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Effect of gastrectomy on the pharmacokinetics of tegafur, uracil, and 5-fluorouracil after oral administration of a 1:4 tegafur and uracil combination

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Abstract. The effects of gastrectomy on the pharmacokinetics of UFT, a combined oral preparation of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and uracil at a molar ratio of 1:4, were examined in 26 patients with macroscopic Stage I gastric cancer. In all, 200 mg UFT (in terms of tegafur) was given to 17 patients who underwent partial gastrectomy (9 cases of Billroth I reconstruction, 8 cases of Billroth II reconstruction) and to 9 patients who underwent total gastrectomy with modified Roux-en-Y reconstruction. Before the operation, the area under the curve (AUC) for tegafur, uracil, and 5-fluorouracil (5-FU) was 79.28 ± 26.88, 4.41 ± 1.78, and 0.51 ± 0.20 μg h ml^{-1}, respectively. Partial (Billroth I and II) and total gastrectomy did not alter the AUC of tegafur, and partial gastrectomy using the Billroth I and II methods decreased the AUCs of uracil and 5-FU during the first 2 weeks postoperation. However, plasma levels of uracil and 5-FU reverted to preoperative values at 3 months postsurgery. Our findings show that when UFT is prescribed for patients treated in the early postoperative period following partial gastrectomy for cancer, dose increases and the timing of administration should be given close attention.

Introduction

Malabsorption of nutrients can occur after gastrectomy [2, 24, 32], the cause being rapid intestinal transit, bacterial overgrowth, and/or pancreatic understimulation. In Japan, postoperative chemotherapy combined with oral preparations of 5-fluorouracil (5-FU) [16] or its analogues is often prescribed for patients with gastric cancer [15, 17]. UFT, a combination of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and uracil at a molar ratio of 1:4, was developed by Fujii et al. [5, 6] (Fig. 1). Experimental studies [5, 6, 13] and clinical trials [8, 22] have shown higher 5-FU levels in the blood and in tumor tissues after the administration of UFT as compared with tegafur or 5-FU alone. Figure 2 illustrates the metabolism of UFT. In the postoperative period, microfoci of tumor cells often grow rapidly, and early postoperative chemotherapy including UFT is required to suppress tumor growth. There have been few studies on the influence of gastrectomy with regard to the absorption and pharmacokinetics of orally prescribed preparations [33]. Suda et al. [29] reported on the influence of gastrectomy on pharmacokinetic changes of UFT for patients given UFT for the first 7 postoperative days; however, they did not describe the pharmacokinetic changes in the time trend for each patient who underwent gastrectomy.

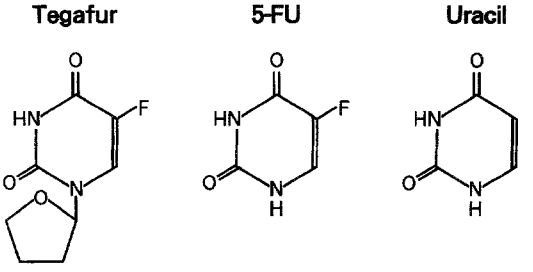

Fig. 1. Molecular structures of tegafur, 5-FU and uracil

Following the peroral administration of 200 mg UFT (in terms of tegafur) to patients with macroscopic Stage I gastric cancer, we examined the concentrations of these drugs in blood samples on the day before operation and at 2 weeks and 3 months postoperation, the objective being to assess the pharmacokinetics of UFT after the ingestion of this drug following gastrectomy.

Patients and methods

Patients. The 26 patients included in this trial underwent macroscopic curative resection for a Stage I gastric cancer, including 9 cases of partial gastrectomy with Billroth I reconstruction, 8 cases of partial

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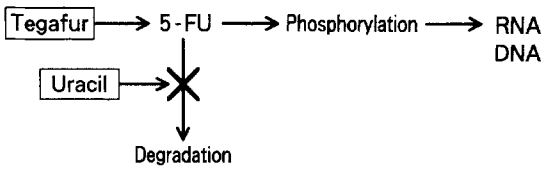

Fig. 2. Schema for metabolism of UFT [9]

gastrectomy with Billroth II reconstruction, and 9 cases of total gastrectomy with modified Roux-en-Y reconstruction (Fig. 3). Preoperative pulmonary, liver, kidney, and heart functions were within the normal ranges. Peroral nutrition was started on postoperative days 4–7, the time at which the first fecal evacuations occurred. All these patients were free of postoperative complications.

