

Changes induced by surgical and clinical factors in the pharmacology of intraperitoneal mitomycin C in 145 patients with peritoneal carcinomatosis

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Abstract

Background Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are a combined treatment modality considered for selected patients with peritoneal carcinomatosis from colorectal and appendiceal cancer. Mitomycin C is a drug often used in this clinical setting. The surgical and clinical factors that may influence the pharmacokinetics of hyperthermic intraperitoneal chemotherapy should be further elucidated.

Materials and methods The patients included were 145 who had colorectal or appendiceal carcinomatosis resected using cytoreductive surgery prior to treatment with hyperthermic intraperitoneal chemotherapy with mitomycin C as part of a multidrug regimen. The effect of clinical and surgical factors on drug distribution after single intraperitoneal bolus administration with mitomycin C was determined.

Results The pharmacokinetics of 145 patients treated with intraperitoneal mitomycin C showed a 27 times greater exposure to peritoneal surfaces when compared to plasma.

At 90 min, 29% of the drug remained in the chemotherapy solution, 62% was retained in the body, and 9% was excreted in the urine. The extent of peritonectomy increased the clearance of mitomycin C from the peritoneal space ($p = 0.051$). A major resection of visceral peritoneal surface and a contracted peritoneal space reduced drug clearance. A contracted peritoneal space significantly reduced ($p = 0.0001$) drug concentrations in the plasma.

Conclusions Surgical and clinical factors may require modifications of drug dose or timing of chemotherapy administration. A large visceral resection and a contracted peritoneal space caused a reduced mitomycin C clearance. Total diffusion surface is an important determinant of mitomycin C pharmacokinetics.

Keywords Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy (HIPEC) · Mitomycin C · Intraperitoneal chemotherapy · Appendix cancer · Colorectal cancer · Chemotherapy pharmacokinetics

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Introduction

A validated treatment option for patients with carcinomatosis from colorectal or appendiceal cancer is a comprehensive management plan using cytoreductive surgery and perioperative intraperitoneal chemotherapy [1, 2]. The intraperitoneal chemotherapy used in the operating room is combined with moderate hyperthermia for optimal effects [3, 4]. Mitomycin C has received the greatest amount of preclinical and clinical work and is mostly widely used for peritoneal carcinomatosis [5–8]. It has been used for peritoneal carcinomatosis from colorectal cancer, appendiceal cancer, ovarian cancer, gastric cancer, and diffuse malignant peritoneal mesothelioma [1, 2, 9–12].

Controversies still exist regarding the proper dosimetry of the chemotherapy solution. Some institutions use a single dose of mitomycin C, others a double dose, and still others triple dose the drug over a 90-min time period [13–15]. Also, the volume of carrier solution used to fill the peritoneal space with the chemotherapy solution varies greatly at different institutions [16, 17]. Design of an optimal hyperthermic intraperitoneal chemotherapy regimen is difficult because randomized clinical trials to identify a best treatment option are unlikely to be successful. Our group has concluded that continued pharmacologic study of this new route and new timing of chemotherapy administration will assist in better defining the optimal management plan.

Despite a large amount of clinical and preclinical data, pharmacokinetic studies in a large number of patients treated in a uniform manner with cytoreductive surgery prior to hyperthermic intraperitoneal mitomycin C do not exist. For example, the effects of the extent of the cytoreductive surgery on the pharmacology of hyperthermic intraperitoneal mitomycin C in a large number of patients have yet to be described. In this manuscript, we confirm and expand prior pharmacokinetic information regarding hyperthermic intraperitoneal mitomycin C used in the operating room. The goal of this manuscript is to study the impact of surgical and clinical factors on the pharmacology of mitomycin C.

Materials and methods

Patients

All 145 patients were treated at the Washington Hospital Center. They carried a diagnosis of peritoneal carcinomatosis from colorectal cancer or appendiceal cancer. The carcinomatosis was resected at a cytoreductive surgical procedure using a uniform surgical approach [18–20]. All of the data were accumulated prospectively and then gathered for a critical statistical analysis. The data accumulation and its statistical analysis were approved by the Institutional Review Board at the Washington Cancer Institute.

Methods

This treatment regimen of bidirectional intraperitoneal and intravenous chemotherapy was initiated in August 2005. Data collection for this study ceased in December 31, 2009. In this interval, 162 patients were candidates for treatment. There were 17 patients in whom the pharmacologic analysis could not be completed. Indications for exclusion were palliative treatment with treatment time reduced to 60 min (5), reduced renal function (4), prophylactic treatment with treatment time reduced to 60 min (2), technical

complication with patients or drug delivery (6). With these patients excluded, a total of 145 consecutive patients were available for a 90-min pharmacologic study of the hyperthermic intraperitoneal mitomycin C.

