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Optimisation of Intraperitoneal Cisplatin Therapy with Regional Hyperthermia in Rats

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The purpose of this study was to optimise intraperitoneal chemotherapy by combining this modality with regional hyperthermia. *In vitro* data demonstrated that both the uptake of cisplatin into CC531 tumour cells and cytotoxicity were increased at temperatures of 40°C (factor 4) and 43°C (factor 6) compared to 37°C. The increase of intracellular platinum concentration correlated well with the decrease in survival of these cells. *In vivo*, rats were treated intraperitoneally with cisplatin (5 mg/kg) in combination with regional hyperthermia of the abdomen (41.5°C, 1 h). The mean (S.D.) temperature in the peritoneal cavity was 41.5 (0.3)°C and outside the peritoneal cavity 40.5 (0.3)°C. Enhanced platinum concentrations were found in peritoneal tumours (factor 4.1) and kidney, liver, spleen and lung (all around a factor 2.0), after combined cisplatin-hyperthermia treatment. The platinum distribution in peritoneal tumours was more homogeneous after the combined treatment than after cisplatin alone, possibly due to increased penetration of cisplatin into peritoneal tumours. Pharmacokinetic data demonstrated an increased tumour exposure for unfiltered platinum in the peritoneal cavity (area under the curve [AUC] increased from 339 μmol/l/min to 486 μmol/l/min at 37°C and 41.5°C, respectively), and for total and ultrafiltered platinum in the blood. The AUC for total platinum increased from 97.9 to 325.8 μmol/min and for ultrafiltered platinum from 22.2 to 107 μmol/l/min at 37°C and 41.5°C respectively. The latter might be due to a slower elimination of platinum from the blood. The combined treatment, intraperitoneal cisplatin and regional hyperthermia, also increased toxicity. The thermal enhancement ratio (TER) using lethality as endpoint was 1.8.
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INTRODUCTION

CISPLATIN IS the major component of drug therapy of ovarian cancer [1]. Unfortunately systemic therapy results in less than 50% pathological complete remission. Even many of these and all the others are associated with subsequent progression or relapse [2]. The therapeutic index has been improved by changing the route of administration for cisplatin from intravenous to intraperitoneal in patients with residual small volume ovarian cancer who had failed to respond completely to intravenous cisplatin [2, 3]. Further improvement might be obtained by combining intraperitoneal cisplatin treatment with whole body hyperthermia (WBH) or regional hyperthermia which might be potentially effective for this disease. The basic principle of this combination is that heat may increase cell membrane permeability to drugs, improve membrane transport of drugs [4] and alter cellular metabolism [5]. In addition, drug pharmacokinetics and excretion may also be changed [6], which can lead to increased cytotoxicity [7–13]. Although the mechanisms responsible for hyperthermic sensitisation of anticancer drugs are not entirely understood, they may result in increased drug reaction rates with DNA and heat induced inhibition of DNA repair [14–16].

Experimental data on the combined treatment of hyperthermia and cisplatin treatment demonstrated improvement of its cytotoxic effect against experimental animal tumours [17–19]. Since both hyperthermia and cisplatin administration, however, may cause renal failure when given as separate modalities [20–24], kidney toxicity as a result of cisplatin combined with WBH may be additive [25]. Gerard *et al.* [26], for example, reported on renal failure in 3 patients after simultaneous intravenous treatment with cisplatin and whole body hyperthermia. Regional hyperthermia, however, is less toxic than WBH, because hyperthermic sensitisation will occur only in the treatment volume [27]. Moreover, some systemic toxicity might be lower after intraperitoneal cisplatin combined with regional hyperthermia of the peritoneal cavity because intraperitoneal cisplatin gives less systemic toxicity than intravenous [3, 28]. Finally, regional hyperthermia will alter the pharmacokinetic profile which may enhance drug exposure of the local tumour. A slower release of the drug from the peritoneal cavity into the systemic circulation is expected due to a decrease in the splanchnic blood flow, as seen in WBH [29].

