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ORIGINAL ARTICLE

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Extent of parietal peritonectomy does not change intraperitoneal chemotherapy pharmacokinetics

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Abstract *Purpose*: To measure the clearance intraperitoneal mitomycin C and doxorubicin in patients having peritonectomy and analyze the impact of the extent of peritoneal resection on pharmacokinetics. *Methods*: A group of 15 patients with peritoneal carcinomatosis were submitted to cytoreductive surgery and heated intraperitoneal chemotherapy. Ten patients received mitomycin C and five, doxorubicin. Six patients underwent total parietal peritonectomy and nine had less-extensive peritonectomy. Pharmacokinetics were determined by sampling peritoneal fluid and blood. Drug concentrations over time, area under the curve ratios and the amount of drug recovered from the peritoneal cavity were calculated and compared between the groups. *Results*: The concentrations of mitomycin C over time in the peritoneal fluid and plasma were similar in five patients with total parietal peritonectomy as compared to five patients with less-extensive peritonectomy ($P = 0.5350$ and 0.6991; Mann-Whitney test). Mitomycin C area under the curve ratio in total peritonectomy patients was 20.5 and 25.7 in patients with less-extensive peritonectomy. The difference in total amount of drug recovered from the peritoneal cavity was not significant ($30.6 \pm 6.188\%$ versus $22.6 \pm 3.84\%$, $P = 0.095$). In the studies with doxorubicin, one patient underwent total parietal peritonectomy with similar pharmacokinetics to four patients submitted to partial peritonectomy. *Conclusions*: The extent of parietal peritoneal resection did not affect the pharmacokinetics of intraoperative intraperitoneal chemotherapy. The pharmacological barrier between the abdominopelvic cavity and plasma is not directly related to an intact peritoneum.

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Introduction

The treatment of peritoneal surface dissemination of gastrointestinal cancer, abdominopelvic sarcoma or primary peritoneal mesothelioma with aggressive cytoreductive surgery and maximal regional chemotherapy has shown long-term survival benefits and acceptable morbidity and mortality in selected patients [11, 18, 19, 20]. All natural history studies have documented short-term survival in these patients using conventional treatment [3, 16]. Clinical reports clearly establish that complete cytoreduction is an absolute requirement for long-term survival benefit [4, 13, 19, 20, 21]. Both visceral resection and parietal peritonectomies are necessary to treat peritoneal surface malignancies; the extent of resection is variable and depends on the distribution of disease. Non-mucinous tumors involve both the parietal and visceral surfaces, whereas mucinous tumors rarely develop large-volume disease on parietal peritoneal surfaces [2]. In order to achieve acceptable long-term results in a larger proportion of patients, the extent of peritonectomy has gradually increased, and currently a substantial percentage of patients require a total parietal peritonectomy for complete cytoreduction to occur.

In order to deal with small-volume residual disease, intraperitoneal chemotherapy is delivered intraoperatively and in the early postoperative period [18]. The use of drugs with high molecular weight, such as mitomycin C, via the intraperitoneal route presents a favorable area under the curve (AUC) ratio of intraperitoneal to intravenous exposure, which results in a high intraperitoneal cell kill with reduced systemic toxicity [12]. The use of chemotherapy in the perioperative period not only destroys the tumor cells, but also eliminates viable

platelets, white blood cells and monocytes from the peritoneal cavity. This may diminish the promotion of tumor growth associated with the wound-healing process. The drugs used intraoperatively are those whose cytotoxicity is augmented by heat [1, 23].

Increasingly aggressive peritonectomy is now being combined with a standardized intraoperative chemotherapy regimen in order to achieve a complete cytoreduction. In some patients with peritoneal surface malignancy, less than half of the peritoneal surface is stripped away. These patients have limited peritoneal seeding. In other patients a greater volume and distribution of implants requires a total parietal peritonectomy. Profound systemic toxicity could occur in these complete resections if the peritoneum-plasma barrier is extensively disrupted. This study was performed to measure the clearance of intraperitoneal mitomycin C and doxorubicin in patients having a variable extent of parietal peritonectomy.

Material and methods

Between May and August 2002, 15 patients underwent cytoreductive surgery followed by heated intraoperative intraperitoneal mitomycin C or doxorubicin. Of the patients treated by intraperitoneal mitomycin C, five required total parietal peritonectomy, and five had less-extensive peritonectomy. Five patients were treated with intraperitoneal doxorubicin, one had a complete parietal peritonectomy and four did not. All the patients had a biopsy-confirmed diagnosis of peritoneal carcinomatosis.

