

Evaluation of oxaliplatin exposure of healthcare workers during heated intraperitoneal perioperative chemotherapy (HIPEC)

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Abstract: The aim of this study was to evaluate air and surface contaminations, and internal contamination of healthcare workers during open-abdomen HIPEC using oxaliplatin. Platinum (Pt) was measured in urine of exposed workers and in multiple air and surface samples. Three successive HIPEC procedures were investigated in each of the two hospitals participating in the study. Analysis of air samples did not detect any oxaliplatin contamination. Heavy contamination of the operating table, the floor at the surgeon's feet, and the surgeon's overshoes were observed. Hand contamination was observed in surgeons using double gloves for intra-abdominal chemotherapy administration, but not in those using three sets of gloves. Pt was not detected in urine samples obtained after HIPEC (<5 ng/L). The main risk of HIPEC is related to direct or indirect skin exposure and can be prevented by correct use of adapted protective equipment.

Key words: Oxaliplatin, HIPEC, Occupational exposure, Biomonitoring, Atmospheric samples, Surface samples

Introduction

Peritoneal carcinomatosis is a common complication

of gastrointestinal tract cancer that, up until recently, was considered to have a poor prognosis. A new strategy combining maximal cytoreductive surgery with heated intraperitoneal perioperative chemotherapy (HIPEC) has been introduced over the last decade and appears to constitute a major therapeutic progress in selected patients¹. During HIPEC, heated (42–43 °C) cytotoxic agents are

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administered directly into the abdominal cavity; as heat synergizes the cytotoxic effects of chemotherapy. Several HIPEC methods have been proposed^{2, 3)}, corresponding to two main types: closed-abdomen HIPEC and open-abdomen HIPEC. The technique most commonly performed in France at the present time is the “coliseum technique”, an open-abdomen HIPEC procedure. The coliseum technique allows homogeneous distribution of heat and cytotoxic agents throughout the abdominal cavity. The main drawbacks of this technique are heat loss due to the wide operative field and risks of leakage and contamination of healthcare workers.

HIPEC is associated with a risk of cytotoxic agent exposure of surgical staff, who are not familiar with this type of hazard and the associated risks. Originally reserved to a small number of specialized surgical units, HIPEC is now used by a rapidly increasing number of surgical teams. The occupational health risk is consequently, a growing concern. Healthcare workers involved in these new procedures must be adequately informed about the associated hazards and risks, and appropriate safety measures. However, very few published data are available on the significant routes of exposure, and the risk of local and systemic contamination. Over the last decade, two studies have assessed mitomycin C exposure of operating room staff during one⁴⁾ and 10⁵⁾ successive HIPEC procedures, respectively. More recently, four articles reported platinum salt exposure associated with HIPEC procedures: a German study measured oxaliplatin/cisplatin atmospheric and surface contamination in the operating room during HIPEC⁶⁾; a French experimental study evaluated the risk of oxaliplatin air contamination associated with HIPEC⁷⁾; a first publication by our team⁸⁾ and a Swedish study⁹⁾ assessed the risks of external exposure and internal contamination of a limited number of healthcare workers during HIPEC. We therefore conducted a larger study evaluating external exposure and internal contamination of surgeons and nurses from three different teams in each of the two hospitals taking part in the study, during successive HIPEC procedures. Multiple atmosphere, surface, and urine samples were analyzed during each procedure.

Methods

Study sites

Two hospitals performing HIPEC in the Paris area were contacted and enrolled in the study, after providing their consent. They will be subsequently designated as sites A and B. Both sites have performed HIPEC procedures

for many years with a total of more than 100 procedures in each site. In both sites, the HIPEC procedure was performed using the coliseum technique with oxaliplatin as cytotoxic agent administered into the peritoneal cavity. The oxaliplatin perfusion bag was prepared in the hospital central pharmacy and connected to the heating machine immediately prior to delivery. The dose of oxaliplatin delivered was 460 mg/m², diluted in 2 L/m² glucose solution (50 mg/ml). Patients concomitantly received intravenous 5-fluorouracil and/or irinotecan. Duration of oxaliplatin administration was 30 min.

