Investigations on safety of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with Mitomycin C

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Abstract

Aims: Previous safety monitoring of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with Mitomycin C (MMC) did not demonstrate any detectable safety hazard to the personnel. Nevertheless, those results have been discussed controversially because of the methodological problems employed in the evaluation of potential exposure. We re-evaluated possible safety hazards of HIPEC by applying different monitoring strategies.

Methods: We monitored air samples in the operation room during HIPEC. In addition, we measured MMC in plasma of the surgeon with a newly developed analytical method. All samples were analysed by HPLC−UV at 360 nm. The permeability of the gloves was tested using two in vitro techniques: diffusion cells and a glass cell chamber. In-use and worst-case exposure scenarios were imitated for in vitro experiments.

Results: The analysis of the air samples ($n = 3$) could not detect any MMC. We found no drug above the limit of detection (1 μg MMC/L) in the plasma samples of the surgeons ($n = 5$). A breakthrough of latex glove material was detected in only one (worst-case exposure scenario) of 40 diffusion cell experiments.

Conclusions: Established methods of safety monitoring could not reveal any detectable risk on in-use exposure conditions. The wearing of doubled latex gloves should prevent the surgeon from dermal exposure to MMC during HIPEC.
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Keywords: Hyperthermic intraoperative intraperitoneal chemotherapy; Mitomycin C; Latex gloves; Safety monitoring

Introduction

Aggressive cytoreductive surgery together with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is a new and promising therapy in treating peritoneal carcinomatosis.[1] Handling chemotherapy moves from an oncology centre into the operating room. More critical than the acute toxic effects are the mutagenic, teratogenic, and carcinogenic effects of antineoplastic agents. As advantageous as HIPEC may be for patients, it presents yet a potential occupational health risk for the operative and participating personnel. One of the most commonly used chemotherapy agents in HIPEC procedures described by

Sugarbaker et al.[2] is Mitomycin C (MMC). In the open technique the HIPEC procedure includes manual manipulation of patient's viscera by the surgeon to ensure adequate distribution of the chemotherapeutic substance. During this procedure surgeons may accidentally come in contact with this substance.

Reasonable concern about the personnel's risk of handling chemotherapeutic drugs has led to improved safety standards. For the preparation and handling of cytostatic drugs guidelines require the use of approved biological safety cabinets. The use of appropriate personal protective equipment and avoidance of hazardous handling practices are obligatory. As HIPEC is carried out in operating rooms, some of those requirements cannot be fulfilled. Therefore, a special risk assessment has to be carried out to evaluate possible routes of exposure.[3]

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Up to now, safety monitoring of the HIPEC technique included the assessment of the permeability of the gloves to MMC and the analysis of urine samples from the surgeon and from the perfusionist. Different types of gloves were demonstrated to be permeable for MMC with a 10-fold range of MMC penetration.[4] Analysis of urine samples from the surgeon and the perfusionist had shown no detectable levels of Mitomycin C.[4] Nevertheless, those results have been discussed controversially due to the methodological problems employed in the evaluation of potential exposure of personnel.[5]

Previous pharmacokinetic studies reported that the elimination of the intact drug in urine was fairly low in humans (10–30%[2]). Therefore we decided to re-evaluate possible safety hazards by applying a newly developed, more sensitive analytical method to measure MMC in the plasma of the surgeon. Besides, we monitored air samples in the operation room. Furthermore, we assessed the permeability of latex gloves using two in vitro techniques: diffusion cell and a glass cell chamber.

