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Effect of Application Volume and Area on the Absorption of Phenol Red, as a Model Drug, from the Liver Surface in Rats

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Abstract

To determine the influence of the method of administration of a pharmaceutical formulation we have examined the importance of application volume and area in the absorption of phenol red, as a model drug, from the rat-liver surface.

When 1 mg phenol red was applied to the rat-liver surface, in-vivo, in three volumes (0·1, 0·2 or 0·334 mL) using a cylindrical glass cell (i.d. 9 mm), the shape of the plasma concentration profile differed greatly, particularly the maximum concentration. These patterns were well fitted by a two-compartment model with first-order absorption, and the absorption-rate constant K_a obtained was inversely proportional to the application volume. The absorption ratio and biliary recovery of phenol red after 6 h increased with glass cell area (i.d. 6, 9 or 14 mm; area 0·28, 0·64 or 1·54 cm^2). Furthermore, the permeability coefficient P_{app} derived from K_a did not depend on application area, indicating no difference in the absorption characteristics of the liver surface. This also implies transport of the drug by passive diffusion from the liver surface. After intraperitoneal administration to the rat-liver surface for clinical application, increasing the application volume resulted in the delayed disappearance of phenol red from the plasma. However, the difference was not as marked as that obtained by use of the glass cell. The assumption that the effective area relating to the absorption changed with the application volume enabled us to estimate P_{app}. Consequently, we speculate that absorbability can be estimated precisely by consideration of application volume and area.

We have previously reported on drug absorption from the liver surface in rats, and demonstrated that direct application to the liver surface is useful for drug delivery to the target site in the liver (Nishida et al 1994). Furthermore, we examined the mechanism of drug absorption from the liver surface using, as model drugs, several organic anions and FITC-labelled dextrans of different molecular weights (Nishida et al 1995a, b, 1996).

An appropriate pharmaceutical modification for enhancement of drug release, and adhesion to the liver surface, should be considered to improve drug targeting to the liver. Therefore, application conditions such as volume and area are very important factors in absorption from the liver surface.

In this study we selected phenol red as a model drug for which the mechanism of absorption has already been clarified (Nishida et al 1994, 1995a, b), and examined the influence of application volume and area of a glass cell on the absorption characteristics from the liver surface in rats. We also studied intraperitoneal administration of phenol red to the rat-liver surface for clinical application.

Materials and Methods

Phenol red was purchased from Nacalai Tesque (Kyoto, Japan). Other chemicals were reagent-grade products.

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In-vivo experiment

All animal procedures in the study conformed to the Guideline for Animal Experimentation in Nagasaki University.

Male Wistar rats (230–250 g) were anaesthetized with sodium pentobarbitone (50 mg kg^{-1}, i.p.) and the left femoral artery was cannulated with polyethylene tubing (0·5 mm i.d., 0·8 mm o.d.; Dural Plastics, Dural, Australia). A 3-cm incision was made in the middle abdomen, and the common bile duct was cannulated with polyethylene tubing (0·28 mm i.d., 0·61 mm o.d.; Becton Dickinson, Parsippany, NJ).

Application of phenol red solution to the rat-liver surface

A cylindrical glass cell (6, 9 or 14 mm i.d., effective area 0·28, 0·64 or 1·54 cm^2) was attached with Aron Alpha (Sankyo, Tokyo, Japan) to the left lobe of the rat-liver surface. Throughout the experiment the rats' body temperatures were kept at 37°C by means of a heat lamp. Phenol red solution (0·1, 0·2 or 0·334 mL containing 1 mg) was prepared in isotonic phosphate buffer (pH 7·4) and added directly to the glass cell. The top of the glass cell was sealed with a piece of aluminium foil to prevent evaporation of the applied solution.

Intraperitoneal administration of phenol red solution to the rat-liver surface

Phenol red solution (1 mg in volumes of 0·2, 1 or 5 mL) in isotonic phosphate buffer (pH 7·4) was administered intraperitoneally to the rat-liver surface, the point of injection being the division between the right and left lobes.

