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PHARMACOKINETICS AND DISPOSITION

Pharmacokinetics of cisplatin during hyperthermic intraperitoneal treatment of peritoneal carcinomatosis

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Abstract
Purpose Cisplatin during hyperthermic intraperitoneal chemotherapy (HIPEC) has not previously been measured with a selective technique. The primary aims were to examine the pharmacokinetics of active cisplatin and its monohydrated complex (MHC) during HIPEC using a specific measuring technique, to compare cisplatin's systemic absorption with oxaliplatin, and to compare active cisplatin levels to that of total platinum.
Methods Ten patients treated with cytoreductive surgery and HIPEC (cisplatin 50 mg/m^2,doxorubicin 15 mg/m^2) were recruited. Blood and perfusate samples were drawn during and after HIPEC. Cisplatin analysis was conducted using liquid chromatography (LC) with post-column derivatization with diethyldithiocarbamate and compared with inductively coupled plasma-mass spectrometry (ICP-MS).
Results The mean half-life (t1/2) of perfusate cisplatin was 18.4 min, with area under the time-concentration curve (AUC) 0–90 min of 2.87 mM·min and estimated 0–60 min of 2.45 mM·min. The absorption t1/2 was 9.0 min for cisplatin and 18.2 min for oxaliplatin. The ratio of total platinum to active cisplatin increased in a linear manner by time of perfusion.
Conclusions Cisplatin is absorbed quicker than oxaliplatin. Lowering the perfusion time to 60 min does not significantly change the pharmacokinetics of cisplatin, and is therefore to be considered. As the HIPEC perfusion progresses, the ICP-MS technique does not adequately reflect active cisplatin levels in the perfusate.

Keywords Pharmacokinetics · Cisplatin · Hyperthermic intraperitoneal chemotherapy · HIPEC · Cytoreductive surgery · Perfusion time

Abbreviations

AAS	Flameless atomic absorption spectrophotometry
AUC	Area under the time-concentration curve
BMI	Body mass index
BSA	Body surface area
CC	Completeness of cytoreduction
CRS	Cytoreductive surgery
HIPEC	Hypthermic intraperitoneal chemotherapy
ICP-MS	Inductively coupled plasma mass spectrometry
IV	Intravenous(ly)
MHC	Monohydrated complex of cisplatin
PCI	Peritoneal cancer index
PMP	Pseudomyxoma peritonei
UF	Ultrafiltrate

Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) treatment is a growing field. It is being used intra-operatively during cytoreductive surgery (CRS). *cis*-Diamminedichloroplatinum, also known as cisplatinum or cisplatin, is a commonly used drug in this setting, particularly for ovarian and gastric tumors [1, 2]. The drug's target molecule is DNA producing intra-strand and inter-strand adducts. The main intracellular form of the drug thought to react in this way is the monohydrated complex (MHC) [3–5].

In 2002, Elias et al. conducted a study using oxaliplatin instead of cisplatin in HIPEC for colorectal peritoneal

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carcinomatosis (PCs) [6]. They chose a 30 min perfusion time, using the maximum intraperitoneal concentration and the concentration in tumor nodules as the end point of the chemoperfusion. The area under the time-concentration curve (AUC) of oxaliplatin in the perfusate was not an endpoint in the study. This is in contrast to earlier cisplatin studies with 90 min perfusion, where comparisons have been made primarily using the perfusate AUC as a measure of efficacy. As oxaliplatin is a derivative of cisplatin, a third generation platinum compound, the question arises whether the same rationale used in oxaliplatin can be used in cisplatin. One justification given for the two different perfusion times between the platinum compounds is that oxaliplatin has been proposed to have a quicker systemic uptake, which would warrant a shorter perfusion time using a higher concentration [7].

