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ORIGINAL ARTICLE

Extracellular fluid concentrations of cisplatin, carboplatin, and oxaliplatin in brain, muscle, and blood measured using microdialysis in nonhuman primates

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Abstract
Purpose Cisplatin, carboplatin, and oxaliplatin are chemically reactive anticancer drugs with modest activity in brain tumors. Previously, we have demonstrated that drug exposure in cerebrospinal fluid (CSF) for these platinum analogs is <5% of the plasma ultrafiltrate (UF) drug exposure in nonhuman primates. Microdialysis is a minimally invasive in vivo method for sampling small molecules in the blood and tissue extracellular fluid (ECF). The purpose of this study was to estimate the penetration of platinum analogs into the brain ECF.
Methods We measured free concentrations of cisplatin, carboplatin, and oxaliplatin in ECF of brain, muscle, and blood of nonhuman primates using microdialysis and compared ECF platinum concentrations in blood and brain to plasma UF and CSF concentrations obtained using conventional sampling methods.
Results For all three platinum analogs, $AUC_{0\text{-}4h}$ for microdialysis sampling from the vein was similar to standard plasma UF sampling. The median $AUC_{0\text{-}4h}$ ratio for vein to plasma UF was 1.1 (range, 0.9–1.4). The platinum analogs had limited distribution (<5%) to the CSF and brain ECF. CSF penetration predicts for the limited penetration of the platinum analogs into brain ECF, but concordance between CSF and brain ECF measurements was poor. CSF oxaliplatin concentrations ($AUC_{0\text{-}4h}$, 0.4–0.9 μM h) were substantially lower than brain ECF concentrations ($AUC_{0\text{-}4h}$, 2.0–8.6 μM h).
Conclusions The penetration of platinum analogs into CSF and brain is limited. The differences in the CNS penetrations among the three platinum analogs are not clinically significant. For cisplatin and carboplatin, CSF penetration appears to be a surrogate for brain extracellular free drug exposure.

Keywords Platinum analogs · CNS penetration · Microdialysis

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Introduction

The platinum analogs—cisplatin, carboplatin, and oxaliplatin—are chemically reactive anticancer drugs that produce a cytotoxic effect through platination of DNA and the formation of cross links. These agents have a broad spectrum of antitumor activity, including modest activity against brain tumors [12, 13, 24, 25]. Recently, the clinical utility of platinum-based chemotherapy in some brain tumors has been challenged [3, 4]. We previously studied the cerebrospinal fluid (CSF) penetration (as a surrogate of

blood–brain barrier [BBB] penetration) of these three platinum analogs in nonhuman primates, and found that drug exposure in CSF was <5% of the plasma ultrafiltrate (UF) drug exposure for all three analogs [14].

Microdialysis is an in vivo method for sampling small molecules in the blood and tissue extracellular fluid (ECF). Microdialysis is based on the principle of diffusion. Concentric microdialysis probes with a semi-permeable membrane (10 mm × 0.5 mm 20 kDa mol. wt. cut off) are inserted into the tissue. A physiological solution is perfused into the probe at a low flow rate. Free drug in the tissue diffuses across the probe membrane and is collected in the outflow dialysate [6]. The concentration of drug in the outflow dialysate is proportional to the drug concentration in tissue ECF. Microdialysis is quantitative if recovery, which is the proportionality factor that relates dialysate drug concentration to tissue drug concentration, is determined by a calibration method, such as retrodialysis [5].

Quantitative microdialysis has several potential advantages over standard sampling of plasma, CSF, or tissue at discrete time points for pharmacokinetic studies. Microdialysis continuously samples drug at the measurement site, providing an estimate of drug exposure at the site over the sampling period. Microdialysis measures free drug concentration, which is the parameter most closely related to drug effect for most agents. Tumor ECF free concentrations of cisplatin measured by microdialysis have been shown to correlate with platinum–DNA adducts better than total platinum concentrations in tumor [30]. The small size of microdialysis probes also allows sampling from the target site in a minimally invasive manner [15, 17]. The small dialysate sample size can be a limitation of the method if sensitive assays are not available for the drug or the drug is highly protein bound.

In this study, we measured free elemental platinum concentrations in the ECF of the brain, muscle, and blood of nonhuman primates using microdialysis after systemic adminstration of cisplatin, carboplatin, and oxaliplatin. We compared the tissue drug concentration obtained using microdialysis to plasma and CSF concentrations obtained by conventional sampling methods, and we compared CSF drug penetration to BBB drug penetration.