Cytoreductive surgery

The cytoreductive surgery involved up to five different peritonectomy procedures and as many as eight visceral resections. The peritonectomy procedures included peritoneal stripping of the parietal surface of the anterior abdominal wall, stripping of the undersurface of the left hemidiaphragm, stripping of the undersurface of the right hemidiaphragm, stripping of the pelvis, and stripping of the omental bursa. Peritonectomies were performed only when cancer nodules were present at the designated anatomic site [18]. The visceral resections included right colon resection, rectosigmoid colon resection, transverse and descending colon resection, greater omentectomy, splenectomy, hysterectomy and bilateral salpingo-oophorectomy, small bowel resection, and partial or complete gastrectomy. Patients were scored as having a total colectomy if all 3 portions of the colon required resections. Visceral resections were performed when the extent of carcinomatosis precluded simple debridement of tumor nodules from the organ.

Completeness of cytoreduction

In order to evaluate the effect of residual disease on the pharmacokinetics, the extent of residual disease was recorded at the end of cytoreductive surgery. Completeness of cytoreduction (CC) was scored as follows: A CC-0 resection indicated patients in whom no visible tumor nodules remained or a few patients who had a complete response to neoadjuvant chemotherapy. In CC-1 resections tumor nodules less than 2.5 mm in both diameters remained. CC-2 resections were in patients in whom tumor from 2.5 mm up to 2.5 cm in diameter remained. CC-3 resections were in patients in whom tumor greater than 2.5 cm in diameter were left behind. Patients with tumor nodules less than 2.5 mm (CC-0 and CC-1) in diameter were considered a complete resection [22]. A CC-2 or CC-3 resection was scored as an incomplete cytoreduction.

Hyperthermic intraperitoneal chemotherapy

Following complete or near complete resection of all visible carcinomatosis, the skin edges were elevated on a self-retaining retractor to create an expanded reservoir of the peritoneal space. A single dose of mitomycin C at 15 mg/m² was instilled into the carrier solution as part of a multidrug treatment. This treatment regimen combined intraperitoneal administration of 15 mg/m² of doxorubicin along with the

mitomycin C. The carrier solution was always 1.5% dextrose peritoneal dialysis solution at a volume of 1.5 L/m² instilled into the abdominopelvic space. The patients received a simultaneous intravenous bolus administration over 6–8 min of 5-fluorouracil at 400 mg/m² both in 250 ml normal saline in separate intravenous lines and leucovorin at 20 mg/m² [21]. The heated chemotherapy solution was instilled with the abdomen open but covered by a plastic drape. Two smoke evacuators (Surgimedics, Buffalo, NY) were placed beneath the plastic drapes to help control possible environmental chemotherapy contamination. The heated chemotherapy solution was manually distributed by the surgeon's double-gloved hand during the 90 min of treatment. The target temperature within the peritoneal space was 42°C. A heater circulator was used to maintain the hyperthermic conditions within the peritoneal cavity (Belmont Heater Circulator, Billerica, MA). If the patient's core temperature exceeded 39°C, the inflow temperature of the chemotherapy solution was decreased and upper body warming was stopped.

Sampling

Prior to treatment a 3 ml reference sample of the chemotherapy solution was obtained along with a 3 ml sample of blood and urine. Subsequently, 2-ml aliquots of blood, peritoneal fluid, and urine were obtained at 15-min intervals from all patients. These samples were centrifuged to remove debris or red blood cells. The cell-free solutions were frozen and stored for high performance liquid chromatography (HPLC) analysis which was performed within 1 week.

Peritoneal fluid volumes

The total volume of chemotherapy solution was always 1.5 L/m² of body surface area. The volume of chemotherapy solution that would fill the peritoneal space at the initiation of the intraperitoneal chemotherapy treatment was recorded in all patients. We defined patients with limited peritoneal space as those whose peritoneal cavity was filled by 65% or less of the total initial volume of chemotherapy solution.

Urine volumes during chemotherapy treatment

A forced diuresis was maintained in all patients using normal saline. The goal was to maintain 2 ml/kg for every 15-min interval. Furosemide was used in 5 mg doses if urine output was judged to be inadequate. The volume of urine produced every 15 min was recorded as well as the total volume for the 90-min hyperthermic intraperitoneal chemotherapy treatment.

High performance liquid chromatography analysis of plasma, peritoneal fluid, and urine

The concentration of mitomycin C in plasma, peritoneal fluid, and urine samples was determined by HPLC using an adaptation of the techniques as described by Dalton et al. [23]. The HPLC system consisted of a Shimadzu LC7A instrument equipped with a SPD-6AV spectrophotometer set at 365 nm. The stationary phase was a reversed-phase C₁₈ column ('Microsorb 100', 150 × 4.6 mm, 5-μm particle size, Varian Inc., Lake Forest, CA). The mobile phase consisted of 15% acetonitrile in 0.01 M phosphate buffer (pH 6.5) which ran isocratically at 1.5 ml/min.

