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Lymphatic Delivery of Oral Anticancer Tegafur by Emulsion Formulations

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ABSTRACT

The influence of emulsion type of tegafur, an oral anticancer agent, on lymphatic transport was studied in rats. The water-in-oil-type of emulsion and the oil-in-water-type emulsion of tegafur each in 50 mg, calculated in terms of tegafur, were prepared by adding tegafur aqueous solution to sesame oil containing hydrogenated castor oil following ultrasonic treatment, and then the prepared emulsions and aqueous solution as a comparative formulation were administered orally to rats (50 mg/5 ml/kg). The concentration levels of tegafur in plasma of femoral artery and lymph from thoracic duct cannula were measured simultaneously along a time course after administration and the pharmacokinetic parameters were investigated. At the same time, we examined the above described factors of 5-FU which is known as an active metabolite of tegafur. In comparison with tegafur solution, AUC and mean residence time of plasma tegafur were significantly increased in w/o-emulsion but significantly decreased in o/w-emulsion. Lymph flow rates were similar in both solution and w/o-emulsion but half in o/w-emulsion. Ratios between area under the lymph and plasma concentration-time curves were always less than 1 reflecting the passive lymphatic delivery after oral administration of the prepared tegafur emulsions, but those to the 5-FU in the case of w/o-emulsion were more than 1. These results suggested that lymphatic delivery of tegafur by w/o-emulsion was more effective than that by o/w-emulsion due to its differences of formation ability of chylomicrons.

1. INTRODUCTION

The lymphatic contribution to the overall systemic transport and bioavailability following oral administration has been particularly interested for compounds which are subject to first pass metabolism as well as for anticancer agents in order to prevent the metastasis within the lymphatics.

Lymphatic delivery of drugs was widely studied in the routes of intramuscle,[1,2] intraperitoneum,[3,4] intraduodenum,[3,5-8] rectum,[9,10] large intestine[11-14] and stomach wall,[3,15] but oral administration[16-20] was poorly performed. This was probably due to the complexity of intestinal absorption process. But the oral route is the safest and most convenient method to administer drugs to the patients, so we tried to study lymphatic delivery of drug through oral route.

The candidate carriers for lymphatic delivery are liposome,[4] emulsion,[2,5,9,15,21] macromolecular conjugate,[1,8,12] mixed micelle[6,7,11,13,14] and so on. In order to introduce drugs into the lymphatic system from oral route, two methods can be considered. One is the pharmaceutical preparation of drugs as lipid emulsions and mixed micelles. The other is the chemical modification[16,18,19] of drugs, although there is little known about this method. Because the emulsion can be prepared simply, rapidly and orally effective, we introduced the emulsion as a carrier.

It has been suggested that the lymph con-

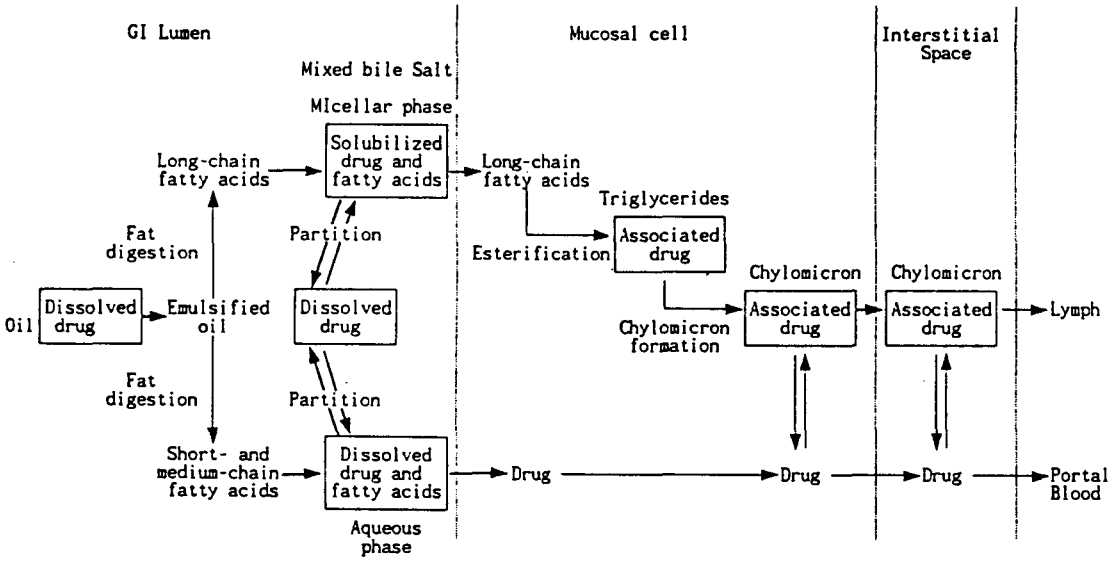

Figure 1—Luminal and mucosal processing of an administered oil containing dissolved drug.

