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Lymphatic uptake of water-soluble drugs after rectal administration

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Certain drugs appear to avoid first-pass liver metabolism following rectal administration (de Boer & Breimer 1980). This indicates that the hepatic portal system is not the only pathway by which rectally absorbed drugs enter the general circulation. Historically, first-pass avoidance after rectal administration was rationalized in terms of a partial direct shunt provided by certain haemorrhoidal veins connecting the rectal vasculature to the inferior vena cava. This study demonstrates the influence of lymphatic cannulation and diversion on bioavailability after rectal drug administration. A significant fraction of highly polar test compounds is shown to be absorbed into the lymphatic system after rectal administration in the presence of salicylate-type absorption adjuvants.

Methods

Male Sprague-Dawley rats (200–225 g) were anaesthetized with pentobarbitone 50 mg kg^{-1} i.p. Rectally administered drugs and absorption adjuvants were delivered as a 0·2 ml aqueous microenema containing 1/15 M phosphate at pH 7·4 (pH 5·0 for insulin). The microenema was restricted to the rectal compartment by ligation at both ends. Parenteral administration was with the same drug - buffer solutions without the addition of absorption adjuvant. Lymph was collected from the thoracic duct according to the method of Bollman et al (1948). Blood samples were withdrawn from the external jugular vein at predetermined sampling times after dosing. Lymph fractions and plasma samples were deproteinized with acetonitrile before the assay for drug concentration. Phenol red concentration was determined at 540 nm after adding 1·0 M NaOH to the samples. Insulin was assayed using an immunospecific enzyme assay kit supplied by Toyo Jozo, Ltd, Japan. Cefoxitin, theophylline, sodium salicylate and sodium 5-methoxysalicylate concentrations were determined using high pressure liquid chromatography techniques at 254 nm.

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Results and discussion

Four compounds were chosen as model drugs: phenol red, insulin, sodium cefoxitin and theophylline. Under ordinary conditions, these compounds are poorly absorbed from the rectal compartment. However, Nishihata and coworkers (1980, 1981a,b) have demonstrated improved rectal absorption of several polar drug species, including theophylline and insulin, by co-administration of sodium salicylate or one of its analogues. Although improved rectal absorption is not the issue in this report, it is necessary to show a certain degree of rectal absorption in test animals in order to evaluate the impact of lymphatic transport. Data

Table 1. Integrated drug profiles (AUC) after parenteral and rectal dosing in the rat: influence of lymphatic transport.

	Parenteral administration			Rectal administration				
Compound	Dose	Plasma [AUC] mg min^{-1} ml^{-1} mean (s.d.) (n)	Drug recovered from thoracic dose[c] mean	Dose	Adjuvant[a]	Plasma [AUC] mg min^{-1} ml^{-1} normal thoracic duct mean ± (s.d.) (n)	Plasma [AUC] mg min^{-1} ml^{-1} cannulated thoracic duct mean ± (s.d.) (n)	Drug recovered from thoracic duct[c] mean
Sodium Phenol red	2·0 mg rat^{-1} i.v.	4·69 (0·28) (3)	24 µg	10 mg rat^{-1}	A	13·3 (1·8) (3)	2·92 (0·83) (10)	300 µg
Insulin	0·8 iu rat^{-1} i.m.	13·4 (1·86[b]) (6)	3·4 miu	2 iu rat^{-1}	A	6·43 (1·01[b]) (6)	2·64 (0·42[b]) (8)	24 ml
Sodium cefoxitin	2·5 mg rat^{-1} i.v.	1·09 (0·18) (3)	8·5 µg	7·5 mg rat^{-1}	A B	1·62 (0·23) (3) 0·74 (0·13) (3)	0·20 (0·04) (12) 0·068 (0·026) (6)	195 µg 75 µg
Theophylline	6·0 mg rat^{-1} i.v.	6·66 (0·33) (3)	61 µg	15 mg rat^{-1}	A	10·9 (0·8) (3)	3·02 (0·60) (8)	1300 µg
Sodium 5-methoxy-salicylate	6·0 mg rat^{-1} i.v.	6·06 (0·28) (3)	79 µg	15 mg rat^{-1}	none	11·3 (1·0) (3)	4·38 (0·46) (8)	1645 µg
Sodium salicylate	6·0 mg rat^{-1} i.v.	6·97 (0·33) (3)	not determined	15 mg rat^{-1}	none	12·1 (2·0) (3)	5·98 (0·39) (8)	not determined

[a] A = sodium 5-methoxysalicylate 15 mg rat^{-1}, B = sodium salicylate 15 mg rat^{-1}.
[b] AUC for insulin expressed in (m i.u. min)/ml. $[AUC]_0^{20}$ not extrapolated to infinity.
[c] Lymph collected for 120 min.

presented in Table 1, both the AUC after parenteral injection and the AUC after rectal absorption, indicate appreciable rectal uptake of the model drugs in the presence of an absorption adjuvant.

