



## Evaluation of the risk of contamination of surgical personnel by vaporization of oxaliplatin during the intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC)

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### Abstract

**Aims:** To evaluate if oxaliplatin is likely to vaporize under HIPEC conditions and to see if it could be a source of pulmonary contamination for surgeons.

**Methods:** Three oxaliplatin concentrations (230, 460 and 920 mg oxaliplatin/l), 3 heating temperatures (41, 43 and 45 °C) and 3 bubbling durations (30, 60 and 90 min) were tested. Drug vaporization was evaluated by using inductively coupled plasma mass spectrometry (ICP-MS) to analyze platinum concentrations in the trap solutions.

**Results:** At all concentrations of oxaliplatin solutions, heating temperatures and bubbling trap periods, the quantities of vaporized platinum were always insignificantly lower than 1 µg/l.

**Conclusions:** The experimental risk of pulmonary contamination of hospital staff during HIPEC procedure appears to be negligible. However a monitoring study with an analysis of samples of the operating theatre and urine from surgical personnel should be carried out to confirm these conclusions.

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**Keywords:** Oxaliplatin; Intraperitoneal chemotherapy; Vaporization; Safety; Occupational exposure

### Introduction

Hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is a promising therapy for peritoneal carcinomatosis. Various studies have shown that some 30% of colorectal cancer patients can be cured.<sup>1</sup> In the open technique, the HIPEC procedure is based on continuous manual handling of patient's viscera by the surgeons to ensure a good distribution of the heated agent.<sup>2</sup> Technical conditions vary among surgical teams concerning chemotherapeutic agents (5-fluorouracil, mitomycin, cisplatin etc.), heating temperature (40–43 °C) and handling duration (30–90 min).<sup>3</sup>

The safety of the surgical staff is very important. The adverse effects of antineoplastic drug exposure have been well documented and monitoring occupational exposure using analytical and biological methods are widely used.<sup>4</sup> The heating of chemotherapy drugs is specific to the HIPEC protocol and constitutes a risk of exposure of surgeons to their vapours.<sup>5,6</sup> Physical, chemical and toxicological data are available for most of the agents and can be efficiently analyzed to take safety measurements.<sup>7</sup> Data about oxaliplatin are weak although this drug is clinically important for colorectal carcinomas.<sup>8,9</sup>

We wished to see whether oxaliplatin is likely to vaporize under HIPEC conditions and could be a source of pulmonary contamination for surgeons. The other compounds from platinum (carboplatin, cisplatin) are well documented in literature and it appears that they are not volatile.<sup>10</sup>

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## Material and method

The experimental conditions were set on the basis of the clinical HIPEC protocol that is applied at Rouen University Hospital. The medical team uses 1 l of oxaliplatin solution to obtain a concentration of 460 mg of drug/m<sup>2</sup> of body area of the patient. As average body area is approximately 2 m<sup>2</sup>, HIPEC protocol is conducted with a solution containing 920 mg of oxaliplatin diluted in 1 l of 5% glucose solution. When the patient is brought to the surgical operating room, the abdominal operative field is initially preheated with 3 l of glucose solution until the temperature reaches 43 °C. The oxaliplatin solution is then added to obtain a concentration of 230 mg/l in the peritoneal cavity in the end. Thermal probes give continuous temperature intra-abdominal feedback so that the temperature is maintained between 42 and 44 °C. The treatment is given for 45 min before the solution is completely removed.

### Preparation of oxaliplatin solutions

For our laboratory study, we evaluated the possibility of vaporization of oxaliplatin under different experimental conditions selected to enclose the clinical HIPEC protocol.

- 3 Oxaliplatin concentrations: 230, 460 and 920 mg oxaliplatin/l, respectively, corresponding to  $1.13 \times 10^5$ ,  $2.27 \times 10^5$  and  $4.54 \times 10^5$  mg platinum/l (Pt/l),
- 3 heating temperatures: 41, 43 and 45 °C,
- 3 bubbling durations: 30, 60 and 90 min.

