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ORIGINAL ARTICLE

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Pharmacokinetics and tissue distribution of intraperitoneal paclitaxel with different carrier solutions

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Abstract *Background*: For cancers that have disseminated to peritoneal surfaces, intraperitoneal chemotherapy administration results in high drug concentration locally with low systemic toxicity. Using a rat model we compared the pharmacokinetics and tissue absorption of paclitaxel infused intraperitoneally in two isotonic carrier solutions: 1.5% dextrose peritoneal dialysis solution (peritoneal dialysis solution) and hetastarch (6% hydroxyethyl starch), a high molecular weight solution. *Methods*: A total of 60 Sprague Dawley rats were randomized into groups according to the carrier solution administered. Rats were given a single dose of intraperitoneal paclitaxel (40 mg/m^2) in 0.1 ml/g body weight of each carrier solution. Each group was further randomized according to the intraperitoneal dwell period (3, 6, 12, 18 and 24 h). At the end of the procedure the rats were killed, the peritoneal fluid was withdrawn completely and the volume recorded. Blood and tissues were sampled using a standardized protocol. Drug concentrations in peritoneal fluid, plasma, and tissues were determined by high-performance liquid chromatography. *Results*: Fluid clearance from the peritoneal cavity was lower in the presence of hetastarch than in the presence of peritoneal dialysis solution. The mean volumes remaining in the peritoneal cavity were significantly higher with hetastarch at 18 h ($P=0.0079$). No excess peritoneal fluid remained with peritoneal dialysis solution at 24 h. Mean plasma paclitaxel concentrations were significantly lower with hetastarch at 3 h ($P=0.0079$), 12 h ($P=0.0079$), and 18 h ($P=0.0317$). The mean total quantity of drug remaining in the peritoneal cavity was significantly greater with hetastarch at 12 h ($P=0.0079$) and 18 h ($P=0.0317$). There was a 105% increase in the area under the curve ratio of peritoneal fluid to plasma paclitaxel concentrations with hetastarch (391) vs peritoneal dialysis solution (191). Paclitaxel concentrations were significantly greater with peritoneal dialysis solution at 6 h in colon, abdominal wall, and myocardium. *Conclusions*: The use of intraperitoneal paclitaxel with hetastarch carrier solution provides a pharmacologic advantage for a local-regional killing of residual tumor cells with decreased systemic toxicity. Clinical investigations into the use of 6% hetastarch with high molecular weight chemotherapeutic agents are warranted.

Keywords Carrier solutions · Intraperitoneal chemotherapy · Paclitaxel · Pharmacokinetics · Tissue concentrations

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Introduction

The peritoneal cavity is a common site of tumor dissemination for gastrointestinal and ovarian malignancies. Over the past decade, clinical researchers have examined the potential of intraperitoneal administration of antineoplastic drugs in the treatment of patients with intraabdominal malignancies. The major aim of this strategy is to expose tumor within the peritoneal cavity to greater concentrations of cytotoxic agents for longer periods than can be accomplished safely with intravenous drug administration [3]. The strong rationale behind intraperitoneal chemotherapy has translated into a survival benefit 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 [20].

The main factors determining the theoretical and practical limitation of intraperitoneal therapy are the pharmacologic properties of the peritoneal plasma barrier, the ability of cytostatic drugs to penetrate

intraabdominal tissues and the rate of systemic drug degradation. Tissue penetration of intraperitoneal chemotherapeutic agents depends on drug characteristics including concentration, time of exposure, molecular weight, lipophilicity, and temperature.

