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edited by

James M. Anderson

and

Sung Wan Kim

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Advances in Drug Delivery Systems

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Edited by

James M. Anderson

Institute of Pathology, Case Western Reserve University,
Cleveland, OH 44106, U.S.A.

and

Sung Wan Kim

Department of Pharmaceutics, University of Utah,
Salt Lake City, UT 84112, U.S.A.

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PREFACE

The Second International Symposium on Recent Advances in Drug Delivery Systems was held in Salt Lake City, Utah, from February 27 through March 1, 1985. Our goal in organizing this symposium has been to provide a vehicle by which scientists could come together to discuss recent advances and state-of-the-art technology in drug delivery systems. Given the time constraints which are always a problem with symposia, we elected to invite pharmaceutical scientists, polymer chemists, bioengineers, pharmacologists and physicians whose efforts were at the leading edge of the research and development of drug delivery systems. We also sought to include speakers whose research we felt would be important to future efforts in the area of drug delivery systems.

The multidisciplinary nature of drug delivery systems is reflected in the wide variety of topics which were presented at the symposium. To provide perspective and focus in the research, development and clinical application of drug delivery systems, we divided the symposium presentations into six significant areas. These are: gastrointestinal drug delivery systems, skin and topical delivery systems, insulin delivery systems, biodegradable polymers, hydrophilic polymers and hydrogels, and other applications.

This book contains manuscripts which were generated from the topics presented in the symposium. They are presented to provide the reader with in-depth knowledge and perspective regarding the individual topics. The multi-faceted and interdisciplinary nature of drug delivery systems mitigates toward broad, as well as in-depth, perspectives when viewing the science and technology of drug delivery systems. With this approach in mind, the editors present the Proceedings from the Second International Symposium on Recent Advances in Drug Delivery Systems.

The task of reviewing and editing the papers was shared between Dr. Jorge Heller, Professor Jan Feijen, and ourselves.

The editors extend their appreciation to sponsors of the Symposium who are the CIBA-GEIGY Corporation, the Monsanto Company, Pennwalt Corporation, Pfizer Central Research, Riker Laboratories/3M, Smith Kline and French Laboratories, the Upjohn Company and Travenol Laboratories, Inc. Symposium contributors included Abbott Laboratories; Alcon Laboratories; Biomaterials International; CIBA-GEIGY Pharmaceuticals, U.K.; E.R. Squibb and Sons; Genentech; Hoffmann–La Roche; Merck Sharp and Dohme Research Laboratories; Nelson Research and Development; Sandoz Research Institute; Schering Corporation; and Syntex Research. The generosity of these sponsors and contributors permitted the Second International Symposium on Recent Advances in Drug Delivery Systems to be held.

JAMES M. ANDERSON
Case Western Reserve University, Cleveland, Ohio
SUNG WAN KIM
University of Utah, Salt Lake City, Utah

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CONTENTS

Preface v

I. Gastrointestinal Drug Delivery Systems 1

Targeting drugs to the enterohepatic circulation: Lessons from bile acids and other endobiotics
A.F. Hofmann (La Jolla, CA, U.S.A.) 3

Improving the intestinal mucosal cell uptake of water insoluble compounds
G.L. Amidon, B.H. Stewart (Ann Arbor, MI, U.S.A.) and S. Pogany (Lawrence, KS, U.S.A.) 13

The design and evaluation of controlled release systems for the gastrointestinal tract
S.S. Davis (Nottingham, Great Britain) 27

Rate controlled rectal drug delivery in man
D.D. Breimer, A.G. de Boer and L.G.J. de Leede (Leiden, The Netherlands) 39

Physico-chemical properties of water insoluble polymers important to mucin/epithelial adhesion
H. Park and J.R. Robinson (Madison, WI, U.S.A.) 47

II. Skin and Topical Delivery Systems 59

Mechanisms of topical delivery of liposomally entrapped drugs
N.F.H. Ho (Kalamazoo, MI, U.S.A.), M.G. Ganesan (Pearl River, NY, U.S.A.), N.D. Weiner and G.L. Flynn (Ann Arbor, MI, U.S.A.) 61

