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PLASMA LEVELS OF 5-FLUOROURACIL AFTER ORAL AND INTRAVENOUS ADMINISTRATION IN CANCER PATIENTS

R.E. FINCH[1], M.R. BENDING[2] & A.F. LANT[1]

Department of Therapeutics[1] and Medical Unit[2] Westminster Hospital, London SW1P 2AP

1 Plasma levels of 5-fluorouracil (5FU) have been determined in eleven cancer patients after 0.5 g and 1.0 g intravenous doses, and in one patient after paired 1.0 g oral and intravenous doses.

2 The plasma half-life after the 0.5 g intravenous dose was relatively constant, irrespective of the stage and spread of the disease.

3 Plasma kinetics of the drug were dose dependent. Doubling of the intravenous dose produced a 1.5-fold increase in plasma half life, a two-fold increase in initial plasma drug concentration, and a three-fold increase in area under the concentration/time curve.

4 In one patient receiving paired 1.0 g intravenous and oral doses nine weeks apart, an increase in the bioavailability of the drug coincided with a marked clinical regression in palpable intra-abdominal metastases.

5 The significance of measuring plasma drug kinetics and their relationship to drug efficacy and toxicity are discussed.

Introduction

Cytotoxic agents used in cancer chemotherapy generally show a low therapeutic index. Most agents are not tumour specific and drug efficacy is dependent on a greater recovery rate of normal as compared with malignant tissue. Disposition of these drugs in the body is complex (Chabner, Myers & Oliverio, 1977; Bender, Zwelling, Doroshow, Locker, Hande, Murinson, Cohen, Myers & Chabner, 1978) and minor increases in dose may produce severe toxicity. Because of these limitations, and the individual variation in response to these drugs, cytotoxic therapy regimes are largely empirical.

5-fluorouracil (5FU) has been used over the past 20 years in the treatment of carcinoma of the breast, ovary, and gastrointestinal tract. (Heidelberger & Ansfield, 1963; Bruckner & Creasey, 1974; Seifert, Baker, Reed & Vaitkevicius, 1975). The parent drug is distributed throughout extra-cellular fluid and is extensively metabolized, mainly in the liver. Pharmacokinetics of the unchanged drug have been investigated in attempts to optimize conditions of treatment (Cohen, Irwin, Marshall, Darvey & Bateman, 1974; Finn & Sadee, 1975; Sadee & Wong, 1977).

It is possible that both the therapeutic effect and toxicity of 5FU may relate to its rate of disappearance from plasma. We have therefore, monitored the pharmacokinetic properties of 5FU in plasma following standard intravenous and oral doses, with the aim of characterising the variation in drug handling in individual patients.

Methods

Patients

Eleven patients were included in the study: all had primary gastro-intestinal, ovarian, or breast cancer. The range in body weight was between 43 and 79 kg. In each case drug studies were carried out where 5FU was indicated as part of the therapeutic management of the patient.

All eleven patients received an 0.5 g intravenous dose of 5FU, six of them on one occasion only, four on two occasions, with the eleventh patient, W.M., receiving four identical 0.5 g injections. In patient F.C., the two doses were given 1 day before and 17 days after resection of a primary rectal tumour. Patient V.B. received two doses 7 days apart, before and after a 5-day course of quadruple chemotherapy. S.H. received two doses, comprising days 1 and 3 of a 5-day course of quadruple chemotherapy, and F.B. received two doses, 2 days apart. Patient W.M. received four 0.5 g doses of 5FU (1) prior to 5-day quadruple chemotherapy, (2) and (3) on days 1 and 3

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respectively of the 5-day course, and (4) 6 weeks later.

Seven of the eleven patients received both 0.5 g and 1.0 g intravenous doses of 5FU. The two injections were given between 3 and 7 days apart.

In patient W.M., it proved possible to do repetitive studies over several months. As well as receiving four 0.5 g intravenous doses of 5FU, and comparative 0.5 g and 1.0 g doses on two occasions, this patient also received paired 1.0 g oral and 1.0 g intravenous doses. The 1.0 g doses were given 7 days apart in week 1 and 4 days apart in week 9.

