Investigations on Permeation of Mitomycin C Through Double Layers of Natural Rubber Gloves

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Treating peritoneal carcinomatosis by the aggressive cytoreductive surgery with the hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) surgeons expose their gloved hands for up to 90 min to a peritoneal dialysis solution (PDS) containing mitomycin C (MMC). We investigated the permeation of MMC through the material of three different natural rubber gloves under conditions similar to the in-use during HIPEC as well as under worst-case exposure scenario. Two different methods, a two-chamber diffusion cell and a single-chamber glass chamber method, were used to demonstrate the permeation capability. The permeation of MMC dissolved in 0.9% NaCl solution and PDS through double natural rubber glove material was tested over 2 h using four concentrations (c = 0.004, 0.008, 0.016 and 0.4 mg ml^{-1}) and three receptor fluids (0.9% NaCl solution, PDS and a novel artificial sweat). In none of four glass chamber experiments and in only one of 40 diffusion cell experiments was permeation through glove material detected. The permeation occurred between 15 and 30 min under worst-case exposure scenario at a ~100-fold higher MMC concentration than under in-use conditions during HIPEC.

The double-layer natural rubber gloves tested were effective to prevent a permeation of MMC in vitro under HIPEC-similar exposure. Our results support the glove wearing procedure in our university hospital. However, occupational exposure to antineoplastic drugs should be minimized, since there is insufficient knowledge regarding harmful effects from a long-term exposure to low doses.

Keywords: antineoplastic drugs; artificial sweat; diffusion cell; intraperitoneal chemotherapy; mitomycin C; natural rubber gloves; permeation

INTRODUCTION

The use of gloves at workplaces has been recommended as an appropriate personal protective measure to protect the hands of workers from dermal contact with hazardous substances when engineering controls cannot be implemented (Klingner and Boeniger, 2002; Korinth et al., 2007). Whereas a significant number of studies investigated the efficacy of chemical-resistant gloves regarding the permeation of industrial hazardous substances (e.g. Forsberg and Fanidiadis, 1986; Mellström et al., 1991; Moody and Nadeau, 1994; Vo et al., 2000; Korinth et al., 2003; Gao et al., 2005), data quantifying the permeation of the antineoplastic drug mitomycin C (MMC) through natural rubber gloves are limited (Stuart et al., 2002). However, since health care workers are also handling antineoplastic drugs, such an exposure might represent a potential occupational health risk.

MMC (molar mass: 334.33 g mol^{-1}) is a solid heterocyclic compound carcinogenic in animals and probably also in humans (IARC, 1976). It is most commonly used as antineoplastic drug in the aggressive cytoreductive surgery with the new therapeutic option, the hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in treating peritoneal carcinomatosis (Stuart et al., 2002; Schmid et al., 2006). Surgeons involved in the open HIPEC manipulate manually patient’s viscera in an aqueous MMC glucose solution to achieve adequate intraperitoneal distribution of MMC. During this procedure, surgeons have a repeated glove contact of ~90 min to
MMC. In a recent study, we could not detect MMC in the ambient air of operating rooms of our university hospital as well as in biological material of surgeons (Schmid et al., 2006). These results are in agreement with the findings of Stuart et al. (2002), who also could not demonstrate health risks resulting from occupational exposure to MMC in medical operating personnel. However, surgeons may also accidentally come in dermal contact with this substance, e.g. after a permeation of glove material.

According to manufacturers’ safety data sheets, recommended natural rubber gloves for handling antineoplastic drugs, e.g. MMC formulations, are effective, as a breakthrough time of several hours could be observed (Berner, 2007). Most data on the effectiveness of glove material against permeation of chemicals are obtained in vitro using two-chamber permeation cells. Manufacturers test their gloves usually according to the European standard EN 374. This standard specifies the testing of the permeability of glove material at a temperature of 23 ± 1°C (CEN, 2003). The permeation data are, therefore, often valid only for this temperature. However, these standardized test conditions mostly do not reflect the real workplace exposure situations (Evans et al., 2001; Klingner and Boeniger, 2002).

