Cancer Chemother. Pharmacol. 4, 189–193 (1980)

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of 1-Alkylcarbamoyl-5-fluorouracils in Plasma and Ascites Fluid after Oral Administration in Mice

M. Iigo, A. Hoshi, and K. Kuretani

Pharmacology Division, National Cancer Center Research Institute, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan

Summary. *Pharmacokinetics of 1-alkylcarbamoyl-5-fluorouracils was examined in mice bearing sarcoma 180. The alkylcarbamoyl derivatives were absorbed rapidly as intact form through the gastrointestinal tract and distributed into ascites fluid. Concentration-×-time (C-×-t) values of 5-fluorouracil formed in plasma and ascites fluid decreased in order by extension of the carbon chain of the alkyl moiety. C-×-t value of 5-fluorouracil formed in ascites fluid after hexylcarbamoyl derivative was higher than that in plasma. Antitumor activity of the compounds was correlated with both maximum concentration (Cmax) and C-×-t values of 5-fluorouracil formed and Cmax of total (intact form plus 5-fluorouracil formed) in ascites fluid ($P < 0.01$), and with C-×-t values in ascites fluid and Cmax and C-×-t values of 5-fluorouracil formed in plasma ($P < 0.05$). Alkylcarbamoyl structure was valuable for rapid absorption through the gastrointestinal tract and blood-ascites barrier and for maintenance of 5-fluorouracil level in plasma and ascites fluid.*

Introduction

5-fluorouracil (5FU) is the most effective agent in chemotherapy of adenocarcinoma of the gastrointestinal tract, but is very toxic at higher doses [2]. Clinical response correlates with the plasma concentration of 5FU [6] and maintenance of a high level of 5FU over a considerable period of time produces an enhanced antitumor effect [1]. Similarly, a positive correlation between plasma levels of 5FU and tumor response was found in colonic cancer [3]. To maintain a high level of 5FU, by administration of a 'masked form' of 5FU but not by continuous infusion of 5FU itself, antitumor activity of various derivatives of 5FU has been examined [4]. Through these studies, 1-alkylcarbamoyl-5-fluorouracils have been found to be a group of active derivatives [4]. These compounds are more active than 5FU against adenocarcinoma 755 and the ascites form of sarcoma 180 when administered orally [4]. Especially methyl- and ethylcarbamoyl derivatives completely inhibit the growth of the ascites sarcoma, but 5FU is only moderately active at the optimal dose [4].

In this report, absorption through the gastrointestinal tract and distribution into ascites fluid of the 1-alkylcarbamoyl-5-fluorouracils were quantitatively examined. Moreover, relationships between concentrations in plasma and ascites fluid or antitumor activity of the derivatives was examined.

Materials and Methods

Compounds. Chemical structures of ten 1-alkylcarbamoyl-5-fluorouracils are shown in Table 1. 5FU and 1-(2-tetrahydrofuryl)-5-fluorouracil (FT) were used as reference compounds. These compounds were supplied by Mitsui Pharmaceuticals, Tokyo, Japan. The compounds were homogenized with 0.5% carboxymethyl cellulose in physiological saline and administered orally in a volume of 0.01 ml/g body weight.

Evaluation of Antitumor Activity. Female ddN mice (20–23 g) were used. A group of six mice were implanted IP with 1×10^7 cells of the tumor. All compounds to be tested were administered orally on day 1 at 1.5 mmol/kg. Antitumor activity of the compounds against the tumor was evaluated by total packed cell volume (TPCV) ratio (T/C, %) on day 7 as previously reported [4].

