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Docetaxel Accumulates in Lymphatic Circulation Following Subcutaneous Delivery as Compared to Intravenous Delivery in Rats

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Abstract

Background—The circulatory pathway for particles deposited outside of blood capillaries has not been well characterized for non-traditionally-delivered chemotherapeutics.

Materials and Methods—Blood and lymph pharmacokinetics of docetaxel (5 mg/kg) and carboplatin (14 and 28 mg/kg) following subcutaneous (s.c.) versus intravenous (i.v.) delivery were determined in a rodent model with catheterizations of both the thoracic lymphatic duct and jugular vein for prolonged synchronous blood and lymph sampling.

Results—Subcutaneous docetaxel demonstrates preferential lymphatic accumulation based on the area under the time-concentration curve ($AUC_{0–24h}$) whereas i.v. docetaxel resulted in a greater plasma maximum concentration measured (C_{max}). The apparent elimination half-life ($t_{1/2}$) in lymph for docetaxel is greater following i.v. or s.c. delivery as compared to $t_{1/2}$ in blood. Carboplatin demonstrates a dose-dependent increase in plasma C_{max} regardless of delivery route; the total carboplatin exposure over 24 hours in lymph and plasma are comparable.

Conclusion—Subcutaneous docetaxel achieves lymphatic accumulation greater than with i.v. delivery.

Keywords

Lymph; subcutaneous administration; docetaxel pharmacokinetics; carboplatin pharmacokinetics

Introduction

The pharmacokinetics of intravenous (*i.v.*) chemotherapy, including carboplatin and docetaxel, are well delineated. The use of *i.v.* chemotherapy is an indisputable pillar of cancer therapy; however, it can be associated with unfavorable systemic toxicity. The application of locally delivered chemotherapy, whether subcutaneous (*s.c.*), surgical placement or intracavitary routes, similarly yields beneficial effects, yet with decreased

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systemic toxicity and positive tumor control at dosages less than traditionally given *i.v.* (1–6). A possible reason may be increasing drug levels within the lymphatic system. The lymphatic system is an integral scavenge system or accessory route of fluid and large particulate matter accumulating in the interstitial space for return to the blood (7). While drugs have been targeted for delivery to the lymph, either by route of delivery or by specific formulation, drug levels in the lymph fluid have not been well characterized to date for non-traditionally delivered chemotherapy agents (8–10).

The lymphatic system differs from the vascular system with its unidirectional flow of lipophilic-rich fluid, albumin, lymphocytes and scavenged cells from peripheral lymphatics through lymph nodes to collecting lymph ducts prior to emptying into the cranial vena cava. The lymphatic system is also a pathway for metastasis; the presence of metastasis in lymph nodes is of clinical import (11). As revealed in breast cancer, tumor production of lymphangiogenic growth factors stimulates lymphatic vessel formation and resulting in trafficking of metastatic cells through lymph fluid that aids their survival *via* protective high concentrations of hyaluronic acid and low flow rates (12). Local delivery of chemotherapy, demonstrating preferential lymphatic uptake into or near tumors or resection sites, may be beneficial to more successfully treat cancers having locoregional lymphatic metastasis.

Recent research efforts have focused attention on the strategy of *s.c.* drug delivery and enhancing lymphatic drug uptake (13–16). These strategies include use of lipoproteins, formulation of dendritic polymers, microspheres, micelles and liposome encapsulation (17–20). Other efforts have included direct *s.c.* deposition of desired drug or protein (3, 14). The size of *s.c.* drug particles and structures have also been increased to preclude direct vascular access for obligate entry into the lymphatic system and is the strategy for lymphatic targeting with binding drugs to large dendrimers. Another approach has altered drug hydrophobicity of smaller molecules to improve targeting to lipophilic lymph (16, 21). Thus, there is practicality and importance in delineating the lymphatic and hemovascular pharmacokinetics and bioavailability of a drug when delivered both *i.v.* and *s.c.*.

The purpose of this study was to describe and compare the lymphatic and hemovascular pharmacokinetics of two common and physiochemically different chemotherapeutics, docetaxel and carboplatin, when delivered *s.c. versus i.v.* in a rodent model with catheterizations of both the thoracic lymphatic duct and jugular vein for prolonged synchronous blood and lymph sampling. We hypothesized that docetaxel and carboplatin, when administered *s.c.*, would accumulate within lymph fluid resulting in delayed and sustained vascular concentrations as compared to the traditional *i.v.* delivery.

Materials and Methods

Animals

Study underwent ethical review and was approved by the Colorado State University Institutional Animal Care and Use Committee (protocol# 12-3320A), according to the United States Department of Agriculture/Animal and Plant Health Inspection Service Animal Welfare Act and Public Health Service Policy. The care and use of study animals

complied with local animal welfare laws, guidelines and policies. Thirty-two male Sprague Dawley rats (Charles River Laboratories, Inc., Wilmington, MA, USA) were used.