For a 6-h period after dosing, blood samples (200 μL) were collected at selected times from the heparinized cannula inserted into the femoral artery and centrifuged at

15 000 rev min^{-1} for 5 min. Bile samples were collected at appropriate times during the same 6-h period. At the end of the 6-h period the urine remaining in the bladder was collected with a syringe and the solution remaining in the glass cell or peritoneal cavity was withdrawn.

Analytical method

The concentrations of phenol red in the plasma, bile and urine, and in the solution remaining in the glass cell or peritoneal cavity were determined. The concentration of free phenol red was determined spectrophotometrically at 560 nm after dilution with 1 M NaOH solution. The total concentrations of free phenol red and its metabolite were similarly measured after acid hydrolysis (1 M HCl at 100°C for 30 min) (Hart & Schanker 1966).

Compartment model analysis

The plasma-concentration (C_p) profile of phenol red after intravenous administration was fitted to the biexponential equation:

$$C_p = [Dose(\alpha - K_{21})e^{-\alpha t}]/[V_c(\alpha - \beta)] + [Dose(K_{21} - \beta)e^{-\beta t}]/[V_c(\alpha - \beta)] \quad (1)$$

by the non-linear least-squares method (Yamaoka et al 1981). Hybrid parameters α and β are defined as $\alpha+\beta = K_{12}+K_{21}+K_{el}$ and $\alpha\beta = K_{21}K_{el}$. V_c is the volume of the central compartment and K_{el} is the first-order elimination rate-constant from the central compartment. K_{12} and K_{21} are the first-order transfer rate-constants between the central and peripheral compartments. These parameters were substituted into equation 2 for the plasma concentration after application to the rat-liver surface. The result for intravenous administration has already been reported (Nishida et al 1995a).

Next, in the same way, the plasma concentration profile of phenol red after application to the rat-liver surface was fitted in the two-compartment model with first-order absorption, by the non-linear least-squares method (Yamaoka et al 1981). In this model, the equation for plasma concentration is given by the equation:

$$C_p = FDoseK_a/V_c\{(K_{21} - K_a)e^{-k_a t}/[(\beta - K_a)(\alpha - K_a)] + (K_{21} - \alpha)e^{-\alpha t}/[(\beta - \alpha)(K_a - \alpha)] + (K_{21} - \beta)e^{-\beta t}/[(\alpha - \beta)(K_a - \beta)]\} \quad (2)$$

where K_a is the first-order absorption rate-constant for absorption into the blood stream from the rat-liver surface or peritoneal cavity and F is the availability after application to the rat-liver surface or after intraperitoneal administration around the rat-liver surface.

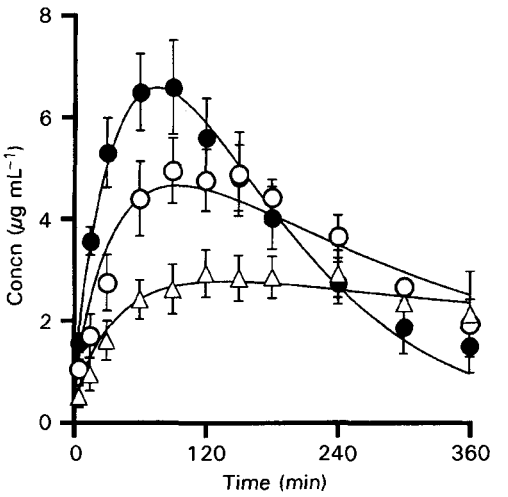

FIG. 1. Plasma-concentration profiles of phenol red after application of a dose of 1 mg in 0·1 (●), 0·2 (○) or 0·334 (△) mL vehicle to the rat-liver surface. Fitted curves show simulated functions based on the pharmacokinetic parameters shown in Table 1. Each point represents the mean ± s.e. of results from four experiments.

Statistical analysis

Statistical analysis was performed by applying Student's unpaired *t*-test. $P < 0.05$ was considered to be indicative of statistical significance. All results were expressed as the mean ± s.e. of results from at least four experiments.