Extraction of mitomycin C from plasma was accomplished using acetonitrile instead of ethyl acetate. This facilitated a more efficient sample preparation with a shorter evaporation time and a cleaner HPLC chromatogram. Two milliliters of acetonitrile was added to a 0.2 ml sample of plasma in a 15-ml polypropylene centrifuge tube. After mixing on a Vortex mixer followed by centrifugation, the liquid portion was transferred to another 15-ml tube and evaporated to dryness under a steady stream of N₂ at 39°C. The residue was redissolved in 0.4 ml of 0.01 M phosphate buffer for HPLC injection. Peritoneal fluid and urine samples, which contained much higher levels of mitomycin C, were diluted appropriately with 0.01 M phosphate buffer. All solutions were filtered through 0.45-μL nylon syringe filters before HPLC injection. The injection volume was 50 μL. All solvents were HPLC grade (Fisher Scientific, Norcross, GA).

Data retrieval and statistics

All data were prospectively recorded along with the clinical features of these patients. All data presented on the graphs are mean ± 1 standard deviation. Calculations of area under the curve and subsequent area under the curve ratios were obtained using GraphPad Prism analyses (GraphPad Software, Inc., La Jolla, CA). The Pearson's correlation coefficient was calculated to test the association of the extent of peritonectomy with the area under the curve ratio of mitomycin C. A similar calculation was used to test the association of extent of visceral resection and area under the curve ratio. For comparison of peritoneal fluid mitomycin C area under the curve and plasma mitomycin C area under the curve in patients with average or limited peritoneal space, the Wilcoxon rank test was used.

Results

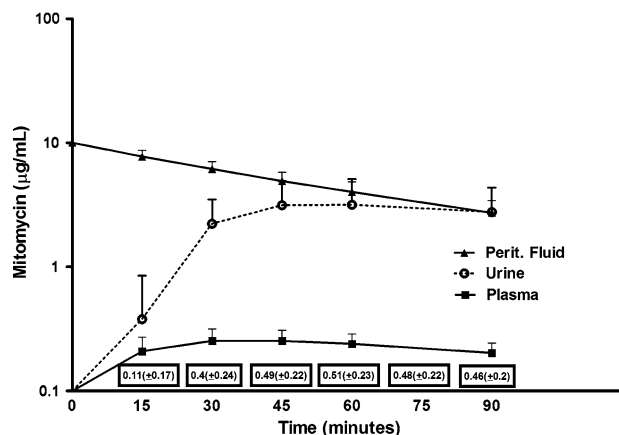
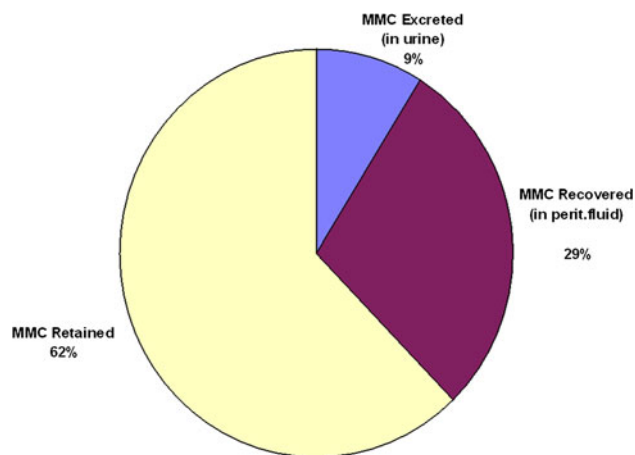
The demographics and clinical features of this group of 145 patients are summarized in Table 1. The plasma, peritoneal

Table 1 Demographics and surgical variables in 145 patients with colorectal or appendiceal carcinomatosis

Total number of patients	Number	% of total
Age (years)		
Median	49.6	
Range	23–71	
Gender		
Male	66	45.5
Female	79	54.5
Cancer diagnosis		
Colorectal	11	7.6
Appendiceal	131	90.3
Other	3	2.1
Peritonectomy procedures		
Anterior parietal peritonectomy	53	36.6
Left upper quadrant peritonectomy	73	50.3
Right upper quadrant peritonectomy	108	74.5
Pelvic peritonectomy	125	86.2
Omental bursa peritonectomy	71	49.0
Visceral resections		
Right colectomy	57	39.3
Rectosigmoid colon resection	67	46.2
Transverse colon resection	19	13.1
Greater omentectomy	142	97.9
Splenectomy	85	58.6
Hysterectomy	48	33.1
Small bowel resection	31	21.5
Partial or complete gastrectomy	4	2.8
Completeness of cytoreduction		
Complete cytoreduction (CC-0 or CC-1)	125	86.2
Incomplete cytoreduction (CC-2 or CC-3)	20	13.8

fluid and urine concentrations at 15-min intervals following bolus intraperitoneal administration of mitomycin C are shown in Fig. 1. The area under the curve ratio of peritoneal fluid concentration times time to plasma concentration times time was 26.6 (± 7.1). The peak plasma concentration was 0.25 (± 0.06) $\mu\text{g/ml}$ at 30 min. Also recorded in the lower portion of Fig. 1 is the amount of mitomycin C excreted in the urine in 15-min intervals.