centration of chylomicrons should be a major factor in controlling the uptake of drug molecules into the lymphatic vessels. Fig. 1 illustrates the various pathways whereby compounds incorporated into lipids may be handled by the body. For the short- or medium-chain triglycerides, the primary digestion products, fatty acids and monoglycerides, are transported in systemic circulation via the portal blood. The longer chain fatty acids and monoglycerides from long-chain triglyceride digestion, after absorption, may be resynthesized into triglycerides via at least two pathways.[22] The re-formed triglycerides are incorporated into lipid microspheres, chylomicrons, having a core consisting of triglycerides, esterified cholesterol, and other fat-soluble components, are coated with apoprotein, lipoprotein, and free cholesterol. The chylomicrons are then secreted from the intestinal cell by an exocytosis process and transverse the vasement membrane to enter the interstitial space and subsequently the lymph vessels.[23] The lymphatics are able to transport the chylomicrons due to the larger gaps between the cells of the lacteals preferentially to portal blood transport.[24] Lipid-soluble vitamins and other lipophilic compounds are generally transported in the lacteals of the mesenteric lymphatic system[25] in association with the chylomicrons. Materials transported in this manner reach systemic circulation without passing through the liver (Fig. 2). Therefore, long chain fatty acid can be used to promote selectively the intestinal absorption of lipophilic drugs via the lymphatic system.[26] From this point of view, vegetable oils are useful as a lymphagogue.

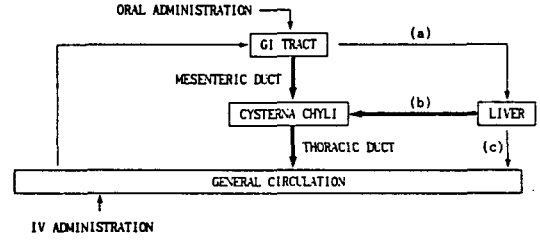

Figure 2—Physiological model for the determination of the contributions of lymphatic delivery process. Narrow and bold lines represent blood and lymph pathways, respectively.

From this standpoint, we studied the lymphatic delivery of tegafur emulsions via oral route, which contained long chain fatty acid

in its oily phase. Tegafur has shown significant activity in gastrointestinal and breast carcinomas with less myelotoxicity but more central nervous system toxicity than those of 5-FU.[27,28] It is considered to be a slow-release form of 5-FU which undergoes metabolic activation *in vivo*. Microsomal drug-metabolizing enzymes such as cytochrome P_{450} may participate in the mechanism of tegafur activation, and the liver has been proposed as the primary site of activation.[29,30] Also tegafur may be converted into 5-FU in tumor tissues by a thymidine phosphorylase.[31]

In this study, w/o- and o/w-emulsions of tegafur were orally administered to rats to compare with their lymphatic delivery effects. And also in order to demonstrate the lymph targeting associated to the oral route, it was deemed necessary to investigate the fate of solution after oral administration as a control. Lymph and plasma samples were periodically taken from each subject. Then, lymph and plasma levels of tegafur and 5-FU were observed. Also pharmacokinetic parameters were compared with each others.

On the other hand, most previous studies of lymphatic transport have not addressed the question of whether an increase in mesenteric or thoracic lymph transport by the manipulation of a suspected variable was due to a selective delivery to the intestinal lymphatics or an overall increase availability. In the future, we are going to determine the contribution of mesenteric lymph transport versus portal blood transport of the oral anticancer drug. Therefore, in this article we coverved not only lymphatic delivery of a fat-emulsified tegafur but also characteristics of lymphatic absorption for the future.

2. CHARACTERISTICS OF LYMPHATIC ABSORPTION

The lymphatic vessels in the small intestine originate as elongated, blind-ended vessels (lacteals) in the center of each villus. Finger-like villi host one central lacteal, whereas flattened villi, such as those found in rats, host several vessels. The lacteals lie approximately 50 μm beneath the epithelium and their radius is about 20 μm. These vessels join a network of capillaries in the glandular layer of the mucosa and are linked to collecting lymphatics. At the mesenteric border the lymphatics leave the intestine in association with the blood vessel. In contrast to the small intestine, large-intestinal lymphatic vessels are fewer in number and smaller in diameter and lie deep in the mucosa 300-400 μm beneath the mucosal epithelium.

