Hyperthermic intracavitary chemotherapy in abdomen and chest

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Citation for published version (APA):
CHAPTER SIX

Pharmacokinetics of intraperitoneal mitomycin C

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Surgical Oncology Clinics of North America
Management of Peritoneal Surface Malignancy
2003; In Press
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Introduction

The pharmacokinetic advantage is the most important rationale for applying cytostatic drugs in the peritoneal cavity in patients with peritoneal surface malignancies. Mitomycin C (MMC) is one of the available cytostatic drugs for intraperitoneal administration of chemotherapy. It belongs to the group of anti-tumor antibiotics. MMC binds with DNA, resulting in inhibition of DNA synthesis. In higher doses, MMC also suppresses the cellular RNA synthesis and protein synthesis. The advantages of using MMC as intraperitoneal application are several: 1) it is non-cell-cycle-specific, thus has direct cytotoxic effect even after a short exposure, 2) MMC has a large molecular weight of 334 Dalton keeping it for a longer period confined to the peritoneal cavity, the aimed target region, 3) MMC is water-soluble, 4) MMC is rapidly cleared from the systemic circulation and 5) The cytotoxic effect can be increased by hyperthermia.

Intraperitoneal chemotherapy with MMC has been applied in patients with peritoneal carcinomatosis of colorectal origin, gastric cancer and pseudomyxoma peritonei. Colorectal carcinoma cell lines are relatively resistant to chemotherapy, however there is a clear dose-response relation. Both instillation and perfusion can be used for application cytostatic drugs in the peritoneal cavity. Instillation is the simplest technique but leads to very unequal distribution and is at present rarely used. We will concentrate this paper on pharmacokinetics of perfusions with intraperitoneal MMC. Perfusion has the advantage of a more uniform distribution of the cytostatic drug throughout the abdominal cavity, a key factor in effective intraperitoneal therapy. Several variables may influence the pharmacokinetics of intraperitoneal (i.p.) MMC. Perfusion before, during and after operation have been tested. Hyperthermia has only been tested during operation because it can not be tolerated by the awake patient. The dose of MMC, the perfusate volume, the temperature and the duration of perfusion are other factors that have been varied in different studies on pharmacokinetics. Due to all these variables it is extremely difficult to compare data. The data we present in this review should be seen as being of an exploratory nature rather than comparative analysis.

The pharmacokinetics of MMC

We confine our review to clinical studies dealing with hyperthermic intraperitoneal perfusion with MMC (Table 1). Ten studies have been reported. Our own experience on pharmacokinetics with MMC is wide discussed.

Intraperitoneal MMC kinetics

The pharmacokinetics of intraperitoneal chemotherapy perfusion can best be described using a pharmacokinetic model as shown in Figure 1. Assuming a dose-effect relation, the aim is to expose the peritoneal surface to a maximal concentration over time, while maintaining systemic toxicity within acceptable limits. When MMC is administered to the perfusion system,
Table 1. An overview of clinical studies dealing with the pharmacokinetics of MMC in intraperitoneal chemotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Dose (mg/L)</th>
<th>Ip Temperature (°C)</th>
<th>Duration (min)</th>
<th>Technique</th>
<th>Absorption (%)</th>
<th>T1/2 (min)</th>
<th>Cmax Plasma (mg/L)</th>
<th>Cpe/pl</th>
<th>Ratio</th>
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<tr>
<td>Loggie</td>
<td>7</td>
<td>20</td>
<td>40.5 inflow</td>
<td>120</td>
<td>closed</td>
<td>NA</td>
<td>97</td>
<td>NA</td>
<td>27</td>
<td>NA</td>
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<td>Beaujard</td>
<td>83</td>
<td>10</td>
<td>42</td>
<td>90</td>
<td>closed</td>
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<td>NA</td>
<td>0.5</td>
<td>20</td>
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<td>10</td>
<td>42</td>
<td>90-120</td>
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<td>54 i.p.</td>
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<td>0.4</td>
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<td>Fernandez</td>
<td>10</td>
<td>5-10</td>
<td>41-43</td>
<td>120</td>
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<td>71 i.p.</td>
<td>58</td>
<td>0.25</td>
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<td>22</td>
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<td>Jacquet</td>
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<td>10</td>
<td>41-43</td>
<td>120</td>
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<td>70 i.p.</td>
<td>58</td>
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<td>Koga</td>
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<td>8-10</td>
<td>40-42 outflow</td>
<td>60</td>
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<td>39 i.p.</td>
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<td>28</td>
<td>10</td>
<td>45 outflow</td>
<td>120</td>
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<td>NA</td>
<td>0.16-0.19</td>
<td>10-28</td>
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<td>Schneebaum</td>
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<td>10-20</td>
<td>41-42</td>
<td>60</td>
<td>closed</td>
<td>21 i.v.</td>
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<td>0.24</td>
<td>NA</td>
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<td>NA</td>
<td>0.25</td>
<td>29</td>
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<tr>
<td>NKI</td>
<td>118</td>
<td>18</td>
<td>40-41</td>
<td>90</td>
<td>open</td>
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<td>49</td>
<td>0.44</td>
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<td>13</td>
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</table>

