

Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution

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Purpose: This article reports the pharmacokinetics (PK) of heated intra-operative intraperitoneal oxaliplatin and its tolerance profile. Oxaliplatin has demonstrated significant activity in advanced colorectal cancer, and this is the first publication concerning its intraperitoneal administration.

Methods: Twenty consecutive patients with peritoneal carcinomatosis (PC) of either gastrointestinal or uniquely peritoneal origin underwent complete cytoreductive surgery followed by intra-operative intraperitoneal chemo-hyperthermia (IPCH) with increasing doses of oxaliplatin. We performed IPCH using an open procedure (skin pulled upwards), at an intraperitoneal temperature of 42–44 °C, with 2 l/m² of 5% dextrose instillate in a closed circuit. The flow-rate was 2 l/min for 30 min. Patients received intravenous leucovorin (20 mg/m²) and 5-fluorouracil (400 mg/m²) just before the IPCH to maximize the effect of oxaliplatin. We treated at least three patients at each of the six intraperitoneal oxaliplatin dose levels (from 260 to 460 mg/m²) before progressing to the next. We analysed intraperitoneal, plasma and tissue samples with atomic absorption spectrophotometry.

Results: The mean duration of the entire procedure was 8.4 ± 2.7 h. Half the oxaliplatin dose was absorbed in 30 min at all dose levels. Area under the curve (AUC) and maximal plasma concentration (C_{max}) increased with dose. At the highest dose level (460 mg/m²), peritoneal oxaliplatin concentration was 25-fold that in plasma. AUCs following intraperitoneal administration were consistently inferior to historical control AUCs after intravenous oxaliplatin (130 mg/m²). Intratumoral oxaliplatin penetration was high, similar to absorption at the peritoneal surface and 17.8-fold higher than that in non-bathed tissues. Increasing instillate volume to 2.5 l/m² instead of 2 l/m² dramatically decreased oxaliplatin concentration and absorption. There were no deaths, nor severe haematological, renal or neurological toxicity, but we observed two fistulas and three deep abscesses.

Conclusions: Heated intraperitoneal chemotherapy gives high peritoneal and tumour oxaliplatin concentrations with limited systemic absorption. We recommend an oxaliplatin dose of 460 mg/m² in 2 l/m² of 5% dextrose for intraperitoneal chemo-hyperthermia, at a temperature of 42–44 °C over 30 min. We may be able to improve these results by increasing the intraperitoneal perfusion duration or by modifying the instillate composition.

Key words: colorectal cancer, cytoreductive surgery, hyperthermia, intraperitoneal chemotherapy, oxaliplatin, peritoneal carcinomatosis

Introduction

Cisplatin is one of the antineoplastic agents most frequently used in intraperitoneal chemo-hyperthermia (IPCH) [1–5].

The rationale for its use is its potentiation at high temperatures and its ability to act at any stage of malignant cell replication [1, 6]. However, if this drug has proven activity in the treatment of intraperitoneal malignancies such as gastric and ovarian carcinomas [7–9], no such efficacy has been demonstrated in colorectal or appendix adenocarcinomas. Oxaliplatin is a third-generation platinum complex with a diamino cyclohexane (DACH) carrier group and an oxalate leaving ligand, with no

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renal or hepatic toxicity but with cumulative sensory neuropathy as its dose-limiting toxicity. It gives high response rates and improved survival parameters in metastatic colorectal cancer patients. The objective response rate was 24% as a single agent in second line intravenous chemotherapy [10], and around 50% in first line combined with 5-fluorouracil (5-FU) and folinic acid at a dose intensity of 40–50 mg/m²/week [11, 12].