Macro- and molecular physical—chemical considerations in understanding drug transport in the stratum corneum
K. Knutson (Salt Lake City, UT, U.S.A.), R.O. Potts, D.B. Guzek, G.M. Golden, J.E. McKie (Groton, CT, U.S.A.), W.J. Lambert and W.I. Higuchi (Salt Lake City, UT, U.S.A.) 67

A new transdermal delivery system for estradiol
W.R. Good (Ardsley, NY, U.S.A.), M.S. Powers, P. Campbell (Palo Alto, CA, U.S.A.) and L. Schenkel (Basel, Switzerland) 89

Release kinetics of polymeric laminates for transdermal delivery: Experimental evaluation and physical modelling
H.P. Merkle (Bonn, F.R.G.), A. Knoch and G. Gienger (Heidelberg, F.R.G.) 99

Dermal drug delivery — Improvement by choice of vehicle or drug derivative
A. Hoelgaard and B. Møllgaard (Copenhagen, Denmark) 111

Adhesive topical drug delivery system
T. Nagai (Tokyo, Japan) 121

III. Insulin Delivery Systems 135

Microencapsulation of living cells — A long-term delivery system
A.M. Sun and G.M. O'Shea (Toronto, Ontario, Canada) 137

Self-regulating insulin delivery systems. III. *In vivo* studies
S.Y. Jeong, S.W. Kim, D.L. Holmberg and J.C. McRea (Salt Lake City, UT, U.S.A.) 143

Glucose sensitive membranes for controlled delivery of insulin: Insulin transport studies
G. Albin, T.A. Horbett and B.D. Ratner (Seattle, WA, U.S.A.) 153

IV. Biodegradable Polymers. 165

Controlled drug release from poly(ortho esters) — A surface eroding polymer
J. Heller (Menlo Park, CA, U.S.A.) 167
Release of antibiotic from composites of hydroxyapatite and poly(lactic acid)
Y. Ikada, S.-H. Hyon, K. Jamshidi, S. Higashi, T. Yamamuro, Y. Katutani and T. Kitsugi (Kyoto, Japan). 179
Controlled delivery of an LHRH analogue from biodegradable injectable microspheres
L.M. Sanders, G.I. McRae, K.M. Vitale and B.A. Kell (Palo Alto, CA, U.S.A.) 187
The effect of hydrocortisone acetate loaded poly(DL-lactide) films on the inflammatory response
K.L. Spilizewski, R.E. Marchant, C.R. Hamlin, J.M. Anderson (Cleveland, OH, U.S.A.), T.R. Tice, T.O. Dappert and W.E. Meyers (Birmingham, AL, U.S.A.). 197
Optimization of macromolecular prodrugs of the antitumor antibiotic adriamycin
C.J.T. Hoes, W. Potman, W.A.R. van Heeswijk, J. Mud, B.G. de Grooth, J. Greve and J. Feijen (Enschede, The Netherlands) 205

V. Hydrophilic Polymers and Hydrogels. 215

Osmotic flow through controlled porosity films: An approach to delivery of water soluble compounds
G.M. Zentner, G.S. Rork and K.J. Himmelstein (Lawrence, KS, U.S.A.). 217
The release of prostaglandin E_2 from a novel crystalline-rubbery poly(ethylene oxide) network crosslinked by 3,4-dihydro-2H-pyranyl-2-methyl-(3,4-dihydro-2H-pyran-2-carboxylate)
N.B. Graham, M.E. McNeill and A. Rashid (Glasgow, Great Britain) 231
Synthesis and characterization of some modified polysaccharides containing drug moieties
E. Schacht, J. Vermeersch, F. Vandoorne, R. Vercauteren and J.P. Remon (Ghent, Belgium). 245
Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues
N.A. Peppas (West Lafayette, IN, U.S.A.) and P.A. Buri (Geneva, Switzerland). 257
Kinetics of drug release from hydrogel matrices
P.I. Lee (Philadelphia, PA, U.S.A.) 277
Biological properties of targetable poly[*N*-(2-hydroxypropyl)methacrylamide]—antibody conjugates
B. Říhová and J. Kopeček (Prague, Czechoslovakia) 289

