysis rate due to intestinal microorganisms and subsequent deconjugated product reabsorption can be simulated by changing the value of k_{21}.

The amount of drug in the body, A, as a function of time after different administration routes can be solved easily to yield the following analytic expressions.

After intravenous bolus injection of dose D, the drug level in the body is:

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

where:

$$\alpha = \tfrac{1}{2}(k_{21} + k_{20} + k_{12} + k_{10} + \nabla) \quad \text{(Eq. 2)}$$

$$\beta = \tfrac{1}{2}(k_{21} + k_{20} + k_{12} + k_{10} - \nabla) \quad \text{(Eq. 3)}$$

and:

$$\nabla^2 = (k_{21} + k_{20} + k_{12} + k_{10})^2 - 4(k_{12}k_{20} + k_{10}k_{21} + k_{10}k_{20}) \quad \text{(Eq. 4)}$$

The area under the intravenous injection plasma decay curve is then obtained by integrating Eq. 1:

$$CXT_{iv} = \left(\frac{D}{V}\right)\left(\frac{k_{21} + k_{20}}{k_{12}k_{20} + k_{21}k_{10} + k_{10}k_{20}}\right) \quad \text{(Eq. 5)}$$

where V is the distribution volume.

After oral administration of dose D, the drug level in the body is:

$$A_{oral} = \frac{Dk_{21}}{\alpha - \beta}[\exp(-\beta t) - \exp(-\alpha t)] \quad \text{(Eq. 6)}$$

Since the area under the plasma decay curve for oral dosing is:

$$CXT_{oral} = \left(\frac{D}{V}\right)\left(\frac{k_{21}}{k_{12}k_{20} + k_{21}k_{10} + k_{10}k_{20}}\right) \quad \text{(Eq. 7)}$$

the oral dose availability (or the fraction absorbed into the body) is:

$$F = \frac{k_{21}}{k_{21} + k_{20}} \quad \text{(Eq. 8)}$$

Following the oral dose, the peak drug level and the time required to reach it are:

$$A_{max} = \frac{Dk_{21}}{\alpha}\left(\frac{\alpha}{\beta}\right)^{-\beta/\alpha-\beta} \quad \text{(Eq. 9)}$$

$$t_{peak} = \frac{1}{\alpha - \beta}\ln\frac{\alpha}{\beta} \quad \text{(Eq. 10)}$$

Following intravenous drug infusion at constant rate k_0, the drug level in the body as a function of time is:

$$A_{infusion} = \frac{k_0(k_{21} + k_{20})}{\alpha\beta} - \frac{k_0(\alpha - k_{21} - k_{20})}{\alpha(\alpha - \beta)}\exp(-\alpha t) - \frac{k_0(k_{21} + k_{20} - \beta)}{\beta(\alpha - \beta)}\exp(-\beta t) \quad \text{(Eq. 11)}$$

As time proceeds, the drug level reaches a steady state:

$$A_{ss} = \frac{k_0(k_{21} + k_{20})}{k_{21}k_{10} + k_{12}k_{20} + k_{10}k_{20}} \quad \text{(Eq. 12)}$$

The drug half-lives are then given by:

$$T^{\alpha}_{1/2} = \frac{\ln 2}{\alpha} \quad \text{(Eq. 13)}$$

and:

$$T^{\beta}_{1/2} = \frac{\ln 2}{\beta} \quad \text{(Eq. 14)}$$

where $T^{\beta}_{1/2}$ is the terminal drug half-life.

The influences of biliary excretion and reabsorption processes on drug disposition can be simulated by changing the rate constants k_{12} and k_{21}. It can be shown (*Appendix*) that:

$$\frac{\partial\beta}{\partial k_{12}} > 0 \quad \text{if } k_{20} > k_{10} \quad \text{(Eq. 15)}$$

$$\frac{\partial\beta}{\partial k_{12}} = 0 \quad \text{if } k_{20} = k_{10} \quad \text{(Eq. 16)}$$

$$\frac{\partial\beta}{\partial k_{12}} < 0 \quad \text{if } k_{20} < k_{10} \quad \text{(Eq. 17)}$$

The physical meaning of a multivariable function partial differentiation with respect to one of its variables is the rate of change of that function with respect to the variable while the other variables are held constant. Therefore, β will increase as k_{12} increases and will decrease as k_{12} decreases if $k_{20} > k_{10}$. If $k_{20} < k_{10}$, β will decrease while k_{12} is increased. If $k_{20} = k_{10}$, the value of β will be independent of the changes in k_{12}.

