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ORIGINAL ARTICLE

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Impact of carrier solutions on pharmacokinetics of intraperitoneal chemotherapy

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Abstract *Purpose*: In the treatment of gastrointestinal malignancies with dissemination to peritoneal surfaces the principal advantage of intraperitoneal chemotherapy over intravenous chemotherapy is the high drug concentration achieved locally with low systemic toxicity. This advantage can be optimized by maintaining a large area of contact between the chemotherapy solution and the surfaces within the abdomen and pelvis over a prolonged time period. Using a rat model we compared the pharmacokinetics of two drugs infused intraperitoneally, 5-fluorouracil and gemcitabine, in five different carrier solutions. *Methods*: A total of 120 Sprague Dawley rats were randomized into groups according to the carrier solution and the drug administered. Rats were given a single dose of intraperitoneal 5-fluorouracil (20 mg/kg) or gemcitabine (12.5 mg/kg) in 0.1 ml/g body weight of each carrier solution. The carrier solutions used varied in their tonicity (0.3%, 0.9% or 3% sodium chloride), or were isotonic and varied in molecular weight (0.9% sodium chloride, 4% icodextrin and 6% hetastarch). With the hypotonic, isotonic and hypertonic sodium chloride solutions, only 5-fluorouracil was used. Each group was further randomized according to the intraperitoneal dwell period (1, 3 or 6 h). At the end of the procedure the rats were killed, the peritoneal fluid was withdrawn completely and the blood was sampled using a standardized protocol. The volume of the peritoneal fluid was recorded, and the drug concentrations in the peritoneal fluid and plasma were determined by high-performance liquid chromatography. *Results*: Measurements of peritoneal fluid volume showed a more rapid clearance of hypotonic and isotonic sodium chloride solutions from the peritoneal cavity as compared to hypertonic sodium chloride and high molecular weight solutions. When comparing the remaining intraperitoneal volumes at 6 h, the differences were statistically significant for both 5-fluorouracil and gemcitabine when hetastarch ($P < 0.0001$ and $P = 0.0004$) and icodextrin ($P = 0.002$ and 0.008) were compared with isotonic sodium chloride solution. Similarly, there was a significant difference in the volumes recorded at 6 h when hypotonic ($P < 0.0001$) and isotonic sodium chloride solutions ($P = 0.0002$) were compared with hypertonic sodium chloride solution. The concentrations of chemotherapy in the different carrier solutions varied little. The total amount of drug in the peritoneal cavity decreased with all solutions and more quickly with 5-fluorouracil than with gemcitabine. There was a significant difference in the total intraperitoneal 5-fluorouracil between hypotonic and isotonic sodium chloride solutions at 1 h ($P = 0.0003$) and 3 h ($P = 0.0043$), as well as between the isotonic and hypertonic sodium chloride solutions at 1 h ($P = 0.03$) and 3 h ($P < 0.0001$). Similarly, there was a significant difference in the total peritoneal gemcitabine at 6 h between icodextrin and isotonic sodium chloride solution ($P = 0.01$) and between hetastarch and isotonic sodium chloride solution ($P = 0.05$). There were no significant differences in plasma 5-fluorouracil and plasma gemcitabine concentrations obtained with the five solutions. *Conclusions*: These findings show that the clearance of 5-fluorouracil and gemcitabine from the peritoneal cavity can be significantly modified by varying the tonicity or the molecular weight of the carrier solution. Peritoneal fluid clearance was slower with hypertonic sodium chloride and high molecular weight solutions and this resulted in a reduced clearance of chemotherapy. By using a high molecular weight carrier solution the exposure of intraperitoneal cancer cells to gemcitabine was prolonged and drug availability at the peritoneal surface was increased. Similarly, by using a hypertonic carrier solution the

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exposure to 5-fluorouracil was prolonged and drug availability at the peritoneal surface was also increased.

Key words Carrier solutions · Intraperitoneal chemotherapy · Peritoneal carcinomatosis · Pharmacokinetics

Introduction

Peritoneal carcinomatosis is a frequent cause of surgical treatment failure for intraabdominal cancers. Resection of the primary cancer may be followed by local-regional recurrence, peritoneal seeding, and subsequent death. For cancers that disseminate to peritoneal surfaces the therapeutic index of a cytotoxic agent may be improved by changing the route of administration. The major advantage of intraperitoneal chemotherapy is a high drug level at the peritoneal surface with low systemic exposure [3]. Intraperitoneal administration of cisplatin has been shown to be superior to intravenous administration for patients with ovarian cancer [1]. For gastric cancer a significant improvement in survival has been shown when patients are treated with perioperative intraperitoneal chemotherapy [18]. However, there remain many unanswered questions in the attempt to optimize intraperitoneal chemotherapy delivery.