Oxaliplatin solutions were prepared from Eloxatine<sup>®</sup> (Sanofi Aventis, France) which contains 5 mg oxaliplatin/ml of water. All dilutions were carried out with ultrapure

water in small polystyrene flasks with a 2-way cap for the entry and the exit of the bubbling air (Fig. 1).

### Sample collection

Oxaliplatin solutions (10 ml) were placed in a water bath (41, 43 or 45 °C) until temperature equilibrium was reached. The second flask (trap) was filled with 10 ml ultrapure water and joined before the air pump was started (15 l/min). The water in every trap flask was replaced with fresh ultrapure water every 30 min in order to have 3 samples corresponding to 3 bubbling periods (0–30 min, 30–60 min, 60–90 min). Simultaneously a control with ultrapure water was treated for a duration of 90 min heating. The samples were stored at +4 °C until analysis.

### Platinum quantification

Platinum was quantified using inductively coupled plasma mass spectrometry (ICP-MS) according to a method previously described.<sup>11</sup> A Thermo Elemental X7CCT bench top series with PlasmaLab<sup>®</sup> software and without a dynamic reaction cell (Thermo Optek, Courtaboeuf, France), was used. The limit of quantification for platinum was 0.01 µg/l.

## Results

Whatever were the concentrations of oxaliplatin solutions (230–920 mg/l), the heating temperatures (41–45 °C) and the bubbling trap periods (30–90 min) the quantities of vaporized platinum measured were always not significant (Table 1). Platinum concentrations were always lower than 1 µg Pt/l with an average concentration  $0.40 \pm 0.27$  µg/l

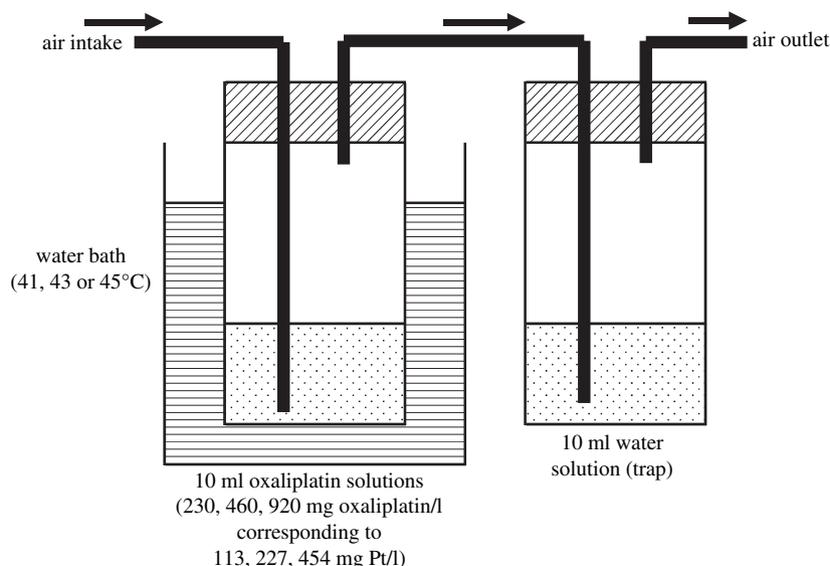


Figure 1. Experimental apparatus for testing the oxaliplatin vaporization.