Unlike blood vessels, the lacteals are composed of endothelial cells with no fenestrations. Nevertheless, since the junctions are widely separated, macromolecules such as chylomicrons (75-600 nm diameter) can pass readily into the lymphatic lumen. Moreover, the lymphatic capillaries have a fragmented basement membrane offering little barrier to the passage of solutes, fluids, and large particles. Consequently the major pathway for the transport of fluids and particulate components from the interstitium into the lymphatic lumen is the intercellular route. Particles ranging in diameter from 3 to 50 nm have been shown to pass through intermediate junctions of the endothelial cells but not the tight junctions. Substances in this group can be taken up by vesicles approximately 50 nm in diameter for transport across the cell.

The lacteals lie in a gel-like structure (interstitium) through which water and solutes slowly percolate. The interstitium is composed of mainly collagen fibers and hyaluronic acid, a polymer of N-acetylglucosamine and glucuronic acid with a molecular weight ranging from a few thousand to several million daltons. Cross-linking between hyaluronic acid and collagen and other proteins creates a fine interstitial mesh, with a pore size about 25 nm. Since hyaluronic acid is anionic, the gel has a net negative charge at physiological pH and ionic strength. When intersti-

tial fluid volume rises during a meal from its normal 25 ml/100 g, the porosity of the matrix increases from 20 nm to approximately 100 nm. The net result is reduced frictional resistance to diffusion of macromolecules and an increased hydraulic conductivity.

The interstitial-to-lacteal hydrostatic pressure gradient is the major driving force for lymphatic filling and therefore determines lymph flow. During net fluid absorption, the increase can be 5-20 times higher than normal lymph flow in the nonabsorptive state. The magnitude of increase is quite variable, due possibly to such factors as tonicity of the fluid ingested, portal vein pressure, intraenteric pressure, and GI motility. Should these factors be held constant or eliminated, the rate of fluid absorption would become a major determinant of intestinal lymph flow.

Chylomicrons, with diameters ranging from 75 to 600 nm, are barred from the blood capillaries whose open fenestrae are only 40-60 nm in diameter. Once formed in the enterocytes, they leave the cell by exocytosis and pass through pores in the basement membrane of the epithelial cell. Chylomicrons traverse approximately 50 μm of interstitium to the lacteal, where the particles are taken up by cell gaps via an unidentified transport mechanism.

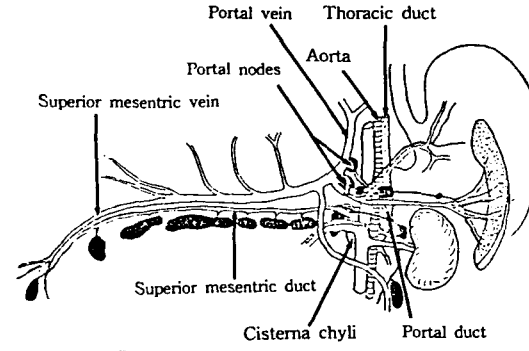

Figure 3—Lymphatics of the abdominal viscera drain into three lymph ducts which enter the cisterna chyli.

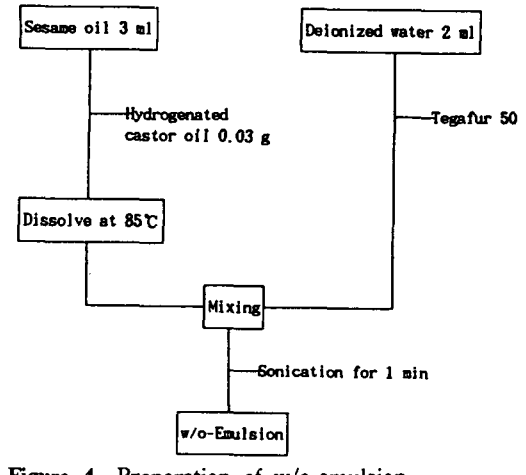

Figure 4—Preparation of w/o-emulsion.

3. FORMULATION AND PREPARATION OF EMULSIONS

3-1. Aqueous Solution

Fifty mg of tegafur was dissolved in 5 ml of water.

3-2. W/O- and O/W-Emulsions

The w/o-emulsion was prepared in accordance with the method of Hanaue *et al.*.[21] Briefly, tegafur w/o-emulsion was prepared following the procedure outlined in Fig. 3. Thirty mg of hydrogenated castor oil was dissolved in 3 ml of sesame oil at 85℃ and 2 ml of water containing 50 mg of tegafur was added to this oil phase. This mixture was then exposed to ultrasonic treatment in an ultrasonic generator for 1 min. On the other hand, o/w-emulsion was prepared in the same ingredients and the same manner of w/o-emulsion following the procedure outlined in Fig. 4 in order to eliminate the changes of lymphatic transport due to the composition.