Current techniques for intraperitoneal chemotherapy administration most often utilize isotonic salt solutions. However, the ideal carrier solution should expose the cancerous surfaces within the peritoneal cavity to high levels of cytotoxic agents for as long as possible. Slow clearance would benefit the use of cell cycle-specific drugs, such as 5-fluorouracil and gemcitabine, and facilitate daily administration of ambulatory intraperitoneal chemotherapy. Recently, a successful attempt has been made to prolong retention of intraperitoneal chemotherapy by using icodextrin [6, 8]. Icodextrin 7.5% is an isomolar glucose polymer-based dialysate solution originally prepared for once-daily use in peritoneal dialysis for patients with end-stage renal failure. Subsequent use in other clinical areas has established its tolerability and safety profiles. The high intraperitoneal fluid volume over many hours has led to its use as an intraperitoneal drug carrier solution for treatment of peritoneal carcinomatosis [11]. Also in a phase III clinical trial icodextrin has been successfully used for continuous ambulatory intraperitoneal chemotherapy in combination with 5-fluorouracil [5]. Another isomolar glucose polymer solution with a potentially long intraperitoneal dwell time is 6% hydroxyethyl starch, referred to here as hetastarch.

The purpose of these animal experiments was to determine the pharmacokinetics of two drugs, 5-fluorouracil and gemcitabine, after intraperitoneal infusion in five different carrier solutions: three salt-based carrier solutions (0.3%, 0.9% and 3% sodium chloride) varying in their tonicity, and three isotonic solutions varying in their molecular weight (0.9% sodium chloride, 4% icodextrin and 6% hetastarch).

Materials and methods

Rats

Male Sprague Dawley rats weighing between 250 and 400 g were obtained from a single breeding colony (Harlan Sprague Dawley, Indianapolis, Ind.). Animals were individually housed and were allowed free access to food and water. These experiments were conducted after approval by the Animal Care and Use Committee.

Surgical procedure

All rats were briefly anesthetized by inhalation of halothane (Halothane, USP, Abbott Laboratories, North Chicago, Ill.). Using a 25-gauge needle the solutions, made up of the cytotoxic agent and the carrier, were administered intraperitoneally. The volume of solution administered was 0.1 ml/g body weight when 5-fluorouracil was infused and 80 ml when gemcitabine was infused. Rats were returned to their cages to recover and were allowed free access to food and water. Rats were killed 1 min before the end of the dwell time with a lethal inhalation of halothane. Through a midline laparotomy the peritoneal fluid was carefully removed and quantitated, and intracardial blood was taken in a standardized fashion.

Experimental design

The doses of 5-fluorouracil and gemcitabine used in this study were chosen to approximate the systemic dosage used in humans, 20 mg/kg and 12.5 mg/kg respectively. Five carrier solutions (0.1 ml/g body weight) were used with each drug: 0.3%, 0.9%, 3% sodium chloride (Abbott Laboratories), 4% icodextrin (ML Laboratories, Liverpool, UK), and 6% hetastarch (Abbott Laboratories). A total of 120 rats were randomized into eight groups according to the carrier solution and the drug administered. With the hypotonic and hypertonic sodium chloride solutions, only 5-fluorouracil was used. Each of the eight groups of 15 rats was further randomized according to the length of the dwell period of chemotherapy (1, 3 or 6 h). A reference sample of 500 µl was retained before each intraperitoneal administration. At the end of the procedure rats were killed. A small midline abdominal incision was made, and all peritoneal fluid was aspirated. The volume of peritoneal fluid was recorded and a 500-µl sample was retained. Blood was also sampled. The 5-fluorouracil and gemcitabine concentrations in peritoneal fluid and plasma were analyzed by high-performance liquid chromatography (HPLC).

5-Fluorouracil and gemcitabine assays by HPLC

5-Fluorouracil levels were determined using the method described by Sugarbaker et al. [16], with some modifications to the HPLC system. The HPLC system consisted of a Shimadzu LC7 A instrument equipped with an SPD-6AV detector set at 270 nm-UV, along with a C-R6A Chromopac data processor. A reversed-phase column of 250 × 4.6 mm of Dynamax 300A 5 µm silica was used, coupled to a guard column of the same chemical consistency. The mobile phase consisted of a mixture of 20 m*M* acetic acid in 1% acetonitrile run isocratically at 0.9 ml/min. Sample injections were 50 µl. All solvents used were HPLC grade (Fisher Scientific, Norcross, Ga.). Gemcitabine levels were determined as outlined by Pestieau et al. [12].