Paclitaxel is a unique cytotoxic antineoplastic drug that results in tumor cell kill by producing excessive polymerization of tubulin and dysfunctional microtubules. Recent reports suggest that paclitaxel undergoes metabolism in the liver [14], which makes it an ideal candidate for intraperitoneal drug delivery. Agents undergoing extensive hepatic metabolism such as 5-fluorouracil and doxorubicin possess the greatest regional advantage with intraperitoneal instillation [7, 9, 18]. Evaluation of several established cell lines has shown that the biologic effects of paclitaxel depend on both duration of exposure and drug concentration, features that potentially can be optimized with intraperitoneal instillation [17]. Phase I/II studies have demonstrated paclitaxel's suitability as an intraperitoneal agent [10, 12].

Current techniques for intraperitoneal chemotherapy administration most often utilize isotonic solutions such as 1.5% dextrose peritoneal dialysis solution. However, the low molecular weight of this solution results in its rapid peritoneal absorption [19]. The ideal carrier solution should expose cancerous surfaces or residual tumor cells within the peritoneal cavity to high levels of cytotoxic agent for as long as possible. Slow clearance would benefit the use of cell cycle-specific drugs whose apoptotic effects enhance penetration in solid tumor. Recently, 4% icodextrin, an iso-osmotic solution of the α-1,4-linked glucose polymer, has been successfully used to prolong retention of intraperitoneal chemotherapy [5]. Another iso-osmolar glucose polymer solution with a potentially long intraperitoneal dwell-time is 6% hydroxyethyl starch (hetastarch) which has been used to successfully prolong intraperitoneal retention of gemcitabine in recent animal studies [15].

The purpose of these animal experiments was to determine the pharmacokinetics and tissue concentrations of paclitaxel after intraperitoneal infusion in two isotonic carrier solutions: 1.5% dextrose peritoneal dialysis solution, a low molecular weight solution, and hetastarch, a high molecular weight solution.

Materials and methods

Male Sprague Dawley rats weighing between 300 and 500 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 1-inch 20-gauge needle, the cytotoxic agent plus the carrier solution was administered intraperitoneally. The volume of solution administered was 0.1 ml/g body weight. Rats were returned to their cages to recover and were allowed free access to food and water. At the end of the dwell-time, rats were killed by inhalation of CO_2. Through a midline thoracolaparotomy the peritoneal fluid was carefully removed and quantitated. A sample of intracardiac blood was taken in a standardized fashion and tissue samples were taken from the colon, stomach, abdominal wall and heart.

Experimental design

A total of 60 rats were randomized into two groups according to the carrier solution administered. Paclitaxel (Bristol-Myers Squibb Pharmaceutical Group, New Brunswick, N.J.) was administered in 50% Cremophor EL and 50% dehydrated alcohol. The dose of drug used in this study was chosen to approximate the intraperitoneal dosage used in humans (paclitaxel 40 mg/m^2) and to be above the analytic detection limit in fluid samples. Based on this dosage, paclitaxel was administered at a concentration of 60 μg/ml. Two isotonic carrier solutions (0.1 ml/g body weight) were used: 1.5% dextrose peritoneal dialysis solution (Dianeal, Baxter Healthcare Corporation, Deerfield, Ill.) and 6% hetastarch (Abbott Laboratories, North Chicago, Ill.). Each group was further randomized according to the length of the dwell period of chemotherapy (3, 6, 12, 18 or 24 h). A reference sample of 500 μl was retained before each intraperitoneal administration. At the end of the procedure the rats were killed. A midline thoracoabdominal incision was made and all peritoneal fluid removed. The volume of peritoneal fluid was recorded and a 500-μl sample was retained for analysis. Blood and tissue were also sampled. Paclitaxel concentrations in plasma, peritoneal fluid, and tissue samples were analyzed by high-performance liquid chromatography (HPLC).

HPLC analysis

Paclitaxel levels were determined in plasma, peritoneal fluid and tissue samples, using a modification of the HPLC procedures described by Lee et al. [8]. The HPLC system consisted of a Shimadzu LC7A instrument equipped with an SPD-6AV (UV-VIS) detector set at 227 nm UV, along with a C-R6A Chromopac data processor. A reversed-phase Dynamax 300A 5-μm silica column 250×4.6 mm was used, coupled to a guard column of the same chemical consistency (Varian Associates, Walnut Creek, Calif.). The mobile phase consisted of an isocratic mixture of acetonitrile and 0.1% phosphoric acid in deionized water (50:50, v/v), run at a flow rate of 1.1 ml/min. Sample injections were 50 μl. All solvents used were HPLC grade (Fisher Scientific, Norcross, Ga.).