Pharmacokinetic changes of UFT (Taiho Pharmaceutical Co., Japan) were examined at three different times: on the day before operation and at 2 weeks and 3 months postsurgery. In all, 200 mg UFT (in terms of tegafur) per patient was given orally before breakfast (8:00 a.m.) on the day before the operation and at 2 weeks and 3 months postsurgery. Blood samples were collected prior to administration and at 30 min, 1 h, 3 h, 6 h, 12 h, and 24 h postadministration. Hematopoietic function (WBC, RBC, platelets, hematocrit, and hemoglobin) and liver (albumin, total protein, total bilirubin, alkaline phosphatase, GOT, GPT, and γ-GTP) and kidney (blood urea nitrogen and creatinine) functions were routinely examined. Informed consent to participate in this study was obtained from all patients prior to blood testing.

Assay of drug concentration. The concentrations of tegafur, uracil, and 5-FU in plasma were determined using the gas chromatographic-mass spectrographic method [18–20]. In all, 1 ml plasma was adjusted to pH 2.0 with 5 *N* HCl, chloroform was added, and the preparation was shaken vigorously. The aqueous layer was used to determine the levels of uracil and 5-FU, and the chloroform layer was used to determine the level of tegafur.

Pharmacokinetic analysis. The area under the curve (AUC) was calculated using the logarithmic trapezoidal method [7, 28].

Statistical analysis. The data were analyzed using Student's paired *t*-test. A *P* value of less than 0.05 was considered to be statistically significant.

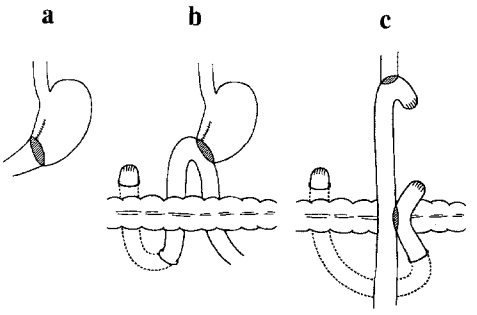

Fig. 3a–c. Mode of gastrectomy for surgical operation. **a** Partial (Billroth I). **b** Partial (Billroth II). **c** Total (modified Roux-en-Y reconstruction)

Results

The plasma levels of tegafur, uracil, and 5-FU in the patients were determined three times during a 24-h period, on the day before the operation and at 2 weeks and 3 months postsurgery (Tables 1–3). No prominent difference in hematopoietic,liver, or renal function was found between the preoperative values and those obtained at 2 weeks or 3 months postsurgery in patients treated with either partial or total gastrectomy. At 2 weeks postsurgery, diarrhea occurred in 33.3% (3/9) of the patients treated by Billroth I partial gastrectomy, in 25.0% (2/8) of those treated by Billroth II partial gastrectomy, and in 33.3% (3/9) of those who underwent total gastrectomy.

In this study, Cpeak was the highest plasma concentration of each drug actually achieved at 30 min, 1 h, 3 h, 6 h, 12 h, and 24 h after oral ingestion of UFT and was expressed as the mean value obtained for the patients in each group listed in Tables 1–3. Tpeak was defined as the time required to reach Cpeak for each drug and was expressed as the mean value obtained for the patients in each group.

First, 200 mg UFT (in terms of tegafur) was given to each patient on the day before surgery and the pharmacokinetics of tegafur, uracil and 5-FU were examined. The

Table 1. Changes in plasma levels of tegafur after peroral administration of 200 mg UFT

Treatment	Time of test	Tegafur		
		Cpeak (μg/ml)	Tpeak (h)	AUC (μg h ml^{-1})
None	Preoperation[a] (n = 26)	8.68±2.29	1.44±1.51	79.28±26.88
Partial gastrectomy (Billroth I, n = 9)	Preoperation[b]	9.43±2.38 *	1.33±1.76 *	84.68±31.30
	Postop – 2 weeks	6.53±1.77	5.00±1.50	84.28±28.94
	Postop – 3 months	9.68±2.42 *	1.50±1.69 *	119.18±34.49
Partial gastrectomy (Billroth II, n = 8)	Preoperation[c]	8.38±2.88	1.94±1.95	77.65±33.64
	Postop – 2 weeks	6.94±3.19	3.50±2.32	80.09±33.80
	Postop – 3 months	8.27±2.41	1.94±1.95	90.63±34.95
Total gastrectomy (n = 9)	Preoperation[d]	8.21±1.76	1.11±0.74	75.32±18.06
	Postop – 2 weeks	8.53±1.32	0.72±0.26	80.29±18.18
	Postop – 3 months	8.75±1.58	0.94±0.81	86.63±19.78