A new therapeutic concept [13] has already led to definitive cure of some cases of peritoneal carcinomatosis (PC) [7, 14, 15]. This concept is to treat macroscopic PC with complete cytoreductive surgery and residual microscopic PC with IPCH. Complete cytoreductive surgery is necessary because experimental studies show that drug penetration is limited to a few cell layers under the surface [16]. Intraperitoneal chemotherapy must be immediate, avoiding trapping residual tumour cells in the post-operative intraperitoneal fibrin adhesions [17, 18]. IPCH leads to high local concentrations of antineoplastic agents [1, 2] and their cytotoxicity is improved by hyperthermia [1, 2], that of oxaliplatin increasing by 180% [19]. Finally, IPCH proved to be superior to intraperitoneal chemotherapy alone and to intraperitoneal hyperthermia alone for curative treatment of PC in a randomised study in rats [20]. The same conclusion was observed in a randomised study aimed at preventing peritoneal recurrences from gastric cancer in humans [21].

Theoretically, oxaliplatin should be a more interesting agent for IPCH in colorectal carcinomatosis than the currently used drugs, mainly mitomycin [1–3, 5–7], which has a limited efficacy on such tumours, and 5-fluorouracil, which is a long-acting drug not potentiated by hyperthermia [22].

In this article we report the results of a phase I clinical study of IPCH with oxaliplatin following complete cytoreductive surgery for PC.

Materials and methods

Patient eligibility

From December 1998 to March 2000, we included 20 patients with pre-operatively identified PC in this prospective phase I study. The protocol was reviewed and approved both by our institution's clinical trial review board and by an independent ethics committee. All patients gave their written informed consent for participation in the study and were not amenable to standard treatment or other ongoing trials.

There were nine men and 11 women, of mean age 44.5 ± 9.1 years. Origin of primary tumour was colorectal ($n = 6$), appendix pseudomyxoma ($n = 7$), malignant mesothelioma ($n = 4$) and other ($n = 3$: stomach, ovary, uterus). Five of them had associated extraperitoneal lesions: liver metastases ($n = 2$) and lymph nodes ($n = 3$), which were resected during the same procedure. In this phase I pharmacokinetic study, patients with extraperitoneal sites could be included provided disease was completely resectable.

Surgical procedures

At laparotomy, we confirmed macroscopic PC by frozen section and scored the extent of PC according to Sugarbaker's peritoneal index [3].

Macroscopically detectable disease had to be completely resected before including the patient in the trial. Such surgery resulted in an R0–R1 resection. If, at the beginning of the procedure, we considered PC to be incompletely resectable, we immediately abandoned the operation. Resection of PC obeyed principles described elsewhere [23]. Intestinal anastomoses were delayed until after IPCH in order to treat the bowel margins. There were no temporary stomas. During each procedure we chose one 5 mm-sized tumour nodule (or two or three nodules of 2–3 mm), marked it and left it in place during IPCH. We then resected it after IPCH to analyse intratumoral oxaliplatin penetration. Patients were informed of this procedure.

Intraperitoneal chemo-hyperthermia

We first checked that oxaliplatin was stable *in vitro* in 5% dextrose solution at 46°C during 4 h (stability testing: gas chromatography). We performed IPCH with a continuous closed circuit using four 36-French drains (two inlet and two outlet) connected to two pumps. We used one heating unit and two heat exchangers to eliminate a Y connector that could reduce flow rates and heat homogeneity [5]. We used an open abdominal cavity procedure with the skin pulled upwards, after demonstrating that this technique was the only one that allowed temperature homogeneity and complete spatial diffusion of the peritoneal instillate in the whole peritoneal cavity [5]. Flow rate was 1 l/min for each pump. Four thermal probes inside the peritoneal cavity gave continuous temperature feedback, and we monitored the whole process and saved the data to a computer. The intra-abdominal temperature was maintained between 42 and 44°C during IPCH (this is the most powerful and tolerable temperature). Perfusion duration was exactly 30 min from the time when optimal temperature (42–44°C) was reached. Usually, 8–10 min were necessary to reach high homogeneous temperature, leading to a total peritoneal infusion duration of close to 40 min. Afterwards, we completely evacuated the infusion. We delivered the total oxaliplatin dose as a bolus mixed with 5% dextrose solution at the beginning of the procedure. The total amount of peritoneal liquid used was based, as for oxaliplatin, on the body surface area: 2 l/m² (the dimension of the abdominal cavity varying with size and weight). One hour before IPCH we delivered systemic intravenous leucovorin 20 mg/m² and 5-FU 400 mg/m² because 5-FU potentiates the action of oxaliplatin [11]. However, as 5-FU cannot be mixed with oxaliplatin in the peritoneal cavity due to pH incompatibility, it was delivered intravenously. Following this systemic perfusion, tumour and healthy tissue were soaked with 5-FU before the beginning of the IPCH. A low dose of 400 mg/m² was chosen to avoid intensifying the aggressiveness of combined complete cytoreductive surgery and IPCH.