Sample preparation and analysis

Blood samples were centrifuged and the plasma was separated from the cells. Using a 15-ml polypropylene conical tube, a 300-μl sample of plasma was treated with 6 ml acetonitrile and mixed thoroughly in a vortex mixer. After centrifugation, the acetonitrile was transferred to another polypropylene tube and evaporated at approximately 45°C by blowing with a gentle stream of nitrogen. The residue was resuspended in 150 μl mobile phase and filtered through a 0.45-μm syringe filter before HPLC injection. Peritoneal fluid samples were diluted with mobile phase as required and filtered through a 0.45-μm nylon syringe filter for HPLC injection.

Tissue samples were processed after drying surface moisture. A sample of tissue (250 mg) was accurately weighed and homogenized in 5 ml acetonitrile. The tissue sample site was consistent for all animals. The homogenate was centrifuged and the acetonitrile extract was removed and evaporated as with plasma samples. The residue was redissolved in 1 ml mobile phase and filtered for injection into the HPLC system.

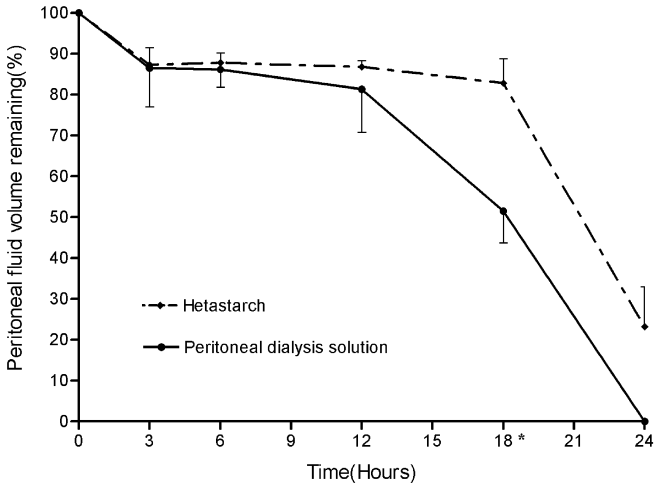

Fig. 1 Mean peritoneal fluid volume remaining as a percentage of initial chemotherapy solution volume administered

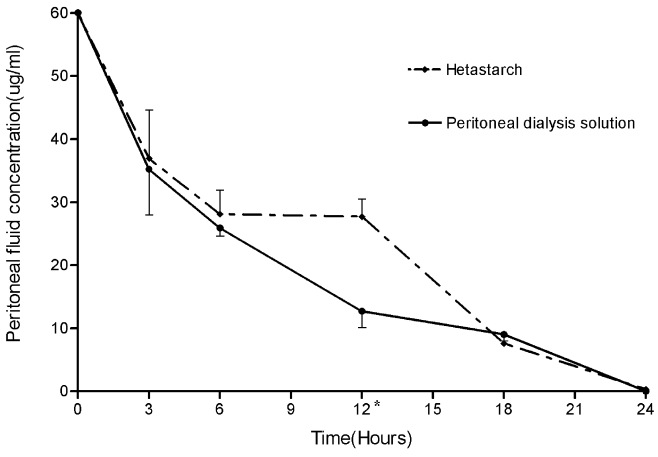

Fig. 2 Mean peritoneal fluid concentration of paclitaxel with different carrier solutions

Statistical procedures

The areas under the curve were determined using Prism for Windows, version 3 (GraphPad Software, San Diego, Calif.). All pharmacokinetic data were compared between groups at each time-point with the Mann-Whitney test (two-tailed) using Prism for Windows, version 3.0. For all statistical procedures, P values <0.05 were considered significant.

