Pharmacokinetics of doxorubicin and cisplatin used in intraoperative hyperthermic intrathoracic chemotherapy after cytoreductive surgery for malignant pleural mesothelioma and pleural thymoma

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Cytoreductive surgery combined with intraoperative hyperthermic intrathoracic chemotherapy (HITHOC) is studied in a phase I study in the treatment of malignant pleural mesothelioma and pleural thymoma. We studied the pharmacokinetics of doxorubicin and cisplatin used during the HITHOC procedure. Furthermore, the penetration characteristics of doxorubicin were examined. Between 1998 and 2001, 24 perfusions were performed with a solution containing doxorubicin and cisplatin for 90 min at 40–41°C. The dose was first based on square meters body surface, whereas in later studies a fixed concentration of the perfusion fluid was used. Samples of blood and perfusion fluid were collected for doxorubicin and cisplatin measurements. The penetration characteristics of doxorubicin in tissue were determined by fluorescence microscopy. The mean $AUC_{perfusate}$:AUC_{plasma} ratios for doxorubicin and cisplatin (ultrafiltration for plasma) were 99 and 59, respectively. During perfusion the concentration in the perfusate declined essentially according to first-order elimination kinetics for both doxorubicin and cisplatin with half-lives of 74 and 138 min, respectively. At the end of the perfusion, about 35 and 52% of the dose of doxorubicin and cisplatin, respectively, was recovered in the perfusion fluid. One patient developed a nephrotoxicity grade II. No leukopenia or hair loss was seen. Doxorubicin penetrated into the intercostal muscle specimen, albeit that there was considerable variation in distribution throughout the specimen. We conclude that HITHOC with doxorubicin and cisplatin is relatively a safe procedure with the advantage of high intrathoracic cytostatic drug concentrations, while having limited systemic side effects. *Anti-Cancer Drugs* 14:57–65 © 2003 Lippincott Williams & Wilkins.

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Introduction

Malignant pleural mesothelioma (MPM) and pleural thymoma are diseases mostly confined to the thoracic cavity [1]. When untreated, the prognosis of MPM is poor with a median survival of less than 1 year [2]. Surgery alone is associated with a high recurrence rate and therefore surgery combined with adjuvant therapies has gained popularity in recent years [3,4]. For pleural thymoma no curative therapy is known [5]. Systemic chemotherapy has been reported to be of limited value. Multimodality treatment seems to result in a better outcome [6,7].

One of these experimental multimodality treatments is the combination of cytoreductive surgery with intraoperative hyperthermic intrathoracic chemotherapy (HITHOC). Intracavitary chemotherapy has the advantage of a high local concentration of the cytostatic drug with limited systemic side effects [8]. Hyperthermia is known to enhance the cytotoxicity of some chemotherapeutics and to increase the penetration depth, and is, therefore, considered to be a useful addition [9,10]. As the penetration depth of intracavitary chemotherapy is limited to a few millimeters at most, cytoreductive surgery aimed to remove all macroscopically visible lesions is mandatory [11–14]. In the abdomen there is now ample experience with this multimodality treatment [15,16]. In theory, the same principles should also apply to the thoracic cavity.

Patients with limited MPM or pleural thymoma are treated in our hospital in a phase I study with the combination of cytoreductive surgery and subsequent HITHOC [17]. We used doxorubicin and cisplatin because of the reported sensitivity of MPM and pleural thymoma for these cytostatic drugs [6,7,18,19]. In this paper we present the pharmacokinetics of doxorubicin and cisplatin used as cytostatic drugs during the HITHOC procedure. Furthermore, we studied the penetration characteristics of doxorubicin.

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Patients and methods

Patients

A total of 23 patients were treated in our institute in the period from 1998 and 2001. One patient underwent a second HITHOC procedure because of contralateral recurrence. Patients with a good general condition (WHO 0–1 performance status) were asked to participate in this study. Inclusion criteria included normal cardiac, renal and liver functions. A sufficient pulmonary function for thoracotomy and, if needed, pneumonectomy was mandatory. The maximum age for inclusion was 70 years. Both patients with stage I malignant pleural mesothelioma (TNM of IMIG classification [20]) on pre-operative staging or patients with isolated unilateral pleural metastases of thymoma were included. The ethics committee of the Institute approved the study protocol.

Surgery

After thoracotomy an extrapleural dissection was performed between the parietal pleura and the chest wall, diaphragm and mediastinum. When the dissection reached the hilar structures, the decision was made whether to perform a pneumonectomy when the lung was too much involved or damaged, or to limit resection to a decortication of involved pleura. Aggressive surgical cytoreduction was carried out with the aim to reach complete resection or, if not possible, to leave only visible tumor residue smaller than 2.5 mm.