Determination of 1-Alkylcarbamoyl-5-fluorouracil and 5-Fluorouracil in Plasma or Ascites Fluid. A group of ten mice were implanted IP with 1×10^7 cells of the tumor. All compounds were administered orally at 1.5 mmol/kg 7 days after tumor implantation. After oral administration, the mice were killed at 15, 30, 60, 120, 180, 360, and 720 min. Blood samples were collected from the axillary artery under light ether anesthesia at specified time intervals after oral administration. Plasma samples (about 1 ml) obtained from two mice were pooled and were deproteinized, by the addition of an equal volume of 1 N HCl-methanol (1 : 1, by volume), mixed, and centrifuged. The supernatant was transferred to a fresh tube. An equal volume of chloroform was added to the supernatant to extract 1-alkylcarbamoyl-

Send offprint requests to: M. Iigo at the above address

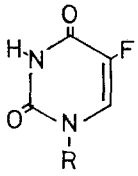
0344-5704/80/0004/0189/$ 01.00

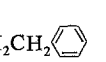
5-fluorouracil. The chloroform layer was evaporated at room temperature in vacuo. The water layer was combined with methanol (3 volumes) and the precipitate formed was removed by centrifugation. The supernatant was dried in vacuo, dissolved in methanol, and an aliquot was spotted on thin-layer chromatograph plate (precoated silica gel 60 F_{254} plate, Merck, Germany). 1-Alkylcarbamoyl-5-fluorouracil and FT in chloroform extract were separated by thin-layer chromatography using a chloroform-methanol (10 : 1) solvent system. 5FU in methanol extract was separated by thin-layer chromatography using the following solvent systems: *n*-propanol-formic acid (10 : 1) and chloroform-methanol (10 : 1). A UV-absorbing spot at Rf similar to authentic sample was scraped off and eluted with methanol. The optical density of each extract was measured at 260 nm. The amounts of 1-alkylcarbamoyl-5-fluorouracils, 5FU, and FT were calculated from the calibration curves of each compound.

On the other hand, ascites fluid (3 ml) which removed tumor cells by centrifugation was pooled, and intact compound and 5FU were separated by thin-layer chromatography similar to plasma.

The recovery of 1-alkylcarbamoyl-5-fluorouracils, 5FU, and FT were 70—80, 70.1, and 80.0%, respectively.

Table 1. Antitumor activity of 5-fluorouracil derivatives. Compounds were administered orally (1.5 mmol/kg) 1 day after tumor implantation. The antitumor activity of the compounds was evaluated with the total packed cell volume ratio 7 days after tumor implantation



Compound no.	—R	Tumor growth (T/C, %)
I	—H (5FU)	27
II	(FT)	89
III	—CONHCH$_3$	7
IV	—CONHC$_2$H$_5$	15
V	—CONHC$_3$H$_7$	53
VI	—CONHC$_4$H$_9$	49
VII	—CONHC$_5$H$_{11}$	60
VIII	—CONHC$_6$H$_{13}$	62
IX	—CONHC$_7$H$_{15}$	88
X	—CONHC$_8$H$_{17}$	82
XI		87
XII		44

Results and Discussion

Plasma Levels of Compounds. Plasma concentration of 5FU varied considerably among 5FU, FT, and 1-alkylcarbamoyl-5fluorouracils (Tables 2 and 3). When 5FU (I) was administered orally, the maximum plasma concentration of intact 5FU was 0.780 μmol/ml at 15 min, but it rapidly decreased and was not detectable at 180 min. Plasma concentration of 5FU derived from FT (II) was low, though intact FT was very high for 720 min. As shown in Table 2, 5FU derived from methyl-(III) and ethylcarbamoyl (IV) derivatives was higher at maximum, then slowly decreased but was still detected at 360 min. Intact methylcarbamoyl derivative was not so highly concentrated, but intact ethylcarbamoyl derivative was very high. 5FU derived from propylcarbamoyl derivative (V) was similar to that of methylcarbamoyl derivative (III). When the carbon chain was extended stepwise, the maximum concentration of intact alkylcarbamoyl derivative and 5FU formed gradually decreased, but were retained for a long period. Phenethylcarbamoyl derivative (XII)

Table 2. Changes in 5-fluorouracil formed in plasma following oral administration of 5-fluorouracil derivatives