NA = not available. * = The Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital.
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the dose will be diluted by the amount of fluid needed to fill the peritoneal cavity. Usually an isotonic dialysis fluid is used in order to prevent interactions with MMC and unwanted electrolyte shifts. After a few cycles perfusion, the concentration of MMC in perfusate is about 90-95% of the expected concentration by the initial dose. Loss due to adsorption to any component of the perfusion tubing or equipment seems therefore minimal. The concentration of MMC in perfusate decreases over time according to a one-compartment kinetic model with first-order elimination. The half-life of MMC in perfusate is our series is 49 minutes, comparable with data of Jacquet et al. At the end of perfusion about 50% of the initial dose can be recovered from the perfusate, indicating that 50% of the total dose represents the uptake in the patient.

What is happening with the absorbed MMC? A part will bind to tissue structures in the peritoneal cavity. Another part will pass the peritoneal-plasma barrier. In Figure 1 K12 represents the rate constant from the perfusate to the systemic circulation. In plasma the pharmacokinetics can be described according to a two-compartment kinetic model with first-order absorption and elimination.

The plasma concentration gradually increases until the end of perfusion (Figure 2 and 3). The half-life of MMC in plasma after cessation the perfusion in our series is 76 minutes. Intravenous administration of MMC shows first a rapid half-life of distribution (2-10 minutes) and thereafter an elimination half-life of MMC between 25 and 90 minutes. In intraperitoneal chemotherapy the mean plasma Cmax is reported to vary between 0.11 to 0.50 mg/L. Most colon cancer cell lines will undergo extensive lysis if the drug concentration reaches approximately 1 mg/L. The plasma level is relatively low, not reaching this therapeutic level. The ratio concentration MMC in perfusate and in plasma is reported to vary between 10 and 29. MMC in plasma will also move to the third space and vice versa with an inter-compartmental clearance (Q).

A more exact measurement of the drug exposure is the time concentration or Area Under the Curve (AUC). The ratio AUC perfusate/plasma is reported to vary between 13 and 107 (Table 1). Some reported ratios may represent overestimates because AUC was calculated on-

![Figure 1. Pharmacokinetic model for HIPEC with MMC. K12: rate constant from the perfusate to the systemic circulation, Q: inter-compartment clearance, CL: clearance from the central compartment.](image-url)
Figure 2. Example of a time profile MMC concentrations in perfusate (full line) and plasma (dotted line) after a single administration of MMC at \( t=0 \) minutes.

Figure 3. Example of a time profile MMC concentrations in perfusate (full line) and plasma dotted line) after administration of MMC in three divided doses; half of the dose at \( t=0 \) minutes, a quarter of the dose at \( t=30 \) minutes and a quarter of the dose at 60 minutes.
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ly over the perfusion time (usually 90 minutes), whereas plasma AUC does not stop at the end of the perfusion. Ratio calculation would be more exact when calculated with a plasma AUC, extrapolated to infinity. The true AUC of MMC in perfusate appears to be between 10 and 20 times that in plasma.

MMC is predominantly metabolized in the liver. Urinary recovery after intravenous administration ranges from 1-20%. There are two reports of excretion of MMC in urine after intraperitoneal MMC administration; 7-8% of the initial dose was excreted by urine 2 hours after administrating MMC. The low urinary recovery cannot explain the rapid plasma clearance, therefore it has been suggested that MMC is rapidly cleared from plasma by biodegradation.