The terminal half-life (t1/2) in the perfusate of oxaliplatin is around 30 min, which has been demonstrated both by a general measuring technique, flameless atomic absorption spectrophotometry (AAS) or inductively coupled plasma mass spectrometry (ICP-MS); and a specific technique, liquid chromatography with post-column derivatization using diethyldithiocarbamate as the reagent [6, 8]. Using the AAS or ICP-MS technique, which will codetermine low-molecular-weight complexes of platinum with endogenous compounds, cisplatin has a terminal t1/2 in the perfusate of between 25.8 and 99.6 min [9–12]. No studies have investigated the pharmacokinetic profile of cisplatin using a specific measuring technique, and considering the great range in t1/2, there is a need of determining the pharmacokinetic profile using a specific measuring technique (measuring only active cisplatin). Moreover, this may have important implications for the future of cisplatin in HIPEC, if the perfusion time can be decreased.

The monohydrated form of cisplatin (MHC), which has been implicated in the nephrotoxicity [13] of cisplatin in intravenous administration [14], has never previously been measured during HIPEC. As such, the primary aim of this study was to examine the pharmacokinetics of active cisplatin and MHC during HIPEC using a specific measuring technique, and to compare the systemic absorption of cisplatin with that of oxaliplatin. The secondary aim was to compare the results of the specific technique (liquid chromatography with post-column derivatization using diethyldithiocarbamate as the reagent) with measurements of total platinum using ICP-MS.

Methods and patients

Patients

A recent study on sample size has shown that a reasonable estimate on pharmacokinetics can be achieved at a minimal sample size of five [15]. Thus, a sample size of ten was chosen, in order to compensate for possible technical difficulties. Ten consecutive patients treated at Uppsala University Hospital for peritoneal carcinomatosis (PC) where the drug of choice was cisplatin were invited into the study. The eligibility requirements for treatment were the following: histologically confirmed diagnosis of PC; no distant metastases; adequate renal, hematopoietic and liver functions; and World Health Organization (WHO) performance status less than or equal to 2. Exclusion citeria were the following: pregnancy, disease preventing chemotherapy administration (such as immunological deficiencies), other cancer disease still under follow-up. There were six patients with pseudomyxoma peritonei (PMP), two with mucinous colorectal tumors, one with ovarian cancer, and one with small bowel adenocarcinoma. The following clinical data was collected: age, gender, body surface area (BSA), body mass index (BMI), tumor histopathology, cisplatin dose given, volume of perfusate, erythrocyte fraction volume preoperatively and postoperatively, postoperative plasma albumin, and surgical parameters (such as blood loss and operating time). The regional ethics committee approved the study and informed consent was obtained from each patient.

Surgery and HIPEC

The patients were operated on with peritonectomy and visceral resections, as described by Sugerbaker [16]. The extent of tumor load and result of the surgical procedures were recorded at surgery as peritoneal cancer index (PCI) and completeness of cytoreduction score (CC) respectively. The PCI lesion score divides the abdomen into 13 sections according to size: 0=no visible tumor, 1=tumor up to 0.5 cm, 2=tumor up to 5 cm, and 3= tumor >5 cm. Maximum PCI is 39 (13×3) with lesions > 5 cm in all 13 sections. The CC score is based upon the remaining tumor nodules after cytoreduction: 0=no peritoneal seeding visible, 1=nodules up to 2.5 mm, 2=nodules up to 2.5 cm, and 3=nodules > 2.5 cm.

After cytoreduction, the patients received HIPEC with cisplatin and doxorubicin. It was administered using the coliseum technique, as described earlier [17]. Briefly, a Tenchoff inflow catheter was centrally placed in the abdomen and four outflow catheters were inserted through separate stab incisions through the abdominal wall. Both the inflow and outflow catheters were connected to a perfusion pump and a heat exchanger. The skin of the abdomen was attached to a retractor ring and covered with a plastic film. Prior to the start of the treatment, the patient's core temperature was reduced to 35 °C with a cooling blanket. A dose of 50 mg/m^2 cisplatin and 15 mg/m^2 doxorubicin was injected into the circulating perfusate (dianeal peritoneal dialysis fluid) that was kept at a temperature of 41.1–43 °C. This

treatment was given during 90 min. Afterward, the abdomen was rinsed and closed up. Four intra abdominal drains were left in place after surgery in all the patients as part of the postoperative care.