Chemotherapy schedules

Single agent therapy 5FU (0.5 g or 1.0 g) was given intravenously or orally. When given intravenously the drug was administered by rapid bolus injection, over less than 10 s. The oral dose was buffered to pH 7.8 and given in orange juice, on an empty stomach.

Combined agent therapy A 5 day cyclical regime of quadruple therapy was used (Costanzi & Coltman, 1969; Hanham, Newton & Westbury, 1971), as follows:

5-fluorouracil	500 mg	Days 1, 2, 3, 4, 5.
Cyclophosphamide	300 mg	Days 1 and 5.
Methotrexate	10 mg	Days 1 and 4.
Vincristine	1 mg	Days 2 and 5.

The other three cytotoxic drugs were administered intravenously as described for 5FU. An intravenous dose of metoclopramide preceded each course of cytotoxic therapy throughout the study. Blood samples for analysis were collected from the opposite arm, by indwelling catheter, into lithium-heparin tubes. Plasma was separated immediately and stored at −20°C.

Samples were collected up to 1.5 h after the intravenous dose and 4 h after the oral dose.

Drug analysis

Plasma samples were analysed by gas liquid chromatography using a nitrogen detector. The internal standard was thymine (Finch, Bending & Lant, 1978). The method is specific for 5FU, even in the presence of other cytotoxic drugs used in the quadruple regime above. Reproducible results were obtained down to 0.1μg 5FU/ml plasma.

Calculations

For each intravenous study a plot of log drug concentration/time was obtained, which was biphasic, showing a rapid alpha phase (less than 5 min), and a linear beta phase. From the plot, the following indices were derived: Co (computed concentration of the drug

Table 1 Diagnostic and pharmacokinetic data for eleven patients after an 0.5 g intravenous dose of 5-fluorouracil

Patient	*Sex*	*Age (years)*	*Site of primary tumour *proven metastases*	$T_{\frac{1}{2}}$ *(min)*	*Co (μg ml⁻¹)*	*AUC (μg min ml⁻¹)*	V_d *(l)*
FB	F	64	Ovary*	7.4	38.8	413	10.7
				9.7	26.0	364	19.2
VB	F	44	Breast*	7.2	50.4	520	9.9
				8.4	46.1	555	10.8
FC	F	40	Gastrointestinal tract	7.2	31.9	333	15.7
			(G.I.T.)	7.3	46.8	498	10.7
RG	F	41	G.I.T.*	9.5	49.5	678	10.1
SG	M	55	G.I.T.	9.0	22.4	290	22.3
PH	M	70	G.I.T.	6.5	51.0	481	11.2
RH	M	74	G.I.T.	13.9	20.6	411	24.3
SH	F	50	Breast*	7.5	50.4	548	9.9
				9.8	30.9	436	16.2
WM	F	55	Breast*	7.2	48.6	506	10.3
				7.5	48.1	517	10.4
				8.5	50.1	611	10.0
				5.4	61.7	479	8.1
HR	M	71	G.I.T.*	10.3	60.6	904	8.3
JT	F	34	G.I.T.	6.6	60.6	577	8.3
Mean				8.3	44.1	507	12.6
s.e. mean				0.45	3.0	32.8	1.15

$T_{\frac{1}{2}}$ = plasma half-life of 5FU; Co = computed concentration of 5FU at zero time; AUC = area under the plasma concentration/time plot; V_d = apparent volume of distribution of 5FU in the body.

at zero time, μg ml^{-1}) by extrapolating the beta phase of the plot to zero time; $T_{\frac{1}{2}}$(min) from the relationship 0.693/k (k = elimination rate constant); AUC (calculated area under the concentration/time curve, μg min ml^{-1}) from the relationship Co/k and V_d (apparent volume of distribution of the drug in the body, l) from the equation dose mg/Co.