HITHOC

After completion of cytoreductive surgery the perfusion system was set up [17]. A Tenckhoff inflow catheter and three silicone outflow catheters were placed in the thoracic cavity. A temperature sensor was attached to each catheter. The skin wound was firmly closed with sutures. The catheters were connected with a fluid filter, roller pump and heat exchanger. Thereafter the closed system was filled with an isotonic dialysis fluid (Dianeal PD1; Baxter, Uden, The Netherlands). When the temperature of 40–41°C was reached in all regions, the cytostatic agents were added as bolus to the perfusion system. The first 18 procedures were performed using a fixed dose of cisplatin (80 mg/m^2) and doxorubicin starting at 15 mg/m^2 with increments of 5 mg/m^2 per dose step. A different dose method was applied for the last six patients. Doxorubicin was given in three patients at a dose of 18 mg/l; three other patients were given 21 mg/l (Table 1). Cisplatin was given at a fixed dose of 40 mg/l perfusion liquid.

The body temperature, measured in the pharynx, was maintained below 39.5°C. If the body temperature exceeded 39°C, the temperature of the perfusion fluid was reduced to 40°C. The duration of perfusion was 90 min at a flow rate of 1 l/min. During the perfusion the contralateral lung was ventilated separately. The ipsilateral lung, if reserved, was inflated at a pressure of 15 cm water using oxygen, keeping the lung semi-inflated, thus allowing sufficient space between lung parenchyma and the chest wall for adequate perfusion, but limiting the possible toxicity of cytostatic drugs to collapsed lung parenchyma. At the completion of the procedure, the perfusion fluid was removed, leaving drains in the pleural top and sinus. Thereafter the chest was closed using standard procedures.

Pharmacokinetics

Blood and perfusate samples were collected for doxorubicin measurements at several time points during and after completion of the perfusion (perfusate 1–30–90 min; blood 1–10–15–30–45–60–75–90–120–180–240 min and 18 h). After centrifugation for 10 min at 1000 *g*, the supernatant perfusate and plasma samples were separated and stored at −20°C until analysis. Cisplatin was determined in plasma ultrafiltrate prepared only from samples taken during the perfusion. Samples of 24-h urine were collected from two patients for cisplatin measurements. Doxorubicin levels were determined by high-performance liquid chromatography [21,22]. Cisplatin levels were determined by flameless atomic absorption spectrometry [23]. The area under the curve during the 90 min perfusion fluid ($AUC_{0–90}$) values of doxorubicin and cisplatin in perfusate and cisplatin in plasma ultrafiltrate were calculated using the linear trapezoidal rule without extrapolation to infinity. The distribution and elimination half-lives of doxorubicin after cessation of the perfusion were calculated using the software program Mediware [24]. The total $AUC_{0-\infty}$ of doxorubicin in plasma was calculated by summation of the $AUC_{0–90}$ plus the $AUC_{90-\infty}$ of doxorubicin calculated from the exponential analysis in Mediware. The results of the first four procedures were excluded from further analysis because of technical problems in sample collection.

Doxorubicin absorption test

To exclude the possibility that doxorubicin would disappear due to adsorption to any component of the perfusion equipment, we performed a perfusion experiment using the same system and conditions, except that a glass box replaced the patient. Either polypropylene or polystyrene tubes, used for sample collection, were tested.

Statistics

Statistical analysis was performed with Statistical Package for the Social Sciences software (SPSS 10.0; Chicago, IL). Linear regression was applied by univariate analysis with covariates (ANCOVA) to test relationships between the variables $AUC_{perfusate}$, AUC_{plasma}, liters perfusion fluid and the event of pneumonectomy. $p < 0.05$ was considered significant.