The type of emulsion was determined by dilution test and dye solubility test with Sudan-III.

4. SPECIFIC SURGICAL PROCEDURES AND ADMINISTRATION OF DRUG

4-1. Experimental Animal

Male Sprague-Dawley rats weighing 100-150 g were obtained from Seoul National University Hospital. Water and feed (Jeil Co., Korea) were freely supplied for more than two weeks at 20-25℃, 50-60% RH and the rats weighing 200-300 g were used.

4-2. Thoracic Duct Catheterization

The thoracic duct was cannulated with polyethylene tubing (PE-50, Intramedic®, Clay Adams Co., USA) under light ether anesthesia according to the modified Bollman's method.[32]

One end of the catheter was made into a U-shaped loop of about 5 mm diameter. A transverse incision was made across the abdomen starting in the xiphoid cartilage and proceeding down the left side. The left kidney was loosened by gently tearing the connective tissue, and the kidney, gut and liver were pulled to the right by a gauze pack. The exteriorization was made through the dorso-posterior skin and muscle with 17 gauge needle, another PE-50 tubing was inserted into peritoneal cavity as the same method for the purpose of introducing normal saline intraperitoneally. The duct was separated from dorsal aorta. A U-shaped end was inserted into the duct and two threads were tied around the duct. After catheterization, the internal organs were returned to their normal anatomical positions and the muscle and skin incisions were sutured.

4-3. Mesenteric Lymphatic Duct Catheterization

All rats used in the experiments were fasted for 24 hr prior to each experimendt with frfee access to water. The animals were anesthetized for the duration of the experiment using 50 mg/kg sodium pentobarbital given by an intraperitoneal injection. Additional injections were given as needed (approx. every 2 hr).

The animals were shaved from ventral midline to dorsal midline on the animal's right side also on the ventral side of the neck.

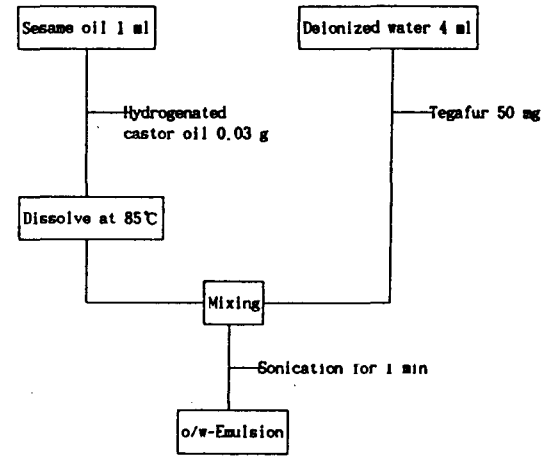

Figure 5— Preparation of o/w-emulsion.

With the rat on its back, both of the front legs were taped to the table on the animal's left side. A 7-8 cm lateral incision was made 1 cm below the libs from the animal's right side to the ventral midline cutting through both skin and muscle layers. The intestines were gently pushed towards the animal's left side (into the body cavity). A 2×2×7 cm piece of cotton was placed into the body cavity to hold the relocated intestines in place. A pair of 4 inch pointed forceps were then placed into the fat pad beneath the right kidney. The forceps, with tips together, were gently pushed through the fat, under the vena cava, raising the peritoneal membrane on the opposite side of the vena cava. Once the membrane had been raised, it was cut to leave the mesenteric artery and the mesenteric lymph duct exposed. While the forceps are under the vena cava the lymphatic cannula can be pulled through. A syringe, filled with heparinized saline (200 U/ml), was used to flush the cannula to help prevent clotting of the lymph. Carefully, only the top of the lymph duct was cut. (The mesenteric lymphatic duct is usually located to the left, anterior, of the mesenteric artery.) (Fig. 5) The polyethylene end of the cannula was inserted into the lymph duct approx. 3-4 mm. At this time, the syringe can be removed tempora-

rily to check for lymph flow. Any auxiliary lymph ducts to the right of the artery were cut to ensure all lymph flow into the main mesenteric duct. One drop of superglue was placed over the area to hold the cannula and to seal the auxiliary ducts. A 5×5 mm piece of muscle tissue, which had been cut from the abdominal wall, was placed over the superglue area to help secure the cannula and to prevent adhesions of the intestines. At this point, the cotton plug was removed from the abdominal cavity and the intestines were gently brought back to their original position.