For the oral studies, AUC was estimated using the trapezoidal rule. Bioavailability was obtained from the relationship AUC (oral)/AUC (intravenous), expressed as a percentage.

Results

Three aspects of the handling of 5FU were investigated. First, drug kinetics after 0.5 g intravenously. Second, a comparison of drug kinetics after 0.5 g and 1.0 g intravenously and, third, a comparison of systemic availability after paired 1.0 g oral and intravenous doses of the drug.

Intravenous dose of 5FU (0.5 g)

5FU 0.5 g was given by rapid intravenous injection to eleven patients on eighteen separate occasions. The results of kinetic analysis are shown in Table 1. Mean plasma $T_{\frac{1}{2}}$ of the drug for patients receiving the 0.5 g dose was 8.3 min ($n=18$). Co for the group lay between 20.6 and 61.7 μg ml^{-1} (mean = 44.1). There was a three-fold range in calculated V_d after the 0.5 g intravenous dose, between 8.1 and 24.3 l (mean = 12.6 l). Computed AUC showed a 3.1-fold range between 290 and 904 μg min ml^{-1} (mean = 507).

Comparison of 0.5 g and 1.0 g intravenous 5FU

In seven patients, eight comparisons were made between plasma levels achieved after 0.5 g and 1.0 g 5FU intravenously (Table 2).

Mean plasma $T_{\frac{1}{2}}$ after the 0.5 g dose was 8.2 min, and after the 1.0 g dose was 12.7 min ($n=8$, $P=0.001$). Doubling of the intravenous dose produced a two-fold increase in Co, with a mean of 44.2 μg ml^{-1} after the 0.5 g dose, and 86.8 μg ml^{-1} after the 1.0 g dose. Comparison of the mean AUC following the 0.5 g and 1.0 g doses showed a disproportionate three-fold increase from 480 to 1537 μg min ml^{-1}. Mean V_d after 0.5 g intravenously was 13.3 l and, after 1.0 g intravenously, was 12.4 l. A doubling of the intravenous dose in individual patients gave values for V_d which were not significantly different when analysed by a paired t-test ($P=0.4$-0.5).

Comparison of 1.0 g oral and 1.0 g intravenous doses

Figure 1 shows the plasma log concentration/time plot for patient W.M. after paired 1.0 g oral and intravenous doses of 5FU given 8 weeks apart. The bioavailability was 33% during week 1 and 58% during week 9.

Discussion

Measurements of plasma concentration/time curves of 5FU reported here are of similar magnitude to results found by other workers (Cohen *et al.*, 1974; Finn & Sadee, 1975; Garrett, Hurst & Green, 1977).

After 0.5 g 5FU intravenously, the plasma half-life of the drug was remarkably consistent, despite gross differences in state of nutrition, type of carcinoma, stage of disease, and the other drugs which these patients with neoplasia were receiving. Other kinetic parameters measured at the 0.5 g level showed a wider

Table 2 Comparison of pharmacokinetic data in seven patients after paired 0.5 g and 1.0 g intravenous doses of 5-fluorouracil

	0.5 g			*Dose 5FU (i.v.)*	*1.0 g*			
Patient	$T_{\frac{1}{2}}$ *(min)*	*Co (μg ml^{-1})*	*AUC (μg min ml^{-1})*	V_d *(l)*	$T_{\frac{1}{2}}$ *(min)*	*Co (μg ml^{-1})*	*AUC (μg min ml^{-1})*	V_d *(l)*
FB	7.4	38.8	413	12.9	10.7	85.0	1312	11.8
RG	9.5	49.5	678	10.1	14.1	89.3	1822	11.2
SG	9.0	22.4	290	22.3	13.0	54.7	1015	18.3
PH	6.5	51.0	481	9.8	11.2	83.2	1351	12.0
RH	13.9	20.9	416	24.3	19.3	60.5	1679	16.5
WM	7.2	48.6	506	10.3	10.3	99.0	1477	10.1
	5.4	61.7	479	8.1	10.8	139.0	2171	7.2
JT	6.6	60.6	577	8.3	12.2	83.7	1468	11.9
Mean	8.2	44.2	480	13.3	12.7	86.8	1537	12.4
s.e. mean	0.95	5.55	41.0	2.3	1.1	9.1	124.4	1.2