Surgical model

Each rat was premedicated with buprenorphine (0.05 mg/kg *s.c.*), either carprofen (1 mg/kg *s.c.*) or meloxicam (0.2 mg/kg), and dexmedetomidine (0.3 mg/kg IP) and induced with isoflurane *via* face mask. A 24-gauge over the needle catheter was placed in the tail vein for continuous intravenous delivery of sterile 0.09% saline for surgical support. Following aseptic preparation, a left paracostal laparotomy was done. Sterile methylene blue dye, 0.01 ml (10 mg/ml), was injected into a mesenteric lymph node to aid in thoracic duct coloration and localization. The abdominal portion of the thoracic lymph duct was isolated immediately cranial to the left kidney, adrenal gland and cisterna chylii. A 60 cm length of sterile 2Fr polyurethane tubing (flushed with heparinized saline) was tunneled from the abdominal cavity through the left lateral flank with an 18-gauge needle. The thoracic duct was isolated, incised and the polyurethane catheter was threaded into the thoracic duct and secured with a combination of 6.0 encircling nylon suture and sterile N-butyl cyanoacrylate adhesive. The presence of free flowing lymph was confirmed *via* visualization of passive fluid movement from the free end of the polyurethane catheter. The abdominal cavity was closed with 4-0 polyglyconate in two layers and covered with wound clips. The polyurethane catheter was tunneled to exit dorsal to the cervical region. The rat was repositioned and the ventral cervical region was aseptically prepared. The left jugular vein was isolated and a second 60 cm length of 2Fr sterile polyurethane tubing flushed with heparinized saline was threaded and secured within the left jugular vein with two 6-0 nylon encircling ligatures. The wound was closed in a single intradermal layer with 4-0 polyglyconate. The catheter was tunneled to exit dorsal to the cervical region adjacent to the thoracic duct catheter. A tethered silicone harness was fitted to each animal such that the catheters were protected within the spring wire tether to exit through the floor of a rat housing box. The tethered animal was allowed unrestricted movement within the box and free access to food and water *ad libitum*. Tethered restraint permitted non-stressful distance collection for serial sample collections. Lymph was allowed to flow continuously and passively at a gravity dependent distance below the rat to prevent clotting. All animals received buprenorphine (0.05 mg/kg *s.c.* q 8 h) for additional analgesia.

Sample collection

Carboplatin (14 or 28 mg/kg) or docetaxel (5 mg/kg) was injected either into the right subcutaneous mammary fat pad or intravenously through the tail vein catheter. Lymph and blood were collected at 0, 0.5, 1, 2, 3, 4, 12 and 24 h. As lymph was free flowing, it was collected for ten-minute intervals, starting five minutes prior to blood collection times. Blood samples were collected *via* a three syringe technique. Briefly, a syringe filled with 0.05 ml heparinized saline (50 IU/ml) was used to draw out 0.3 ml of reserved blood. A second syringe, rinsed with 143 IU heparin/ml saline, was used to collect 0.15 ml of blood for analysis. Reserved blood was returned through the jugular catheter and the catheter was flushed with 0.2 ml heparinized saline (50 IU/ml) and plugged. Blood samples once collected were centrifuged for 10 minutes and plasma was obtained. Plasma and lymph

aliquots were frozen at −80°C until analysis. Rats were humanely euthanized at the 24-h time point.

Pharmacokinectics and sample analysis

Docetaxel concentrations in lymph and plasma were determined *via* liquid chromatography-tandem mass spectrometry (LC-MS/MS) as described previously by Gustafson *et al.* (22). Total platinum quantification in lymph and plasma was determined *via* total platinum analysis by inductively coupled plasma mass spectrometry. Prior to shipping total platinum samples to Midwest Laboratories Inc (Omaha, NE, USA) for inductively coupled plasma mass spectrometry (ICP-MS) analysis, 50 – 100 μl of lymph or plasma was tared in 15 ml conical tubes to which 10 volumes of freshly prepared aqua regia (concentrated nitric acid and hydrochloric acid in a 1:3 (v:v) ratio) were added and incubated overnight at room temperature. The following day samples were diluted 1:2 with Milli-Q water and shipped to Midwest Laboratories. Amounts of aqua regia and Milli-Q were determined gravimetrically and total platinum concentrations are reported in μg/ml of plasma or lymph.

