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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Comparison of Tissue and Blood Concentrations of Oxaliplatin Administrated by Different Modalities of Intraperitoneal Chemotherapy

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ABSTRACT

Background. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new technology for delivering intraperitoneal chemotherapy. It is generally assumed that with PIPAC, the ratio of peritoneal to systemic drug concentration is superior to liquid hyperthermic intraperitoneal chemotherapy (HIPEC). To date, no direct comparative data are available supporting such an assumption.

Materials and Methods. Twelve 65-day-old pigs were randomly separated into three groups of four pigs each, all of which received intraperitoneal chemotherapy using the following administration methods: PIPAC with oxaliplatin 92 mg in 150 ml dextrose 5% (Group 1); PIPAC with electrostatic aerosol precipitation (ePIPAC; Group 2); or laparoscopic HIPEC (L-HIPEC) with oxaliplatin 400 mg in 4 L dextrose 5% at 42 °C (Group 3). Serial blood and peritoneal tissue concentrations of oxaliplatin were determined by spectrometry.

Results. In all three groups, the maximum concentration of oxaliplatin in blood was detected 50–60 min after onset of the chemotherapy experiments, with no significant differences among the three groups ($p = 0.7994$). Blood oxaliplatin concentrations (0–30 min) were significantly higher in the L-HIPEC group compared with the ePIPAC group ($p < 0.05$). No difference was found for the overall systemic oxaliplatin absorption (area under the curve). Overall concentrations in the peritoneum were not different among the three groups ($p = 0.4725$), but were significantly higher in the visceral peritoneum in the PIPAC group ($p = 0.0242$).

Conclusions. Blood and tissue concentrations were comparable between all groups; however, depending on the intraperitoneal area examined and the time points of drug delivery, the concentrations differed significantly between the three groups.

Currently, liquid intraperitoneal chemotherapy (L-IPC) is delivered, in most cases, as intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) immediately after complete macroscopic tumor resection has been achieved. In selected cases, this combined approach has been reported to achieve good results, with improved survival.[1] More recently, laparoscopic HIPEC (L-HIPEC) has been proposed as a palliative tool to deliver intraperitoneal chemotherapy (IPC) to patients suffering from debilitating malignant ascites, or in neoadjuvant therapy settings for patients with synchronous peritoneal metastases (PM).[2] Small case series and phase II trials report that L-HIPEC is well tolerated, efficient to control malignant ascites, can improve quality of life, and can induce objective regression of PM.[2–6]

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Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a newer technology for delivering IPC to patients suffering from end-stage PM. Drugs are injected as aerosolized IPC (A-IPC) into a constant capnoperitoneum. Although never systematically analyzed, based on in vitro and in vivo studies performed in both animals and humans, it is currently assumed that A-IPC has a higher ratio between peritoneal and systemic drug concentrations compared with all modes of L-IPC.[7,8] An electrostatic aerosol precipitation device has recently been developed and used during PIPAC (ePIPAC). This new modality is assumed to enhance aerosol deposition and to improve the efficacy of conventional PIPAC.[9]

The present study was the first quantitative analysis of systemic and local tissue concentration of chemotherapy administered by A-IPC (PIPAC/ePIPAC) in direct comparison with L-IPC (L-HIPEC). In order to compare drug concentrations in both tissue and blood, the study was conducted according to the same strict protocols for PIPAC/ePIPAC and L-HIPEC used in daily clinical practice. For study relevance, it was necessary to use a drug that is delivered for both HIPEC and (e)PIPAC. Oxaliplatin was therefore selected since it has a similar application time for both PIPAC and HIPEC, is the standard drug for PIPAC to treat PM of colorectal origin, and is also widely used for HIPEC.

MATERIALS AND METHODS

Legal Background, Animals, and Anesthesia

The animal study protocol (#2017122310302649.V1–11660) was approved by the local Animal Ethics Committee, Val de Loire, France, and all experiments were performed in accordance with relevant guidelines and regulations. A total of 12 animals (*Sus scrofa domesticus)* weighing from 23 to 26 kg were used. Anesthesia was induced by intramuscular injection of ketamine 20 mg/kg, xylazine 2 mg/kg, and a subcutaneous injection of atropine 0.02 mg/kg, and then completed by endotracheal intubation. Animals were maintained under anesthesia by isoflurane 3%, intravenous sufentanil, and cisatracurium.