Table 1 **Pharmacokinetics of doxorubicin and cisplatin during the HITHOC procedure**

No.	Perfusion fluid (l)	Doxorubicin						Cisplatin				
		Dose	Target concentration (mg/l)	AUC_{0-90} perfusate (μmol · l/h)	AUC_{0-90} plasma (μmol · l/h)	$AUC_{0-\infty}$ plasma (μmol · l/h)	AUC ratio (ratio)	Dose	Target concentration (mg/l)	AUC_{0-90} perfusate (μmol · l/h)	AUC_{0-90} plasma (μmol · l/h)	AUC ratio (ratio)
1	5	21 mg/l	21	36.0	0.046	0.23	157	40 mg/l	40	131.5	1.95	67
2	4	21 mg/l	21	34.9	0.049	0.27	129	40 mg/l	40	130.1	1.8	72
3	4	21 mg/l	21	38.6	0.068	0.35	110	40 mg/l	40	131.4	2.26	58
4	3	18 mg/l	18	19.8	0.048	NA	NA	40 mg/l	40	122.5	2.55	48
5	7	18 mg/l	18	29.6	0.081	NA	NA	40 mg/l	40	154.1	2.85	54
6	6	18 mg/l	18	31.9	0.086	0.38	84	40 mg/l	40	108.8	2.01	54
7	6	35 mg/m^2	10.8	13.5	0.042	0.29	47	80 mg/m^2	24.7	72.6	ND	ND
8	4	35 mg/m^2	17.5	17.1	0.040	0.25	68	80 mg/m^2	40	89.0	ND	ND
9	6	35 mg/m^2	11	10.7	0.062	0.32	33	80 mg/m^2	25.3	40.0	ND	ND
10	2	25 mg/m^2	16.6	15.4	0.029	NA	NA	80 mg/m^2	53	100.4	ND	ND
11	6	30 mg/m^2	10.5	21.5	0.061	0.30	72	80 mg/m^2	28	58.7	ND	ND
12	5.8	30 mg/m^2	10.3	15.1	0.035	NA	NA	80 mg/m^2	27.6	58.2	ND	ND
13	4.5	30 mg/m^2	12	17.5	0.016	NA	NA	80 mg/m^2	32	83.6	ND	ND
14	4	25 mg/m^2	10	17.8	0.035	0.19	94	80 mg/m^2	32	85.6	ND	ND
15	5	25 mg/m^2	8.8	13.9	0.025	NA	NA	80 mg/m^2	28	52.7	ND	ND
16	5	25 mg/m^2	10	16.9	0.022	0.15	113	80 mg/m^2	32	ND	ND	ND
17	4.5	25 mg/m^2	9.7	15.2	0.010	NA	NA	80 mg/m^2	31.1	62.1	ND	ND
18	4	25 mg/m^2	13.1	14.7	0.022	NA	NA	80 mg/m^2	42	125.5	ND	ND
19	3	25 mg/m^2	14	17.4	NA	NA	NA	80 mg/m^2	44.8	91.0	ND	ND
20	5	25 mg/m^2	9.2	23.3	0.027	0.13	179	80 mg/m^2	29.6	80.2	ND	ND
mean				21	0.042	0.26	99			93.6	2.24	59

NA: not available because of incomplete series of samples.
ND: not determined.

Penetration characteristics of doxorubicin

After cessation of the perfusion a piece of perfused intercostal muscle (about 1 cm^3) was removed to determine the penetration characteristics of doxorubicin. The side in contact with the perfusion fluid was marked. After rinsing the specimen with saline, it was frozen to -80°C in a tissue medium (Cryoblock; Klinipath, Duiven, The Netherlands). Cryosections of 4 μm thickness were prepared and stored at -20°C. Fluorescence of doxorubicin was visualized to determine the penetration characteristics by using fluorescence microscopy. An Axiovert S-100 microscope (Zeiss, Oberkochen, Germany) was used with a mercury light source and a filter block provided with band-pass filter of 450–490 nm for excitation, a FT510 beam splitter and an emission long-pass filter of 520 nm. Objectives (Plan-Apochromat) of $\times 10$ and $\times 20$ magnifications were used. Images were sampled using an Axiocam HR camera in combination with AxioVision software (version 3.1). Next, the same slides were stained with hematoxylin & eosin and images of the same areas were sampled by transmission light microscopy using the same equipment.

Results

Surgery and HITHOC procedure

Twenty-four procedures were performed in four females (one malignant pleural mesothelioma and three pleural thymoma patients) and 19 males (all malignant pleural mesothelioma patients). One patient underwent a second HITHOC procedure because of contralateral recurrence of thymoma. The median age of patients was 57 years (range 34–68). The side of localization was 11 times left and 13 times right. To achieve optimal removal of the tumor mass the pericardium was opened in 17 cases. In 14 cases the diaphragm was partial opened or removed. A pneumonectomy was necessary in nine cases; in 15 cases only a decortication was performed. The median duration of the procedure was 6.5 h (range 4.5–8.5) including 90 min of perfusion. Median blood loss was 1.8 l (range 0.4–5.1). The median given number of packed cells was 2 units (range 0–9).