From an occupational hygienist’s point of view, glove safety data are relevant when simulating the in-use exposure conditions as realistically as possible. The temperature inside of gloves in workers is ~35°C, which may significantly reduce the breakthrough time and increase the permeation rate of chemicals relative to test data of manufacturers generated at a temperature of 23°C (Evans et al., 2001). In our particular situation, surgeons manipulated the patient’s viscera with a heated chemotherapy solution even at temperatures between 40°C and 41°C. Since it is evident that MMC is carcinogenic, it is to demand that surgical gloves must prevent any permeation of MMC to avoid occupational health risks. Furthermore, when dealing with carcinogenic chemicals, it is of great concern for occupational hygienists to know about the risks also under worst-case exposure scenario.

Previous in vitro investigations demonstrated that single natural rubber gloves of different manufacturers do not prevent the permeation of MMC under HIPEC-type exposure (Stuart et al., 2002). These findings are contrary to data of previous studies (Connor, 1999; Connor et al., 2000) and indicate occupational risks handling MMC formulations. When facing the challenge to prove the safety of natural rubber gloves used in our university hospital during HIPEC, we evaluated their MMC permeability in aqueous media. Double layers of gloves were tested using two in vitro methods, the diffusion cell and a glass chamber, under conditions as realistic as possible to in-use exposure. Additionally, the experimental conditions were modified to represent a worst-case exposure scenario.

MATeRIALS AND METHODS

Test compound and chemicals

MMC (CAS: 50-07-7) was purchased from Zhejiang Hisun Pharmaceutical (Taizhou City, China). An aqueous MMC test formulation (20 mg MMC dissolved in 50 ml 0.9% NaCl solution) was prepared on the day of experiments in our local university pharmacy. Dianeal® PD1 glucose 1.36% (w/v) peritoneal dialysis solution (PDS) was purchased from Baxter (Unterschleissheim, Germany). NaH2PO4·H2O and methanol for High Performance Liquid Chromatography (HPLC) eluent preparation were obtained from Merck (Darmstadt, Germany).

Receptor fluids and gloves

In our studies, three different receptor fluids were used. In diffusion cell experiments to test the permeability of surgical, powder-free natural rubber Biogel Indicator™ gloves (Regent Medical, Norcross, GA), the receptor phase contained artificial sweat (preparation procedure, see below), 0.9% NaCl or PDS solutions. To test the permeability of Z®PLUS cytostatic protective, powder-free natural rubber gloves (Berner International, Elmshorn, Germany) and Biogel™ powder-free natural rubber gloves (Regent Medical) using the glass chamber, the receptor phase contained only artificial sweat.

Preparation of artificial sweat

Artificial sweat was used as collecting medium in the receptor compartment in a few diffusion cell experiments and in all experiments with the glass chamber. The sweat was prepared on the basis of the data of Patterson et al. (2000) on the composition of sweat in male humans excreted from hands during physical exercise. Distilled water served as a basis for the artificial sweat to which NaCl, KCl, NaHCO3 (all from Merck) and lactic acid (Fluka, Buchs, Switzerland) were added (Table 1). The composition of our artificial sweat is similar as described by Patterson et al. (2000) with the exception of HCO3−. The concentration of lactic acid may marginally differ from values given by Patterson et al. (2000), since it was also used to adjust the pH of the sweat to 5.68.

Analysis of MMC in the receptor fluid

The analytical method was based on an online sample clean-up using a restricted access material RP-18 phase followed by a HPLC separation and UV detection. Thus, no sample preparation besides a dilution step was necessary prior to analysis. Three hundred microlitres of each sample, obtained in the permeation experiments, were diluted with 300 μl
Table 1. Concentrations of constituents of artificial sweat

<table>
<thead>
<tr>
<th>Compound</th>
<th>Amount (mg l⁻¹)</th>
<th>[Na⁺] (mmol l⁻¹)</th>
<th>[K⁺]</th>
<th>[Cl⁻]</th>
<th>[HCO₃⁻]</th>
<th>Lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>697.3</td>
<td>30.33</td>
<td>—</td>
<td>19.67</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>KCl</td>
<td>220.93</td>
<td>—</td>
<td>5.65</td>
<td>6.23</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>93.55</td>
<td>4.07</td>
<td>—</td>
<td>—</td>
<td>1.53</td>
<td>—</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>992.68</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>~11.02</td>
</tr>
</tbody>
</table>