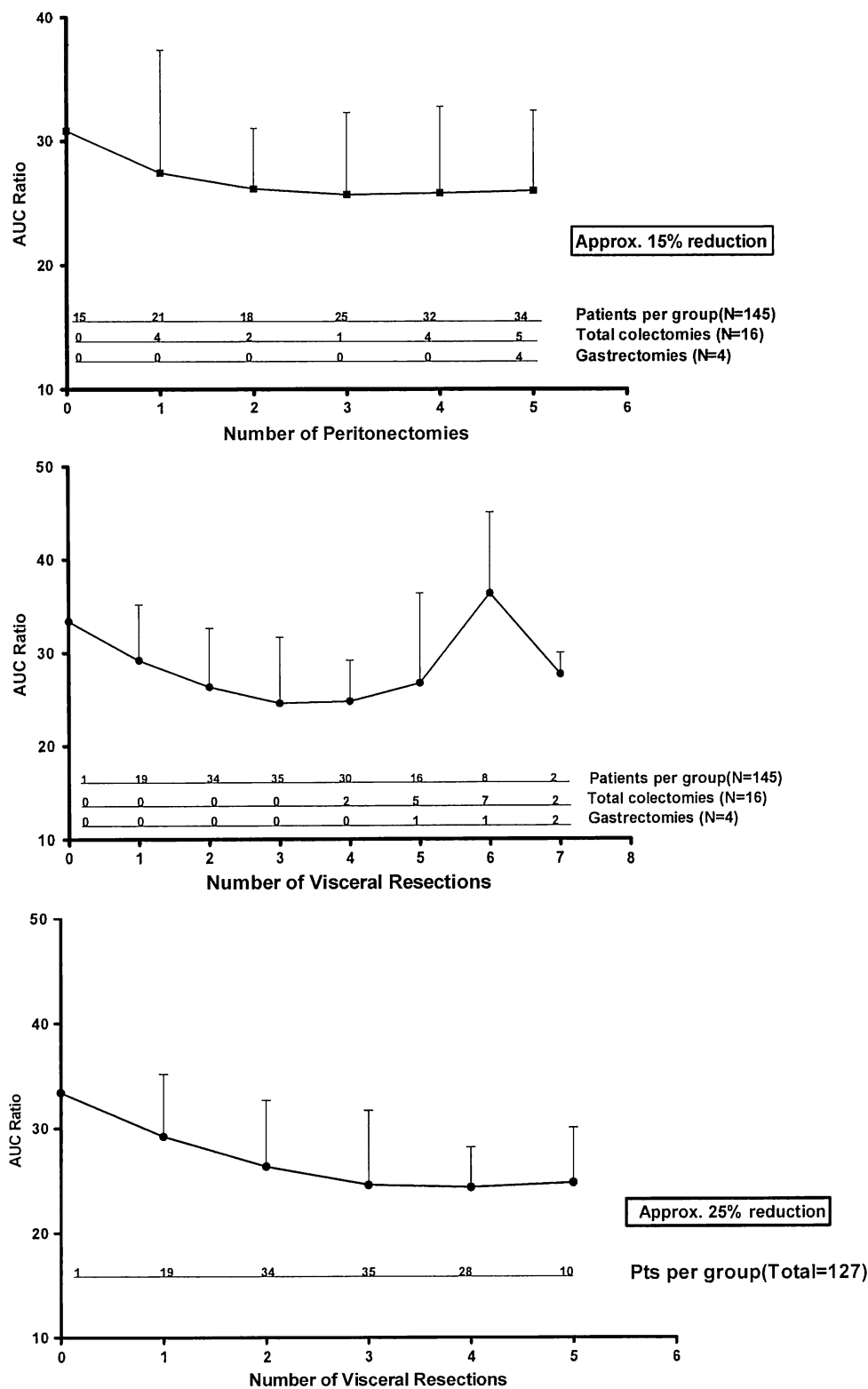
In these patients, the total amount of mitomycin C within the chemotherapy solution at the start of the procedure was recorded; also, the total amount of drug excreted in the urine during the 90 min of peritoneal lavage was determined. At the conclusion of the hyperthermic treatment, the final volume and final concentration in the peritoneal cavity was obtained and from these amounts the total amount of mitomycin C in the residual chemotherapy solution was calculated. Figure 2 shows that 62.1 (± 7.4)% of the total