Results

Intraperitoneal volume

Measurements of peritoneal fluid volume at each time-point showed slower clearance from the peritoneal cavity of hetastarch when compared to peritoneal dialysis solution (Fig. 1). The mean percentage of fluid volume remaining in the peritoneal cavity was significantly higher with hetastarch at 18 h ($P=0.0079$). No excess peritoneal fluid remained at 24 h when peritoneal dialysis solution was used. At each time-point, animals randomized to hetastarch had the highest volume of fluid remaining in the peritoneal cavity.

Peritoneal fluid drug concentration

At each time-point drug concentrations were determined within the peritoneal cavity (Fig. 2). The mean peritoneal fluid paclitaxel concentration was significantly greater at 12 h when hetastarch was used ($P=0.0079$). There was no significant difference between carrier solutions in terms of peritoneal fluid paclitaxel concentrations at other time-points.

Plasma drug concentration

Plasma paclitaxel concentrations were significantly lower when the drug was administered with hetastarch

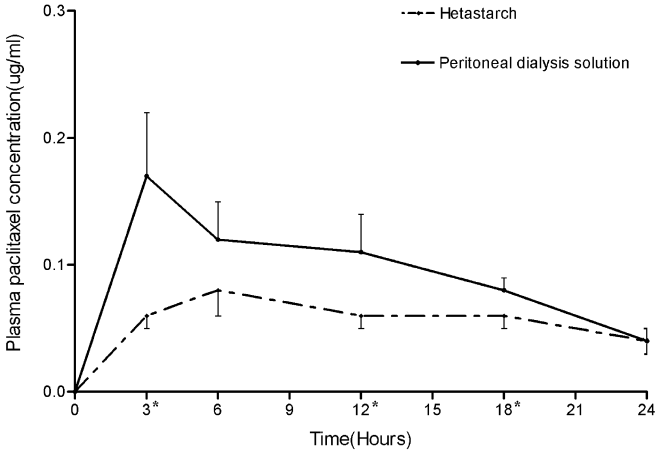

Fig. 3 Mean plasma concentration of paclitaxel with different carrier solutions

at 3, 12 and 18 h ($P=0.0079$, $P=0.0079$ and $P=0.0317$; Fig. 3).

Total quantity of drug in peritoneal fluid

The mean total quantity of paclitaxel in the peritoneal fluid decreased with time for both hetastarch and peritoneal dialysis solution, but was significantly greater with hetastarch at 12 h ($P=0.0079$) and 18 h ($P=0.0317$; Fig. 4). No measurable drug or excess peritoneal fluid was present at 24 h when peritoneal dialysis solution was used. When hetastarch was used, the mean volume of peritoneal fluid remaining at 24 h was $23.2\pm9.9\%$ ($\pm$SD) of the initial peritoneal fluid volume. The mean total quantity of paclitaxel in this fluid was extremely low (2.5 ± 1.9 μg).

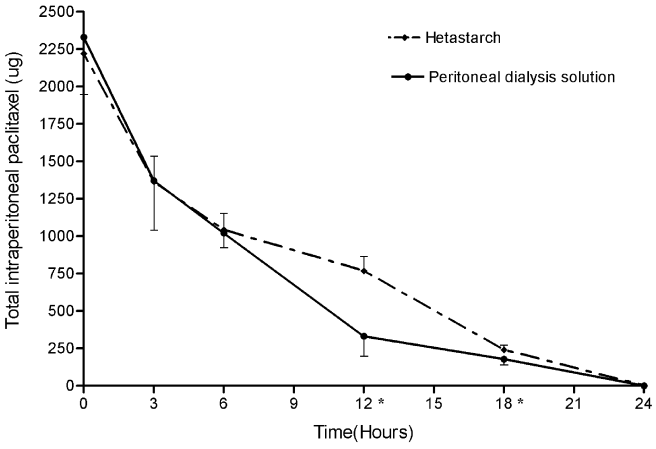

Fig. 4 Mean total quantity of paclitaxel in peritoneal fluid with different carrier solutions

