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Pharmacokinetic study of doxifluridine given by 5-day stepped-dose infusion*

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Summary. Doxifluridine (5′-deoxy-5-fluorouridine, 5′-dFUR) metabolism has been reported to be saturable and associated with a fall in clearance of the drug as the dose is increased. The aim of the present study was to determine the disposition of 5′-dFUR and 5-fluorouracil (5-FU) when 5′-dFUR was given as a 5-day infusion, with the infusion rate increased stepwise every 24 h. Measurement of plasma and urinary levels of 5′-dFUR and 5-FU at steady-state for each infusion rate enabled the estimation of 5′-dFUR renal (Cl_R) and nonrenal (Cl_{NR}) clearance and 5-FU renal clearance. A total of 28 patients with histologically proven malignancy received 5-day courses of 5′-dFUR ranging in dose from 3.75 to 20 g/m^2 per 120 h. The lowest dose given over 24 h was 0.25 g/m^2, and the highest was 5 g/m^2. Steady-state plasma levels of 5′-dFUR ranged from 167 to 6,519 ng/ml. At these plasma levels there was no evidence of significant saturation of 5′-dFUR metabolism; steady-state plasma levels of 5′-dFUR increased approximately linearly with dose, and nonrenal clearance did not change significantly with dose. There was also no evidence of nonlinearity in 5′-dFUR renal clearance. The mean (±SD) Cl_R of 5′-dFUR was 108.9 ± 53.6 ml/min per m^2 (range, 45.7–210 ml/min per m^2), and the Cl_{NR} was 728 ± 181 ml/min per m^2 (range, 444–1,119 ml/min per m^2). Renal clearance comprised 13% of the total 5′-dFUR clearance. The mean renal clearance of 5-FU was 100.8 ± 48.6 ml/min per m^2 (range, 23.5–198 ml/min per m^2). There was considerable interpatient variability in 5′-dFUR renal and nonrenal clearance, even at the same dose level. We concluded that the administration of 5′-dFUR by the infusion method described avoided the saturation of nonrenal elimination processes reported to occur with shorter infusion schedules.

Introduction

Doxifluridine (5′-deoxy-5-fluorouridine, 5′-dFUR, Ro 21-9738) is a fluoropyrimidine that was synthesized in the search for new cytostatic antimetabolites with greater therapeutic indices than 5-fluorouracil (5-FU) [4, 7]. 5′-dFUR is a prodrug of 5-FU [2, 6, 11] that releases 5-FU in tumour cells as a result of the action of intracellular pyrimidine nucleoside phosphorylases [9]. Higher concentrations of 5-FU are released in tumours than in normal tissues [10], probably as a result of higher concentrations of pyrimidine phosphorylase in tumour tissues. By contrast, slower conversion of 5′-dFUR to 5-FU in bone marrow has been reported [1, 7].

5′-dFUR metabolism is saturable and is associated with a fall in clearance of the drug as the dose is increased [3, 5, 8, 13, 15]. The initial decline in levels after a short infusion of 5′-dFUR indicated zero-order elimination, which eventually became first-order below concentrations of approximately 50 mM (~12 μg/ml). The decline in 5-FU plasma levels paralleled the decline in 5′-dFUR leves, suggesting that 5-FU formation was rate-limiting [13]. Dihydrofluorouracil (5-FUH_2) formation or transport also appeared to be saturated under these conditions.

The aim of the present study was to determine the disposition of 5′-dFUR and 5-FU when 5′-dFUR was given as a 5-day infusion, with the infusion rate increased stepwise every 24 h. This method of administration was chosen to avoid the high peak plasma levels and toxicity associated with shorter infusion regimens. Although dependent on the dose and rate of administration, the half-lives of 5′-dFUR and 5-FU are relatively short, and steady-state levels are readily attained with a 24-h infusion of 5′-dFUR. Measurement of plasma and urinary levels of 5′-dFUR and 5-FU at steady-state for each infusion rate enabled the estimation of 5′-dFUR renal and nonrenal clearance and 5-FU renal clearance. The dose dependency of 5′-dFUR disposition with this administration schedule could then be examined.

