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Abstract:

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a technique to directly deliver chemotherapeutic drugs in the abdomen for the treatment of peritoneal metastases. Pressurization improves the treatment efficacy but increases the risk of exposure for the medical/non-medical staff who can be contaminated by dermal or ocular contact, or inhalation of aerosols containing the cytotoxic drugs. The aim of this study was to evaluate the risk of contamination for the medical/non-medical staff (nurses, surgeons, anaesthesiologists and cleaning personnel; n=13) during PIPAC with oxaliplatin or cisplatin-doxorubicin performed according to the protocol recommended in France. Blood samples were collected 1 hour before and immediately after PIPAC, and urine samples 1 hour before, and then 3 hours and the morning after PIPAC. In the control, non-exposed group (n=7), only one urine and blood sample were collected. Surface contamination in the operating room was assessed in water- and Surfanios-impregnated wipe samples. The total elemental platinum in each sample was quantified by inductively coupled plasma mass spectrometry, using a method adapted to quantify trace amounts ($ng.L^{-1}$) in very low volumes (100µl). No surface contamination was detected. Although 25% of urine samples in the exposed group contained platinum, no statistical difference was observed in urine and plasma samples collected before and after PIPAC and with the control group samples. These findings suggest that the French PIPAC protocol does not increase the risk of exposure to platinum in all staff categories involved. This protocol could be considered in future occupational policies and consensus statements.

Keywords: PIPAC, oxaliplatin, occupational safety, occupational hazard, personal protective equipment.

Abbreviations

EG: exposed group

NEG: non-exposed group

PIPAC: pressurized intraperitoneal aerosol chemotherapy

PIPAC-CD: pressurized intraperitoneal aerosol chemotherapy with cisplatin-doxorubicin

PIPAC-Ox: pressurized intraperitoneal aerosol chemotherapy with oxaliplatin

Pt: platinum

1. Introduction:

Life-threating peritoneal metastases from various cancers respond poorly to intravenous drugs. Therefore, innovative loco-regional strategies and systemic chemotherapy are currently combined to improve the prognosis of these patients (Ceelen and Flessner, 2010). For instance, pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an intraperitoneal drug delivery method performed in the operating room during laparoscopy (Alyami et al., 2019). Oxaliplatin (PIPAC-Ox) and the cisplatin and doxorubicin combination (PIPAC-CD) are frequently used for PIPAC. PIPAC-Ox is mainly proposed to patients with peritoneal metastases of colorectal origin, but also for other indications (Di Giorgio et al., 2020; Sgarbura et al., 2019). During PIPAC, microdroplets of the chosen chemotherapeutic drug are delivered by constant flow after establishment of a stable pressure capnoperitoneum in the purpose of improving their intra-abdominal distribution and penetration in the peritoneal tissue (Solass et al., 2014). PIPAC

efficacy is based on the delivery of the chemotherapeutic drug(s) in the form of pressurized aerosols during 37 minutes, but this delivery could also increase the risk of exposure to such cytotoxic drugs and represents an occupational hazards for the involved medical/non-medical staff (CDC, n.d.). Specifically, inhalation is considered to be the main contamination route associated with PIPAC, whereas contamination via the dermal and oral routes should be less common. Therefore, in Germany, very rigorous safety protocols have been put in place with at least three containment levels (zero flow abdominal pressure, laminar airflow system in the operating room, and remote controlled administration of the drug) (Solaß et al., 2013). The French safety protocol also includes a plastic sheet around the patient and a toxic gas aspiration device under the sheet during the procedure (Cazauran et al., 2018) as the fourth level of containment. However, a French study suggested that the laminar air flow could be replaced by any advanced airflow system (Delhorme et al., 2019).