The highest dose of doxorubicin given was 35 mg/m^2. The median amount of Dianeal needed to fill the thoracic cavity and the perfusion circuit was 4.3 l (range 2–7), and depended strongly upon gender and whether a pneumonectomy was performed. The median difference in volume of perfusion fluid before and after perfusion was nil (ranging from -1.5 to $+0.7$ l). During the perfusion the maximum temperature of the perfusate was 40.2–43°C (inflow catheter). The maximum body temperature varied between 36.8 and 39.4°C. Only in one case was the perfusion aborted after 80 min because of hemodynamic instability of the patient.

Systemic toxicity was encountered in the first patient only, who showed transient nephrotoxicity grade II (Common Toxicity Criteria). In the following procedures the per-operative hydration was improved by maintaining a diuresis of at least 40 ml/h. After this precaution similar nephrotoxicity was not observed. Doxorubicin-related side effects such as leukopenia and hair loss were not

observed. Nausea and vomiting were not scored because the combination with thoracic surgery makes it difficult to differentiate chemotherapy-related effects from post-operative symptoms. Major surgical complications were observed in 14 patients (58%). There was no 30-day mortality. The median hospital stay was 16 days (range 11–77).

Pharmacokinetics

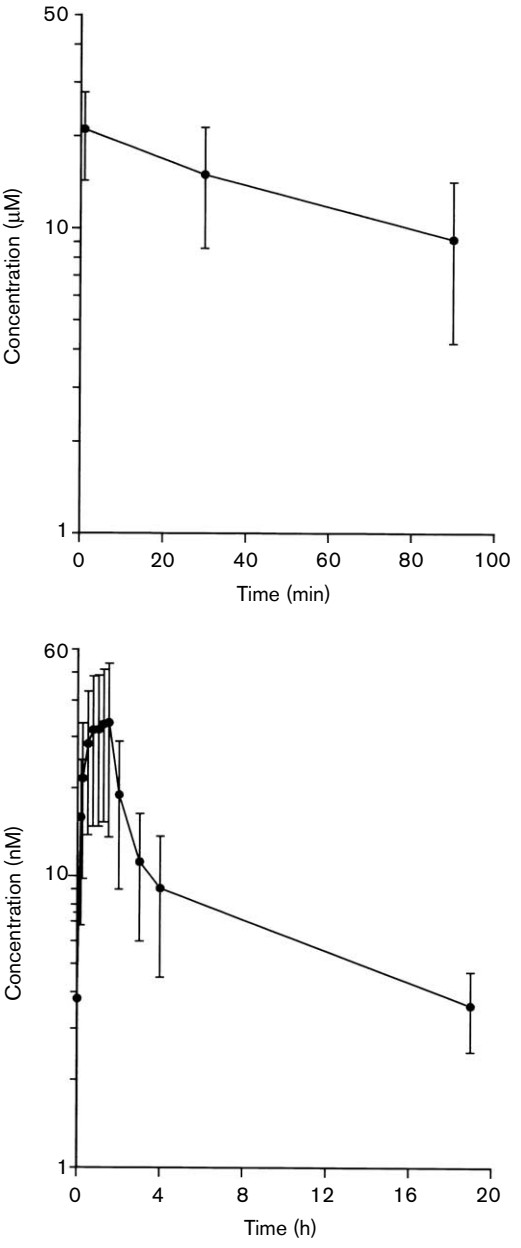
Dose-finding steps of doxorubicin were 15 (one patient), 20 (two patients), 25 (nine patients), 30 (three patients) and 35 (three patients) mg/m^2, whereas the cisplatin dose level was not increased (Table 1). As the amount of fluid used for the perfusion varied from patient to patient, the actual concentration of both drugs in perfusate varied between 8.3 and 17.5 mg/l for doxorubicin and between 24.7 and 53 mg/l for cisplatin. Because of this, the last six patients received both drugs at fixed concentrations per liter perfusion fluid.

In 20 procedures the concentration of doxorubicin in perfusate was measured. At 1 min after injection of the drug into the perfusion system, the concentration of doxorubicin was 21.1 ± 6.8 μmol/l (mean $\pm$ SD), corresponding to 81 ± 12% of the administered dose. During the following 90 min the concentration in the perfusate declined essentially according to first-order elimination kinetics with a half-life of approximately 74 ± 34 min (Fig. 1). At the end of perfusion about 35 ± 17% of the dose was recovered in the perfusate fluid. In plasma the concentration of doxorubicin increased gradually, reaching almost steady-state levels within 90 min with a C_{max} ranging between 9.3 and 76 nmol/l (Fig. 1). After cessation of the perfusion the doxorubicin concentration decreased according to two-compartmental decay kinetics with mean distribution and elimination half-lives of 21 min and 13.5 h, respectively. Unfortunately the plasma sample that was scheduled to be drawn at approximately 20 h after the HITHOC procedure was missing in a number of patients, whereas this sample was essential for an accurate calculation of the elimination half-life and $AUC_{0-\infty}$. The area under the curves of doxorubicin in plasma increased linearly with dose.