Results

Effect of application volume on absorption of phenol red from the rat-liver surface

The plasma concentrations of phenol red were determined for 6 h after application of 1 mg of the compound to the rat-liver surface in three volumes, 0·1, 0·2 or 0·334 mL, in a 9-mm i.d. glass cell, as illustrated in Fig. 1. We observed a marked decrease in maximum concentration and a prolongation of the time the compound remained in the plasma as the application volume was increased. The biliary excretion rate patterns of free phenol red and its metabolite showed a similar tendency (data not shown).

Table 1 lists the recovery of phenol red from the bile, urine and glass cell 6 h after application to the rat-liver surface at a dose of 1 mg in the three volumes. The recovery ratio in the glass cell after 6 h was significantly affected by the application volume. The extent of absorption of phenol red in 6 h was calculated from the recovery ratio to be 91·8, 71·5 and 46·8% for dose volumes of 0·1, 0·2, and 0·334 mL, respectively. The biliary recovery of phenol red in 6 h also tended to decrease as

Table 1. Recovery after 6 h and pharmacokinetic parameters of phenol red after application to the rat-liver surface at a dose of 1 mg in three different volumes.

Volume (mL)		0·1	0·2	0·334
Recovery (% of dose)	Glass cell	8·2 ± 2·0	28·5 ± 0·6**	53·2 ± 2·7**
	Bile	50·7 ± 5·0	29·6 ± 3·2*	18·0 ± 3·6**
	Urine	29·3 ± 5·8	21·5 ± 4·7	22·7 ± 1·6
Absorption rate-constant K_a	($min^{-1} \times 10^{-3}$)	9·20 ± 1·00	4·83 ± 0·52**	3·01 ± 0·41**
Apparent absorption clearance $CL_{a,app}$	(mL $min^{-1} \times 10^{-3}$)	0·92 ± 0·10	0·97 ± 0·10	1·01 ± 0·14
Permeability coefficient P_{app}	(cm $min^{-1} \times 10^{-3}$)	1·44 ± 0·16	1·51 ± 0·16	1·57 ± 0·21

Each value is the mean ± s.e. of results from four experiments. *$P < 0.05$, **$P < 0.01$, significantly different from the result for 0·1 mL

Table 2. Recovery after 6 h and pharmacokinetic parameters of phenol red after application to the rat-liver surface at a dose of 1 mg under different conditions.

Area (cm^2)		0·28	0·64	0·64	1·54
Volume (mL)		0·1	0·1	0·334	0·334
Recovery (% of dose)	Glass cell	32·6 ± 2·0**	8·2 ± 2·0	53·2 ± 2·7	17·6 ± 1·1**
	Bile	23·9 ± 3·4**	50·7 ± 5·0	18·0 ± 3·6	33·0 ± 5·6
	Urine	35·8 ± 2·3	29·3 ± 5·8	22·7 ± 1·6	33·4 ± 6·3
Absorption rate-constant	($min^{-1} \times 10^{-3}$)	4·91 ± 0·57**	9·20 ± 1·00	3·01 ± 0·41	7·88 ± 0·77**
Apparent absorption clearance	($mL\ min^{-1} \times 10^{-3}$)	0·49 ± 0·06**	0·92 ± 0·10	0·97 ± 0·10	2·63 ± 0·26**
Permeability coefficient	($cm\ min^{-1} \times 10^{-3}$)	1·74 ± 0·20	1·44 ± 0·16	1·57 ± 0·21	1·71 ± 0·17

Each value is the mean ± s.e. of results from four experiments. **$P < 0·01$, significantly different from the result for 0·64 cm^2.

the absorption ratio decreased according to the application volume.

We also tried to examine the effect of application volume by applying a two-compartment model with first-order absorption (Nishida et al 1995a, 1996). As shown in Fig. 1, each curve fitted the experimental values, suggesting the validity of the pharmacokinetic analysis. The calculated K_a values listed in Table 1 were inversely proportional to the application volume.