Cytoreductive surgery

The cytoreductive approach used to treat these patients included visceral and parietal peritonectomy procedures, as previously described [17]. The goal of the surgery was to remove all visible evidence of tumor within the abdominal cavity. Four different parietal peritonectomy procedures were used as necessary to strip or resect peritoneal implants. The parietal peritonectomy procedures were: (1) total anterior parietal peritonectomy, (2) left-upper quadrant peritonectomy, (3) right-upper quadrant peritonectomy, and (4) pelvic peritonectomy with resection of the rectosigmoid colon. The approximate extent of each parietal peritonectomy procedure was quantitated as shown in Fig. 1.

Patients treated in this study had mucinous peritoneal carcinomatosis. The distribution of the disease was such that little if any dissection of small bowel was necessary in any of the 15 patients. Some individual tumor nodules were removed from stomach and proximal small bowel. The major site for mucinous tumor distribution requiring peritoneal stripping was the parietal peritoneum [2].

For statistical analysis the patients were divided into two groups according to the extent of peritoneal resection. The first group comprised those in whom 100% of the parietal peritoneum was stripped and the second group those who did not have anterior parietal peritonectomy. The indication for the extent of peritonectomy was the amount of disease; the objective of the surgery was to clear all visible tumor.

Heated intraoperative intraperitoneal chemotherapy

At the end of the surgery, but before the surgical reconstruction, closed suction catheters were placed through the abdominal wall. A Tenckhoff catheter and a temperature probe were similarly placed in the abdominal cavity. The Tenckhoff catheter was used as an inflow line. The closed suction catheters were used as drainage lines. The skin edge was sutured to a self-retaining retractor, and a plastic sheet was incorporated into these sutures to create an open space beneath. A slit in the plastic cover was made to allow the surgeon's double-gloved hand access to the abdomen and pelvis [18].

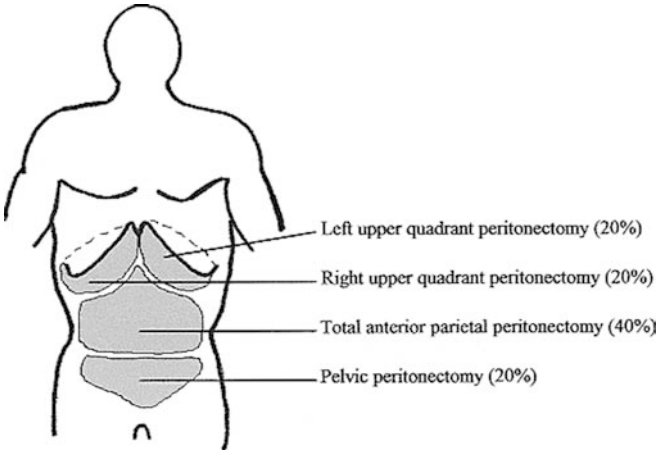

Fig. 1 Quantitation of the extent of parietal peritonectomy

The heated mitomycin C or doxorubicin treatment continued for 90 min. The dose of mitomycin C was 12.5 mg/m^2 for males and 10 mg/m^2 for females. Doxorubicin was given at 15 mg/m^2. The drugs were delivered in 3 l 1.5% dextrose peritoneal dialysis solution. Using an external heater, a heat exchanger, and infusion pumps, the temperature in the abdominal cavity was kept near 41.5°C. During the perfusion, the surgeon vigorously manipulated all viscera to uniformly distribute the chemotherapy solution.

Upon completion of the 90-min chemotherapy perfusion the intraperitoneal fluid was collected, quantitated, and the drug concentration determined. The bowel anastomosis and other reconstruction procedures were performed after completion of the peritoneal perfusion.

Pharmacokinetics studies

During the heated intraoperative intraperitoneal chemotherapy procedure, perfusate and blood samples were collected at 15-min intervals. An additional plasma sample was collected 30 min after the end of the procedure. Assays of mitomycin and doxorubicin concentrations were determined by high-performance liquid chromatography (HPLC), as described elsewhere [6, 7, 9, 22]. Briefly, isolation of mitomycin C from plasma was done by solid-phase extraction. Doxorubicin was isolated by liquid/liquid extraction with methanol/chloroform (3:2). Perfusate samples, which contained relatively high concentrations of drug were appropriately diluted with water (mitomycin C) and mobile phase (doxorubicin) and filtered through 0.2-μm nylon syringe filters for HPLC injection.