Postop, Postoperation
* P <0.01
[a] Data were calculated by the cumulation of b, c, and d

Table 2. Changes in plasma levels of uracil after peroral administration of 200 mg UFT

Treatment	Time of test	Uracil		
		Cpeak (μg/ml)	Tpeak (h)	AUC (μg h ml^{-1})
None	Preoperation[a] (n = 26)	1.98±0.99	1.23±0.89	4.41±1.78
Partial gastrectomy (Billroth I, n = 9)	Preoperation[b]	1.97±1.03 } *	1.11±0.74 } *	4.42±2.23 } **
	Postop – 2 weeks	0.50±0.79	3.78±1.79	2.02±2.89
	Postop – 3 months	1.96±1.05 } *	1.33±1.77 } *	4.14±1.75 } **
Partial gastrectomy (Billroth II, n = 8)	Preoperation[c]	1.98±1.15 } **	1.06±0.82 } **	4.35±1.81 } **
	Postop – 2 weeks	0.86±1.11	2.94±2.15	2.39±1.80
	Postop – 3 months	1.83±1.96 } *	1.69±1.39	4.30±2.21 } **
Total gastrectomy (n = 9)	Preoperation[d]	1.99±0.99	1.50±1.15	4.46±1.56
	Postop – 2 weeks	1.50±0.81	0.98±0.26	3.37±1.42
	Postop – 3 months	1.70±0.93	0.94±0.81	3.41±1.29

Postop, Postoperation
*P <0.01, **P <0.05

[a] See Table 1

Table 3. Changes in plasma levels of 5-FU after peroral administration of 200 mg UFT

Treatment	Time of test	5-FU		
		Cpeak (μg/ml)	Tpeak (h)	AUC (μg h ml^{-1})
None	Preoperation[a] (n = 26)	0.14±0.08	1.17±1.23	0.51±0.20
Partial gastrectomy (Billroth I, n = 9)	Preoperation[b]	0.15±0.08 } *	1.33±1.77 } *	0.58±0.25 } **
	Postop – 2 weeks	0.04±0.07	5.00±3.00	0.32±0.19
	Postop – 3 months	0.13±0.07 } *	2.06±3.74 } *	0.55±0.18 } **
Partial gastrectomy (Billroth II, n = 8)	Preoperation[c]	0.14±0.09	0.75±0.25 } *	0.54±0.16 } **
	Postop – 2 weeks	0.07±0.07	4.00±3.92	0.29±0.15
	Postop – 3 months	0.13±0.12	1.94±1.96	0.53±0.18 } **
Total gastrectomy (n = 9)	Preoperation[d]	0.14±0.07	1.17±1.06	0.48±0.21
	Postop – 2 weeks	0.11±0.05	1.00±0.79	0.51±0.19
	Postop – 3 months	0.12±0.07	1.50±1.87	0.53±0.18

Postop, Postoperation
*P <0.01, **P <0.05

[a] See Table 1

Cpeak was 8.68±2.29 μg/ml and the Tpeak was 1.44±1.5 h for tegafur. At the first 2 weeks postoperatively, the Cpeak was decreased and the Tpeak was delayed for tegafur in cases of partial gastrectomy with Billroth I reconstruction (P <0.01) but not for patients treated by Billroth II partial gastrectomy or total gastrectomy (Table 1). The AUC of tegafur remained unchanged on the day before the operation and at 2 weeks and 3 months postsurgery in cases of either partial (Billroth I and II) or total gastrectomy.

Before the operation, the Cpeak of uracil and 5-FU was 1.98±0.99 and 0.14±0.08 μg/ml, respectively, and the Tpeak was 1.23±0.89 and 1.17±1.23 h, respectively (Tables 2, 3). The Cpeak was decreased and the Tpeak was delayed for uracil and 5-FU at 2 weeks postoperatively in patients who underwent partial gastrectomy using Billroth I and II methods (P <0.05), but these changes were not evident in cases of total gastrectomy. The AUCs of uracil and 5-FU decreased to about 50% at 2 weeks postsurgery in cases of partial gastrectomy with Billroth I and II reconstruction (P <0.05) but not for total gastrectomy.