Group 1: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

Four animals underwent a standard PIPAC procedure as described elsewhere.[10] Oxaliplatin 92 mg (Pfizer; product number 00363003) diluted with dextrose 5% to a total of 150 ml was delivered. The PIPAC nozzle (Capnopen®; Capnomed GmbH, Villingendorf, Germany) was introduced into the abdominal cavity in a stable perpendicular position (Fig. 1).

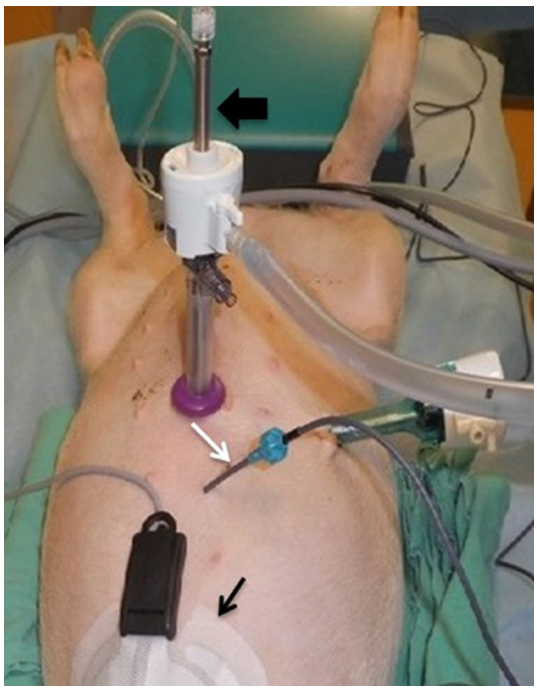

FIG. 1 Operative set-up for (e)PIPAC. The white grounding plate (*black arrow*) was attached to the skin of the inferior ventral thoracic cavity, and the 'Ionwand' electrode (*white arrow*) was placed percutaneously into the abdominal cavity via puncture between the 12-mm trocar with the PIPAC nozzle in situ (*black bold arrow*) and the xiphoid. Conventional PIPAC experiments were performed using a similar operative set-up, but without the application of electro-precipitation. *ePIPAC* electrostatic PIPAC, *PIPAC* pressurized intraperitoneal aerosol chemotherapy

Group 2: Electrostatic Precipitation PIPAC (ePIPAC)

Four pigs underwent ePIPAC experiments. In addition to a standard PIPAC procedure, an aerosol electro-precipitator device (Ultravision™; Alesi Surgical Ltd, Cardiff, UK) was used, as previously reported.[9] At the end of every PIPAC/ePIPAC procedure, the capnoperitoneum was evacuated via a closed air waste suction system (Fig. 1).

Group 3: Laparoscopic Hyperthermic Intraperitoneal Chemotherapy (L-HIPEC)

Four pigs underwent L-HIPEC as previously reported by Ferron et al.,[11] with minor technical modifications (Fig. 2). The abdomen was filled with dextrose 5% and heated to 42 °C at a steady flow rate of 1000 ml/min (Belmont®; Hyperthermia Pump, Billerica, MA, USA). After a steady intra-abdominal temperature of 42 °C had been reached, oxaliplatin 400 mg (Pfizer; product number 00363003) was added so that a total perfusate volume of 4 L was obtained. The HIPEC procedure was then continued for another 30 min. At the end of the L-HIPEC procedure, the perfusate was evacuated and the abdominal cavity rinsed with

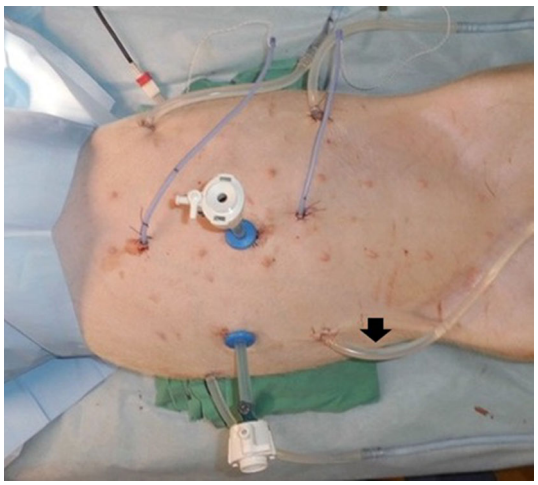

FIG. 2 Operative set-up for laparoscopic HIPEC. One 5-mm trocar was placed at the umbilicus, and the second trocar was inserted in the left lateral hemi-abdomen. Two thermal probes (*blue*) were used, and one inflow (*black bold arrow*) and three outflow drainage tubes. *HIPEC* hyperthermic intraperitoneal chemotherapy

4 L of Ringer's lactate. Determining the platinum concentrations from the solutions at the beginning and end of the chemotherapy exposure allowed assessment of an actual delivered dose of oxaliplatin.