Exposed healthcare workers

For each HIPEC procedure, the exposed group included all members of the medical staff (senior surgeon, junior surgeon, anesthesiologist, operating room nurse, and nurse anesthetist), the operating room cleaner and the staff member who transported drugs from the pharmacy to the operating room. During oxaliplatin administration, only the senior surgeon was directly exposed to oxaliplatin. He used a protective disposable impervious gown, latex gloves, a surgical mask, shoe covers (always in site B, in most cases in site A), and a facial screen for possible droplet protection. Nurses used a protective disposable impervious gown, latex gloves, a surgical mask, and shoe covers.

Informed consent was obtained from all subjects, and the study was approved by the local ethical committee.

Air sampling

Air samples were obtained using materials supplied by CRAMIF (Caisse régionale d'assurance maladie de l'Île-de-France): Gilian 3500[®] and MSA Escort elf[®] sampling pumps, with constant flow control, set at a 2 l/min flow rate and connected to QMA Whatman[®] quartz fiber filters. Pumps were placed at three different locations: above the operating field, next to the oxaliplatin perfusion machine; at the anesthesiologist's working station, both inside the operating room: the last one was placed outside the operating room, next to the operating room door. Two unused filters were used as controls.

Air sampling started at the beginning of the HIPEC procedure and stopped at its end.

Wipe and glove sampling

Wipes were Linget'Anios (impregnated with ethanol, chlorhexidine digluconate and alkylaminoalkylglycine). A 900 cm square template was dropped on to the floor. The interviewer wiped the square in two directions with

a Linget'Anios, which was then placed into a clean container. Sampling of hands was performed by the workers themselves, by successive wiping of the palms, dorsal areas and interdigital spaces. Fifteen different locations were sampled before and/or after each HIPEC procedure, including the operating table, several areas in the operating room, the oxaliplatin perfusion bag, and the surgeons' and nurses' shoes and hands. Gloves and overshoes were also analyzed.

Urine sampling

Urine specimens were collected from all exposed workers for platinum analysis. Each participant was asked to collect a sample from the first void in the morning after the procedure, in a 40 ml bottle (red cap PP bottle; CEB Laboratory, France). Samples were immediately stored at -20°C , until analysis.

Urine samples were also obtained from a control group of 7 healthcare workers in the same hospitals.

Each participant filled in a questionnaire concerning previous participation in HIPEC procedures, present or past exposure to antineoplastic drugs, and other possible exposures to platinum (especially, breast or dental prostheses).

Control subjects had no known present or past exposure to platinum compounds or cytostatic drugs.

Analytical procedures

Sample preparation

Platinum (Pt) was extracted from the wipes (surface sampling) and filters (air sampling) using 1 ml hot (80°C) concentrated nitric acid (65%, Suprapur[®], VWR, Fontenay-sous-Bois, France) for 48 h. This process was performed 4 times successively, to ensure complete Pt extraction. The extraction product was then diluted with 4 ml ultrapure water (MilliQ[®], Millipore, Molsheim, France) before analysis. Gloves were treated with 140 ml of 1 M nitric acid for 2 h at 80°C . Urine was diluted five times with 0.1 M nitric acid.

Analysis

Pt concentration was measured using inductively coupled plasma mass spectrometry (ICP-MS) on a DRCE quadrupole spectrometer (Perkin Elmer, Les Ulis, France). The three major platinum isotopes (194, 195 and 196) were initially measured in urine; as the results were similar for all three isotopes, only ^{195}Pt was subsequently measured¹⁰.