Material and methods

Subjects

We analysed plasma samples of surgeons before ($n = 1$) and after ($n = 5$) performing HIPEC. These surgeons manipulated the patient's viscera with the heated chemotherapy solution (temperature: 40–41 °C) for the entire 90 min of treatment. Intraoperative dose rate of 30–35 mg MMC per square meter body surface area, subdivided in three portions, was used. Two pairs of natural rubber, powder-free latex gloves (either Biogel Indicator™, Regent medical, Norcross, GA or Z⁺®PLUS gloves, Berner International, Elmshorn, Germany combined with Biogel™, Regent medical, Norcross, GA) were used during the procedure (double-gloving). The outer gloves were changed every 30 min. MMC was determined in plasma samples of patients before ($n = 1$) and immediately after ($n = 5$) a HIPEC treatment. Informed consent from all subjects and approval from the Hospital Ethics Committee (University Erlangen-Nuremberg, Germany) were obtained prior to the participation in the study.

Determination of MMC in plasma

In order to measure the plasma samples we developed an easy, fast and sensitive HPLC–UV method with an online sample clean-up [M.I. Boettcher, unpublished data]. The limit of detection was 1 µg MMC/L plasma.

Air sampling and sample preparation

We conducted an air sampling in the operating room close to the open abdomen during the approximately 90 min lasting HIPEC procedure. For that purpose we adapted a commonly used air-sampling technique from the polycyclic aromatic hydrocarbon (PAH) ambient monitoring studies[6] as described elsewhere [M. Boettcher, unpublished data]. The limit of detection was estimated to be 10.3 ng/m³ air (1.3 ng MMC absolute on the adsorbent tube).

In vitro penetration experiments

The studies were conducted using two techniques: static Franz diffusion cells[7] and a glass cell chamber similar to that described previously.[4] For experiments with glass cell chamber, Z⁺®PLUS gloves combined with Biogel™ gloves were used. Forty diffusion cell test sets with latex glove materials (Biogel Indicator™) and three different receptor fluids were carried out. Diffusion cell experiments were designed to represent an in-use workplace exposure (exposed MMC dose: 1.6 µg) as well as a worst-case scenario (exposed MMC dose: up to 160 µg) [M.I. Boettcher, unpublished data].

Results

Determination of MMC in plasma

We analysed plasma samples of surgeons before ($n = 1$) and after ($n = 5$) performing HIPEC. In all cases we found no drug above the limit of detection in the plasma of the surgeon. In contrast, MMC was detected in all plasma samples of the patients after the HIPEC procedure ($n = 5$, mean value: 361 µg/L, range: 208–733 µg/L at the end of the surgery) but not before the therapy ($n = 1$).

Determination of MMC in air samples

The analysis of the air samples could not detect any MMC.

In vitro penetration experiments

No breakthrough of MMC through Biogel™ and Z⁺®PLUS gloves was detected in experiments with glass cell chamber. Only in one diffusion cell experiment (worst-case scenario) of 40 a breakthrough was observed for latex glove material (Biogel Indicator™). In the other 39 diffusion cell experiments no breakthrough was detected.

Discussion

The results of epidemiological studies investigating the risk due to the occupational exposure to cytostatic drugs are inconsistent.[8] Very limited data are available to address cancer risk in health care workers.[9] According to animal carcinogenicity data, Mitomycin C was classified as possibly carcinogenic to humans (group 2B) as indicated by the International Agency for Research on Cancer (IARC).[10]

Detailed recommendations concerning policies and procedures for the safe handling of cytostatic agents used in HIPEC have been developed.[3] Possible routes of exposure during HIPEC are inhalation and dermal absorption.

For some groups of hazardous substances (e.g. pesticides) the dermal uptake can be the most important route of absorption.[11] In certain exposure situations, e.g. dermal contact to aqueous solutions of the glycol ether 2-butoxyethanol, the dermal uptake can exceed the uptake by inhalation even at the current occupational threshold values in air.[12]

A previous study, that examined penetration of MMC through latex gloves as well as MMC concentrations in air samples during and in urine samples after HIPEC, stated that there is no occupational health risk for personnel in operating rooms.[4] Yet, the methods used in this study were questioned as they appeared to be unproven and insensitive.[5] Therefore we decided to re-evaluate possible safety hazards by applying state-of-the-art techniques as well as a newly developed analytical method to conduct in vitro penetration experiments, ambient air monitoring in the operation room and biological monitoring of the surgeons.