4-4. Drug Administration and Sampling of Lymph and Plasma

After thoracic duct catheterization, PE-50 tubing was inserted in the left femoral artery. The animal was put in a restraining cage. Ordinarily the animal awoke in about 5-15 min. Then, 5 m*l*/kg of test sample was orally administered by oral zonde. Two ml of normal saline was administered intraperitoneally every hour to obtain a constant flow rate of the lymph.[5,33,34]

After dosing, lymph and blood samples were taken from each subject at 0.5, 1, 2, 4, 6, 8, 10, 14, 19, 24 and 29 hours, which were immediately centrifuged for 2 min at 12000 rpm. And then 100 μ*l* of plasma and lymph were frozen below −20℃ until the assay. The amount of lymph was measured with gravimetry.

As shown in Fig. 6, lymph flow rates were similar in both solution and w/o-emulsion but half in o/w-emulsion and all reached to constant at 10-15 hours. Milk-like chyle was observed at 1-2 hours after administration of w/o-and o/w-emulsion. Therefore, it suggested that w/o-emulsion made more chylomicrons than o/w-emulsion did.

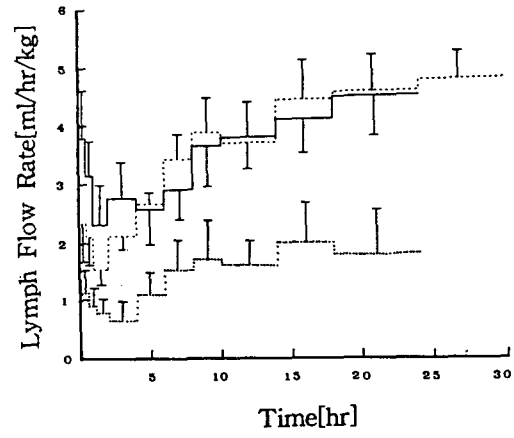

Figure 6— Lymph flow rate of tegafur after oral administration of its aqueous solution, w/o-, and o/w-emulsion (50 mg/5 m*l*/kg) (n=3~5).
Key: —, aqueous solution; ---, w/o-emulsion; ···, o/w-emulsion

5. SIMULTANEOUS DETERMINATION OF TEGAFUR AND 5-FU BY HPLC

We used a modified HPLC method of Wu, *et al.*.[35] One hundred μ*l* of plasma and lymph samples were mixed with 100 μ*l* of water containing 100 μg/m*l* of theophylline as an internal standard and adjusted with water to a total volume of 1 m*l*, then 0.1 m*l* of 0.5 M sodium biphosphate solution and 8 m*l* of ethyl acetate were added. After extraction and centrifugation, the organic layer was taken and evaporated with centrifugal vaporizer. The residue was redissolved in 100 μ*l* chromatographic mobile phase, and 20 μ*l* of this solution was injected on the column. Since it was reported that 5-FU was adsorbed on glass surfaces, silicon coated glass tube and polypropylene tubes were used in all procedures. Table I shows HPLC condition for determination.

For the construction of calibration curves, blank rat plasma was spiked with known amounts of tegafur and 5-FU, subjected to the HPLC determination procedure described above. The standard curves include 2, 5, 10, 20, 50, 100 and 200 μg of tegafur and 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1 and 2 μg of 5-FU standard in 1 m*l* of plasma. The serial experiments were performed at three times a day for three days and intra-day and inter-

Table I—HPLC Condition for Determination of Tegafur and 5-FU.

Parameters	Conditions
Mobile phase	0.01 M Sodium acetate buffer (pH 4): Methanol (1000:90)
Column	μ-Bondapak C_{18} Column (10 μm, 3.9 mm×300 mm)
Flow rate	2 ml/min
Detector	UV (270 nm)
Temperature	Ambient
Injection volume	20 μl