In earlier work, we demonstrated that the area under the concentration × time curve (AUC) in the peritoneal cavity contributed to the ultimate platinum concentration in the tumour [27] and since the total platinum concentration in the tumour should be related to the antitumor response, the increase in AUC may be very important. In the present paper we have studied cisplatin pharmacokinetics, platinum tissue concen-

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trations, platinum distribution in peritoneal tumours and toxicity after intraperitoneal cisplatin treatment alone or combined with regional hyperthermia at 41.5°C for 1 h of the rat peritoneal cavity.

MATERIALS AND METHODS

Tumour model

Male WAG/Rij rats, 8–12 weeks old at the time of the experiments were obtained from the animal department of the Netherlands Cancer Institute. The CC531 tumour is a well characterised carcinoma [30] and grows subcutaneously and intraperitoneally in the WAG/Rij rat. Rats were inoculated intraperitoneally with 2×10^6 CC531 tumour cells in 2 ml phosphate buffered saline (PBS) on day 0. 4 weeks later small tumour nodules (2–5 mm in diameter) on the diaphragm, peritoneum and on the mesothelium between the intestines were present in 80–100% of the rats [31]. Treatment started 28 days after inoculation. Tumours and various normal tissues were collected at set times to determine platinum concentrations. Before tissue sampling, animals were killed by ether.

Sensitivity of CC531 for cisplatin in vitro at 37°C, 40°C and 43°C

Sensitivity of CC531 for cisplatin at different temperatures was tested by a clonogenic assay. The tumour cells were plated at a density of 1×10^5 cells in fresh Dulbecco's modified medium (DMEM) with 10% fetal calf serum (FCS, Flow). The doubling time of the CC531 tumour cells *in vitro* was 16 h.

Drug sensitivity curves were determined using clonogenicity in 6 well tissue culture plates (Costar, UK). CC531 cells in single cell suspension were plated in 6 well plates (150 cells/well) in a volume of 2.9 ml medium (Dulbecco's modified medium + 10% fetal calf serum [Flow]). Cisplatin (Platinol®, Bristol Myers, Weesp, The Netherlands) was added after 24 h. The final drug concentration in each well differed in the different experiments for cisplatin from 0.01 to 10 μmol/l. After 1 h incubation at different temperatures (37°C, 40°C, 43°C), cells were washed 3 times with PBS and fresh medium was added. Colonies containing more than 50 cells were scored visually 7 days after plating the cells. Every experiment was performed in triplicate.

Thermometry and heating technique

Animals were anaesthetised by giving intramuscular 0.05 ml (6 mg/kg) xylazine followed by 50 mg/kg ketanine 12 min later. Then the rats were positioned in a thermostatically controlled water bath at 41.5°C. The temperature in the peritoneal cavity of the animal steadily increased from normal body temperature (around 38°C) to 41.5°C in about 30–40 min. At the desired temperature, cisplatin was administered intraperitoneally in a 0.9% NaCl solution (20 ml) at 41.5°C. The duration of the heat treatment at 41.5°C was 60 min. During treatment, intraperitoneal temperatures were monitored every 5 min using copper-constant thermocouple probes (IT-18, diameter 0.62 mm, Sensortek, USA) at three locations in the peritoneal cavity (near the bladder, the spleen and right kidney). In addition to the temperatures in the peritoneal cavity, the rectal temperature at a distance of 6 cm into the rectum and the temperature in the oesophagus were monitored.

Tissue platinum concentrations after intraperitoneal chemotherapy

Rats with peritoneal tumours were treated with cisplatin (5 mg/kg in 20 ml 0.9% NaCl solution) alone or combined with regional hyperthermia (41.5°C). Several tissues were collected (tumour, liver, kidney, spleen, intestines and lung) 24 hours after treatment and prepared for platinum analysis.

Table 1. Uptake of cisplatin into CC531 cells in vitro

Concentration ng platinum/10^6 cells			Ratio	
37°C	40°C	43°C	40°/37°C	43°/37°C
29 (11)	93 (1)	99 (10)	3.2	3.4

Incubation time 1 h, cisplatin 5 μg/ml.
Mean (S.D.).