VI. Other Applications 311

PGE_1—heparin conjugate releasing polymers
H. Jacobs, T. Okano, J.Y. Lin and S.W. Kim (Salt Lake City, UT, U.S.A.) 313
Long acting thrombolytic immobilized enzymes
V.P. Torchilin and A.V. Mazaev (Moscow, U.S.S.R.) 321
Controlled release of macromolecules: Biological studies
R. Langer (Cambridge, MA, U.S.A.), D. Lund (Boston, MA, U.S.A.), K. Leong (Cambridge, MA, U.S.A.) and J. Folkman (Boston, MA, U.S.A.) 331
Preparation of injectable controlled-release microcapsules by a solvent-evaporation process
T.R. Tice and R.M. Gilley (Birmingham, AL, U.S.A.). 343
Ocular therapy with nanoparticulate systems for controlled drug delivery
R. Gurny, T. Boye and H. Ibrahim (Geneva, Switzerland) 353
Triggered drug delivery systems
C.G. Pitt, Z-W. Gu, R.W. Hendren, J. Thompson and M.C. Wani (Research Triangle Park, NC, U.S.A.) 363

The immobilization of L-asparaginase on porous hollow fiber plasma filters
  W.R. Gombotz, A.S. Hoffman, G. Schmer and S. Uenoyama (Seattle, WA, U.S.A.) 375
Passive and active vectoring with microparticles: Localisation and drug release
  E. Tomlinson (Horsham, Great Britain) 385
Controlled drug delivery: Veterinary applications
  J.R. Cardinal (Groton, CT, U.S.A.) 393
Controlled release: Challenges and opportunities for the next decade
  A.S. Michaels (Boston, MA, U.S.A.) 405

Author Index 411

I. Gastrointestinal Drug Delivery Systems

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TARGETING DRUGS TO THE ENTEROHEPATIC CIRCULATION: LESSONS FROM BILE ACIDS AND OTHER ENDOBIOTICS*

Alan F. Hofmann

Department of Medicine, T-013, University of California, San Diego, La Jolla, CA 92093 (U.S.A.)

The pharmacology of chenodeoxycholic acid (chenodiol) and ursodeoxycholic acid, two naturally occurring bile acids which are used for cholesterol gallstone dissolution, is compared with that of common drugs. These bile acids are "enterohepatic" drugs, in that their distribution is limited to the intestine, portal and systemic circulation, liver, and biliary tract; and their target tissue is bile. They also differ from common drugs in being excreted efficiently into bile after amidation with glycine or taurine in the liver. The amidates are efficiently reabsorbed from the small intestine by active ileal transport, whereas sulfates and glucuronides of common drugs are not reabsorbed from the intestine. Efficient intestinal reabsorption results in a flux through the liver and biliary tract many fold greater than the administered dose. Bile acids are completely biotransformed by bacterial enzymes before excretion. The biotransformation products are reabsorbed from the distal intestine and in some species are toxic. It is suggested that the unique pharmacology of enterohepatic drugs should be considered in developing drugs for treatment of diseases of the liver, biliary tract, and small intestine.

OVERVIEW: ENTEROHEPATIC DRUGS VERSUS CONVENTIONAL DRUGS

Traditionally, most systemic drugs are designed to be well absorbed, to have a low first-pass hepatic clearance, and to attain high blood concentrations. A high blood concentration is considered desirable to obtain high tissue concentrations. Elimination of drugs is via renal excretion of the unchanged compound or its tissue metabolites.

During the past decade, two naturally occurring bile acids have been introduced as therapeutic agents for the dissolution of cholesterol gallstones [1,2]. These two bile acids, chenodeoxycholic acid, which has the USAN name has as yet been adopted, have epimer, ursodeoxycholic acid, for which no USAN name has as yet been adapted, have been widely used in Europe and have recently been licensed in the United States. The agents have been shown to be rather effective and safe for the treatment of early cholesterol cholelithiasis. The mechanism of action is to induce the secretion of bile whose micelles are unsaturated in cholesterol; cholesterol moves from the surface of the gallstone to the micelle, and gallstones slowly dissolve.

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*Paper presented at the Second International Symposium on Recent Advances in Drug Delivery Systems, February 27, 28 and March 1, 1985, Salt Lake City, UT, U.S.A.

