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Pharmacokinetic study of 5-fluorouracil in a novel dialysate solution: a long-term intraperitoneal treatment approach for advanced colorectal carcinoma

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Summary Five patients with advanced colorectal and gastric carcinoma with peritoneal deposits were treated by continuous weekdays intraperitoneal (i.p.) instillation of 5-fluorouracil (5-FU) 200 mg m^{-2} day^{-1} in a novel dialysate solution that ensures maximal exposure of peritoneal areas liable to bear tumours for 24 h. A solution of icodextrin, a glucose polymer, in a 2 l twin-bag delivery system allowed a single daily exchange and demonstrated the feasibility of long-term continuous ambulatory treatment with up to 17.4 g of 5-FU, delivered intraperitoneally, in this initial study. During the entire study, there were 235 fluid exchanges or 470 connections and disconnections and no bacterial peritonitis or exit site infection were observed. There was no treatment-associated toxicity worse than WHO grade 2. Drug concentrations in both peritoneal and plasma compartments followed a first-order model with similar half-life value of 1.3 h. 5-FU pharmacokinetic parameters (half-life values, total body clearance, peritoneal clearance and pharmacological advantage of the i.p. route) with this novel icodextrin carrier solution were similar to those obtained in other referenced pharmacokinetic studies with other carrier solutions (dextrose dialysate and lactated Ringer's solutions). This confirms that icodextrin solution is physiologically neutral, drug compatible and allows adequate dwell times with constant fluid balance for long-term continuous intraperitoneal chemotherapy. The pharmacokinetic parameters from this study will be used to design a loading dose infusion schedule in an attempt to maintain steady-state i.p. 5-FU levels in a new multicentre phase I trial.

Intraperitoneal (i.p.) and intracavity administration of antitumour drugs has been performed since the early days of modern cancer chemotherapy. Intraperitoneal infusion of an appropriate cytotoxic agent is still in many patients the most efficient palliative therapy for malignant ascites arising from carcinomatosis peritonei (Weisberg *et al.*, 1955; Clarkson *et al.*, 1964; Suhrland & Weisberger, 1965; Casper *et al.*, 1983). The ability to deliver drugs into the abdominal cavity on a regular or continuous basis has frequently been frustrated by the non-availability of a safe delivery system. High complication rates due to catheter flow obstruction, infection and abdominal pain or discomfort (Piccart *et al.*, 1985) have limited the use of this route of administration. Similarly, available carrier solutions tend to be rapidly absorbed, thus making peritoneal exposure to the drugs patchy and erratic.

Up to 2 l of fluid is required for adequate immersion of all peritoneal areas liable to bear tumours (Wahl *et al.*, 1989). Thus, continuous, peritoneal coverage requires frequent regular administration of large volumes of electrolyte solution, which may result in fluid overloading and or unacceptable excretion of massive urine volumes.

Continuous, ambulatory peritoneal dialysis (CAPD) has revolutionised our knowledge, experience and ability to employ the peritoneal cavity for therapeutic purposes, and anephric patients have now been maintained on CAPD for up to 15 years (Bengmark, 1989). From these developments have come proven, safe delivery systems which protect the patient from peritonitis (Verger & Luzar, 1986; Rottembourg *et al.*, 1987) and new carrier solutions, based on the use of glucose polymers as osmotic agents, which remain within the peritoneal cavity for 24 h with minimal exchanges of fluid or electrolytes (Mistry *et al.*, 1985, 1987).

Thus, the technology and practical clinical experience of peritoneal dialysis has now provided, for the first time, the opportunity to meet the long sought after therapeutic requirements for adequate, long-term continuous exposure of peritoneal tumour deposits to cytotoxic agents.

Previous studies (Speyer *et al.*, 1981; Speyer, 1985; Sugarbaker *et al.*, 1985; Ekberg *et al.*, 1988; Goldberg *et al.*, 1988; Sugarbaker, 1991; Hallenbeck *et al.*, 1992) have shown that 5-FU has single-agent activity in the treatment of the colorectal carcinomas confined to or recurrent in the peritoneal cavity and has a large pharmacokinetic regional advantage following i.p. instillation, i.e. the drug is cleared much more rapidly from the systemic circulation than from the peritoneal cavity.