Blood, Peritoneal Liquid, and Tissue Samples

All samples were taken as triplicates. For each animal, central venous blood samples (10 ml) were collected immediately before the application of chemotherapy and at 10, 20, 30, 40, 50, and 60 min after the beginning of the chemotherapy procedure. In the group of animals that underwent L-HIPEC, four samples of peritoneal fluid (10 ml) were collected in the chemotherapy perfusate circuit immediately before starting the procedure and then at 10, 20 and 30 min. All samples were stored immediately at − 20 °C.

At the end of the procedure, the animals underwent median laparotomy, and standardized tissue samples (approximately 5.0 g) from the parietal peritoneum (A = central; B = right upper; C = epigastric; D = left upper; E = left flank; F = left lower; G = pelvis; H = right lower; I = right flank) and visceral peritoneum (J = upper jejunum; K = lower jejunum; L = upper ileum; M = lower ileum) were obtained as triplicates according to a previously described peritoneal map inspired by Sugarbaker's Peritoneal Carcinomatosis Index (PCI) [12] (Fig. 3). Samples of the small bowel always comprised a full-depth tissue fragment. The tissue samples were rinsed rapidly once with ultrapure distilled water and then immediately frozen at − 20 °C. After completing tissue sampling (60 min), to avoid hemodynamic disturbance due to intra-abdominal bleeding, the animals were immediately euthanized by intravenous injection of pentobarbital. The blood pharmacokinetics were therefore limited to the first hour of duration.

Determination of Oxaliplatin with Inductively Coupled Plasma-Mass Spectrometry

All samples were analyzed by an independent pharmaceutical laboratory (Antellis, Toulouse, France) according to the International Organization for Standardization (ISO)/CEI 17025:2005) and Principles of Good Laboratory Practice (GLP) standards. Weighted blood and tissue samples (AL204 Analytical Balance; Mettler Toledo, Columbus, OH, USA) were digested with nitric acid (HNO_3), heated for 12 h at 90 °C, and diluted with hydrochloric acid (HCl) to a total volume of 25 and 50 ml, respectively. Perfusate samples and intra-abdominal liquid samples harvested after the (e)PIPAC procedures were also weighted and diluted with HCl to a total volume of 50 ml. Additional dilution was performed for some samples that were out of calibration. The platinum concentration was measured using inductively coupled plasma-mass spectrometry (Thermo Fisher Scientific, Massachusetts, MA, USA). A total of six analytical runs were performed for each sample. The results were corrected according to the dilution and the sample weight, and a concentration in micrograms per gram was obtained. Since platinum is approximately half the molecular mass of oxaliplatin, platinum concentrations must be multiplied by 2.03 to obtain oxaliplatin concentrations.

Statistical Analysis

Concentrations of oxaliplatin (μg/g), temperature (°C), and time (minutes) are presented as mean ± standard deviation in the text and tables. Nonparametric tests were used to analyze the concentrations of oxaliplatin. A Kruskal–Wallis test was performed to compare the distribution and medians of the three groups, and, when different, the Mann–Whitney test was used for 2 × 2 comparisons between groups. Student's *t* test was employed to examine the statistical significance of the blood concentration of oxaliplatin. Decimals were always conserved for the calculations, but only two decimals are shown for oxaliplatin concentrations. For all tests, two-tailed *p*-values inferior to 0.05 were considered significant. Data collection and statistical calculations were performed using GraphPad software (GraphPad Software Inc., San Deigo, CA, USA).