The limit of detection (LOD) (defined as three times the standard deviation of the blank) was 0.03 ng/filter, i.e. 0.2

to 0.5 ng/m^3 (depending on the volume of air sampling) for air concentrations; 0.25 ng/wipe, i.e. 0.27 pg/cm^2 for surface concentrations; 0.7 ng/unit for gloves and 5 ng/L for urine concentrations. The limit of quantification (LOQ) was 3.3 times the LOD, i.e. 0.1 ng/filter, 0.66 to 1.65 ng/m^3 , 0.83 ng/wipe, 0.89 pg/cm^2 , 2.3 ng/glove, and 16 ng/L, respectively.

Results

Three HIPEC procedures were studied in each participating hospital, resulting in a total of six different datasets.

Atmospheric samples

Pt was undetectable ($<0.03\text{ ng/filter}$) in the filters from all three locations of each HIPEC procedure in the 2 hospitals. Taking into account the volume of air sampled, the atmospheric concentrations were respectively:

- less than $0.28\text{--}0.5\text{ ng/m}^3$ Pt above the operating field during oxaliplatin delivery at site A, and less than $0.23\text{--}0.27\text{ ng/m}^3$ for the same location at site B;
- less than $0.23\text{--}0.5\text{ ng/m}^3$ Pt at the anesthesiologist's work station at site A, and less than $0.23\text{--}0.38\text{ ng/m}^3$ for the same location at site B;
- less than $0.18\text{--}0.28\text{ ng/m}^3$ Pt outside the operating room on site A, and less than $0.20\text{--}0.39\text{ ng/m}^3$ for the same location at site B;

Surface samples

Pt surface concentrations on HIPEC devices, floor, shoes and hands are presented in Tables 1 and 2.

At site A, a slight residual contamination of the floor under the operating table was observed before HIPEC 3, six days after the previous HIPEC procedure. During all three procedures, the Pt concentration on oxaliplatin perfusion bags was slightly elevated, using Pt concentrations on 5-FU and/or irinotecan bags as reference values. At this site, the floor was heavily contaminated at the surgeon's feet after each HIPEC procedure. On the other hand, no significant contamination was observed five meters from the operating table. Wipe sampling of the surgeons' hands showed contamination of one of the 2 surgeons after HIPEC 2 and 3 (not studied after HIPEC 1). Contamination of a nurse's hands was also observed after HIPEC 3. Slight contamination of the shoes (under overshoes) was observed in a surgeon after HIPEC 2 and 3.

At site B, very slight residual contamination of the floor under the operating table was present before HIPEC 2 and 3, seven days after the previous HIPEC procedure. Slight

Table 1. Pt surface concentrations in site A

Sampling time	Sampling location	Platinum					
		HIPEC n°1		HIPEC n°2		HIPEC n°3	
		ng/wipe	pg/cm ²	ng/wipe	pg/cm ²	ng/wipe	pg/cm ²
Before HIPEC	Floor, under the operating table, at the surgeon's feet	3.7	4	5.6	6	73	82
	Floor, 5 m from the operating table	5.4	6	5	6	33	36
	Stretcher	-	-	<0.25	-	0.6	1
	5-FU infusion bag	1.9	-	-	-	16.9	-
	Oxaliplatin infusion bag	12	-	15	-	88	-
	Irinotecan infusion bag	3.2	-	0.7	-	-	-
After HIPEC	Floor, under the operating table, at the surgeon's feet	970	1,078	17,512	19,458	5,951	6,613
	Floor, 5 m from the operating table	8.2	9	1	1	29	33
	Operating table	1.9	2	14	15	5.2	6
	Oxaliplatin delivering machine	75	-	3.8	-	10.2	-
	Hands surgeon 1	-	-	0.6	-	32	-
	Hands surgeon 2	-	-	941	-	273	-
	Hands operating room nurse 1	<0.25	-	-	-	706	-
	Hands operating room nurse 2	4.9	-	8.9	-	3.7	-
	Operating field clamp	15	-	-	-	<0.25	-
	Shoes surgeon 1	13	-	-	-	-	-
	Right shoe surgeon 2	-	-	44	-	6.5	-
	Left shoe surgeon 2	-	-	163	-	134	-