Recently, it has been shown that prolongation of intravenous infusion (e.g. to 10 weeks) of 5-FU is associated with an increased response rate in patients with advanced colorectal carcinoma (Seifert, 1975; Lokich *et al.*, 1989; Leichman *et al.*, 1993). The aim of the present study was to determine the pharmacokinetics of 5-FU following intraperitoneal administration in a novel dextrin carrier solution during a 24 h dwell time and to assess the peritoneal fluid balance profile (in and out i.p. fluid volumes), peritoneal cytology and associated toxicity.

Patients and methods

Patients and eligibility criteria

Five patients with a histologically documented intra-abdominal malignancy (four colorectal and one gastric carcinoma) were enrolled in this study. The patients' characteristics are given in Table I.

The patients had normal haematological, renal and hepatic indices and a WHO performance status of better than 2. The protocol was approved by the institutional ethics committee review board and all patients provided written, informed consent.

Treatment plan

Four to 5 weeks prior to initiation of chemotherapy, all patients had a Tenckhoff catheter peritoneal access system surgically placed in theatre. Immediately following catheter placement, several washout exchanges with icodextrin solutions were performed to prevent clogging of the catheter and

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Table I Patient characteristics and i.p. chemotherapy treatment duration

Sex	Age (years)	Site of primary	Peritoneal disease	Ascites	Disease elsewhere	Previous treatment	Total number of days on i.p. chemotherapy	Total 5-FU dose delivered i.p. (g)
M	58	Caecum and liver	At laparotomy widespread peritoneal nodules (positive biopsy)	No	Liver metastases	5-FU folinic acid and PALA	19 (over 4 weeks)	6.624
F	64	Sigmoid colon adherent to anterior abdominal wall	Laparotomy for liver and peritoneal metastases	No	Liver metastases	No	21 (over 5 weeks)	5.657
M	59	Sigmoid colon	Retroperitoneal lymph nodes	No	No	No	18 (over 4 weeks)	5.709
M	48	Stomach inoperable	Inoperable	Yes	Pancreas Retroperitoneal and pelvic lymph nodes	No	38 (over 8 weeks)	11.797
F	62	Caecum	Satellite tumours Retroperitoneal lymph nodes	No	No	No	65 (over 14 weeks)	17.435

to assess catheter drainage. The peritoneal cavity was then left dry until 1 week prior to initiation of chemotherapy.

The i.p. 5-FU dose of 200 mg m^{-2} daily was selected to provide an intermediate dose (compared with previous studies of intermittent, high-dose 5-FU therapy) which might be tolerated for the relatively prolonged period of 3 months. The 5-FU dose of 200 mg m^{-2} daily was aseptically admixed in 2 l of 7.5% icodextrin solution (icodextrin 7.5%, ML Laboratories) in a twin-bag configuration, prewarmed to 37°C and instilled into the peritoneal cavity by gravity flow as rapidly as possible (10–20 min). The intraperitoneal drug delivery system design is shown in Figure 1. Following a 24 h dwell time, the peritoneal space was drained as completely as possible in the empty bag of the twin-bag container and drainage fluid volume was accurately monitored. This procedure was applied from Monday to Friday. Friday's 5-FU i.p. instillation was only drained on the following Monday after a 72 h dwell time.

In addition, peritoneal dialysis effluents were examined cytologically. A total cell count was first performed using an improved Neubauer counting chamber and a duplicate count was carried out using a Coulter counter to confirm the accuracy of these manual counts. Differential cell counts were performed on cytospin preparations with an optimum cell dilution to produce an even spread of cells. To obtain a differential count five standard-sized fields per cytospin were examined with a minimum of 200 cells counted. The following cell types were characterised separately: macrophages, lymphocytes, neutrophils, eosinophils and mesothelial cells.

Treatment was continued daily for 3 months or until development of intolerable toxicity or progressive disease.