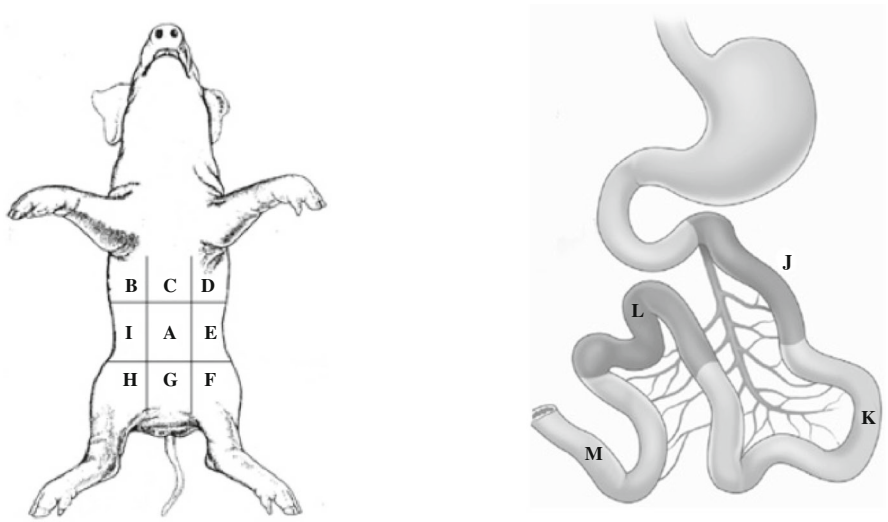

FIG. 3 Sketch of areas of peritoneal tissue sampling according to Jacquet and Sugarbaker[12] A–I = parietal peritoneum (A = central; B = right upper; C = epigastric; D = left upper; E = left flank; F = left lower; G = pelvis; H = right lower; I = right flank), and J–M = visceral peritoneum (J = upper jejunum; K = lower jejunum; L = upper ileum; M = lower ileum)

A – I = parietal peritoneum: A= central; B = right upper; C = epigastric; D = left upper; E = left flank; F = left lower; G = pelvis; H = right lower; I = right flank; J – M = visceral peritoneum: J = upper jejunum; K = lower jejunum; L = upper ileum; M = lower ileum

RESULTS

Overall and Blood Absorption of Oxaliplatin

At the end of the L-HIPEC procedures (30 min), a mean of 104.6 ± 11 mg of oxaliplatin was delivered; this result was obtained by calculation of the absorption of oxaliplatin. After 30 min, the mean of oxaliplatin in the intraperitoneal liquid was 74 ± 11 mg/l. Therefore, the absorption was 26% (100 mg/l oxaliplatin [oxaliplatin added at the initial intra-abdominal perfusate] − 74 mg [oxaliplatin in the intraperitoneal liquid at the end of the procedure]/100 mg). Hence, total oxaliplatin absorbed corresponded to 26% of 400 mg (104 mg). Compared with 92 mg in the PIPAC/ePIPAC groups, no statistically significant difference was observed. The maximum blood concentration in all three groups occurred 50–60 min after the onset of chemotherapy (Group 1, PIPAC: 1.60 ± 0.14 µg/g; Group 2, ePIPAC: 1.30 ± 0.16 µg/g; Group 3, L-HIPEC: 1.20 ± 0.18 µg/g). No overall significant differences were observed between the three groups (p = 0.7994). The mean area under the curve (AUC) of oxaliplatin blood absorption (0–60 min) between the three groups (Group 1, PIPAC: 38.30 ± 5.40; Group 2, ePIPAC: 32.80 ± 2.31; and Group 3, L-HIPEC: 50.80 ± 5.40) did not show a statistically significant difference (L-HIPEC vs. PIPAC: p = 0.5653; L-HIPEC vs. ePIPAC: p = 0.5653; ePIPAC vs. PIPAC: p = 0.7983).

However, significant differences in absorption kinetics were found between Group 3 (L-HIPEC) and the remaining two groups. Indeed, the PIPAC and ePIPAC groups exhibited a very reproducible biphasic pattern with a very discrete increase in blood concentration during the first 30 min, and then with rapid progression until 50–60 min. The first phase with low blood absorption was always strictly concomitant from the presence of the capnoperitoneum. Mean systemic oxaliplatin blood concentrations and overall absorption (AUC) for all three groups are summarized in Fig. 4.