The HPLC system consisted of a Shimadzu LC7A instrument equipped with a SPD-6AV (UV-vis) detector (set at 365 nm for mitomycin C and 290 nm for doxorubicin), along with a C-R6A Chromatopac data processor. Reversed-phase columns (250×4.6 mm of 300 Å 5-μm silica for mitomycin and 150×4.6 mm of 100 Å 5-μm silica for doxorubicin) bonded to C18 (Dynamax; Rainin Instruments, Emeryville, Calif.) were used, coupled to a guard column of the same chemical consistency. The mobile phase consisted of methanol/water (3:7) for mitomycin and acetonitrile (32% v/v) in 0.1% ammonium formate buffer (pH 4) for doxorubicin, run isocratically at 0.9 ml/min. Sample injections were 50 μl. All solvents were Fisherbrand, HPLC grade (Fisher Scientific, Norcross, Ga.).

Statistical analysis

Raw data for statistical analysis were generated from the HPLC analysis. The mitomycin C pharmacokinetic data of patients treated with total parietal peritonectomy were compared to data from patients treated with less-extensive peritonectomy using a non-parametric Mann-Whitney test (two-tailed). The statistical comparison of body surface area was made using a non-parametric Mann-Whitney test (two-tailed). AUCs of perfusate concentrations versus time and plasma concentration versus time were calculated. The AUC ratio was defined as the ratio of the AUC for peritoneal concentrations to the AUC for plasma concentrations. For all calculations and statistical analyses, Prism for Windows, version 3.0 (GraphPad Software, San Diego, Calif.) was used. P values <0.05 were taken as significant.

Results

Mitomycin C pharmacokinetics

Table 1 shows the extent of peritonectomy for individual patients. The five patients submitted to total parietal peritonectomy received a median dose of 22 ± 4.5 mg of intraperitoneal mitomycin C, and the five patients submitted to standard surgery 23.4 ± 2.6 mg of intraperitoneal mitomycin C ($P = 0.84$). The concentrations of drug over time are shown in Fig. 2. There was no significant difference between plasma and peritoneal fluid concentrations in the two groups ($P = 0.5350$ and 0.6991, respectively). The AUC ratios was 20.5 in the total peritonectomy patients and 25.7 in the less-extensive peritonectomy patients. The mean total amount of drug recovered from the peritoneal cavity was greater in the total parietal peritonectomy patients than in the less-extensive peritonectomy patients, but the difference was not significant ($30.6 \pm 6.188\%$ versus $22.6 \pm 3.84\%$, $P = 0.095$). The volume recovered from the peritoneal cavity at the end of procedure was significantly greater in the total peritonectomy group (2.85 ± 0.57 l vs 2.18 ± 0.24 l, $P = 0.0317$). The mean body surface area was 1.85 ± 0.158 m^2 in patients with total parietal peritonectomy and 2.0 ± 0.158 m^2 in those with less-extensive parietal peritonectomy ($P = 0.2222$).

Table 1 Description of peritonectomy in ten patients who had cytoreductive surgery plus heated intraoperative intraperitoneal mitomycin C

Procedure	Total parietal peritonectomy					Partial parietal peritonectomy				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Total anterior parietal peritonectomy	●	●	●	●	●					
Left-upper quadrant peritonectomy	●	●	●	●	●	●	●			
Right-upper quadrant peritonectomy	●	●	●	●	●	●	●	●	●	
Pelvic peritonectomy	●	●	●	●	●	●	●	●	●	●
Percentage parietal peritoneum resected	100	100	100	100	100	60	60	40	40	20