Sampling and pharmacokinetic analysis

Perfusate and arterial blood samples were drawn immediately before start of HIPEC (time 0) and then at seven different intervals—2, 5, 10, 15, 30, 60, and 90 min during the HIPEC perfusion. Additional samples (arterial blood only) were drawn at 1, 15, 45, 75, and 105 min after completing the HIPEC perfusion.

The samples were collected in pre-chilled vacutainer tubes and stored on ice. The blood and a portion of the perfusate samples were ultrafiltrated centripetally at 4 °C (4000×g, 20 min) within 30 min. After centrifugation, the resulting filtrates were promptly put on dry ice, stored at −80 °C, and analyzed within 3 weeks. This is in accordance with the known stability of cisplatin and MHC [18]. The analysis was done by liquid chromatography using a post-column derivatization technique, as described earlier, to determine the concentrations of cisplatin[19]. MHC was analyzed using the same conditions, but with a pH 8.2 HEPES buffer, and this method has been previously shown to clearly distinguish between mono and dihydrated forms of platinum [20, 21]. While these methods have been internally validated; as of yet, they lack a full Food and Drug Administration (FDA) standardised bioanalytical method validation. The area under the concentration time curve (AUC), peak concentration, and terminal t1/2 for cisplatin in blood ultrafiltrate (UF) were calculated using the WIN NONLIN 1.5 SCI software in a compartmental model. The AUC for MHC in both perfusate and blood was determined using the trapezoidal rule, as it provided a better model of MHC levels than the NONLIN compartmental model. Pharmacokinetic calculations for the perfusate samples were performed by Graph Pad Prism (version 3.02, Graph Pad Software, San Diego, CA, USA). The AUC ratio was calculated by dividing the perfusate AUC of the 90 min cisplatin perfusion by the resulting systemic blood UF AUC. The perfusate AUC between 0 and 60 min was also estimated.

Cisplatin versus oxaliplatin

The comparison between the absorption of cisplatin and oxaliplatin was conducted by calculating the absorption constant (k_a) during the HIPEC phase. Unpublished data on oxaliplatin's absorption constant (k_a) was retrieved from an earlier study on oxaliplatin pharmacokinetics in eight patients, performed at our institution using the same HIPEC coliseum method (only the carrier solutions differed: oxaliplatin with electrolyte-free glucose and cisplatin with dianeal peritoneal dialysis fluid) [8]. Further characteristics of these patients are detailed in the previous study [8]. The mean value was calculated with the standard deviation and 95 % confidence interval. The absorption constant as calculated from the systemic uptake was expressed in terms of a t1/2 in min. The Mann–Whitney *U* test was used to evaluate the statistical difference between cisplatin and oxaliplatin. A p value <0.05 was considered statistically significant.

Inductively coupled plasma mass spectrometry versus liquid chromatography in perfusate samples

Two samples from every patient were sent for total platinum analysis using ICP-MS. These samples were taken at 10 min and 90 min during the HIPEC perfusion. For patient 2, samples were taken from all seven sampling time points during the HIPEC perfusion and sent for total platinum analysis. The ICP-MS results were then compared with the liquid chromatography results by a ratio (ICP-MS/liquid chromatography).

Results

Clinical results

Basic patient descriptive data are displayed in Table 1. The tumor load, as estimated by PCI, had a mean value of 24.4; and out of the ten patients, seven reached a CC score of 0, two had a CC score of 0–1, and one had CC score of 2. The mean operating time was 10.75 h (range: 6.5–12.67) with a mean blood loss of 675 ml (range: 200–2,000). The mean loss of EVF (erythrocyte volume fraction) during surgery was 30 % (absolute value 12.4 % from 40.8 % to 28.4 %). The mean postoperative value of albumin was 29.8 g/L. No grade III–IV hematological or renal toxicity was observed. However, in four patients, there was a transient grade I increase in creatinine an average of 7 days after treatment.