Tissue Concentrations of Oxaliplatin

Between the three groups, the global Kruskal–Wallis test did not show significant differences (p = 0.4725). However, regardless of the different techniques used to

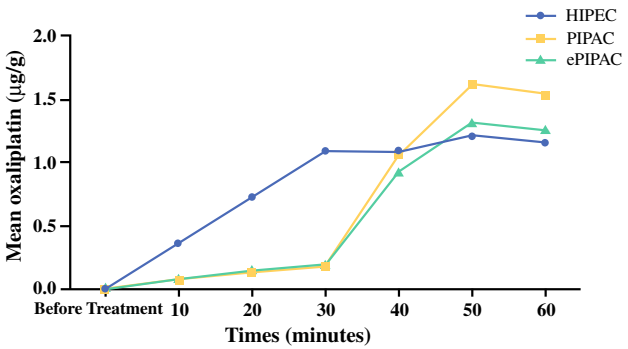

FIG. 4 Systemic oxaliplatin absorption. Mean blood concentrations of oxaliplatin, as well as AUC, are presented for each group. Oxaliplatin absorption during the first 30 min of the experiments was significantly higher in the two A-IPC groups compared with the L-HIPEC group. Nevertheless, no statistically significant difference was found for the AUC between all three groups (0–60 min). *AUC* area under the curve, *A-IPC* aerosolized intraperitoneal chemotherapy, *L-HIPEC* laparoscopic hyperthermic intraperitoneal chemotherapy, *PIPAC* pressurized intraperitoneal aerosol chemotherapy, *ePIPAC* electrostatic PIPAC, *HIPEC* hyperthermic intraperitoneal chemotherapy

deliver IPC, the overall oxaliplatin concentrations found in the parietal peritoneum were significantly higher compared with those found in the visceral peritoneum (25.80 ± 2.14 vs. 2.20 ± 0.26 μg/g; $p = 0.0001$).

In the parietal peritoneum, no significant difference was observed between the three groups (Group 1, PIPAC: 37.16 ± 5.80 μg/g; Group 2, ePIPAC: 32.50 ± 8–60 μg/g; Group 3, L-HIPEC: 38.28 ± 3.80 μg/g; $p = 0.3452$). However, the overall tissue concentrations in the visceral peritoneum in the PIPAC group (3.22 ± 0.64 μg/g) was significantly higher compared with those of the other two groups (Group 2, ePIPAC: 1.14 ± 0.30 μg/g; Group 3, L-HIPEC: 2.18 ± 0.20 μg/g; $p = 0.0242$). The following differences were observed: in tissue sampling area C (Group 1, PIPAC: 12.80 ± 3.80 μg/g; Group 2, ePIPAC: 8.8 ± 4.4 μg/g; Group 3, L-HIPEC: 34.6 ± 4.4 μg/g), significantly higher values were observed in the L-HIPEC group versus the PIPAC group ($p = 0.0286$), and in the L-HIPEC group versus the ePIPAC group ($p = 0.0286$). Additionally, in tissue areas H (Group 1, PIPAC: 41.22 ± 10.0 μg/g; Group 2, ePIPAC: 15.6 ± 1.8 μg/g; Group 3, L-HIPEC: 32.6 ± 4.0 μg/g), I (Group 1, PIPAC: 71.0 ± 8.6 μg/g; Group 2, ePIPAC: 16.10 ± 9.4 μg/g; Group 3, L-HIPEC: 34.50 ± 9.2 μg/g), L (Group 1, PIPAC: 3.56 ± 0.4 μg/g; Group 2, ePIPAC: 0.70 ± 0.70 μg/g; Group 3, L-HIPEC: 2.4 ± 0.24 μg/g), and M (Group 1, PIPAC: 3.80 ± 0.74 μg/g; Group 2, ePIPAC: 0.84 ± 0.40 μg/g; Group 3, L-HIPEC: 2.12 ± 0.38 μg/g), significantly lower concentrations were found in the ePIPAC group versus the PIPAC group ($p < 0.05$). In tissue area H, there was a significant difference between the L-HIPEC and ePIPAC groups ($p = 0.0286$). Results from the local tissue concentrations, side-by-side with the 2 × 2 Mann–Whitney *U* test, are presented in a synthetic manner in Fig. 5.