Methods

Animals

Nine adult male rhesus monkeys (*Macaca mulatta*) ranging in weight from 7.3 to 17.5 kg were used in the study. Prior to the conduct of the study, all experimental procedures were reviewed and approved by the National Cancer Institute Animal Care and Use Committee. All animals were fed and group housed in accordance with the Guide for the Care and Use of Laboratory Animals [1]. All animals were anesthetized prior to and during the experiments. Due to the anticipated toxicity from high-dose platinum therapy, animals that received high-dose oxaliplatin ($n = 3$) or high-dose cisplatin ($n = 2$) underwent planned euthanasia at the end of the experiment. In addition, one animal was euthanized following carboplatin administration due to complications of a subcutaneous leak in the chronically indwelling central venous catheter and intractable seizures in the postoperative period.

Drugs

Drugs were obtained commercially and diluted in 5% dextrose or 0.9% saline for infusion. Oxaliplatin (Sanofi Synthelabo, Bedford, OH) 21–25 mg/kg (maximum single dose 300 mg, human equivalent, 460–550 mg/m^2) was administered intravenously (IV) over 2 h to three animals. Cisplatin (Bristol-Meyers Squibb, Princeton, NJ) 2 mg/kg was administered IV over 1 h to one animal and 10 mg/kg IV over 1 h to two animals (human equivalent, 40 mg/m^2 or 200 mg/m^2). The fivefold higher than standard doses of cisplatin and oxaliplatin were required to achieve measurable platinum concentrations in brain microdialysate. Carboplatin (Bristol-Meyers Squibb, Princeton, NJ) 10 mg/kg (human equivalent, 200 mg/m^2) was administered IV over 1 h to three animals.

Standard sampling

Blood samples were drawn through a temporary saphenous vein catheter, placed contralateral to the site of drug administration. CSF was obtained from a temporary lumbar catheter ($n = 4$), from subarachnoid fluid at the vertex ($n = 1$), or from a chronic indwelling fourth ventricular Pudenz catheter attached to a subcutaneously implanted Ommaya reservoir ($n = 4$) [19]. Blood (3 ml) and CSF (0.3 ml) samples were obtained prior to infusion, at 30 and 60 min (and 120 min for oxaliplatin) after the start of infusion, and then 15 and 30 min and 1 and 2 h after the end of infusion. Whole blood was immediately centrifuged, and plasma UF was prepared by centrifuging the plasma through a Microcon 10 kDa mol. wt. cut-off filter (Millipore Corporation, Bedford, MA) at 12,000 rpm for 40 min at 10°C. The UF was then frozen at −70°C. CSF samples were immediately frozen at −70°C without ultrafiltration.

Microdialysis sampling

Animals were anesthetized, intubated, and immobilized in a cranial stereotaxic unit (David Knopf Instruments, Tunga, CA). Anesthesia was maintained throughout the

experiment using isofluorane (1–2%). Microdialysis probes (CMA 20, 10 mm × 0.5 mm polycarbonate membrane mol. wt. cut-off 20 kDa; CMA Microdialysis, North Chelmsford, MA) were inserted into the frontal lobe of the brain, the temporalis muscle, and a peripheral vein of each animal using surgical techniques described previously [8]. In two animals that received carboplatin, two ipsilateral brain probes were placed approximately 3 cm apart. For one animal (G4), samples from each brain probe were analyzed separately; however, for the second animal (RQ1357), only data from a single probe is presented due to questions regarding probe positioning and recovery. For all other sites, a single probe was inserted.

In vivo recovery was measured for each probe using retrodialysis prior to drug administration [29, 32]. Briefly, a known concentration of drug (1 μM for brain, 5 μM for muscle or blood) was perfused through each probe at a flow rate of 0.5 μl/min. After equilibration, a sample of the outflow dialysate was collected and the drug concentration was measured. Recovery was calculated from the following equation:

$$\text{Recovery} = \frac{[\text{Perfusate}] - [\text{Dialysate}]}{[\text{Perfusate}]}$$

where [Perfusate] and [Dialysate] are the drug concentrations in the inflow (perfusate) and outflow (dialysate) fluids, respectively. Upon completion of in vivo recovery, the probes were flushed with drug-free dialysate, equilibrated and continuously perfused (0.5 μl/min) with Elliott's B solution (Orphan Medical, Minnetonka, MN) for brain microdialysis or Lactated Ringer's for muscle and blood microdialysis. Microdialysis samples were collected in 1 or 2 h intervals for 4 hours after the start of drug administration. Microdialysis samples were frozen at −70°C until analyzed.