Concentrations of constituents in our artificial sweat

*Values are identical as published in Patterson *et al.* (2000) for human sweat with exception of HCO₃⁻ (c = 1.07 mmol l⁻¹) in Patterson *et al.*, 2000). The pH of the artificial sweat was 5.68.

water, so that a volume of 500 µl could be injected. Calibration was carried out with aqueous standard solutions in the concentration range of 5–500 µg l⁻¹. The limit of detection (LOD) was estimated to be 1 µg l⁻¹ based on a signal to noise ratio of 3.

This analytical method was originally developed for the determination of MMC in human plasma samples (Schmid *et al.*, 2006). For plasma samples, the method proved to be reliable with imprecision data of 6.3% for the intra-day and 9.6% for the inter-day assay. In addition, we found recovery rates of 94.4 ± 4.2% (intra-day assay) and 97.2 ± 6.8% (inter-day assay).

Permeation studies

Permeation of aqueous MMC formulations through natural rubber glove material was tested using two *in vitro* methods, static Franz diffusion cells (Franz, 1975) and a glass chamber (Fig. 1), which was principally similar to the test chamber described previously (Stuart *et al.*, 2002). In both methods, the outside glove material was in contact to MMC test formulation and the inside against the receptor phase. Experimental details, e.g. MMC concentrations, receptor fluids, temperature of glove material, are presented in Table 2. Ambient air and glove material temperatures of the exposure side were measured using the digital precision thermometer GMH 3230 (Greisinger Electronic, Regenstauf, Germany).

Diffusion cell experiments

In total, 40 diffusion cell experiments were carried out. Diffusion cells (FDC-400 9FF; Crown Glass, Somerville, NJ) with a circular (diameter 9 mm) exposure area of 0.64 cm² were connected by a water jacket to a thermostatic circulating water bath (MV-4; Julabo, Seelbach, Germany) at a temperature of 43.5°C and continuously stirred with a teflon-coated magnetic bar at 500 r.p.m. The vertical cells consist of two compartments where the upper compartment represents the exposure chamber and the lower compartment the receptor chamber. Circular pieces (diameter 26 mm) of Biogel Indicator™ gloves were excised near to the gauntlet and fixed both the outer (straw) glove (exposure side) and the inner (green) glove (receptor side) on diffusion cells between the exposure and receptor chambers. The glove material was exposed to four MMC concentrations (c = 0.004, 0.008, 0.016 and 0.4 mg ml⁻¹) in 0.9% NaCl and PDS without occlusion. The MMC concentration applied in diffusion cell experiments was similar to that during HIPEC (c = 0.004 mg ml⁻¹) as well as 2-fold (c = 0.008 mg ml⁻¹), 4-fold (c = 0.016 mg ml⁻¹) and 100-fold (c = 0.4 mg ml⁻¹) higher.

Glass chamber experiments

The glass chamber was filled with PDS (5 l) and with the MMC test formulation (20 mg MMC dissolved in 50 ml 0.9% NaCl solution). The MMC concentration (c = 0.004 mg ml⁻¹) in these experiments was the same as the concentration used during HIPEC. This solution in the glass chamber was warmed up on a hot plate to a temperature of 40°C and continuously stirred with a large teflon-coated magnetic bar. Z⁺@PLUS™ gloves were put over Biogel™ gloves and filled with 500 ml of artificial sweat, which served as receptor phase. The gloves were dipped into the glass chamber and fixed on the border of the chamber by a clamp holding device. The permeation of MMC through gloves was also tested using a reverse wearing procedure (outer glove: Biogel™, inner glove: Z⁺@PLUS™) (N = 2 for each glove wearing procedure). This experimental design was adapted according to glove wearing procedure by surgeons at our university hospital during HIPEC.