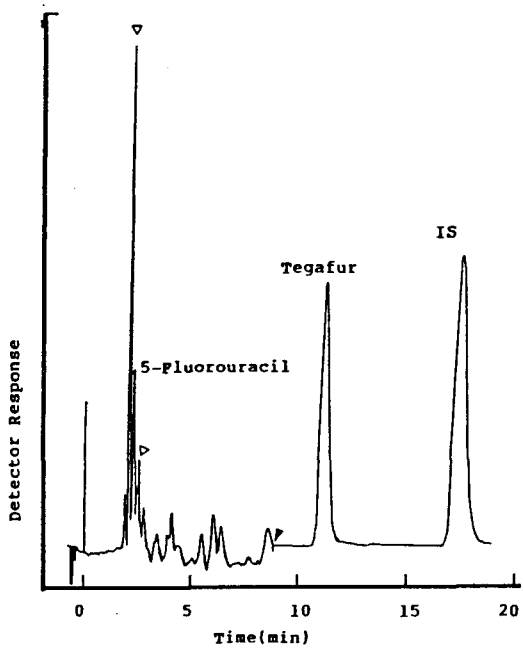

Figure 7—HPLC chromatogram of rat plasma extract 4hr after oral tegafur solution 50 mg/kg administration.
I.S.: Theophylline
▽: present in control plasma, —: attenuation 0.005 → 0.2

day coefficients were calculated. Coefficient of variation (C.V.%) was calculated by (S.D./mean)×100.

Fig. 7 shows the chromatogram of tegafur and 5-FU in rat plasma. The peaks corresponding to 5-FU, tegafur and theophylline (internal standard) were well resolved with retention times of 2.7, 12, 17 min, respectively. The procedure was quantified by the internal standard method using peak height ratios.

Table II—Calibration Curve Data of Tegafur#.

Plasma tegafur concentration (μg/ml)	Intra-day CV(%) (n=3)	Inter-day CV(%) (n=3)
2	10.78	1.71
5	8.82	3.01
10	6.86	1.61
20	6.44	1.30
50	9.27	3.94
100	3.24	1.52
200	6.45	1.04

Height ratio=0.0160×Concentration+0.0368 (γ=0.9995)

Table III—Calibration Curve Data of 5-FU.

Plasma 5-FU concentration (μg/ml)	Intra-day CV(%) (n=3)	Inter-day CV(%) (n=3)
0.01[a]	11.25	7.42
0.02[a]	6.71	5.56
0.05[a]	10.21	4.89
0.1[a,b]	2.50	1.71
0.2[a,b]	5.75	7.60
0.5[b]	7.55	6.22
1[b]	2.24	8.49
2[b]	4.52	9.75

[a]Height ratio=4.1381×Concentration+0.0815:0.01-0.2 μg/ml (r=0.9994)
[b]Height ratio=2.8613×Concentration+0.3248:0.1-2 μg/ml (r=0.9970)

The calibration curves obtained from plasma were $y=0.0160x+0.0368$(r=0.9995) for tegafur, $y=2.8613x+0.3248$(r=0.9970) for the higher concentration of 5-FU, and $y=4.1381x+0.0815$(r=0.9994) (y=height ratio, x=concentration) for the lower concentration of 5-FU over the concentration range of 2-200 μg/ml, 0.1-2 μg/ml and 0.01-0.2 μg/ml,

respectively.[36] The detection limits of tegafur and 5-FU were 1 and 0.01 μg/ml, respectively. The extraction ratios of tegafur and 5-FU determined by the peak height ratio of extracted and blank samples were 98% and 92%, respectively. The coefficients of variation showed somewhat high accuracy and good reproducibilities (Table II and III).

6. PHARMACOKINETIC EVALUATION OF THE PREPARED EMULSIONS

6-1. Lymph and Plasma Level of Tegafur and 5-FU

Fig. 8, 9, 10 and 11 show the concentration-time profiles of tegafur and 5-FU in plasma and lymph, respectively. After oral administration, it took 1 hr to reach plasma peak level of tegafur in both formulation.

When aqueous solution was administered, there were not so many differences between lymph and plasma level of tegafur at any time, but in the case of emulsions, lymph level was slightly lower than plasma level. It has been shown that tegafur is metabolized in the body to form 5-FU. Although the concentration of 5-FU was extremely lower than that of the parent compound, it was similar to tendency of tegafur. The observed initial high concentration of 5-FU probably resulted from the 5-FU contamination of the tegafur powder.[37,38]

6-2. Pharmacokinetic Parameters

According to the concentration-time curves, we obtained the pharmacokinetic para-

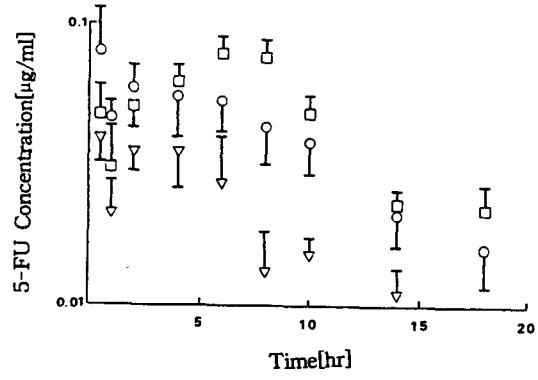

Figure 9—Mean plasma concentration of 5-FU after oral administration of its aqueous solution, w/o-, and o/w-emulsion (50 mg/5 ml/kg) (n=3~5).
Key: ○, aqueous solution; □ , w/o-emulsion; ▽, o/w-emulsion