**Fig. 1** Concentration times time graph of mitomycin C in peritoneal fluid, plasma, and urine in 145 patients. The area under the curve ratio of peritoneal fluid to plasma was 26.6 (± 7.1). Peak plasma concentration was 0.25 (± 0.06) $\mu\text{g/ml}$ at 30 min. Also shown are the total milligrams of mitomycin C excreted in the urine at 15-min intervals**Fig. 2** Distribution of mitomycin C following 90 min of hyperthermic intraperitoneal treatment. After this time interval, 62.1 (± 7.4)% of the mitomycin C remained within the patient's body (MMC = mitomycin C)

mitomycin C was retained within the patients body, 8.8 (± 3.5)% was excreted in the urine and 29 (± 7.6)% was removed from the peritoneal cavity at the termination of the treatment to be discarded.

Area under the curve ratios are correlated with extent of peritonectomy and extent of visceral resections in Fig. 3. The number of peritonectomies varied between 0 and 5 and the number of resections between 0 and 8. The top of Fig. 3 shows the extent of peritonectomy caused the clearance of mitomycin C to increase with borderline significance ($p = 0.051$). The area under the curve ratio decreased approximately 15% between 0 and 5 peritonectomy procedures. The middle graph in Fig. 3 shows that the extent of visceral resections decreased the area under the curve ratio if relatively minor visceral resections were

Fig. 3 Plot of the area under the curve ratios by extent of peritonectomy and extent of visceral resection. As extent of peritonectomy increased the area under the curve ratio diminished (*top*). Visceral resection diminished the area under the curve ratio except in patients requiring total colectomy or gastrectomy. Larger visceral resections were associated with an increased area under the curve ratio (*middle*). The *bottom* graph shows a plot of area under the curve ratio by extent of visceral resection in patients with total colectomy and gastrectomy removed from the analysis



performed. However, if patients required a total abdominal colectomy (right colon resection, transverse and descending colon resection, and rectosigmoid colon resection) or a gastrectomy, the area under the curve ratio increased.

The lower graph in Fig. 3 shows the change in area under the curve ratio if patients who had extensive visceral resections are removed from the analysis. This included the patients with total colectomy and gastrectomy. If these

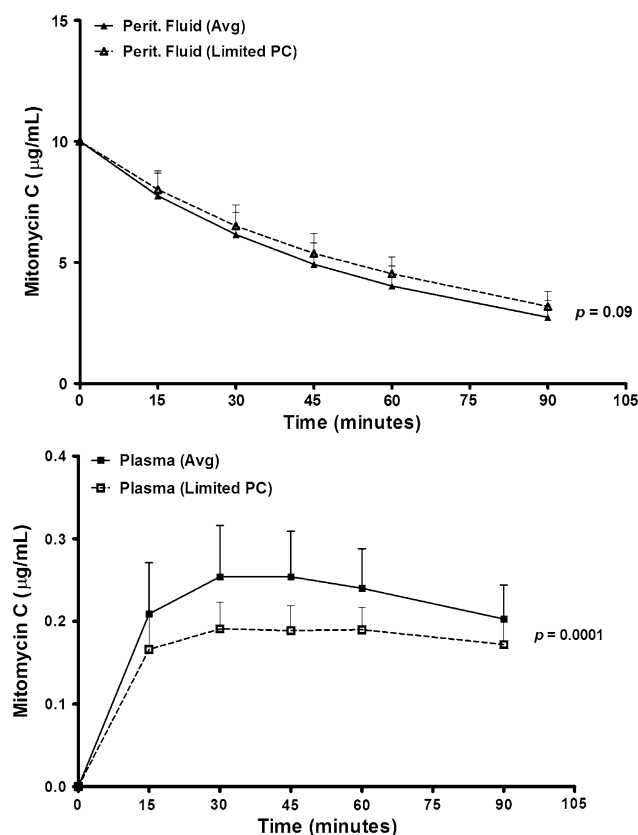


Fig. 4 Study of a limited peritoneal space and its effect on pharmacokinetics. The peritoneal fluid (*top*) and plasma (*bottom*) area under the curve are plotted in two groups of patients. One subgroup of 10 patients could receive into the intraperitoneal space only 65% or less of the total volume of chemotherapy solution. The concentrations of mitomycin C in this group was compared to the average of that in the 145 patients. With a limited peritoneal space, there is less mitomycin C absorbed into the plasma ($p = 0.0001$)

patients with large resection of peritoneal diffusion surface are removed from analysis, clearance of mitomycin C from the peritoneal space increases minimally with visceral resection.