Pharmacokinetics

The results of the pharmacokinetic analysis are displayed in Tables 2, 3, and 4. The mean t1/2 of cisplatin in the perfusate UF was 18.4 min with an AUC of 2.87 mM × min. The mean t1/2 of cisplatin in the blood UF was 36.6 min with an AUC of 0.46 mM × min. The AUC perfusate UF/blood UF ratio was 6.28 for cisplatin and the mean perfusate and blood concentrations are displayed in Fig. 1. The AUC of the MHC in the perfusate UF was 0.66 mM × min, whereas the blood UF was 0.09 mM × min (Table 4). The mean

Table 1 Patient characteristics and cisplatin dosage

Patient	Age	Gender	Weight (kg)	BMI (kg/m2)	Tumor (kg)	Tumor Type	Dose (mg)	Adjusted SA[a] (m2)	Adjusted Dose[a] (mg/m2)	Volume Perfusate
1	45	F	88	29.1	2.5	Ovarian	100	2.00	50.0	4.1
2	56	M	93	31.4	2.7	mCRC	100	2.08	48.1	2.6
3	66	F	73	25.3	4.8	PMP	92	1.79	51.4	3.6
4	39	M	76	26.3	5.0	PMP	94	1.82	51.6	2.6
5	67	M	84	27.1	1.4	PMP	100	1.99	50.3	3.1
6	67	F	62	23.3	3.0	mCRC	83	1.63	50.9	3.2
7	60	M	99	29.2	1.1	SBAC	110	2.21	49.8	3.0
8	69	M	125	33.9	5.3	PMP	125	2.48	50.4	2.6
9	71	F	61	23.0	11.4	PMP	83	1.52	54.6	5.2
10	53	F	73	27.1	4.0	PMP	90	1.75	51.4	4.1
Mean	59.3		83.9	27.7			97.7	1.93	50.9	3.4

SA surface area; *BMI* body mass index; *PMP* pseudomyxoma peritonei; *mCRC* mucinous colorectal cancer; *SBAC* small bowel adenocarcinoma

[a] These columns are calculated using an adjusted weight where the weight of the tumor removed is subtracted from the preoperative weight.

perfusate UF AUC from 0 to 60 min was 2.45 mM × min ± 0.62 (SD).

Cisplatin versus oxaliplatin

The absorption constant (k_a)±standard deviation for cisplatin was 0.077±0.026 (95 % CI: 0.059–0.096) as compared with 0.038±0.007 for oxaliplatin (95 % CI: 0.033–0.043), p=0.005. The corresponding t1/2 was 9.0 min for cisplatin and 18.2 min for oxaliplatin.

Inductively coupled plasma mass spectrometry versus liquid chromatography in perfusate samples

The ratio of total cisplatin (as measured by ICP-MS) to active cisplatin (as measured by liquid chromatography)

Table 2 Pharmacokinetic parameters of cisplatin in perfusate ultrafiltrate

Patient	Calc C_{max} Perfusate UF (μM)[a]	Found C_{max} Perfusate UF (μM)[b]	C_{max} perfusate UF found/calc	AUC perfusate UF (mM × min)[c]	t1/2 perfusate UF (min)	Dose absorbed (%)[d] (30 min)	Dose absorbed (μmole)[d] (30 min)
1	81.2	83.7	1.03	2.93	15.6	74	245
2	128	106	0.83	3.50	21.0	63	209
3	85.0	80.6	0.95	2.50	18.2	68	209
4	120	86.5	0.72	2.83	19.6	65	205
5	107	99.1	0.93	3.19	22.1	61	203
6	86.4	83.3	0.96	2.17	14.4	76	211
7	122	114	0.93	3.47	19.2	66	242
8	160	144	0.90	3.49	13.5	79	327
9	52.2	49.0	0.94	2.30	33.8	45	127
10	74.9	75.9	1.01	2.36	18.1	68	205
Mean±SD	102±31.6	92.2±25.5	0.92±0.09	2.87±0.52	18.4[e]	67±10	218±50

C_{max} Maximal concentration; AUC=Area under concentration–versus–time curve; *t1/2* Elimination half-life; *UF* Ultrafiltrate

[a] Dose (μmole)/perfusate volume (l)

[b] Rate of elimination extrapolated to time zero, assuming first order kinetics

[c] AUC integrated until time of influx of saline=perfusion stop

[d] Due to a very low degradation rate in perfusate (3 %), dose absorbed was calculated: $100 \cdot (C_o – C_{30'})/C_{o,}$ where C is the cisplatin concentration in perfusate at 0 min and 30 min.