Sampling procedure

In diffusion cell experiments, for analysis 300 µl samples were withdrawn from the receptor compartment at five sampling times up to 2 h (Table 2) and replaced with fresh receptor fluid. Samples in glass chamber experiments were taken in 30-min intervals also up to 2 h of exposure (Table 2) without replacing the receptor fluid as the withdrawn sample volume (1 ml) was small compared to the volume of the receptor compartment (500 ml). Samples were frozen immediately at −20°C and analysed a few days later to avoid a degradation of MMC.
RESULTS

In total, 40 diffusion cell tests with four MMC concentrations in a vehicle consisting of 0.9% NaCl and PDS and three different receptor fluids were carried out (Table 2). Only in one of the 10 parallel tests using 0.9% NaCl solution as receptor fluid a breakthrough of Biogel Indicator/C212 glove material was observed using the highest MMC concentration of 0.4 mg ml\(^{-1}\) (Fig. 2). The cumulative permeated amount after 30 min of exposure was 6.87 \(\mu\)g/0.64 cm\(^2\) of glove material approximating a permeation rate of 0.36 \(\mu\)g cm\(^{-2}\) min\(^{-1}\). The term 'breakthrough' was defined as the detection of MMC in a sample above LOD. This does not conform to the term ‘breakthrough time’ of glove material according to the definition of EN 374 (CEN, 2003). The first sample did not contain MMC above the LOD (Fig. 2). The breakthrough detection time of glove material ranged between 15 and 30 min of exposure. The MMC value at 30 min represents the maximum permeated amount, since no significant additional permeation could be observed subsequently. In the other 39 diffusion cell experiments, no permeation of MMC through glove material was observed.

No permeation of MMC through Biogel™ and Z\(^+\)@PLUS gloves was detected in any of the four experiments with the glass chamber.

DISCUSSION

The wearing of gloves should primarily protect surgeons and patients against a transfer of pathogens. Additionally, gloves should be used at workplaces when technical measures cannot provide an adequate controlling of dermal exposure (Evans et al., 2001). This is the case in surgeons manually manipulating patient’s viscera to achieve adequate intraperitoneal distribution of chemotherapeutic MMC formulations during HIPEC. Since no evaporation of MMC from aqueous solutions was detectable even at 37°C (Connor et al., 2000), the main exposure of surgeons during HIPEC should result from dermal route in case of leaky gloves or after permeation of the glove material.

Various methods can be applied to investigate the permeability of hazardous substances through glove materials (Laidlaw et al., 1984; Stuart et al., 2002; CEN, 2003; Korinth et al., 2003). Diffusion cells
are established not only in percutaneous absorption studies (van de Sandt et al., 2004) but also for the investigation of permeability through synthetic membranes (Chilcott et al., 2005). The present study was conducted to evaluate the effectiveness of double-layer natural rubber gloves under experimental conditions simulating the exposure during HIPEC as realistically as possible. During the HIPEC procedure, our surgeons wore powder-free natural rubber gloves either Biogel Indicator™ (double gloves) or Z⁺®PLUS (single gloves) gloves combined with Biogel™ (single gloves) gloves.

In the present study, we extended and improved considerably the method spectrum in comparison to the study of Stuart et al. (2002). The permeation of continuously exposed aqueous MMC formulations through three different natural rubber gloves was tested using two different methods. Continuous exposure is indicated to be a worst-case scenario producing the fastest breakthrough time of gloves (Roder, 1990). In our experiments, we attempted particularly to design the exposure and the receptor side to simulate HIPEC. Diffusion cell experiments imitated an in-use (MMC concentration: 0.004 mg ml⁻¹) as well as a worst-case exposure scenario (MMC concentrations: >0.004 mg ml⁻¹) in terms of test formulation and exposure duration. During HIPEC, surgeons have a repeated glove contact for 90 min (outer gloves were changed in 30-min intervals) to the same MMC concentration (0.004 mg ml⁻¹) as in a few of our diffusion cell and in all glass chamber experiments (Table 2). In all experiments, the exposed dose of MMC over 2 h was infinite. Also
the exposure of surgeon’s gloves to MMC at the workplace represents an infinite MMC dose. An aqueous receptor phase was used for sampling as MMC is very water soluble (8430 mg l⁻¹ at 25°C). The thickness of glove material (Table 2) at the excision area was the lowest from the whole glove according to the manufacturers’ safety data sheets. Furthermore, a novel artificial sweat, the composition of which corresponds well with human sweat as described by Patterson et al. (2000), was used as receptor fluid to imitate the inside of gloves in surgeons under in-use conditions. All these experimental conditions comply with a worst-case exposure scenario.