-: no sample

contamination of the stretcher was also observed before HIPEC 2. Slight surface contamination of the oxaliplatin perfusion bag was observed only before HIPEC 3. After the procedure, contamination of the floor at the surgeon's feet was observed after HIPEC 2 and 3, but not after HIPEC 1. No contamination of the operating table was observed after HIPEC 3; with slight contamination after HIPEC 2, and much heavier contamination after HIPEC 1. Wipe sampling of the hands showed no contamination of any of the surgeons, nurses or nurse-aides. One surgeon had contaminated shoes after HIPEC 2.

Glove and overshoe samples

The results for protective gloves and overshoes are presented in Tables 3 and 4. As expected, the surgeon's outer gloves were heavily contaminated at both sites, as these gloves were in direct contact with oxaliplatin during surgery. The outer glove of the guiding hand was more heavily contaminated. Inner gloves at site A and intermediate gloves at site B (where surgeons used three sets of gloves for intraperitoneal oxaliplatin administration) were less constantly and much less heavily contaminated. At site B, inner gloves were not contaminated or only very slightly

contaminated. Moderate contamination of outer gloves was observed for several nurses, with no contamination of inner gloves.

The surgeon's overshoes were heavily contaminated at site A. Most surgeons at site B did not use overshoes (Table 2) and their shoes were heavily contaminated.

Urine Pt concentrations

Globally, 44 workers (23 women and 21 men, aged 26–59 yr) participated in the study. Urine samples were obtained from 29 workers (14 women and 15 men, aged 27–59 yr) in the morning after the procedure. Pt was undetectable (<5 ng/L) in all workers. The Pt concentration was situated between the LOD and the LOQ (16 ng/L) in one of the 42 samples obtained before HIPEC; the worker concerned had participated in another HIPEC procedure one month previously.

Pt concentration was also below the LOD in urine samples from the control group (4 women and 3 men, aged 21–53 yr).

Table 2. Pt surface concentrations in site B

Sampling time	Sampling location	Platinum					
		HIPEC n°1		HIPEC n°2		HIPEC n°3	
		ng/wipe	pg/cm ²	ng/wipe	pg/cm ²	ng/wipe	pg/cm ²
Before HIPEC	Floor, under the operating table, at the surgeon's feet	1.7	2	17	19	34	37
	Floor, 5 m from the operating table	5.6	6	6.4	7	13	15
	Stretcher	4.8	5	47	52	3.4	4
	5-FU infusion bag	<0.25	-	<0.25	-	0.25	-
	Oxaliplatin infusion bag	0.4	-	0.6	-	141	-
After HIPEC)	Floor, under the operating table, at the surgeon's feet	30	34	1,737	1,930	3,659	4,066
	Floor, 5 m from the operating table	11	13	5.7	6	10.9	12
	Operating table	2,816	3,129	173	192	5	6
	Oxaliplatin delivering machine	15	-	24	-	2.3	-
	Hands, surgeon 1	1.5	-	0.6	-	27	-
	Hands, surgeon 2	1	-	-	-	-	-
	Hands, surgeon 3	-	-	3.8	-	1.2	-
	Hands, nurse-aides	-	-	4.6	-	-	-
	Hands, operating room nurse 1	31	-	19	-	1.4	-
	Hands, operating room nurse 2	-	-	-	-	-	-
	Hands, operating room cleaner 1	1.9	-	-	-	-	-
	Hands, operating room cleaner 2	4.4	-	-	-	-	-
	Operating field clamp	15	-	13	-	1.6	-
	Right shoe, surgeon 3	0.7	-	1505	-	23	-
	Left shoe, surgeon 3	<0.25	-	584	-	47	-

-: no sample

Discussion

With the growing use of HIPEC for the treatment of peritoneal carcinomatosis, the resulting occupational risk for operating room personnel deserves more thorough evaluation. This new treatment strategy combines meticulous cytoreductive surgery (by peritonectomy, visceral resections and electroevaporation of small tumor nodules) and perioperative intraperitoneal chemotherapy. During the first surgical phase of the procedure, electrocautery generates a large amount of smoke composed of steam, particulate matter, organic and inorganic substances, and microorganisms¹¹). During the second chemotherapeutic phase, health workers are exposed to antineoplastic agents. Both steps of the HIPEC procedure generate poorly evaluated dangers and risks. The aim of this study was to characterize the risks during perioperative chemotherapy.

