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 weekly dialysate (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 values 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 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; Lohk 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 (i.e. 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

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 (Picart 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
Table 1 Patient characteristics and i.p. chemotherapy treatment duration

| Age | Sex | 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      | No      | Liver metastases  | 5-FU folic acid and PALA | 19 (over 4 weeks)                  | 6.624                             |
|     |     |                 | widespread         |         |                   |                   |                                          |                                  |
|     |     |                 | peritoneal         |         |                   |                   |                                          |                                  |
|     |     |                 | nodules (positive |         |                   |                   |                                          |                                  |
|     |     |                 | biopsy)            |         |                   |                   |                                          |                                  |
|     |     |                 |                    |         |                   |                   |                                          |                                  |
| F   | 64  | Sigmoid colon   | Laparotomy for     | No      | Liver metastases  | No               | 21 (over 5 weeks)                  | 5.657                             |
|     |     | adherent to     | liver and          |         |                   |                   |                                          |                                  |
|     |     | anterior wall   | peritoneal         |         |                   |                   |                                          |                                  |
|     |     |                 | metastases         |         |                   |                   |                                          |                                  |
| M   | 59  | Sigmoid colon   | Retroperitoneal     | No      | No                | No               | 18 (over 4 weeks)                  | 5.709                             |
|     |     |                 | lymph nodes        |         |                   |                   |                                          |                                  |
| M   | 48  | Stomach         | Inoperable         | Yes     | Pancreas          | No               | 38 (over 8 weeks)                  | 11.797                            |
|     |     | inoperable      |                    |         | Retroperitoneal   |                   |                                          |                                  |
|     |     |                 |                    |         | and pelvic lymph  |                   |                                          |                                  |
|     |     |                 |                    |         | nodes             |                   |                                          |                                  |
| F   | 62  | Caecum          | Satellite tumours   | No      | No                | No               | 65 (over 14 weeks)                 | 17.435                            |
|     |     |                 | Retroperitoneal     |         |                   |                   |                                          |                                  |
|     |     |                 | lymph nodes        |         |                   |                   |                                          |                                  |

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 21 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 compatibility

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 21 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 subvisial 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 consecutively 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 21 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-fluourouracil. 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 compatibility

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.

Pharmacokinetic studies

Peritoneal and plasma concentration versus time (semilogarithmic) 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:

\[ \ln C_p(t) = \ln C_{i.p.}(0) - k_{P.i}t \]

where \( C_{P.i} \) is the drug concentration in peritoneal fluid or

\[ \ln C_{d}(t) = \ln C_{p}(0) - k_{d}t \]

where \( C_{d} \) is the drug concentration in plasma. Peritoneal clearance (PA) can be expressed as \( PA = k \times V_p \). If the β-phase half-life (β-phase \( t_b \) in both compartments is expressed by \( t_b = 0.693 \times k_p \); then the β-phase 5-FU apparent elimination constants (\( k_p \) and \( k_d \)) can be deduced.

Peritoneal clearance obtained from this equation was found to be 15.8 ± 5.6 ml min⁻¹, whereas a value of 16.5 ± 5.2 ml min⁻¹ was found when calculated as the conventional dose peritoneal AUC ratio. Peritoneal clearance (PA) can be expressed as \( PA = k \times V_p \). If the β-phase half-life (β-phase \( t_b \) in both compartments is expressed by \( t_b = 0.693 \times k_p \); then the β-phase 5-FU apparent elimination constants (\( k_p \) and \( k_d \)) can be deduced.

Peritoneal fluid balance profile

During the whole study a total of 344.551 (or kg) of carrier solution was instilled (ranging from 29.75 to 125.001 per patients) and 344.911 (or kg) was drained (ranging from 15.95 to 138.361 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 21 of carrier solution with 5-FU instilled 2–31 were drained 24 h later). This was not associated with electrolyte disturbance or dehydration.

| Table II 5-Fluourouracil stability results in icodextrin solutions |
|---------------------------------|---------------------------------|------------------|------------------|
| Storage intervals (days) | 5-FU content (% of initial | Mean ± s.d.) | pH | Osmolality (mMol kg⁻¹) | |
| 5-FU at 25 mg l⁻¹ | 100.0 ± 0.1 | 5.25 | 288 |
| 14 | 97.3 ± 0.1 | 5.26 | 289 |
| 30 | 99.7 ± 0.2 | 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 | 100.0 ± 0.1 | 5.49 | 287 |
| 14 | 98.1 ± 0.2 | 5.51 | 290 |
| 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 | 100.0 ± 0.1 | 7.18 | 287 |
| 14 | 98.4 ± 0.2 | 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 | 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 |

*Mean of three samples. **Mean and standard deviation of three samples analysed in duplicate.
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 receiving CAPD (Fok et al., 1989).

On the weekdays, total cell counts and the percentage of neutrophil polymorphs regularly exceeded the criteria for peritonitis (2 x 10^9 cells l^-1 and >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 weekday 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 much more viable, a proper prospective 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 in continuous long-term i.p. treatment for 3 months in patients with advanced colorectal, gastric and ovarian cancer.

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