Constant intraperitoneal 5-fluorouracil infusion through a totally implanted system

Five-day continuous intraperitoneal (ip) infusions of 5-fluorouracil (FU) were injected into five patients as part of a phase I clinical pharmacology study. They received 20 courses through a totally implanted catheter/injection port system. Six courses are evaluable for kinetic parameters and all courses are evaluable for toxicity. In each course a 2 to 3 log FU concentration differential in favor of the peritoneal cavity was achieved and maintained. Steady-state venous plasma FU concentrations averaged 0.34 μM, whereas steady-state ip FU concentrations averaged 697 μM. Mean total body clearance (TBC) in these patients was 18.4 l/min and mean permeability-area (PA) product for diffusion from the peritoneum was 13.7 ml/min. Mean TBC of 20 l/min with ip FU infusion was observed in one patient who also received a 24-hr IV FU infusion for comparison. The TBC during the later infusion was 5.9 l/min. In this patient, calculations indicate 75% extraction of drug during the passage from the peritoneum to the systemic circulation, presumably representing in large part hepatic extraction of FU taken into the portal venous circulation. Ip constant infusion and bolus kinetics were compared in one patient. TBC for the ip bolus was 14.3 l/min, which was approximately half of the TBC of 29.5 l/min determined during the 5-day constant ip infusion. Thus constant ip infusion of FU (1 gm/day) can provide an improved regional advantage over bolus ip FU because of an increased TBC. Toxicity was acceptable in all courses. Dose limiting toxicity was regional, namely moderate chemical peritonitis seen in two of the five patients on repeated courses. There was no myelosuppression, alopecia, nausea, or vomiting. There were no infectious complications. The only patient with measurable disease had an objective response in hepatic metastases from gastric cancer. The implanted device was well tolerated and facilitated peritoneal fluid sampling.

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Disseminated intraperitoneal (ip) cancer occurs frequently in gastrointestinal and gynecologic malignancies. Malignant ascites can be a major problem in other cancers as well. The unique restricted volume of distribution in the

peritoneal cavity makes it possible to devise regimens to provide selective concentrated drug exposure by ip injection. The kinetic rationale for ip injection of antineoplastic drugs has been elegantly delineated by Dedrick et al.[8] They have shown that, at steady state, the selective advantage (R_d) of a direct drug infusion into the peritoneal cavity relates directly to the total body clearance (TBC) of the drug infused and inversely to the permeability-area product (PA), a measure of peritoneal clearance, of the peritoneal surface exposed.[8, 26] Initial pilot studies of ip chemotherapy in man used 5-fluorouracil (FU),[26, 27] methotrexate,[15, 18] adriamycin,[24] melphelan,[14] and cisplatin.[16, 17, 20] The studies demonstrated that these drugs can be injected ip with acceptable regional toxicity and that the drug concentrations achieved in the peritoneal cavity can be 10 to 1000 times as high as in the plasma. Drugs with significant hepatic extraction are ideal since a portion of such drugs may be metabolized by the liver through portal venous uptake before reaching the sytemic circulation. This first pass effect would be expected to increase the TBC of the drug and maximize the difference between plasma and peritoneal fluid drug concentration.

Other studies have generally used exchanges of large volumes of drug containing solutions injected through Tenkhoff peritoneal dialysis catheters. Since antimetabolites generally induce cytotoxicity as a function of duration of exposure above critical concentrations[5] we have investigated protracted infusions of the antimetabolite FU as a means of selectively sustaining high regional drug levels in the peritoneal cavity, whereas the lower systemic levels achieved may avoid systemic toxicity. In addition, to circumvent the inconvenience and morbidity associated with indwelling peritoneal catheters, we have used a new, totally implanted silastic catheter/port system that facilitates peritoneal fluid sampling yet obviates the need for dressing changes and may avoid potential infectious complications associated with chronic externalized catheters.

Methods

Our subjects were five male patients with histologic proof of malignancy (four colon cancer, one gastric cancer) aged 28 to 62. Two patients had residual macroscopic but nonmeasurable, intra-abdominal extrahepatic cancer after resection of a primary colon carcinoma and two patients with Dukes C_2 lesions were treated as part of an adjuvant study. The fifth patient had unresectable gastric cancer with measurable liver metastases by computerized tomography (CT) and peritoneal seeding with tumor and symptomatic malignant ascites. No patient had received chemotherapy.