Pharmacokinetic parameters were determined *via* non-compartmental analysis performed with Phoenix™ WinNonlin® v6.3 (Certara Inc., Princeton, NJ, USA). Plasma and lymph values for docetaxel and plasma values for carboplatin are reported as the mean and standard deviation (SD) of individual rat pharmacokinetic parameters. Maximum plasma concentration (C_{max}) data was available for all rats; only rats with plasma/lymph concentrations measured out to 24 h were used for estimation of elimination rate constant (λ_z), half life ($t_{1/2}$) and area under the plasma concentration time curve ($AUC_{0–24h}$). Due to difficulties during sampling of lymph for carboplatin treated rats, not all rats were able to provide a lymph sample at each time point and, thus, full time course data for each rat could not be used for pharmacokinetic (PK) analysis. A non-compartmental sparse sampling method was used to obtain one mean concentration-time profile, Phoenix™ WinNonlin® v6.3 (Certara Inc.). This method utilizes an algorithm that allows intersubject variability on C_{max} and $AUC_{0–24h}$ to be obtained; thus, the C_{max} and $AUC_{0–24\ h}$ for lymph data in carboplatin treated mice are reported as Mean±standard error of the mean (SEM). Bioavailability for *s.c.* delivered docetaxel and carboplatin were determined by the ratio of $AUC_{0–24}$ values for *s.c.* administration divided by values for *i.v.* administration and is reported as a percent.

Statistical analysis

Comparisons of plasma pharmacokinetic parameters between administration routes and between plasma and lymph parameters for docetaxel administration were made using two-tailed student's *t*-test. Significance was determined as a p value < 0.05. Statistical analysis was carried out with Graphpad Prism® (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Plasma and lymph disposition of docetaxel following i.v. and s.c. administration

Docetaxel administered *s.c.* demonstrates preferential lymphatic accumulation when comparing total exposure in lymph and plasma from 0 to 24 h ($AUC_{0–24h}$) *via* both

administration routes (Figure 1, Table I). The $AUC_{0–24h}$ in the lymph was 1,563±216 h*ng/ml when docetaxel was administered *s.c.* compared to 1,022±339 h*ng/ml following *i.v.* delivery (p=0.110). There was a larger difference in the AUC values for plasma between the two routes with *i.v.* and *s.c.* having values of 1,297±344 and 799±226 h*ng/ml, respectively (Table I). This difference was not statistically significant (p=0.066) but the small number of animals with full time course samples available in the *i.v.* group (n=2) may have been the cause. The ratio of docetaxel exposure in the lymph to exposure in the plasma in the *i.v.* and *s.c.* groups was 0.787 and 1.96, respectively. The C_{max} in lymph was comparable regardless of the route of delivery (172±63 ng/ml following *i.v.* and 161±54 ng/ml when administered *s.c.; p*=0.830). Not surprisingly, plasma C_{max} was significantly greater following *i.v.* delivery (2,857±560 ng/ml) than with *s.c.* delivery (80.8±19.0 ng/ml; p=0.0001; Table I). The time to maximal concentration (T_{max}) in plasma and lymph following *s.c.* delivery was quite similar (3.0±1.2 h and 2.3±1.5 h, respectively) while T_{max} in lymph following *i.v.* delivery occurred at 30 minutes (Table I). Taken together, the data for *i.v.* and *s.c.* delivered docetaxel suggests that *s.c.* administration provides comparable, slightly higher lymphatic exposure with a lower plasma exposure based on C_{max} and $AUC_{0–24h}$.

Plasma and lymph disposition of carboplatin following i.v. and s.c. administration at two dose levels

Following *i.v.* delivery of carboplatin at 14 mg/kg, the C_{max} in the plasma and lymph for total platinum was 23.0±5.1μg/ml and 13.1±4.1μg/ml (Figure 2, Table II). The $AUC_{0–24h}$ for plasma and lymph was 27.8±15.1 h*μg/ml and 31.0±9.0 h*μg/ml, respectively (Table II). Thus, while the maximum concentration in lymph is lower following *i.v.* delivery, the total exposure over 24 hours in lymph and plasma are comparable. When delivered *s.c.* at 14 mg/kg, the carboplatin C_{max} in the plasma and lymph was 7.22±1.9 μg/ml and 9.40±6.6 μg/ml (Table II). Twenty-four hour exposures in plasma and lymph following *s.c.* delivery were also comparable (16.7±2.8 h*μg/ml and 22.8±2.7 h*μg/ml, respectively) (Table II). Following *s.c.* administration of a 28 mg/kg carboplatin dose, there was a dose proportional increase in the plasma and lymph C_{max} and $AUC_{0–24h}$ with values approximately twice those following the 14 mg/kg dose (Figure 3, Tables II and III). Similar to the 14 mg/kg *s.c.* dose, the lymph C_{max} following 28 mg/kg *s.c.* was slightly higher than the plasma C_{max} (17.3±1.6 μg/ml *versus* 13.0±2.6 μg/ml). Unexpectedly, a dose proportional increase in C_{max} and $AUC_{0–24h}$ was not seen following the 28 mg/kg *i.v.* dose. However, the same trend in plasma *versus* lymph that was observed with the 14 mg/kg *i.v.* dose was seen in the 28 mg/kg *i.v.* dose with a higher plasma C_{max} (26.2±4.9 μg/ml *versus* 16.7±3.0 μg/ml) and comparable 24 h exposure (29.1±4.5 h*μg/ml in plasma *versus* 30.3±5.4 h*μg/ml in lymph) (Figure 3, Table III). In comparing the plasma carboplatin between the two administration routes, there is a significantly higher C_{max} for both 14 mg/kg and 28 mg/kg doses (p<0.0001 and p=0.003, respectively) but no significant difference in $AUC_{0–24h}$ (p=0.105 and p=0.297) (Tables II and III). Taken together, this data suggests that the maximum lymph concentration and the 24 h lymph exposure are comparable with either *i.v.* or *s.c.* administration and there is no apparent accumulation of carboplatin in lymph. While it might appear that there is substantial accumulation in lymph following *s.c.* delivery of the 28 mg/kg dose ($AUC_{0–24}$ of 74.0±29.3 h*μg/ml *versus* 36.3±9.8 h*μg/ml in plasma) it is important to note the substantial