Plasma extraction

Blood samples were centrifuged and the plasma was separated from the cells. For 5-fluorouracil, extraction was performed as previ-

ously described [16]. For gemcitabine, a 200-µl sample of plasma was treated with 6 ml isopropanol (15%) in ethyl acetate and mixed thoroughly. After centrifugation the organic phase was transferred to another polypropylene tube and evaporated under nitrogen in a water-bath at 45 ºC. The residue was redissolved in 1 ml of the mobile phase (a 5× dilution) and filtered through a 0.45-µm nylon syringe filter for HPLC injection.

Peritoneal fluid

These samples were diluted with mobile phase as required and filtered through 0.45-µm nylon syringe filters for HPLC injection.

Statistical procedures

To obtain the area under the curve of peritoneal fluid vs time, and plasma vs time, the polygon equation was used with Microsoft Excel (Microsoft, Redmond, Wash.). All pharmacokinetic data were compared between groups by the Wilcoxon Rank Test using Prism for Windows, version 2.0 (GraphPad Software, San Diego, Calif.). For all statistical procedures P-values < 0.05 were taken as significant.

Results

Intraperitoneal volume

Measurements of peritoneal fluid volume at 1, 3, and 6 h showed more rapid absorption from the peritoneal cavity of 0.9% sodium chloride than the high molecular weight solutions with 5-fluorouracil (Fig. 1a, b). This was also observed with gemcitabine (Fig. 1e, f), 0.9% sodium chloride being cleared more rapidly than the high molecular weight solutions. Similarly, there was a tendency for more rapid clearance of 0.3% and 0.9% sodium chloride from the peritoneal cavity as opposed to 3% sodium chloride (Fig. 1c, d). When 5-fluorouracil was used, the percentages of remaining peritoneal fluid volume of 0.9% sodium chloride, icodextrin, and hetastarch were respectively 68%, 72%, and 78% at 1 h, 52%, 73%, and 79% at 3 h, and 40%, 68%, and 84% at 6 h. The difference in the clearance of peritoneal fluid became more evident as the dwell time increased, with 60% of 0.9% sodium chloride being absorbed at the end of the 6-h experiment as opposed to 32% of icodextrin ($P = 0.002$) and 16% of hetastarch ($P < 0.0001$). This was also observed amongst the three concentrations of sodium chloride: only 18% of 3% sodium chloride was absorbed at the end of 6 h as opposed to 60% of 0.9% sodium chloride ($P = 0.0002$) and 99.9% of 0.3% sodium chloride ($P < 0.0001$).

When gemcitabine was used, the percentages of remaining peritoneal fluid volume of sodium chloride, icodextrin, and hetastarch were, respectively, 84%, 84%, and 89% at 1 h, 75%, 80%, and 84% at 3 h, and 60%, 82%, and 92% at 6 h. There was a significant difference in the volumes recorded at 6 h comparing icodextrin with sodium chloride ($P = 0.008$) and hetastarch with sodium chloride ($P = 0.0004$). At each time-point and for both drugs, animals randomized to hetastarch and hypertonic sodium chloride had the highest volume of fluid remaining in the peritoneal cavity. Although the volumes of the intraperitoneal fluid varied markedly, the concentration of 5-fluorouracil and gemcitabine varied little as a result of the differences in carrier solution (Fig. 1a–f).

Peritoneal fluid total drug level

The total amount of drug in the peritoneal fluid decreased with time for the five solutions. The drug clearance from the peritoneal cavity occurred more rapidly for 5-fluorouracil than for gemcitabine. The amounts of intraperitoneal 5-fluorouracil remaining in 0.9% sodium chloride, icodextrin and hetastarch were, respectively, 29%, 34%, and 36% at 1 h, 1%, 1%, and 2.5% at 3 h, and 0.1%, 0.05%, and 0.1% at 6 h (Fig. 2a). The area under the curve (AUC) ratios of remaining intraperitoneal 5-fluorouracil over the 6-h experiment in icodextrin vs 0.9% sodium chloride and in hetastarch vs 0.9% sodium chloride were both equal to one. The amounts of intraperitoneal gemcitabine remaining in 0.9% sodium chloride, icodextrin and hetastarch were, respectively, 63%, 68%, and 70% at 1 h, 37%, 44%, and 45% at 3 h, and 11%, 19%, and 15% at 6 h (Fig. 2c). The levels of gemcitabine remaining in the peritoneal cavity at 6 h with icodextrin ($P = 0.01$) and hetastarch ($P = 0.05$) were significantly different from the levels remaining with 0.9% sodium chloride ($P = 0.01$, $P = 0.05$, respectively).