Compound no.	Concentration (μmol/ml)						
	15 min	30 min	60 min	120 min	180 min	360 min	720 min
I	0.780 ± 0.131	0.515 ± 0.040	0.108 ± 0.034	0.038 ± 0.024	< 0.02	< 0.02	< 0.02
II	< 0.02	0.040 ± 0.014	0.026 ± 0.004	0.026 ± 0.011	0.027 ± 0.017	0.026 ± 0.006	< 0.02
III	0.509 ± 0.083	0.413 ± 0.050	0.310 ± 0.064	0.277 ± 0.064	0.174 ± 0.014	0.026 ± 0.010	< 0.02
IV	0.404 ± 0.038	0.441 ± 0.043	0.391 ± 0.030	0.377 ± 0.054	0.131 ± 0.088	0.080 ± 0.036	< 0.02
V	0.600 ± 0.075	0.306 ± 0.031	0.347 ± 0.092	0.132 ± 0.030	0.057 ± 0.044	0.046 ± 0.036	< 0.02
VI	0.472 ± 0.058	0.202 ± 0.003	0.175 ± 0.026	0.158 ± 0.068	0.021 ± 0.004	< 0.02	< 0.02
VII	0.246 ± 0.104	0.201 ± 0.026	0.178 ± 0.064	0.063 ± 0.051	0.021 ± 0.010	< 0.02	< 0.02
VIII	0.152 ± 0.031	0.092 ± 0.036	0.074 ± 0.026	0.041 ± 0.014	0.030 ± 0.018	< 0.02	< 0.02
IX	0.178 ± 0.017	0.211 ± 0.061	0.031 ± 0.021	0.017 ± 0.017	< 0.02	< 0.02	< 0.02
X	0.205 ± 0.030	0.155 ± 0.021	0.064 ± 0.044	0.068 ± 0.026	0.033 ± 0.021	< 0.02	< 0.02
XI	0.297 ± 0.067	0.132 ± 0.065	0.145 ± 0.036	0.104 ± 0.012	0.058 ± 0.007	0.040 ± 0.014	< 0.02
XII	0.320 ± 0.121	0.178 ± 0.011	0.149 ± 0.046	0.145 ± 0.026	0.195 ± 0.050	0.132 ± 0.026	0.065 ± 0.017

Each compound was administered orally at 1.5 mmol/kg
After each administration, plasma of two mice were pooled and analysed
Each value is the mean ± SE for five experiments

Table 3. Changes in intact 5-fluorouracil derivatives in plasma following oral administration of 5-fluorouracil derivatives

Compound no.	Concentration (μmol/ml)						
	15 min	30 min	60 min	120 min	180 min	360 min	720 min
II	0.548 ± 0.074	0.479 ± 0.080	0.490 ± 0.081	0.346 ± 0.023	0.361 ± 0.038	0.179 ± 0.060	0.074 ± 0.036
III	0.070 ± 0.014	0.172 ± 0.035	0.110 ± 0.021	0.096 ± 0.017	0.063 ± 0.032	0.045 ± 0.024	< 0.02
IV	0.799 ± 0.061	0.416 ± 0.036	0.425 ± 0.007	0.403 ± 0.053	0.199 ± 0.042	0.062 ± 0.008	< 0.02
V	0.282 ± 0.053	0.239 ± 0.036	0.208 ± 0.060	0.097 ± 0.020	0.069 ± 0.008	0.036 ± 0.010	< 0.02
VI	0.330 ± 0.013	0.228 ± 0.016	0.223 ± 0.039	0.173 ± 0.035	0.120 ± 0.036	0.061 ± 0.018	< 0.02
VII	0.427 ± 0.119	0.132 ± 0.005	0.171 ± 0.049	0.147 ± 0.049	0.075 ± 0.019	0.077 ± 0.049	< 0.02
VIII	0.288 ± 0.050	0.162 ± 0.011	0.057 ± 0.014	0.057 ± 0.006	0.052 ± 0.023	0.040 ± 0.013	< 0.02
IX	0.133 ± 0.019	0.181 ± 0.046	0.103 ± 0.033	0.054 ± 0.004	0.063 ± 0.006	0.046 ± 0.026	< 0.02
X	0.208 ± 0.008	0.134 ± 0.039	0.084 ± 0.024	0.063 ± 0.018	< 0.02	< 0.02	< 0.02
XI	0.265 ± 0.066	0.154 ± 0.086	0.125 ± 0.026	0.097 ± 0.030	0.111 ± 0.029	0.046 ± 0.014	< 0.02
XII	0.198 ± 0.021	0.112 ± 0.012	0.123 ± 0.032	0.153 ± 0.028	0.175 ± 0.041	0.179 ± 0.018	0.0147 ± 0.021