Similarly, no matter what the relative values of k_{20} and k_{10}, the partial derivative of α with respect to k_{12} is always greater than zero. Thus, a biliary excretion reduction will decrease α and produce a longer α-phase half-life. However, by observing Eqs. 5, 7, and 12, it is obvious that a reduction of k_{12} will increase CXT_{iv}, CXT_{oral}, and A_{ss}.

The influence of changing the reabsorption rate k_{21} on the drug elimination can be studied similarly. It can be proved that:

$$\frac{\partial\beta}{\partial k_{21}} < 0 \quad \text{if } k_{20} > k_{10} \quad \text{(Eq. 18)}$$

$$\frac{\partial\beta}{\partial k_{21}} = 0 \quad \text{if } k_{20} = k_{10} \quad \text{(Eq. 19)}$$

$$\frac{\partial\beta}{\partial k_{21}} > 0 \quad \text{if } k_{20} < k_{10} \quad \text{(Eq. 20)}$$

Thus, an increase in the drug reabsorption rate will have the same effect on β and $T^{\beta}_{1/2}$ as a biliary excretion reduction. However, $\partial\alpha/\partial k_{21}$ is always positive for any combination of variables. An enhancement in the reabsorption rate will thus increase α and shorten the α-phase half-life.

The effect of k_{21} on the values of CXT_{iv}, CXT_{oral}, and A_{ss} cannot be as easily observed as with k_{12}. However, Eqs. 5, 7, and 12 can be rewritten in the form:

$$CXT_{iv} = \left(\frac{D}{V}\right)\left[\frac{1}{k_{10}} - \frac{k_{12}k_{20}}{k_{10}(k_{12}k_{20} + k_{21}k_{10} + k_{10}k_{20})}\right] \quad \text{(Eq. 21)}$$

An increase in k_{21} will decrease the second term in the parenthesis and increase CXT_{iv}. Hence, an increase in the drug reabsorption rate will increase CXT_{iv}, CXT_{oral}, and A_{ss} while a reduction of k_{21} will decrease these quantities.

DISCUSSION

The influence of the biliary excretion and reabsorption rates on the disposition of drugs subject to enterohepatic circulation was studied analytically using the model of Harrison and Gibaldi (2). The results are:

1. If $k_{20} > k_{10}$, a biliary excretion reduction or reabsorption rate increase will decrease β and produce a longer half-life $T^{\beta}_{1/2}$. If $k_{20} < k_{10}$, a decrease in biliary excretion or reabsorption enhancement will increase β and shorten the drug half-life. If $k_{20} = k_{10}$, the terminal half-life will be independent of the changes in either rate.
2. A reduction of biliary drug excretion will always decrease the value of α and increase the α-phase half-life, while an increase in the reabsorption rate will have the reverse effects, regardless of the combination of variables.
3. A biliary excretion reduction or an increase in the reabsorption rate will always increase the area under the plasma decay curve for intravenous and oral doses and will also raise the steady-state drug level in the body following a constant-rate intravenous infusion.

Biliary excretion enhancement or drug reabsorption decrease will produce the opposite effects on drug disposition.

Although the terminal half-life may be reduced by biliary dysfunction or reabsorption enhancement (when $k_{20} < k_{10}$), CXT_{iv}, CXT_{oral}, and A_{ss} will always be increased by these changes. Since drug effectiveness and toxicity are closely related to CXT values after intravenous or oral dosing and to A_{ss}, the steady-state drug level, after infusion, they will increase for patients with biliary dysfunction or enhanced reabsorption. To avoid toxicity, the drug dosage may have to be reduced accordingly.

APPENDIX

From Eq. 3, partial differentiation of β with respect to k_{12} yields:

$$\frac{\partial\beta}{\partial k_{12}} = \frac{1}{2\nabla}[\nabla - (k_{21} + k_{12} + k_{10} - k_{20})] \quad \text{(Eq. A1)}$$

