Effect of gastrectomy on the pharmacokinetics of 5-fluorouracil and gimeracil after oral administration of S-1

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The effect of gastrectomy on pharmacokinetics after S-1 administration was investigated in a total of 12 cases – nine in which partial gastrectomy was performed and three in which total gastrectomy was performed. A single oral dose of S-1, 50 mg as tegafur, was administered, serial peripheral blood samples were collected, and the concentrations of 5-fluorouracil (5-FU) and gimeracil (CDHP) were measured. The pre-operative S-1 dose was administered about 7 days before surgery and the post-operative dose was administered around post-operative hospital day 14. In the partial gastrectomy cases the maximum post-operative blood concentration (C_{max}) of 5-FU and CDHP tended to be lower than before surgery, and the difference in 5-FU concentrations was significant. The area under the blood concentration–time curve ($AUC_{0-8\,h}$) for CDHP was significantly smaller post- than pre-operatively, but no significant difference was observed with regard to 5-FU. In the total gastrectomy cases the post-operative t_{max} of both 5-FU and CDHP was shorter than the pre-operative t_{max}, and no significant differences were observed between the pre- and post-operative $AUC_{0-8\,h}$ values. Thus, the results of the present study showed that around post-operative hospital day 14, when total oral feeding had become possible after surgery for gastric cancer, the $AUC_{0-8\,h}$ values of 5-FU and CDHP after S-1 administration were almost the same as before surgery and that gastrectomy had hardly any effect on the pharmacokinetics of S-1. *Anti-Cancer Drugs* 17:393–399

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Introduction

S-1 is an oral anti-cancer drug in which two modulators, gimeracil (CDHP), which inhibits the 5-fluorouracil (5-FU)-degrading enzyme dihydropyrimidine dehydrogenase (DPD), and oteracil potassium (Oxo), which inhibits the 5-FU-phosphorylating enzyme orotate phosphoribosyltransferase in the normal mucosa of the digestive tract, are combined with the 5-FU pro-drug tegafur (FT) in an FT:CDHP:Oxo molar ratio of 1:0.4:1 [1–3]. Thus, S-1 was developed as a formulation that possesses properties that maintain high 5-FU blood concentrations, that increase its anti-tumor effect and that mitigate its digestive system toxicity. S-1 has been found to have a high efficacy rate of 46.5% in phase II clinical trials in advanced gastric cancer [4–6] and it is currently being widely used as monotherapy or in combination with other drugs to treat advanced gastric cancer in Japan.

After oral administration S-1 is absorbed in the small intestine [7]; when used as post-operative adjuvant therapy the transit rate of the drug into the small intestine is different because it is being ingested after gastrectomy and it is thought that its pharmacokinetics may be affected. Hirata *et al.* [8] and Kochi *et al.* [9] investigated the effect of gastrectomy on the pharmacokinetics of S-1 by comparing kinetics in the blood after S-1 administration before and after gastrectomy, and suggested that gastrectomy had hardly any effect on the in-vivo kinetics of S-1. Their studies, however, were on only small numbers of subjects. Moreover, while there have been several reports on 5-FU [10–12] and UFT (FT and uracil) [13] in studies based on differences in surgical procedure, there have been none on S-1. We therefore conducted a comparative study of the pre- and post-operative pharmacokinetics of S-1 in gastric cancer patients who underwent partial gastrectomy or total gastrectomy.