Pharmacokinetic studies

Pharmacokinetic studies were performed in rats after cannulation of the carotid artery. Cisplatin (5 mg/kg) was administered intraperitoneal in a volume of 20 ml 0.9% NaCl. At different time points after treatment with cisplatin, blood samples were taken from the carotid artery. Platinum concentrations in plasma and plasma ultrafiltrate were determined by flameless atomic absorption spectroscopy (FAAS). The cisplatin clearance from the peritoneal cavity was studied by sampling the installed peritoneal fluid. For the total platinum and the ultrafiltrated platinum the AUC were determined, as well as the maximum concentration (C_{max}), the maximal time (T_{max}) and the half-life time ($t_{1/2\beta}$). AUC were calculated by means of the trapezoidal rule [32]. Other pharmacokinetic parameters were calculated from the semilogarithmically plasma concentration time curves according to standard methods [32].

Detection of platinum by FAAS and proton induced X-ray emission (PIXE)

A model AA40 Atomic Absorption Spectrometer with a GTA 96 Graphite Tube Atomiser (with Zeeman background correction) or Varian (Victoria, Australia), was used for platinum analysis. Platinum concentrations were determined in plasma, peritoneal fluid, tumour tissue, tumour cells and target tissues. Sample preparation has been described elsewhere [28]. A 4-stage heating program was used, consisting of drying at 110°C for 64 s, ashing at 1400°C for 75 s, atomising at 2650°C for 3 s, using maximum power, and conditioning at 2550°C for 5 s. The inert gas was nitrogen.

The PIXE facility at the Eindhoven University of Technology was used to study the platinum distribution in peritoneal tumours. The technical conditions and sample preparation have been described elsewhere [28, 33–35]. For the measurements of spatial distributions, cryostat sections of 40 μm were used. Platinum concentrations were determined in areas of 1600 μm^3 (beam size of about 40 μm diameter).

Statistics

The Wilcoxon test was used to study the significance, with P values > 0.05 considered to be not significant.

RESULTS

In vitro studies

The uptake of cisplatin into CC531 cells was increased at incubation temperatures of 40° and 43°C (Table 1). Parallel with the increased drug uptake, clonogenic assays on CC531 colon carcinoma cells showed a decrease in cell survival with an increase in cisplatin concentration (Fig. 1). At a fixed cisplatin dose (2.5 mg/l), cytotoxicity increased with elevated temperatures; survival decreased from 40% at 37°C to 5.5% at 40°C and to 2.5% at 43°C. The enhanced intracellular drug concentration

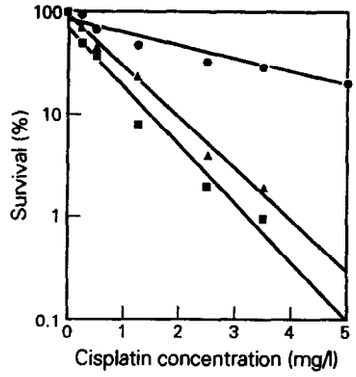

Fig. 1. Clonogenic assay of CC531 cells. Incubation with cisplatin at 37°C (●), at 40°C (▲) and at 43°C (■). All curves were adjusted for the control values at 37°C, 40°C and 43°C, and were performed in triplicate.

at higher temperatures correlated with the increase in cytotoxicity at higher temperatures ($r = 0.9$) (Table 1 and Fig. 1).

Thermometry

Animals were positioned in a thermostatically controlled water bath at 41.5°C. During treatment, temperatures were monitored every 5 minutes by six thermocouple probes positioned in the peritoneal cavity, the oesophagus and the rectum. Figure 2 shows the temperature as a function of heating time in these sites. Temperatures measured at different sites in the peritoneal cavity varied slightly, resulting in a mean (S.D.) temperature of the whole peritoneal cavity of 41.5 (0.3) (Table 2). The mean temperature at a distance of 6 cm into the rectum was 41.4°C while the temperature outside the heated area, as measured in the oesophagus, was more than 1°C lower, an important fact in view of the toxicity of WBH (Table 2, Fig. 2).

