Chapter 63

The Enterohepatic Circulation

G. L. Plaa

I. Introduction

Substances are said to undergo an enterohepatic circulation (EHC) when they are excreted into the bile, pass into the lumen of the intestine, are reabsorbed and then return to the liver via the circulation. Many endogenous and exogenous substances can undergo an EHC. Among the endogenous substances are the bile salts, the biliary lipids and biliary phospholipids; the degree of reabsorbability varies considerably for each of these types of substances. Other endogenous substances include estrone and estriol (Sandberg et al., 1967), folic acid (Baker et al., 1965; Herbert, 1965), vitamin B12 (Grasbeck et al., 1958), and urobilinogen (Lester et al., 1965). Ibrahim and Watson (1968) demonstrated that an EHC exists for protoporphyrin in man. The oral administration of cholestyramine, an anionic exchange resin, improves the clinical condition of patients suffering from porphyria cutanea tarda (Stathers, 1966) or from erythropoietic protoporphyria (Lischner, 1966) apparently by interrupting the EHC for the porphyrins.

Biliary secretion is an important excretory pathway for a great variety of drugs and chemicals or their metabolites (Stowe and Plaa, 1968; Plaa, 1971; Smith, 1971). Becker and co-workers (Gibson and Becker, 1967; Becker et al., 1968) reported that the lethality of ouabain, promazine, perphenazine and meprobamate is markedly increased in mice with ligated bile ducts. Klaassen (1973) has shown that the toxicity of colchicine, diethylstilbestrol, digoxin, ouabain, indocyanine green, rifampin and iopanoic acid was greater in mice and rats with ligated bile ducts than in normal animals.

The studies in which lethality was measured by no means established that merely the reduction in biliary excretion led to the enhanced lethality. The effect of accumulated bile salts during cholestasis on processes of drug inactivation was not evaluated. Nor were possible changes in distribution assessed. However, the data strongly suggest that alterations in biliary excretion are involved.

Several drugs exhibit an EHC. Potentially, all substances that are excreted by the biliary route could undergo such a circulation if reabsorption occurs in the intestine. Keberle et al. (1962) demonstrated that in the rat the presence of an EHC can have a marked effect on the persistence of glutethimide metabolites in the body. The glucuronide conjugate of chloramphenicol is excreted in the bile of rats, converted to arylamine and reabsorbed in this form; this arylamine can exert a toxic action on the thyroid (Thompson et al., 1954). Williams et al. (1965) point out the possibility that intestinal carcinogenic activity of aromatic amines in rats may be caused by o-hydroxyamines which are formed in the liver and excreted into the bile as glucuronides and finally degraded in the intestine to the free hydroxyamines, which are carcinogenic. Unfortunately, no generalizations can be made about the relative importance of the EHC in the overall response of the animal to a particular chemical agent since it depends not only upon the particular

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compound and the pharmacologic activity of its metabolites, but also the animal species being tested.

II. Methods for Studying the Enterohepatic Circulation

One method of studying the EHC is to compare the biologic half-lives of a substance and its metabolites in normal animals with that in animals with a bile fistula (Keberle et al., 1962; Charytan, 1970). Another approach is to compare the amounts of substances excreted in the bile of animals with bile fistulas to the amounts excreted in the feces and urine of normal animals (Woods, 1954; Dobbs and Hall, 1969; Caldwell et al., 1971). Others have used “linked animals”; in this preparation, the bile cannula from one animal is inserted into the duodenum of a second animal; the substance is given to the first animal and biliary excretion of the substance in the second animal is monitored (Hucker et al., 1966; Ladomery et al., 1967).

Recently, two methods have been described in which repeated bile collections can be made from the uninterrupted EHC in chronic preparations. Den-Besten (1971) has described a method used in dogs in which a duodenal pouch containing the intact sphincter of Oddi has been prepared. This pouch drains into the duodenum through a Gregory cannula. The duodenal section has been surgically prepared to contain a Thomas cannula through which the bile samples can be collected. During the times the bile is not collected, the cannula can be arranged to permit an uninterrupted EHC.

The second method has been devised for the collection of bile in rhesus monkeys (Dowling et al., 1968). In this preparation, the extrahepatic biliary pathway is brought to the exterior; the bile flows through a stream-splitter connected to an electronic circuit and is collected into reservoirs. One reservoir is also connected to an electronic leveling system that controls a pump draining this reservoir and reinfuses the bile into the duodenum of the animal. When bile is needed for analysis, the stream-splitter is put in the diverted position and bile is collected directly rather than being reinfused. This particular technique obviously requires that the animal be restrained during the entire experiment.

To study the absorption of metabolic products, the metabolites can be infused into the duodenum and their subsequent biliary excretion monitored using an animal with a cannulated bile duct (Fischer et al., 1966; Eriksson, 1971). The role of intestinal microorganisms in the hydrolysis of conjugates and the subsequent reabsorption of deconjugated products has been demonstrated by comparing responses obtained in animals whose intestinal lumen has been sterilized to those obtained in nonsterilized animals (Dobbs et al., 1970; Clark et al., 1969).

III. The Enterohepatic Circulation of Bile Salts

A number of reviews deal with this subject (Hofmann, 1965; Lack and Weiner, 1967; Hofmann and Small, 1967; Dietschy, 1968; Dowling, 1972). Therefore, only highlights of this information will be covered in this chapter.

The body normally conserves bile acids by reabsorption from the intestine. In man, a 3 to 5 g bile salt pool circulates through the EHC about 6 to 10 times per day (Borgstrom et al., 1957; Lindstedt, 1957). Between 20 to 25% of the total bile salt pool escapes reabsorption and is excreted in the feces (Bergstrom, 1962). In the steady state, synthesis of bile salts must equal loss and this loss is due primarily to fecal excretion. Therefore, an enhanced fecal excretion of bile salts can have a marked effect on net synthesis of these substances. Norman and Sjovall