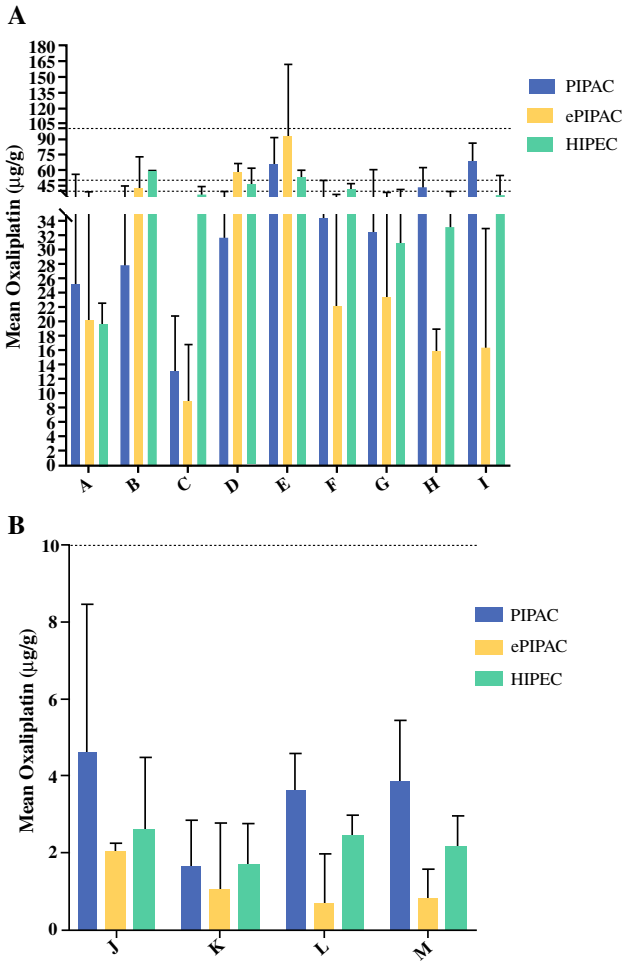

FIG. 5 Oxaliplatin concentrations in the parietal and visceral peritoneum. **a** A–I = the corresponding area from which the tissue samples were taken from the parietal peritoneum (A = central; B = right upper; C = epigastric; D = left upper; E = left flank; F = left lower; G = pelvis; H = right lower; I = right flank). **b** J–M = corresponding localization of tissue samples from the visceral peritoneum (*J* = upper jejunum; *K* = lower jejunum; *L* = upper ileum; *M* = lower ileum). *HIPEC* hyperthermic intraperitoneal chemotherapy, *PIPAC* pressurized intraperitoneal aerosol chemotherapy, *ePIPAC* electrostatic PIPAC

DISCUSSION

Suboptimal spatial drug distribution patterns, as well as low drug penetration into tumor tissue, remain technically and clinically unsolved limitations of all L-IPC regimens.[13,14] PIPAC is a new technology that aims to optimize the treatment of PM patients by overcoming the above-outlined limitations of L-IPC. Such theoretical assumptions are supported by both in vitro and in vivo animal experiments that suggest improved local bioavailability, as well as a better spatial drug distribution pattern, than obtained by L-IPC.[7,8,15,16] Compared with historic HIPEC data, deeper in-tissue penetration, higher tissue concentrations, and lower systemic drug absorption were observed. The systemic AUC of 'low-dose' doxorubicin after PIPAC is assumed to be approximately 1% that of intravenous chemotherapy, and 5% for HIPEC.[8] More recently, it has been hypothesized that the additional use of an electrostatic precipitation device may further enhance the pharmacologic properties of PIPAC as so-called electrostatic precipitation PIPAC (ePIPAC). In vivo animal experiments with tracer substances assumed that ePIPAC furthermore increases the efficiency of tissue drug uptake compared with conventional PIPAC.[9] Currently, PIPAC therapy for patients suffering from end-stage PM of colorectal origin is delivered with oxaliplatin at a dose that corresponds to approximately 20% that of HIPEC.[17]

In the present study, in contrast to general expectations, there was neither an overall difference of the maximum systemic blood concentrations nor the overall absorption of oxaliplatin (AUC) between the three groups. On the

contrary, although not statistically significant, the highest systemic oxaliplatin concentrations were measured in the two A-IPC groups; however, the time course of systemic oxaliplatin absorption showed significant differences between the A-IPC and L-HIPEC experiments. While systemic absorption remained minimal during application of the 'therapeutic capnoperitoneum' in both A-IPC groups, systemic absorption in the L-HIPEC group showed a linearly and significant increase from the beginning of L-HIPEC administration. Nevertheless, with evacuation of the 'therapeutic capnoperitoneum', there was a steep, parallel, and relevant increase in oxaliplatin absorption in both A-IPC groups. Although speculative, the delayed oxaliplatin absorption pattern during A-IPC is very likely to be related to increased intra-abdominal pressure. Increased intra-abdominal pressure by 5 mmHg (from 10 to 15 mmHg) decreases the blood flow to the liver and the peritoneum by 39% and 60%, respectively.[18] Blanco et al. previously proposed that an increase in intra-abdominal pressure during the application of PIPAC is advantageous over other delivery routes because the decreased splanchnic blood flow leads to higher tissue bioavailability and lower systemic plasma concentration.[19] Our current findings support such an assumption that not only the increased intra-abdominal pressure of the capnoperitoneum but also the duration of the capnoperitoneum might be an important parameter to delay systemic drug absorption. This effect could favor drug delivery to peritoneal tissue, including peritoneal tumor, to potentially increase its antitumoral activity.

