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Site of drug absorption after oral administration: Assessment of membrane permeability and luminal concentration of drugs in each segment of gastrointestinal tract

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ABSTRACT

This study was conducted to assess the site of drug absorption in the gastrointestinal (GI) tract after oral administration. Drug permeability to different regions of rat intestine, jejunum, ileum and colon, was measured by *in situ* single-pass perfusion method. It was revealed that the epithelial surface area should not be a determinant of the regional difference in the intestinal permeability of highly permeable drugs. Effects of the mucus layer at the surface of the epithelium and the fluidity of the epithelial cell membrane on the drug permeability were investigated. These factors are demonstrated to contribute to the regional differences in intestinal drug permeability. The luminal drug concentration in each segment of the GI tract after oral administration was measured directly in fasted rats. Water ingested orally was absorbed quickly in the jejunum and the luminal fluid volume was diminished in the middle to lower part of the small intestine. According to the absorption of water luminal concentration of atenolol, a drug with low permeability, was elevated and exceeded the initial dose concentration. In contrast, the concentration of highly permeable drugs, antipyrine and metoprolol, decreased quickly in the upper part of the intestine and a significant amount of drugs was not detected in the lower jejunum and the ileum. From the time-profiles of luminal drug concentration, fraction of dose absorbed from each segment of the GI tract was calculated. Both antipyrine and metoprolol were found to be absorbed quickly at the upper part of the small intestine. In addition, the possible contribution of gastric absorption was demonstrated for these drugs. The pattern of site-dependent absorption of atenolol showed the higher absorbability in the middle and lower portion of the jejunum. These informations on site-dependent absorption of drugs are considered to be important for effective oral delivery systems.

1. Introduction

Oral drug administration is the most convenient and common method of medication and now more than 60% of marketed drugs are used as oral products. Drugs administered orally are absorbed into systemic circulation mainly from the small intestinal tract. Although the upper part of the small intestine is considered to have the higher capacity for drug absorption,

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some drugs are known to be absorbed from other specific portions of the intestinal tract including the colon. In order to develop efficient dosage forms, therefore, detailed information on the site-dependent absorption of drugs should be necessary. Especially for sustained of controlled release products, high absorbability of drugs in the lower part of the intestine is desired.

Drug absorption rate and amount are expressed by the following equations as:

$$\text{absorption rate} = P_{\text{eff}} S C_{\text{GI}} \quad (1)$$

$$\text{absorption amount} = P_{\text{eff}} S \int_0^t C_{\text{GI}}\, dt = P_{\text{eff}} S\, \text{AUC}_{\text{GI}} \quad (2)$$

where P_{eff} is an effective permeability of drugs, S the surface area of the intestinal membrane and C_{GI} is a luminal concentration of drugs. AUC_{GI} expresses the area under the drug concentration–time curve in the GI tract during the intestinal transit time, t. In order to calculate the fraction absorbed of drugs in each segment of the GI tract, these parameters in the equations should be assessed.

Among above parameters, gastrointestinal transit time of drugs has been researched in detail using polyethylene glycol 4000 (Murata et al., 1987), and phenol red (Sawamoto et al., 1997) as non-absorbable markers. There are reviews indicating the importance of the gastrointestinal transit rate in considering the absorption kinetics and the bioavailability of orally administered drugs (Kimura and Higaki, 2002).

Generally, drug permeability to the intestinal membrane is considered to be higher in the upper region of the intestine than in the lower. Well-developed villous structure in the upper intestine spreads the surface area of the membrane. Relatively leaky structure of the membrane might also contribute to the high permeability of hydrophilic drugs to the upper intestinal membrane. However, some drugs have been reported to show fairly high permeability even to the lower part of the intestine, ileum and colon (Patel and Kramer, 1986; Gramatte, 1994). The pattern of regional difference in permeability should be dependent on the physicochemical properties of drugs.

Water volume for oral dosing is an important factor to determine the dose concentration of drugs. Usually, 250 mL of water is recommended in the clinical study to be ingested with drugs. However, drug concentration in the GI tract should be changing according to the fluid absorbed from the GI tract. Also, gastrointestinal secretion of fluids, such as bile and pancreatic juice, might affect the fluid volume in the intestine. However, since information on real fluid volume or the concentration of drugs in the each part of the GI tract *in vivo* are very limited, ingested water volume (250 mL) has been used to calculate the drug concentration in the intestine to estimate or simulate the oral drug absorption so far (Yu et al., 1996a).

In this report, first we have tried to clarify factors that contribute to the regional differences in the intestinal drug permeability by taking into account the physicochemical properties of drugs. Then, the luminal drug concentration in each segment of the GI tract after oral administration was measured directly in fasted rats. In addition, the change in water volume in each segment was estimated from the concentration of non-absorbable marker, FITC-dextran (FD-4).

2. Materials and methods

2.1. Materials

[^{14}C]Mannitol and [^{14}C]Urea was purchased from New England Nuclear (Boston, MA). Antipyrine, atenolol, griseofulvin, metoprolol and naproxen were purchased from WAKO Pure Chemical Industries, Ltd. (Japan). FITC-dextran (FD-4, MW 4400) was purchased from Sigma–Aldrich (St. Louis, MO). All other chemicals were commercial products of reagent grade.

2.2. Intestinal drug permeability

The permeability of rat intestinal membrane was evaluated by *in situ* single-pass perfusion method and closed loop method. Male Wistar rats (body weight, 200–250 g) fasted overnight were anesthetized with pentobarbital. The abdominal cavity was opened and an intestinal loop (length, 10 cm) was made at three regions (proximal jejunum, distal ileum, and colon) by cannulation with a silicone tube (i.d., 3 mm), then the intestinal contents were removed by a slow infusion of saline and air.

Following the above procedure, in the perfusion experiment, test solution (phosphate buffered solution, adjusted to pH 6.5) containing each compound (20 μM) and FD-4 (10 μM) was perfused with an infusion pump at a flow rate of 0.5 mL/min. The effluent was collected from 30 min after starting the perfusion to 90 min at 10-min intervals, because steady-state absorption usually was achieved by 30 min under these conditions. The drug permeability was calculated according to the following equation:

$$P_{\text{eff}} = \frac{Q(1 - C_{\text{out}}/C_{\text{in}})}{2\pi RL} \quad (3)$$

where Q is the flow rate and $C_{\text{out}}/C_{\text{in}}$ is the ratio of outlet/inlet drug concentration. The effect of water transport during perfusion on C_{out} was corrected using the concentration ratio of a non-absorbable marker (FD-4). L and R represent the length and the radius of the used segment of intestine, respectively, thus, the value of $2\pi RL$ corresponds to its surface area. As a radius of each intestinal segment, the value reported by Fagerholm et al. (1997) was used (0.18 cm for jejunum and ileum, 0.25 cm for colon).

In the closed loop experiment, test solution containing each compound (20 μM) was introduced into intestinal loops and both ends of the loop were ligated. After a certain period of time, the luminal solution in the loop was collected. The drug permeability was evaluated by the percentage of dose absorbed, by subtracting the remaining amount of the drug from the administered amount. The following equation was used to calculate the permeability:

$$P_{\text{eff}} = \frac{k_a V}{2\pi RL} \quad (4)$$

where k_a is the absorption rate constant of the drug estimated from the percentage of dose absorbed during the defined