ABSORPTION CHARACTERISTICS OF DRUGS FROM SMALL INTESTINAL SEROSAL SURFACE IN RATS FOR PREDICTION OF DRUG DISPOSITION AFTER INTRAPERITONEAL ADMINISTRATION

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ABSTRACT SUMMARY

We examined absorption characteristics of drugs from the small intestinal serosal surface in rats to predict drug disposition after intraperitoneal administration. There was a significant correlation between the absorption rates and molecular weights. Furthermore, we clarified contribution of each organ surface by comparison of the absorption clearance.

Keywords: pharmacokinetics, drug absorption

INTRODUCTION

The intraperitoneal (i.p.) route of drugs has attracted attention because the peritoneal cavity is a potential space for peritoneal dialysis as a long-term renal replacement therapy and i.p. chemotherapy of cancer restricted to the peritoneal cavity such as peritoneal carcinomatosis and ovarian cancer. As a series of our investigation to clarify whether drug absorption from the peritoneal cavity occurs through the specific organs1,2, it should be important to study drug absorption from the small intestinal serosal surface because of its large surface area.

In this study, we have examined the absorption characteristics of phenolsulfonphthalein (PSP) and fluorescein isothiocyanate-dextrans (FD-4, MW 4400: FD-10, MW 9500: FD-40, MW 40500) as model compounds after application to the rat small intestinal serosal surface. Furthermore, we compared the absorption rates among the peritoneal organs to predict the disposition characteristics of drugs after i.p. administration.

EXPERIMENTAL METHODS

Male Wistar rats (260 - 290 g) were anesthetized with sodium pentobarbital, and the left femoral artery and common bile duct were cannulated with a polyethylene tube. A cylindrical diffusion cell (i.d. 4 mm, area 0.13 cm²) was attached to the small intestinal serosal surface with adhesive chemical Aron Alpha. The drug solution (30 mg/ml x 0.334 ml) in an isotonic phosphate buffer (pH 7.4) was added to the diffusion cell.

Blood samples were collected from the femoral artery, followed by centrifugation. Bile was collected at the selected time intervals. At 6 hr after application, the urine and the solution remaining in the diffusion cell were withdrawn. The concentrations of PSP and FDs were determined by spectrophotometer and spectrophotofluorometer, respectively.

RESULTS AND DISCUSSION

We established an experimental system utilizing a diffusion cell attached to the small intestinal serosal surface to examine the possibility of drug absorption. This system enables us to study the drug absorption from the small intestinal serosal surface without interference by absorption from other sites.

After application to the rat small intestinal serosal surface, PSP appeared in the plasma with a maximum at 1 hr, and decreased gradually thereafter. PSP and its metabolite were excreted into the bile and urine. We studied the time course of PSP amount remaining in the diffusion cell to assess the absorption characteristics. A semi-log plot of the time course gave a straight line (r² = 0.973), indicating that the absorption of PSP from the rat small intestinal serosal surface proceeds via a first-order process. The absorption rate constant Kₐ was calculated to be 6.1 x 10⁻³ min⁻¹.
Both FD-4 and FD-10 were absorbed from the rat small intestinal serosal surface with low plasma concentrations as compared with PSP, followed by excretion into the urine (21.4 and 12.2 % of dose in 6 hr, respectively). The remaining amount of FD-4 and FD-10 in the diffusion cell declined linearly on a semi-log scale, suggesting that the absorption of macromolecules from the rat small intestinal serosal surface obeys first-order kinetics.

The absorption ratios in 6 hr of the model compounds having different molecular weights from the rat small intestinal serosal surface were calculated from the amount recovered from the diffusion cell, as 89.2 % for PSP, 34.6 % for FD-4, 14.9 % for FD-10 and 2.1 % for FD-40. Accordingly, the drug absorption from the rat small intestinal serosal surface was dependent on the molecular weight, similar to the other organs3,4.

As shown in Fig. 1, a linear relationship was observed between the apparent permeability coefficients ($P_{app}$) and the reciprocal values with square root of molecular weights of the model compounds for the small intestinal serosal surface in rats ($r^2 = 0.997$). Similar tendency was seen in the other organs reported previously3,4. Also, the limit of molecular weight for the drug absorbed from the rat small intestinal serosal surface can be estimated to be approximately 27,000 from the intercept of x-axis.

Since small intestine occupies about 40 % for the total peritoneal area in rats, we suppose its marked contribution to the drug absorption from the peritoneal cavity. We compared the drug absorption rate from the small intestinal serosal surface with the other organ surfaces (liver, kidney, stomach and cecum). As listed in Table 1, kidney has the highest $P_{app}$ for PSP, FD-4 and FD-10, whereas no marked difference was seen in the other organs.

### Table 1: $P_{app}$ (µm/min) and $CL_a$ (µl/min) for PSP, FD-4 and FD-10 after application to several organ surfaces.

<table>
<thead>
<tr>
<th>Route</th>
<th>$P_{app}$</th>
<th>$CL_a$</th>
<th>$P_{app}$</th>
<th>$CL_a$</th>
<th>$P_{app}$</th>
<th>$CL_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine</td>
<td>15.9</td>
<td>296.2</td>
<td>2.62</td>
<td>48.81</td>
<td>1.18</td>
<td>21.98</td>
</tr>
<tr>
<td>Liver</td>
<td>10.9</td>
<td>77.9</td>
<td>2.56</td>
<td>18.36</td>
<td>1.51</td>
<td>10.83</td>
</tr>
<tr>
<td>Kidney</td>
<td>24.7</td>
<td>32.1</td>
<td>7.11</td>
<td>9.24</td>
<td>3.90</td>
<td>5.07</td>
</tr>
<tr>
<td>Stomach</td>
<td>12.3</td>
<td>20.1</td>
<td>2.47</td>
<td>4.03</td>
<td>0.76</td>
<td>1.24</td>
</tr>
<tr>
<td>Cecum</td>
<td>11.2</td>
<td>28.2</td>
<td>2.11</td>
<td>5.32</td>
<td>0.83</td>
<td>2.09</td>
</tr>
</tbody>
</table>

Furthermore, we derived the absorption clearance $CL_a$ by the assumption of uniform drug absorption from the peritoneal cavity according to the area of organ surface. The $CL_a$ for PSP, FD-4 and FD-10 in the small intestine was the highest among the organ surfaces probably due to its large surface area in the peritoneal cavity (Table 1), despite the fastest absorption from the kidney surface. This implies that small intestine contributes considerably to drug absorption from the peritoneal cavity in rats.

**CONCLUSION**

We demonstrated considerable contribution of the small intestinal serosal surface to drug disposition from the peritoneal cavity, leading to estimate overall drug absorption rate after i.p. administration.

**REFERENCES**


**ACKNOWLEDGEMENTS**

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.