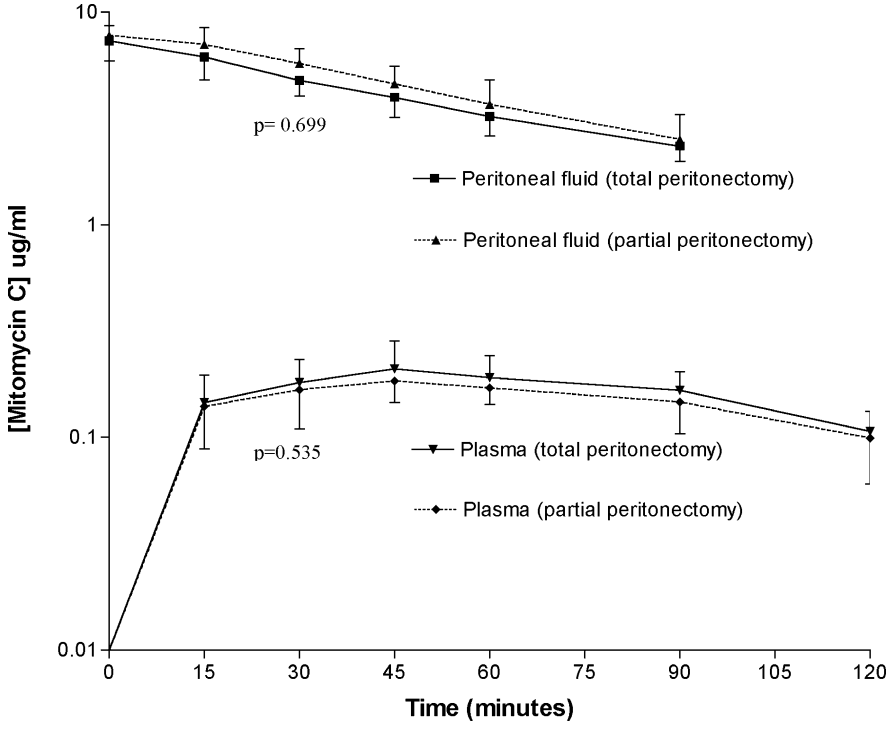

Fig. 2 Peritoneal and plasma concentration curves of heated intraoperative mitomycin C. The means ± SD of five patients in each group are shown

It has been established that body size correlates directly with peritoneal surface area [5, 15]. To test the influence of body size on mitomycin C pharmacokinetics the AUC peritoneal fluid, the AUC plasma and the peritoneal fluid to plasma AUC ratio were determined for the five largest patients treated with mitomycin C and for the five smallest patients similarly treated. The dose of mitomycin C varied with body surface area but the volume of perfusate did not. The mean peritoneal fluid AUC was 467.9 ± 48.6 μg/ml·min in the larger patients and 359.1 ± 72.38 μg/ml·min in the smaller patients ($P = 0.0556$, borderline significance). The mean plasma AUCs were 12.54 ± 4.14 μg/ml·min and 15.75 ± 1.74 μg/ml·min, respectively ($P = 0.15$), and the mean peritoneal fluid to plasma AUC ratios were 40.31 ± 11.7 and 22.92 ± 4.54, respectively ($P = 0.0556$).

Doxorubicin pharmacokinetics

In the group of five patients treated with heated intraperitoneal doxorubicin, one patient had total parietal peritonectomy and four had less-extensive peritonectomy. The concentrations of drug over time are shown in Fig. 3.

Discussion

Pharmacokinetic studies of the intraperitoneal route of administration of cancer chemotherapy demonstrate a protracted local concentration as compared to systemic levels. The distribution model was proposed by Dedrick et al. to explain this phenomenon [5]. In this model, delayed systemic drug distribution is predictable and dependent on drug diffusivity within the adjacent tissues in the peritoneal cavity and the rate of drug removal from tissue by capillary blood. Low systemic drug concentrations are maintained by a rapid systemic metabolism or excretion by the kidneys and liver. The phenomenon is referred to as the peritoneum-plasma barrier [10]. An intact peritoneum is presumed to be required to maintain the marked concentration differences between plasma and peritoneal fluid.