degree of variability in the lymph data that was due to a single rat with a high concentration measured at a late time point. Additionally, this large apparent increase in exposure was not seen following the 14 mg/kg *s.c.* dose, which also suggests that the $AUC_{0–24h}$ data in the 28 mg/kg *s.c.* group should be interpreted with caution. Plasma exposures over 24 h are comparable between administration routes but, not surprisingly, maximum plasma concentrations are higher following *i.v.* delivery.

Discussion

Non-traditional *s.c.* delivery of docetaxel achieves intended lymphatic accumulation greater than with traditional *i.v.* delivery; yet there was no apparent lymphatic accumulation with *s.c.* delivery of carboplatin in this rodent model. The different pharmacokinetic patterns between these two drugs may be explained by the differing physiochemical properties of each. Lymph is a lipophilic-rich fluid; docetaxel is lipophilic and carboplatin has partial hydrophilicity. The finding of lymphatic accumulation with *s.c.* delivery of docetaxel has possible implication for dosing strategies of at least docetaxel antineoplastics for susceptible cancers that metastasize predominantly *via* lymphatic pathways. Additionally, while the area under the time concentration curve in plasma with either *i.v.* or *s.c.* dosing of carboplatin (28 mg/kg) and docetaxel were similar, the maximum plasma concentration measured was less with *s.c.* dosing for both chemotherapeutics. This may also have possible application for cancer patients susceptible to toxicity resulting from peak maximum hemovascular chemotherapy concentrations that may be lessened *via s.c.* delivery while maintaining comparable overall plasma drug exposures.

Use of locally delivered chemotherapy has been explored extensively for dogs with naturally occurring canine tumors (2, 3, 6, 23–25). Wound implantation of cisplatin-impregnated open-cell polylactic acid (OPLA-Pt) was shown to be tolerated and effective against metastasis and local recurrence in dogs receiving limb-sparing surgery (2, 6, 23–25). Following wound implantation of either 82 or 54 mg/m^2 OPLA-Pt, the combined mean area under the curve for total serum platinum concentration was almost 30 times greater than that after a single *i.v.* infusion of 70 mg/m^2 of cisplatin (23); in another study dogs receiving single *s.c.* cisplatin injections of 70 mg/m^2 had detectable serum platinum concentrations all through the 21 days measured (26). Simcock *et al.* reported a median survival time of 365 days in 17 client-owned dogs having curative-intent surgical treatment for naturally occurring primary bone tumors and which received only a single adjuvant slow *s.c.* infusion of 300 mg/m^2 carboplatin over a 3 to 7 day delivery period (3). This is comparable to historical median survival times of 10–14 months following four 300 mg/m^2 *i.v.* adjuvant carboplatin doses delivered every three weeks (3) and demonstrates a poorly understood benefit of non-traditional extravascular carboplatin delivery resulting in comparable tumor control at doses less than traditionally given. Extravascular delivered carboplatin experiences lymphatic uptake, which may explain, in part, the observed therapeutic advantage. Advancing the concept of locally delivered chemotherapeutics, several studies have also demonstrated lymphatic targeting of various formulations of locally delivered chemotherapeutics (27–37). Effectiveness of lymphatic penetration of these various formulations had been inferred from indirect lymphatic sampling methods to estimate the amount of product penetrating the lymphatics *via* lymph node tissue sampling, but have not

been measured in lymph fluid prior to this study (8, 21, 38). Definitive lymph fluid sampling to assess lymphatic pharmacokinetics of locally delivered drug has occurred very rarely to date (10, 14, 39).

It is unknown what injection site reaction might result from slow sustained *s.c.* delivery of some chemotherapeutics. Carboplatin has been described as a possible irritant if extravasation following bolus *i.v.* delivery in people. Effects of extravasated docetaxel are less defined with case reports describing irritant events as vesicant-type reactions (40). Future studies are planned assessing long-term toxicities associated with *s.c.* delivery of docetaxel in this model.