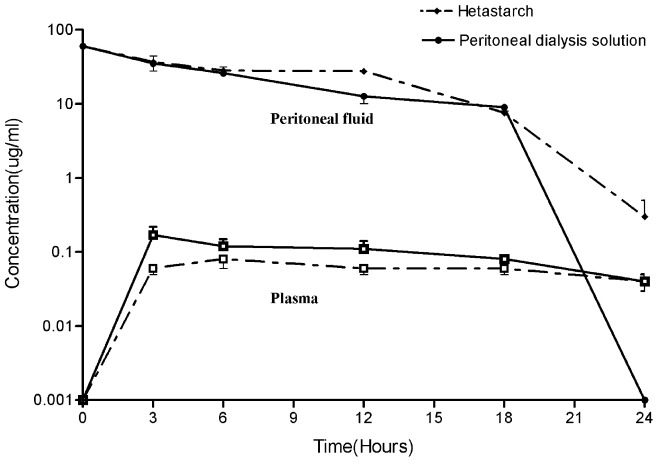

Fig. 5 Mean concentrations of paclitaxel in peritoneal fluid and plasma with different carrier solutions. The peritoneal fluid to plasma AUC ratio with hetastarch was 391, and with peritoneal dialysis solution was 191

Area under the curve ratio of peritoneal fluid to plasma paclitaxel concentration

The area under the concentration over time curve (AUC) ratio with hetastarch was 540 for peritoneal fluid and 1.38 for plasma. The AUC ratio for peritoneal dialysis solution was 442 for peritoneal fluid and 2.31 for plasma. The AUC ratio of peritoneal fluid to plasma was 391 for hetastarch, and 191 for peritoneal dialysis solution. There was an increase of 105% in the AUC ratio of peritoneal fluid to plasma with hetastarch (391 vs 191; Fig. 5).

Tissue drug concentration

Mean tissue concentrations of paclitaxel were greater in colon, abdominal wall and myocardium with peritoneal dialysis solution. These differences were significant at

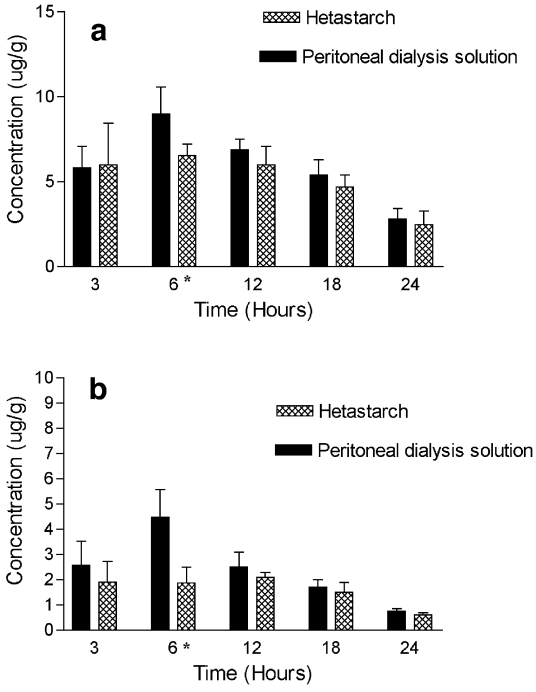

Fig. 6 **a** Mean colonic tissue concentrations of paclitaxel with different carrier solutions. **b** Mean abdominal wall concentrations of paclitaxel with different carrier solutions. *Significant using the Mann-Whitney two-tailed test

6 h ($P=0.0159$) for colonic tissue and abdominal wall ($P=0.0079$; Fig. 6), and at 3 and 6 h for cardiac tissue ($P=0.0317$, $P=0.0079$). No significant differences were seen in gastric tissue concentrations of paclitaxel.