Already at 1 min after administration of doxorubicin, we recovered only 80% of the dose in the perfusion circuit.

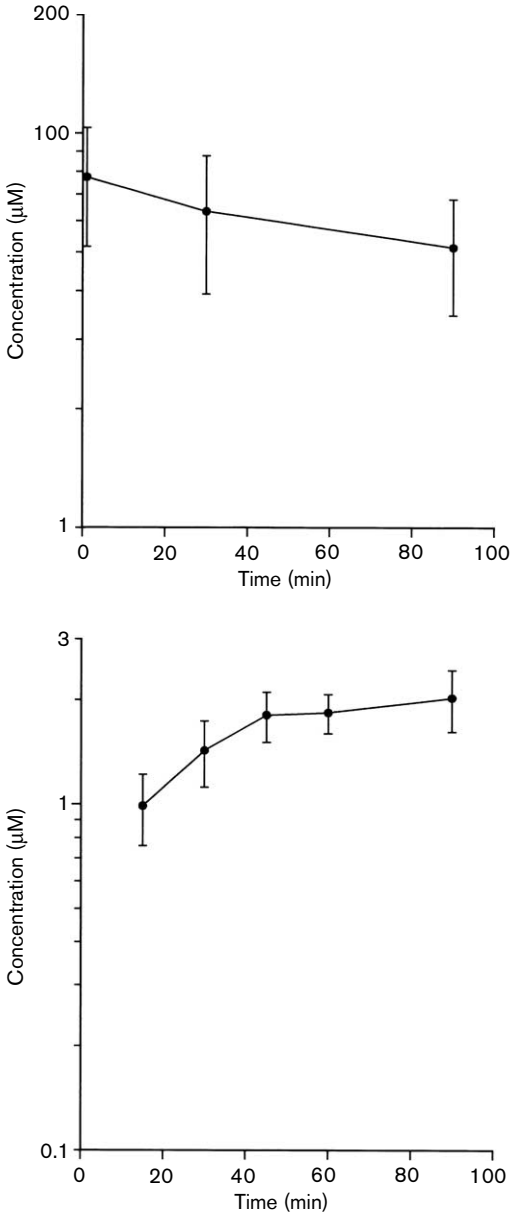
The concentration of cisplatin in perfusate was measured in 19 procedures and in the last six patients also in plasma ultrafiltrate during the perfusion period of 90 min. At 1 min after injection of the drug into the perfusion system, the concentration of cisplatin was 77.5 ± 25.9 μmol/l (mean $\pm$ SD), corresponding to only about 68 ± 21% of the administered dose. When taking into account only the last six patients who received cisplatin at a fixed concentration of 40 mg/l, the recovery was 82 ± 5% of the dose at 1 min. During the following 90 min the concentration in the perfusate of these latter patients declined essentially according to first-order elimination kinetics with a half-life of approximately 138 ± 20 min and at the end of perfusion about 52 ± 7% of the dose was recovered in the perfusate fluid (Fig. 2). In plasma the concentration of cisplatin increased gradually reaching almost steady-state levels at 90 min (Fig. 2). The C_{max} in plasma ultrafiltrate was 2.03 ± 0.41 μmol/l

Fig. 1



The course of doxorubicin concentration (mean $\pm$ SD) on a logarithmic scale in relation to time measured in perfusate (top) and plasma (bottom).

Fig. 2



The course of cisplatin concentration (mean ± SD) on a logarithmic scale in relation to time measured in perfusate (top) and plasma (bottom).

and the AUC_{0-90} was $2.24 \pm 0.40\ \mu mol \cdot l/h$. The $AUC_{0-\infty}$ could not be calculated, as no plasma ultrafiltrate was prepared from samples drawn after the end of the perfusion. A 24-h urine sample was collected from two of the patients receiving cisplatin at a fixed dose of 40 mg/l and showed that 7.5% of the total dose cisplatin was recovered in the urine. The measured concentration in perfusate of these two patients declined from 33 mg/l (82% of the dose) to 19.5 and 21.8 mg/l (49 and 55% of the dose), respectively, after 90 min of perfusion.