**Studying the most optimal dose**

In The Netherlands Cancer Institute/ Antoni van Leeuwenhoek hospital intra-operative hyperthermic intraperitoneal chemotherapy (HIPEC) has been extensively studied in over 200 patients. The semi open perfusion technique has been used, as propagated by Sugarbaker, with a basic volume of 3 liters, a perfusion rate of 1 L/min, at 40-41°C for a duration of 90 minutes. An important issue is the dose method. A single administration of MMC has the disadvantage that the concentration of MMC in perfusate decreases in time (Figure 2). Figure 3 shows the time profile MMC concentrations in perfusate after administration of MMC in three divided doses; half of the dose at t=0 minutes, a quarter of the dose at t=30 minutes and a quarter of the dose at 60 minutes. The advantage of administration of MMC in three divided doses is the maintenance of a certain MMC concentration in the perfusate. The AUC for MMC – when divided in three doses – is higher when compared with single administration, while peak concentrations are constant.

We studied different dose levels to determine the most suitable dose of MMC. Dose steps of 5 mg/m² were performed from 15 mg/m² until 40 mg/m² (Table 2) in three divided doses of 50%, 25% and 25%. The Maximal Tolerated Dose was at 40 mg/m² resulting in two deaths out of seven patients (29%) due to the combination of severe leucopenia and surgical complications. The dose of 35 mg/m² resulted in the highest perfusate/plasma AUC ratio. The mean ratio AUC perfusate/plasma was 13 (range 3-19).

<table>
<thead>
<tr>
<th>Dosage (mg/m²)</th>
<th>Patients (n)</th>
<th>Cmax perf. (mean) (ng/ml)</th>
<th>Cmax pl. (mean) (ng/ml)</th>
<th>AUC perf. (mean) (ng/ml/min)</th>
<th>AUC pl. (mean) (ng/ml/min)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>8</td>
<td>6967</td>
<td>339</td>
<td>276</td>
<td>24</td>
<td>11.7</td>
</tr>
<tr>
<td>25</td>
<td>3</td>
<td>7600</td>
<td>447</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>6860</td>
<td>261</td>
<td>335</td>
<td>32</td>
<td>10.9</td>
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<tr>
<td>35</td>
<td>95</td>
<td>10036</td>
<td>443</td>
<td>605</td>
<td>54</td>
<td>13.2</td>
</tr>
<tr>
<td>40</td>
<td>7</td>
<td>15600</td>
<td>627</td>
<td>968</td>
<td>81</td>
<td>12.4</td>
</tr>
</tbody>
</table>

*: not available
A major safety issue in peritoneal chemotherapy perfusion is the resulting systemic drug exposure, and the resulting toxicity, mainly in bone marrow suppression. In our series, using $35 \, \text{mg/m}^2 \, \text{MMC}$, we observed in 28% of the patients severe leucopenia (grade II/IV according to the Common Toxicity Criteria). Careful monitoring the course of white blood cells and accompanied adequate action is essential. The nadir is reached around 10 days after perfusion. It is important that surgical problems are solved before the neutropenic period. In case of neutropenic fever wide spectrum antibiotics are given. With this regimen we have not encountered any permanent complications related to leucopenia. We feel therefore that $35 \, \text{mg/m}^2$ is a safe dose for i.p. chemotherapy.

There are no data proving a dose response relation between the AUC of MMC in perfusate and survival. However a high AUC in plasma has been reported to be of prognostic value. Of course MMC in perfusate itself does not do any good, besides killing free floating tumor cells. The true target cells for i.p. therapy are the cells on the peritoneal surface. To be effective, MMC has to enter the superficial tissue layers. It seems therefore understandable that more penetration, resulting in a higher AUC in plasma, has more effect. The assumption being that the tissue layer between the peritoneal surface and the first capillaries is exposed to the higher and effective dose level. Our understanding of the exact movements of MMC is limited by our inability to visualize MMC molecules in tissue samples. Pharmacokinetics of MMC shows that we deal with linear pharmacokinetics. This is an important finding: increase of the intraperitoneal dose results in a proportional increase of plasma exposure. An increased plasma exposure will result in more hematotoxicity. Some groups have based dose of i.p MMC on body surface area, assuming that abdominal volume has some relation to body surface area as does systemic toxicity. Others have used a constant concentration of MMC in perfusion fluid, assuming that concentration dominates the movement of MMC molecules over the peritoneal-plasma barrier. In practice the differences between the two approaches are not so big. In case of dosing on surface area, big people tend to have a big abdomen, needing more perfusion fluid, leveling the concentration differences. The same phenomenon makes that when a fixed concentration in perfusate is used, the extra fluid needed in big people results in a higher total dose.