Compared with L-HIPEC and ePIPAC, significantly higher tissue concentrations in the visceral peritoneum were found in the PIPAC group. This finding is attributed to the behavior of the particles delivered by the PIPAC spraying device. Indeed, state-of-the-art technical and granulometric analysis of this device, as well as scintigraphy analysis of technetium delivered in a post mortem PIPAC animal model, uniformly revealed that more than 98 vol% of the delivered aerosol droplets directly impact with the underlying peritoneum of the small bowel.[20,21] Consequently, locoregional high-tissue concentrations in the peritoneum of the small bowel can occur, but enhanced clinical efficacy of that effect remains to be confirmed.[17,19]

The highest tissue concentrations observed in this study were found in the ePIPAC group and were observed in one tissue sampling area of the parietal peritoneum in the left upper abdominal quadrant facing the electrode location. This finding does not confirm previous data obtained from in vivo animal experiments with ePIPAC delivering methylene blue staining solution and another tracer molecule.[9] An homogeneous and more intensive peritoneal methylene blue staining pattern, compared with PIPAC, was observed. Moreover, an increased uptake of a tracer substance into the peritoneal tissue was also found.[9] To interpret our findings, some details regarding aerosol electro-precipitation technology used for ePIPAC must be considered. Only 2 vol% of the PIPAC aerosol had a particle size to remain airborne in the capnoperitoneum during PIPAC application and is therefore potentially amenable for electro-precipitation.[20,21] Furthermore, the electrode tip of the electro-precipitation device creates a concentric electrical field around the point charge at the tip of the electrode inside the abdominal cavity. According to the Gaussian law, the field strength drops by one-quarter by doubling the distance from the point charge. Thus, aerosol deposition mainly occurs on the peritoneum, which is located close to the electrode tip. Based on such basic physical principles, as well as previous animal experiments, aerosol deposition by electro-precipitation in the abdominal cavity is not uniform.[22] Taken together, high tissue concentrations of oxaliplatin found in the parietal peritoneum of the upper abdominal quadrant are probably directly linked to the position of the electrode.

However, we are aware that our present study also has some limitations. First, the results obtained in our animal model cannot be extrapolated one-to-one to human patients, and, second, systemic absorption was only monitored for 60 min.

CONCLUSIONS

Irrespective of the delivery technique used, the overall oxaliplatin concentrations in the visceral and parietal peritoneum showed no significant differences among the three groups. Similar findings were also observed for the overall and maximum oxaliplatin blood absorption.

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AUTHOR CONTRIBUTIONS UG-P: Study design, animal experiments, data acquisition, data interpretation, manuscript drafting, and critical revision for important intellectual content of the manuscript. PB, ALP: Study design, study protocol, and critical revision for important intellectual content of the manuscript. SR, ALP, SL: Critical revision for important intellectual content of the manuscript. TAF: Animal experiments and data acquisition. NT: Data analysis and interpretation. CD: Critical revision for important intellectual content of the manuscript. ES: Critical revision for important intellectual content of the manuscript. MO: Study design, study protocol, animal experiments, data acquisition, data interpretation, manuscript drafting, and critical revision for important intellectual content of the manuscript.

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DISCLOSURE Urs Giger-Pabst, Petru Bucur, Sébastien Roger, Thomas Albert Falkenstein, Nicolas Tabchouri, Alain Le Pape, Stéphanie Lerondel, Cédric Demtröder, Ephrem Salamé, and Mehdi Ouaissi have no conflicts of interest to declare.

AVAILABILITY OF DATA AND MATERIALS The dataset of the current study is available from the corresponding author upon reasonable request.

ETHICAL APPROVAL The study protocol was approved by the local Animal Ethics Committee, Val de Loire, France.

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