Materials and methods

The subjects of this study were patients who underwent partial gastrectomy (distal gastrectomy, with Billroth I reconstruction) or total gastrectomy (with Roux-en-Y reconstruction) for gastric cancer in our department between June 2004 and March 2005, except cases

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complicated by pyloric stenosis pre-operatively and those in which oral feeding was impossible. This study was approved by the institutional ethics review committee. The study was explained to the patients, and those who consented to drug administration and the blood collections were enrolled as subjects. The background of all 16 patients enrolled in the study is shown in Table 1. Their ages ranged from 46 to 78 years old (mean 61.1 years), and there were 13 males and three females. According to the site in the stomach occupied by the tumor, three were in the U region, 10 in the M region and three in the L region. The surgical procedure consisted of partial gastrectomy in 11 cases and total gastrectomy in five cases, and D1 + α lymph node excision was performed in nine cases and D2 lymph node excision in seven cases. According to the histological stage classification, four cases were stage IA, five stage IB, two stage II, two stage IIIA and three stage IIIB. The 12 cases in which it was possible to make serial pre- and post-operative determinations of 5-FU and CDHP concentrations in the same patient (nine partial gastrectomy cases and three total gastrectomy cases) were included as subjects of the analysis. The handling of the gastric cancers was in accordance with the *Japanese Classification of Gastric Carcinoma* (13th ed.) of the Japanese Gastric Cancer Association [14].

A single dose of S-1 (TS-1 capsule; Taiho Pharmaceutical, Tokyo, Japan), 50 mg as FT, was administered orally after breakfast and serial peripheral blood samples were collected. The S-1 dosage time before surgery was approximately 7 days before surgery (ordinary diet) and the dosage time after surgery was around post-operative hospital day 14, when oral rice gruel (cooked with rice and water in a ratio of 1:5) feeding had become possible after surgery. Blood samples were collected a total of 5 times: before, and 1, 2, 4 and 8 h after oral S-1 administration. After isolating the serum, the concentrations of both 5-FU and CDHP were measured by HPLC [3]. More specifically, 0.5 ml of saturated ammonium sulfate solution was added to 0.5 ml of serum. After adding 0.1 ml of 5-bromouracil solution as an internal control for 5-FU and stirring, 5 ml of chloroform was added. After vigorous shaking for 10 min at room temperature, it was centrifuged and the aqueous phase was collected. A 4-ml volume of ethyl acetate was then added to the aqueous phase and the ethyl acetate phase was collected after centrifuging. An additional 4 ml of ethyl acetate was added, and after the same procedure the ethyl acetate phases were combined and evaporated to dryness under a stream of N_2. After adding 0.2 ml of pure water to it and dissolving, the solution was used as the sample for quantitative determination of 5-FU and CDHP. 5-FU was determined by the internal standard method and CDHP by the absolute calibration curve method. The conditions for 5-FU determination were: column Chemcosorb 300-5C18 (4.6 × 250 mm; Chemco Scientific, Osaka, Japan); mobile phase 10 mmol/l potassium phosphate solution (pH 5.0) containing 2 mmol/l tetrabutylammonium; flow rate 1.0 ml/min: UV wavelength 270 nm. The conditions for CDHP determination were: column Chemcosorb 300-5C18 (4.6 × 150 mm); mobile phase 2% acetonitrile containing 0.01 mol/l trifluoroacetate; flow rate 1.0 ml/min: UV wavelength 280 nm. The area under the blood concentration–time curve (AUC) of 5-FU and CDHP was calculated by the trapezoid method as the $AUC_{0-8\,h}$ until 8 h after administration. The paired *t*-test was used to analyze the data for significant differences and $P < 0.05$ was considered significant.

Table 1 **Patient characteristics**

Patient no.	Age (years)	Sex	Tumor location	Stage	Surgical procedure[c]	Lymph node dissection
1	67	male	L	II	DGR	D1 + α
2[a]	51	male	L	IIIB	DGR	D1 + α
3	68	male	M	IA	DGR	D1 + α
4	49	female	M	IB	DGR	D2
5[a]	78	female	U	IB	TGR	D1 + α
6	46	male	U	IIIB	TGR	D1 + α
7	53	male	M	IB	TGR	D2
8[b]	69	male	M	IB	DGR	D1 + α
9	56	male	M	IIIA	DGR	D2
10	63	male	U	IB	TGR	D2
11	60	male	L	IA	DGR	D2
12	70	female	M	IA	DGR	D2
13	53	male	M	II	DGR	D2
14[b]	47	male	M	IIIB	TGR	D1 + α
15	70	male	M	IIIA	DGR	D1 + α
16	78	male	M	IA	DGR	D1 + α

The handling of the gastric cancers was in accordance with the *Japanese Classification of Gastric Carcinoma* (13th ed.) of the Japanese Gastric Cancer Association.
[a]Only post-operative blood samples were collected in patients 2 and 5.
[b]Only pre-operative blood samples were collected in patients 8 and 14.
[c]DGR: distal gastrectomy; TGR: total gastrectomy.