Drug stability and compatability

A long-term stability study up to 3 months was conducted on 5-FU from two different sources (Fluoro-Uracil, Roche; and Fluorouracil injection BP, David Bull Laboratories) aseptically admixed into two lots of 2 l glucose polymer solution (icodextrin 7.5%, ML Laboratories) at the concentrations of 25 mg l^{-1}, 100 mg l^{-1}, 250 mg l^{-1} and 500 mg l^{-1} at 25°C. Three containers were monitored by combination (drug content, manufacturer and carrier solution lot) up to 112 days of storage when protected from light. At weekly intervals, the admixtures were tested for pH and for 5-FU content by high-performance liquid chromatography (HPLC) using a method similar to the HPLC method described by Christophidis *et al.* (1979) and fully validated for stability assessment, visual and subvisual particulate matters and osmolality.

Pharmacokinetic studies

Following instillation of an early-morning exchange of 200 mg m^{-2} 5-FU in the carrier solution during the first week of treatment, multiple samples were taken from the peritoneal dialysate (5 ml aliquots) and from a peripheral vein via an indwelling catheter (10 ml aliquots into a lithium heparin tube).

Peritoneal fluid and blood samples were withdrawn concurrently prior to instillation, at the end of instillation (10–20 min after the start of instillation) and at 30 min, 1, 2, 4, 8, 12 and 24 h after start of instillation.

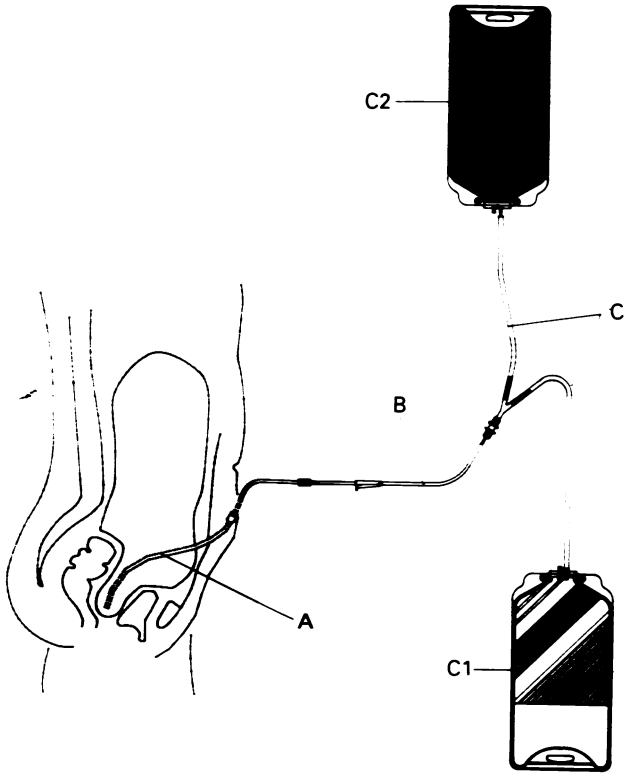

Figure 1 Intraperitoneal drug delivery system. The system contains an intraperitoneal implantable Tenckhoff catheter (A) connected to the integrated twin-bag disconnected system (C) via a CAPD extension line (B). A drainage container (C1) and a 2 l carrier solution container (C2) constitute the integrated twin-bag system.

The blood and peritoneal dialysate samples were kept on ice, spun at 2,000 r.p.m. for 5 min and the plasma separated and then frozen at −20°C until analysis. Plasma 5-FU concentrations which are below quantitative determination limit (50 μg l^{-1}) of the HPLC method were measured by a sensitive and specific gas chromatography (GC) – negative ion chemical ionisation mass spectrometry (NICIMS) method as previously described (Bates *et al.*, 1991) and peritoneal samples by a HPLC method previously used by Goldberg *et al.* (1988) and described in detail by Christophidis *et al.* (1979).

To achieve long-term steady-state drug concentration in the plasma and peritoneal compartments, it is necessary to determine the drug elimination constants (β-phases) in both compartments in order to establish the rate of continuous administration of 5-fluorouracil. Therefore, the 5-FU peritoneal and plasma concentration values were simply fitted to a first-order linear regression model (ln C versus time) in a linear regression SAS program and goodness of fit was evaluated by the correlation coefficient. Areas under the curve (AUC) were calculated from time 0 to 12 h by the trapezoidal rule.