Experimental design

The first dose level was 260 mg/m², twice the 3-weekly intravenous dosage. Dose escalation was in 50 mg/m² steps up to a maximum of 460 mg/m². Before moving to the next dose level, we had to treat at least three patients at each level without them presenting any severe chemotherapy-related toxicity or unexplained post-operative complication. One aim of the pharmacokinetic study was to compare ultrafiltrable platinum levels and AUCs to historical intravenous controls to eliminate the possibility of severe systemic toxicity due to the administration of such high doses. Should one of these complications occur, two more patients had to be treated at the same dose level without incident before escalating to the next step, and then only after a multidisciplinary committee approved its ethical legitimacy. Since one postoperative gastric fistula occurred in one patient at the first dose level, five patients received 260 mg/m². Only three patients were treated at each subsequent dose level (310, 360, 410 and

460 mg/m²), because no serious complications occurred. At 410 mg/m² after protocol amendment, we treated three patients with our standard instillate volume (2 l/m²) and three with 2.5 l/m² of instillate, to evaluate the effect of dilution on pharmacokinetics. Thus we included a total of 20 patients in this study.

Oxaliplatin assay by flameless atomic absorption spectrophotometry

Plasma sample preparation. We collected fourteen 5 ml heparinized blood samples from each patient: before IPCH, when IPCH began, when IPCH reached 42°C, then every 10 min during the procedure. Samples were then collected at 15 and 30 min, 1, 2, 6, 12 and 24 h after IPCH. Each sample was immediately centrifuged at +4°C, 1500 g to separate the plasma. An aliquot of plasma was saved and stored at -20°C for total platinum determination. Another aliquot was ultrafiltered by centrifugation through an Ultrafree Millipore membrane (cut-off 5000 Da) for ultrafilterable platinum determination. The ultrafiltrate was stored at -20°C until analysis.

Peritoneal fluid sample preparation. We collected five 5 ml peritoneal samples from each patient: at the start of the procedure (37 °C), at 42°C and then every 10 min. These were immediately centrifuged at 1500 g and frozen at -20°C.

Tissue sample preparation. We studied three types of solid tissue for each patient: the 5 mm-sized tumour nodules, a 5 cm diameter piece of normal peritoneal tissue treated with IPCH and one piece of parietal muscle, which was not in contact with IPCH. We changed gloves and surgical instruments before resecting the muscle sample.

Platinum determination. We performed platinum assay using flameless atomic absorption spectrophotometry at 265.9 nm with a Perkin Elmer AA300 spectrophotometer equipped with an HGA 800 furnace, an AS-72 autosampler and its AA Winlab software. We used Pyrocoated graphite tubes of the same brand. Platinum levels were quantitated after preparing calibration curves with atomic platinum. Solid tissue measurements were performed on desiccated tissue, reflecting the actual intracellular drug concentration. Each tissue sample was desiccated to reach constant weight, digested in 65% nitric acid (90–95°C for 96 h) and evaporated to dryness. The solid residue was dissolved in 1 ml of a mixture of Triton X100 (0.1%) and nitric acid (0.2%).