Pharmacokinetics

Pharmacokinetics in plasma for both total and ultrafiltered platinum differed significantly ($P < 0.05$) in rats treated with cisplatin alone or in combination with heat at a temperature of 41.5°C (Fig. 3 and 4A). The AUC for both total and ultrafiltrated platinum in plasma was 4 times larger in rats receiving regional hyperthermia, the $t_{1/2\beta}$ for total and ultrafiltrated platinum were

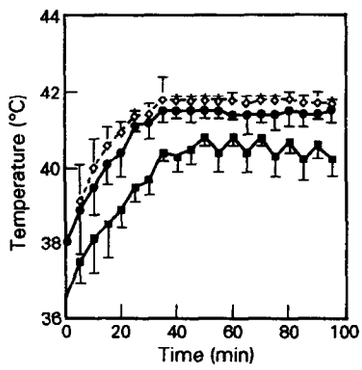

Fig. 2. Temperature measured in the peritoneal cavity (●), rectum (◇), and esophagus (■) plotted versus heating time in a water bath at a temperature of 41.5°C. Systemic heat loss during anaesthesia before the start of heating accounts for initial temperatures of approximately 37°C. Data points represent mean (S.D.) of 3 measurements.

Table 2. Thermometry in rats during regional hyperthermia at 41.5°C

Site	Temperatures (°C)*	Mean temperatures (°C)*
Intraperitoneally		
near spleen	40.5–41.8	41.5 (0.2)
near bladder	40.5–41.8	41.5 (0.2)
near right kidney	40.4–41.8	41.4 (0.1)
Rectum	41.3–42	41.4 (0.2)
Oesophagus	39.3–41	40.3 (0.1)
Water bath	41.3–41.5	41.5 (0.05)

Data were obtained during 8 heating sessions.
*During plateau phase.

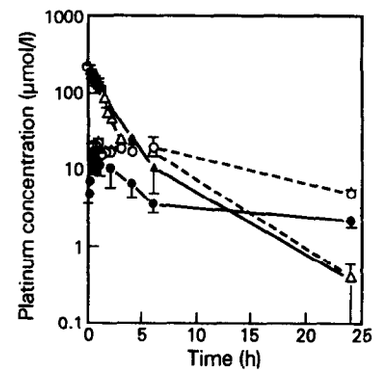

Fig. 3. Semilogarithmic concentration vs. time plots of total cisplatin (●) and cisplatin combined with regional hypethermia [41.5°C] (○) in plasma; and cisplatin (▲) and cisplatin + regional hyperthermia (△) in peritoneal fluid after intraperitoneal administration of 5 mg/kg cisplatin.

3 times longer in rats receiving heat and the T_{max} in plasma for ultrafiltered platinum occurred later (Table 3). The AUC for ultrafiltered platinum in the peritoneal cavity altered with heat, and significantly increased in rats receiving hyperthermia treatment (Table 3, Figs 4a and 4b). The other parameter, $t_{1/2\beta}$, did not change.

These pharmacokinetic findings indicate that peritoneal tumours were better exposed to drug via the installed fluid in

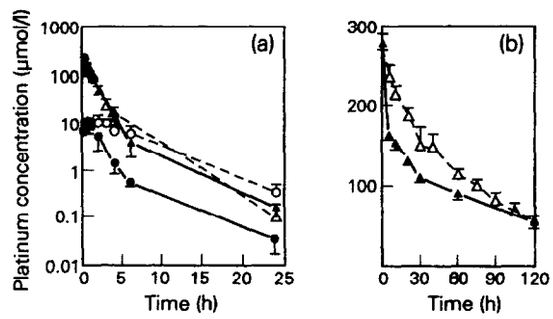

Fig. 4. (a) Semilogarithmic concentration vs. time plots of ultrafiltered cisplatin (●) and cisplatin + regional hyperthermia [41.5°C] (○) in plasma and peritoneal fluid (cisplatin: ▲, cisplatin + regional hyperthermia: △) after intraperitoneal administration of 5 mg/kg cisplatin (b). A detail of a from 0 to 120 minutes on a linear scale.