Some German groups have already evaluated the occupational exposure risk to platinum linked to PIPAC with platinum-based drugs (Ametsbichler et al., 2018; Solaß et al., 2013). They determined air and surface contamination by quantifying platinum concentration in air and wipe samples, respectively. Operating room air sampling revealed low platinum contamination levels (<9 pg/m^3), and surface contamination ranged from 0.01 to 1733 pg/cm², depending on the area (higher contamination on the injector and trocars) (Ametsbichler et al., 2018). No platinum was detected in the operating room air at the places where the surgeon and anaesthesiologist work during PIPAC (Solaß et al., 2013). These data suggest a low exposure risk when PIPAC is performed following the safety protocol implemented in Germany. Few studies focused on the biological monitoring of the medical staff. In 2016, Graversen et al. showed the absence of contamination in two surgeons after two consecutive PIPAC procedures, by quantifying platinum in blood samples. However, these authors did not describe the method used for platinum quantification and the limits of detection. Ndaw et al. analysed platinum concentration

in urine samples of the medical staff collected at 24h post-PIPAC-CD and from a control group and did not find any significant difference between groups (Ndaw et al., 2018).

However, to our knowledge, no study measured the platinum concentration in both blood and urine samples. Moreover, despite this encouraging preliminary evidence and the rigorous safety protocol put in place for the medical (Alyami et al., 2020) and non-medical staff (Al Hosni et al., 2020), the use of PIPAC, and also of other types of intraperitoneal chemotherapy procedures, such as hyperthermic intraperitoneal chemotherapy, is still considered as an occupational hazard and requires continuous updating and education (Al Hosni et al., 2020; Clerc D et al., 2021).

The aim of this study was to evaluate the risk of exposure for the operating room medical/non-medical staff during PIPAC-Ox procedures by measuring and comparing platinum concentration in blood and urine samples collected from potentially exposed staff members and from healthy volunteers. Contamination of the operating room surfaces after PIPAC was also evaluated.

2. **Material and methods**:

2.1. PIPAC procedure

The PIPAC procedure is performed in a dedicated operating room with an advanced ventilation system and remote controlled administration according to the French safety protocol (Cazauran et al., 2018). The standardized surgical technique includes a two-port access with double-balloon trocars and aerosolization of the chemotherapeutic drug after evaluation of the metastatic disease, as described elsewhere (Hübner et al., 2017). In PIPAC-Ox, oxaliplatin ($92mg.m^{-2}$) is diluted in 5% glucose solution, and administered with a flow of $0.6ml.sec^{-1}$ and

upstream pressure limit of 290 psi (Dumont et al., 2020; Sgarbura et al., 2020). The total administration time is 37 minutes.

2.2. Study participants

The study was carried out at the Cancer Institute of Montpellier (ICM), France, in 2018. In our centre, more than 70 PIPAC procedures are performed annually since its introduction in 2016 (Al Hosni et al., 2020). The operating room staff members who took part in two different PIPAC-Ox sessions two weeks apart were enrolled in the current study: session 1 (one senior surgeon, one assistant surgeon, one circulating nurse, one scrub nurse, one nurse anaesthetist, one anaesthesiologist, and the cleaner), and session 2 (one senior surgeon, one assistant surgeon, one circulating nurse, one scrub nurse, one nurse anaesthetist, one anaesthesiologist). With the exception of the anaesthesiologists and of the senior surgeon, all staff members involved in PIPAC delivery undergo a 2-week non-exposure period before and between PIPAC sessions. The participation was voluntary and the group was defined as “Exposed group” (EG).

Seven healthy volunteers formed the control “Non-Exposed group” (NEG) and were selected among the ICM researchers and administrative staff who had no identified contact with platinum-containing cytotoxic drugs.

All participants received oral and written information about the study and signed an informed consent. The study was carried out in accordance with the current version of the Declaration of Helsinki and approved by a national ethics committee (2017-A01921-52). The study was registered at ClinicalTrials.gov (NCT04014426).