[e] Mean value calculated from the mean of the rate constants

Table 3 Pharmacokinetic parameters of cisplatin in blood ultrafiltrate

Patient	C_{max} blood UF (μM)	T_{max} blood UF (min)	AUC blood UF (mM × min)	t1/2 blood UF (min)	Cl (l/h/m^2)	AUC perfusate UF/AUC blood UF	C_{max} found perfusate/C_{max} UF
1	5.94	21.6	0.53	41.7	13.3	5.53	14.1
2	4.04	32.8	0.42	30.9	13.1	8..33	26.2
3	5.83	25.5	0.56	39.5	12.4	4.46	13.8
4	4.49	30.1	0.43	31.3	15.3	6.58	19.3
5	5.26	25.7	0.51	37.5	11.9	6.25	18.8
6	5.42	22.9	0.46	37.8	16.4	4.71	15.4
7	4.44	29.3	0.42	38.7	15.6	8.26	25.7
8	5.64	24.0	0.47	38.5	16.5	7.43	25.5
9	3.45	49.9	0.40	30.8	11.1	5.75	14.2
10	4.26	24.4	0.43	45.1	15.8	5.49	17.8
Mean±SD	4.87±0.85	28.6±8.2	0.46±0.05	36.6[a]	14.1±2.0	6.28±1.49	19.1±5.0

C_{max} Maximal concentration; *AUC* Area under concentration–versus–time curve; *t1/2* Terminal elimination half-life; *UF* Ultrafiltrate; *Cl* Clearance

[a] Mean value calculated from the mean of the rate constants

over time in the perfusate is demonstrated in Fig. 2. The ratio of total platinum to cisplatin increased in a linear manner by time of perfusion.

Discussion

This is the first pharmacokinetic analysis of cisplatin and MHC in HIPEC using a selective technique. The t1/2 of active cisplatin in the perfusate UF was 18.4 min. This differs from earlier studies where t1/2 was reported to range between 25.8 and 99.6 min [9–12], or between 43.8 and 48 min with the same dosing (50 mg/m^2) as the current study [9, 11]. This would indicate that after 75 min there is little active cisplatin left in the perfusate, having been either absorbed locally in the abdomen, systemically, or been bound to compounds (low-molecular weight compounds such as thiols) in the perfusate.

There are several findings in this study that would support a change in the current protocol from a 90-min to a 60-min perfusion time for cisplatin in HIPEC. Firstly, considering the short t1/2, reducing from 90 to 60 min would not significantly change the AUC in the perfusate (from 2.87 to 2.45 mM x min). Secondly, the cytotoxic effect of cisplatin is both time and concentration dependent, meaning that its cytotoxic effect can be enhanced by either increasing exposure time or the concentration [22, 23]. One in vitro study, combining both hyperthermia (at different temperatures) and cisplatin (at increasing concentrations), demonstrated only a few percent cell survival after 1 h cisplatin exposure at 7 mg/L (23.3 μM) with

Table 4 Pharmacokinetic parameters of MHC in blood UF and perfusate UF

Patient	C_{max} blood UF (μM)	T_{max} blood UF (min)	AUC blood UF (mM × min)	C_{max} perfusate UF (μM)	T_{max} perfusate UF (min)	AUC perfusate UF (mM × min)
1	0.88[a]	30[a]	0.07	7.45	30	0.51
2	1.01	60	0.12	9.27	15	0.60
3	1.18	60	0.14	7.90	15	0.51
4	0.98	60	0.09	11.0	15	0.65
5	1.16	60	0.11	14.0	15	0.85
6	0.96	30	0.06	7.90	10	0.51
7	0.80	30	0.06	13.0	30	0.90
8	1.25	30	0.09	18.3	10	1.05
9	1.02	90	0.09	6.68	60	0.51
10	1.00	60	0.09	8.66	15	0.53
Mean±SD	1.02±0.14		0.09±0.03	10.4±3.7		0.66±0.20