Results

A total of five patients received 161 exchanges of chemotherapy out of the total 235 fluid exchange procedures during this study; individual treatment duration is listed in Table I. Out of the five patients, only one patient completed the full treatment plan of 14 weeks of continuous 5-FU weekdays exchanges. Another patient received an 8 week treatment of continuous 5-FU weekdays exchanges. In the three other patients, IPC treatment was discontinued after 4–5 weeks of continuous weekday exchanges owing to progressive disease.

Drug stability and compatability

Stability of 5-FU when diluted in the glucose polymer carrier solution was studied over a period of up to 4 months.

The data (listed in Table II) show that the pH of the admixed solutions ranged from 5.2 to 8.0 depending on 5-FU content. Those initial pH values remained unchanged throughout the test period. The drug concentration of solutions containing 25–500 mg l^{-1} 5-FU remained stable for up to 112 days when stored at 25 ± 3°C protected from light. No precipitations or increase in subvisible particulate matter occurred throughout the storage period.

Table II 5-Fluorouracil stability results in icodextrin solutions

Storage intervals (days)	*5-FU content (% of initial)* Mean[b]	s.d.[b]	*pH*[a]	*Osmolality*[a] (*Mosmol* kg^{-1})
5-FU at 25 mg l^{-1}				
0	100.0	0.1	5.25	288
14	97.3	0.1	5.26	289
30	99.7	0.1	5.23	288
70	99.9	0.2	5.22	280
112	101.1	0.2	5.18	289
5-FU at 100 mg l^{-1}				
0	100.0	0.1	5.49	287
14	98.1	0.4	5.51	289
30	100.2	0.1	5.49	286
70	100.5	0.1	5.45	278
112	101.0	0.1	5.44	288
5-FU at 250 mg l^{-1}				
0	100.0	0.1	7.18	287
14	98.4	0.1	7.15	288
30	100.0	0.1	7.09	287
70	100.3	0.2	6.98	281
112	100.7	0.2	6.94	288
5-FU at 500 mg l^{-1}				
0	100.0	0.1	7.90	288
14	98.7	0.9	7.86	289
30	99.4	0.2	7.82	289
70	101.6	0.6	7.71	281
112	101.2	0.6	7.60	288

[a]Mean of three samples. [b]Mean and standard deviation of three samples analysed in duplicate.

Pharmacokinetic studies

Peritoneal and plasma concentration versus time (semi-logarithmic) curves on the five tested patients are shown in Figure 2. The i.p. 5-FU concentrations are approximately 1,000-fold higher than plasma concentrations. After a relatively short lag time, drug appears in the plasma compartment, where a maximum peak level is achieved within 30 min post i.p. instillation. After this quick absorption distribution phase (α-phase), the elimination phase (β-phase) also follows a first-order model, and 5-FU was still detectable in both fluids 12 h post instillation. This apparent first-order 5-FU clearance in both compartments can be expressed by the following equations:

$$\ln C_{i.p.}(t) = \ln C_{i.p.}(0) - k_{i.p}\, t$$

where $C_{i.p.}$ is the drug concentration in peritoneal fluid or

$$\ln C_{pl}(t) = \ln C_{pl}(0) - k_{pl} t$$

where C_{pl} is the drug concentration in plasma. Peritoneal clearance (PA) can be expressed as $PA = k \times V_{i.p.}$. If the β-phase half-life (β-phase $t_{\frac{1}{2}}$) in both compartments is expressed by $t_{\frac{1}{2}} = 0.693/k$, then the β-phase 5-FU apparent elimination constants ($k_{i.p.}$ and k_{pl}) can be deduced.

Peritoneal clearance obtained from this equation was found to be 15.8 ± 5.6 ml min^{-1}, whereas a value of 15.6 ± 5.2 ml min^{-1} was found when calculated as the conventional dose/peritoneal AUC ratio. β-phase half-life values are respectively 1.28 ± 0.21 and 1.28 ± 0.15 for peritoneal and plasma compartments, and 5-FU apparent elimination constants are similar in both compartments (0.51 ± 0.02 and 0.56 ± 0.04 in peritoneum and plasma respectively).

Total body clearances (expressed as total absorbed dose plasma AUC ratio) varied between 5 and 26 l min^{-1} (Table III).