2.3. Analysis of biological samples

In the EG group, blood samples were collected in heparinized tubes 1hour before and immediately after the PIPAC intervention. Urine samples were collected 1 hour before (T0), 3

hours after (T1), and the morning (T2) after the PIPAC procedure. In the NEG group, only one sample of urine and one sample of plasma were collected. Plasma was separated from blood by centrifugation at 2000g for 5 minutes. All biological samples were stored at -80°C until analysis.

Several methods using mineralization or direct dilution in acidic or alkaline media were previously published for platinum quantification in biological samples (Abduljabbar et al., 2019; Chantada-Vázquez et al., 2019; Gong et al., 2017; Lu et al., 2015). Nevertheless, due to the very small concentrations ($ng.L^{-1}$) and small sample volume, these methods could not be used directly. Therefore, the method was optimized using oxaliplatin-spiked samples. Briefly, mineralization was optimized in acidic (69% HNO_3/H_2O_2) or alkaline (25% tetramethyl ammonium hydroxide, TMAH) solutions at different ratios, but important matrix effect and nebulization clogging was observed. A 5- or 10-fold dilution in nitric acid did not improve platinum recovery as protein precipitation leads to the loss of platinum. Finally, a direct 10-fold dilution in 0.1% TMAH/0.1% Triton X-100 was retained to minimize the matrix effect, with a >75% recovery.

Thus, a 100µL aliquot of each plasma and urine sample was 10-fold diluted in 0.1% TMAH/0.1% Triton X-100 (Sigma Aldrich, St Quentin Falavier, France). Tantalum (PlasmaCAL, SCP Science, Courtaboeuf, France) was added at a concentration of 1 $ng.L^{-1}$ as internal standard. After stirring, samples were centrifuged at 11000rpm, 4°C for 15 min, and analysed by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Matrix-dependent calibration curves were obtained by spiking known concentrations of pure oxaliplatin in the control urine or plasma samples to study the matrix effect. Then, the limit of detection (LOD) and of quantification (LOQ) were estimated as 3 and 10 times, respectively, the standard deviation of the intercept divided by the calibration curve slope.

175 *2.4. Analysis of samples from contaminated surfaces and determination of the Limits of*
176 *quantification (LOQ).*
177 *2.4.1 Standardization and LOQ determination:*
178 An oxaliplatin standard solution (platinum concentration ranging from 70 fg.cm^{-2} to 250
179 ng.cm^{-2}), water, or the surface disinfectant Surfanios (blanks) were deposited onto 4 cm² glass
180 surfaces and allowed to dry under moderate heating (50°C). After complete dryness, each
181 surface was rubbed with a 2.25 cm² multi-layered wipe wetted with 150 µl of water or
182 Surfanios. Wipes were then mineralized by addition of 400 µl pure nitric acid and 150 µl of
183 hydrogen peroxide (Sigma Aldrich, St Louis Missouri, United States) at 75°C for 3 hours, and
184 centrifuged at 15000 g for 15min. Platinum in the supernatant was then quantified by ICP-MS
185 after addition of 1µg.L^{-1} indium as internal standard (SCP Science, Courtaboeuf, France). The
186 LOQ after recovery was determined as the lowest concentration that can be measured with an
187 accuracy within 30% of the nominal value deposited onto the test surface.
188 *2.4.2 Operating room surface contamination:*
189 Six potentially contaminated surfaces were identified on the basis of previous publications
190 and the operating room staff's experience: anaesthesia monitoring screen, surgical lamp,
191 laparoscopy tower, surgical gas aspirator, surgical gas aspiration filter, and laparoscopic
192 monitor (Fig. 1). To evaluate their contamination, surfaces (area=9 cm²) were rubbed twice
193 with water- or Surfanios-impregnated multi-layered wipes in both directions by the same
194 experienced person who collected the wipe samples also for the standardization experiment.
195 Wipes were handled as described in 2.4.1 and platinum quantified by ICP-MS.
196
197 *2.5. Analytical quantification*
198 Diluted serum and urine samples were analysed using an Agilent 7700x quadrupole ICP-
199 MS (Agilent Technologies, Tokyo, Japan) equipped with a Scott spray chamber (cooled at 2°C),

a MicroMist nebulizer (400µL.min^{-1}), X-Lenses and nickel cones. Plasma power was set to 1550W. Platinum determination was performed by quantifying three major isotopes (^{194}Pt, ^{195}Pt, ^{196}Pt) with an integration time of 999msec per isotope. Quantification was performed by internal calibration with tantalum-181 (integration time 100ms).