In the 6-h experiment, the AUC ratio of the remaining intraperitoneal gemcitabine in icodextrin vs 0.9% sodium chloride and in hetastarch vs 0.9% sodium chloride were, respectively, equal to 1 and 1.3. When 5-fluorouracil was used with the sodium chloride solutions, the drug clearance increased as the concentration of the solution decreased (Fig. 2b). There was a significant difference between the total amount of peritoneal 5-fluorouracil remaining in 0.9% sodium chloride and 0.3% sodium chloride at 1 h ($P = 0.0003$) and at 3 h ($P = 0.0043$). Similarly, there was a significant difference between the total amount of peritoneal 5-fluorouracil remaining in 0.9% sodium chloride and 3% sodium chloride at 1 h ($P = 0.03$) and at 3 h ($P < 0.0001$).

Plasma drug concentration

There were no significant differences in plasma 5-fluorouracil or gemcitabine concentrations obtained with the five solutions at any time-point. The mean plasma concentrations of 5-fluorouracil when the drug was infused in 0.9% sodium chloride, 0.3% sodium chloride, 3% sodium chloride, 4% icodextrin, and 6% hetastarch were, respectively, 0.9 ± 0.4, 0.7 ± 0.2, 0.9 ± 0.4, 1.5 ± 1, and 2.4 ± 2.4 µg/ml at 1 h; 0.2 ± 0.1, 0.7 ± 0.2, 0.9 ± 0.4, 0.1 ± 0, and 0.3 ± 0.2 µg/ml at 3 h; and 0.9 ± 0.4, 0.7 ± 0.2, 0.9 ± 0.4, 1.5 ± 1, and 2.4 ± 2.4 µg/ml at 6 h