Discussion

Although the theoretical rationale for intraperitoneal drug delivery has been clearly established [3], translation into successful treatment of peritoneal surface malignancies has been limited. No standard treatment in terms of schedule, dwell-time, drug or carrier solution has been established. When considering intraperitoneal chemotherapy as an adjunct to cytoreductive surgery, the selection of chemotherapeutic agent depends on the target tissue for treatment. After cytoreductive surgery, tumor recurrence within the peritoneal cavity may be due to residual tumor nodules on the peritoneal surface or to implantation of residual tumor cells circulating within peritoneal fluid. The ideal cytotoxic agent must be able to penetrate peritoneal surface tumor nodules effectively, but also be able to eradicate microscopic residual disease within the peritoneal fluid. A prolonged, even distribution of chemotherapy solution within the peritoneal cavity is required to maximize exposure of tumor cells and nodules to cytotoxic drug. Small volumes of fluid do not flow freely in the peritoneal cavity and a better distribution is obtained with a large volume of intraperitoneal chemotherapy resulting in mild

abdominal distension [16]. A prolonged high intraperitoneal fluid volume would improve distribution of a drug over a longer time period and improve the efficacy of intraperitoneal chemotherapy.

In order to optimize intraperitoneal chemotherapy, an appropriate matching of chemotherapeutic agent and carrier solution must be achieved. Agents with medium or high molecular weight have a slower peritoneal clearance because of their low permeability [2]. The molecular weight of paclitaxel (853.9 Da), makes it considerably heavier than drugs such as 5-fluorouracil (130.08 Da). Favorable characteristics such as high molecular weight and bulky structure have made paclitaxel an attractive drug for intraperitoneal use. Recent studies have shown a marked pharmacologic advantage with intraperitoneal use of paclitaxel in patients with ovarian cancer [11].

In the study reported here, the use of hetastarch, a high molecular weight carrier solution, delayed the clearance of chemotherapy solution from the peritoneal cavity when compared to peritoneal dialysis solution. The total quantity of intraperitoneal drug at each time-point was also higher with hetastarch. By delaying the clearance of intraperitoneal fluid and thereby maintaining a large distribution, starch-based solutions may optimize intraperitoneal chemotherapy treatments. At the 12-h time-point an increased concentration of intraperitoneal paclitaxel was demonstrated. Intraperitoneal concentrations of drug were similar for both carrier solutions at other times, but the larger intraperitoneal volumes achieved using hetastarch suggest no decrease in mass of drug within the peritoneal cavity. This may expose a larger number of residual tumor cells or minute nodules on the peritoneal surface to the same concentration of drug over a given time period.

Our results demonstrates a minimal volume change of peritoneal dialysis solution for 12 h and hetastarch for 18 h followed by rapid disappearance from the peritoneal cavity. A possible explanation for this is that the peritoneal surface area was consistent throughout the experiment; therefore, one would expect a consistent volume of fluid to be removed over a given time period. Towards the end of the experiment this consistent volume would have a greater impact on the total volume remaining. Although the volume of fluid removed would be the same as time progresses the percentage of fluid removed would increase.

