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Received June 29, 1981.
Accepted for publication August 26, 1981.

Pharmacokinetic and Biopharmaceutic Parameters During Enterohepatic Circulation of Drugs

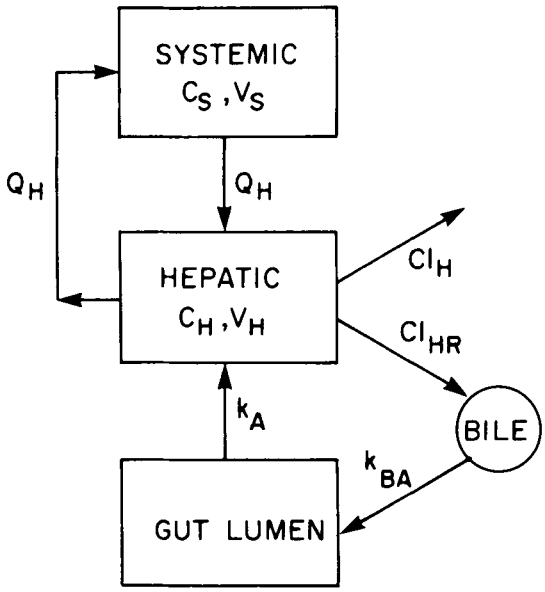
Keyphrases □ Enterohepatic circulation—model, evaluation of pharmacokinetic parameters □ Pharmacokinetics—evaluation of parameters, enterohepatic circulation model

To the Editor:

As research in the area of enterohepatic circulation continues in this laboratory, several aspects of its impact on the interpretation of pharmacokinetic and biopharmaceutic studies have become apparent. Simulation techniques have been used to investigate the effect of enterohepatic circulation on various pharmacokinetic and biopharmaceutic parameters under various conditions.

The simple first-pass perfusion model in Scheme I was used for the simulations. In the model, V_H and V_S are the effective hepatic and systemic volumes[1], Q_H is the blood flow to the liver, and Cl_H and Cl_{HR} are the irreversible and recirculating hepatic organ clearances, respectively. The biliary excretion component was assumed to be continuous in the present model to avoid the complexities associated with gallbladder storage and subsequent excretion into the duodenum. The more complex model was addressed previously (1) and will be investigated further, but the concepts presented here are generally applicable to both situations. For the purpose of the oral absorption simulations, the absorption rate constant, k_A, was set at 0.693 hr^{-1}. Simulations were performed under conditions of intact enterohepatic circulation (k_{BA} = 1.0) and under conditions of bile duct cannulation, *i.e.*, interrupted enterohepatic circulation (k_{BA} = 0.0).

Blood concentration–time data following intravenous and oral doses were simulated using several sets of parameter values. Representative examples from the total number of simulations are presented in Tables I–III. The



Scheme I—Pharmacokinetic first-pass perfusion model used to describe the systemic blood concentrations of drugs that undergo enterohepatic recycling. Key: Q_H, hepatic blood flow; Cl_H and Cl_{HR}, irreversible and recirculating hepatic organ clearances, respectively; and k_A and k_{BA}, the absorption and bile transport processes, respectively.

effect of enterohepatic circulation on blood clearance (Cl_B), oral clearance (Cl_O), elimination half-life ($t_{1/2\beta}$), and the volume of distribution ($V_{d_{area}}$) are presented in Table I. The influence of enterohepatic circulation on the time (T_{max}) of the maximum observed blood concentration (C_{max}) and the elimination half-life following oral dosing are presented in Table II. Table III contains the blood clearance (Cl_B) and oral clearance (Cl_O) parameters along with the absolute bioavailability under intact (F_I) as well as bile duct-cannulated (F_C) conditions. In addition, the ratio of the area under the curves following intravenous doses (AUC_{IV}) under intact and bile-duct-cannulated conditions (R_{IV}) as well as the ratio of the area under the curves following oral doses (AUC_O) under intact and bile duct-cannulated conditions (R_O) are presented in Table III.

The results of these simulations indicate that enterohepatic circulation increases the apparent volume distribution and prolongs the half-life of elimination when compared to identical blood clearances without it. The more extensive the recycling, the more prolonged the half-life and greater the volume increase (Table I). The data presented in Table II indicate that the pharmacokinetic complexities associated with enterohepatic circulation are affected by the effective hepatic and systemic volumes of distribution. The time (T_{max}) of the maximum observed blood concentrations (C_{max}) following oral doses are a function of both the interrelationship of systemic to hepatic effective volumes of distribution as well as the extent of enterohepatic circulation (Table II).

For example, comparison of cases G–I with cases J–L in Table II indicates that when the effective systemic volume of distribution is smaller than the effective hepatic volume of distribution, more extensive recycling results in longer elimination half-lives and lower C_{max} values, but results

[1] Effective volume is the product of the physiological volume of the organ or pooled tissues times its retention factor.