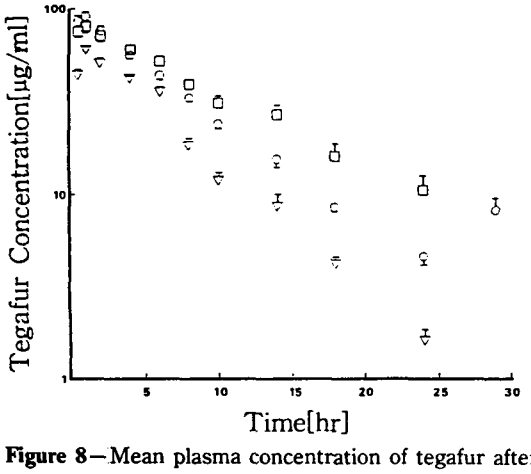

Figure 8—Mean plasma concentration of tegafur after oral administration of its aqueous solution, w/o-, and o/w-emulsion (50 mg/5 ml/kg) (n=3~5).
Key: ○, aqueous solution; □, w/o-emulsion; ▽, o/w-emulsion

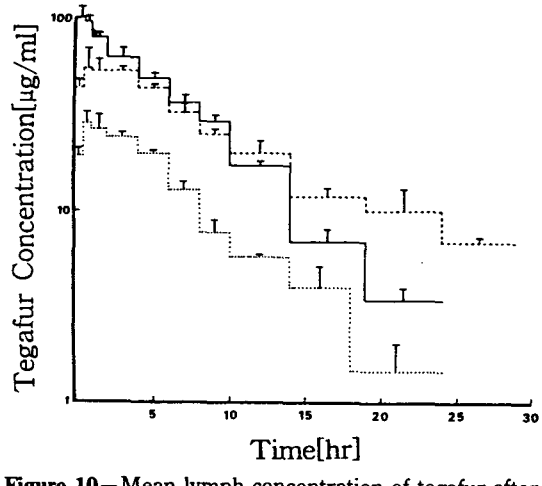

Figure 10—Mean lymph concentration of tegafur after oral administration of its aqueous solution, w/o-, and o/w-emulsion (50 mg/5 ml/kg) (n=3~5).
Key:—, aqueous solution; --, w/o-emulsion; ···, o/w-emulsion

meters, taking advantage of 'Moment' program.

In comparison with control group, AUC and MRT of tegafur were significantly ($p<0.05$) increased in w/o-emulsion but significantly decreased in o/w-emulsion (Table IV).

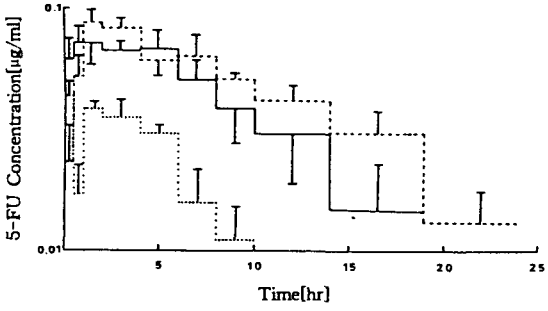

Figure 11— Mean lymph concentration of 5-FU after oral administration of its aqueous solution, w/o-, and o/w-emulsion (50 mg/5 ml/kg) (n=3~5).

Key : —, aqueous solution; ---, w/o-emulsion; ···, o/w-emulsion

Lymph flow rate, an important factor in lymphatic transport of drugs, was similar in both formulations. This result agree with that of Nakamoto *et al.*.[5]

Nakamoto *et al.* reported that w/o-emlsion produced higher lymph tegafur level than that of aqueous solution. It was suggested that the w/o-emulsion should be converted to a w/o/w type within the luminal fluid and water soluble drugs should be mostly included inner aqueous phase of the oil droplets in contrast to the case of o/w-emulsion.[5] Therefore, w/o-emulsion may be more effective than o/w-emulsion. This may be an important factor for the lymphatic transport of drugs. But our results showed that initial tegafur concentrations were higher in the case of aqueous solution but terminal concentrations were reversed. And also ratios between area under the lymph and plasma concentration-time curves were always less than 1 ref-

Table IV—Pharmacokinetic Parameters of Tegafur and its Metabolite 5-FU in Plasma#.