Manufacturers are testing their glove material usually according to EN 374–3 at the standard temperature of 23 ± 1°C (CEN, 2003). This temperature, however, does not represent the in-use conditions during HIPEC, since the MMC chemotherapy solution is warmed up intraperitoneally to 40–41°C (Schmid et al., 2006) or to 43°C (Stuart et al., 2002). To consider this in our experiments, we kept the temperature of the outer glove material at ~40°C. A temperature rise of already 10°C may lead to a doubled permeation rate and a significantly decreased breakthrough time (Comyn, 1985).

The gloves are also stressed physically during HIPEC. In our diffusion cell study, the glove material remained static, since it is difficult to stress gloves in vitro similarly like in use. In the glass chamber experiments, the glove material was minimally stretched by the volume of the receptor fluid of 500 ml. Rego and Roley (1999) showed that due to physical stress gloves often do not accomplish the recommendations of manufacturers’ safety data sheets. In a recent study, the permeation of 13 antineoplastic drugs through 13 different gloves (eight of them were natural rubber gloves) was tested under dynamic conditions, such as rubbing, stretching and tension (Wallenmacq et al., 2006). During 60 min of exposure, a permeation rate of >1 ng cm⁻² h⁻¹ was detected in all gloves materials for at least one antineoplastic drug. On the other hand, double-layer gloves do not show a significant permeation alteration by flexing (Colligan and Horstman, 1990).

In this study, a breakthrough of MMC through double layers of glove material was detected in one of 40 diffusion cell experiments but in none of the glass chamber experiments. The breakthrough was observed when testing Biogel Indicator™ glove material exposed to a 100-fold higher MMC concentration in comparison to the exposure of surgeons during HIPEC. The permeation of MMC through double-layer natural rubber glove material could not be affirmed in any other diffusion cell experiment with various MMC test formulations and different receptor fluids. Artificial sweat in the receptor phase did not influence the permeability of glove material to MMC. As the first sample did not contain MMC, the permeation kinetics indicate that there was probably no contamination of the samples. Contamination would have rather occurred during the application phase of the test compound than during the exposure phase, as a contact to the exposure chamber after the application of MMC formulations was avoided. Furthermore, for the analysis no sample preparation, which may be susceptible for contamination, was necessary. A reliable aqueous calibration performed the ruggedness of our analytical method regarding matrix influences.

Similar permeation kinetics as in our study has been observed also in studies testing the permeation of pesticides through butyl glove material (Krzeminska and Szczecinska, 2001) and of disinfectants through natural rubber and vinyl glove material (Mellström et al., 1992). A declined permeation course after achieving a permeation maximum is attributed to a structural modification of the glove material by the impact of chemicals (Mellström et al., 1992).

The results of our diffusion cell experiments are opposite to the findings of Stuart et al. (2002), who detected a permeation of MMC dissolved in PDS through all tested single natural rubber gloves (18 gloves of three brands) using a single-chamber method similar to our glass chamber. However, in their study, single Biogel™ gloves showed significant lower total permeation of MMC than it was found in the one experiment in our study with Biogel Indicator™ double gloves (0.4 μg versus 6.9 μg). According to EN 374–3, the breakthrough time of MMC through the glove material is reached at a permeation rate of 1 μg cm⁻² min⁻¹ (CEN, 2003). Based on the data of our experiment showing a permeation of MMC, the breakthrough time of MMC through Biogel Indicator™ glove material according to EN 374–3 was not reached, since the permeation rate was ~0.36 μg cm⁻² min⁻¹ (6.87 μg MMC/0.64 cm²/30 min). However, the significance of the parameter ‘breakthrough time’ for risk assessment purposes is questionable, since in surgeons during HIPEC theoretically an MMC permeation of up to 90 mg may occur at the breakthrough time (permeation rate: 1 μg cm⁻² min⁻¹, exposed glove area of both hands: ~1000 cm², duration of HIPEC: 90 min). From the occupational hygienist’s point of view, such a potential dermal exposure would represent a high risk for workers and cannot be accepted for probably carcinogenic compounds (DFG, 2006).