Table 3. Pharmacokinetic data in plasma and peritoneal cavity after intraperitoneal cisplatin at 37°C and 41.5°C

Parameter	Total platinum		Ultrafiltered platinum	
	37°C	41.5°C	37°C	41.5°C
AUC_{plasma} (0–24 h)	97.9 (14)	325.8 (85)*	22.2 (7)	107.0 (33)*
T_{max} (min)	40 (9)	55 (6)	40.0 (10)	110.0 (17)*
C_{max} (μM)	17.0 (2.6)	24.6 (3.0)	11.0 (1.7)	11.8 (1.2)
$t_{1/2\beta plasma}$ (min)	160 (30)	644 (114)*	74 (15)	227 (50)*
$AUC_{p.c.}$ (0–24 h)	482.0 (110)	566 (64)	339 (38)	486 (68)*
$t_{1/2\beta p.c.}$ (min)	78.0 (23)	68.6 (35)	65 (13)	60.3 (6.7)

p.c. = peritoneal cavity; AUC = area under the concentration × time curve (μmmol/l/min).
Results were obtained from at least four concentration × time curves for each treatment modality.
*Significant difference between treatment at 37°C and 41.5°C ($P < 0.05$), mean (S.D.).

the peritoneal cavity and the blood circulation after the combined treatment than after cisplatin treatment alone. The higher exposure by the blood circulation might be due to a lower excretion from the plasma.

Toxicity

Intraperitoneal administration of cisplatin in combination with regional hyperthermia (60 min at 41.5°C) led to a decrease in the cisplatin dose to reach maximum tolerated dose (MTD) from 5 mg/kg to 3.5 mg/kg. The calculated thermal enhancement ratio (TER), using lethality as endpoint (TER = LD_{50} cisplatin without hyperthermia/LD_{50} cisplatin with hyperthermia) was 1.8. Functional damage in the kidney, monitored by measuring creatinine levels at day 5, was expressed as a $TER_{creatinine}$ (calculated at 0.35 μmol/l) of 1.6 (Table 4). These data suggest that the increased mortality as a result of the combined treatment is due to renal failure.

In vivo biodistribution of cisplatin

Rats with peritoneal tumours were treated intraperitoneally with cisplatin, 5 mg/kg, at 37°C or in combination with regional hyperthermia at 41.5°C for 1 h. The animals were killed 24 h after cisplatin administration and tissues such as peritoneal tumours, liver, kidney, intestines, spleen and lung, were collected. Enhanced platinum concentrations were measured in all the selected tissues after the combined cisplatin plus regional hyperthermia treatment (Table 5). A striking difference was seen in the platinum concentration in tumour and intestine. Comparing 41.5°C with 37°C, platinum concentrations were 4.1 times higher in tumours but only 1.4 times higher in the intestines, despite the fact that both tissues were lying within the peritoneal cavity. The intestine result might be due to a decrease in the splanchnic blood flow initiated by higher temperatures. Of more importance with respect to toxicity was an increase in platinum concentration in the kidney of only 2, compared to 4.1 in the peritoneal tumours (Table 4).

Distribution of platinum in peritoneal tumors after intraperitoneal treatment with cisplatin alone or combined with regional hyperthermia

Platinum levels were determined quantitatively in tissue sections (thickness 40 μm) by PIXE, using a line scan from the center of the tumour outward to the periphery. Figure 5 shows platinum concentration profiles in tumours treated with 5, 12 mg/kg and 5 mg/kg cisplatin combined with regional hyperthermia (41.5°C, 1 h). Intratumoral platinum concentrations after combined treatment of cisplatin (5 mg/kg) with regional hyperthermia were larger than after a comparable cisplatin treatment at 37°C at every point measured. Increasing the cisplatin dose at 37°C to 12 mg/kg resulted in local tumour platinum concentrations comparable with 5 mg/kg cisplatin at 41.5°C for 60 minutes. Figure 5 also shows the absence of a platinum concentration gradient in the combined treatment group, in contrast to the 12 mg/kg group for drug alone. The homogeneous platinum distribution after the combined treatment of cisplatin and regional hyperthermia was probably due to a better penetration of cisplatin directly from the peritoneal cavity as well as from the circulation.