After acid digestion, wipes were analysed by high resolution ICP-MS using an Element XR (ThermoScientific, Bremen, Germany) equipped with a Scott spray chamber (cooled at 2°C), a MicroMist nebulizer (200µL.min-^{1}) and nickel cones. To improve sensitivity, the instrument operating conditions were plasma power of 1200W and low resolution (m/Δm 400). Internal calibration was performed for platinum quantification using indium as internal standard. ^{194}Pt, ^{195}Pt and ^{115}In were monitored (50 sample/peak, mass window 20%, sample time 5 sec for ^{194}Pt and ^{195}Pt and 10 msec for ^{115}In). Platinum concentrations were determined using the ^{194}Pt and ^{195}Pt values, but only the ^{195}Pt concentration was reported, if not otherwise mentioned. All standard solutions were from SCP Science (Courtaboeuf, France).

2.6. Statistical analysis

The descriptive analysis was performed using median and range for continuous parameters, frequency and percentage for categorical variables. The comparative analysis was based on non-parametric tests (Mann Whitney, Wilcoxon) and was performed with STATA 16 (Stata Corporation, College Station, Tx, USA). A p-value <0.05 was considered significant.

3. Results

3.1. Platinum concentration in biological samples

The instrument LOD and LOQ of platinum were estimated at 0.3 $ng.L^{-1}$ and 0.9 $ng.L^{-1}$ respectively. This corresponded to 5 and 16 $ng.L^{-1}$, respectively, in plasma, and to 3 and 9 $ng.L^{-1}$, respectively, in urine, by taking into account the matrix effect and dilution factor.

In the EG, 37 urine samples were collected from 13 medical/non-medical staff members implicated in the two PIPAC procedures (Table 1). Before PIPAC (T0), platinum concentration was below the LOQ in 9/13 urine samples (69%), and could not be detected (<LOD) in 7/13 samples (54%). Only 4/13 samples (31%) contained platinum (from 9.8 to 42 $ng.L^{-1}$). After PIPAC, platinum concentration in urine samples was below the LOQ in 18/24 samples (75%) (18/24) and remained undetectable in 10/24 samples (42%). Platinum could be quantified in 6/24 urine samples (25%) and the concentration ranged from 12.5 to 367 $ng.L^{-1}$. The two anaesthesiologists' and the senior surgeon's urine samples at T0 were positive (4 and 11). One surgeon, one assistant surgeon, one circulating nurse and one scrub nurse had positive urine samples at T2. In all plasma samples, platinum concentration was below the LOQ (7/25; 28%) or the LOD (18/25; 72%) before and also after PIPAC.

There was no statistical difference in platinum concentration in urine and plasma samples collected before and after PIPAC (p=0.2).

In the NEG (n=7), all plasma samples were below the LOQ, and platinum could not be detected (<LOD) in 6/7 samples (86%). Conversely, in two urine samples, platinum concentration was slightly above the LOQ and in two slightly below the LOD. There **was** no statistical difference in the platinum concentrations in the EG and NEG urine and plasma samples (p=0.2).

3.2. *Surface contamination*

Water- and Surfanios-impregnated wipes with known concentrations of oxaliplatin (from 70 $fg.cm^{-2}$ to 250 $ng.cm^{-2}$) were used to determine the platinum recovery yield that was higher

with water-impregnated wipes (Fig. 2). The LOQ with water-impregnated wipes was 2.5 pg.cm^{-2}.