Patients and methods

Patients. A total of 28 patients with histologically proven malignancy were studied (Table 1). To be eligible for the study, patients must have been considered refractory to conventional therapy or had a tumour for which no established effective therapy existed. At least 3 weeks must have elapsed since prior chemotherapy (6 weeks in the case of mitomycin C or the nitrosoureas). Liver and renal function tests must have been shown to be normal prior to entry into the study. All patients were older than 18 years of age and gave informed consent before proceeding with the

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Table 1. Patient characteristics

Patient number	Sex/ age (years)	Surface area (m^2)	Dose (g/m^2 per 24 h): Day					Dose (g/m^2 per 120 h)	Diagnosis
			1	2	3	4	5		
1	M/43	1.75	0.25	0.5	0.75	1	1.25	3.75	Rectal cancer
2	F/54	1.7	0.25	0.5	0.75	1	1.25	3.75	Small-cell lung cancer
3	F/45	1.4	0.25	0.5	0.75	1	1.25	3.75	Breast cancer
4	F/69	1.4	0.25	0.5	1	1.5	1.75	5	Non-small-cell lung cancer
5	M/48	2.0	0.25	0.5	1	1.5	1.75	5	Colon cancer
6	M/43	1.65	0.25	0.5	1	1.5	1.75	5	Pancreatic cancer
7	M/66	1.7	0.5	1	1.5	2	2.5	7.5	Head and neck cancer
8	M/74	1.9	0.5	1	1.5	2	2.5	7.5	Prostate cancer
9	M/69	1.75	0.5	1	1.5	2	2.5	7.5	Non-small-cell lung cancer
10	F/57	1.9	1	1.5	2	2.5	3	10	Ovarian cancer
11	F/61	1.45	1	1.5	2	2.5	3	10	Kidney cancer
12	F/54	1.7	1	1.5	2	2.5	3	10	Renal cell cancer
13	Patient withdrew from study								
14	F/67	1.9	1.5	2	2.5	3	3.5	12.5	Melanoma
15	M/67	2.0	1.5	2	2.5	3	3.5	12.5	Non-small-cell lung cancer
16	F/47	1.6	2	2,5	3	3.5	4	15	Colon cancer
17	M/76	1.6	2	2.5	3	3.5	4	15	Stomach cancer
18	M/75	1.5	2	2.5	3	3.5	4	15	Colon cancer
19	M/57	1.9	2.5	3	3.5	4	4.5	17.5	Rectal cancer
20	F/36	1.55	2.5	3	3.5	4	4.5	17.5	Colon cancer
21	F/50	1.8	2.5	3	3.5	4	4.5	17.5	Colon cancer
22	F/40	1.6	3	3.5	4	4.5	5	20	Colon cancer
23	M/22	1.9	3	3.5	4	4.5	5	20	Head and neck cancer
24	F/60	1.4	3	3.5	4	4.5	5	20	Adenocarcinoma
25	M/48	1.9	3	3.5	4	4.5	5	20	Non-small-cell lung cancer
26	F/43	1.8	3	3.5	4	4.5	5	20	Breast cancer
27	F/26	1.75	3	3.5	4	4.5	5	20	Sarcoma
28	M/48	2.1	3	3.5	4	4.5	5	20	Non-small-cell lung cancer
Mean 54		1.73							
SD 14		0.20							

study. The study was approved by the Ethics Committee of the Peter MacCallum Cancer Institute, Melbourne. Patients did not receive other anti-neoplastics or biological modifiers during the study period; radiotherapy to an isolated lesion was permitted. Subjects did not have other serious medical or psychiatric illnesses during the study. They were excluded if they had had previous adverse reactions to 5-FU.

Drug administration. Doxifluridine was given by continuous 24-h infusion for 5 days. Groups of three patients received the same total dose and dose increments before new patients were studied at the next dose level. Seven patients received the maximum tolerated dose of 20 g/m^2 per 120 h. The total 5-day dose was given in stepwise increments over 5 days. A starting dose of 3.75 g/m^2 per 120 h was derived from previous studies using prolonged continuous-infusion schedules (personal communication, Hoffmann-La Roche, Basel). Subjects received up to four courses of treatment, 4 weeks apart. The doses given to each patient on each day of the study are shown in Table 1. In all cases the drug was infused into an arm vein using an infusion pump.

Specimen collection. Blood specimens (10 ml) were collected via an indwelling Teflon catheter from a forearm vein into ice-cold tubes containing heparin. Specimens were collected preinfusion and at 22 and 24 h after the start of each daily infusion for each day of the first course of 5′-dFUR treatment. Blood was kept ice-cold and centrifuged within 1 h of collection, and the plasma was stored at −70° C. Under these conditions no significant loss of 5′-dFUR was expected prior to analysis [14]. Urine samples were collected pre-infusion and all urine voided between 20 and 24 h was also collected. The actual time over which the urine was collected was recorded, as was the volume, and a 10-ml aliquot was immediately frozen and stored at −70° C to await analysis.