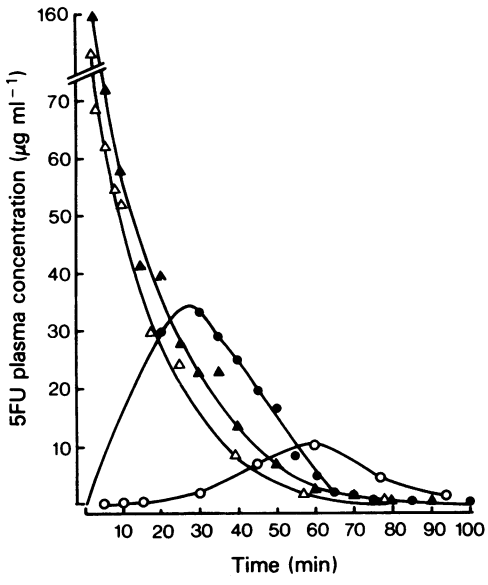

Figure 1 Plasma concentration/time plot for patient W.M. given paired 1.0 g oral and intravenous doses of 5FU over a period of 9 weeks. △ i.v., ○ oral week 1, ▲ i.v., ● oral week 9.

variability. A three-fold variation in Co and AUC was observed which was not related to body weight. There was a tendency for high Co and high AUC in patients with advanced metastatic disease, although this trend did not reach statistical significance.

When the intravenous dose of 5FU was increased from 0.5 g to 1.0 g, the plasma kinetics of the drug showed marked dose dependency. Plasma half-lives averaged 8.2 min for the 0.5 g dose, and 12.7 min for the 1.0 g dose. Doubling of the intravenous dose produced a corresponding two-fold increase in Co from 44.2 μg ml^{-1} to 86.8 μg ml^{-1}. However, there was a disproprotionate three-fold increase in AUC from 480 μg min ml^{-1} to 1537 μg min ml^{-1}. A similar discrepency has been reported by Garrett *et al.* (1977) in two out of three patients studied. This dose dependency could imply that significant rate limiting steps occur in the enzymatic pathways of 5FU biotransformation, as has been suggested for other drugs (Shane, Iazzetta, Chisholm, Berka & Leung, 1978).

From our observations it can be seen that plasma levels of 5FU are highly dependent on dosage. The degree of drug efficacy and toxicity may relate to these variations in pharmacokinetic properties. An analogy may be drawn between cytotoxic and antibacterial chemotherapy. Plasma levels of the aminoglycoside antibiotics, particularly gentamicin, are frequently monitored because of their relevance to the therapeutic and toxic effects of the drug. Gentamicin has an optimum plasma level below which efficacy is significantly reduced and above which ototoxicity commonly occurs. It is not clear which characteristics of the plasma concentration/time curve is most important in predicting toxicity. Peak and trough plasma levels and area under the concentration/time curve have all been suggested (Mawer, Ahmad & Dobbs, 1974; Barza & Lauermann, 1978). Similarly, it has been shown (Stoller, Hande, Jacobs, Rosenberg & Chabner, 1977) that monitoring of plasma levels after high dose methotrexate infusion can identify patients at high risk of toxicity. This risk is related to critical plasma levels of the drug at 48 h and duration of exposure to the drug.

With respect to 5FU, several workers have related toxicity to both dose and route of administration of the drug. Seifert *et al.* (1975) showed that administration by continuous infusion produced considerably less haematologic suppression than after bolus injection. This is compatible with observations that plasma clearance of the drug after continuous infusion is double that seen after bolus injection (Garrett *et al.*, 1977). In relation to dose levels of 5FU, a marked increase in toxicity with relatively small increases in dosage has been described. (Ansfield, 1964; Horton , Olson & Sullivan, 1970; Jacobs, Reeves & Wood, 1971; Kaufman, 1973). We have shown a disproportionate increase in AUC on increasing the dose of 5FU administered by bolus injection, and suggest that toxicity of 5FU may be directly related to this parameter.