The decreases in Cpeak and AUC and the delay of Tpeak recorded for tegafur, uracil, and 5-FU at 2 weeks following partial gastrectomy had recovered to preoperative levels by 3 months after the operation.

Discussion

5-FU and its analogues, including UFT, a combined oral preparation of tegafur and uracil at a molar ratio of 1:4, have been prescribed for patients with gastric cancer [15, 17]. We found that UFT was more antineoplastic than 5-FU, tegafur, or 1-hexylcarbamoyl-5-fluorouracil against gastric cancer tissues as determined using the in vivo chemosensitivity test [12]. The mechanisms of the antineoplastic effects of UFT are as follows; tegafur is converted to 5-FU mainly in liver microsomes [31] and the phosphorylated antimetabolites of 5-FU inhibit RNA and DNA synthesis in

the tumor. Concomitant administration of uracil suppresses the degradation of 5-FU in the liver but does not suppress the phosphorylation of 5-FU in the tumor (Fig. 1) [9]. Higher levels of 5-FU remain in the blood and in tumor tissues when UFT is given to rodents [5, 6] or to patients [8] as compared with the findings obtained with tegafur or 5-FU alone.

We have found that postoperative chemotherapy with mitomycin C and UFT extends the 5-year survival of patients with stage IV gastric cancer to 23% as compared with the 13% reported for the combination of mitomycin C and tegafur [15]. Rates of side effects are not increased by the administration of a daily dose of UFT, because UFT is selectively toxic against tumor tissue [5]. In this protocol, 600 mg UFT (in terms of tegafur) given orally and daily for 2 years was started at 2 weeks after the surgery.

Tegafur was developed as a lipophilic masked derivative of 5-FU so as to improve the absorbability and to retain the antitumor effect after oral ingestion; it is absorbed by passive diffusion from the intestine [4, 25–27]. Anttila et al. [1] have reported that tegafur is well absorbed from the intestine, is distributed into each organ in the body in patients with a nonresectable hepatic tumor, and that there is no need to give this drug intravenously. In case of uracil, active transport is the predominant mode of absorption [26], and passive diffusion occurs when the concentration of uracil in the small intestine is increased and active processes are saturated.

The Cpeak was decreased and the Tpeak was delayed for both tegafur and uracil in patients undergoing partial gastrectomy because of a diminished movement of the remnant stomach and a lower degree of transit of these agents in the time trend from the remnant stomach to the small intestine during the early postoperative period. On the other hand, the liver is the main organ in which drugs are metabolized [3, 11]. As no changes were noted in perioperative liver and renal functions in cases of partial and total gastrectomy, there should be no difference in the rate of drug metabolism measured on the day before the operation and that determined postoperatively. Therefore, the absorption of water-soluble uracil in the small intestine would be decreased and the level of AUC would be lower in cases of partial gastrectomy. As uracil suppresses the degradation of 5-FU in the liver of the patient, the lower absorption of uracil in cases of partial gastrectomy is closely related to the lower plasma level of 5-FU. These decreased levels of drugs in the early postoperative period have also been reported for patients treated by Billroth I partial gastrectomy [29]. In cases of total gastrectomy, tegafur and uracil are immediately transferred to the intestine after oral ingestion of UFT and are well absorbed.

The minimal inhibitory concentration of 5-FU has been reported to be 0.05 μg/ml both experimentally and clinically [10, 23, 30]; however, the Cpeak of 5-FU was lower than this concentration following the administration of 200 mg UFT (in terms of tegafur) after partial gastrectomy with Billroth I reconstruction. When the oral prescription of UFT was continued, 5-FU accumulated [21] and the blood level of 5-FU exceeded 0.05 μg/ml. As the cytotoxicity of 5-FU is also dose-dependent [14], the antineoplastic effect of UFT should be lower in cases of partial gastrectomy when the preparation is prescribed during the early postoperative period. The decreased absorption of uracil was overcome within 3 months postoperatively and functions of the digestive organs recovered to normal levels.

Our findings show that partial gastrectomy with Billroth I and II reconstruction alters the pharmacokinetics of UFT following its oral ingestion. Such being the case, when UFT is prescribed in the early postoperative period, dose increases and the timing of administration should be given due consideration.

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