Results

Blood concentration of 5-FU and CDHP in all of the cases included in the analysis

The changes in the blood 5-FU concentrations of the 12 patients in whom it was possible to collect blood both pre- and post-operatively among the 16 patients enrolled in the study are shown in Fig. 1. The pre-operative 1-, 2-, 4- and 8-h concentrations (means ± SD) were 25 ± 35, 88 ± 45, 118 ± 46 and 24 ± 9 ng/ml, respectively; the peak blood concentration (C_{max}) was 122 ± 48 ng/ml; the time to reach the C_{max} (t_{max}) was 3.8 ± 0.6 h; and $AUC_{0-8\,h}$ was 564 ± 219 ng · h/ml (Table 2). The post-operative 1-, 2-, 4- and 8-h concentrations were 42 ± 49, 84 ± 57, 90 ± 40 and 25 ± 11 ng/ml, respectively; C_{max} was 101 ± 46 ng/ml; t_{max} was 2.9 ± 1.2 h; and $AUC_{0-8\,h}$ was 496 ± 246 ng · h/ml (Table 2). The post-operative 1-h concentration tended to be slightly higher than the pre-operative value and the post-operative 4-h concentration tended to be slightly lower than the pre-operative concentration, but no significant differences were found between the C_{max}, t_{max} or $AUC_{0-8\,h}$ values before and after the operation.

The pre- and post-operative blood CDHP concentrations in the same patients are shown in Fig. 2. The pre-operative 1-, 2-, 4- and 8-h concentrations were 83 ± 88, 225 ± 92, 185 ± 63 and 51 ± 15 ng/ml, respectively; C_{max} was 240 ± 85 ng/ml; t_{max} was 2.4 ± 1.0 h; and $AUC_{0-8\,h}$ was 1071 ± 318 ng · h/ml (Table 3). The post-operative 1-, 2-, 4- and 8-h concentrations were 124 ± 131, 175 ± 98, 121 ± 43 and 46 ± 18 ng/ml, respectively; C_{max} was 210 ± 115 ng/ml; t_{max} was 2.4 ± 1.2 h; and $AUC_{0-8\,h}$ was 844 ± 347 ng · h/ml (Table 3). The 1-h concentration tended to be slightly higher post- than pre-operatively. The post-operative 2- and 4-h concentrations tended to be slightly lower than the pre-operative values, and the difference at 4 h was significant. No significant differences, however, were found between the C_{max}, t_{max} or $AUC_{0-8\,h}$ values before and after the operation.

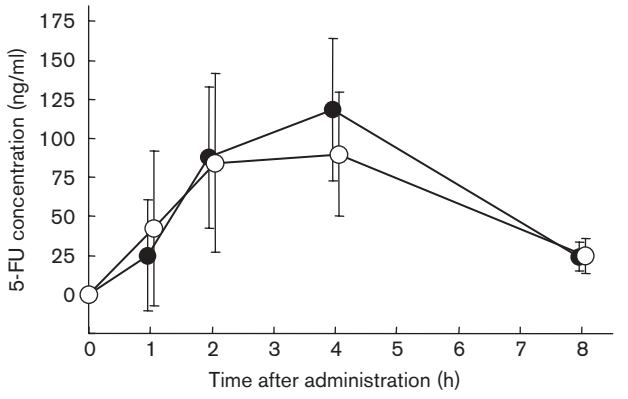
Investigation of the correlations between the $AUC_{0-8\,h}$ of the blood 5-FU concentrations and the CDHP concentrations in these 12 patients revealed positive correlations between them, both pre- ($r = 0.774$) and post-operatively ($r = 0.769$) (Fig. 3).