Peritoneal fluid balance profile

During the whole study a total of 344.55 l (or kg) of carrier solution was instilled (ranging from 29.75 to 125.00 l per patients) and 344.91 l (or kg) was drained (ranging from 15.95 to 138.36 l per patient). For the two patients undergoing long-term i.p. dialysis (Figure 3) the volume balance percentages after 24 h exchanges were mostly stable with time and ranged from 0 to −50% (which means that for 2 l of carrier solution with 5-FU instilled 2–3 l were drained 24 h later). This was not associated with electrolyte disturbance or dehydration.

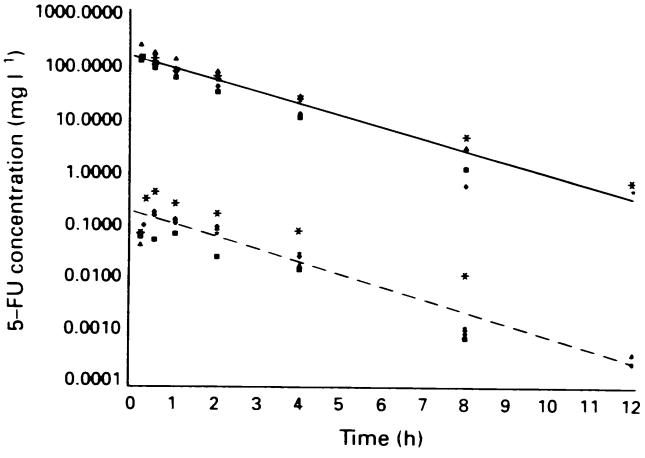

Figure 2 5-Fluorouracil peritoneal (——) and plasma (– – –) levels achieved post i.p. installation of 200 mg m^{-2} 5-fluorouracil in the carrier solution in five patients (*, ▲, ◆, ■, ★).

Table III Pharmacokinetics data results for i.p. 5-fluorouracil (200 mg m^{-2}) on five patients

Patient no.	5-FU dose delivered i.p. (mg)	Intraperitoneal data				PA (ml min^{-1})	Plasma data			TBC (l min^{-1})	Peritoneal/ plasma ratio	
		Volume (l)	Peak level (mg l^{-1})	AUC (0 12 h) (mg l^{-1} × h)	$t_{\frac{1}{2}}$ (h)		Peak level (mg l^{-1})	AUC (0 12 h) (mg l^{-1} × h)	$t_{\frac{1}{2}}$ (h)		Peak conc.	AUC
1	299.4	2.0	149.7	338.9	1.53	15.1	0.400	0.927	1.53	5.4	374	366
2	260.1	1.0	260.1	474.8	1.26	9.2	0.168	0.367	1.31	11.8	1,548	1,294
3	301.7	2.0	150.9	241.7	1.00	23.2	0.179	0.390	1.17	12.9	843	620
4	256.6	2.0	128.3	204.9	1.19	19.4	0.067	0.167	1.20	25.6	1,915	1,227
5	239.3	1.5	159.5	324.1	1.44	12.0	0.151	0.375	1.17	10.6	1,056	864
Mean ± s.d.	271.4 ± 27.7	1.7 ± 0.5	169.7 ± 51.8	316.9 ± 104.5	1.28 ± 0.21	15.8 ± 5.6	0.193 ± 0.124	0.445 ± 0.284	1.28 ± 0.15	13.3 ± 7.5	1,147 ± 602	874 ± 395
(range)	(239 302)	(1 2)	(128 260)	(205 475)	(1 1.5)	(9 23)	(0.07 0.4)	(0.17 0.93)	(1.2 1.5)	(5 26)	(374 1,915)	(366 1,294)

PA, permability area product or peritoneal clearance = $k \times V_{(t_0)}$; TBC, total body clearance = total absorbed dose/AUC (plasma); AUC, area under curve ($C \times T$) determined by the trapezoidal rule.

