Absorption of iodipamide from the biliary system of the rabbit

In a recent letter, Clark, Hirom & others (1971) presented data suggesting that high molecular weight organic molecules (mol wt > 300) are poorly absorbed from the bile duct following retrograde administration into the common duct of the rat. This conclusion was based on the relatively low amounts (< 2% of dose), of such drugs recovered from the urine, as well as the fact that relatively large amounts of these high molecular weight molecules can be recovered in the bile within 5 min after stopping the retrograde infusion (30–40% of dose for compounds with mol wt > 300; 5–12% of dose when mol wt < 300). Although no blood measurements were made, Clark & others (1971) suggest that some absorption of these high molecular weight molecules may occur since the amounts recovered from the bile after retrograde biliary infusion slowly increase with time.

Stimulated by the report of Clark & others, we have examined the absorption of the radio-opaque agent megluamine iodipamide (Cholografin mol wt 1138; and pK 3·5) following retrograde biliary administration. We used a rapid and accurate assay for iodine in biologic fluids and tissues (Moss, Nelson & Kaufman, 1972). The influence of the hydrostatic bile pressure head on the absorption of the drug from the bile duct was also observed.

Six male white New Zealand rabbits (~ 4 kg) were anaesthetized via an ear vein with ketamine HCl (Vetalar) and the common bile duct cannulated. The cystic duct was not tied. A supra-pubic urinary bladder catheter was placed.

In 5 rabbits the common duct pressure was measured after cannulation by determining the vertical pressure head of bile observed in the cannula above the estimated height of the porta hepatis. Using PE 90 tubing, an average opening pressure of 12·6 ± 1·6 cm was observed in the 5 rabbits. After this measurement, 1 to 2·5 ml of bile was removed from the ductal system by aspiration. The cannula was then connected to an open funnel syringe and 1 ml (0·25 ml/kg or 0·13 g/kg) of iodipamide was allowed to drain by gravity (5–10 min) into the bile duct at a pressure 1 cm above opening pressure. The dose was followed by 0·5 to 1 ml of bile given by gravity drainage. The bile colour showed above the drug dose column in the cannula so that relatively complete dose administration could be assured. The common duct cannula was then transected at the perfusion pressure level and was allowed to vent into an open syringe reservoir. In the sixth rabbit, 1 ml of iodipamide was diluted with 9 ml of saline and the total 10 ml dose was injected into the common bile duct by syringe. No pressure measurements could be made with this system.

Timed blood collections were obtained via an ear artery at 0 time and at 30 min intervals after the completion of gravity flow for a total of 4 h in 3 rabbits, including the animal receiving the 10 ml injection. One rabbit receiving a low pressure infusion died after 1 h. In 2 rabbits, blood was obtained after 0, 1, 3, 5, 10, 15, 20, 25 and 30 min, and at 30 min intervals thereafter for 4 h. Urine was collected from all rabbits at 0 time and at 30 min intervals for 4 h. Bile was collected at 0 time and throughout the experiment whenever at least 1 ml had accumulated in the reservoir which was maintained at a height 1 cm above opening pressure.

In the 5 rabbits that received the low pressure retrograde gravity perfusion, bile flow averaged 1·6 ± 0·4 ml/h. Two rabbits received a constant intravenous infusion via an ear vein of 0·5% sodium taurocholate at 5 ml/h with no significant change in bile flow. That these bile flow rates are much lower than those stated by Scratcherd (1963) is because we left the gallbladder untouched, and the flow was measured against a vertical fluid pressure rather than by siphon (Vanlerenberghe, Guislain & Delabre, 1968).