At the conclusion of each experiment, microdialysis probes were removed from the tissue and in vitro retrodialysis was performed to verify probe integrity. Microdialysis probes were immersed in continuously mixed normal saline at 38°C and perfused with a known concentration of drug (1 μM for brain, 5 μM for muscle or blood) at a flow rate of 0.5 μl/min. In vitro recovery was determined as described for in vivo recovery.

Sample analysis

After systemic administration of cisplatin, carboplatin, or oxaliplatin, inactive protein-bound elemental platinum in plasma is separated from low molecular weight platinum species by ultrafiltration. Elemental platinum in plasma UF, CSF, and microdialysis dialysates were measured with a Perkin-Elmer AAnalyst 800 Atomic Absorption Spectrometer (Perkin-Elmer Corp., Norwalk, CT) with an AS autosampler and HGA-800 graphite furnace. A 10-μl sample was injected and the furnace was heated slowly to 2,550°C. The absorbance of atomized platinum was measured at 265.7 nm. The assay for total platinum was validated according to the FDA guidelines [2] and were reported previously [14]. The standard curve was linear over the range of 0.1–5 μM. The lower limit of quantification of 0.02 μM for CSF and 0.03 μM for plasma UF and dialysates was achieved using concentration of samples by drying 3–5× 10 μl samples on the graphite tube prior to initiation of the furnace burn. The interday and intraday coefficients of variation were <10%; precision and accuracy exceeded 80%.

The ECF free platinum concentration in each microdialysis sample was calculated by dividing the measured drug concentration in the dialysate by the in vivo recovery at that site. The microdialysis sample is collected continuously. Therefore, the measured drug concentration in the microdialysis sample is the average concentration over the sampling interval.

Pharmacokinetic analysis

The area under the platinum concentration–time curve (AUC) for plasma UF and CSF was calculated over the 4-h sampling period using the linear trapezoidal method [9]. The ECF $AUC_{0\text{-}4h}$ for each tissue was calculated by summation of ECF platinum concentrations multiplied by the sampling interval. Central nervous system penetration was calculated from the ratio of the CSF $AUC_{0\text{-}4h}$ to plasma UF $AUC_{0\text{-}4h}$ for conventional sampling or the ratio of brain ECF $AUC_{0\text{-}4h}$ to vein $AUC_{0\text{-}4h}$ for microdialysis sampling.

Results

Recovery

In vivo recovery measured by retrodialysis was tissue dependent (Table 1). Recoveries were highest in the vein ranging from 75 to 82% and lowest in the brain, ranging from 30 to 46%. Within each tissue, recovery was similar for the three platinum analogs, and variability in recovery was low across animals for a given drug in each tissue (median CV 14%).

In vitro recovery was measured by retrodialysis in each microdialysis probe immediately following each experiment and demonstrated that the dialysis membranes of all probes were intact at the end of the experiments. In vitro recovery was higher than in vivo recovery and ranged from 74 to 98%. In vitro recovery did not accurately reflect the in vivo recovery, especially for the brain probes.

Table 1 In vivo recovery for microdialysis probes measured by retrodialysis prior to drug administration for each probe in the three tissue sites

Tissue	Mean recovery (CV)		
	Cisplatin	Carboplatin	Oxaliplatin
Vein	0.75 (14%)	0.79 (17%)	0.82 (7%)
Muscle	0.57 (20%)	0.45[a] (28%)	0.50 (12%)
Brain	0.46 (5%)	0.30[b] (19%)	0.34 (30%)

Recovery is expressed as mean (coefficient of variation) for three animals

[a] Recovery for one muscle microdialysis probe was excluded due to technical problems with flow, therefore, $n = 2$. Recovery for the individual probes was 0.36 and 0.54

[b] Recovery from four individual probes (data from one animal with two probes inserted, data from a single probe in two animals)

Platinum concentrations

The $AUC_{0\text{-}4h}$ for each platinum analog measured by conventional methods and by microdialysis is listed in Table 2 and representative concentration–time curves for each drug are presented in Fig. 1. For all three platinum analogs, $AUC_{0\text{-}4h}$ for microdialysis sampling from the vein yielded similar estimates of the $AUC_{0\text{-}4h}$ as standard plasma UF sampling (Fig. 2a). The median $AUC_{0\text{-}4h}$ ratio for vein to plasma UF was 1.1 (range, 0.9–1.4). This close agreement between plasma UF and vein microdialysis platinum $AUC_{0\text{-}4h}$ validates the accuracy of microdialysis sampling of blood for pharmacokinetic studies. The muscle and vein $AUC_{0\text{-}4h}$ were also similar, indicating that free (ultrafiltered) fraction of these drugs is well distributed to tissues. The median $AUC_{0\text{-}4h}$ ratio for muscle to vein was 0.78 (range, 0.54–1.2).