Each compound was administered orally at 1.5 mmol/kg
After each administration, plasma of two mice were pooled and analysed
Each value is the mean ± SE for five experiments

Table 4. Changes in 5-fluorouracil formed in ascites following oral administration of 5-fluorouracil derivatives

Compound no.	Concentration (μmol/ml)						
	15 min	30 min	60 min	120 min	180 min	360 min	720 min
I	0.784 ± 0.067	0.504 ± 0.074	0.135 ± 0.031	0.055 ± 0.026	< 0.01	< 0.01	< 0.01
II	0.054 ± 0.009	0.074 ± 0.013	0.112 ± 0.040	0.033 ± 0.014	0.036 ± 0.011	0.032 ± 0.018	< 0.01
III	0.391 ± 0.074	0.313 ± 0.026	0.302 ± 0.014	0.320 ± 0.028	0.182 ± 0.021	0.048 ± 0.007	< 0.01
IV	0.300 ± 0.074	0.373 ± 0.050	0.321 ± 0.048	0.213 ± 0.026	0.156 ± 0.021	0.040 ± 0.007	< 0.01
V	0.248 ± 0.037	0.253 ± 0.073	0.168 ± 0.030	0.149 ± 0.054	0.139 ± 0.016	0.037 ± 0.016	< 0.01
VI	0.341 ± 0.103	0.108 ± 0.007	0.104 ± 0.006	0.125 ± 0.017	0.058 ± 0.011	0.036 ± 0.004	< 0.01
VII	0.078 ± 0.011	0.092 ± 0.001	0.099 ± 0.020	0.040 ± 0.026	0.054 ± 0.007	0.031 ± 0.007	< 0.01
VIII	0.071 ± 0.026	0.107 ± 0.018	0.079 ± 0.014	0.064 ± 0.021	0.051 ± 0.011	0.068 ± 0.011	< 0.01
IX	0.060 ± 0.006	0.060 ± 0.011	0.044 ± 0.011	0.050 ± 0.016	0.051 ± 0.010	0.018 ± 0.007	< 0.01
X	0.043 ± 0.007	0.081 ± 0.031	0.040 ± 0.007	0.034 ± 0.007	0.034 ± 0.016	< 0.01	< 0.01
XI	0.117 ± 0.026	0.129 ± 0.030	0.090 ± 0.014	0.078 ± 0.030	0.092 ± 0.028	0.050 ± 0.011	< 0.01
XII	0.115 ± 0.043	0.083 ± 0.018	0.067 ± 0.009	0.061 ± 0.017	0.060 ± 0.007	0.060 ± 0.017	0.054 ± 0.017

Each compound was administered orally at 1.5 mmol/kg
Each value is the mean ± SE for ten mice

Table 5. Changes in intact 5-fluorouracil derivatives in ascites following oral administration of 5-fluorouracil derivatives