The four types of liquid samples assayed were spiked with a set volume of matrix modifier. Appropriate dilutions were programmed in a run including calibration and quality control samples. Results are expressed as platinum concentration in micrograms per millilitre (µg/ml) for liquid samples or in nanograms per milligram (ng/mg) of dry tissue.

Pharmacokinetics. We used Micropharm® software to analyse PK results. Because IPCH is not a standard route of administration, no modelling was available. We used the trapezoid rule to calculate the area under the curve (AUC) for concentration versus time values. We compared plasma platinum levels with administered oxaliplatin doses rather than with the quantity of oxaliplatin absorbed, since the principal concern was to remain at safe systemic levels relative to the total i.p. dose given, irrespective of how much drug was absorbed.

Results

Intra-operative parameters

Mean duration of surgery including IPCH was 8.4 ± 2.7 h, mean blood loss 1138 ± 930 ml (range 700–3000) and mean number of intestinal anastomoses was 1.5 ± 1.1 per patient (range 0–4). Mean peritoneal index (reflecting the extent of PC) was 19.6 ± 2.2 (median, 21; range 4–31). In all cases, we performed complete macroscopic resection of PC. Intraperitoneal temperature was always maintained between 42 and 44°C for exactly 30 min. We did not abandon any procedures prematurely.

Postoperative toxicity

There was no hospital mortality. Only two intestinal fistulas (10%) occurred during the postoperative course at the first and last dose levels. In the first group, since the cause of the fistula was not clear, we included two additional patients. Other complications occurred in eight patients at all dose levels: three abscesses drained percutaneously, three pneumonias, three urinary tract infections and two central venous catheter infections. These effects were not unusual for the post-operative period in such patients. There was no renal failure and no neutropenia. However, as with our previous studies using hyperthermia, all patients presented a transient biological renal dysfunction with phosphoruria and glucosuria. There was no neurotoxicity. Mean hospital stay was 24.8 ± 15 days (median 21; range 11–71). The longest hospital stay was for the patient with the gastric fistula.

Pharmacokinetics

Time course of oxaliplatin in the peritoneal perfusate. Figure 1 shows a rapid, constant and exponential decrease of platinum concentration in the peritoneal perfusion during the procedure. Half of the drug was absorbed during the 40 min of the procedure.

Time course of oxaliplatin in the peripheral blood. We observed peak plasma concentration of platinum 30 min after starting IPCH (Figure 2). Subsequently platinum concentra-

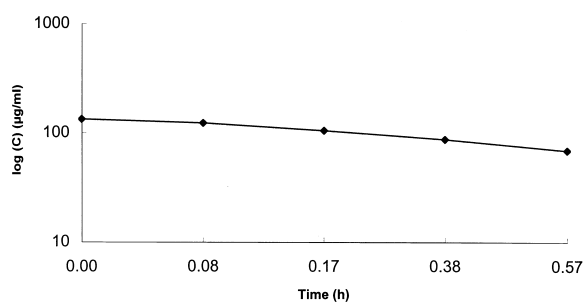


Figure 1. Decrease of ultrafiltered platinum concentrations in heated peritoneal instillate.

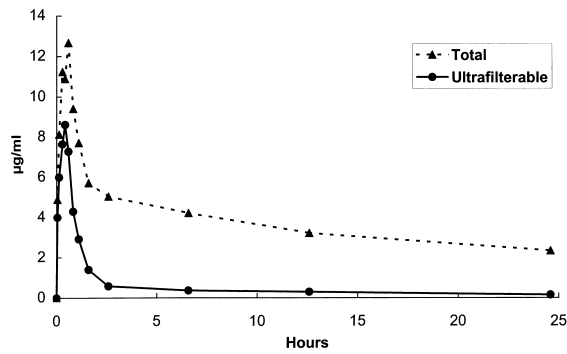


Figure 2. Oxaliplatin pharmacokinetics in plasma after heated intraperitoneal chemotherapy. Oxaliplatin dose: 460 mg/m^2 in 2 l/m^2 of 5% dextrose.