Parameters	Solution	W/O-Emulsion	O/W-Emulsion†
$AUC_p^{0-\infty}$(μg·hr/ml)[a]	696.29± 7.68	1083.11± 71.24*	426.00± 11.45*
MRT(hr)[b]	7.82± 0.33	12.70± 1.46*	6.65± 0.42*
CL/F(ml/hr)[c]	0.072± 0.001	0.046± 0.003*	0.117± 0.004*
$AUC_M^{0-\infty}$ (μg·hr/ml)[d]	0.979± 0.098	1.030± 0.102	0.40± 0.103*

[a] $AUC_p^{0-\infty}$ is calculated by trapezoidal (AUC^{0-lm}) and extrapolated ($AUC^{lm-\infty}$) method.
[b] MRT is $AUMC^{0-\infty}/AUC_p^{0-\infty}$.
[c] CL/F is the Dose/$AUC_p^{0-\infty}$.
[d] $AUC_M^{0-\infty}$ is AUC_p of 5-FU.
*$p<0.05$, between aqueous solution and the prepared emulsion.
†$p<0.05$, between the prepared emulsions.
#Mean± S.E. (n=3~5).

Table V—Pharmacokinetic Parameters of Tegafur and its Metabolite 5-FU in Lymph#.

Parameters	Tegafur			5-FU		
	Solution	W/O	O/W	Solution	W/O	O/W
$AUC_l^{0-\infty}$ (μg·hr/ml)[a]	756.10± 60.25	784.80± 55.94	234.03± 28.26*	0.942± 0.154	1.237± 0.140	0.331± 0.036*
$AUC_l^{0-\infty}/AUC_p^{0-\infty}$	1.087± 0.095	0.727± 0.064*	0.538± 0.039*	0.968± 0.071	1.202± 0.096*	0.818± 0.075

[a] $AUC_l^{0-\infty}$ calculated by trapezoidal and extrapolated method represents $AUC^{0-\infty}$ in lymph.
*$p<0.05$, between the one and the others.
#Mean± S.E. (n=3~5).

lecting the passive lymph delivery after oral administration of the prepared emulsions (Table V). We suppose that this disagreement results from several reason. First, it was due to the difference of administration routes. They administered the formulation via intraduodenum. Therefore, in the case of oral administration, it is suggested that w/o-emulsion should be disrupted by gastric environment. Second, because of the viscosity of w/o-emulsion, the absorption can be delayed.[20] Third, since oil-water partition coefficient of tegafur is not high,[39] the probability of lymphatic selectivity may be rare. High levels of tegafur in lymph at terminal period are supposed to result from the delivery of tegafur from plasma, and this phenomenon shows the intact function of lymphatic system.

Therefore, we propose that lipid solubilities of drugs influence greatly lymphatic delivery and the stable preparation in gastric environment is desirable to increase the lymphatic delivery of drugs via oral route.

7. CONCLUSIONS

Indeed, lymphatic channels are frequently the route by which tumors metastize, with micrometastases lodging in regional or distant lymph nodes. It would be therefore be of potential therapeutic advantage in the treatment of cancer to selectively concentrate antitumor agents in lymph channels and lymph nodes. Cancers such as colon, rectum or ovarian cancers which associate either dissemination of metastases targeting to local and regional nodes (thoracic) could benefit of the emulsions. Therefore, in order to demonstrate the lymph targeting associated to the oral route, we prepared w/o- and o/w-emulsions of tegafur which is oral anticancer agent and they were orally administered to rats. And then we compared with their lymphatic delivery effects by use of thoracic duct concentration.

1) In comparison with tegafur solution, AUC and MRT of plasma tegafur were significantly increased in w/o-emulsion but significantly decreased in o/w-emulsion.

2) Lymph flow rates were similar in both solution and w/o-emulsion but half in o/w-emulsion.

3) AUC of lymph tegafur was similar in both solution and w/o-emulsion but significantly decreased in o/w-emulsion.

4) AUC of lymph 5-FU was significantly increased in w/o-emulsion but significantly decreased in o/w-emulsion to the solution.

5) Ratios between area under the lymph and plasma concentration-time curves were always less than 1 reflecting the passive lymphatic delivery after oral administration of the prepared tegafur emulsions, but those to the 5-FU in the case of w/o-emulsion were more than 1.

These results suggested that lymphatic delivery of tegafur by w/o-emulsion was more effective than that by o/w-emulsion due to its differences of formation ability of chylomicrons.

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