Platinum concentration was below this LOQ in all wipe samples from the six tested surfaces.

4. Discussion:

The current study shows that exposure to oxaliplatin during PIPAC-Ox performed following the current French safety protocol is non-existent for all the involved medical/non-medical staff members. This is the first study to extensively investigate PIPAC-Ox occupational exposure risk by analysing both environmental and biological samples.

PIPAC-Ox was initially used for colorectal cancer peritoneal metastases (Demtröder et al., 2016), and was then enlarged to other types of gastrointestinal cancers (Di Giorgio et al., 2020; Sgarbura et al., 2019). Although there is no report on the exact number of healthcare centres performing PIPAC-Ox worldwide, the recently published PIPAC survey identified 62 centres that carried out at least 5972 procedures in 20 countries, and 74% of all respondents confirmed the use of oxaliplatin (Sgarbura et al., 2020). However, **studies** on PIPAC-Ox-linked surface and biological contamination are scarce (Graversen et al., 2016) and based on limited data. The findings of the current study confirm that PIPAC-Ox use in the operating room following specific protection regulations (i.e. the French safety protocol) does not increase the risk of exposure to platinum compared with controls. Moreover, platinum concentration in all environmental samples was below the LOQ, although previous studies identified the injector surface as a safety hazard (Ametsbichler et al., 2018; Ndaw et al., 2018).

The results of the present study are based on the analysis of two different biological samples (urine and blood) and environmental samples. Moreover, before the analysis of environmental samples, the recovery yield was evaluated by ICP-MS quantification of the

platinum concentration in water- or Surfanios-impregnated wipes that were used to clean surfaces with a known oxaliplatin concentration. In previous studies, only the extraction (mineralization, liquid extraction) and/or quantification methods were evaluated (Ndaw et al., 2018). A better sensitivity was obtained with water-impregnated wipes. Platinum concentrations of the operating room samples after PIPAC were all below the LOQ. As we assumed a recover yield above 70% from the surface to the test tube, we considered that the operating room was not contaminated after the PIPAC procedure.

Human exposure to platins in intraperitoneal drug delivery is usually carried out through blood and/or urine samples based on the known pharmacokinetic properties of oxaliplatin (Graham et al, 2000; Ceelen and Flessner, 2010; Villa et al, 2015; Ndaw et al, 2018). Our analytical method gave LOD and LOQ for urine and blood samples that are within the previously published ranges. Urinary platinum concentration is commonly used to evaluate contamination by platinum salts because platinum is rapidly cleared from the plasma, and urinary excretion is considered the predominant route of elimination (Graham et al., 2000). As previous studies used 24h urine samples (Konate et al., 2011) or pre-shift and post-shift urine samples (Ndaw et al., 2018), we cannot directly compare our results (1 hour before, 3 hours after, and the morning after the PIPAC procedure). We chose this sampling schedule on the basis of pharmacokinetic data obtained after intravenous injection of oxaliplatin that showed a concentration decreases by 50% at 6h post-injection (Graham et al., 2000). After PIPAC, 25% of urine samples in the EG were positive. However, the urine samples of the anaesthesiologists and of the senior surgeon were positive already at T0. These staff members did not have a 2-week non-exposure period before and between PIPAC procedures. That is not the case for the scrub nurse of the second procedure where urine sample was also positive at T0 without any identified exposure. The other positive samples at T2 were from the surgeon, assistant surgeon, circulating nurse, and scrub nurse implicated in the second PIPAC session. However, these

results (platinum ranging from 10.5 to 367 $ng.L^{-1}$) are in the same range but cannot be directly compared with the maximum concentration of 136 $ng.L^{-1}$ detected in 24h urine collected after PIPAC (Ndaw et al., 2018), or the 1300 $ng.L^{-1}$ in post-shift urine samples from nurses or pharmacy technicians (Turci et al., 2002). Furthermore, no statistical difference was observed for urine samples collected before and after PIPAC and between EG and NEG samples, strongly suggesting that the level of contamination in urine is not significant.