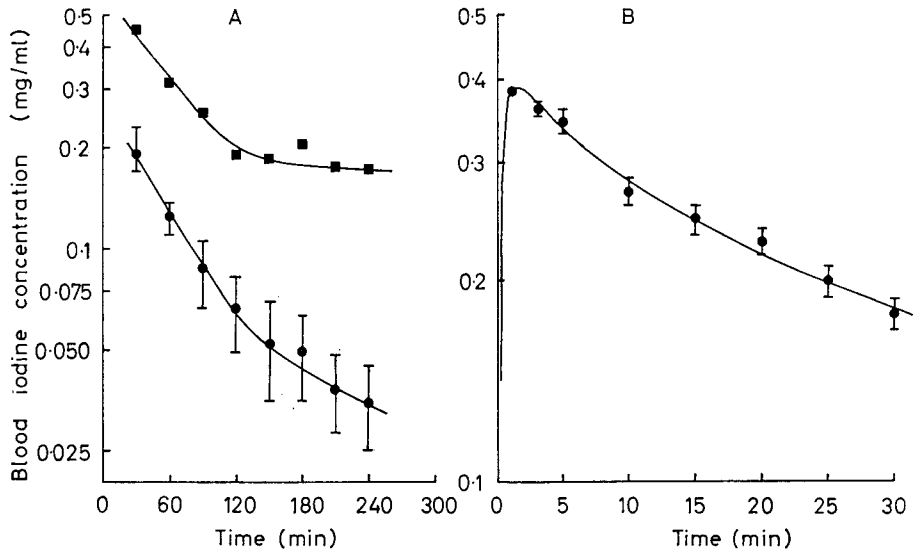

FIG. 1. A. Semilogarithmic plots of blood iodine curves in one animal with high pressure retrograde infusion (■) compared with five animals with low pressure retrograde infusion (●). Bars indicate standard deviation. All rabbits received a 1 ml dose of iodipamide.
B. Early blood curve in two rabbits with low pressure infusion. Bars indicate standard deviation.

All blood, urine, and bile samples (1 ml samples) were analysed for iodine by K-shell activation analysis as described by Moss & others (1972) and the concentrations expressed as mg of iodine per ml. Percent of dose excreted in bile and urine per collection period was determined by dividing mg of iodine in the bile and urine by mg of iodine in the administered iodipamide. Previous work has shown that iodipamide is excreted unchanged in both bile and urine (Billing, Maggiore & Cartter, 1963).

Fig. 1A compares the average blood iodine concentration curve for the 5 rabbits with low pressure retrograde dose administration with the concentration curve seen for the rabbit receiving the high pressure infusion of an identical dose of iodipamide. Greater hepatic absorption or breakthrough is seen at the higher pressure. Fig. 1B illustrates the early, zero–30 min average blood iodine curve seen in 2 rabbits following retrograde injection of 1 ml of iodipamide at low pressure. The maximum blood level was found within 1 min of low pressure retrograde infusion, indicating that absorption of iodipamide from the biliary tract occurs relatively rapidly under the experimental conditions employed.

Table 1 shows the percentage of total administered dose recovered in 4 h in the 4

Table 1. *Percentage of total dose recovered in both bile and urine and the percentage of total dose recovered only from the urine after retrograde biliary administration of iodipamide and subsequent maintenance of an hydrostatic bile pressure head identical to the measured opening pressure in the common bile duct in 4 rabbits for 4 h.*

Rabbit	% Total dose recovered in both bile and urine	% Recovered in urine
1	67%	64
2	72%	48
3	44%	33
4	56%	42
Mean ± s.d.	60 ± 12	47 ± 13

rabbits receiving a low dose infusion, and the percent of dose recovered from the urine. Bile iodine recovery represents the difference in each individual study.

Previous studies of similar doses of iodipamide in rabbits showed a 47% biliary excretion and 22–34% urinary excretion in 2 h when bile was collected by gravity from the common bile duct (Novek, 1959). We found about 47% urinary excretion after 4 h, with an average of 35% after 2 h (range 25–47%). The lower biliary excretion in our work is probably related to the fact that biliary excretion occurred at a constant secretory back-pressure, usually approximately 14 cm of bile in a PE 90 cannula, and that the gallbladder was left intact. Preliminary results after iodipamide was given intravenously to rabbits with the cystic duct tied off where bile is collected by siphon (no hydrostatic back pressure) show approximately 30% of the dose excreted in the urine and 40% in the bile at the end of 4 h. Bile flow under these conditions increased to 7–10 ml/h.

This study also points out the importance of measuring blood concentrations of a drug when evaluating the possibility of reabsorption from the bile duct. There is no *a priori* reason to expect that any molecule reabsorbed into the blood stream from the biliary tract would not be partitioned between bile and urine in the same way as intravenously administered agents unless a different back-pressure toward biliary excretion was maintained in the two studies. Thus, it is possible for a molecule to reach high plasma concentrations during retrograde infusion (see Fig. 1A) when a back pressure is exerted by the infusion, yet to exhibit rapid biliary clearance when the back pressure is removed following the infusion.

After retrograde common duct infusion of iodipamide into the rabbit at low pressures, blood, urine, and bile concentrations of the drug show rapid absorption or leakage from the hepatic ducts into the systematic circulation. When an hydrostatic bile pressure head, identical to the measured opening pressure in the common bile duct is maintained throughout, 1/3 to 2/3 of the dose of iodipamide can be recovered in the urine. This reabsorption and urinary excretion occurs despite the high molecular weight of iodipamide and is similar to the excretion of iodipamide after intravenous administration of a similar dose (Novek, 1959) (the slightly higher urinary excretion in our rabbits is probable due to the presence of the hydrostatic bile pressure head).

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