TABLE 1

Properties of CDC and UDC, the first enterohepatic drugs versus those of conventional systemic drugs

	CDC and UDC	Conventional systemic drugs
Absorption	passive	passive
Albumin-binding	high	variable
Hepatic extraction	50—60%	as low as possible
$t_{1/2}$ for plasma disappearance	5—10 min	variable, usually longer
Hepatic biotransformation	amidation	glucuronidation, sulfation many others
Biliary secretion of metabolite	complete	variable
Daily biliary secretion, multiple of dose	10—40	probably <1
Fate of biliary metabolites	reabsorbed	not reabsorbed
Site and mechanism of absorption of metabolites	ileum, active	colon, passive
$t_{1/2}$, days for body pool	2—3	usually less than 1
Route of excretion	fecal	mostly urinary
Desired plasma level	low	high
Target tissue	gallbladder bile	variable
Tissue distribution	gut, portal and systemic circulation, liver and biliary tract	variable; many tissues
Degree of bacterial degradation of compound	extensive	usually extremely low
Absorption of bacterial biotransformation product	yes	rarely
Toxicity in animals	severe in non-sulfating species	usually none
Monitoring of compliance	bile levels	blood levels

If considered as drugs, these two bile acids have a pharmacology which is quite different than that of most other drugs [3], as summarized in Table 1. It has been suggested that these compounds should be classified as the first "enterohepatic" drugs, since these drugs may be considered to be targeted to the enterohepatic circulation [3]. In this article, I would like to review the clinical pharmacology of these bile acids and relate this to other recent studies on modified bile acids from our laboratory, in order to define some of the chemical and biological features that appear necessary for drugs to be "enterohepatic" drugs. Bile acids are "endobiotics" as distinguished from xenobiotics, and an understanding of their metabolism may well provide new insights into the pharmacology of traditional drugs.

This article is based on the assumption that there will be therapeutic utility for enterohepatic drugs, and new enterohepatic drugs will be developed in the future. Since enterohepatic drugs are limited in their anatomical distribution to the intestinal lumen, enterocytes, portal and systemic circulation, hepatocytes, and biliary tract (including biliary ductular cells), such drugs should be useful for disease processes involving these tissues. Diseases of these organs are a major health problem in the United States as has been well documented in recent reports to Congress [4].

SPECIAL FEATURES OF CDC AND UDC PHARMACOLOGY

CDC and UDC are weak acids (pK_a about 5) and because of the insolubility of the protonated acid, their molecules must be solubilized in the mixed micelles present in small intestinal content for efficient absorption [3]. The passive membrane permeability of CDC is extremely high, and perfusion studies in rodents suggest that diffusion through the aqueous boundary layer is rate limiting [5]. UDC is more hydrophilic than CDC, and its membrane permeation is lower; for this bile acid, both unstirred water layer resistance and membrane resistance influence its kinetics of absorption [5].

CDC and UDC pass through the enterocyte without appreciable biotransformation and enter the portal circulation. Their binding to albumin is great — in plasma, both bile acids are >97% bound [6]. Despite this, hepatic first-pass clearance is high, the fractional clearance averaging 60% for CDC [7,8] and 50% for UDC [9]. As a consequence, levels of CDC and UDC remain extremely low in systemic plasma. In the hepatocyte, the bile acids are immediately converted to thioesters by linkage with Coenzyme A [10]. The CoA derivatives then interact with a second enzyme, cholyl CoA amino acid transferase, which acylates glycine or taurine with the bile acid to form the glycine or taurine conjugated bile acid [11]. The transferase has absolute specificity for glycine and taurine; despite the wealth of amino acids in the hepatic cytosol, only these two amino acids are used for conjugation [12]. For CDC, and presumably for UDC, there is no appreciable formation of sulfates or glucuronides.

The glycine and taurine conjugates of CDC or UDC, which may be termed amidates, are efficiently secreted into bile. This rapid first-pass uptake and the complete vectoriality of hepatic transport — into bile rather than back into plasma — is the first major difference between bile acids and conventional drugs.

The bile acid conjugates are strong acids — the pK_a of glycine conjugated bile acids is about 2.6 and that of taurine conjugated bile acids <1 [13]. In addition, the conjugates also possess a polar amide bond. Thus, in bile, which is quite alkaline, bile acids are fully charged and as a consequence of their charge and polarity, the CDC and UDC amidates pass down the biliary tree without appreciable absorption in the biliary tree. A major fraction of the bile acids are stored in the gallbladder which contracts and discharges its contents into the small intestine when a meal is ingested [14].