C_{max} Maximal concentration; *AUC* Area under concentration–versus–time curve; *UF* ultrafiltrate

[a] Analysis of MHC in blood UF not performed in all samples from patient 1

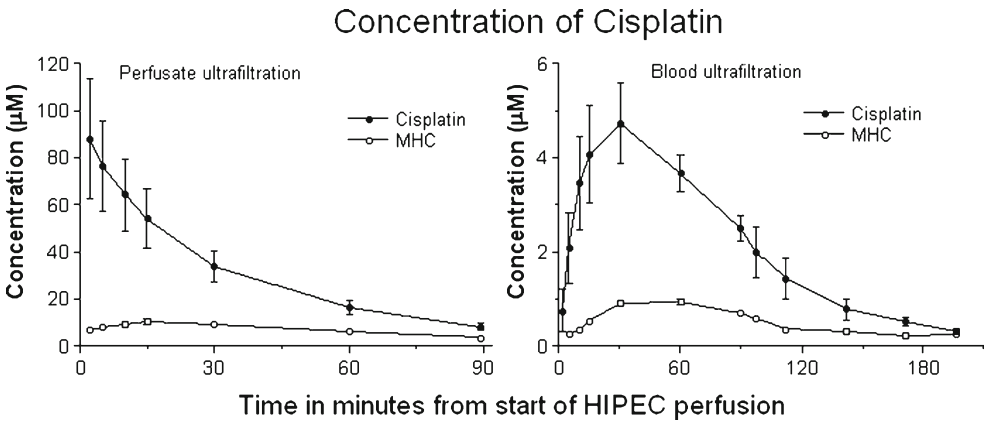

Fig. 1 Mean cisplatin and MHC concentrations in perfusate and blood ultrafiltrate. The error bars represent the standard deviation

42 °C hyperthermia [24]. Our study has an average concentration of 40 μM (2.4 mM x min/60 min) during the first 60 min with a hyperthermic temperature between 41 and 43 °C, which is consistent with a good cell kill rate according to Barlogie and colleagues. Thirdly, our comparison with oxaliplatin systemic absorption clearly shows that cisplatin is absorbed twice as fast as oxaliplatin (t1/2: 9.0 min vs. 18.2 min). This refutes the earlier rationale that cisplatin should have a longer perfusion time based on longer systemic absorption [7]. One weakness in this study is the low number of patients, which may limit the generalizability of the results. However, the results are quite congruent as shown in Tables 2 and 3, where the standard deviation of the AUC of the perfusate is only 18 % of the mean value and only 11 %of the blood UF. Therefore, with such consistency, it was deemed unnecessary to increase the sample size. Using the current protocol with 50 mg/m^2 dosing, it appears feasible to reduce the perfusion time to 60 min.

Could the perfusion time be reduced even more, to 30 min, as used for oxaliplatin? Considering the more rapid systemic uptake and the shorter perfusate t1/2 in this study compared to oxaliplatin, it seems relevant to perform a dose escalating study on cisplatin within the framework of 30 min. However, there is some contention as to what should be the pharmacological endpoint. Some stress the exposure time as important, arguing in favour of repeated dosing [25], while others stress the local uptake in the tumor nodule as the endpoint, which is much more concentration dependant [6, 26]. In either case, it appears important to confirm pharmacokinetic models with in vitro studies in order to verify that there indeed is a similar or improved rate of tumor cell death.

Figure 2 displays the ratio between total platinum and cisplatin, and it appears that the longer the perfusion continues, the less reliable total platinum measurements of cisplatin are, with a median difference in the concentration of cisplatin of more than 40 % at the end of the perfusion. This difference is important, as it affects the pharmacokinetic modelling. The AAS or ICP-MS techniques measure all the platinum in a sample, but cisplatin can bind to various other low-molecular-weight endogenous compounds in the ultrafiltrate, such as thiols, leading to a lowering of bioactive platinum [27, 28]. There is a time-dependent increase of protein and albumin levels in the perfusate during HIPEC, probably due to raw peritoneal surfaces [9]. This could explain the skewed difference over time, as cisplatin can continue to react with new endogenous compounds that continuously leak into the peritoneal cavity during the perfusion. This also explains why this study's pharmacokinetics differs from earlier studies, as they have not taken into account the continuous inactivation of cisplatin in the perfusate by new compounds leaking into the abdominal cavity from raw dissected peritoneal surfaces. These studies only measure total platinum, which cannot differentiate between active and inactive cisplatin (even after ultrafiltration). This supports the use of more specific measurements than total platinum as a basis for pharmacokinetic modeling of cisplatin in the perfusate during HIPEC.