Assay methods. 5′-dFUR and 5-FU were kindly provided by Roche Australia. 5-Chlorouracil (5-CU) was obtained from Sigma Chemical Co. Plasma and urinary levels of 5′-dFUR and 5-FU were quantitated by the method of Schaaf et al. [12] with the following modifications. As suggested in the original publication, the source and treatment of the silicas used were found to be important variables in the optimization of the assay. Silica gel obtained from Sigma Chemicals (St. Louis, USA) was used in place of Koch-Light silica gel. It was washed four times with 5 ml ethyl acetate-methanol (90 : 10) before use. 5-CU was used in place of 5-bromouracil as an internal standard, as it had a more convenient retention time relative to

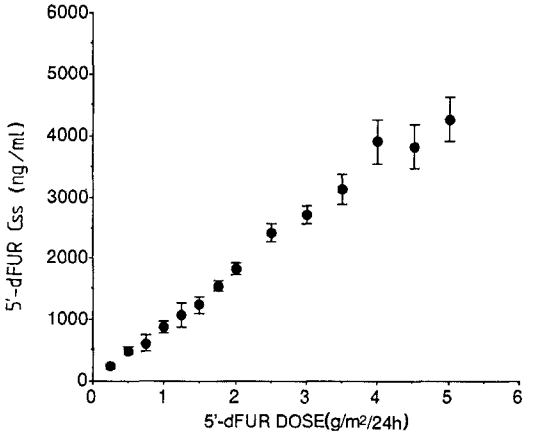

Fig. 1. Mean (± SE) steady-state plasma levels of 5′-dFUR vs the 5′-dFUR dose for the first course of treatment given as a constant i. v. infusion over 24 h and increased stepwise each day for 5 days

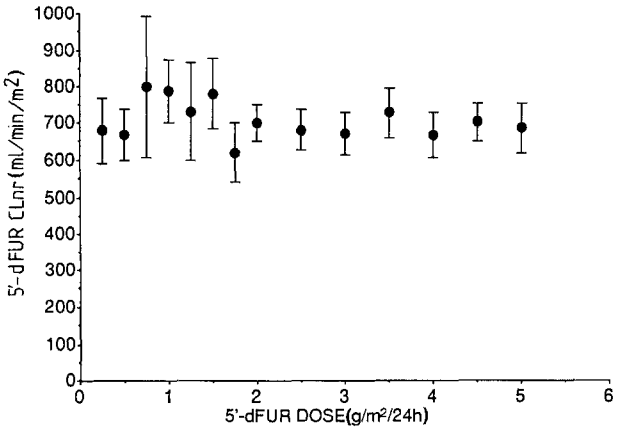

Fig. 2. Mean (±SE) Cl_{nr} of 5′-dFUR vs the 5′-dFUR dose given as a constant i. v. infusion over 24 h and increased stepwise each day for 5 days

5′-dFUR and 5-FU. Retention times of 5-FU, 5-CU, and 5′-dFUR were 4.3, 6.5, and 7.9 min, respectively. Detection limits for 5′-dFUR and 5-FU in plasma were 50 and 20 ng/ml, respectively. In urine the detection limits were approximately 10 and 1 μg/ml, respectively, although these limits could be lowered by subjecting urine to the second extraction step used for plasma.

Intra-assay reproducibility of the HPLC assays was assessed at three different concentrations in plasma and urine. Reproducibility of the assay for 5′-dFUR was 16.9%, 5.0% and 5.5% at plasma concentrations of 200, 500 and 1,000 ng/ml, respectively. For 5-FU, reproducibility was 17.3%, 18.2% and 9.6% at plasma concentrations of 20, 50 and 100 ng/ml, respectively. For 5′-dFUR in urine, reproducibility was 6.6%, 4.5% and 6.6% at urinary concentrations of 10, 50 and 100 μg/ml, respectively. For 5-FU in urine, reproducibility was 19.0%, 6.2% and 4.4%, respectively, at concentrations of 1, 5 and 10 μg/ml, respectively. Reproducibility was poorer at the extremes of the detection limits of the assay, as would be expected; at these limits, specimens were assayed in duplicate.

Inter-assay variability of the HPLC assays was assessed at four different concentrations in plasma and urine. Depending on the expected concentration of 5′-dFUR and 5-FU in the biological fluids, the two most appropriate control samples were included in the run; controls were included in all assay runs. Reproducibility was 12.6%, 7.2%, 8.8% and 7.4% at 5′-dFUR plasma concentrations of 200, 500, 1,000 and 2,000 ng/ml, respectively, and 13.2%, 16.1%, 16.4% and 7.6% at 5-FU plasma concentrations of 20, 50, 100 and 200 ng/ml, respectively. Reproducibility was 10.0%, 10.1%, 9.0% and 7.1% at 5′-dFUR urinary concentrations of 10, 50, 100 and 500 μg/ml, respectively, and 14.6%, 10.1%, 8.8% and 10.1% at urinary 5-FU concentrations of 1, 5, 10 and 50 μg/ml, respectively.