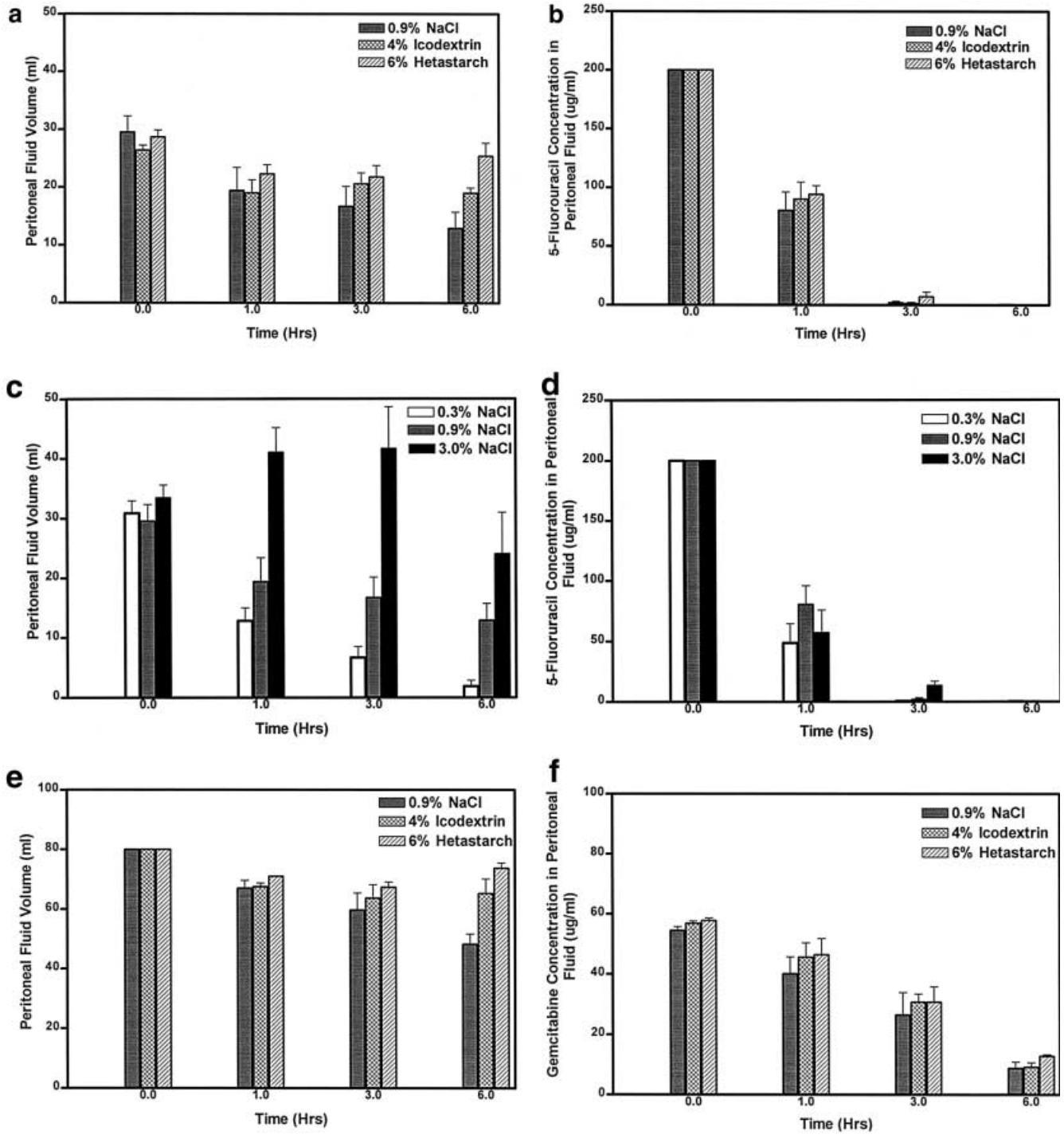

Fig. 1a–f **a,b** Peritoneal fluid volume (**a**) and 5-fluorouracil concentration (**b**) over time with 0.9% sodium chloride, 4% icodextrin and 6% hetastarch. The average weights of the animals were, respectively, 296 ± 33 g, 271 ± 12 g, and 286 ± 12 g when 0.9% sodium chloride, 4% icodextrin and 6% hetastarch were infused; these weights were not significantly different. **c**,**d** Peritoneal fluid volume (**c**) and 5-fluorouracil concentration (**d**) over time with 0.3%, 0.9% and 3% sodium chloride. The average weights of the animals were, respectively, 310 ± 23 g, 296 ± 33 g, and 334 ± 38 g when 0.3%, 0.9% and 3% sodium chloride were infused; these weights were not significantly different. **e**,**f** Peritoneal fluid volume (**e**) and gemcitabine concentration (**f**) over time with 0.9% sodium chloride, 4% icodextrin and 6% hetastarch. The average weights of the animals were, respectively, 349 ± 12 g, 364 ± 8 g, and 370 ± 13 g when 0.9% sodium chloride, 4% icodextrin and 6% hetastarch were infused; these weights were not significantly different

(Fig. 3a, b). The mean plasma concentrations when gemcitabine was infused in 0.9% sodium chloride, 4% icodextrin, and 6% hetastarch were, respectively, 3 ± 0.5, 2.8 ± 0.3 and 2.8 ± 0.6 μg/ml at 1 h; 4.7 ± 1.2, 4.4 ± 0.8 and 4.8 ± 0.8 μg/ml at 3 h; and 3.2 ± 0.4, 3.9 ± 0.1 and 3.8 ± 0.5 μg/ml at 6 h (Fig. 3c).