All three platinum analogs had limited distribution into the CSF and brain (Tables 2, 3). Although CSF penetration predicts for the limited penetration of the platinum analogs into brain ECF, the concordance between CSF and brain ECF measurements was poor compared to plasma UF and microdialysis vein measurements (Table 2, Fig. 2b). The range of the ratios of brain ECF to CSF across the three drugs was 0.28–12, and the $AUC^{Brain}_{0\text{-}4h}$:$AUC^{CSF}_{0\text{-}4h}$ appears to be drug dependent. The ratio is <1 for cisplatin, 0.8–4.3 for carboplatin, and 4.7–12 for oxaliplatin, for which CSF concentrations were substantially lower than brain ECF concentrations measured by microdialysis (Table 2, Fig. 2b). The CSF penetration of oxaliplatin (median, 0.3%) at the higher doses used for these microdialysis experiments is lower than the 2.0 ± 0.2% CSF penetration that we previously measured with standard doses (5 mg/kg) of oxaliplatin in the same nonhuman primate model [14]. The CSF penetration of oxaliplatin from the prior standard dose studies were recalculated using the ratio of the CSF to plasma UF $AUC_{0\text{-}4h}$ (sampling interval used in microdialysis studies) rather than the $AUC_{0\text{-}24h}$, and the median CSF penetration of oxaliplatin was 1.2% at the 5 mg/kg dose (see supplementary data).

The mean $AUC_{0\text{-}4h}$ of oxaliplatin in plasma UF after the higher doses (21–25 mg/kg) used in the microdialysis studies was 4.7-fold greater than the $AUC_{0\text{-}4h}$ of oxaliplatin in plasma UF at the 5 mg/kg dose in the prior study. The lower CSF penetration ($AUC^{CSF}_{0\text{-}4h}$:$AUC^{Plasma\ UF}_{0\text{-}4h}$) at the higher dose resulted from a less than proportional increase in CSF oxaliplatin concentrations at the higher dose.

Table 2 Platinum $AUC_{0\text{-}4h}$ in plasma UF and CSF from standard sampling methods and in vein, muscle, and brain using microdialysis sampling for the platinum analogs cisplatin, carboplatin, and oxaliplatin

	Animal	Dose (mg/kg)	$AUC_{0\text{-}4h}$ (μM h)				
			Plasma UF	Vein	Muscle	CSF[a]	Brain
Cisplatin	T68	2	14	13	12	0.69 (V)	ND[b]
	R842	10	92	112	72	4.0 (S)	1.1
	B9884	10	89	89	103	4.8 (V)	2.8
Carboplatin	V29	10	84	109	59	4.2 (V)	3.4
	RQ1357	10	136	131	NA[c]	2.0 (L)	3.9
	G4	10	118	133	153	1.6 (V)	4.1
Oxaliplatin	HH351	25	144	196	119	0.4 (L)	4.3
	9SL	23	133	146	94	0.4 (L)	2.0
	R829	21	112	107	110	0.9 (L)	8.6

[a] Letter in parentheses denotes CSF sampling site: *V* ventricular CSF from Ommaya reservoir, *S* subarachnoid CSF from the vertex, *L* CSF from a lumbar catheter

[b] *ND* platinum was not detectable in dialysate

[c] *NA* not analyzed due to technical problems with flow rate that precluded calculation of in vivo recovery and measurement of tissue concentration

In prior studies of oxaliplatin at a 5 mg/kg dose, the median $AUC_{0\text{-}4h}$ in plasma UF was 25.7 μM h (range, 15.1–41.4 μM h) and the median CSF $AUC_{0\text{-}4h}$ was 0.3 μM h (range, 0.2–1.3 μM h), resulting in a median CSF penetration of 1.2% (range, 0.9–3.2%). With the high dose of oxaliplatin, the median $AUC_{0\text{-}4h}$ in plasma UF was 133 μM h (range, 112–144 μM h), the median CSF $AUC_{0\text{-}4h}$ was 0.4 μM h (range, 0.4–0.9 μM h), and the median CSF penetration was 0.3% (range, 0.3–0.8%). The median brain $AUC_{0\text{-}4h}$ by microdialysis was 4.3 μM h (range, 2.0–8.6 μM h) and the median $AUC^{Brain}_{0\text{-}4h}$:$AUC^{Vein}_{0\text{-}4h}$ was 2.2% (range, 1.4–8.0%). In contrast, the CSF penetration of cisplatin at a dose of 10 mg/kg (Table 3) was similar to the CSF penetration at a dose of 2 mg/kg (4.9% for animal T68 and a mean of 3.3% in three animals from the prior study).