Doxorubicin absorption test

To exclude the possibility that the 20% of doxorubicin had disappeared due to adsorption to any component of the perfusion equipment, we performed a perfusion experiment using the same system and conditions, except that a glass box replaced the patient. When using this system we recovered nearly 100% of doxorubicin in the samples throughout the complete period of 90 min. Either polypropylene or polystyrene tubes could be used for sample collection.

Statistics

No relation was found between $AUC_{perfusate}$ or AUC_{plasma} for doxorubicin and for cisplatin and the covariates liters perfusion fluid and the event of pneumonectomy.

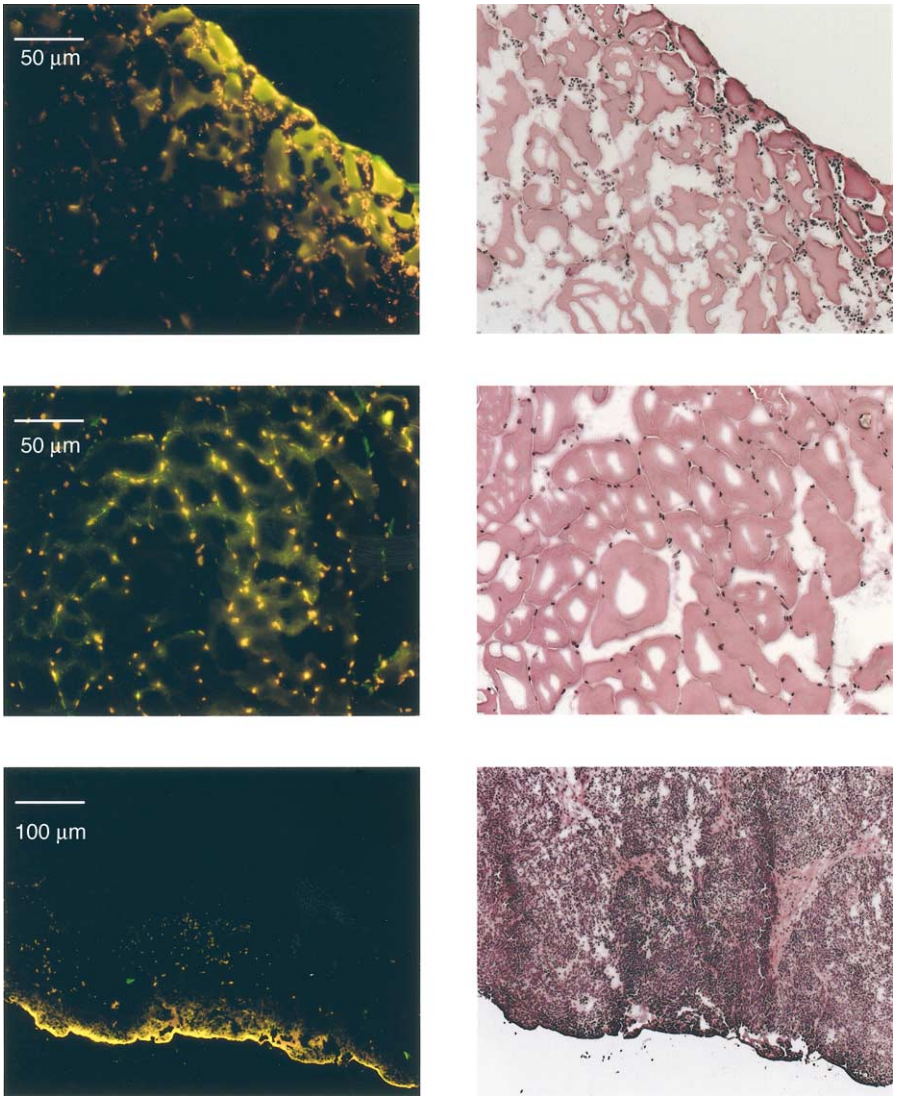
Penetration characteristics of doxorubicin

After perfusion, a piece of intercostal muscle was obtained from several patients to examine the penetration characteristics of doxorubicin under hyperthermic conditions. In two patients residual tumor was also found after perfusion and was resected for analysis. Fluorescence microscopy could visualize doxorubicin in the cells of intercostal muscle in all cases (Fig. 3). However, the penetration of doxorubicin in the intercostal muscle specimen was not very uniform throughout the tissue. Some areas showed intense doxorubicin fluorescence, whereas other areas were virtually dull. Intense fluorescence was present at the peripheral side of the tissue that was exposed to doxorubicin; however, there was a sharp concentration gradient (Fig. 3, upper panel). Within these areas infiltrating white blood cells with doxorubicin-bright nuclei were observed. These areas may contain tumor cells seeded throughout the thoracic cavity. Even at more distant sites from the periphery, doxorubicin-bright nuclei were found in some areas (Fig. 3, middle panel). This involved both muscle cells and supporting endomysial cells. In the tumor sample doxorubicin could only be detected in the outer rim, although in some areas of the tumor more distant from the periphery some clusters of doxorubicin nuclei were detected (Fig. 3, lower panel).