In 10 of these 145 patients, the peritoneal space was markedly contracted and would only allow a portion of the full 1.5 L/m^2 volume to enter. In these 10 patients, only 65% or less of the calculated volume for the chemotherapy solution could be instilled into the abdominal space. Figure 4 demonstrated that the reduced total diffusion surface non-significantly decreased the peritoneal fluid area under the curve ($p = 0.090$). It significantly reduced the plasma area under the curve ($p = 0.0001$).

In 6 of 145 patients (4%), the HPLC chromatogram indicated an absence of the expected metabolites of mitomycin C (18). The top portion of Fig. 5 shows the peritoneal fluid, plasma, and urine HPLC chromatograms in a single patient; these patterns are very similar to those observed in 139 patients. The bottom portion of Fig. 5

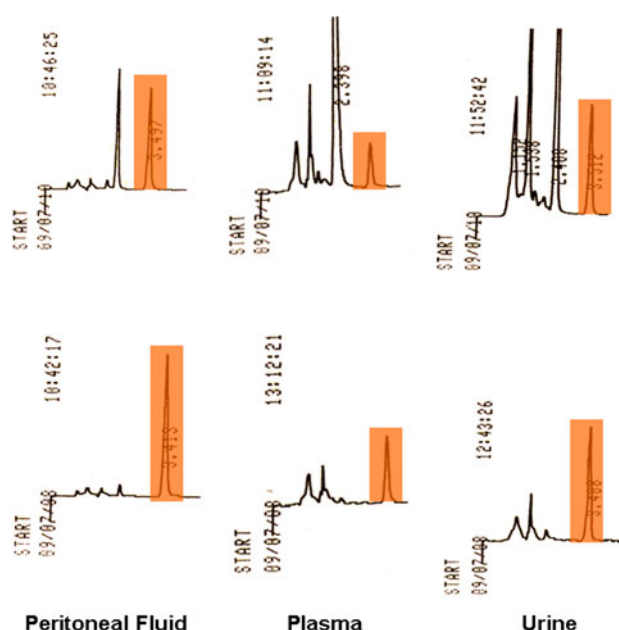


Fig. 5 Unusual mitomycin C chromatograms. In the top portion is a representative HPLC chromatogram of mitomycin C (*shaded*) and its metabolites in peritoneal fluid, plasma, and urine. This pattern was observed in 139 patients. The lower graphs show the HPLC chromatograms of a single patient who showed no evidence of mitomycin C metabolites. Six patients (4%) had this unusual pattern. The top and lower chromatograms are from samples taken at 60 min

shows the HPLC chromatograms in a single patient who showed no evidence of mitomycin C metabolites. Five additional patients showed a similar pattern of the HPLC chromatogram. In a statistical analysis of the pharmacokinetics of these 6 patients when compared to the other 139, no significant differences were present. These 6 patients were not in the group with a contracted peritoneal space.

There was a marked variation in total urine output over 90 min of hyperthermic intraperitoneal chemotherapy in these 145 patients. Patients were divided into three groups by the total output of urine during the 90 min of chemotherapy. The low urine output group had less than 1,000 ml excreted in 90 min. Moderate output was 1,001–1,999 ml in 90 min. In the high output group, patients had greater than 2,000 ml excreted. Figure 6 shows the mitomycin area under the curve in plasma in these 3 groups of patients. There is no change in plasma area under the curve in the patients with different urine output.

In 125 patients, all evidence of cancer was removed by the cytoreductive surgery. In 20 patients, scar from prior surgery, an invasive component of the disease, or a large volume of disease prevented the complete removal of cancer. The complete cytoreduction group had a reduced area under the curve ratio and a more rapid mitomycin C clearance ($p = 0.046$).

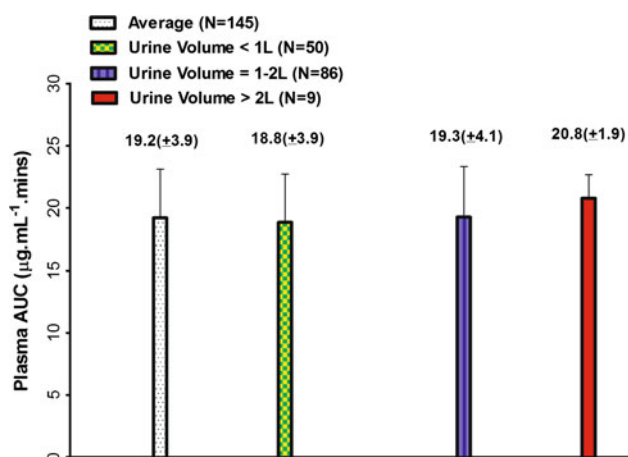


Fig. 6 Pharmacokinetic study of patients by urine output. Patients were divided into three groups by the total output of urine during the 90 min of chemotherapy. The low urine output group had less than 1,000 ml excreted in the 90 min. Moderate output was 1,001–1,999 ml in 90 min. In the high output group, patients had greater than 2,000 ml excreted. The graph shows a similar mitomycin area under the curve in plasma in these 3 groups of patients