Tenkhoff (four patients) or Toronto (one patient) Silastic peritoneal dialysis catheters were implanted in the abdominal cavity through a subcutaneous tunnel under local anesthesia and attached to an injection port (Pharmacia Nu Tech) placed subcutaneously and affixed to the fascia of the lower anterior chest wall. The port consists of a low profile stainless steel cylindrical chamber with a self-sealing silicone rubber septum. An IVAC 530 infusion pump (IVAC Corp.), or an IMED 960 infusion pump (IMED Corp.) and Luer-lok extension tubing were used for drug infusions. A three-way stopcock was inserted into the infusion line and attached to a Huber-point needle bent at 90° so that the hub of the needle lay parallel to the skin when inserted percutaneously into the port. The needle and adjacent tubing were placed under sterile conditions and secured with steri-strips (3M Corp.) and op-site (Acme United Corp.) for the 5-day infusion. At the completion of an infusion the needle was removed and no further maintenance was required. This methodology had been used successfully for continuous intravenous infusions with another implanted injection port system.[13]

Before therapy, 1.5 *l* lactated Ringers (LR) solution was infused into the abdomen over 90 min followed by a constant infusion of LR at 42 ml/hr. This rate was selected based on technetium 99m sulfur colloid (TcSC) isotopic dilution studies in which only a 10% to 20% change in ip volume was found on day 5 from day 1 using this initial volume and subsequent rate of infusion. In addition, in one patient the abdomen was drained and a volume of 1.3 *l* recovered after completing the 5-day infusion. The ip distribution of the fluid was determined by radionuclide scan.[16, 17, 29] Before chemother-

apy, 1 mCi of TcSC was injected ip and the patients scanned after 1 hr of ambulation. Patients were candidates for pharmacology studies if the scan demonstrated free distribution of the radiopharmaceutical.

The ip infusion therapy consisted of 1 gm FU each day (1 gm FU in 1 *l* LR injected ip at 42 ml/hr) for 5 days repeated monthly. Simultaneous peritoneal fluid and venous plasma samples were obtained twice daily beginning 12 hr after initiation of the ip infusion. Patients ambulated for one hour before peritoneal fluid sampling. Peritoneal fluid samples (5 ml) for FU assay were obtained through the three-way stopcock after withdrawing 20 ml peritoneal fluid to flush the catheter and avoid sampling error. The 25-ml volume was then replaced and the infusion-rate resumed in an effort to maintain a constant ip volume. The adequacy of this sampling technique was determined in two patients in whom random simultaneous samples were obtained from a second temporary silastic catheter placed into the peritoneal cavity on the contralateral side. Under these circumstances the ip FU concentration determined from the two sites was equivalent (within 5%).

A total of 20 ip FU infusions were injected into the five patients. Six courses were evaluable for kinetic studies, and all courses were evaluable for toxicity. One patient was evaluable for response. In addition to the 5-day ip infusion one patient received a 24-hr IV infusion of FU (1 gm/24 hr) and a second patient received an ip bolus of FU (1 gm over 1 min) for comparison with the ip infusion kinetic data.

FU was assayed by a HPLC assay. To measure FU concentrations greater than 1 μg/ml, a 200-μl sample of plasma or peritoneal fluid was added to 400 μl methanol and 40 μl internal standard solution (10 μg 5-chlorouracil/40 μl). The mixture was vortexed and centrifuged at 4000 rpm for 15 min at 4°. The supernatant (1 to 10 μl) was injected for HPLC analysis. Samples were analyzed on a RCM-100 Radial-Pak C_{18} column system (Waters) using a 0.01M ammonium phosphate (pH = 6.7) mobile phase. The flow rate was set at 2 ml/min and peak detection was accomplished with a Waters Model 440 UV-VIS detector with a 254 mμ filter. Calibration curves were constructed by