Since ∇ is always positive, if $k_{20} \geq k_{21} + k_{12} + k_{10}$, then $\partial\beta/\partial k_{12}$ will be positive. If $k_{21} + k_{12} + k_{10} > k_{20}$, $\partial\beta/\partial k_{12}$ has the same sign as $\nabla^2 - (k_{21} + k_{12} + k_{10} - k_{20})^2$. Thus:

$$\nabla^2 - (k_{21} + k_{12} + k_{10} - k_{20})^2 = 4k_{21}(k_{20} - k_{10}) \quad \text{(Eq. A2)}$$

and, therefore:

$$\frac{\partial\beta}{\partial k_{12}} > 0 \quad \text{if } k_{20} > k_{10} \quad \text{(Eq. A3)}$$

$$\frac{\partial\beta}{\partial k_{12}} = 0 \quad \text{if } k_{20} = k_{10} \quad \text{(Eq. A4)}$$

$$\frac{\partial\beta}{\partial k_{12}} < 0 \quad \text{if } k_{20} < k_{10} \quad \text{(Eq. A5)}$$

Similarly, partial differentiation of β with respect to k_{21} gives:

$$\frac{\partial\beta}{\partial k_{21}} = \frac{1}{2\nabla}[\nabla - (k_{21} + k_{12} + k_{20} - k_{10})] \quad \text{(Eq. A6)}$$

which is similar to Eq. A1 except that the order of k_{20} and k_{10} is reversed. Therefore:

$$\frac{\partial\beta}{\partial k_{21}} < 0 \quad \text{if } k_{20} > k_{10} \quad \text{(Eq. A7)}$$

$$\frac{\partial\beta}{\partial k_{21}} = 0 \quad \text{if } k_{20} = k_{10} \quad \text{(Eq. A8)}$$

$$\frac{\partial\beta}{\partial k_{21}} > 0 \quad \text{if } k_{20} < k_{10} \quad \text{(Eq. A9)}$$

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Progestin Permeation through Polymer Membranes III: Polymerization Solvent Effect on Progesterone Permeation through Hydrogel Membranes

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Received August 4, 1978, from the *Department of Pharmaceutics, College of Pharmacy, University of Utah, Salt Lake City, UT 84112.* Accepted for publication November 13, 1978.

Abstract □ Hydrogels prepared from poly(hydroxyethyl methacrylate) are biocompatible and highly permeable to low molecular weight solutes. Permeation rates can be varied by altering the cross-linker concentration or using copolymers; the latter are chosen to alter the hydrogel equilibrium hydration. These factors suggest that hydrogels are good candidates for controlled-release drug delivery devices. Hydrogels may be synthesized using various temperatures, initiators (nature and concentration), and solvents (nature and concentration). This study demonstrated that progesterone permeation through poly(hydroxyethyl methacrylate) films is independent of polymerization solvent (nature and concentration) for the solvents, water, ethanol, and *tert*-butyl alcohol. The importance of hydrogel equilibrium hydration in progesterone permeation is emphasized.

Keyphrases □ Hydrogels, poly(hydroxyethyl methacrylate)—progesterone permeation, effect of various nonaqueous polymerization solvents □ Hydroxyethyl methacrylate—hydrogel films, progesterone permeation, effect of various nonaqueous polymerization solvents □ Progesterone—permeation through hydrogel membranes, effect of various nonaqueous polymerization solvents □ Delivery devices, controlled—hydrogel membranes, progesterone permeation, effect of various nonaqueous polymerization solvents

Hydrogels are biocompatible (1) and potentially useful for controlled-release drug delivery systems (2–9). Monomer composition and cross-linker type and composition determine hydrogel drug release rates.

The physical–chemical properties of hydrogels depend on polymerization conditions (10). In poly(hydroxyalkyl methacrylate) synthesis, polymerization at the gel equilibrium water content is convenient. However, varying the initial solvent composition is often advantageous in fabricating controlled-release drug delivery devices. Certain fabrication problems may be overcome through nonaqueous polymerization (4, 7). However, polymer chain organization, degree of cross-linking, and other properties may be altered, resulting in a different polymer when water is omitted. These changes could affect the permeability of these films relative to those polymerized in the presence of water.

For these reasons, a systematic study of polymerization solvent effects on progesterone permeability through films polymerized from hydroxyethyl methacrylate was undertaken. Films prepared without cross-linker were chosen because the permeabilities of these films are highly sensitive to small changes in cross-link density (9, 11, 12).

Also included in the present study are the effects of the solvents ethanol and *tert*-butyl alcohol. Based on thermodynamic (13) and swelling arguments (14), ethanol and, to a greater extent, *tert*-butyl alcohol are better solvents for poly(hydroxyethyl methacrylate) than is water. These solvents are expected to offer certain advantages in the polymerization of films containing high concentrations of cross-linking agents and aid in dissolving drugs that nor-

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