This model is unique for several reasons. (i) Techniques employed in this study permitted direct lymph sampling in awake and freely mobile animals, which may potentially be more representative of actual lymph circulatory patterns as opposed to studies requiring sustained general anesthesia of the patient for lymph sampling or studies sampling lymph node tissue without lymph fluid for drug measurements. (ii) This model permits free unrestricted movement of the animal that also increases lymph pharmacokinetic accuracy as compared to studies strictly impeding animal movement. Lymph circulation moves as the function of both the intrinsic and extrinsic lymphatic pumps. The extrinsic lymphatic pump is partially dependent upon contraction of surrounding skeletal muscle, movement of body systems, including peristaltic bowel, lung insufflation and pulsation of adjacent arteries. (iii) All animals had the same surgical catheterizations performed on each creating uniformity of the investigative insult though increasing the technical challenge in performing these studies (14).

A challenge of this study is that thoracic duct catheterizations are not always successful, as it has been reported in experienced hands this procedure is successful 80% of the time that echoes this group's experience (41). Another challenge of this model is the finite amount of time possible for serial lymph and blood collection prior to lymph catheter clotting and iatrogenic life-threatening hypoalbuminemia and anemia without active replacement measures. Future studies are planned to utilize sequential lymph and blood sampling at different time points in a larger population of cannulated rats. Additional work is also needed to correlate lymphatic and hemovascular pharmacokinetics with pharmacodynamics in tumor-bearing animal models to better understand the impact of prolonged drug exposure from greater AUCs *versus* the impact of greater C_{max} for optimal antineoplastic effect.

In conclusion, this study demonstrates non-traditional *s.c.* delivery of docetaxel achieves enhanced lymphatic accumulation greater than with traditional *i.v.* delivery and that paired serial blood and lymph collection is achievable in a rodent model.

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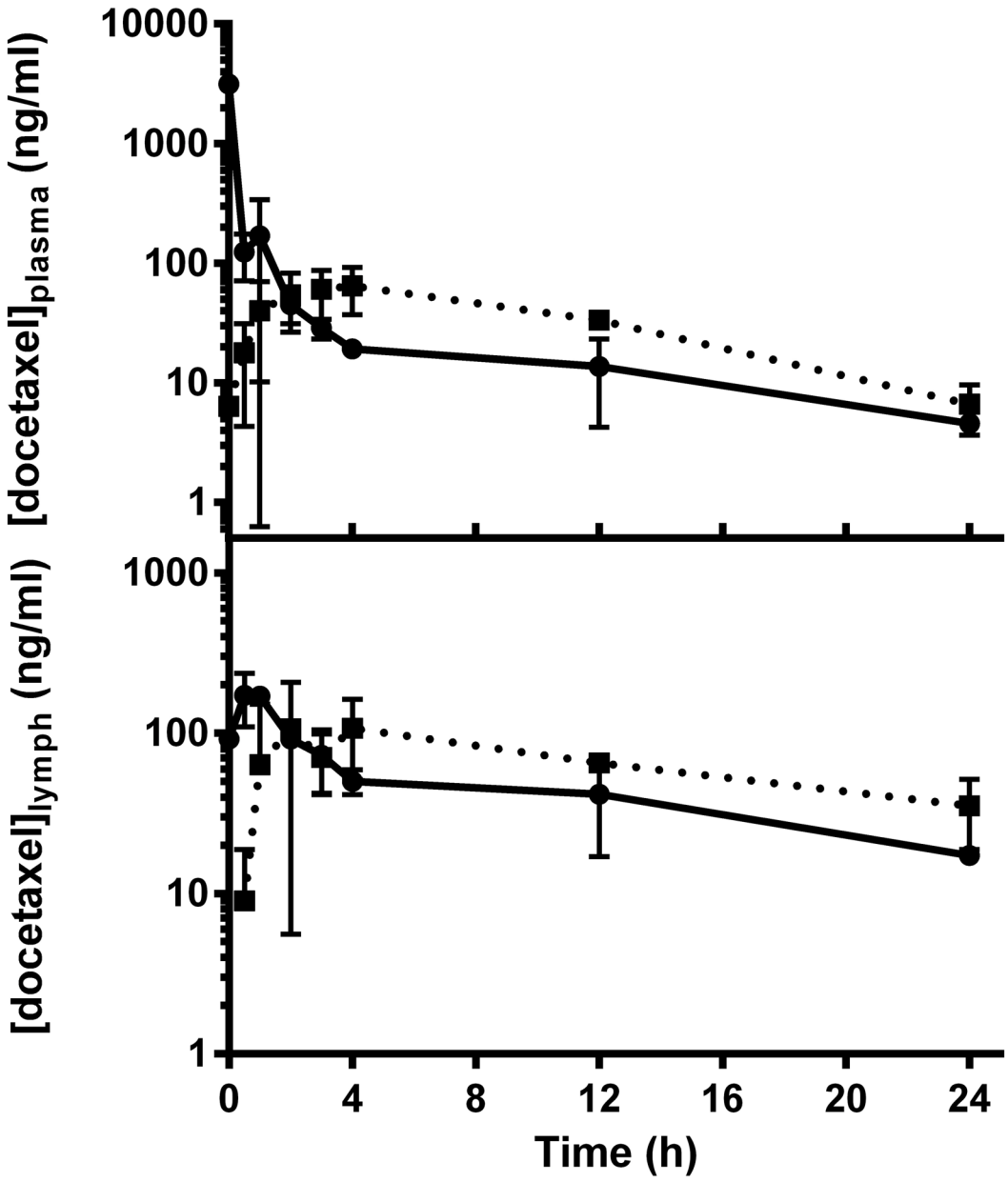