When comparing results with intravenously (IV) administered cisplatin using the same liquid chromatography technique, the AUC of plasma UF (0.46 mM × min—Table 3) in HIPEC was 46 % of the AUC of plasma UF (1 mM × min) in IV administration [14]. This is interesting as the dose given

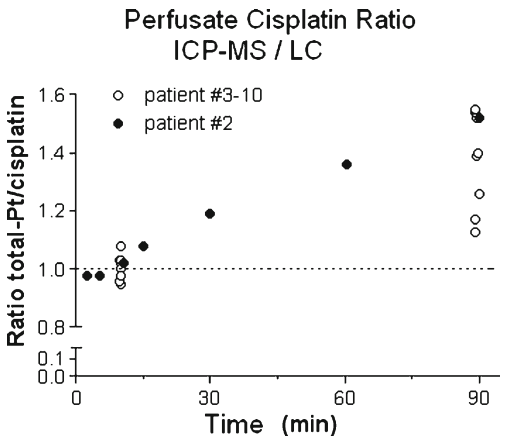

Fig. 2 Ratio of total platinum/cisplatin in the perfusate. ICP-MS inductive coupled plasma mass spectrometry, LC—liquid chromatography

during HIPEC is exactly half that given during IV administration (50 mg/m^2 vs. 100 mg/m^2). This is in contrast to earlier findings, where the AUC of plasma UF was similar for HIPEC at 50 mgm^2 (0.8 mM × min) and IV at 100 mg/m^2 (0.7 mM × min) measured as total platinum [9, 29]. The locoregional treatment of peritoneal carcinomatosis is not aimed at reaching therapeutic systemic levels. However, this may mean there is a margin on which to increase the cisplatin dose, particularly if the perfusion time were to decrease. There is one dose escalation study with a cisplatin perfusion of 90 min that increased the dose from 100 to 400 mg/m^2. However, this study simultaneously administered sodium thiosulfate intravenously as a protective agent against nephrotoxicity, but how much that leaks into the peritoneal cavity inactivating cisplatin is yet unknown [30]. Furthermore, Cotte observed that they could not increase the dose (1–1.5 mg/kg which is a similar dose as 50 mg/m^2) without sodium thiosulfate, as they were already observing temporary renal failures [31]. As such, one needs to either add sodium thiosulfate IV (maybe also determine its presence in the perfusate) or decrease the perfusion time if the dose is to be increased.

MHC presence in the perfusate UF and blood UF, as measured by the AUC, was 18 % in both. This metabolite is a very toxic form of cisplatin, both in terms of tumor cytotoxicity and nephrotoxicity [13, 14]. Its production appears to be similar in both the perfusate and blood ultrafiltrate. It should be important to quantify the concentration of MHC when evaluating the influence of the composition of the perfusion solution, since both chloride concentration and pH will affect the formation and thus, the cytotoxicity of cisplatin [32].

In conclusion, the pharmacokinetics of cisplatin demonstrates that the absorption of active cisplatin is more rapid than oxaliplatin and quicker than previously known. Lowering the perfusion time from 90 to 60 min does not significantly change the pharmacokinetic profile of active cisplatin during HIPEC and may, therefore, be considered. Further studies are needed to discern if a high-dose cisplatin and 30 min perfusion is possible. As the HIPEC perfusion progresses, the ICP-MS technique does not adequately reflect active cisplatin levels. Thus, pharmacokinetic modelling of cisplatin in HIPEC is improved by using a selective measuring technique, such as the one used in this study.

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