Various anticancer drugs have been used, either alone or in combination, for HIPEC (mitomycin C¹²⁻¹⁴), doxorubicin¹⁵), cisplatin^{16, 17}) or oxaliplatin^{6, 18}). The main risk resulting from exposure to anticancer agents is a carcinogenic risk, which has been well documented in treated patients¹⁹⁻²⁴). Two epidemiological studies also showed

elevated risks of leukemia²⁵), breast cancer²⁶) and rectal cancer²⁶) in nurses occupationally exposed to anticancer drugs. The International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of three of the cytostatic drugs used for HIPEC: cisplatin, doxorubicin and mitomycin C ; the first two drugs were considered to be probably carcinogenic for humans (group 2A) and the last one only possibly (group 2B) carcinogenic for humans²⁷). There is no published epidemiological or experimental study on oxaliplatin carcinogenicity. Available data on cisplatin carcinogenicity are more consistent, and oxaliplatin is both chemically and pharmacologically related to cisplatin. According to IARC, there is sufficient evidence for cisplatin carcinogenicity in animals, and sufficient evidence of its genotoxic effects; it can therefore be considered to be probably carcinogenic for humans, despite the absence of suitable epidemiological data²⁷).

Health worker exposure to cytostatic drugs during HIPEC may result from inhalation, or direct or indirect skin or eye contact. There are two types of HIPEC: closed abdomen during chemotherapy, and open abdomen. The closed abdomen technique prevents anticancer drug exposure, but as distribution of the heated liquid in the

Table 3. Pt in protective gloves and overshoes during and after HIPEC – Site A

Item sampled and sampling time	Amount of platinum per item		
	HIPEC n°1	HIPEC n°2	HIPEC n°3
Operating room nurse's right outer glove. End of surgery (after wound closure)	12	78	39
Operating room nurse's left outer glove. End of surgery (after wound closure)	12	173	99
Operating room nurse's right inner glove. End of surgery (after wound closure)	3	-	-
Operating room nurse's left inner glove. End of surgery (after wound closure)	2.8	-	-
Operating room nurse's right outer glove (change of gloves during the procedure)	361	18	1,050
Operating room nurse's: left outer glove (change of gloves during the procedure)	3.1	120	<0.7
Surgeon 1. Right outer glove End of HIPEC (before wound closure)	-	41,328	6,237
Surgeon 1. Left outer glove. End of HIPEC (before wound closure)	-	50,120	11,218
Surgeon 1. Right outer glove. End of surgery (after wound closure) ¹	-	6,314	349
Surgeon 1. Left outer glove. End of surgery (after wound closure) ¹	-	4,155	625
Surgeon 1. Right inner glove. End of surgery (after wound closure)	500	35	152
Surgeon 1. Left inner glove. End of surgery (after wound closure)	281	154	166
Surgeon 2. Right outer glove. End of HIPEC (before wound closure)	7,149	-	8,315
Surgeon 2. Left outer glove. End of HIPEC (before wound closure)	244	-	3,631
Surgeon 2. Right outer glove. End of surgery (after wound closure) ¹	640	3,824	120
Surgeon 2. Left outer glove. End of surgery (after wound closure) ¹	355	1,047	3,030
Surgeon 2. Right inner glove. After the end of the procedure	<0.7	-	170
Surgeon 2. Left inner glove. After the end of the procedure	<0.7	-	80
Operating room nurse. Right and left gloves after connecting oxaliplatin perfusion bag to the delivering machine	2.5	-	-
Operating room nurse. Right and left gloves after cleaning the oxaliplatin delivering machine	194	-	-
Operating room nurse. Right glove after the end of the procedure	-	621	-
Operating room nurse. Left glove. End of surgery (after wound closure)	-	378	-
Surgeon 1. Right overshoe. End of surgery (after wound closure)	2,472		
Surgeon 1. Left overshoe. End of surgery (after wound closure)	3,538		
Surgeon 2. Right overshoe. End of surgery (after wound closure)		95,970	6,677
Surgeon 2. Left overshoes. End of surgery (after wound closure)		157,458	19,930
Control overshoe	0.9	-	-