An important parameter for pharmacokinetic analyses of a drug is the AUC which represents the total drug exposure integrated over time. The AUC is traditionally the relationship between time and plasma concentration, but can also be applied to concentration of drug in peritoneal fluid for intraperitoneal chemotherapy. Cancer chemotherapy pharmacokinetics assumes a definite relationship of drug response to drug dose. Following intraperitoneal administration of a drug, the AUC reflects the degree of exposure of peritoneal surfaces to chemotherapeutic agent. It is the best estimate of drug delivery and a predictor of response. By comparing the AUC of a drug after intraperitoneal administration in hetastarch to the AUC after administration in peritoneal dialysis solution an estimate of the optimum carrier solution that will prolong contact of peritoneal surfaces and residual tumor cells with chemotherapy solution can be obtained. The ratio of the AUC of paclitaxel in peritoneal fluid to that in plasma after intraperitoneal administration reflects exposure of peritoneal surfaces to chemotherapy solution in relation to plasma concentrations of drug, which govern systemic toxicity. The higher AUC ratio of peritoneal fluid to plasma paclitaxel concentration with hetastarch suggests that better regional exposure of paclitaxel and lower systemic toxicity can be achieved than with peritoneal dialysis solution. Using intraperitoneal paclitaxel with hetastarch provides a potential for a favorable antitumor effect on small peritoneal surface tumor deposits or microscopic residual disease.

At 6 h, tissue concentrations of paclitaxel in colon, abdominal wall and myocardium were significantly higher when peritoneal dialysis solution was the carrier. This would suggest that paclitaxel moved from the peritoneal fluid into tissues more rapidly in peritoneal dialysis solution than in hetastarch. The differences in tissue concentration were significant at early time-points. The higher plasma levels seen with paclitaxel and peritoneal dialysis solution would seem to confirm this.

Our results have not established the precise mechanism whereby this paclitaxel retention occurs. The concentration of intraperitoneal paclitaxel in hetastarch and peritoneal dialysis solution was remarkably similar over the 24 h of the experiment. No driving force for paclitaxel diffusion based on drug concentration was evident. Rather the longer clearance time for hetastarch solution allowed a larger proportion of the total paclitaxel mass to remain in the peritoneal fluid for a longer time. It may be suggested that fluid mechanics rather than tissue barriers control the drug clearance from the peritoneal cavity. A diffusion model in which the larger molecular size of hetastarch causes it to move more slowly from the peritoneal space to the plasma is the simplest explanation for these observations [11]. If there is little return from the plasma into the peritoneal cavity, and no metabolism of drug within the peritoneal cavity, then this hypothesis regarding chemotherapy clearance would be supported. Further investigation into the nature and anatomic site of the ''peritoneal fluid to plasma barrier'' is indicated.

This study suggests that hetastarch, by remaining longer in the peritoneal cavity, provides wider intraperitoneal distribution of paclitaxel, and an increased exposure of peritoneal surfaces to high molecular weight drugs such as paclitaxel with lower systemic toxicity than peritoneal dialysis solution. The potential impact of our study has been demonstrated in recent clinical studies using starch carrier solutions for intraperitoneal chemotherapy delivery. Mohamed and colleagues compared intraperitoneal paclitaxel delivery in hetastarch with peritoneal dialysis solution in patients following

cytoreductive surgery for peritoneal surface malignancy [13]. Clearance of hetastarch from the peritoneal cavity was lower than that of peritoneal dialysis solution. Both the volume of solution remaining in the peritoneal cavity and total drug amount were greater with hetastarch, resulting in an increased exposure of peritoneal surfaces to paclitaxel. Hosie and colleagues studied 4% icodextrin as a carrier solution for adjuvant intraperitoneal 5-fluorouracil delivery in patients with surgically resected colorectal carcinoma [6]. The 4% icodextrin solution provided a similar pharmacokinetic advantage in maximizing the serosal surfaces in contact with chemotherapeutic agent by maintaining the instilled volume over a prolonged time.

Maintenance of an expanded intraperitoneal space with the use of hetastarch may in addition ensure separation of loops of bowel to allow direct contact of chemotherapy solution with bowel surfaces prone to adhesion formation and subsequent disease recurrence. This reduction in adhesion formation has been shown with the use of intraperitoneal 4.5% icodextrin lavage and instillation following laparoscopic gynecologic surgery [4]. Further clinical investigation into the use of 6% hetastarch for intraperitoneal administration of high molecular weight chemotherapeutic agents is warranted.

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