Pharmacokinetic analyses. Total plasma clearance (Cl) of 5′-dFUR was determined from the 5′-dFUR steady-state plasma level ($C_{SS,5'\text{-dFUR}}$) obtained 22 h after the start of each daily infusion, using the equation Cl = 5′-dFUR infusion rate /$C_{SS,5'\text{-dFUR}}$. The 24 h level was found to be unsatisfactory for this purpose since it was often collected just after the infusion had ceased and therefore did not accurately reflect steady-state conditions. The renal clearance of 5′-dFUR ($Cl_{R,5'\text{-dFUR}}$) was calculated from the urinary excretion rate of 5′-dFUR (determined over the period approximately 20–24 h after the start of each 24 h infusion) divided by $C_{SS,5'\text{-dFUR}}$. The nonrenal clearance of 5′-dFUR ($Cl_{NR,5'\text{-dFUR}}$) was determined from the difference between the total clearance and the renal clearance, i.e. $Cl - Cl_{R,5'\text{-dFUR}}$. The renal clearance of 5-FU ($Cl_{R,5\text{-FU}}$) was calculated from the urinary excretion rate of 5-FU (determined over the period approximately 20–24 h after the start of each 24-h infusion) divided by the steady-state plasma level of 5-FU ($C_{SS,5\text{-FU}}$).

Statistical analyses. All statistical analyses were carried out using the Statview 512$^+$ program (BrainPower, Calabasas, Calif) run on a Macintosh Plus PC.

Results

A total of 28 patients received 5-day courses of 5′-dFUR ranging in dose from 3.75 to 20 g/m^2 per 120 h. Patient 13 withdrew early from the study; thus, no useable pharmacokinetic data was obtained in this case. The lowest dose received over 24 h was 0.25 g/m^2 and the highest was 5.0 g/m^2. Steady-state plasma levels of 5′-dFUR ranged from 167 to 6,519 ng/ml and increased approximately linearly with dose (Fig. 1). The nonrenal clearance of 5′-dFUR did not change significantly with dose (Fig. 2, Table 2). There was also no evidence of nonlinearity in 5′-dFUR renal clearance (Table 2). The nonrenal clearance of 5-FU could not be determined because the fraction of the 5′-dFUR dose that is converted to 5-FU is unknown.

The mean (± SD) Cl_R of 5′-dFUR was 108.9 ± 53.6 ml/min per m^2 (range, 45.7–210 ml/min per m^2) and the Cl_{NR} was 728 ± 181 ml/min per m^2 (range, 444–1,119 ml/min per m^2). The renal clearance comprised 13% of the total 5′-dFUR clearance. The mean renal clearance of 5-FU was 100.8 ± 48.6 ml/min per m^2 (range, 23.5–198 ml/min per m^2). There was considerable interpatient variability in the renal and nonrenal clearance of 5′-dFUR even at the same dose level.

Only patients who received the highest dose (20 g/m^2 per 120 h) experienced significant toxicity. Patient 22 had mucocitis (ECOG grade 3); patient 23, thrombocytopenia

and neutropenia (grade 4); patient 24, mucositis (grade 3), thrombocytopenia and neutropenia (grade 4), nausea and vomiting (grade 3) and mucositis (grade 4); patient 25, mucositis (grade 3) and rash (grade 2); patient 26, mucositis (grade 3); patient 27, nausea and vomiting (grade 2); and patient 28, nausea (grade 2). Patient 23, with nasopharyngeal carcinoma, was the only subject to show an objective response and achieved a complete response after the second course of treatment. The details of the clinical outcome and toxicity will be discussed in a separate report. All patients receiving $\geqslant 7.5$ g/m^2 5′-dFUR reported mild nausea or vomiting (grades 1, 2). At each dose level from 12.5 g/m^2 onward single patients developed maculopapular truncal rashes.

Discussion

There was no evidence of saturation of 5′-dFUR elimination in patients in the present study. Renal and nonrenal clearance of 5′-dFUR were unaffected by doses over the range of 0.25–5 g/m^2 per 24 h. From the literature [15] it appears that plasma levels of 5′-dFUR above approximately 10 μg/ml are associated with saturation of 5ė-dFUR metabolism. The maximal plasma levels of 5′-dFUR attained in the present study were only 6–7 μg/ml; hence, saturation was not observed.