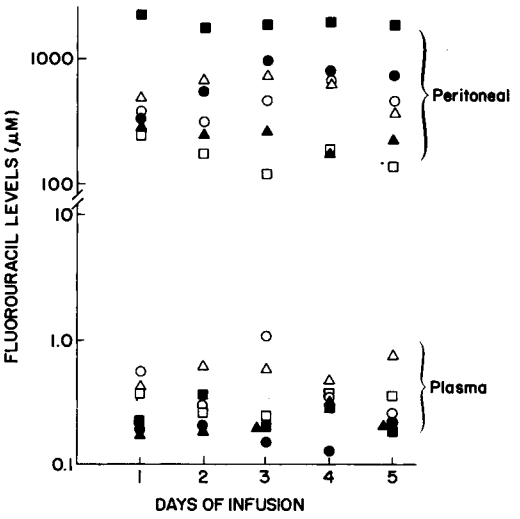

Fig. 1. Concurrent peritoneal fluid and plasma fluorouracil levels during continuous ip infusions in five patients. Each patient is represented by a symbol of different configuration (note repeated course in one patient, empty box and solid triangle) and each point represents the mean of two samples obtained on each of 5 days.

plotting the ratio of the peak height of FU to that of the internal standard as a function of the plasma FU concentration. This assay has a coefficient of variation[4] of 5% over the range from 5 to 40 μg/ml and is accurate to within 5% of the theoretical values.

To measure FU concentrations under 1 μg/ml, 1 ml plasma, or peritoneal fluid was added to 50 μl internal standard solution (500 ng 5-chlorouracil) and 2 ml saturated ammonium sulfate. The mixture was vortexed and extracted twice with 8 ml ethyl acetate by shaking for 10 min at room temperature. The samples were then centrifuged at 3000 rpm for 10 min at room temperature and the pooled ethyl acetate fractions were transferred to conical-bottomed glass tubes. After adding 400 μl 5N KOH, the drug was back-extracted by shaking for 5 min. The samples were again centrifuged (2000 rpm, 15 min, room temperature) and the ethyl acetate phase discarded. The alkaline aqueous phase, 1 to 20 μl, was injected for HPLC analysis with an Altex Ultrasphere-ODS, 5 μ column (Beckman). The mobile phase was a 0.1M ammonium phosphate buffer (pH = 6.7), and the flow rate was set at 1.2 ml/min. The detection system

Table I. *Kinetic parameters for continuous ip infusion of 5-fluorouracil 1 gm/day for 5 days (six courses, five patients)*

Patient	Venous plasma		Peritoneal fluid		TBC (l/min)	PA (ml/min)	Selective regional advantage (R_d)
	$C_{SS_{PV}}$ (μM)	CV	$C_{SS_{IP}}$ (μM)	CV			
1	0.32	18%	176	27%	16.6	30.2	550
	0.22	27%	243	16%	24.1	21.8	1108
2	0.26	30%	2004	9%	20.4	2.6	7852
3	0.51	68%	475	31%	10.4	11.1	939
4	0.18	22%	694	35%	29.5	7.6	3880
5	0.58	24%	588	26%	9.2	9.0	1023
Group mean (±SD)	0.34 (0.16)	32% (18.3)	697 (670)	24% (9.7)	18.4 (7.9)	13.7 (10.3)	2559 (2860)
Group median	0.29	25.5%	532	26.5%	18.5	10.1	1066

CV = Coefficient of variation.

was as described above. Accuracy and precision studies with drug-spiked control plasma at a final concentration of 100 ng FU/ml resulted in a coefficient of variation[4] of 8.8%, whereas the mean of these estimates was within 2% of their theoretic value.

Results

Concurrent peritoneal fluid and plasma FU levels obtained during the continuous ip infusion are shown in Fig. 1. For the entire group, the plasma levels ranged from 0.13 to 1.1 μM, whereas the ip levels ranged from 0.12 to 2.3 mM. This 2-3 log differential was maintained over the 5-day course in each case.