In our pharmacokinetics study we found that dosing based on body surface area resulted in comparatively little variations in the plasma AUC, and therefore in systemic toxicity. We are somewhat worried that dosing on constant concentration in perfusate might result in more variation and more risks on serious toxicity. This is not so much a point if doses are kept relatively low (10-12 mg/L), which typically means a total dose of 30-40 mg of MMC. If, however, the objective is to dose just below the maximal tolerated dose (total dose 70-80 mg of MMC), these variations might represent real danger.

**The impact of minimal or maximal surface peritoneal surface trauma**

The peritoneal-plasma barrier (PPB) has been described as a complex diffusion barrier, consisting of the capillary endothelium, the peritoneal mesothelium and the tissue in between. This physiologic barrier limits the movement of hydrophilic drugs, such as MMC, from the
peritoneal cavity into the blood. Removal of visceral organs does not alter the peritoneal-plasma barrier. Often in peritoneal surface malignancies peritoneectomy procedures precede intraperitoneal chemotherapy. It is a valid question whether the extent of peritoneal stripping influences the characteristics of the PPB. Sugarbaker et al has extensively studied this question. Earlier on they reported that peritoneectomy procedures did not influence the pharmacokinetics of post-operative i.p. MMC, suggesting that the functional peritoneal-plasma barrier remains in tact. In a more recent study they found with more than two peritoneectomy procedures exhibited a significantly higher peak plasma level, a higher AUC and a decreased perfusate/plasma ratio of MMC than patients with none or one peritoneectomy procedure, suggesting a change in membrane property. There are no data on pharmacokinetics after repeated surgery and intraperitoneal MMC.

Summary

The favorable pharmacokinetics of MMC, used during intraperitoneal chemotherapy, has been reported in several studies. A major safety issue in studies using intraperitoneal chemotherapy perfusion is the resulting systemic drug exposure. The AUC is determined by dose, the clearance and the fraction absorbed from the peritoneal cavity. The reported mean plasma peak concentrations are about 1/3 of the systemic exposure following a therapeutic dose of MMC given by intravenous administration. The best method to quantify the exposure to MMC are the time concentration profiles (AUC). Because MMC can still be found in plasma the day after intraperitoneal administration, the AUC is an underestimate of the real AUC; extrapolation to infinity gives the most reliable AUC value. In our series the AUC is about half the AUC when given a therapeutic dose MMC intravenously. What is the best dose in intraperitoneal chemotherapy perfusion? The ideal amount of MMC should include a high AUC, a high AUC and limited systemic toxicity. In our series grade II/IV leucopenia was observed in 28% patients. We find this rather high percentage acceptable as the problem has proved transient and we have experienced no toxic deaths in recent years. In a model study it was estimated that a dose of 25 mg/m² would result in approximately 10% of grade III/IV leucopenia. Our data indicate that dosing based on body surface area is rational and reliable. The inter-individual variation is low. Dosing based on a fixed concentration per liter perfusion fluid is probably more liable to unforeseen variations, given the fact that we deal with linear pharmacokinetics of MMC. As represented in Figure 3, the dose of MMC can best be administered MMC in three divided doses, resulting in more equal exposure of peritoneal structures to MMC during the perfusion. It must be emphasized that our findings only hold true for the perfusion system as used in The Netherlands Cancer Institute. This concerns semi open abdomen, basic perfusate volume of 3 litres, perfusion rate of 1 L/min, abdominal temperature of 40°C, 90 minutes of perfusion and three drug additions (50% at t=0, 25% at t=30 and t=60 minutes). The differences in perfusion techniques make comparison of published pharmacokinetics data difficult. Cautious
comparison suggest that most groups are dosing far below the maximal tolerated dose. We assume that there is a dose-effect relation for MMC. This means that obtaining a maximal safe dose is important to get a maximal result. It seems that better dosing of i.p. MMC can still improve results. The pharmacokinetics of i.p. MMC can however be influenced by many details. Open or closed perfusion for instance may make some essential differences. It is therefore important that each treatment group performs its own pharmacokinetics studies on i.p. MMC, to come to the optimal dose method for their chemotherapy perfusion setting.

In conclusion, the major advantage of intraperitoneal chemotherapy is the regional dose intensity provided. Following intraperitoneal MMC administration, the affected peritoneal surface is exposed to high concentrations while the systemic toxicity is limited. Comparative analyses on MMC pharmacokinetics are difficult to perform because the diversity of treatment techniques. We recommend administration of MMC, divided in three drug additions, based on BSA.

References