¹ A new pair of outer gloves was used for wound closure. -: no sample

abdominal cavity is not uniform with this technique, open-abdomen HIPEC is generally preferred at the present time²⁸). The open-abdomen technique was used in the two hospitals participating in this study.

Exposure of healthcare workers to anticancer drugs during open-abdomen HIPEC is a subject of concern: healthcare workers in the operating room generally have no experience in handling these drugs; cytostatic drugs are heated before administration which facilitates their vaporization; the open-abdomen technique implies manual control of the distribution of the chemotherapy solution in the abdomen, with the associated risks of splashes and direct contamination of the surgeon.

No significant atmospheric oxaliplatin contamination was observed in this study. As the oxaliplatin LOD was situated between 200 and 500 pg/m³ in this study (accord-

ing to the pump flow rate and sampling duration) and as the platinum concentration in urban air is generally less than 10 pg/m³,^{29, 30}) this study did not clearly establish the presence of any atmospheric contamination. However, our results indicate the absence of any toxicologically significant production of vapors or aerosols during oxaliplatin perfusion, in this series of six procedures by different teams in two different hospitals. No significant atmospheric contamination was observed in a preliminary study of open-abdomen HIPEC using oxaliplatin⁸). In a realistic experimental study, Guerbet *et al.*⁷) also showed no risk of atmospheric oxaliplatin contamination during the HIPEC procedure. These results can probably be extrapolated to the other platinum salts used for HIPEC. However, as oxaliplatin (vapour pressure at 25 °C: 0.46 mmHg)³¹) and the other platinum-containing cytostatic drugs are poorly

Table 4. Pt in protective gloves and overshoes during and after HIPEC – Site B

Item sampled and sampling time	Amount of platinum per item		
	HIPEC n°1	HIPEC n°2	HIPEC n°3
Operating room nurse Right outer glove. End of surgery (after wound closure)	128	52	16
Operating room nurse Left outer glove. End of surgery (after wound closure)	138	7.4	108
Operating room nurse Right inner glove. End of surgery (after wound closure)	-	-	2.9
Operating room nurse Left inner glove. End of surgery (after wound closure)	-	-	1.8
Surgeon 1. Right outer glove. End of the surgery (after wound closure) ¹	1,077	-	94
Surgeon 1. Left outer glove. End of surgery (after wound closure) ¹	50	-	54
Surgeon 1. Right inner glove. End of surgery, after wound closure ¹	16	-	-
Surgeon 1. Left inner glove. End of surgery (after wound closure) ¹	17	-	-
Surgeon 2. Right outer glove. End of HIPEC (before wound closure)	4,152	-	34,118
Surgeon 2. Left outer glove. End of HIPEC (before wound closure)	6,055	-	42
Surgeon 2. Right intermediate ² glove. End of HIPEC (before wound closure)	26	-	20,210
Surgeon 2. Left intermediate ² glove. End of HIPEC (before wound closure)	47	-	40
Surgeon 2. Right inner glove. End of HIPEC (before wound closure)	15	-	24
Surgeon 2. Left inner glove. End of HIPEC (before wound closure)	10.3	-	77
Surgeon 3. Right outer glove. End of HIPEC (before wound closure)	-	3,143	19,568
Surgeon 3. Left outer glove. End of HIPEC (before wound closure)	-	11,324	1,731
Surgeon 3. Right intermediate ² glove. End of HIPEC (before wound closure)	-	7.8	-
Surgeon 3. Left intermediate ² glove. End of HIPEC (before wound closure)	-	19	-
Surgeon 3. Right inner glove. End of HIPEC (before wound closure)	-	<0.7	1.5
Surgeon 3. Left inner glove. End of HIPEC (before wound closure)	-	2.8	2.5
Surgeon 2. Right overshoe. End of surgery (after wound closure)	58	-	-
Surgeon 2. Left overshoe. End of surgery (after wound closure)	42	-	-