The kinetic parameters evaluated during the 5-day ip infusions in the five patients are listed in Table I. The mean plasma FU concentration, for individual courses ranged from 0.18 to 0.58 μM. This mean plasma concentration represents the steady-state venous plasma concentration ($C_{SS_{PV}}$). The coefficient of variation[4] for $C_{SS_{PV}}$ in each course ranged from 18% to 68% (mean 32%; median 25.5%). The mean $C_{SS_{PV}}$ for the entire group was 0.34 μM (median 0.29 μM). The mean peritoneal fluid FU concentration for individual courses ranged from 176 to 2004 μM. The mean concentration over the 5-day infusion represents the steady-state ip FU concentration ($C_{SS_{IP}}$) for that course. The coefficient of variation for $C_{SS_{IP}}$ for individual courses ranged from 9% to 35% (mean 24%; median 26.5%). The mean $C_{SS_{IP}}$ for the entire group was 697 μM (median 532 μM).

Total body clearance (TBC) was calculated from the ratio of the constant infusion dose rate and the venous plasma steady-state concentration. In these six treatment courses TBC averaged 18.4 l/min (median 18.5 l/min). The permeability area product (PA) was determined from steady-state levels ($C_{SS_{PV}}$ and $C_{SS_{IP}}$) and the TBC.[26] The mean PA in these patients was 13.7 ml/min (median 10 ml/min).

The selective regional advantage (R_d) of ip infusion FU was directly determined as the ratio of $C_{SS_{IP}}$ to $C_{SS_{PV}}$ and also calculated from values derived for TBC and PA.[8, 11] Both methods gave equivalent results. In these patients the mean R_d was 2559 (median 1066).

Forty-eight hours before his second course of ip FU, patient 1 received a 24-hr intravenous infusion of FU (1 gm/24 hr) after loading the abdomen as described for the ip infusion treatment followed by constant infusion of LR ip at 42 ml/hr. Peritoneal fluid and venous blood samples were obtained during the infusion and assayed for FU. Based on the formula derived by Collins et al.[7] the extraction of FU by the liver and peritoneal surface was calculated from steady-state venous plasma levels obtained from the intravenous and subsequent ip infusions. In this case the extraction of FU was found to be 75%. TBC during the 24-hr intravenous infusion was calculated as described above and

Table II. *Drug related toxicity associated with intraperitoneal infusion of 5-fluorouracil 1 gm/day for 5 days (20 courses, 5 patients)*

Patient	No. of courses	Myelosuppression	Courses with: Nausea/Vomiting	Courses with: Mucositis	Courses with: Symptomatic chemical peritonitis*
1	4	0	0	0	0
2	7	0	0	0	0
3	2	0	0	0	2
4	5	0	0	0	3
5	2	0	0	0	0

*All patients experienced mild abdominal discomfort related to intraperitoneal fluid volume. There was no evidence of bacterial peritonitis.

found to be 5.9 *l*/min. TBC for this patient during two separate ip infusion courses was 16.6 and 24.1 *l*/min. This difference in TBC is consistent with the regional extraction noted.

Patient 4 received a single IP bolus of FU (1 gm) on a separate treatment course. The abdomen was loaded with fluid and the LR infused as described above before injecting the FU. Peritoneal fluid and venous plasma samples were obtained over 16 hr and were assayed for FU. Fluorouracil was not detectable in venous plasma 8 hr later although ip levels were 0.42 μM at 16 hr. TBC was calculated from the ratio of dose and AUC. AUC was determined by the trapezoidal rule from time zero to the last measurable plasma point and then extrapolated to infinity (by first order extrapolation). As described by Speyer et al.[26] this formula is valid for any linear kinetic model regardless of the number of compartments. If TBC varies with dose, then the drug kinetics are nonlinear. The TBC for this patient given the ip bolus was 14.3 *l*/min whereas there was a TBC of 29.5 *l*/min during the 5-day ip infusion in the same patient.

The five patients received a total of 20 ip infusions of FU. Toxicity was minimal (Table II). There was no evidence of systemic toxicity (mucositis or myelosuppression), but all patients experienced mild abdominal discomfort related to the fluid volume infused, e.g., with ip fluid loading before FU infusion. Symptomatic chemical peritonitis occurred repeatedly in two patients who received a total of seven courses. There was no change in the distribution of ip fluid as determined by TcSC scans and ip levels of FU did not change significantly during the infusion in these two patients who experienced symptomatic chemical peritonitis. One might expect such changes to occur if peritoneal surface characteristics and the PA were affected by significant, severe peritonitis. Peritoneal fluid was sampled on the third day of each infusion for cell count, differential, and bacterial culture, and evidence of a mild sterile inflammatory reaction was present in most patients.