As oxaliplatin binds to plasma proteins (Casini and Reedijk, 2012; Chalret du Rieu et al., 2014; Turci et al., 2002), we analysed also blood samples collected before and after PIPAC. Several methods using mineralization or direct dilution in acidic or alkaline media were previously described (Abduljabbar et al., 2019; Chantada-Vázquez et al., 2019; Gong et al., 2017; Lu et al., 2015). Nevertheless, due to the very small concentrations of platinum ($ng.L^{-1}$) and the small sample volume, these methods could not be used directly. Therefore, we optimized them using oxaliplatin-spiked samples and we chose a direct 10-fold dilution in 0.1% TMAH/0.1% Triton X100 to minimize the matrix effect compared with mineralization in HNO_3 or TMAH alone. Indeed, the combination of TMAH, which improves protein solubilization by cutting protein disulphide bridges, and Triton X-100, which improves cell lysing, protein and fat solubilization, allowed us to efficiently recover platinum from plasma and urine. For all plasma samples, the platinum concentration never exceeded the LOQ, without any significant difference between pre- and pots-PIPAC values and with the NEG. These results indicate the effectiveness of the implemented PIPAC safety protocol.

It would be now important to review all the available evidence concerning PIPAC safety for the involved medical/non-medical staff to define international guidelines. These recommendations could then be considered as the expert opinion to be taken into account by regulatory bodies to define a homogenous safety protocol for PIPAC procedures worldwide.

The limitations of the study include the low number of tested PIPAC procedures (n=2) and the fact that the included staff members have been repeatedly exposed to oxaliplatin. Moreover, the number of samples collected from each participant was limited in time (before, after and the morning after PIPAC). The current findings cannot be extended to ePIPAC that has administration times shorter than 30 minutes (Taibi et al., 2020) because in this case the operating room staff return in the room earlier after the remote administration, and this might modify the risk of exposure.

In conclusion, PIPAC-Ox performed following the French safety protocol does not seem to increase the risk of platinum exposure for the involved medical/non-medical staff. Therefore, this safety protocol could be considered in future occupational policies and consensus statements.

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Larroque et al Figure 1

Figure 1: Sampling areas in the operating room: monitoring screen (1), surgical lamp (2), laparoscopy tower (3), surgical-gas aspiring device console (4), surgical gas aspiration filter (5), and laparoscopic monitor (6).