Blood concentration of 5-FU and CDHP in the partial gastrectomy cases

The changes in blood 5-FU concentrations in the nine cases in which it was possible to collect blood both pre- and post-operatively among the 11 patients who underwent partial gastrectomy (distal gastrectomy) are shown in Fig. 4. The pre-operative 1-, 2-, 4- and 8-h concentrations were 26 ± 40, 85 ± 35, 121 ± 41 and 24 ± 9 ng/ml, respectively; C_{max} was 126 ± 44 ng/ml; t_{max} was 3.8 ± 0.7 h; and $AUC_{0-8\,h}$ was 567 ± 178 ng · h/ml (Table 2). The post-operative 1-, 2-, 4- and 8-h concentrations were 29 ± 37, 75 ± 50, 88 ± 36 and 24 ± 11 ng/ml, respectively; C_{max} was 97 ± 36 ng/ml; t_{max} was 3.0 ± 1.2 h; and $AUC_{0-8\,h}$ was 463 ± 203 ng · h/ml (Table 2). The post-operative 2- and 4-h concentrations tended to be lower than the pre-operative concentrations, and C_{max} was significantly lower post- than pre-operatively ($P = 0.046$). No significant differences, however, were found between t_{max} or $AUC_{0-8\,h}$ before and after the operation.

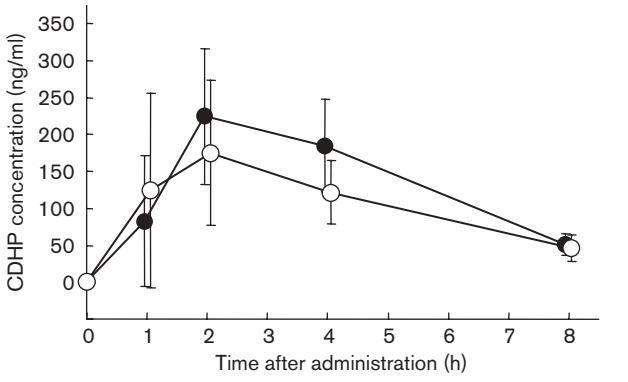
The pre- and post-operative changes in blood CDHP concentrations in the same patients are shown in Fig. 5. The pre-operative 1-, 2-, 4- and 8-h concentrations were 81 ± 96, 218 ± 60, 184 ± 72 and 50 ± 16 ng/ml, respectively; C_{max} was 226 ± 66 ng/ml; t_{max} was 2.3 ± 1.0 h; and $AUC_{0-8\,h}$ was 1054 ± 318 ng · h/ml (Table 3). The post-operative 1-, 2-, 4- and 8-h concentrations were 73 ± 67, 155 ± 104, 118 ± 49 and 45 ± 19 ng/ml, respectively; C_{max} was 179 ± 93 ng/ml; t_{max} was 2.8 ± 1.2 h; and $AUC_{0-8\,h}$ was 749 ± 314 ng · h/ml (Table 3). The post-operative

Fig. 1



Changes in blood 5-FU concentrations in all cases included in the analysis ($n = 12$). Closed circles, pre-operation; open circles, post-operation; points, mean; bars, SD.

Fig. 2



Changes in blood CDHP concentrations in all cases included in the analysis ($n = 12$). Closed circles, pre-operation; open circles, post-operation; points, mean; bars, SD.