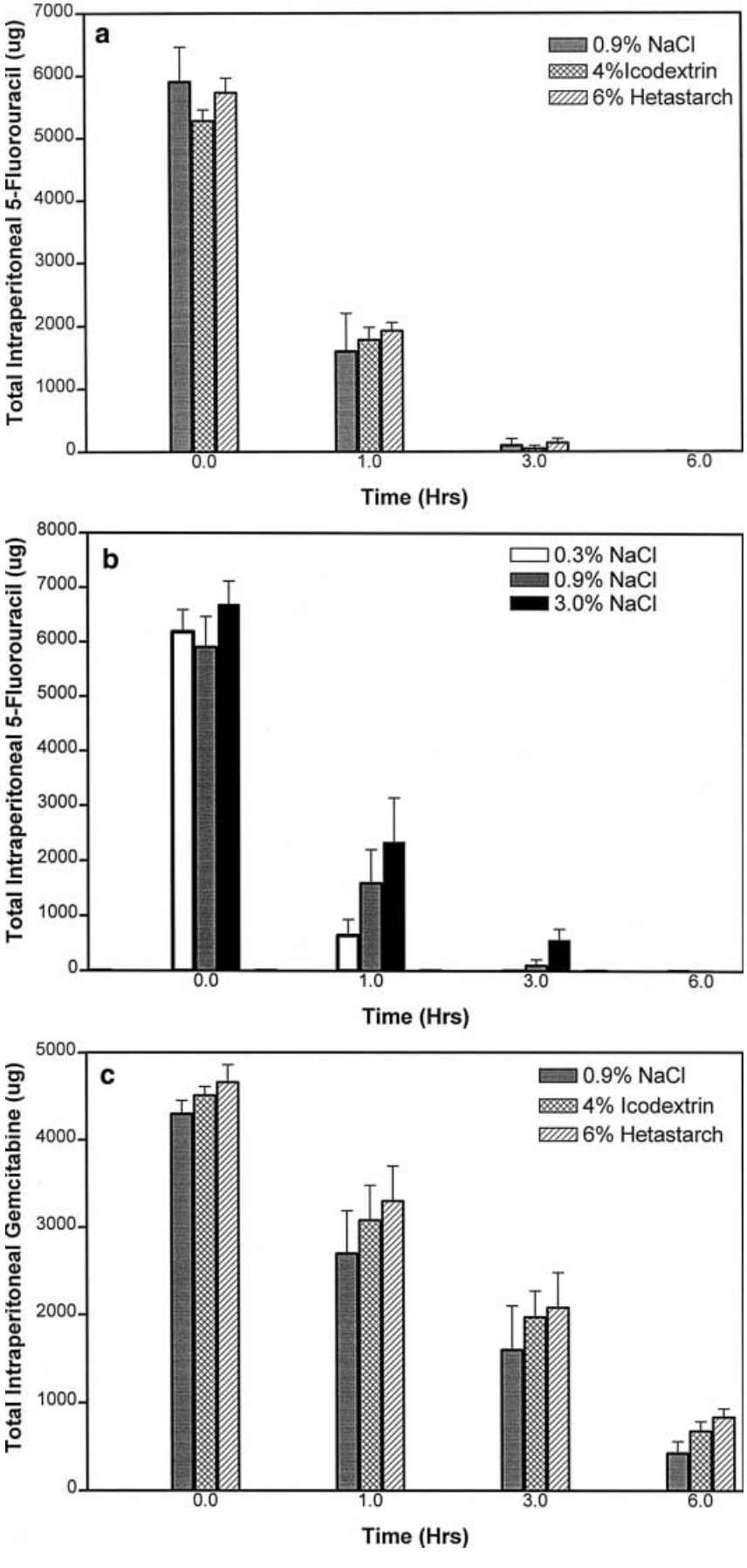

Fig. 2 **a** Total intraperitoneal 5-fluorouracil over time with 0.9% sodium chloride, 4% icodextrin and 6% hetastarch. **b** Total intraperitoneal 5-fluorouracil over time with 0.3%, 0.9% and 3% sodium chloride. **c** Total intraperitoneal gemcitabine over time with 0.9% sodium chloride, 4% icodextrin and 6% hetastarch