Effect of application area on absorption of phenol red from the rat-liver surface

We examined the effect of the application area of the glass cell on the absorption of phenol red from the rat-liver surface. Figs 2a and 2b illustrate the plasma-concentration profiles of phenol red applied at a dose of 1 mg (10 mg mL^{-1} × 0·1 mL (a) or 3 mg mL^{-1} × 0·334 mL (b)) after application to the rat-liver surface using three different glass cells (6, 9 or 14 mm i.d., effective area 0·28, 0·64 or 1·54 cm^2). For application of 10 mg mL^{-1} × 0·1 mL (Fig. 2a), the plasma concentration pattern for the 0·64-cm^2 cylinder was sharper and the maximum concentration was twofold higher than for the 0·28-cm^2 cylinder. A similar relationship between the small and large glass cells was observed for application of 3 mg mL^{-1} × 0·334 mL, as shown in Fig. 2b. The biliary excretion rate profiles of free phenol red and its metabolite changed with the area of glass cell (data not shown).

Table 2 summarizes the recovery of phenol red after 6 h in the bile, urine and solution remaining in the glass cell under several experimental conditions. For application volumes of 0·1 and 0·334 mL, the absorption ratio from the rat-liver surface after 6 h increased significantly, by 1·4- and 1·8-fold, respectively, with increasing application area. A similar trend was seen in the biliary recovery ratio of phenol red.

Good agreement was observed between experimental values and the fitting lines (Figs 2a and 2b); the K_a values calculated are listed in Table 2. In general, the K_a value increased in proportion to the application area, indicating that application area determines the rate of absorption from the rat-liver surface.

Effect of application volume on the pharmacokinetics of phenol red after intraperitoneal administration to the rat-liver surface

For clinical application, we studied the peritoneal absorption of phenol red in different application volumes. Fig. 3 shows the plasma-concentration profiles of phenol red after intraperitoneal administration to the rat-liver surface at a dose of 1 mg in three volumes (0·2, 1 or 5 mL). The plasma-concentration profiles after intraperitoneal administration were delayed by increasing the application volume. However, there was no significant difference in the plasma-concentration profiles resulting from the three application volumes, irrespective of the large variation (0·2–5 mL) relative to that obtained using a glass cell (0·1 to 0·334 mL).

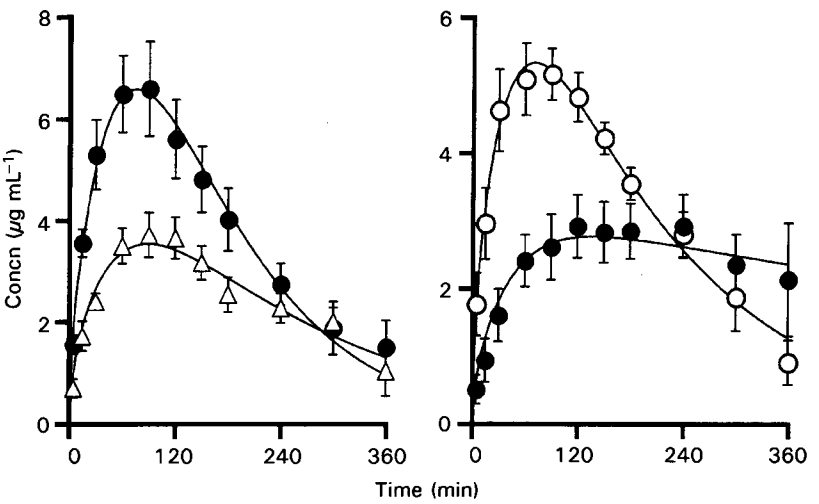

FIG. 2. Plasma concentration profiles of phenol red after application of a dose of 1 mg (10 mg mL^{-1} in 0·1 mL (left)) or 3 mg mL^{-1} (3 × 0·334 mL (right)) to application areas of three different sizes on the rat-liver surface. △ 0·28 cm^2, ● 0·64 cm^2, ○, 1·54 cm^2. Curves show simulated functions based on the pharmacokinetic parameters shown in Table 2. Each point represents the mean ± s.e. of results from four experiments.