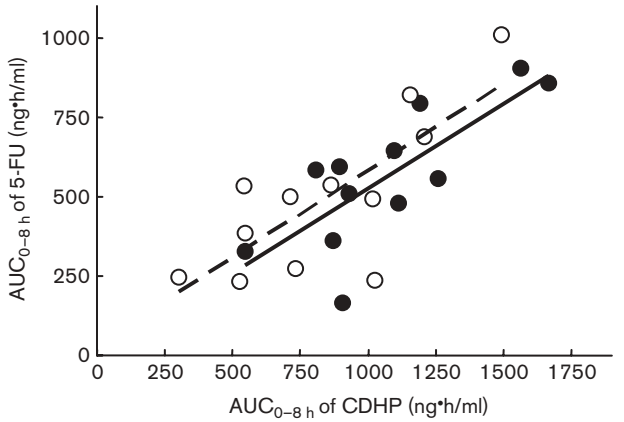
Table 2 **Pharmacokinetic parameters (means ± SD) of 5-FU after a single dose of S-1**

Treatment	*n*	Time of test	C_{max}(ng/ml)	*P*	t_{max}(h)	*P*	$AUC_{0-8\,h}$(ng · h/ml)	*P*
Gastrectomy	12	pre-operation	122 ± 48	0.076	3.8 ± 0.6	0.017	564 ± 219	0.083
		post-operation	101 ± 46		2.9 ± 1.2		496 ± 246	
Distal gastrectomy	9	pre-operation	126 ± 44	0.046	3.8 ± 0.7	0.080	567 ± 178	0.090
		post-operation	97 ± 36		3.0 ± 1.2		463 ± 203	
Total gastrectomy	3	pre-operation	109 ± 68	0.790	4.0 ± 0.0	0.184	554 ± 371	0.511
		post-operation	114 ± 78		2.7 ± 1.2		593 ± 388	

Table 3 Pharmacokinetic parameters (means ± SD) of CDHP after a single dose of S-1

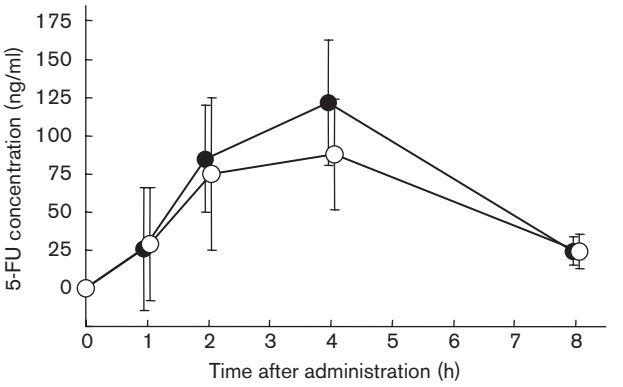
Treatment	*n*	Time of test	C_{max}(ng/ml)	*P*	t_{max}(h)	*P*	$AUC_{0-8\,h}$(ng · h/ml)	*P*
Gastrectomy	12	pre-operation	240 ± 85	0.265	2.4 ± 1.0	1.000	1071 ± 318	0.051
		post-operation	210 ± 115		2.4 ± 1.2		844 ± 347	
Distal gastrectomy	9	pre-operation	226 ± 66	0.168	2.3 ± 1.0	0.426	1054 ± 318	0.044
		post-operation	179 ± 93		2.8 ± 1.2		749 ± 314	
Total gastrectomy	3	pre-operation	281 ± 139	0.075	2.7 ± 1.2	0.270	1121 ± 383	0.927
		post-operation	305 ± 142		1.3 ± 0.6		1127 ± 326	

Fig. 3



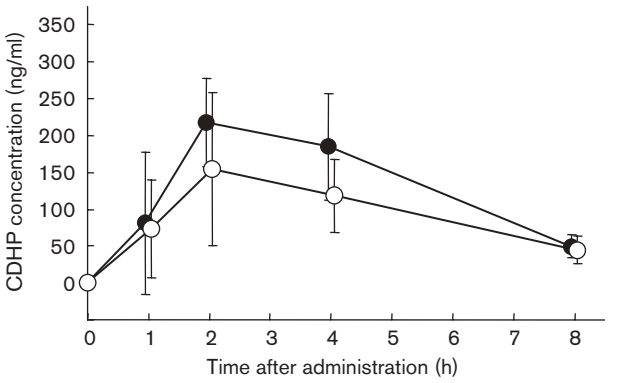
Correlations between the AUCs of the blood 5-FU concentrations and blood CDHP concentrations in all cases included in the analysis ($n=12$). Closed circles, pre-operation, $y=0.534x-7.661$, $r=0.774$; open circles, post-operation, $y=0.546x-34.84$, $r=0.769$.