Several workers have reported a large variation in absorption of 5FU after oral administration (Bruckner & Creasey, 1974; Cohen *et al.*, 1974; Finn & Sadee, 1975; Garrett *et al.*, 1977). Recently it has been demonstrated that 5FU can profoundly depress adsorptive and enzymatic activities of perfused rat small intestine (Gardner, Samson & Heading, 1978). In the present study, where 1.0g oral and intravenous doses were given on two occasions, there was an increase in bioavailability from 33% to 58% after an interval of 8 weeks (Figure 1). This change coincided with a marked clinical regression in palpable intra-abdominal metastases. Monitoring of plasma levels after oral administration of 5FU would, therefore, seem particularly relevant to ensure that appropriate drug levels reach the systemic circulation.

5FU is extensively metabolized to active, intracellular metabolites. The major species is believed to be 5-fluorodeoxyuridine monophosphate (5 FdUMP), which inhibits thymidilate synthetase, thus restricting DNA synthesis (Heidelberger & Ansfield, 1963). Using mice bearing L1210 lymphocytic leukemia (Chadwick & Rogers, 1972), it was found that 5 FdUMP persisted in the body for up to 72 h after dosing, particularly in malignant tissue. High levels of metabolite were also found in small intestine and bone marrow, which may be correlated with the

observed toxic effects of 5FU. Nothing is known of the levels of 5 FdUMP in human tissues after 5FU administration. Metabolite levels in malignant and surrounding healthy tissue could be measured if 5FU therapy was used as an adjuvant to surgical excision of the tumour. However, this would produce only a single estimate in contrast to the serial estimates obtained when plasma levels of the parent drug are monitored.

Plasma levels of 5FU may give a useful indication of therapeutic effect, although the contribution of an active metabolite remains undefined. Further work is needed to determine the relationship between plasma levels of the parent drug and tissue levels of the active metabolite.

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Addendum

Since this study was completed, Christophidis, Vajda, Lucas, Drummer, Moon & Louis (1978) have reported from Australia on the pharmacokinetics of fluorouracil after oral, rectal, or intravenous administration to twelve patients with cancer of the large bowel. These authors demonstrated a wide range in plasma levels of 5FU after different dose schedules and routes of administration, and a disproportionate increase in bioavailability with increasing oral dose. Their findings agree with those presented in this paper.

References

ANSFIELD, F.J. (1964). A less toxic fluorouracil dosage schedule. *J. Am. med. Ass.*, **190**, 686–688.

BARZA, M. & LAUERMANN, M. (1978). Why monitor serum levels of gentamicin? *Clin. Pharmacokin.*, **3**, 202–215.

BENDER, R.A., ZWELLING, L.A., DOROSHOW, J.H., LOCKER, G.Y., HANDE, K.R., MURINSON, D.S., COHEN, M., MYERS, C.E. & CHABNER, B.A. (1978). Antineoplastic drugs: clinical pharmacology and therapeutic use. *Drugs*, **16**, 46–87.

BRUCKNER, H.W. & CREASEY, W.A. (1974). The administration of 5 fluorouracil by mouth. *Cancer*, **33**, 14–18.

CHABNER, B.A., MYERS, C.E. & OLIVERIO, V.T. (1977). Clinical pharmacology of anticancer drugs. *Seminars in Oncology*, **4**, 165–191.

CHADWICK, M. & ROGERS, W.I. (1972). The physiological disposition of 5 fluorouracil in mice bearing solid L1210 lymphocytic leukemia. *Cancer Res.*, **32**, 1045–1056.