Bile acids are secreted into the small intestinal lumen, whose pH is considerably lower than that of bile because of the discharge of acidic gastric contents. When the pH is sufficiently low in the duodenum, a small fraction of the glycine conjugates of UDC and CDC will be protonated and probably undergo passive absorption in the protonated form; whether this occurs to an appreciable extent is unknown [3]. In the more distal jejunum and ileum, the pH of intestinal content increases, and bile acids probably undergo little passive absorption. The amide bond of the conjugated bile acids is quite resistant to pancreatic enzymes so that the conjugated bile acids remain intact in the proximal small intestine [15]. An active transport mechanism for conjugated bile acids is located in the distal ileum [16]. This removes the conjugated CDC and UDC and returns them to the liver, where they are promptly resecreted in bile. The first-pass clearance of these conjugates is even higher than the unconjugated form — probably 70–80% [3]. This efficient active absorption of the hepatic biotransformation products from the intestine is the second major difference between the pharmacology of bile acids and that of conventional drugs.

It may be of interest to contrast the intestinal conservation of bile acid conjugates with the lack of conservation of bilirubin diglucuronide conjugates. These are not reabsorbed from the intestine [17].

In principle, this active intestinal conservation of conjugated bile acids should result in an ever increasing amount of CDC and UDC in the body when they are ingested chronically. In fact, a steady state obtains after some weeks of ingestion, in which the input of newly ingested (unconjugated) molecules is balanced by loss of conjugated bile acid molecules. The degree of enrichment is striking for CDC — biliary bile acids may become composed of >95% CDC; with UDC, the enrichment is less [18,19]. For a dose of 8–12 mg/kg day, UDC eventually composes 40 to 50% of biliary bile acids. (The reasons for the differing steady state enrichments during CDC and UDC ingestion are complex, and have been reviewed elsewhere [3].) As a consequence of this accumulation of CDC and UDC in the enterohepatic circulation, the secretion of the administered bile acid into the biliary system (and the intestine) is far greater than the administered dose. The intestinal conservation of the amidates of CDC and UDC amplifies the input of unconjugated molecules, and an amplification term may be defined quite simply:

$$\text{Amplification} = \frac{\text{daily secretion into bile}}{\text{daily dose}}$$

For CDC and UDC, this factor is about 8 to 20. Northfield et al. [20], for example, found a daily bile acid secretion of 450 μmol/kg day in subjects ingesting a dose of about 50 μmol/kg day of CDC.

In the distal small intestine, the normally sterile small intestinal content begins to develop an appreciable bacterial flora, and some of these bacteria possess deconjugating activity [21]. Some of the CDC and UDC conjugates are deconjugated, so that absorption also involves the absorption of unconjugated species. The unconjugated bile acids, however, are absorbed passively as well as actively.

The small fraction of CDC and UDC conjugates not absorbed passes into the bacteria-rich cecum, where complete deconjugation occurs. In addition, there is 7-dehydroxylation which converts CDC and UDC to lithocholate (LC), which, at least in some species, is a potent hepatotoxin [22]. Evidence suggests that about 20% of the LC formed in the colon is absorbed [23]; this passes to the liver, where it is not only amidated with glycine or taurine, but is sulfated at the 3 position [12]. The sulfated amidates are secreted into bile and, in contrast to the nonsulfated amidates (which are the predominant species in bile), are not appreciably reabsorbed from the small intestine [24]. As a result, LC and its conjugates do not accumulate in the enterohepatic circulation in man.

The formation of bacterial metabolites of CDC and UDC would not appear particularly important, but in species, such as the rabbit and rhesus monkey, that cannot sulfate LC in the liver, it is secreted into bile as its amidates; and these are reabsorbed from the intestine, resulting in accumulation in the enterohepatic circulation causing severe hepatotoxicity (reviewed in Ref. [25]). The hepatotoxicity, which consists of portal tract inflammation, bile duct proliferation, and fibrosis, is the result of the defective detoxification of LC, a bacterial metabolite of CDC and UDC. It does not occur in species such as man which sulfate LC efficiently. Thus, for enterohepatic drugs, toxicity studies must consider not only the toxicity of the administered compound and its tissue biotransformation products, but also the toxicity of any absorbed bacterial biotransformation products, as well as their respective tissue biotransformation products.