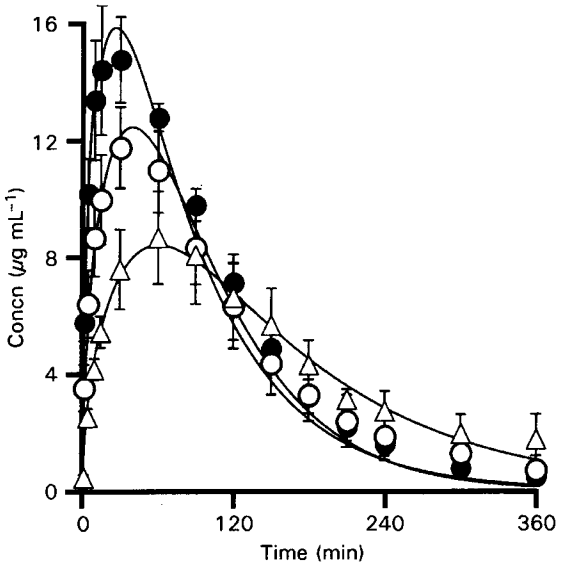

FIG. 3. Plasma-concentration profiles of phenol red after intraperitoneal administration of a dose of 1 mg in 0·2 (●), 1 (○) or 5 (△) mL vehicle to the rat-liver surface. Curves show simulated functions based on the pharmacokinetic parameters shown in Table 3. Each point represents the mean ± s.e. of results from four experiments.

Table 3 lists the biliary and urinary recovery of phenol red 6 h after intraperitoneal administration to the rat-liver surface. For every application volume, more than 97% of the dose was absorbed from the peritoneal cavity in 6 h. Accordingly, no significant difference was seen for the biliary and urinary recovery of phenol red on alteration of the application volume (Table 3).

Moreover, we calculated the K_a value of phenol red by pharmacokinetic analysis of the plasma-concentration profile, on the assumption of first-order absorption from the peritoneal cavity around the liver surface. In the pharmacokinetic analysis, best-fit curves in the three volumes were obtained as shown in Fig. 3, suggesting that this model can explain the pharmacokinetics after intraperitoneal administration. The K_a after intraperitoneal administration to the rat-liver surface decreased with increasing application volume, as shown in Table 3.

Discussion

From the results obtained, application volume and area seem to be significant factors in the absorption of a drug from the liver surface. The characteristics of this absorption can be precisely evaluated by use of the clearance concept. The elimination clearance of phenol red from the glass cell, which is assumed to be the apparent absorption clearance $CL_{a,app}$ (mL min^{-1}), is expressed as:

$$CL_{a,app} = K_a V_a \quad (3)$$

where V_a is the application volume. Furthermore, the absorption clearance per application area is calculated from:

$$P_{app} = K_a V_a / Area \quad (4)$$

where Area is the effective application area of a glass cell (cm^2). P_{app} (cm min^{-1}) is equivalent to the apparent diffusion coefficient, representing drug absorbability from the liver surface. The values of $CL_{a,app}$ and P_{app} of phenol red after application to the rat-liver surface with a glass cell, calculated according to equations 3 and 4, are summarized in Tables 1 and 2.

Although the K_a value decreased with increasing application volume (Table 1), $CL_{a,app}$ (approximately 1×10^{-3} mL min^{-1}) was not affected. This suggests equal absorbability from the liver surface when identical glass cells are used. Accordingly, the area of application is the main factor determining absorption from the liver surface.

Furthermore, we studied the change in absorption from the liver surface as a result of using several glass cells with different application areas (0·28, 0·64 and 1·54 cm^2). In general, judging from the values of $CL_{a,app}$ (Table 2), the absorbability of phenol red increased with application area. On the other hand, use of the three different application areas resulted in no significant difference in P_{app} (Table 2), values ranging from $1{\cdot}44 \times 10^{-3}$ to $1{\cdot}74 \times 10^{-3}$ cm min^{-1}. This result indicates that the liver surface membrane is broadly uniform in respect of absorption characteristics. We also confirmed the simple passive transport of drug across the liver surface (Nishida et al 1995a).