Figure 1.
Time concentration curves of docetaxel (5 mg/kg) in plasma (top graph) and lymph (bottom graph) when delivered either i.v. (solid line) or s.c. (dotted line).

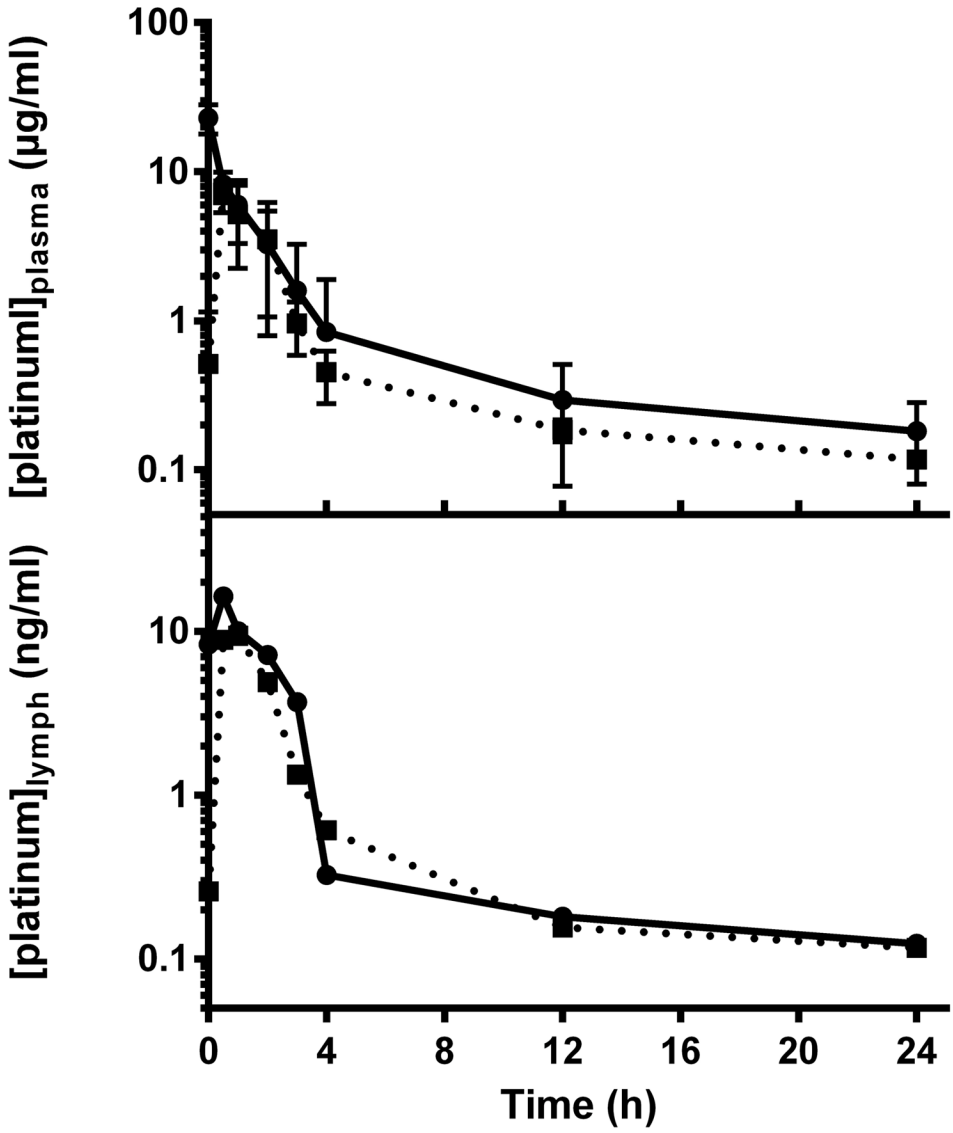

Figure 2.

Time concentration curves of carboplatin (14 mg/kg) in plasma (top graph) and lymph (bottom graph) when delivered either i.v. (solid line) or s.c. (dotted line).