Cytostatic pharmaceuticals may evaporate and form a gas phase during normal handling.[13] As no vaporisation of MMC in water-based solution was detectable even at $37\,^{\circ}C$,[14] no relevant inhalative exposure is expected to occur in operating rooms. For our ambient air monitoring we had adapted a commonly used air-sampling technique from the PAH ambient monitoring studies.[6] The analysed air samples showed that no MMC was detectable during HIPEC in the operation room. We therefore confirmed that, under the circumstances our surgeons were working, no safety hazards from the ambient air are expected.

Another route of exposure might be a dermal exposure in case of leak gloves. Various methods can be applied to investigate the permeability of chemicals through synthetic materials. In experiments using a glass cell chamber we tried to imitate the workplace situation as realistic as possible. A breakthrough of gloves under these conditions near to the in-use exposure situation was not detected. Our results are opposite to the findings of Stuart et al.[4] Even though Biogel™ gloves showed only a low permeability, he was able to detect a breakthrough of latex gloves (single gloves) when using a similar in vitro method.[4] In contrast, Connor had demonstrated among others latex gloves to be impermeable to MMC.[15] As surgeons at our university hospital are wearing only doubled gloves during HIPEC, our in vitro experiments were carried out solely with doubled gloves. This is likely the reason that in our study no breakthrough of glove material was detected not only under in-use conditions, but also under worst-case exposure scenario with the exception of one test set.

In in vitro experiments a breakthrough of Biogel Indicator™ latex gloves (doubled gloves) was observed in only one of the 40 diffusion cell experiments using a 100 times higher concentration of MMC than the gloved hands of surgeons are exposed during HIPEC. However, a breakthrough of MMC through various natural rubber latex gloves could not be affirmed in any other in vitro experiment with various MMC formulations. In summary, also the results of our in vitro study militate for the safety of the used procedure of glove wearing by surgeons.

As a result, the evaluation of possible routes of exposure (dermal and inhalative) did not show any measurable occupational health risks for surgeons performing HIPEC.

To confirm that no detectable exposure of the surgeons had occurred during HIPEC we conducted an additional biological monitoring of plasma samples after HIPEC procedure. There are no data regarding the metabolism and urinary excretion of MMC taken in by inhalation or by dermal absorption. The monitoring of urinary concentrations for some antineoplastic agents, however not MMC, was able to detect incorporations of drugs despite standard safety precautions in operatives of pharmaceutical and oncological departments.[8] Since pharmacokinetic data had shown that the urinary excretion of MMC is rather low[2] the analysis of blood seems to be more promising for a sensitive biological monitoring. To measure the plasma samples we developed an easy, fast and sensitive HPLC−UV method. Analysing the plasma samples we found no MMC in the blood of the surgeon manipulating the patient's viscera after the end of the HIPEC procedure. On the other hand, the values obtained from the patients treated with MMC again confirmed the reliability of the analytical method used. For patients, a major safety issue of HIPEC is the moderate resulting systemic drug exposure. The mean plasma concentrations in patients found by us lay in a range, as it was described also in pharmacokinetic studies during HIPEC.[16]

It has to be kept in mind that biological monitoring cannot exclude an intake below the limit of detection of the analytical methods applied. For the urine measurements, the limits of detection were estimated by Stuart et al. at 25 ng/mL.[4] By applying our newly developed analytical method to measure MMC in the plasma of the surgeon we were able to detect even 1 µg MMC/L plasma (i.e. 1 ng/mL).

In our study we considerably extended and improved the method spectrum used by Stuart et al.[4] As a result, no occupational risks for surgeons handling with MMC during HIPEC under exposure situation as described in our study are expected. This was demonstrated by ambient air and biological monitoring. Furthermore, established in vitro methods showed that the wearing of doubled gloves of natural rubber latex is suitable to protect a breakthrough of MMC.

Acknowledgement

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