Absorption of some organic compounds from the biliary system of the rat

The bile is an important pathway of excretion for many drugs and their metabolites (Smith, 1966). However, it is not clear what factors determine their elimination in the bile rather than in the urine. It has been suggested that bile, during its passage down the biliary tract, may be altered in composition by reabsorption and secretion of water and solutes (Andrews, 1955; Brauer, 1959; Sperber, 1959; Goldfarb, Singer & Popper, 1963; Wheeler, 1968). If reabsorption occurs then it could have a decisive bearing on the extent to which a drug appears in bile. It might be postulated, therefore, that substances poorly eliminated in the bile are those that after being cleared by the liver into the primary bile are then reabsorbed as the bile passes along the biliary tract. Conversely, compounds found in large amounts in bile may be relatively poorly reabsorbed from the primary bile.

We have therefore investigated the absorption from the biliary tree of the rat of two groups of organic compounds given by retrograde biliary infusion and selected on the basis of either low or high biliary excretion in this species. Firstly, we examined hippuric acid, 3-aminophenylsulphate, 2-aminophenylglucuronide and succinylsulphanilamide, which are relatively poorly excreted by the rat in the bile, and then stilboestrol glucuronide, phenolphthalein disulphate, phenolphthalein glucuronide and indocyanine green, which are extensively excreted in the bile.

The compounds used were either available in this laboratory or were purchased commercially. They were estimated in bile and urine by procedures previously described thus, [^{14}C]hippuric acid, 3-aminophenylsulphate and 2-aminophenylglucuronide according to Abou-El-Makarem, Millburn & others (1967); succinylsulphanilamide, Millburn, Smith & Williams (1967b), [^{14}C]stilboestrol glucuronide, phenolphthalein disulphate and phenolphthalein glucuronide, Millburn, Smith & Williams (1967a) and indocyanine green, Levine, Millburn & others (1970). Biliary fistulae were established in female Wistar albino rats (210–250 g wt) as described by Abou-El-Makarem & others (1967). In some experiments the renal pedicles were ligated to prevent urinary excretion. The method of retrograde biliary infusion is described in Table 1.

The extent of biliary excretion of the two groups of compounds following their intravenous administration to rats with ligated renal pedicles is shown in Table 1. Those compounds in Group I are poorly excreted in bile in comparison with those of Group II. Thus, the biliary excretion of the compounds in the first group accounted for about 10% or less of the dose in 3 h. By contrast, more than 75% of the dose of the four compounds in Group II appeared in the bile within 3 h. Paper chromatography of bile samples (for details of solvent systems and detection methods see references to analytical methods above) indicated that all the compounds appeared in bile essentially unchanged.

Table 1 also showed that when the four compounds in Group I are given by retrograde biliary infusion less than 20% of the dose is recovered in the bile in 30 min, in fact the values for 3-aminophenylsulphate and succinylsulphanilamide are less than 10%. These compounds appear to be rapidly absorbed from the biliary tract and excreted by the kidneys since following the retrograde biliary infusion of [^{14}C]hippuric acid and succinylsulphanilamide, 47 and 59% of the dose respectively is found in the urine removed from the bladder 30 min after finishing the infusion. With hippuric acid 70% of the dose is recovered in the urine collected after 1 h.

With compounds in Group II relatively large amounts (50–80% of dose) could be recovered in the bile within 30 min of stopping the retrograde biliary infusion (Table 1). These compounds, compared to those of Group I, appear to be relatively poorly

Table 1. *Recovery of some organic compounds from the bile of rats after either intravenous administration or retrograde biliary infusion.* The compounds (20 μmol/kg) were administered to biliary-cannulated female rats either (*a*) intravenously, in which case the renal pedicles were ligated or (*b*) by retrograde biliary infusion using an "Agla" micrometer syringe joined to a short polythene cannula inserted into the common bile duct. In the latter case the dose (0·1 ml) was washed in with 0·1 ml of an NaCl solution (0·9% w/v), the syringe being held in place for 1 min after the injection of the saline before bile collection was commenced. In some experiments the bladder urine was totally removed at 0·5 or 1 h after the infusion. Results are the means of three or more animals; ranges are given in parentheses.

Compound	Molecular weight	(a) Intravenous administration % dose excreted in bile in 1 h	3 h	(b) Retrograde biliary infusion % dose recovered in bile at 5 min	15 min	30 min
Group I						
[^{14}C]Hippuric acid	179	—	5·4 (4·6–5·8)	12 (11–13)	14 (12–15)	14 (13–14)
3-Aminophenylsulphate	189	—	1·0 (0·5–1·5)	5·5 (2·6–10)	6·7 (2·7–12)	7·0 (3·0–14)
Succinylsulphanilamide	272	—	10 (5·5–17)	7·8 (3·4–15)	9·0 (4·2–17)	9·8 (4·8–18)
2-Aminophenylglucoronide	285	—	4·0 (3·5–4·8)	12 (10–14)	13 (11–16)	14 (12–17)
Group II						
[^{14}C]Stilboestrol glucuronide	445	71 (61–80)	92 (89–94)	43 (35–50)	68 (59–76)	78 (66–93)
Phenolphthalein disulphate	479	60 (55–66)	76 (66–79)	31 (16–35)	47 (33–67)	65 (50–87)
Phenolphthalein glucuronide	495	65 (57–72)	96 (87–98)	29 (20–23)	41 (37–60)	65 (56–81)
Indocyanine green	752*	58 (53–68)	78 (68–86)	39 (31–47)	44 (39–53)	53 (39–73)

* Value for anion.

absorbed from the biliary tract for the following reasons. Firstly, after retrograde biliary infusion, only small amounts (less than 2% of dose) of stilboestrol glucuronide, phenolphthalein disulphate and phenolphthalein glucuronide were found in the urine collected at 60 min. Secondly, relatively large amounts (30–40% of dose) can be recovered in the bile within 5 min after stopping the infusion. However, it appears that some absorption from the biliary system followed by excretion of the Group II compounds may occur since the amounts recovered in bile following retrograde biliary infusion slowly increase with time, whereas for those compounds in Group I the amounts found in bile were approximately the same for bile samples collected at 5, 15 and 30 min.

Consideration of the two groups of compounds in terms of the criteria previously suggested for extensive biliary excretion of foreign compounds to occur in the rat points to molecular size and polarity as being important factors in determining the extent of biliary excretion (Millburn & others, 1967a). Large organic anions (molecular weight > 300) are usually extensively excreted in the bile of the rat whereas smaller ones (molecular weight < 300) are not and are eliminated mainly in the urine. The compounds in Group II occur as anions at physiological pH and have molecular weights between 445 and 752 and are extensively excreted in bile. It may be therefore of significance, in relation to their extensive biliary excretion, that these compounds of relatively large molecular weight are comparatively poorly absorbed from the biliary tract. On the other hand all the compounds of Group I exist as polar anions at body pH and have molecular weights less than 300. These relatively small anions are poorly excreted in the bile of the rat and they appear to be extensively absorbed from the biliary tract.

These preliminary observations suggest that the extensive biliary excretion of compounds of relatively high molecular weight may be a reflection of their poor reabsorption from the primary bile. Conversely, organic anions of lower molecular weight can be readily absorbed from the biliary system of the rat and their low

biliary excretion may be a consequence of their extensive absorption from primary bile.

We thank Professor R. T. Williams for his interest in this work, which was in part supported by a grant from May and Baker Ltd. A.G.C. is grateful to the New Zealand University Grants Committee for financial support and to the Wellcome Foundation for a Travel Grant.

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December 3, 1970

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