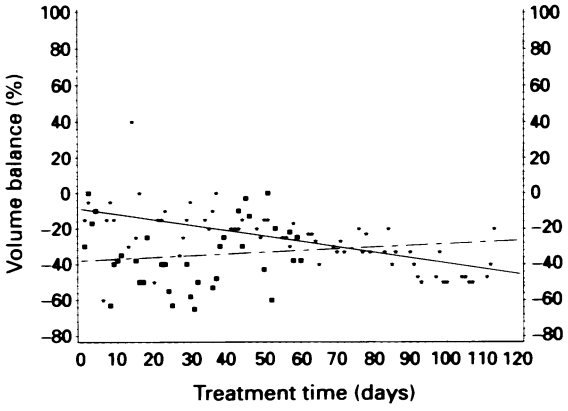

Figure 3 Volume balance percentage levels post 24 h exchange in two patients (■, ★) undergoing long-term i.p. chemotherapy. Volume balance percentage is expressed as the relative difference level between inflow and outflow volumes: [(inflow – outflow) inflow] × 100.

Cytology

For each weekday specimen, the total white cell count and the percentages of mesothelial cells, neutrophil polymorphs, macrophages, eosinophils and lymphocytes were monitored. The percentages of mesothelial cells, macrophages, eosinophils and lymphocytes did not differ significantly from those observed in patients starting CAPD (Fok *et al.*, 1989).

On the weekdays, total cell counts and the percentage of neutrophil polymorphs regularly exceeded the criteria for peritonitis (2×10^8 cells l^{-1} and $\geq 50\%$ polymorphs) in the absence of clinical and bacteriological evidence of peritonitis. Therefore, classical leucocytes and polymorph levels as diagnostic limits for peritonitis in CAPD (Antonsen *et al.*, 1991) are not relevant in these patients. Furthermore, cell counts are apparently unaffected by chemotherapy.

Toxicity and complications

Continuous weekdays i.p. exchanges of 5-FU 200 mg m^{-2} day^{-1} lasting i.p. to 3 months in one patient and for a shorter time for the other patients resulted in no treatment-associated toxicity worse than WHO grade 2. Those WHO grade 2 toxicity incidences included nausea and vomiting and diarrhoea occurring in two patients after 6 weeks of therapy and was treated successfully with antiemetics and loperamide as an antidiarrhoeal agent. During the whole 235 fluid exchanges or 470 connections and disconnections, no bacterial peritonitis or exit site infection events were observed.

Discussion

The study clearly demonstrates the feasibility of long-term continuous weekdays administration of 5-FU i.p. chemotherapy for up to 3 months on an ambulatory treatment basis. This report once again demonstrates the pharmacological advantage that can be achieved by i.p. instillation of chemotherapy. 5-FU concentration ratios between the peritoneal fluid and plasma were about 1,000 for all patients. Interestingly, the peritoneal and plasma 5-FU concentration versus time semilogarithmic curves are parallel for up to 12 h post i.p. instillation, leading to an apparent plasma 5-FU half-life similar to the i.p. 5-FU half-life of around 1.3 h, which is significantly longer than plasma 5-FU half-life of 0.2 h when 5-FU was administered by the i.v. route (Goldberg *et al.*, 1988). Furthermore, the novel carrier solution did not affect the 5-FU pharmacokinetic parameters compared with previous studies with other carrier solutions (1.5% dextrose dialysate or lactated Ringer's solution) (Speyer *et al.*, 1980, 1981; Demicheli *et al.*, 1982; Arbuck *et al.*, 1986; Campora *et al.*, 1987; Schilsky *et al.*, 1990; Sugarbaker *et al.*, 1990).

The relatively constant peritoneal fluid balance achieved with this new carrier solution ensures maximal coverage of peritoneal areas liable to bear tumours for 24 h. This allows a single daily exchange, which is a much more viable prospect for prolonged out-patient dialysis than some of the schedules previously used (for example eight 4-hourly exchanges repeated monthly) (Speyer *et al.*, 1980, 1981; Arbuck *et al.*, 1986). The constant peritoneal fluid balance achieved with the carrier solution combined with the 'state of the art' peritoneal twin-bag delivery system gives long-term and feasible access to the peritoneal cavity with no incidence of exit site infection and bacterial peritonitis in this feasibility study.

Based on the pharmacokinetic parameters from the present study we have designed a loading dose infusion schedule in an attempt to maintain steady-state i.p. 5-FU levels.

We have initiated a multicentre phase I study in collaboration with ML Laboratories to determine the maximum tolerable dose (MTD) values for continuous long-term i.p. treatment for 3 months in patients with advanced colorectal, gastric and ovarian cancer.

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