CHRISTOPHIDIS, N., VAJDA, F.J.E., LUCAS, I., DRUMMER, O., MOON, W.J. & LOUIS, W.J. (1978). Fluorouracil therapy in patients with carcinoma of the large bowel: a pharmacokinetic comparison of various rates and routes of administration. *Clin. Pharmacokin.*, **3**, 330–336.

COHEN, J.L., IRWIN, L.E., MARSHALL, G.J., DARVEY, H. & BATEMAN, J.R. (1974). Clinical pharmacology of oral and intravenous 5 fluorouracil. *Cancer Chemother. Rep.*, **58**, 723–731.

COSTANZI, J.J. & COLTMAN, F.J. (1969). Combination chemotherapy using cyclophosphamide, vincristine, methotrexate and 5 fluorouracil in solid tumours. *Cancer*, **23**, 589–596.

FINCH, R.E., BENDING, M.R. & LANT, A.F. (1978). Use of a nitrogen detector for the GLC determination of fluorouracil in plasma during single and combined agent chemotherapy. *J. pharm. Sci.*, **67**, 1489–1490.

FINN, C. & SADEE, W. (1975). Determination of 5 fluorouracil plasma levels in rats by isotope dilution-mass fragmentography. *Cancer Chemother. Rep.*, **59**, 279–286.

GARDNER, M.L.G., SAMPSON, R.R. & HEADING, R.C. (1978). Changes in absorptive and peptide hydrolase activities in rat small intestine after administration of 5 fluorouracil. *Clin. Sci. mol. Med.*, **54**, 411–418.

GARRETT, E.R., HURST, G.H. & GREEN, J.R. (1977). Kinetics and mechanisms of drug action on microorganisms XXIII: microbial kinetic assay for fluorouracil and its application to human pharmacokinetics. *J. pharm. Sci.*, **66**, 1422–1429.

HANHAM, I.W.F., NEWTON, K.A. & WESTBURY, G. (1971). Seventy five cases of solid tumours treated by a modified quadruple chemotherapy regime. *Br. J. Cancer*, **25**, 462–478.

HEIDELBERGER, C. & ANSFIELD, F.J. (1963). Experimental and clinical use of fluorinated pyrimidines in cancer chemotherapy. *Cancer Res.*, **23**, 1226–1243.

HORTON, J., OLSON, K.B. & SULLIVAN, J. (1970). 5FU in cancer: an improved regimen. *Ann. intern. Med.*, **73**, 897–900.

JACOBS, E.M. REEVES, W.J. & WOOD, D.A. (1971). Treatment of cancer with weekly intravenous 5FU. *Cancer*, **27**, 1302–1305.

KAUFMAN, S. (1973). 5FU in the treatment of gastrointestinal neoplasia. *New Eng. J. Med.*, **288**, 199–201.

MAWER, G.E., AHMAD, R., DOBBS, S.M., MCGOUGH, J.G., LUCAS, S.B. & TOOTH, J.A. (1974). Prescribing aids for gentamicin. *Br. J. clin. Pharmac.*, **1**, 45–50.

SADEE, W. & WONG, C.G. (1977). Pharmacokinetics of 5FU: interrelationship with biochemical kinetics in monitoring therapy. *Clin. Pharmacokin.*, **2**, 437–450.

SEIFERT, P., BAKER, L.H., REED, M.L. & VAITKEVICIUS, V.K. (1975). Comparison of continuously infused 5FU with bolus injection in treatment of patients with colorectal adenocarcinoma. *Cancer*, **36**, 123–128.

SHANE, S.J., IAZZETTA, J.J., CHISHOLM, A.W., BERKA, J.F., LEUNG, D. (1978). Plasma concentrations of isosorbide dinitrate and its metabolites after chronic high oral dosage in man. *Br. J. clin. Pharm.*, **6**, 37–41.

STOLLER, R.G., HANDE, K.R., JACOBS, S.A., ROSENBERG, S.A. & CHABNER, B.A. (1977). Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. *New Eng. J. Med.*, **297**, 630–634.

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