DISCUSSION

Hyperthermia enhances the cytotoxicity of chemotherapeutic agents but often also their toxicity [7, 22, 36]. In the present study, cisplatin was tested in combination with heat *in vitro* and *in vivo* in a peritoneal tumour model. An important observation was that intraperitoneal chemotherapy with cisplatin combined with regional heating of the abdomen resulted in increased

Table 4. Creatinine levels in serum of rats day 5 post treatment of cisplatin or cisplatin in combination with regional hyperthermia

Cisplatin dose (mg/kg)	Creatinine concentration (ng/ml)	
	Cisplatin 37°C	Cisplatin + 41.5°C, 1 h
0	36 (3)	ND
2	ND	160 (133)
3	75 (15)	ND
3.5	98 (30)	350 (350)
5	320 (69)	530 (100)
7	600 (450)	ND

$n = 4$, ND = creatinine levels not determined.

Table 5. Platinum concentrations in tissues after combination treatment with cisplatin intraperitoneally and regional hyperthermia (41.5°C, 1 h) and single treatment with cisplatin (5 mg/kg)

Tissues	μg platinum/g tissue		Factor
	37°C	41.5°C	41.5/37
Liver	3.3 (0.8)	7.1 (0.9)	2.1
Lung	1.8 (0.2)	4.1 (0.9)	2.2
Spleen	2.5 (0.4)	5.4 (1.3)	2.2
Intenstines	1.8 (0.2)	2.5 (0.3)	1.4
Kidney	12.1 (2.6)	24.6 (3.1)	2
Tumour	1.3 (0.6)	5.4 (0.9)	4.1
Plasma*	2.3 (0.4)	4.9 (0.7)	2.1

*Concentration in μmol/l.

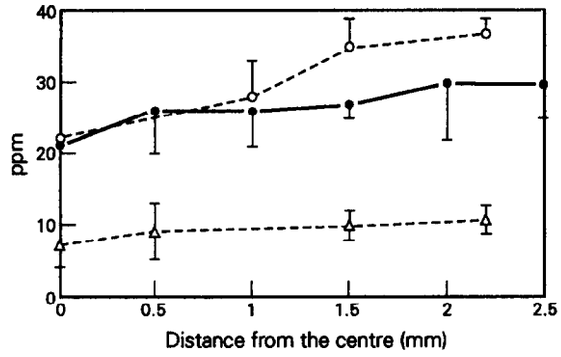

Fig. 5. Platinum distribution in intraperitoneal tumours measured by PIXE. Tumour bearing rats (WAG/Rij rat, CC531 tumour) were treated with 5 mg/kg cisplatin intraperitoneal (△), 12 mg/kg cisplatin (○) or with 5 mg/kg cisplatin intraperitoneally combined with regional hyperthermia (●). The spatial platinum distribution was determined by performing a line scan from the centre to the periphery of the tumour. At fixed distances in a frozen tissue section (thickness 40 μm) the platinum concentration was measured and expressed as ppm (part per million). Mean (S.D.) (n = 4).

platinum levels within peritoneal tumours while renal toxicity increased but remained manageable.

The *in vitro* studies demonstrated that heat facilitated the uptake of cisplatin into tumour cells and increased cytotoxicity. These data are in agreement with other studies, in which the cytotoxicity of cisplatin was enhanced by heat [12, 13, 37, 38]. An increase in temperature from 37°C to 40°C strongly affected the drug uptake of cisplatin into cells and the subsequent survival, while an increase in temperature from 40°C to 43°C resulted in only a marginal extra effect, indicating a possible threshold somewhere between 39°C and 41°C. Such a threshold was also suggested by Wheatly *et al.* [39].

Platinum concentration studies in tissues in our animal model confirmed the potential efficacy of intraperitoneal cisplatin combined with heat. Platinum concentrations in peritoneal tumours were 4.1 times higher if heat was added to the drug therapy. The spatial distribution of platinum in tumours after combined treatment indicated a more homogeneous distribution of the drug in comparison to intraperitoneal cisplatin alone [40]. In other words, the penetration depth of 1 to 2 mm as determined in previous studies [27, 40] was increased by heat, resulting in an additional aliqout of platinum available over the centre. A two-fold increase in platinum concentration in normal tissues was detected after the combined treatment. The platinum levels in tissues may have been over estimated, since platinum concentrations might be partly due to an increase of elevated platinum plasma concentrations at the time of tissue collection.