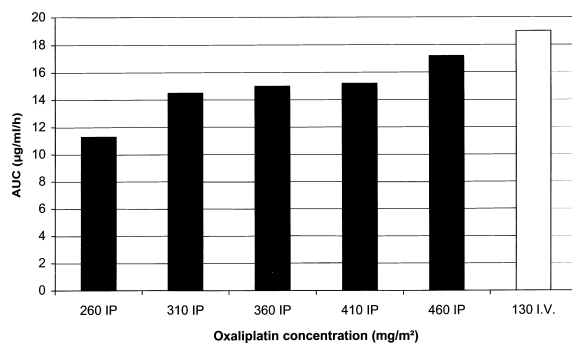


Figure 3. Plasma AUC variations of ultrafiltered platinum versus peritoneal concentration of heated oxaliplatin.

tion dropped very rapidly, resulting in a limited systemic AUC.

C_{max} was 25-fold higher in the peritoneal instillate than in plasma at the 460 mg/m^2 dose level (330 and 13.2 µg/ml , respectively).

Effect of dose escalation

The maximal plasma concentration (C_{max}) and AUC increased progressively at each step (Figure 3), suggesting a dose-related effect. At the maximal dose of 460 mg/m^2 , maximal peritoneal concentration and maximal plasma AUC were obtained with no deleterious effects. In addition, mean plasma AUC of ultrafiltered platinum ($14.8 \pm 3.8 \text{ µg/ml/h}$) were very close to that obtained with systemic intravenous oxaliplatin over 2 h at 130 mg/m^2 ($11.9 \pm 4.60 \text{ µg/ml/h}$) [24].

Tissue concentration

Ultrafiltrable platinum concentrations in solid tissues (tumour, peritoneum in contact with the drug and distant muscle) are reported in Table 1. Concentrations were higher in bathed tissue than in non-bathed tissues. Concentrations were similar in thin tumour tissue and in peritoneum. The drug concentra-

Table 1. Oxaliplatin concentration in tissues, after intraperitoneal chemo-hyperthermia

i.p. level (mg/m^2)	Oxaliplatin (ng/mg dry tissue)		
	Tumour nodule(s)	Peritoneum	Muscle ^a
260	228	230	29
310	248	273	31
360	327	296	20
410	323	287	21
460	339	392	19

^aMuscle was not in direct contact with intraperitoneal chemo-hyperthermia.

i.p., intraperitoneal.

tion in tumour tissue increased with increasing drug dose in the instillate. At the last dose level, it was 17.8-fold higher in bathed tissue than in non-bathed tissue.

Effect of perfusate volume on concentration and pharmacokinetics

In patients treated with oxaliplatin 410 mg/m^2 , three had our standard instillate volume (2 l/m^2) and three had a greater instillate volume (2.5 l/m^2). Pharmacokinetic results differed dramatically with the total volume of the instillate. Platinum intraperitoneal C_{max} decreased by 20% in the 2.5 l/m^2 group compared with the 2 l/m^2 group. Therefore, when we used 410 mg/m^2 oxaliplatin in 2.5 l/m^2 , C_{max} and AUC resembled those observed with 310 mg/m^2 oxaliplatin in 2 l/m^2 , indicating that volume and relative concentration in peritoneal instillate are very important variables for IPCH.

Discussion

Intraperitoneal administration delivers very high local concentrations of cisplatin inside the abdominal cavity and good penetration in superficial local tissue, while avoiding systemic toxicity [1]. The rationale for using IPCH after a primary complete cytoreductive surgery has been described in previous studies [1–9, 13–21].

Oxaliplatin is currently the most interesting drug for local use with hyperthermia for colorectal carcinomas [19]. It has the highest response rate for a single agent in intravenous second-line therapy: 24% of metastatic patients [10]. It is derived from cisplatin, which is a 'minute' drug, rapidly usable and effective, acting through the formation of DNA adducts in malignant cells whatever the cell cycle phase. Platinum compound activity, and oxaliplatin activity in particular, is potentiated by hyperthermia [19, 25].