0022-3549/82/0100-0131$01.00/0

Table I—Effect of Enterohepatic Circulation on Various Pharmacokinetic Parameters

Parameters								
Simulated					Calculated			
V_H, liters	V_S, liters	Q_H, liters/hr	Cl_H, liters/hr	Cl_{HR}, liters/hr	Cl_B, liters/hr	Cl_O, liters/hr	$t_{1/2\beta}$, hr	V_{darea}, liters
100	100	90	10	0	9	10	14.3	185
100	100	90	10	20	9	10	17.8	231
100	100	90	10	80	9	10	28.3	367
100	100	90	10	260	9	10	58.9	765
100	100	90	30	0	22.5	30	5.0	164
100	100	90	30	60	22.5	30	8.8	286
100	100	90	60	0	36.0	60	2.8	143
100	100	90	60	30	36.0	60	3.8	200

Table II—Effect of Enterohepatic Circulation on Various Biopharmaceutic Parameters

	Parameters							
	Simulated					Calculated		
Case	V_H, liters	V_S, liters	Q_H, liters/hr	Cl_H, liters/hr	Cl_{HR}, liters/hr	T_{max}, hr	C_{max}, U/liters	$t_{1/2\beta}$, hr
A	100	100	90	10	0	5	395	14.3
B	100	100	90	10	20	5	331	17.8
C	100	100	90	10	260	4	112	58.9
D	10	100	90	10	0	4	620	8.3
E	10	100	90	10	20	4	474	11.9
F	10	100	90	10	260	4	124	52.8
G	100	10	90	10	0	4	663	7.6
H	100	10	90	10	20	3	524	11.4
I	100	10	90	10	260	1	159	52.7
J	100	1000	90	10	0	8	78.5	83.3
K	100	1000	90	10	20	10	74.5	86.4
L	100	1000	90	10	260	20	49.6	125

Table III—Simulated Effects of Enterohepatic Circulation and Bile Duct Cannulation on Clearance, Bioavailability, and Administration Route Differences

	Parameters										
	Simulated					Calculated					
Recirculation status[a]	V_H, liters	V_S, liters	Q_H, liters/hr	Cl_H, liters/hr	Cl_{HR}, liters/hr	Cl_B, liters/hr	Cl_O, liters/hr	F_I	F_C	R_{IV}	R_O
I	100	100	90	10	0	9.0	10.0	0.900	0.900	1.000	1.000
I	100	100	90	30	0	22.5	30.0	0.750	0.750	1.000	1.000
I	100	100	90	60	0	36.0	60.0	0.600	0.600	1.000	1.000
I	100	100	90	30	60	22.5	30.0	0.750	0.500	0.500	0.333
C				90	0	45.0	90.0				
I	100	100	90	60	30	36.0	60.0	0.600	0.500	0.800	0.667
C				90	0	45.0	90.0				
I	100	100	90	10	20	9.0	10.0	0.900	0.750	0.400	0.333
C				30	0	22.5	30.0				
I	100	100	90	10	80	9.0	10.0	0.900	0.500	0.200	0.111
C				90	0	45.0	90.0				
I	100	100	90	10	260	9.0	10.0	0.900	0.250	0.133	0.037
C				270	0	67.5	270.0				

[a] I, intact, uncannulated; and C, cannulated.

in earlier T_{max} values. However, when the effective systemic volume of distribution is larger than the effective hepatic volume, more extensive recycling not only results in longer elimination half-lives and lower C_{max} values, but also in much later T_{max} values. For comparison with case L, the T_{max} value is 8 hr for a drug with an elimination half-life of 125 hr, but without enterohepatic circulation.

The importance of recycling on estimates of the absolute bioavailability of a drug is shown by comparing the absolute bioavailability simulated in intact, uncannulated (F_I), and bile duct-cannulated (F_C) animals. It is apparent that bioavailability in cannulated animals is less than or equal to the bioavailability in uncannulated animals. This observation is supported by the fact that the ratios of areas under the oral curves (R_O) are decreased more extensively by bile duct cannulation than are the ratios of the areas under the intravenous curves (R_{IV}).

Although enterohepatic circulation affects the shapes of the blood concentration–time curves by increasing the apparent volume of distribution and half-life (Table I) and by altering the C_{max} and T_{max} values (Table II), it will not alter the areas under the blood concentration–time curves unless the enterohepatic circulation is interrupted (Table III) or altered in some way. An interruption can result from bile duct cannulation in the experimental setting, from the oral ingestion of ion-exchange resins, or from changes in the intestinal contents and microflora that may decrease or inhibit drug reabsorption.

Thus, enterohepatic circulation influences the bio-

pharmaceutic and pharmacokinetic parameters associated with a drug. The process needs to be better understood to allow reasonable interpretation of the pharmacokinetic data obtained for drugs that are recycled. The data presented here reflect the simplest case; discontinuous recycling, which is associated with gall bladder storage and emptying, is even more complex (1).