Regional hyperthermia enhanced the toxic side-effects of cisplatin. The thermal enhancement ratio, using lethality as an endpoint (TER = LD_{50} cisplatin without hyperthermia/LD_{50} cisplatin with hyperthermia), was 1.8. Wondergem *et al.* [25] reported a TER of 2.7 after the combination treatment of whole body hyperthermia (120 min, 41.5°C) with cisplatin in rats. It must be noted that our total heating period was around 90 min, composing a 30 min heating period (temperature increased from 37.5°C to 41.5°C) and a 60 min plateau period of 41.5°C, while Wondergem *et al.* had only a 120 min plateau period of 41.5°C. Considering functional damage using creatinine levels at day 5 (TER 1.6), it seemed that the increased mortality as a result of the combined treatment is due to renal failure. This is in agreement with findings of Wondergem *et al.*, who observed a $TER_{creatinine}$ (calculated at 0.4 μmol/l) of 3.4 after whole body hyperthermia (120 min 41.5°C) in combination with cisplatin [41]. Compared with our $TER_{creatinine}$ of 1.6 it can be concluded that a combination of cisplatin with regional hyperthermia is better tolerated than a combination with whole body hyperthermia. In contrast to our animal model, patients receiving cisplatin in the clinic are generally vigourously prehydrated and often get rescue agents such as sodium thiosulphate systemically, in order to lessen cisplatin-induced renal toxicity [42]. Under such circumstances nephrotoxicity due to heat and cisplatin might be avoided.

Two important pharmacokinetic parameters differed for the treatment at 41.5°C compared with that at normal temperatures. The first was that the tumour received a higher exposure by cisplatin in the instilled peritoneal fluid, i.e. the AUC for ultrafiltered platinum was significantly higher after the combined treatment. The second difference was the increased exposure of the tumour by cisplatin in the systemic circulation. The AUC for both ultrafiltered and total platinum in plasma were increased. This was probably due to a reduced renal blood flow [29, 43], which in turn may have affected the renal handling of cisplatin. The latter is supported by a much slower clearance of platinum from the systemic circulation, i.e. the half-life ($t_{1/2\beta}$) was increased by 4 times in comparison with the treatment at normal temperatures. Some of our pharmacokinetic data are in contrast with data published by Zakris *et al.* [44]. In their study, the half-life of cisplatin in the peritoneal cavity of beagle dogs was increased by a factor of 2 after intraperitoneal cisplatin and regional hyperthermia. Our data demonstrated no changes in half-life, as demonstrated in Fig. 4. In addition, the decreased AUC for free drug in the plasma did not correspond with our data. This might, however, be explained by their use of a systemic cooling system, [44]. Our plasma data were more consistent with changes in intravenous cisplatin pharmacokinetics induced by WBH [45].

This investigation demonstrated that regional abdominal hyperthermia in the rat can be consistently and safely achieved and maintained using a simple heating system. The rectal temperature indicated that elevated temperatures of 41.5°C can be reached in peritoneal tissues. Temperatures outside the heated area, measured in the oesophagus, were more than 1°C lower than that in the peritoneal cavity, an important factor in relation to systemic toxicity. In the beagle study mentioned above, the temperature outside the heated area was maintained between 37°C and 39°C using systemic cooling [44].

This study may have clinical relevance, since it has been demonstrated that intraperitoneal cisplatin treatment could improve clinical responses in patients with ovarian cancer who failed to respond to systemic cisplatin treatment [2]. Further improvements in terms of therapeutic index might therefore be achieved by combining intraperitoneal treatment with regional hyperthermia. We demonstrated in our rat model that the drug–heat combination exposed peritoneal tumours to more cisplatin than after cisplatin treatment alone, resulting in higher intratumour platinum concentrations. Renal toxicity was less than that seen after whole body hyperthermia. Furthermore, since regional heating of the abdomen is clinically feasible [46] and can be performed without general anaesthesia, in contrast to total body hyperthermia, this combination treatment might be effective in the treatment of cancers restricted to the peritoneal cavity.

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