In man, CDC and UDC are excreted solely in feces after extensive bacterial biotransformation [3]. There is no appreciable renal elimination, since CDC and UDC and their amidates have low levels in systemic plasma (because of efficient hepatic uptake), do not undergo appreciable glomerular filtration (because of binding to albumin), and even if filtered, would be likely to be reabsorbed in the renal tubules. Thus, a third difference between enterohepatic drugs and conventional drugs is tissue distribution and mode of excretion.

STRUCTURAL REQUIREMENTS FOR ENTEROHEPATIC DRUGS

For drugs to be enterohepatic drugs, there must be efficient transport by the hepatocytes from sinusoidal blood into bile and by the intestine from intestinal content into portal blood.

Hepatic transport involves at least two steps: transport from sinusoid across the sinusoidal membrane and transport from the cell across the canalicular membrane. The hepatic uptake step does not appear to have great specificity since a variety of bile acids and polar drugs are transported into the liver [26]. With bile acids, both neutral and anionic bile acids are taken up by the hepatocyte [27].

The canalicular transport step may have a different structural specificity. Recent studies with bile acids having side chains with differing charged heads suggest that only bile acids with uni-anionic or di-anionic side chains are well transported by the canalicular transport system [27]. It is certainly clear that cationic compounds can be transported into bile [28], but the transport capacity of the liver appears to be far lower for such compounds than for anionic bile acids.

For efficient transport of bile acids by the active transport system of the distal ileum, the bile acids must have one negative charge on the side chain [29]. (It is well known that there are many other active transport systems in the small intestinal epithelial cells.)

When compounds are secreted into canalicular bile, they may or may not undergo efficient reabsorption in the biliary tree. Evidence of Guzelian and Boyer [30] suggests that the biliary ductules actively absorb glucose, but other active absorption mechanisms have not been identified. If bile acids are conjugated, there is likely to be little ductular reabsorption, at least in the rat. On the other hand, if bile acids are secreted in unconjugated form, then the degree of their absorption should depend on their hydrophobicity, and their charge, which is determined by their pK_a in relation to biliary pH. Our laboratory has recently developed fairly convincing evidence that unconjugated dihydroxy bile acids will undergo some ductular reabsorption [31,32]. If unconjugated bile acids are absorbed from the biliary ductules, they return to the liver via the periductular capillary plexus and are once again transported into the hepatocytes. They are once again secreted into the canaliculus, and once again induce an osmotic secretion of bile. Thus each molecule reaching the liver in portal blood may be secreted several times into the bile, the end result being a remarkable choleresis, if bile flow is related to the amount of bile acids recovered in bile. We term this intra-hepatic cycling the "cholehepatic shunt" pathway, and we believe that it is the mechanism by which weak acids induce choleresis. The implications of ductular reabsorption on drug pharmacology are considerable, in our judgement.

The fate of conjugates that reach the small intestine depends on their susceptibility to hydrolysis by pancreatic, brush border, or bacterial enzymes in relation to intestinal transit. The glycine and taurine amidates of bile acids are not hydrolyzed by pancreatic or tissue enzymes, but amidates with other neutral and with basic amino acids are cleaved by pancreatic carboxypeptidases [15]. Sulfates and glucuronides of bile acids (and of drugs) are believed to resist intraluminal and brush border enzymes. Probably, the sulfate, glucuronate, and amino acid moieties of most bile acids and drugs are liberated in the colon. However, little absorption is likely to take place because of the low surface/volume ratio of the colon, as well as binding of the liberated aglycone to bacteria.

COMPLEMENTARITY IN THE TRANSPORT SPECIFICITY OF THE HEPATIC AND ILEAL TRANSPORT SYSTEMS

Smith, in his monograph, has catalogued the array of compounds that are secreted into bile and developed some empirical structure—secretion relationships [33]. It is evident that a great variety of amphipathic substances are secreted into bile, yet of these, only the bile acid amidates are actively reabsorbed from the intestine. Thus, hepatic transport results in efficient elimination of compounds that are not reabsorbed from the intestine.