Fig. 4



Changes in blood 5-FU concentrations in the partial gastrectomy cases ($n=9$). Closed circles, pre-operation; open circles, post-operation; points, mean; bars, SD.

Fig. 5



Changes in blood CDHP concentrations in the partial gastrectomy cases ($n=9$). Closed circles, pre-operation; open circles, post-operation; points, mean; bars, SD.

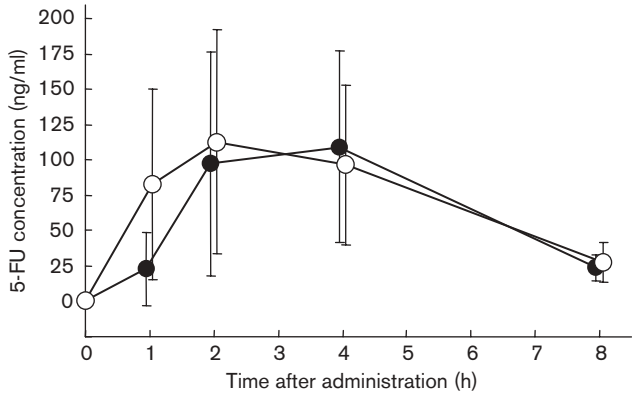
1-, 2- and 4-h concentrations tended to be slightly lower than pre-operatively, and no significant differences were found between the C_{max} and t_{max} values before and after the operation, but the post-operative $AUC_{0-8\,h}$ was significantly smaller than the pre-operative $AUC_{0-8\,h}$ ($P=0.044$).

Blood concentration of 5-FU and CDHP in the total gastrectomy cases

The changes in blood 5-FU concentrations in the three cases in which it was possible to collect blood both pre- and post-operatively among the five patients who underwent total gastrectomy are shown in Fig. 6. The pre-operative 1-, 2-, 4- and 8-h concentrations were 23 ± 26, 97 ± 79, 109 ± 68 and 24 ± 9 ng/ml, respectively; the C_{max} was 109 ± 68 ng/ml; the t_{max} was 4.0 ± 0.0 h; and the $AUC_{0-8\,h}$ was 554 ± 371 ng · h/ml (Table 2). The post-operative 1-, 2-, 4- and 8-h concentrations were 83 ± 68, 113 ± 80 and 97 ± 57 and 28 ± 14 ng/ml, respectively; C_{max} was 114 ± 78 ng/ml; t_{max} was 2.7 ± 1.2 h; and $AUC_{0-8\,h}$ was 593 ± 388 ng · h/ml (Table 2). Although no significant differences were observed in the concentrations 1 and 2 h after S-1 administration, the post-operative concentrations tended to be higher than the pre-operative concentrations, and the 4-h concentration tended to be slightly lower post- than pre-operatively. t_{max} shortened from 4.0 ± 0.0 h pre-operatively to 2.7 ± 1.2 h post-operatively, but no significant differences were found between the C_{max} or $AUC_{0-8\,h}$ values before and after the operation.