¹ A new pair of outer gloves was used for wound closure. ² In site B, surgeons used 3 sets of gloves. -: no sample

volatile. These reassuring results may not apply to more volatile anticancer drugs. Moreover, previous studies also showed no significant atmospheric contamination during HIPEC procedures using mitomycin C^{4, 5)} which is even less volatile than oxaliplatin (vapour pressure: $6.78 \text{ E}^{-10} \text{ mmHg}$ at $25 \text{ }^\circ\text{C}$)³²⁾, probably because in certain circumstances aerosols could be formed.

Heavy oxaliplatin contamination of the operating table and floor at the surgeon's feet was observed during the HIPEC procedure. Slightly heavier contamination was observed at site A, but of the same order of magnitude at both sites. These contaminations probably resulted from spills and splashes during manual supervision of intra-abdominal oxaliplatin perfusion by the surgeon. Consequently, the surgeon's overshoes (or surgeon's shoes when he did not use overshoes) were also contaminated. In surgeons wearing overshoes, slight contamination of the shoes underneath the overshoes was also detected and slight residual contamination of the floor at the surgeon's feet was also observed before HIPEC, indicating that the usual cleaning procedures are not entirely effective.

Our preliminary study of a single HIPEC procedure⁸⁾

showed a similar risk of floor and shoe contamination. In a recent German study, surface sampling was performed in a series of 19 HIPEC procedures using cisplatin or oxaliplatin⁶⁾. This study showed only slight (maximum: 9.7 pg/cm^2) contamination of the floor near the operating table during the HIPEC procedure. However, these results cannot be compared to those obtained in the present study, as only 3 (/19) of the HIPEC procedures were performed according to the open-abdomen (coliseum) technique, floor samples were obtained for only 15 procedures and the authors did not indicate which HIPEC (open- or closed-abdomen) technique was used for this series with floor sampling.

As heavy contamination of the floor and shoes is possible, both should be properly protected. Our study demonstrates the protective effect of overshoes, as well as their limitations. In practice, the use of overshoes is mandatory for surgeons; shoes underneath overshoes must not be personal shoes, but work shoes (disposable shoes, or shoes that can be submitted to a decontamination procedure). The available floor protection devices should be tested for their efficacy and acceptability (they should not limit the

surgeons' movements and/or increase the risk of slipping). The level of floor contamination shows that cleaning staff are also significantly exposed to anticancer drugs. They should therefore wear gloves and overshoes when cleaning the operating room after a HIPEC procedure and their real exposure should be evaluated more precisely.

The low level of external contamination of oxaliplatin perfusion bags observed in this study is consistent with that previously reported in hospital pharmacies preparing anticancer drugs³³⁻³⁵) and justifies the systematic use of gloves when handling these items.

As expected, our study demonstrated heavy contamination of the surgeons' outer gloves that were in direct contact with the oxaliplatin solution. Nurses' outer gloves were not systematically contaminated and always at lower levels. Contamination of the surgeons' gloves immediately underneath the outer gloves was also generally observed, although much lower than contamination of the outer gloves. At site B, surgeons used three sets of gloves for chemotherapy administration, and the inner gloves were never contaminated. Hand wiping showed no or only very slight hand contamination at site B, but significant contamination of several workers at site A. Our preliminary study⁸) was also conducted at site B and showed similar results: heavy contamination of outer gloves, slight contamination of the second set of gloves and no contamination of the surgeon's hands. The German study cited above⁶) also measured platinum contamination of the surgeons' gloves after five HIPEC procedures, but their results cannot be compared to those of this study, as the HIPEC procedures (mainly closed-abdomen HIPEC procedures) and sampling techniques were different.