It is expected that application to the liver surface for clinical use will closely follow conventional administration into the abdominal cavity. We have previously shown (Nishida et al 1995c) that intraperitoneal administration to the liver surface enhances drug delivery to the liver in rats, because the rate of absorption of model drugs from the peritoneal cavity around the liver surface was high, compared with that around the small intestine. Intraperitoneal administration has been extensively used for treatment of cancers, such as ovarian carcinoma, restricted to the peritoneal cavity and is considered to be an effective method of organ-specific drug delivery, owing to the ease of regional delivery of anticancer drugs to the target site.

Several pharmaceutical preparations such as liposomes (Allen et al 1992; Sharma et al 1996), microspheres (Cremers et al 1994; Hagiwara et al 1996) and carbon particles (Hagi-

Table 3. Recovery after 6 h and pharmacokinetic parameters of phenol red after intraperitoneal administration to the rat-liver surface at a dose of 1 mg in three different volumes.

Volume (mL)		0·2	1	5
Recovery (% of dose)	Bile	51·3 ± 9·6	43·6 ± 8·0	57·7 ± 2·3
	Urine	26·0 ± 7·9	36·2 ± 9·8	20·9 ± 7·1
Absorption rate-constant K_a	($min^{-1} \times 10^{-2}$)	3·71 ± 0·57	2·96 ± 0·72	1·34 ± 0·25**
Apparent absorption clearance $CL_{a,app}$	(mL $min^{-1} \times 10^{-2}$)	0·74 ± 0·11	2·96 ± 0·72*	6·75 ± 1·25**
Permeability coefficient P_{app}	(cm $min^{-1} \times 10^{-2}$)	0·45 ± 0·07	0·61 ± 0·15	0·48 ± 0·09

Each value is the mean ± s.e. of results from four experiments. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, significantly different from the result for 0·2 mL.

wara et al 1988, 1992) have recently been used for controlled release of drugs in the peritoneal cavity. For intraperitoneal administration the application volume considerably influences the rate of drug absorption (Nagy et al 1989; Barrett et al 1991; Bredberg et al 1994). However, the effect of application volume on drug absorption from the peritoneal cavity has not been considered in terms of alterations in effective absorption area.

Similar to the application with a glass cell, the plasma concentration patterns of phenol red after intraperitoneal administration to the rat-liver surface were delayed and prolonged (Fig. 3) as the application volume was increased. Obviously, the appearance of phenol red in plasma after intraperitoneal administration was much faster than after use of a glass cell. The absorption area is limited when the drug is applied with a glass cell, whereas drug solution administered intraperitoneally becomes distributed in the peritoneal cavity around the liver surface, resulting in an increase in the effective absorption area.

We calculated the apparent absorption clearance $CL_{a,app}$ on the assumption of first-order absorption from the peritoneal cavity, by regarding the volume of the absorption compartment as the volume applied. However, the derived $CL_{a,app}$ values differed considerably among the three volumes, as shown in Table 3. This result indicates that application area varies with application volume for intraperitoneal administration.

The effective absorption area after intraperitoneal administration is considered to depend on application volume, owing to drug diffusion in the peritoneal cavity. Therefore, we assumed that the administered solution exists in the peritoneal cavity as a sphere, for which the surface area is minimum. The surface area of the sphere for administered volumes 0·2, 1, and 5 mL was estimated according to equation 5 to be 1·7, 4·8 and 14·1 cm^2, respectively.

$$\text{Area} = 4\pi(\sqrt[3]{[3V_a/4\pi]})^2 \quad (5)$$

The corrected absorption clearance, P_{app}, values obtained are listed in Table 3. The values were of the same magnitude for the three application volumes ($0{\cdot}45–0{\cdot}61 \times 10^{-2}$ cm min^{-1}), supporting this assumption.

We do not believe that the administered drug solution actually exists as a globular shape in the peritoneal cavity. Accordingly, it is necessary to understand the change in absorbability caused by dilution of the drug solution with the serous fluid, binding of drug to components of the peritoneal fluid or adhesion of drug to the peritoneal surrounding organs.

In conclusion, the rate of absorption from the liver surface appears to correlate with application volume and area. This should prove useful in the formulation of preparations for pharmaceutical administration.

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