Modeling the enterohepatic circulation

In collaboration with Molino, Milanese, and Belforte of the Politecnico and the University of Turin, we have constructed a pharmacokinetic model which fully describes the enterohepatic cycling and tissue distribution of cholic acid, a major bile acid in man [34]. The model is a general model, but has some unusual aspects, in that the transfer coefficients have functional significance, that is, they denote transport, flow, or biotransformation. The compartments have an anatomical basis, indicating areas of concentration, which in fact, are tissue spaces. The model also includes time-dependent features so that intestinal motility and gallbladder contraction may be changed as desired, for example, when a meal is ingested. We believe that this model can be used for other enterohepatic drugs since only a few of the transfer coefficients are specific for bile acids. Coefficients that describe general human physiology such as systemic or hepatic circulation, flow of intestinal content, gallbladder contraction, etc. should apply to any enterohepatic drug.

Bile acids that are not enterohepatic drugs

The preceding discussion suggests that a bile acid which has biotransformed into a metabolite that was not well transported by the liver or the intestine would not accumulate in the enterohepatic circulation. Two examples of bile acids that are not enterohepatic drugs have recently been discovered.

The first, hyodeoxycholic acid, is a naturally occurring dihydroxy bile acid. In 1971, Thistle and Schoenfield reported that when hyodeoxycholic acid was administered for four months to women with gallstones, it was not detected in biliary bile acids [35]. Under the same conditions, cholic acid administration caused enrichment [36] in both cholate and deoxycholate, its bacterial metabolic product, in biliary bile acids; the effect of CDC on biliary bile acids has already been noted.

The explanation for the lack of enrichment of hyodeoxycholic acid in biliary bile acids was not known. A few years ago, Sacquet et al. [37] showed that hyodeoxycholic acid is glucuronidated in man, and that a major fraction of the glucuronide is excreted in urine.

More recently, in collaboration with Erwin Mosbach, Bert Cohen, Charles McSherry, and Marcus Rothschild, we have found that nor-UDC, when administered to rabbits, does not accumulate in biliary bile acids [38]. In subsequent studies, we found the UDC was biotransformed in the liver exclusively to the 3-glucuronide, which presumably is not reabsorbed from the small intestine [38]. This work suggests that the administration of UDC—glycine, the glycine conjugate of UDC, should accumulate in the enterohepatic circulation, provided the intact conjugate is well absorbed by the terminal ileum.

REPRISE

This work thus indicates that for bile acids or other compounds to circulate enterohepatically and accumulate in the enterohepatic circulation, they must be well transported by the liver and intestine. Glucuronidation and sulfation, the common biotransformation pathways of most drugs, prevent reabsorption in the biliary ductules, which results in the compound being transported to the intestine; however, these conjugates are not subsequently reabsorbed from the small intestine (Fig. 1). Hepatic transport is more versatile than ileal transport,

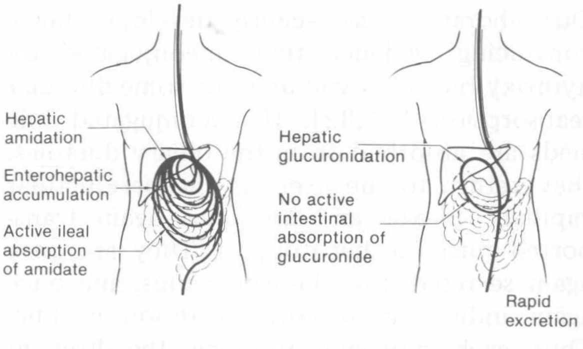
Hepatic amidation
Enterohepatic accumulation
Active ileal absorption of amidate
Hepatic glucuronidation
No active intestinal absorption of glucuronide
Rapid excretion

Fig. 1. Schematic depiction of metabolism of enterohepatic drug (left) and conventional drug that is eliminated solely via bile (right). The natural bile acids are enterohepatic drugs, as they are amidated in the liver and the amidates are actively reabsorbed from the ileum. The C_{23} nor bile acids are glucuronidated and the glucuronide is not reabsorbed actively from the small intestine. Consequently, they do not accumulate in the enterohepatic circulation.

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