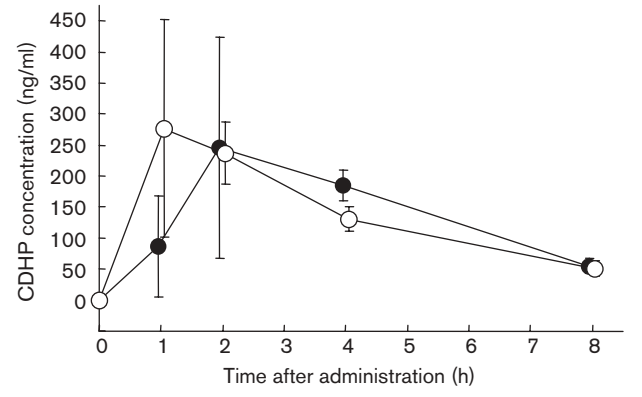
The pre- and post-operative changes in blood CDHP concentrations in the same patients are shown in Fig. 7.

Fig. 6



Changes in blood 5-FU concentrations in the total gastrectomy cases ($n=3$). Closed circles, pre-operation; open circles, post-operation; points, mean; bars, SD.

Fig. 7



Changes in blood CDHP concentrations in the total gastrectomy cases ($n=3$). Closed circles, pre-operation; open circles, post-operation; points, mean; bars, SD.

The pre-operative 1-, 2-, 4- and 8-h concentrations were 88 ± 82, 245 ± 178, 186 ± 23 and 55 ± 13 ng/ml, respectively; C_{max} was 281 ± 139 ng/ml; t_{max} was 2.7 ± 1.2 h; and $AUC_{0-8\,h}$ was 1121 ± 383 ng · h/ml (Table 3). The post-operative 1-, 2-, 4- and 8-h concentrations were 277 ± 175, 237 ± 50, 131 ± 20 and 51 ± 13 ng/ml, respectively; C_{max} was 305 ± 142 ng/ml; t_{max} was 1.3 ± 0.6 h; and $AUC_{0-8\,h}$ was 1127 ± 326 ng · h/ml (Table 3). Although no significant difference was found between the 1-h concentrations after S-1 administration, the post-operative concentration tended to be higher than pre-operatively and the 4-h concentration tended to be slightly lower post- than pre-operatively. t_{max} shortened from 2.7 ± 1.2 h pre-operatively to 1.3 ± 0.6 h post-operatively, but no significant differences were found between the C_{max} or $AUC_{0-8\,h}$ values before and after the operation.

Discussion

S-1 is more capable of maintaining blood 5-FU concentrations to an extent that resembles continuous i.v. infusion of 5-FU than previous oral fluoropyrimidines [8,15] and this is thought to be related to its high efficacy rate. A high incidence of adverse events has, however, been reported when S-1 has been used as post-operative adjuvant therapy for gastric cancer and in some cases treatment has even had to be discontinued [16,17]. Since the subjects of administration are gastrectomy patients when S-1 is used as post-operative adjuvant therapy for gastric cancer, it is important to know the pharmacokinetics of S-1 after gastrectomy from the viewpoint of considering the efficacy and safety of post-operative S-1 administration. Therefore, in the present study, we compared the pharmacokinetics of S-1 after a single dose about 7 days before surgery and on about post-operative hospital day 14, when rice gruel feeding had become possible, in a total of 12 patients, nine of whom underwent partial gastrectomy (distal gastrectomy) and three of whom underwent total gastrectomy. We assessed the pharmacokinetics of S-1 by measuring the blood concentrations of 5-FU and CDHP. Although there was wide variation in the blood 5-FU and CDHP concentrations after S-1 administration from patient to patient, when examined overall the kinetics of 5-FU in the blood correlated with the kinetics of CDHP in the blood (Fig. 3) and, as in the report by Hirata *et al.* [8], the DPD-inhibiting action of CDHP was shown to be important to 5-FU kinetics in the blood after S-1 administration.