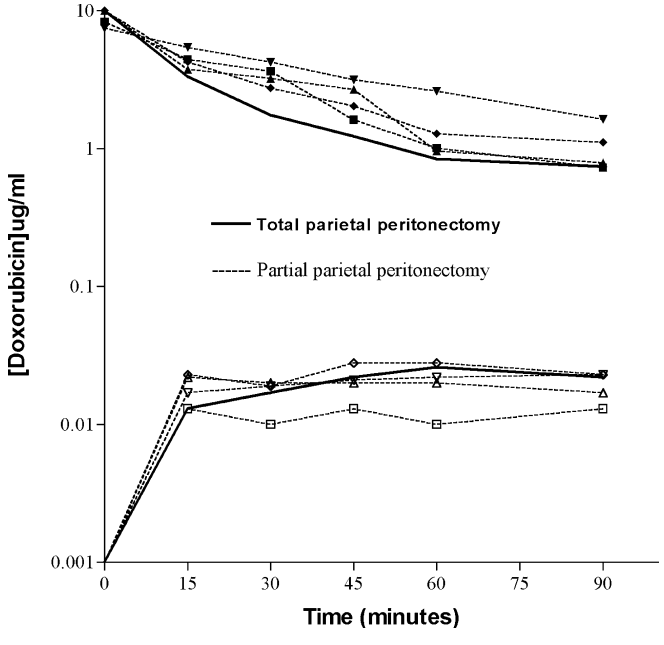

Fig. 3 Heated intraoperative intraperitoneal doxorubicin pharmacokinetics in five patients. The *upper lines* show the peritoneal fluid concentrations and the *lower lines* show the plasma concentrations. The *solid lines* indicate the data from a single patient with total parietal peritonectomy. The percentage parietal peritonectomy in the other four patients were 20% (□), 40% (△), 40% (▽) and 60% (◇)

In this study, the AUC ratio of the five patients having 100% peritonectomy was similar to the ratio of the five who had 60% parietal peritonectomy or less. It is possible that small differences in the clearance of mitomycin C exist as a result of more extensive peritonectomy [12]. It is unlikely that clinical differences requiring modifications of drug dose are necessary in patients requiring complete parietal peritonectomy. Plasma and peritoneal fluid concentrations were remarkably similar for these groups of patients.

The only significant difference that was seen between these two groups was the total volume of fluid remaining after the 90-min perfusion. Patients having total parietal peritonectomy had a mean of 2.85 l and those with less-extensive peritonectomy had 2.18 l ($P = 0.03$). Greater loss of plasma into the peritoneal cavity would be predicted with a larger raw surface. This loss of plasma from the systemic circulation into the peritoneal cavity would work to reduce drug clearance from the peritoneal space by lowering the diffusion gradient between the abdominopelvic space and the plasma compartment. This may help explain the difference in total drug recovered from the peritoneal space in patients with total parietal peritonectomy. These differences in total drug recovery were not statistically significant.

The data from humans would be more convincing if supported by similar studies in animal models. Unfortunately, the fluid and electrolyte support required by total parietal peritonectomy in a prolonged experiment makes this procedure difficult, probably impossible, in an animal model. Rubin et al. have studied the mass transfer coefficients of glucose, urea and inulin in normal dogs and in dogs that had a complete evisceration [14]. The same group has determined that this surgical procedure would remove 50% of the peritoneal surface in a human and 60% in a rat [15]. In the dog model this extensive resection of peritoneal surface caused no changes in clearance of glucose, urea or inulin. Flessner et al. studied the peritoneum as a barrier to mannitol and albumin in the rat [8]. Significant alterations of the membrane were studied using a chamber fixed to the parietal peritoneum. Neither manual drying of the peritoneum nor removal of the peritoneum altered the transport. These authors concluded that the anatomic peritoneum was relatively

unimportant in the transport of molecules from the abdominal and pelvic space.

The data relating body size to peritoneal clearance showed a higher mean AUC of mitomycin in peritoneal fluid for the larger five patients. This would be predicted because less perfusate would be in continuous contact with abdominal and pelvic side walls; there would be a larger open surface with a larger more open abdomen and the same volume of perfusate. The lower mean plasma AUC would be predicted by a more rapid renal excretion in the patients with larger kidneys.

The thinking regarding the anatomic barrier between peritoneal space and systemic blood needs to be revised in the light of these results. The barrier that delays the clearance of large molecules cannot be the peritoneal membrane. Unless fibrosis has markedly altered the peritoneum that persists after surgery these experiments suggest that the peritoneum is of little or no importance to delayed drug clearance. The barrier should no longer be referred to as a peritoneum-plasma barrier; rather peritoneal fluid-plasma barrier may be a more accurate term. The current data may be interpreted to show that all the tissues between these two compartments and the carrier solution itself are important in controlling the pharmacokinetics of intraperitoneal drug administration. It has been established that an intact peritoneum is not required for the marked concentration differences that provide a strong rationale for perioperative intraperitoneal chemotherapy to persist.

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