Compound no.	Concentration (μmol/ml)						
	15 min	30 min	60 min	120 min	180 min	360 min	720 min
II	0.255 ± 0.003	0.331 ± 0.009	0.359 ± 0.055	0.258 ± 0.049	0.300 ± 0.051	0.278 ± 0.034	0.056 ± 0.006
III	0.125 ± 0.025	0.097 ± 0.017	0.083 ± 0.017	0.063 ± 0.006	0.035 ± 0.004	0.024 ± 0.002	< 0.01
IV	0.384 ± 0.077	0.239 ± 0.031	0.292 ± 0.019	0.136 ± 0.013	0.109 ± 0.015	0.039 ± 0.007	< 0.01
V	0.166 ± 0.023	0.141 ± 0.014	0.152 ± 0.025	0.093 ± 0.017	0.102 ± 0.017	0.024 ± 0.004	< 0.01
VI	0.163 ± 0.009	0.150 ± 0.016	0.143 ± 0.019	0.130 ± 0.011	0.083 ± 0.015	0.038 ± 0.005	< 0.01
VII	0.155 ± 0.031	0.064 ± 0.028	0.070 ± 0.015	0.056 ± 0.034	0.052 ± 0.012	0.021 ± 0.009	< 0.01
VIII	0.119 ± 0.030	0.047 ± 0.017	0.052 ± 0.013	0.039 ± 0.006	0.020 ± 0.001	0.021 ± 0.006	< 0.01
IX	0.042 ± 0.008	0.030 ± 0.007	0.028 ± 0.006	0.025 ± 0.001	0.023 ± 0.001	< 0.01	< 0.01
X	0.029 ± 0.008	0.034 ± 0.007	0.041 ± 0.006	0.015 ± 0.004	0.015 ± 0.003	< 0.01	< 0.01
XI	0.050 ± 0.029	0.072 ± 0.018	0.072 ± 0.004	0.058 ± 0.015	0.058 ± 0.007	0.022 ± 0.003	< 0.01
XII	0.078 ± 0.025	0.057 ± 0.006	0.094 ± 0.020	0.089 ± 0.008	0.081 ± 0.005	0.064 ± 0.011	0.072 ± 0.018

Each compound was administered orally at 1.5 mmol/kg
Each value is the mean ± SE for ten mice

and 5FU formed were detected even at 720 min. This is considered to be the reason for higher antitumor potency of the compound in a slow-growing tumor system, such as Lewis lung carcinoma [5]. A large amount of intact alkylcarbamoyl derivatives retained in plasma and 5FU derived from those derivatives was also retained for a long period. It means that all 1-alkylcarbamoyl-5-fluorouracils were rapidly absorbed into plasma in an intact form.

Ascites Fluid Levels of Compounds. As shown in Table 4 and 5, ascites concentration of alkylcarbamoyl derivatives and 5FU formed were varied in compounds. Intact 5FU entered rapidly into ascites fluid but rapidly decreased. In the case of FT (II), intact FT was high and was retained for a long period and 5FU derived from FT in ascites fluid was higher than that in plasma. All of the alkylcarbamoyl derivatives of 5FU were detected in ascites fluid as intact form, and 5FU formed was similar to plasma. Moreover, intact 1-alkylcarbamoyl-5-fluorouracils were retained for a long period. This shows that the intact form can penetrate the bood-ascites barrier without transformation into 5FU.

Relationship Between Concentration of 5FU-×-Time (C-×-t Values) and Chain Length of 1-Alkylcarbamoyl-5-fluorouracil. Concentration of drug-×-time (C-×-t values, mol · hr/ml) were calculated, because a positive correlation between C-×-t values of 5FU in plasma and tumor response was found in colonic cancer [3]. C-×-t values of 5FU in plasma and ascites decreased in order by extension of the carbon chain of the alkyl moiety (Fig. 1). C-×-t values of 5FU formed after administration of phenethylcarbamoyl derivative (XII) showed as high a value as