Discussion

This is the first study describing the pharmacokinetics and penetration characteristics of doxorubicin after intrathoracic perfusion with concomitant cisplatin and hyperthermia. Although the surgical procedure is complex, leading frequently to secondary complications, the therapy is safe from the pharmacokinetics/pharmacodynamics perspective. Only a few other studies dealing with the pharmacokinetics of intrapleural or intraperitoneal instillation of doxorubicin have been reported [13,25–27]. In our series we found a mean ratio for $AUC_{perfusate}$: AUC_{plasma} of 99 for doxorubicin, showing the feasibility of reaching a high local exposure of doxorubicin with only

Fig. 3



The penetration characteristics of doxorubicin visualized by fluorescence microscopy. Fluorescence (left panel) and hematoxylin & eosin stained slides (right panel). Upper panel: intercostal muscle exposed to doxorubicin, peripheral site, magnification × 20. Middle panel: intercostal muscle, example of area more distant from exposed site, magnification × 20. Lower panel: tumor (malignant pleural mesothelioma) exposed to doxorubicin, magnification × 10.

minimal systemic uptake. This ratio is lower than after hyperthermic intraperitoneal perfusion with doxorubicin, as described by Rossi *et al.* [27]. In that study, however, the ratio is somewhat overestimated because for plasma the AUC_{0-90} was used instead of the $AUC_{0-\infty}$. The high ratio is probably due to the moderate to high molecular weight and moderate lipophilicity of doxorubicin, limiting passive diffusion through cellular membranes. A major safety issue in studies using perfusion of cavities with cytotoxic drugs for treatment of locally disseminated cancers is the resulting systemic drug exposure. When perfusions were given at the highest concentration (21 mg/l), the mean systemic exposure ($AUC_{0-\infty}$) was 0.28 μmol · l/h, only 1/10 to 1/15 of the systemic exposure following a therapeutic dose of doxorubicin given by i.v. administration [28–30]. Although the study by Ratto *et al.* [31] showed that pneumonectomy might affect the systemic absorption of cisplatin, we did not find this relation for doxorubicin.

Remarkably, only 81% of the dose was recovered in the perfusate fluid almost immediately after the start of the perfusion. This was not due to adsorption of doxorubicin to the walls of the perfusion device. Most likely,

doxorubicin adheres rapidly to tissue structures in the thoracic cavity (e.g. endothoracic wall, pericardium and mediastinum) during the first passage through the thoracic cavity. At the end of the perfusion the fraction of doxorubicin recovered in the perfusate decreased to 35% of the dose. Rapid systemic uptake in the first minute seems unlikely, given the course of the plasma concentration–time curve and because the $AUC_{0-\infty}$ remains low. This result suggests that doxorubicin is retained in the superficial tissue structures. As shown by fluorescence microscopy, there are substantial deposits of doxorubicin in the intercostal muscle layer (Fig. 3). The distribution of doxorubicin is mainly located in the outer rim of the tissue, although a substantial variation is observed between different regions of the tissue sections. In part, this may be related with the relatively loose structure of this tissue, where drug may be able to penetrate deeper through pores into the tissue. In line with previous observations the penetration of doxorubicin in tumors is limited, probably due to the much more dense structure of tumor tissue [13]. Therefore, effect of the intrathoracic chemotherapy can only be expected in minimal residual disease, emphasizing the importance of the multimodality approach. Only single tumor cells and small clusters of tumors present in the thoracic cavity and/or the superficial cells of the endothoracic wall, pericardium and mediastinum may be targeted by intrathoracic perfusion.