Discussion

This manuscript confirms in a large number of patients having intraperitoneal treatment for peritoneal carcinomatosis after cytoreductive surgery the pharmacokinetic advantage of intraperitoneal mitomycin C delivery for this group of patients. The area under the curve ratio of peritoneal fluid concentration times time to the plasma concentration times time estimates the added chemotherapy exposure a small peritoneal cancer nodule receives as a result of an intraperitoneal route of administration. In our study and in several others, this ratio was between 20 and 35 [13, 15, 22, 24–32]. This pharmacokinetic advantage persists over the 90 min of intraperitoneal chemotherapy lavage. It continues because the tissue uptake, liver metabolism, and urine excretion of mitomycin C is always greater than drug clearance from the peritoneal space into the plasma.

Although the pharmacokinetic advantage of mitomycin C was considerable, the use of intraperitoneal drug in the operating room will maximize the therapeutic advantage. In our patients the chemotherapy solution of mitomycin C was accompanied by moderate heat to augment cytotoxicity and drug penetration. Residual cancer remaining after complete cytoreductive surgery (86% of patients) was at a cellular level or consisted of minute nodules that could be penetrated by chemotherapy diffusion in the expanded peritoneal space. Also, the abdominal and pelvic space had been cleared of all intestinal adhesions that would interfere with the uniform distribution of heated chemotherapy solution. In this clinical setting, the pharmacokinetic advantage of

intraperitoneal mitomycin C administration should translate into a therapeutic advantage for the eradication of peritoneal carcinomatosis.

During the hyperthermic intraperitoneal treatment, the area under the curve ratio was 27 in our study. Van Ruth et al. [15] have suggested that this is an overestimate of the pharmacokinetic advantage. Their area under the curve ratio was calculated at 13. The difference in their data results from an extension of the plasma mitomycin C data extrapolated to infinity. Although intraperitoneal mitomycin C is no longer present after cessation of the lavage, plasma mitomycin C continues. Yet the discrepancy of Van Ruth's data and ours may not be as large as he estimates. It seems probable that mitomycin C remains incorporated in tissues surrounding the peritoneal cavity but, for technical reasons tissue mitomycin C concentrations are not available for measurement. As documented by Fig. 2, large amounts of mitomycin C remain within the body compartment after the 90-min hyperthermic intraperitoneal treatment.

At the cessation of the 90 min of hyperthermic intraperitoneal mitomycin C treatment, 71% of the drug had left the peritoneal space. This means that 29% of the drug was discarded with the removal of the lavage fluid. This fluid represents a considerable environmental safety hazard and must be disposed of properly. Nine percent of the total drug administered had been excreted in the urine, and the urine of these patients should also be considered an environmental safety hazard. The largest proportion (62%) of the total drug administered remained in the body at 90 min. Jacquet et al. [24] and Van Ruth et al. [15] presented similar data. The location and chemical state of this large amount of retained mitomycin C remains to be determined. It is possible that active drug remains in visceral surfaces, parietal peritoneum, and preperitoneal tissues. Unfortunately, a reliable assay of tissue mitomycin C concentrations does not exist; determination of the anatomic site and anticancer activity of this large proportion of the total mitomycin C administered has not been determined.

An important consideration in the safe administration of hyperthermic intraperitoneal chemotherapy following a major surgical intervention is the effects the surgery will have on chemotherapy pharmacokinetics. To determine this, the extent of peritonectomy and the extent of visceral resections were quantitated and then correlated with the plasma area under the curve and area under the curve ratios of mitomycin C. As shown in the top part of Fig. 3, peritoneal resections were associated with a decreased area under the curve ratio and an increased clearance of mitomycin C from the peritoneal space. These data are in agreement with the previous reports of Jacquet et al. [24] and De Lima Vazquez et al. [33]. These authors reported small decreases in the area under the curve ratio as the peritonectomy increased. These data are in conflict with those of

Elias et al. [34] who presented clinical (but not pharmacologic) data to suggest that the extent of cytoreductive surgery would result in an increased systemic adverse effects of the intraperitoneal chemotherapy. It is possible that the extent of liver resection in the patients of Elias but not the extent of peritoneal resection will result in higher plasma levels of intraperitoneal chemotherapy and increased toxicity. However, it is likely that different pharmacokinetic parameters exist for different intraperitoneal chemotherapy agents.

Several pieces of data document that the total diffusion surface in contact with the peritoneal space is a major factor in mitomycin C pharmacokinetics. If patients required total abdominal colectomy or gastrectomy the area under the curve ratio increased. This suggested that a reduction in visceral peritoneal surfaces by large organ resection reduced clearance of mitomycin C from the abdomen and pelvis (Fig. 3).