Table 1  
Analytical results for oxaliplatin vaporization study (results expressed in platinum/l concentrations)

Initial platinum concentration (µg/l) in heated oxaliplatin solutions	Heating temperature (°C)	Platinum concentration (µg/l) in water trap solutions after different heating durations			Final platinum concentration (µg/l) in oxaliplatin solutions after 90 min heating
		0–30 min period	30–60 min period	60–90 min period	
$1.135 \times 10^5$	41	0.47	1.16	0.57	$1.546 \times 10^5$
	43	0.50	0.38	0.37	$1.628 \times 10^5$
	45	0.10	0.12	0.11	$1.400 \times 10^5$
$2.270 \times 10^5$	41	0.13	0.43	0.13	$2.975 \times 10^5$
	43	0.63	0.21	0.26	$2.919 \times 10^5$
	45	0.63	0.67	1.04	$3.394 \times 10^5$
$4.540 \times 10^5$	41	0.30	0.43	0.37	$6.095 \times 10^5$
	43	0.74	0.23	0.10	$5.903 \times 10^5$
	45	0.26	0.33	0.13	$5.618 \times 10^5$
0 (ultrapure water control)	41	—	—	0.04	—
	43	—	—	0.13	—
	45	—	—	0.10	—

LD = limit of detection: 0.01 µg Pt/l.

for all oxaliplatin solutions. Traces of platinum were also detected in water trap control solutions ( $0.09 \pm 0.04$  µg/l). These traces of platinum in control bubbling solutions can be allotted to an urban environmental air contamination in relation to a low release of metals (platinum, palladium etc.) from automobile catalytic converters.<sup>12</sup> It should be noted that the measured platinum concentrations were very low and close to the analytical limit of detection.

By comparing the platinum concentrations in water trap solution corresponding to heated oxaliplatin solutions, only traces of oxaliplatin ( $0.63 \pm 0.46$  µg/l) vaporized during the assay, even for higher conditions of concentration, temperature and duration. The platinum remaining in flasks after 90 min heating was finally measured. It is noted that the concentrations were definitely higher at the end of the experiment than at the beginning. This is logical because approximately one third of the water solution was vaporized, which corresponded to an increased platinum concentration of the solution.

## Discussion

With an increasing number of HIPEC procedures to treat peritoneal surface malignancy, there is a growing concern regarding the safety of the operating room personnel. During the HIPEC open technique, the exposure of surgical personnel to chemotherapy drugs can occur essentially by route of direct contact and inhalation and guidelines for safe administration must be strictly respected. In the operating room, all personnel should wear protective barrier garments.<sup>13</sup> Latex gloves are recommended because they display the highest resistance to permeation of cytotoxic agents although additional factors (i.e. duration of exposure, drug liposolubility and molecular weight) can also affect permeability.<sup>14</sup> Adverse effects of antineoplastic drugs exposure can also result from hazardous exposure in case of splashes or leaky gloves.

Concerning a possible vaporization of cytotoxic drugs and inhalation exposure, there are a few studies on this subject. Although Stuart et al.<sup>15</sup> did not find detectable levels of mitomycin C in environmental air samples from the operating room and in urine from personnel during HIPEC, there are several chemotherapy drugs with widely different physicochemical properties therefore guidelines for safe administration of HIPEC must be adapted to the cytotoxic agent. The use of a smoke evacuator under the plastic sheet continuously working during the perfusion should be preventively adopted to minimize the inhalation exposure of aerosols or vapours.

The aim of our work was to evaluate precisely the vaporization of oxaliplatin under HIPEC conditions and thus the risk of occupational exposure by inhalation for surgical personnel. Whatever were the tested oxaliplatin concentrations, the heating temperatures and the bubbling trap periods, this study showed no obvious vaporization of oxaliplatin. According to the results of this study, it thus appears that the risk of contamination of hospital staff by pulmonary way during the HIPEC procedure is negligible for oxaliplatin. These results go in the same direction as various preliminary studies on antineoplastic agents derived from platinum.<sup>6</sup> However a monitoring study with analysis of samples of operating room and urine from surgical personnel should be done to confirm the conclusions of this experimental laboratory study.

Besides the real medical interest of the hyperthermic intraoperative intraperitoneal chemotherapy, it is imperative not to neglect all the hazards with cytotoxic drugs and always consider the need for taking into account the staff safety.

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