In this study we used different dose methods of doxorubicin. The cytotoxic effect of the chemotherapy is related to concentration of the cytostatic drug in the perfusate fluid. Dosage on a mg/m^2 basis, which was used initially, has the disadvantage that the concentration of the cytostatic drug in the perfusate depends on the amount of perfusion fluid needed to fill the thoracic cavity. We therefore switched to dosing based on a fixed concentration in the perfusion fluid in the last six patients. This resulted in more consistent data on area under the curves (Table 1). The difference in volume of perfusion fluid before and after perfusion, probably due to loss of fluid occurring from an opened diaphragm or, when increased, through leakage of blood into the thoracic cavity, was rather limited. Dosing based on a fixed concentration of the perfusion fluid seems preferable in order to reduce inter-individual variation.

Several studies described the pharmacokinetics of cisplatin when instilled into the pleural cavity either with or without hyperthermia [31–36]. In line with these studies we found high local drug exposure of cisplatin in the thoracic cavity. After administration of cisplatin in the perfusion fluid about 68% of the total dose was recovered in the 1-min sample. During the perfusion period this percentage further decreased by another 26–42%, being about similar to the recovery of doxorubicin. The found mean ratio $AUC_{perfusate}$:AUC_{plasma} of 59 is probably an overestimate because for plasma only the AUC_{0-90} instead of the preferred $AUC_{0-\infty}$ was available. In our series the mean AUC_{0-90} of cisplatin in plasma was 2.24 μmol · l/h. This is approximately 3–5 times lower the level found after a therapeutic dose of cisplatin i.v [35,37–39]. However, as indicated above, the AUC_{0-90} underestimates the true AUC. Bogliolo *et al.* [35], who compared the pharmacokinetics of equal doses of cisplatin given either intrapleurally by instillation without draining or i.v., found that the plasma AUC for ultrafilterable cisplatin following i.v. therapy were similar to those observed after intrapleural therapy. The peak plasma level after intrapleural therapy was 3.4-fold lower, but sustained plasma levels were found after intrapleural administration compared to i.v. administration [35]. These results suggest that the complete intrathoracic dose ultimately reaches the systemic circulation. We found that 7.5% of the dose of cisplatin was recovered as cisplatin in the urine, whereas others have reported that 23% of the dose was recovered in the urine following i.v. administration of cisplatin [39]. Taking the AUC_{plasma} data and the urinary excretion data together, the results suggest that about one-third of the intrathoracic administered dose reaches the systemic circulation within 90 min of perfusion, while only about 50% of the dose is recovered in the perfusate fluid at the end of the perfusion. This discrepancy may be due to irreversible binding of cisplatin to tissue structures in the thoracic cavity. If so, this binding has likely been induced by hyperthermia, since Bogliolo *et al.* [35] did not find any loss in cisplatin. Studies of Ratto *et al.* [31] suggest that the lung plays an important role in cisplatin absorption from the pleural space. Our series, however, do not indicate any relationships between AUC_{plasma} and the event of pneumonectomy, probably due to the limited number of patients.

Overall, the HITHOC procedure proved to be safe. Chemotherapy-related toxicity was absent in all patients except one. This first patient showed a mild nephrotoxicity (grade II), which was most probably related to the combination of cisplatin and inappropriate hydration. This complication was not further observed in subsequent patients upon improving the per-operative hydration. Even in patients with an open pericardium where doxorubicin has free access to the heart muscle, there was no cardiotoxicity, a complication previously described after intrapleural administration of doxorubicin in rabbits [40]. Transient atrial fibrillation was noticed in several patients; however, this is a frequent finding after pneumonectomy and is not necessarily related to doxorubicin. A cardiac tamponade observed in one patient was due to a hemorrhage due to overdose of anticoagulation therapy. All surgery-related complications like diaphragm rupture

and bronchopleural fistula could be managed correctly leading to a WHO 0–1 performance status at discharge in all patients. It seems unlikely that chemotherapy perfusion contributed to surgical complications. It is known that pleurectomy/pleuropneumonectomy by itself is accompanied by a considerable morbidity [41,42]. In future studies the dose of doxorubicin can be increased safely with the knowledge that in this study the systemic exposure remained low. In the case of doxorubicin, local toxicity may become a more restrictive factor than systemic toxicity. Further dose escalation with cisplatin should be done with great caution, since a substantial fraction of the dose reaches the systemic circulation.

In conclusion, HITHOC with doxorubicin and cisplatin is a relative safe procedure with the advantage of high intrathoracic cytostatic drug concentrations with limited systemic exposure. The results indicate that a substantial fraction of drug is adhered to superficial structures within the thoracic cavity, although the penetration of drug into the tissue is not very deep and seems highly variable from region to region. Dosing based on a fixed concentration of the perfusion fluid is preferred in order to reduce inter-individual variation.

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