This study was not specifically designed to assess response, and only one patient had readily measurable disease. The patient with unresectable gastric cancer had symptomatic malignant ascites before ip FU. Peritoneal fluid cytology became negative during the first course of ip FU infusion and remained negative on subsequent evaluations. This patient also had measurable hepatic tumor by CT scan and after two cycles had a partial response (more than 50% reduction in the product of the longest perpendicular diameters of measurable lesions).

Discussion

The rationale for ip dosing in patients with cancer rests primarily upon achieving high local drug concentration in areas where tumor is known to be present.[8, 11] Patients at high risk for tumor recurrence after resection also might benefit from adjuvant therapy. If the drug is injected as an infusion the ratio of the total drug exposure (AUC) for the peritoneal cavity to that for the systemic circulation is determined by the relative clearances from the two spaces. The clearance of a drug from a third space is defined by the permeability-area product (PA) and is related to the molecular weight of the drug

used.[8] Thus drugs with high total body clearance and relatively low PA are rational for ip use. Drugs given ip are cleared primarily by the portal vein and lymphatics.[19, 21] Thus for selected drugs this route may provide an additional advantage since hepatic extraction and metabolism appears to result in enhanced TBC.

Other studies have shown that FU has a TBC of 1 to 2 *l*/min after IV bolus injection and 3 to 7 *l*/min when injected as an intravenous infusion.[6, 9, 22] Speyer et al.[26] reported a TBC ranging from 0.9 to 15 *l*/min in 10 patients receiving repeated ip exchanges of FU. The nonlinearity of FU plasma kinetics after ip exchanges was demonstrated as TBC decreased with increasing doses. Dose dependent variability in TBC with saturable elimination has also been reported for hepatic arterial infusions where the selective advantage of regional dosing can be diminished at higher doses.[12]

Speyer et al.[26] reported a mean PA of 14 ml/min in patients receiving repeated ip exchanges of FU with relatively short ip dwell times.[26] We demonstrated a similar PA for protracted ip FU infusions (Table I). The TBC of 5.9 *l*/min for IV infusion of FU (patient 1) is of the range previously reported[6, 9, 22] and a TBC of 14.3 *l*/min after ip bolus of FU (patient 4) is within the range reported by Speyer et al.[26] Constant ip infusion of FU at the dose-rate selected for our study appears to provide an improved regional advantage because of the maximized TBC.

The plasma levels achieved during these ip infusions are in the range of the systemic levels after protracted intravenous infusions of FU (300 mg/m^2/d).[12] There has been a recent upsurge of interest in the use of protracted infusions of antimetabolites.[15] Such prolonged infusions might lead to improved therapeutic index since most solid tumors have long doubling times and only a small proportion of cells would be expected to be in the drug sensitive DNA synthetic phase at any time. It is possible that chronic exposure may maximize selective differences in drug uptake and activation while killing the increasing fraction of cells accumulating in the drug sensitive phase with time.

The ultimate impact of ip infusion remains to be demonstrated. In colorectal cancer, there is reason to believe that metastatic cancer in the liver initially derives its blood supply from the portal venous circulation.[1] Preliminary reports of adjuvant portal venous infusion FU have been encouraging.[28] This, combined with the concern regarding local recurrence of tumor, has resulted in considerable interest in ip adjuvant therapy as a means of providing high regional concentrations of cytotoxic agents. There are also data that support therapy of small intrahepatic tumor nodules by either the portal venous or hepatic arterial routes.[2, 3, 10, 23, 25] Since the dose limiting toxicity of ip infusion FU is not systemic, but regional (i.e., chemical peritonitis), it is conceivable that this modality could be combined with systemic chemotherapy regimens. The integration of these approaches with hepatic arterial infusion chemotherapy, where the dose limiting toxicity is chemical hepatitis and gastritis,[10] also offers hope for improved therapeutic benefit without overlapping toxicity. The availability of implantable devices for convenient access to the peritoneal cavity and recent developments in portable infusion pumps should greatly facilitate further clinical investigations in this area.

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