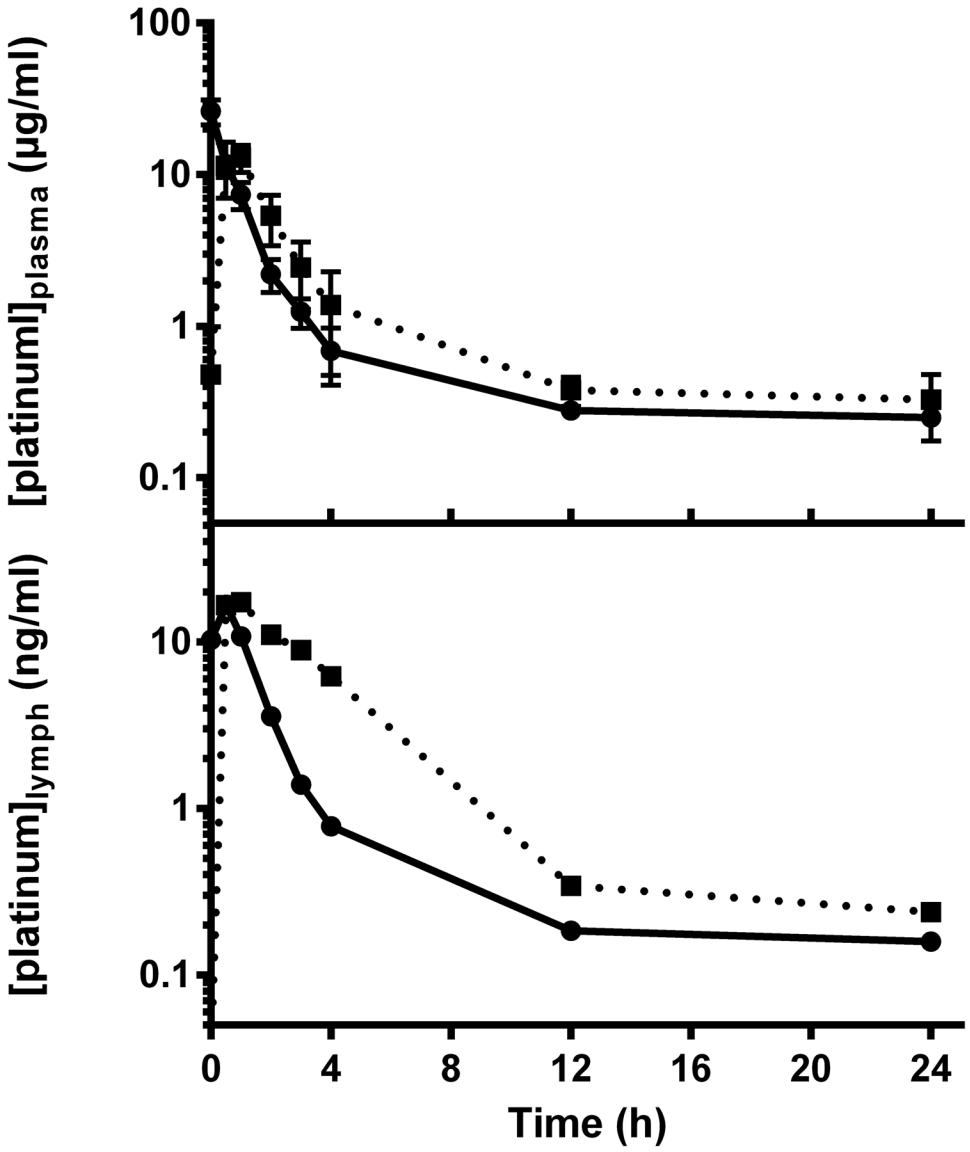

Figure 3.
Time concentration curves of carboplatin (28 mg/kg) in plasma (top graph) and lymph (bottom graph) when delivered either i.v. (solid line) or s.c. (dotted line).

Table I

Non-compartmental pharmacokinetics of docetaxel (5 mg/kg) in plasma and lymph when delivered either i.v. or s.c..

Docetaxel 5 mg/kg

		IV Admin		SQ Admin	
PK parameter		**Plasma ave (S.D.; n)**	**Lymph ave (S.D.; n)**	**Plasma ave (S.D.; n)**	**Lymph ave (S.D.; n)**
C_{max}	ng/mL	2857 (560; *3*)	172 (63; *3*)	80.8 (19.0; *5*)	161 (54; *3*)
T_{max}	hr	-	0.5 (0; *3*)	3.0 (1.2; *5*)	2.3 (1.5; *3*)
λ_z	1/hr	0.073 (0.005; *2*)	0.054 (0.013; *2*)	0.114 (0.024; *5*)	0.084 (0.007; *2*)
$t_{1/2}$	hr	9.6 (0.7; *2*)	13.2 (3.1; *2*)	6.3 (1.3; *5*)	8.3 (0.7; *2*)
$AUC_{0–24\ hr}$	hr*ng/mL	1297 (344; *2*)	1022 (339; *2*)	799 (226; *5*)	1563 (216; *3*)
$AUC_{0\text{-}inf}$	hr*ng/mL	1360 (331; *2*)	1508 (207; *2*)	861 (239; *5*)	1986 (225; *2*)
V_d	L	20.3 (7.8; *2*)		13.4 (6.6; *5*)	
Cl	mL/hr	24.2 (7.6; *2*)		23.7 (8.4; *5*)	
MRT	min	135 (18; *2*)	449 (54; *2*)	405 (91; *5*)	598 (118; *3*)
F	%			61.6%	