Larroque et al Figure 2

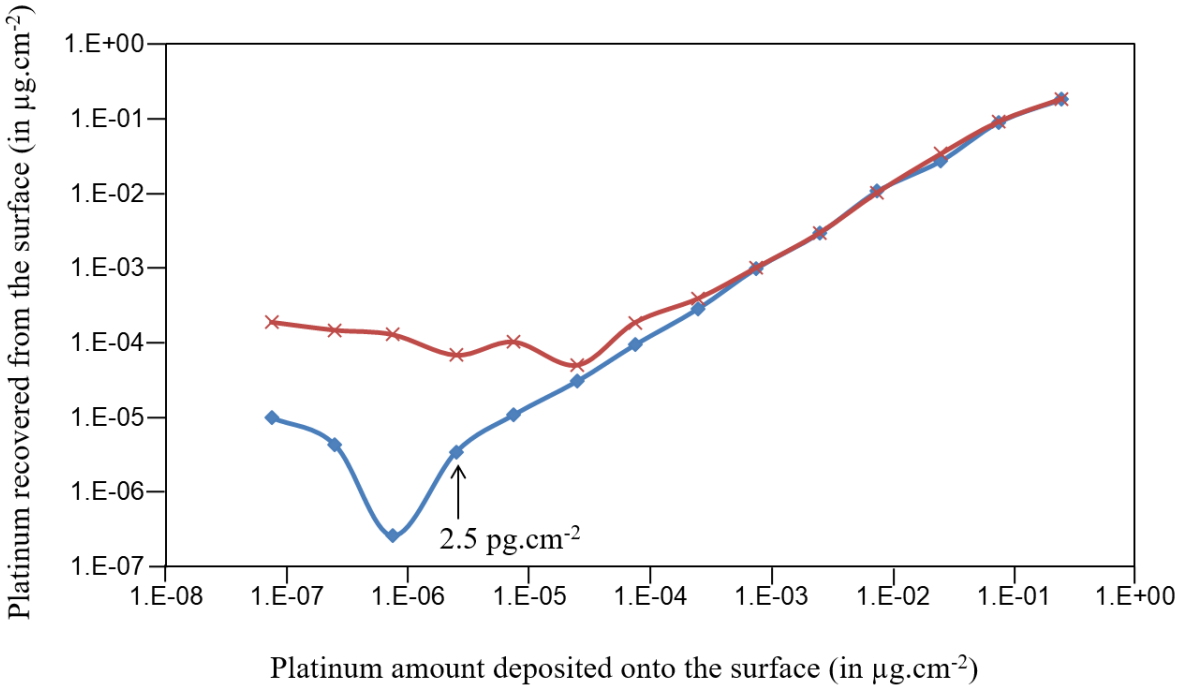

Figure 2: Determination of the platinum recovered from water- (■) or Surfanios- (x) impregnated wipes used to wipe test surfaces contaminated with known platinum concentrations ranging from 100 fg.cm^{-2} to 1 µg.cm^{-2}.

480 Larroque et al Table 1 1
481

	Participant	Pt concentration in urine ($ng.L^{-1}$)			Pt Concentration in plasma ($ng.L^{-1}$)	
		T0	**T1**	**T2**	**T0**	**T1**
Exposed group	1	< LOD	< LOQ	< LOQ	< LOD	< LOQ
	2	< LOQ	< LOQ	< LOQ	< LOD	< LOD
	3	< LOD	< LOD	< LOD	< LOQ	< LOD
	4	10	< LOQ	< LOD	< LOD	< LOD
	5	< LOD	< LOQ	< LOD	< LOD	< LOD
	6	< LOD	< LOD	< LOD	< LOD	< LOD
	7	< LOQ	< LOD		< LOQ	
	8	< LOD	< LOQ	367	< LOD	< LOD
	9	42	< LOD	113	< LOD	< LOD
	10	< LOD	< LOD	13.9	< LOD	< LOQ
	11	< LOD	12.5	< LOD	< LOD	< LOQ
	12	13.8	19.2	< LOQ	< LOD	< LOQ
	13	9.8		49.6	< LOD	< LOQ
Non exposed group	14	< LOQ			< LOD	
	15	< LOD			< LOD	
	16	< LOQ			< LOD	
	17	< LOD			< LOQ	
	18	< LOQ			< LOD	
	19	9.7			< LOD	
	20	11			< LOD	

482
483 **Table 1**. Elemental platinum concentration ($ng.L^{-1}$) in plasma and in urine of participants
484 from the exposed and non-exposed groups. LOD (urine)= 3 $ng.L^{-1}$; LOQ (urine) = 9 $ng.L^{-1}$;
485 LOD (plasma)= 5 $ng.L^{-1}$; LOQ (plasma)= 16 $ng.L^{-1}$. In the Exposed group: participants 1 to 7
486 were involved in the first PIPAC session, and participants 8 to 13 in the second, as follows: 1
487 (senior surgeon), 2 (assistant surgeon), 3 (circulating nurse), 4 (anaesthesiologist), 5 (nurse
488 anaesthetist), 6 (scrub nurse), 7 (cleaner), 8 (assistant surgeon), 9 (senior surgeon), 10
489 (circulating nurse), 11 (nurse anaesthetist), 12 (anaesthesiologist), and 13 (scrub nurse).
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