In partial gastrectomy patients orally administered drugs are temporarily retained in the remnant stomach and then slowly pass into the small intestine, but because the ability of the remnant stomach to retain drugs is reduced, the time until the maximum blood concentration is reached may be shorter, and it is also possible that passage from the stomach into the small intestine may be slowed by stenosis at the site of the anastomosis, etc., and the rise in blood concentration may be late instead. Although the results of this study of partial gastrectomy patients showed that the C_{max} values for the concentrations of 5-FU and CDHP in the blood after S-1 administration were lower after surgery than before surgery, the t_{max} remained unchanged and the $AUC_{0-8\,h}$ values were almost the same. Maehara *et al.* reported on the effects of partial gastrectomy on the pharmacokinetics of UFT, and in the cases in which reconstruction was by the Billroth I method, the C_{max} values for the concentrations of FT, uracil and 5-FU in the blood 2 weeks after surgery were lower than before surgery, the t_{max} values were longer and the AUC values were smaller, and it was assumed that the reason for these results was

that the passage of the drugs from the remnant stomach into the small intestine was late because of the decreased motility of the remnant stomach [13]. They claimed that by 3 months post-operatively the values had recovered to the same level as before surgery. When the pharmacokinetics of S-1 and UFT were compared, there was just a difference in the dose of FT and there was no difference in absorption rate, etc. However, because the uracil combined in UFT is absorbed more rapidly than the CDHP combined in S-1 and it disappears more rapidly from the blood, it is reflected in the kinetics of 5-FU in the blood as well. Thus, UFT appears to be more likely to be affected by the decreased function of the remnant stomach than S-1. Moreover, in the present study we gave the S-1 dose after breakfast, whereas Maehara *et al.* gave the UFT dose before breakfast and it is also possible that administration on an empty stomach is more likely to be affected by the decreased function of the remnant stomach. Based on the above, while it appears possible that decreased function of the remnant stomach and decreased absorption occur in the early post-operative period as a result of the surgical insult, etc., their impact becomes minor by 2 weeks post-operatively and it is inferred that the post-operative pharmacokinetics of S-1 are almost the same as before surgery.

In the patients who underwent total gastrectomy, the t_{max} of CDHP after S-1 administration decreased from 2.7 ± 1.2 h pre-operatively to 1.3 ± 0.6 h post-operatively and the t_{max} of 5-FU decreased from 4.0 ± 0.0 h pre-operatively to 2.7 ± 1.2 h post-operatively, but no significant differences were observed between the pre- and post-operative $AUC_{0-8\,h}$ values of either CDHP or 5-FU. This is presumably because the retention function of the stomach is lost in total gastrectomy patients, and after ingestion the drug rapidly enters the small intestine and is absorbed, but the amounts absorbed themselves are not different before and after surgery. Hirata *et al.* also reported that the t_{max} of 5-FU after S-1 administration was 4 h in patients who had not undergone gastrectomy ($n = 9$) and 2 h shorter in patients who had undergone total gastrectomy ($n = 3$), but that gastrectomy had little effect on the pharmacokinetics of S-1 [8]. Maehara *et al.* reported observing no significant differences between the pharmacokinetics of UFT in total gastrectomy before and 2 weeks after surgery [13]. Based on the above, although the absorption rate of S-1 is increased in total gastrectomy patients, there is no change in the amount absorbed and gastrectomy is inferred to have hardly any effect on the pharmacokinetics of S-1.

Thus, the results of the present study showed that around post-operative hospital day 14, when total oral feeding had become possible after surgery for gastric cancer, the $AUC_{0-8\,h}$ values of 5-FU and CDHP after S-1 administration were almost the same as before surgery, and that gastrectomy had hardly any effect on the pharmacokinetics of S-1. Since the results in partial gastrectomy (distal gastrectomy) cases suggested, however, that the decreased function of the remnant stomach may have an impact in the early post-operative period and the results in the total gastrectomy patients suggested that blood concentrations peak sooner than pre-operatively, because drug absorption is more rapid, it seems especially necessary to exercise care when administering S-1 in the early post-operative period.

Conclusion

Around post-operative hospital day 14, when total oral feeding had become possible after surgery for gastric cancer, the $AUC_{0-8\,h}$ values of 5-FU and CDHP after S-1 administration were almost the same as before surgery, and gastrectomy had hardly any effect on the pharmacokinetics of S-1.

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