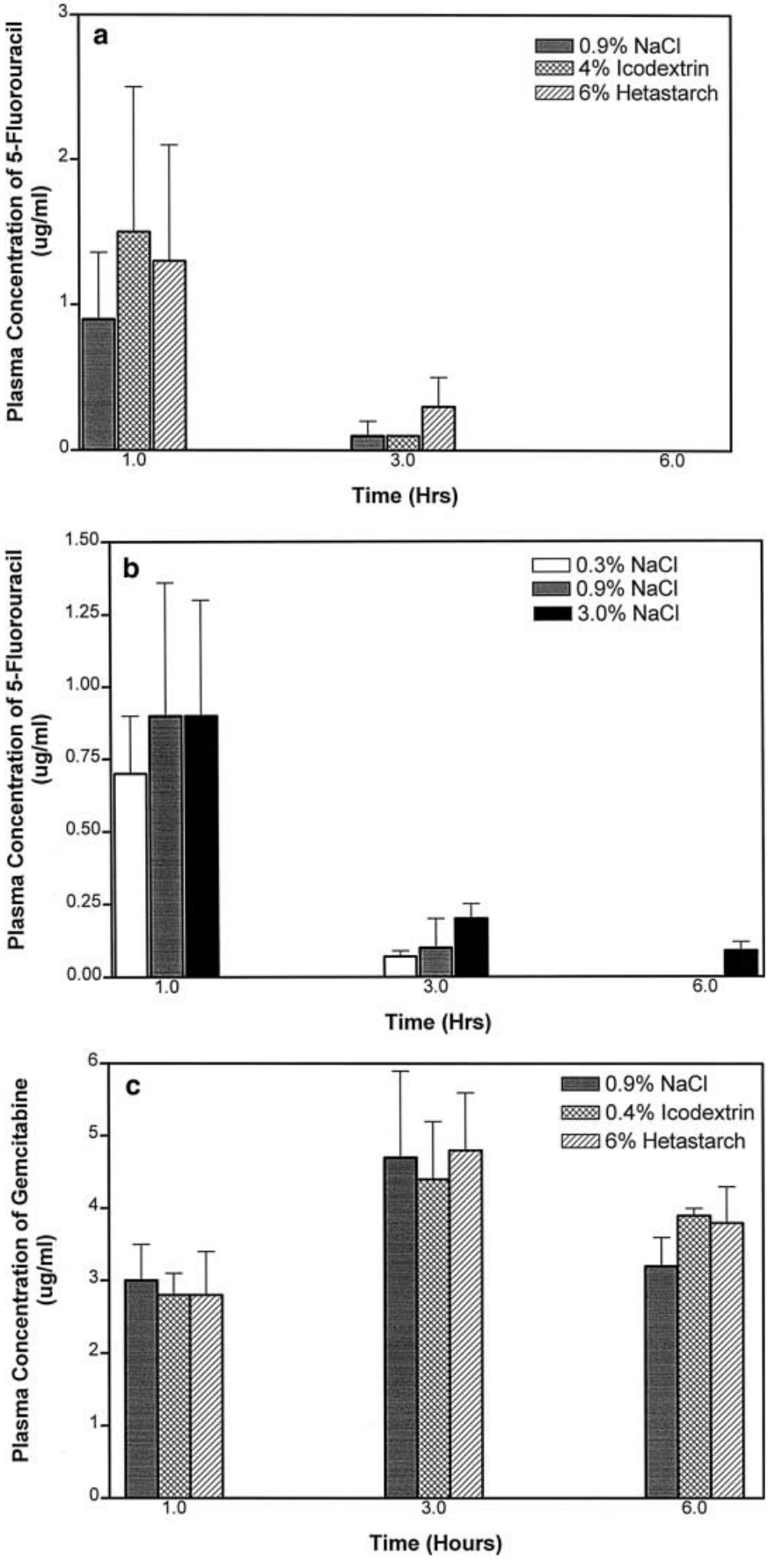

Fig. 3 a Plasma concentration of 5-fluorouracil over time with 0.9% sodium chloride, 4% icodextrin and 6% hetastarch. **b** Plasma concentration of 5-fluorouracil over time with 0.3%, 0.9% and 3% sodium chloride. **c** Plasma concentration of gemcitabine over time with 0.9% sodium chloride, 4% icodextrin and 6% hetastarch

Discussion

Peritoneal carcinomatosis is often widespread and chemotherapy can only be successful if all tumor cells can be treated. Up to now, intraperitoneal chemotherapy has shown limited benefits as treatment for peritoneal surface malignancies. However, no standard treatment in terms of schedule, dwell time, drug and carrier solution has been established. Optimization of intraperitoneal chemotherapy as an adjunct to cytoreductive surgery remains an unrealized goal.

It is necessary for chemotherapy solutions to distribute evenly throughout the entire peritoneal cavity for a prolonged period in order to treat peritoneal surfaces safely and successfully. Maximal cell kill requires that the tumor nodules have prolonged exposure to the cytotoxic drug. Several factors contribute to the drug distribution but intraperitoneal fluid volume is a dominant factor [10]. Rosenheim et al. have demonstrated in monkeys that small volumes of fluid do not flow freely in the peritoneum, even with multiple position changes [13]. Volumes large enough to cause moderate abdominal distention result in more uniform intraperitoneal distribution. Maintenance of a high volume of intraperitoneal fluid over an extended time period would improve the effectiveness of this type of treatment.

Carrier solutions presently in use tend to be rapidly absorbed due to their low molecular weight [17]. In contrast, Icodextrin 20 (7.5%) is an isomolar solution for once-daily use in peritoneal dialysis of patients with end-stage renal failure. Its ability to maintain high intraperitoneal volume over many hours has led to its use as an intraperitoneal drug carrier solution for treatment of peritoneal carcinomatosis [6]. It has been shown to have an intraperitoneal dwell time of 24 h [8]. However, rodents have much higher levels of amylase in their tissues, and therefore metabolize starch more rapidly than humans [9]. In consequence, starch-based solutions are absorbed more rapidly from the peritoneal cavity in these animals and may not mimic the kinetics found in humans.

The osmolality of the solution may also play a role in prolonging the dwell time of intraperitoneal chemotherapy. In a study by Litterst et al., it was shown that slightly hypertonic carrier solutions can prolong the peritoneal retention of chemotherapeutic agents within the peritoneal cavity, probably by inducing a fluid shift inward to the peritoneal cavity [7].

To maintain a high drug concentration as long as possible within the peritoneal cavity the chemotherapeutic agent should also possess a low permeability [2]. It has been shown that medium to high molecular weight agents seem to achieve this condition [4]. With medium molecular weights, 5-fluorouracil (130.08) and gemcitabine (263.2) fall into this category. When used systemically and/or intraperitoneally both agents have proven clinical benefits in many gastrointestinal malignancies [14, 15].

These data show that the use of high molecular weight carrier solutions or a hypertonic sodium chloride solution causes a prolonged dwell of chemotherapy as a result of the intraperitoneal retention of a large volume of fluid. The drug concentrations varied insignificantly between the carrier solutions so that total amounts of 5-fluorouracil and gemcitabine were increased with larger volumes of intraperitoneal fluid. Prolonged intraperitoneal volume was achieved with the high molecular weight solutions, 4% icodextrin and 6% hetastarch, and the hypertonic 3% sodium chloride solution, as compared to 0.9% sodium chloride and 0.3% sodium chloride. At each time-point and for both drugs, animals receiving hetastarch had the highest volume of fluid remaining in the peritoneal cavity. Hypertonic sodium chloride solution (3%) similarly maintained high intraperitoneal volumes throughout the experiment. By slowing down the clearance of intraperitoneal fluid and thereby maintaining a large distribution, starch-based solutions and hypertonic solutions may be considered for optimizing intraperitoneal chemotherapy treatments.