Our trial is the first to study the pharmacokinetics and tolerance of oxaliplatin administered intraperitoneally with hyperthermia in man. The choice of a 30 min duration at an effective ($42\text{--}44^\circ\text{C}$) temperature, with rigorous quality control of the

procedure, was based on our previous experience with IPCH using other agents. In a preliminary trial [5] in which IPCH lasted 60 min, we selected one procedure among seven tested: a closed continuous circuit with four drains and an open abdominal cavity with the skin pulled upwards, because it allows a complete spatial diffusion inside the abdominal cavity to be obtained (demonstrated with blue dye) and temperature homogeneity (monitored with six intracavity thermal probes) [5]. In the present study, we tried to increase drug concentration and decrease IPCH duration to obtain a similar pharmacokinetic result, whilst maintaining plasma levels below those of historical intravenous controls, in order to avoid systemic toxicity. Our intention was to decrease the length of the operation and therefore the cost of the procedure, both in monetary and human terms.

Indeed, we proved that during IPCH, oxaliplatin was rapidly absorbed (half the dose administered during the 30 min of the procedure).

Despite this important uptake, we simultaneously observed low platinum concentrations in plasma, and at the maximal level tested (460 mg/m²), plasma C_{max} and AUC were below the values observed after a 2 h intravenous infusion of oxaliplatin at 130 mg/m². We believe that for this reason there was no systemic toxicity in this trial even at 460 mg/m² oxaliplatin, with concomitant intravenous 5-FU (400 mg/m²) and leucovorin (20 mg/m²).

Finally, at the 460 mg/m² level, the C_{max} was 25-fold greater in the peritoneum, where we want the drug to be active, than in blood. This ratio is greater than those observed previously with cisplatin and carboplatin, which were 15- to 20-fold that of plasma values [1, 15].

When considering intraperitoneal chemotherapy, the usual intravenous dosage is not applicable. The two most important variables are the drug concentration in the instillate and IPCH duration. At the end of the procedure the abdominal cavity is emptied, thereby evacuating the remaining oxaliplatin, which will not be absorbed either in tissues or plasma. The instillate volume determines the concentration, and in our experience modifying volume from 2 to 2.5 l/m² resulted in a dramatic decrease of peritoneal absorption and that of the exposed wounded tissues. So it appears that the volume must be adapted to each individual using the body surface area in accordance with the oxaliplatin dose calculation. Finally, with our IPCH procedure, we advocate an open technique with the skin pulled upwards, which is similar to Sugarbaker's Coliseum technique, basing the cytotoxic dose and the instillate volume on body surface area. We think that a 2 l/m² volume is preferable with this procedure. We recommend a dosage of 460 mg/m² for oxaliplatin because tissue concentrations appear adequate at this level, but we did not reach the maximum tolerated dose in our study.

The discrepancy between the large amount of oxaliplatin absorbed locally and the low serum and muscle levels can be partially explained by a high uptake of oxaliplatin in local

tissues (residual tumour nodules of <1 mm and peritoneum), confirming the local advantage of intraperitoneal chemotherapy. The intratumoural oxaliplatin concentration increased proportionally with the instilled drug concentration. Finally, the concentration was 17.8-fold higher in tissues directly in contact with the drug than in more distant tissue, like muscle. Other methods could increase local intra-tissue penetration and should be the object of future trials: using hypo-osmolar instillate or adding vasopressive drugs or increasing IPCH duration.

In conclusion, this study demonstrates that heated intraperitoneal oxaliplatin is a feasible intra-operative treatment. The pharmacokinetic study indicates a dose-related exposure and efficient intratumoural penetration. The clinical study shows that 460 mg/m² oxaliplatin in 2 l/m² of instillate over 30–40 min at 43°C is well tolerated compared with previous results with IPCH.

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