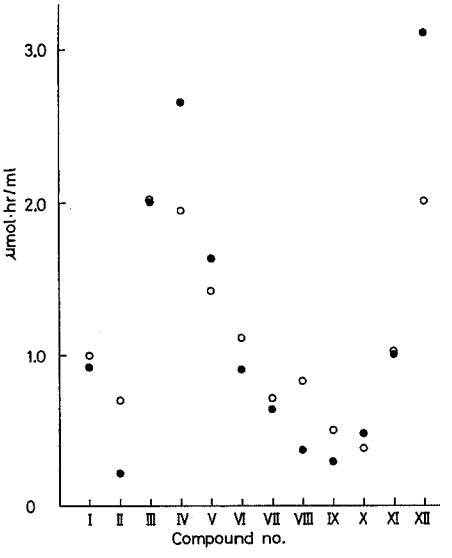


Fig. 1. C-×-t values of 5-fluorouracil formed after oral administration of 1.5 mmol/kg of 5-fluorouracil derivative: (●) plasma; (○) ascites

that of ethylcarbamoyl derivative (IV). C-×-t value of 5FU in ascites fluid of hexylcarbamoyl derivative (VIII) was much higher than that in plasma.

Correlation Among Factors Concerning Plasma and Ascites Levels of Compounds. To clarify properties of the distribution and activation of the masked form of 5FU, the correlation coefficients between each factor concerning maximum concentration (Cmax) and C-×-t values in plasma and that in ascites are calculated in the intact form, 5FU formed or total (intact form plus 5FU formed) (Table 6). Cmax of total in plasma showed a correlation with Cmax of intact form on plasma and with Cmax of total or intact form in ascites fluid ($P < 0.001$). C-×-t values of total in plasma showed a correlation with C-×-t values of intact form and of 5FU formed in plasma and with C-×-t values of total or intact form in ascites fluid. In any case Cmax was not correlated with C-×-t values. Cmax of 5FU in plasma showed a correlation with Cmax of 5FU in ascites. This suggests that 1-alkylcarbamoyl-5-fluorouracils were absorbed in the intact form through the gastrointestinal tract and distributed into ascites fluid in a way similar to 5FU itself.

Antitumor Activity of Compounds Against Ascites Sarcoma 180. As shown in Table 1, 5FU was moderately active but FT was inactive in a single oral administration (1.5 mmol/kg). Methylcarbamoyl derivative (III) of 5FU was markedly active and ethylcarbamoyl derivative (IV) was moderately active. Propyl-(V), butyl-(VI), pentyl-(VII), and hexylcarbamoyl-(VIII) derivatives were weakly active and heptyl-(IX), octyl-(X), and cyclohexylcarbamoyl-(XI) derivatives were inactive.

Relationship Between the Factors and Antitumor Activity. The correlation coefficient is also calculated between factors concerning concentration in plasma or ascites and tumor growth (Table 6). Tumor growth and Cmax of total, 5FU formed, or C-×-t values of 5FU formed in ascites fluid showed negative correlation as expected ($P < 0.01$), and the correlation between Cmax or C-×-t values of 5FU formed in plasma and tumor growth was also significant ($P < 0.05$). These results indicate that 5FU formed in plasma can distribute into ascites fluid and then show antitumor effect, and that a masked form of 5FU in ascites fluid also affects tumor growth. Tumor growth inhibition was more correlated with Cmax than C-×-t value of the intact form in ascites fluid, though C-×-t value was more correlated than Cmax of 5FU formed in ascites fluid with the tumor growth inhibition. Rapid absorption of the intact form into ascites fluid is effective for tumor growth inhibition.

As a result, alkylcarbamoyl structure of the compounds as a mask is considered to be valuable for rapid absorption through gastrointestinal tract and distribution

Table 6. Correlation coefficients between plasma levels, ascites levels and tumor growth when given by oral administration of 1-alkylcarbamoyl-5-fluorouracils