Admin, administration; PK, pharmacokinetic; ave, average; S.D., standard deviation; C_{max}, maximum plasma concentration observed; T_{max}, time of maximum plasma concentration observed; λ_z, elimination rate constant; $AUC_{0–24h}$, area under the plasma concentration time curve from 0 to 24 h; $AUC_{0\text{-}inf}$, area under the plasma concentration time curve from 0 h to infinity; V_d, volume of distribution; Cl, clearance; MRT, mean residence time; F, bioavailability.

Table II

Non-compartmental pharmacokinetics of carboplatin (14 mg/kg) in plasma and lymph when delivered either i.v. or s.c..

Carboplatin 14 mg/kg

		IV Admin		SQ Admin	
PK parameter		**Plasma ave (S.D.; *n*)**	**Lymph mean (SE)**	**Plasma ave (S.D.; *n*)**	**Lymph mean (SE)**
C_{max}	ng/mL	22989 (5099; *10*)	13102 (4070)	7218 (1873; *6*)	9395 (657)
T_{max}	hr	-	0.5	0.9 (0.6; *6*)	1
λ_z	1/hr	0.057 (0.024; *7*)	0.047	0.063 (0.016; *6*)	0.078
$t_{1/2}$	hr	14.1 (5.6; *7*)	14.7	11.6 (2.7; *6*)	8.9
$AUC_{0–24\ hr}$	hr*ng/mL	27798 (15119; *7*)	30990 (8960)	16688 (2763; *6*)	22783 (2661)
$AUC_{0\text{-}inf}$	hr*ng/mL	30997 (15517; *7*)	33619	18658 (3084; *6*)	24287
V_d	L/kg	11.7 (7.0; *7*)		7.61 (1.80; *6*)	
Cl	mL/hr/kg	8.86 (3.15; *7*)		7.67 (1.20; *6*)	
F	%			60	

Admin, administration; PK, pharmacokinetic; ave, average; S.D., standard deviation; SE, standard error; C_{max}, maximum plasma concentration observed; T_{max}, time of maximum plasma concentration observed; λ_z, elimination rate constant; $AUC_{0–24h}$, area under the plasma concentration time curve from 0 to 24 h; $AUC_{0\text{-}inf}$, area under the plasma concentration time curve from 0 h to infinity; V_d, volume of distribution; Cl, clearance; MRT, mean residence time; F, bioavailability.

Table III

Non-compartmental pharmacokinetics of carboplatin (28 mg/kg) in plasma and lymph when delivered either i.v. or s.c..

Carboplatin 28 mg/kg

		IV Admin		SQ Admin	
PK parameter		**Plasma ave (S.D.; *n*)**	**Lymph mean (SE)**	**Plasma ave (S.D.; *n*)**	**Lymph mean (SE)**
C_{max}	ng/mL	26167 (4895; *4*)	16669 (2945)	13025 (2563; *4*)	17325 (1555)
T_{max}	hr	-	0.5	0.9 (0.3; *4*)	1
λ_z	1/hr	0.045 (0.015; *3*)	0.074	0.063 (0.029; *4*)	0.152
$t_{1/2}$	hr	11.5 (4.9; *3*)	9.3	14.9 (11.8; *4*)	4.6
$AUC_{0–24\ hr}$	hr*ng/mL	29144 (4480; *3*)	30255 (5379)	36261 (9844; *4*)	73950 (29259)
$AUC_{0\text{-}inf}$	hr*ng/mL	34994 (3692; *3*)	32380	43008 (8399; *4*)	75521
V_d	L/kg	19.5 (7.6; *3*)		18.7 (16.7; *4*)	
Cl	mL/hr/kg	13.4 (1.5; *3*)		13.8 (2.5; *4*)	
F	%			124	

Admin, administration; PK, pharmacokinetic; ave, average; S.D., standard deviation; SE, standard error; C_{max}, maximum plasma concentration observed; T_{max}, time of maximum plasma concentration observed; λ_z, elimination rate constant; $AUC_{0–24h}$, area under the plasma concentration time curve from 0 to 24 h; $AUC_{0\text{-}inf}$, area under the plasma concentration time curve from 0 h to infinity; V_d, volume of distribution; Cl, clearance; MRT, mean residence time; F, bioavailability.