As surgeons at our university hospital only wear double gloves during HIPEC, we conducted our experiments also solely with double-layer glove material (Biogel Indicator™ gloves) or double gloves (Biogel™ and Z™PLUS gloves). This is probably the reason that in our study, with the exception of
one diffusion cell test, no permeation of MMC through glove material was detected not only under exposure similar to in-use conditions but also under a worst-case exposure scenario. Laidlaw et al. (1984) and Connor (1999), using a different test method (bacterial mutation assay), showed that single natural rubber gloves are impermeable to MMC for 1.5 and 2 h, respectively, also at a significantly higher concentration (0.5 mg ml⁻¹) compared to our concentration (0.004 mg ml⁻¹ in glass chamber experiments and 0.004–0.4 mg ml⁻¹ in diffusion cell experiments). The reliability of the bacterial mutation assay to test the permeation of MMC is questionable, since this test principle allows only a qualitative MMC detection. Furthermore, bacterial mutation assay is not in accordance with EN 374–3 (CEN, 2003), whereas our experimental diffusion cell design basically conforms to this standard also considering the adaptations to in-use conditions.

The test procedures used in our study are more occupationally relevant than in the EN 374–3 (CEN, 2003) especially due to the in-use relevant temperature of glove material. A standard (D 6978–05) designed for testing the permeation of antineoplastic drugs through glove materials under worst-case conditions has recently been approved by ASTM (ASTM International, 2005). The required test temperature of 35 ± 2°C and the defined breakthrough time at a permeation rate of 0.01 µg cm⁻² h⁻¹ should increase the safety for the medical personnel. Our diffusion cell experiments comply well with the standard of ASTM.

Our recent field study (Schmid et al., 2006) evaluating possible exposure routes (inhalative and dermal) did not show detectable occupational health risk for surgeons performing HIPEC. In this study, we showed experimentally that double-layer natural rubber gloves prevent a permeation of MMC. Our results support the glove wearing procedure by surgeons in our university hospital handling MMC formulations during HIPEC. However, it is necessary that the hands of surgeons are dry after disinfection before wearing gloves. Isopropyl alcohol, contained in high concentrations (~70%) in skin disinfectants, permeates through surgical natural rubber glove material partly in <10 min (Mäkelä et al., 2003). It is unknown whether a pre-exposure of natural rubber glove material to skin disinfectants may influence the permeation of antineoplastic drugs.

There is no literature available on the percutaneous absorption of MMC through human skin. Exposure over 2 h in diffusion cell studies using rodent skin could not show a relevant percutaneous absorption of MMC even from isopropyl myristate (Hashida et al., 1985) or azone vehicles (Okamoto et al., 1987) known as strong penetration enhancers. However, considering the results of biological monitoring studies in vitro data must be interpreted with caution.

An intake of antineoplastic drugs in health care workers handling such compounds has been demonstrated (Sessink et al., 1992; Pethran et al., 2003). Furthermore, it can be assumed that macerated skin resulting from occlusion by gloves shows significantly higher percutaneous absorption than unaffected skin. Health care workers without direct dermal contact to antineoplastic drugs may be also exposed by contaminated surfaces (Kromhout et al., 2000; Fransman et al., 2005) or even by the excreta of patients (Kromhout et al., 2000; Ziegler et al., 2002). Due to a low evaporation of many antineoplastic drugs, as of MMC, one can assume that the percutaneous absorption is the main route of intake of such compounds. The occupational exposure to antineoplastic drugs should be avoided or minimized if possible, since their potential harmful effects from a long-term exposure to low doses are still insufficiently investigated.

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**REFERENCES**