We found 10 of our 145 patients to have an unusually small peritoneal space. By the hypothesis offered by Dedrick to predict intraperitoneal pharmacokinetics, the patients with a reduced total diffusion surface would show a reduced mitomycin C clearance from the peritoneal space [35–37]. Also, a reduced plasma area under the curve was predicted. Figure 4 presents data to show a reduced plasma area under the curve.

In patients with an incomplete cytoreduction, both visceral and parietal surfaces will be restricted as a result of residual cancer nodules holding tissues together. In this clinical situation a reduced peritoneal diffusion surface is expected. Also, less extensive peritonectomy and visceral resection would cause a reduced clearance of mitomycin C. Our 20 patients who had an incomplete cytoreduction had a statistically increased area under the curve ratio when compared to 125 patients with a complete removal of all cancer. Mitomycin C clearance was reduced in patients with an incomplete cytoreduction.

These data have relevance to our understanding of an optimal hyperthermic intraperitoneal chemotherapy treatment. Patients who present with *Pseudomyxoma peritonei* and a large volume of mucinous ascites will have an expanded peritoneal diffusion surface. Also, those patients who require resection of a portion of the hemidiaphragm are given hyperthermic intraperitoneal and intrapleural chemotherapy to prevent disease spread to the chest cavity. These patients will also have an expanded total diffusion surface. As a result of the expanded diffusion surface a more rapid clearance of mitomycin C from the peritoneal space and a higher plasma area under the curve for mitomycin C is expected. Consequently, a greater than usual likelihood of bone marrow toxicity occurs. The large variation in total diffusion area in peritoneal carcinomatosis patients poses a challenging problem toward a standardized dosimetry.

In patients treated using an open technique, with drug dose and volume determined by body surface area, patients

with a contracted peritoneal space are likely to be under-treated. The smaller diffusion surface allows limited access of chemotherapy solution and less drug crossing the peritoneal and preperitoneal tissues. In these patients, a closed abdomen intraperitoneal chemotherapy technique may be preferable. An increased intraabdominal pressure will expand the total diffusion surface and increase drug delivery to peritoneal and preperitoneal tissues. Gesson-Paute presented laboratory data to show increased clearance in the experimental animal treated by a laparoscopic intraperitoneal chemotherapy (closed technique) when compared to an open technique [38]. As could be expected this resulted in increased tissue diffusion of the drug [39].

A valid critique of the studies on hyperthermic intraperitoneal chemotherapy concerns a lack of standardized treatment protocols [40]. Currently, most groups employ their individual chemotherapy agents, doses and methodology (open versus closed) for drug delivery. Efforts to use scientific principles as a guide to optimized and standardized protocols are highly desirable. Guidelines cannot be written at this point in time with current data. However, modifications of available protocols will help optimize treatment. For example, more adequate treatment of patients with large variations in diffusion surface will occur by changing the time allowed for the hyperthermic chemotherapy lavage. An increase in time for treatment (120 min) would correct for a decreased peritoneal diffusion surface and a decreased time for treatment (60 min) would correct for an increased total diffusion surface.

Although mitomycin C is not regarded as a prodrug, it is not active against cancerous tissue as the unchanged molecule. The drug is modified as it enters the cell into an active state [41]. As a result of our routine monitoring of mitomycin C by HPLC, we identified six of 145 patients (4%) with an unusual chromatograph. An example of this pattern is shown in the lower portion of Fig. 5. The HPLC chromatogram suggests that the mitomycin C was not metabolized in these patients and likely had no anticancer effects. These patients have a guarded prognosis and deserve special attention in follow-up. This phenomenon may represent a mechanism of absolute drug resistance for these individuals and suggests the need for multidrug treatment regimens. The genetic or metabolic cause for this altered metabolism of mitomycin C is not known. In these 6 patients, we looked for altered mitomycin C metabolism that could be detected by our pharmacologic monitoring. The pharmacologic profile was not different from the majority of patients. Also, no other unusual clinical or surgical factors such as a contracted peritoneal space were apparent in this group of 6 patients.

We calculated the plasma area under the curve for patients with a low, moderate or high urine output during the 90 min of heated intraperitoneal chemotherapy.

The plasma area under the curve of mitomycin C was not elevated with reduced urine output neither were they reduced by a very high urine output. These data suggest that volume of urine excreted has no impact on the amount of mitomycin C eliminated by the kidney.

Conclusions

In an attempt to find an optimal plan for perioperative chemotherapy, we studied the pharmacokinetics of mitomycin C. This is the largest number of patients surgically treated in a uniform manner that have been available for a critical analysis. The total diffusion surface and its effect on drug clearance from within the abdomen and pelvis was the pharmacologic principle that best explained the data we accumulated. These data and the concepts in drug delivery they support contribute to our understanding of intraperitoneal (as contrasted to intravenous) drug delivery.

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