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Received July 17, 1981.
Accepted for publication September 22, 1981.

BOOKS

REVIEWS

Basic Clinical Pharmacokinetics. By MICHAEL E. WINTER, with BRIAN S. KATCHER and MARY ANNE KODA-KIMBLE. Applied Therapeutics, P.O. Box 31-747, San Francisco, CA 94131. 1980. 231 pp. 14.8 × 22.7 cm. Price $22.00.

Pharmacokinetics and biopharmaceutics are well-established disciplines. Their contributions in describing drug disposition, and predicting plasma drug concentrations and changes in drug concentrations are generally recognized. During the past decade, evaluation of drug concentrations in biological fluids has found wide acceptance as part of drug therapy monitoring. The authors view this book as a practical guideline for the clinician in evaluating drug monitoring.

The book is divided into two parts. The first part gives a brief overview of the basic principles of pharmacokinetics dealing with bioavailability, rate of administration, desired plasma concentration, volume of distribution, clearance, elimination, steady-state concentrations, interpretation of plasma drug concentrations, selection of appropriate equations, and creatinine clearance. At the end of the first part, a very instructive diagram is given for evaluation and interpretation of plasma levels. This diagram will be very helpful for any clinician confronted with blood level data interpretation.

Part 2 discusses the clinical pharmacokinetics of drugs usually monitored by a clinical pharmacokinetics service. The following drugs are covered: digoxin, lidocaine, procainamide, quinidine, theophylline, gentamicin, phenobarbital, and phenytoin. For each of these drugs, therapeutic and toxic plasma levels, bioavailability, if applicable, and the most important pharmacokinetic parameters (*i.e.*, volume of distribution, clearance, and elimination half-life) are covered. Where applicable, the influence of age, disease, and other concomitantly given drugs on drug disposition is discussed.

This section, which is well referenced, is followed by a selection of typical clinical cases, along with the pharmacokinetic approach for solution. The calculations are listed stepwise so that even one who is inexperienced in pharmacokinetics can easily follow. This section will be of great value to anyone interested in or practicing clinical pharmacokinetics, as well as for teaching undergraduate and graduate students. Although only a few drugs are discussed in detail, once one masters these problem cases, the principles can be applied and tailored to many more drugs.

The book contains three appendixes: I, nomograms for calculating body surface area of children and adults; II, a listing of equations used throughout the text; and III, a glossary of terms and abbreviations.

In summary, this is a well-written and well-designed text which incorporates the most important basic principles of basic and clinical pharmacokinetics. As such, the book will be of great value to all those involved in clinical pharmacokinetics and drug monitoring, particularly those who are entering the field. The authors have to be congratulated for writing such a well-organized guideline to the practical approach of drug level monitoring.

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GC/MS Assays for Abused Drugs in Body Fluid. NIDA Research Monograph 32. By RODGER L. FOLTZ, ALLISON F. FENTIMAN, and RUTH B. FOLTZ. National Institute on Drug Abuse, Division of Research, 5600 Fishers Lane, Rockville, MD 20857. 1980. 202 pp. 14 × 23 cm. Price $5.00. (Available from Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402. Specify GPO stock no. 017-024-01015-4.)

This monograph, prepared by authors who are well versed in the areas of analytical methodology and drug abuse, should be valuable to investigators interested in quantitating drugs in biological fluids. This work is actually a compilation of assays used for measuring the levels of drugs most often misused.

This volume (13 chapters) includes an introduction and a discussion of experimental considerations and operations common to all of the assays (Chapter 2), and each remaining chapter is devoted to a particular drug that is commonly abused. The inclusion of Chapter 2 (which deals with the basics of obtaining internal standards, preparing calibration curves, sample extractions, performance evaluation of the gas chromatograph–mass spectrometer, *etc.*) is an ideal approach since it greatly reduces excessive repetition that would have been required in each of the succeeding chapters. The authors recommend that investigators concentrate on Chapter 2 along with the specific chapter for the drug in question.

Each succeeding chapter is devoted to one of the following drugs of abuse: phencyclidine, methaqualone, methadone, Δ^9-tetrahydrocannabinol and two of its metabolites (11-hydroxy-Δ^9-THC and 11-nor-9-carboxy-Δ^9-THC), cocaine and its major metabolite (benzoylecgonine), morphine, diazepam and its major metabolite (*N*-desmethyldiazepam), amphetamine, methamphetamine, 2,5-dimethoxy-4-methylamphetamine, and mescaline. Each chapter begins with a brief historical description of the drug followed by a synopsis of its pharmacological effects. A discussion on pharmacokinetics and metabolism examines which biological fluid should be chosen for assay and whether metabolites should be quantitated. Then the sensitivity and selectivity of most of the techniques (*e.g.*, spectrometry, gas chromatography, and radioimmunoassay)