Parenteral injection of the four model compounds produced similar concentration profiles in both lymph and plasma (Fig. 1). These control injections demonstrate uniform drug distribution throughout the haemolymphatic circulation.

In order to assess the relative importance of lymphatic drug uptake from the rectal region, lymphatic drainage was diverted surgically at the level of the abdominal thoracic duct. This vessel carries the lymph produced posterior to the diaphragm back to the general circulation. Surgical intervention allows direct examination of the transport contribution of the lymphatic system. Significant lymphatic transport should be reflected by high concentrations of drug in the collected lymph with concurrent reduced plasma drug levels relative to normal animals receiving the same rectal dose.

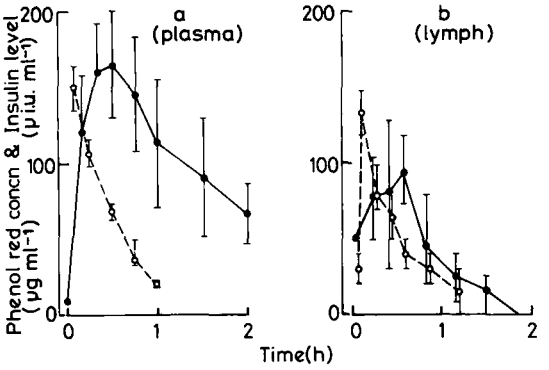

FIG. 1. Concentration in plasma (a) and lymph (b) following i.v. administration of phenol red 2 mg rat^{-1} (○), intramuscular administration of insulin 0·8 iu rat^{-1} (●). Error bars = s.d., n = 3.

As shown in Fig. 2a, the plasma drug levels of rectally administered phenol red after surgical interruption of lymphatic drainage was much lower than plasma drug levels before thoracic duct cannulation. Fig. 2b shows a dramatic increase in lymphatic phenol red concentrations after rectal administration, relative to phenol red levels after the i.v. injection. In this experimental model, the lymphatic cannulation reduced the rectal bioavailability of phenol red by about 80%, as reflected in the reduction in AUC, (area under plasma concentration curve).

Fig. 3 presents similar data for enhanced rectal absorption of insulin. Comparison of insulin plasma profiles, with and without an intact thoracic duct, suggests that a major fraction of rectally absorbed insulin reaches the general circulation via the lymphatic pathway.

The remaining model drugs, cefoxitin and theophylline, also appear to be substantially taken up into the lymphatic system. Table 1 lists the AUC both with and without an intact thoracic duct. With rectal cefoxitin, a reduction of nearly 90% was observed in plasma AUC as a result of thoracic duct cannulation. Similarly, theophylline results indicate that 75% of the absorbed drug (from control experiments) failed to reach the general circulation after interruption of the thoracic duct.

The absorption adjuvants used to facilitate rectal uptake of the model compounds are, in most cases,

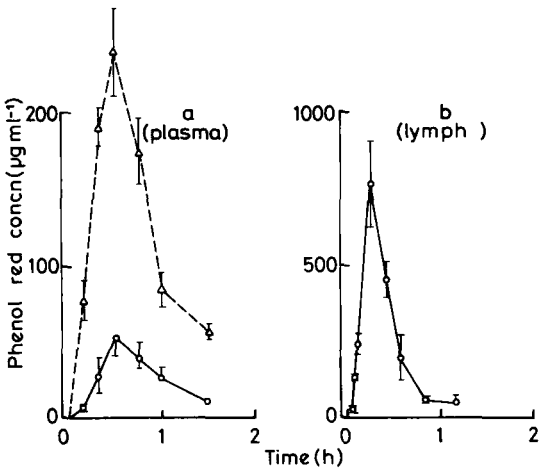

FIG. 2. Concentration of phenol red in the plasma (a) and lymph (b) following rectal administration of 10 mg/body of phenol red in the presence of 5-methoxysalicylate (△) and intact thoracic duct, and rectal administration of 10 mg body phenol red in the presence of 5-methoxysalicylate with the thoracic duct cannulated for collection of lymph (○). Error bars = s.d., n = 3 (△), n = 10 (○).