In the light of our results, surgeons should be advised to systematically use three sets of gloves for administration of perioperative intraperitoneal chemotherapy using the open-abdomen HIPEC procedure. As surgical gloves do not completely prevent anticancer drug penetration during prolonged contact⁵), it is also recommended to change gloves every 30 min when working in contact with cytostatic drugs and also after overt contamination. Surgeons in direct contact with chemotherapy should also wear outer gloves covering the elbow³⁶). As hand contamination is possible, surgeons and nurses should thoroughly wash their hands before leaving the operating room. Protective barrier garments possibly contaminated with anticancer drugs (gloves, gown, pyjamas, overshoes and shoes, etc.) should be left in the operating room in dedicated containers, in order to prevent secondary contamination: gloves, overshoes and surgical gowns to be destroyed; pyjamas

and shoes in a separate container for decontamination.

This study also investigated possible internal contamination of exposed healthcare workers by urinary platinum assays. Urine sampling was performed in the morning after the HIPEC procedure rather than immediately after the procedure, in order to prevent external contamination of the urine. Due to oxaliplatin and platinum elimination kinetics (half-lives >200 h), no significant modification of the urine Pt concentration is expected with this sampling time^{37, 38}); on the other hand, the risk of false-positive results is certainly decreased. Urine Pt was undetectable (<5 ng/L) after HIPEC in all cases of this series. It was between the LOD and the LOQ (16 ng/L) in one of the 42 samples obtained before HIPEC; the surgeon concerned had participated in another HIPEC procedure, one month previously, but this is unlikely to explain the observed result, as platinum was undetectable in the urine of the same person on the following day. In a Swedish study⁹), platinum was also undetectable (<2 ng/L) in the urine from one male surgeon and one female nurse anesthetist after six successive open-abdomen HIPEC procedures with oxaliplatin. The results of these two studies eliminate heavy or moderate internal contamination of surgeons or nurses during open-abdomen HIPEC procedures using platinum salts, but cannot preclude very slight contamination. The LOD of the analytical method was 5 ng/L in our study and 2 ng/L in the Swedish study, while urine platinum concentrations are lower in the general population. No recent data are available for the French population, but, in 1998, in Germany, the median and 95th percentile of urine platinum concentrations were 2 ng/L and 24 ng/L, respectively³⁹). Urine platinum concentrations are probably lower today, as sources of exposure have been significantly decreased over the last 15 yr.

Due to the limited sensitivity of the methods used at the present time for platinum assays in most laboratories, systematic biomonitoring of occupational health workers exposed to platinum salts during HIPEC procedures cannot be recommended, when the LOD of the analytical method is higher than 2 ng/L. However, even in this case, it is still highly advisable to confirm that platinum is undetectable in the urine of any exposed worker, at least the first 2 or 3 times he or she participates in a HIPEC procedure. On the other hand, the urine platinum concentration should be systematically measured to document a possible internal contamination, after any incident or accident responsible for direct skin or eye contact or aerosol production.

Conclusions

The risk of oxaliplatin exposure during open-abdomen HIPEC procedures is low, but not non-existent (this is probably also true for the other platinum salts used for HIPEC). This residual risk is mainly due to the possibility of direct or indirect skin exposure and can be prevented by the correct use of adapted protective equipment. No significant respiratory exposure is expected. Routine biomonitoring is not useful, but urine Pt concentration measurement is recommended to document any possible internal contamination after accidental skin or eye splash or after exposure to accidentally produced aerosols.

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