			Ascites					
			5FU formed		Intact form		Total	
			C-x-t	Cmax	C-x-t	Cmax	C-x-t	Cmax
Plasma	Total[a]	Cmax[b]	+0.482	+0.723[f]	+0.485	+0.936[d]	+0.518	+0.869[d]
		C-x-t[c]	+0.810[e]	+0.301	+0.956[d]	+0.425	+0.944[d]	+0.364
	Intact form	Cmax	+0.229	+0.423	+0.317	+0.937[d]	+0.292	+0.636[f]
		C-x-t	+0.633[f]	+0.103	+0.943[d]	+0.331	+0.484	+0.189
	5 FU formed	Cmax	−0.324	+0.836[e]	+0.425	+0.482	+0.583	+0.794[e]
		C-x-t	+0.940[d]	+0.171	+0.856[e]	+0.496	+0.964[d]	+0.545
Ascites	Total	Cmax	+0.663[f]	+0.921[d]	+0.407	+0.848[e]	−0.381	
		C-x-t	+0.936[d]	+0.547	+0.931[d]	+0.513		
	Intact form	Cmax	+0.496	+0.676[f]	+0.461			
		C-x-t	+0.742[f]	+0.332				
	5 FU formed	Cmax	+0.684[f]					
		C-x-t						

			Plasma						Tumor growth
			5FU formed		Intact form		Total		
			C-x-t	Cmax	C-x-t	Cmax	C-x-t	Cmax	
Plasma	Total[a]	Cmax[b]	+0.492	+0.681[f]	+0.285	+0.842[e]	+0.397	—	−0.598
		C-x-t[c]	+0.923[d]	+0.231	+0.960[d]	+0.293			−0.577
	Intact form	Cmax	+0.293	+0.194	−0.149				−0.422
		C-x-t	+0.793[e]	+0.142					−0.399
	5 FU formed	Cmax	+0.558						−0.643[f]
		C-x-t							−0.738[f]
Ascites	Total	Cmax							−0.836[e]
		C-x-t							−0.739[f]
	Intact form	Cmax							−0.683[f]
		C-x-t							−0.524
	5 FU formed	Cmax							−0.836[e]
		C-x-t							−0.851[e]

[a] Intact form plus 5FU formed
[b] Maximum concentration
[c] Concentration-x-time
[d] $P < 0.001$
[e] $P < 0.01$
[f] $P < 0.05$

into tissues. These results support the superior antitumor effect of 1-hexylcarbamoyl-5-fluorouracil (VIII) from a pharmacological stand point.

Acknowledgements. This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, Japan.

References

1. Ansfield F, Klotz J, Nealon T, Ramirez G, Minton J, Hill G, Wilson W, Davis H, Cornell G (1977) A phase III study comparing the clinical utility of four regimens of 5-fluorouracil. Cancer 39:34
2. Davis HL Jr, Hoff DDV, Rozencweig M, Handelsman H, Soper WT, Muggia FM (1978) Gastrointestinal Cancer: Esophagus, stomach, small bowel, colorectum, pancreas, liver, gallbladder, and extrahepatic ducts. In: Randomized trials in cancer: A critical review by sites. Raven, New York, p 147
3. Hillcoat BL, McCulloch PB, Figueredo AT, Ehsan MH, Rosenfeld JM (1978) Clinical response and plasma levels of 5-fluorouracil in patients with colonic cancer treated by drug infusion. Br J Cancer 38:719
4. Iigo M, Hoshi A, Nakamura A, Kuretani K (1978) Antitumor activity of 1-alkylcarbamoyl derivatives of 5-fluorouracil in a variety of mouse tumors. Cancer Chemother Pharmacol 1:203
5. Iigo M, Hoshi A, Nakamura A, Kuretani K (1979) Antineoplastic effect of orally administered 1-alkylcarbamoyl derivatives of 5-fluorouracil on subcutaneously implanted Lewis lung carcinoma and B16 melanoma. Cancer Treat Rep 63:1895
6. Spiers A, Straus M, Janis M, Polackwick R, Mozden P (1977) High dose intravenous infusions of 5-fluorouracil for refractory tumors: The Hi-FU regimen. Proc Am Soc Clin Oncol 18:292

Received August 27, 1979/Accepted March 14, 1980