Isotonic sodium chloride, icodextrin and hetastarch exerted quite different effects on the total bioavailability of the two drugs at peritoneal surfaces. Gemcitabine appeared to be a "carrier-dependent" drug with total intraperitoneal drug levels (Fig. 2c) showing the same trend as peritoneal fluid volume (Fig. 1e, f). Gemcitabine remained in the peritoneal cavity along with the carrier solution. In contrast, 5-fluorouracil was found to leave the peritoneal cavity independently of the type of carrier. However, in the experiments with 0.3%, 0.9% and 3% sodium chloride, 5-fluorouracil also acted as a "carrier-dependent" drug (Figs. 1c, d and 2b). The bioavailability of 5-fluorouracil at peritoneal surfaces was therefore less affected by the high molecular weight carrier solutions. The more "carrier-dependent" behavior of gemcitabine may be caused by slower peritoneal clearance as a result of its higher molecular weight and its slower metabolism as compared to 5-fluorouracil. The concentration of gemcitabine remaining in the peritoneal cavity at 6 h was higher than that of 5-fluorouracil with all of the solutions.

In summary, the total drug availability depends not only on the molecular structure of the drug but also on the carrier solution that maintains the peritoneal fluid volume.

These results clearly show the premature clearance of 5-fluorouracil from the peritoneal cavity by 0.3% sodium chloride solution. The phenomenon reflects the rapid clearance of intraperitoneal fluid along with the 5-fluorouracil as previously described. It has been suggested that such rapid clearance may facilitate drug delivery into tumor by increasing tumor penetration over a shorter time. Experiments to assess drug concentration in tumor are necessary to answer these questions. In any event, the rapid movement of hypotonic fluid (Fig. 1c, d) and the rapid loss of 5-fluorouracil (Fig. 2b) suggest a carrier-dependency for this drug.

The plasma drug concentration was more dependent on the drug and its metabolism than on the carrier solution. 5-fluorouracil being metabolized systemically and in the liver was cleared much faster from the systemic circulation than gemcitabine. As gemcitabine was cleared from the peritoneal cavity its plasma concentration increased, showing that peritoneal clearance exceeded renal clearance at this dose of drug.

Even though the improvement in the exposure of peritoneal surfaces to chemotherapy was only modest, it is important to realize that this potential improvement in the effects of chemotherapy occurred with no increases in acute toxicity. Also, with this prolonged expansion of the peritoneal space, subsequent applications of chemotherapy to the surfaces will not be jeopardized. They may even be more effective as adhesions are thinned out and the cancer cells retained within become exposed to chemotherapeutic destruction. Maintaining the same concentration of chemotherapy solution but delivering it over an expanded surface is a new and improved concept in the delivery of intraperitoneal chemotherapy. With no additional risk, a substantial theoretical improvement in response has been demonstrated.

From a clinical perspective, the greatest deterrent to adequate treatment with intraperitoneal chemotherapy is not the cytotoxic effects of the chemotherapy. The remarkable responses achieved when small cancer nodules are surrounded by high concentrations of chemotherapy have been well documented. It is the heterogeneity of these responses because of fibrosis from prior surgery that is the major deterrent to a more generalized benefit to patients. Through the maintenance of an expanded intraperitoneal space, the use of high molecular weight carrier solutions may be a step towards the wider application of cytotoxic effects uniformly throughout the abdomen and pelvis. Further studies with these high molecular weight solutions carrying cytotoxic agents within the peritoneal cavity in the early postoperative period is a crucial next step.

Three factors, therefore, are to be considered in optimizing intraperitoneal chemotherapy: the molecular weight of the drug, its pattern of metabolism, and the carrier solution. Medium to high molecular weight cytotoxic agents such as gemcitabine tend to follow the flow of the carrier solution, remaining longer intraperitoneally as does the carrier. For high molecular weight drugs with a slow systemic metabolism, the choice of the carrier solution is an important factor in optimizing prolonged intraperitoneal chemotherapy. For more rapidly cleared and metabolized drugs, their carrier-dependent behavior and the choice of the carrier solution is less determinant. This study suggests that starch-based solutions such as 4% icodextrin and 6% hetastarch by remaining longer in the peritoneal cavity than 0.9% sodium chloride, might provide better distribution of high molecular weight chemotherapeutic drugs.

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