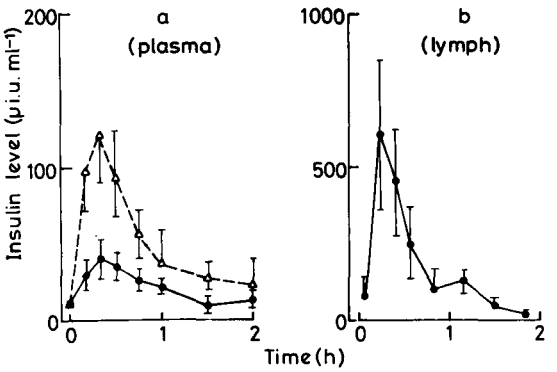

FIG. 3. Concentration of insulin in the plasma (a) and lymph (b) of rats following rectal administration of 2·0 iu/body insulin in the presence of 10 mg/body 5-methoxysalicylate (△) and intact thoracic duct, and rectal administration of 2·0 iu/body insulin in the presence of 10 mg/body 5-methoxysalicylate with the thoracic duct cannulated for collection of lymph (○). Error bars = s.d., n = 6 (△), n = 8 (○).

readily absorbed from the rectal compartent. Surgical disruption of the lymphatic route had a lesser impact on the adjuvant plasma profiles compared with the model drug compounds. Plasma profiles indicate an approximate 60% reduction in AUC of sodium 5-methoxysalicylate and sodium salicylate as a result of the thoracic duct cannulation.

For each compound studied, the total amount recovered from the thoracic duct after rectal administration did not totally account for the reduction in plasma AUC. This apparent discrepancy in the data has been attributed to technical problems with the surgical procedure. Some of the collected lymph was invariably lost through leakage around the catheter insertion site. This leakage was often compounded by back pressure in the catheter from lymphatic coagulation.

These experiments have shown that the gut-associated lymphatic system plays an important role in the transport of water-soluble compounds after rectal absorption. Drug access to this transport mode could help explain the reported instances of apparent direct systemic drug delivery from the rectal compartment. In this study, the rectal bioavailability of one model drug, cefoxitin, was reduced more than 90% by interrupting lymphatic return. Chemical modification of drug substances in conjunction with the use of certin absorption adjuvants may offer a means of targeting drug transport after rectal absorption. The application of directed lymphatic transport may not only permit avoidance of first-pass liver exposure but may also allow site-specific delivery of drugs targeted toward gut-associated lymphoid tissue.

REFERENCES

Bollman, J. L., Cain, J. C., Grindley, J. H. (1948) J. Lab. Clin. Med. 33: 1349

de Boer, A. G. Breimer, D. D. (1980) in: Prescott, L. F., Nimmo, W. S.(eds) Drug Absorption Rectal Absorption: portal or systemic? Adis press, Sydney, pp 61–72

Nishihata, T., Rytting, J. H., Higuchi, T. (1980) J. Pharm. Sci. 69: 744–745

Nishihata, T., Rytting, J. H., Higuchi, T. (1981a) Ibid. 70: 71–75

Nishihata, T., Rytting, J. H., Higuchi, T., Caldwell, L. (1981b) J. Pharm. Pharmacol. 33: 334–335

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Effect of methysergide on renal function

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5-Hydroxytryptamine (5-HT) has been implicated as a possible regulator of renal function (Erspamer 1966). While its antidiuretic effect has been demonstrated in rats (Del Grego et al 1956) and dogs (Spinazzola & Sherod 1957) the mechanism by which this antidiuresis occurs remains obscure. The intravenous infusion of 5-HT has been shown to decrease renal cortical blood flow with a subsequent decrease in glomerular filtration rate and urine (Erspamer & Ottolenghi 1953). However, other studies have shown that its infusion can produce an antidiuresis in the absence of significant changes in either renal blood flow or glomerular filtration rate (Little et al 1961). In the latter study the antidiuresis was characterized by a decrease in urine flow rate and sodium excretion. Similar reductions in sodium excretion and urine flow rate have been observed during animal surgery (Maddox et al 1977). It has been proposed that the decreases in sodium excretion and urine flow rate may be due, in part, to the release of neurotransmitters which presumably affect renal function (Maddox et al 1977). Our recent report has shown that methysergide, a 5-HT antagonist, could produce a diuresis in Sprague-Dawley rats receiving large doses of horseradish peroxidase, a protein known to cause vascular leakage and antidiuresis in rats (Chan & Straus 1980). The present study was undertaken to further elucidate the effect of methysergide on renal function.

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Methods

Male Sprague-Dawley rats 180 to 250 g, were maintained on a regular rat pellet diet and tap water, were anaesthetized with 5-ethyl-5-(L-methylpropyl)-2-thiobarbituric acid (Inactin), 100 mg kg^{-1} i.p. They were placed on a thermostatically controlled animal table where their body temperatures were maintained at 37 °C. The surgical procedures were similar to those of preparing the animal for micropuncture described previously (Chan 1976). Briefly, after tracheotomy, the external jugular vein was cannulated for saline infusion and drug administration. The left carotid artery was cannulated for blood pressure recording as well as for blood sampling. The left kidney was exposed laterally and then immobilized in a double-cup (W. Hampel, Frankfurt, Germany). The left renal artery was exposed to allow arterial injection of the drug through a 30 gauge needle, avoiding constriction of the artery. Pre-warmed mineral oil flowed over the kidney throughout the experiment to maintain the kidney temperature at 37 °C. The ureter was catheterized to allow unhindered flow and for