Sommadossi et al. [15] have shown that the disappearance of 5′-dFUR from plasma approximated first-order kinetics for low doses of between 1 and 2 g/m^2 given by 30-min infusion. With the maximal non-toxic dose of 15 g/m^2, the 5′-dFUR concentration profile was zero-order over 1 h followed by a first-order process thereafter. Plasma levels of 5′-dFUR attained at this dose were 175 μ*M* (43 μg/ml). Information on the renal clearance of 5′-dFUR was lacking in this study and could also have contributed to nonlinearity in the total elimination of the drug. The results of the study indicated that there was saturation of a metabolic or transport process in the formation of 5,6-dihydro-5-fluorouracil. De Bruijn et al. [5] observed convex plasma concentration curves for 5′-dFUR after the i.v. infusion of 3 g/m^2 5′-dFUR over 10 min. Peak plasma levels attained in their study were approximately 400 μg/ml. These levels therefore greatly exceeded those reached in the present study (6.5 μg/ml).

Table 2. Mean pharmacokinetic parameters for the first course of doxifluridine given by continuous intravenous infusion over 5 days to patients with cancer[a]

Patient number	Dose (g/m^2 per 120 h)	$Cl_{R,5'\text{-dFUR}}$[b] (ml/min per m^2)	$Cl_{NR,5'\text{-dFUR}}$[c] (ml/min per m^2)	$Cl_{R,5'\text{-dFUR}}$[d] (ml/min per m^2)
1	3.75	90.2	494	107.2
2	3.75	154.6	1,029	–
3	3.75	156.8	967	–
3	5	168.8	519	158.0
5	5	96.8	591	103.5
6	5	209.9	707	132.8
7	7.5	48.7	1,119	129.5
8	7.5	77.5	708	43.3
9	7,5	48.8	444	129.8
10	10	51.0	585	94.8
11	10	108.7	886	112.0
12	10	45.7	865	75.5
13[e]	12.5	Patient withdrew from study		
14[e]	12.5	(total clearance, 5′-dFUR = 1,268 ml/min per m^2)		
15	12.5	172.0	617	111.3
16	15	78.3	604	81.9
17	15	69.7	545	57.3
18	15	63.0	627	87.7
19	17.5	76.3	742	43.6
20	17.5	41.0	546	23.5
21	17.5	76.8	696	197.6
22	20	84.1	593	42.1
23	20	157.4	971	54.3
24	20	71.0	863	32.0
25	20	204.8	747	155.5
26	20	143.7	843	133.1
27	20	150.3	936	121.3
28	20	184.9	695	192.2
Mean		108.9	728	100.8
SD		53.6	181	48.6

[a] Parameters were determined for each day of the infusion in each patient. When there was no evidence of dose-dependency for the parameters (Figs. 1, 2), mean values were determined for all 5 days of the treatment schedule

[b] Renal clearance of 5′-dFUR

c Nonrenal clearance of 5′-dFUR

[d] Renal clearance of 5-FU

[e] Sufficient information was not available to enable the determination of parameters in these patients. Only plasma collections were made for patient 14

Schaaf et al. [13] recently reported that doubling the 5′-dFUR dose from 2 to 4 g/m^2 (given by i.v. injection) resulted in a 40% decrease in the nonrenal clearance of 5′-dFUR, from 600 to 370 ml/min. The mean body-surface area of patients in their study was 1.8 m^2; hence, the figures equate to approximately 330 and 200 ml/min per m^2, respectively. The mean nonrenal clearance of 5′-dFUR in the present study was 707 ml/min per m^2, suggesting that saturation of this elimination process had occurred in the study of Schaaf et al. [13], even at the 2 g/m^2 dose level. The renal clearance of 5′-dFUR was reported to be approximately 300 ml/min, or 166 ml/min per m^2, by Schaaf et al. [13] and exceeded the expected GFR. These results therefore confirm the suggestion that 5′-dFUR undergoes renal tubular secretion. There was no evidence that the renal clearance of 5′-dFUR was saturable at the dose levels used in either study.

The method of 5′-dFUR administration reported in the present study enables the administration of relatively high total doses and avoids saturation of 5′-dFUR elimination. This is therefore a more predictable situation, where dose increases are less likely to be associated with disproportionately large increases in 5′-dFUR plasma levels. There is an obvious need to determine the Michaelis-Menten constant for the saturable, nonrenal elimination process underlying the nonlinearity in 5′-dFUR disposition so that the point at which saturation occurs can be predicted for different doses and infusion schedules.

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