Adverse events

Animals that received 10 mg/kg cisplatin ($n = 2$) or 21–25 mg/kg oxaliplatin underwent euthanasia at the end of the experiment. One animal (G4) that received carboplatin (10 mg/kg) developed perioperative complications. Upon recovery from anesthesia, a subcutaneous fluid collection in the neck and upper chest was noted. Fluoroscopic evaluation of the jugular central venous catheter revealed an extravascular fluid leak. The animal also developed generalized seizures in the immediate postoperative period. Serum glucose and electrolytes were normal. Seizures did not respond to benzodiazepine therapy, and the animal was euthanized. At necropsy, no gross or microscopic changes related to probe insertion in the brain were observed.

Discussion

The penetration of anticancer drugs, including small molecules, into the central nervous system is limited by the BBB. Delivery of chemotherapeutic agents to tumors within the CNS is also influenced by breakdown of the BBB. CSF drug penetration after systemic administration has been used as a surrogate to estimate blood–brain penetration [23, 27]. Protein levels in CSF are low, and drugs are not protein bound in CSF. As a result, CSF drug concentrations do not exceed free (nonprotein bound) drug concentrations in the plasma [20]. Microdialysis samples free drug concentration in tissue ECF, which may differ substantially from tissue concentration measured in a biopsy sample that includes drug bound to protein in tissue, intracellular drug, and drug within blood vessels in the tissue sample.

This study was designed to compare CSF and brain ECF free drug concentrations of the platinum analogs after intravenous administration. Although the median CSF penetration ($AUC^{CSF}_{0\text{-}4h}$:$AUC^{Plasma\ UF}_{0\text{-}4h}$) and median penetration into brain ECF ($AUC^{Brain}_{0\text{-}4h}$:$AUC^{Vein}_{0\text{-}4h}$) were <5% for the three analogs, the concordance between these ratios was poor when compared to the concordance between plasma UF and vein microdialysis sampling. This may be in part due to the variability in the sampling methods and the assay at the low concentrations found in CSF and brain.

The CSF concentrations of oxaliplatin substantially underestimated brain ECF platinum concentrations at the high doses used in these experiments. CSF penetration of oxaliplatin at doses of >20 mg/kg (range, 0.3–0.8%) was lower than the CSF penetration at doses of 5 mg/kg (range, 0.9–3.2%) in our previous experiments. The oxaliplatin ($AUC^{Brain}_{0\text{-}4h}$:$AUC^{Vein}_{0\text{-}4h}$) ratio at the higher dose (median, 2.2; range 1.4–8.0) was similar to the CSF penetration at the lower dose. Site of CSF sampling (ventricular vs. lumbar) did not alter the CSF concentrations. Dose dependence of CSF penetration was not observed with cisplatin, which was also administered at a fivefold higher dose for the microdialysis experiments. Within the BBB, unsaturated active efflux transporters with increased specificity for oxaliplatin compared to other platinum analogs might account for the lower oxaliplatin brain ECF platinum concentrations at high doses [18, 26]. In colon cancer models, the organic cation transporters (OCT) 1 and 2 have specificity for oxaliplatin compared to cisplatin and carboplatin [30]. However, it is unknown if OCT 1 or 2 are located in the BBB. While a disruption of BBB by the microdialysis probe could result in an overestimate of drug concentration in brain ECF, such a disturbance is unlikely to explain the higher concentrations of oxaliplatin in brain compared to CSF because the $AUC^{Brain}_{0\text{-}4h}$:$AUC^{Vein}_{0\text{-}4h}$ was similar to the ratios for cisplatin and carboplatin.

Johansen et al. used microdialysis to measure cisplatin and carboplatin exposures (AUC) in blood, liver, kidney, and breast tumor xenografts of Fisher 344 rats. They demonstrated extensive distribution of platinum analogs into peripheral tissue [16]. Comparison of platinum exposure in plasma UF, venous, and muscle microdialysis samples in our experiments in nonhuman primates supports extensive peripheral tissue distribution. The similarity of drug exposure for all three analogs in muscle ECF compared with blood, in contrast to the very low penetration into brain ECF, suggests that the insertion of microdialysis probes stereotaxically into the brain does not disrupt the BBB in large animals [7]. Some authors have reported increased BBB permeability around the microdialysis probes [10, 32], but the difference we demonstrated between platinum exposure in peripheral tissue compared with brain tissue suggests that any disruption of the barrier due to probe insertion is not significant in this primate model.

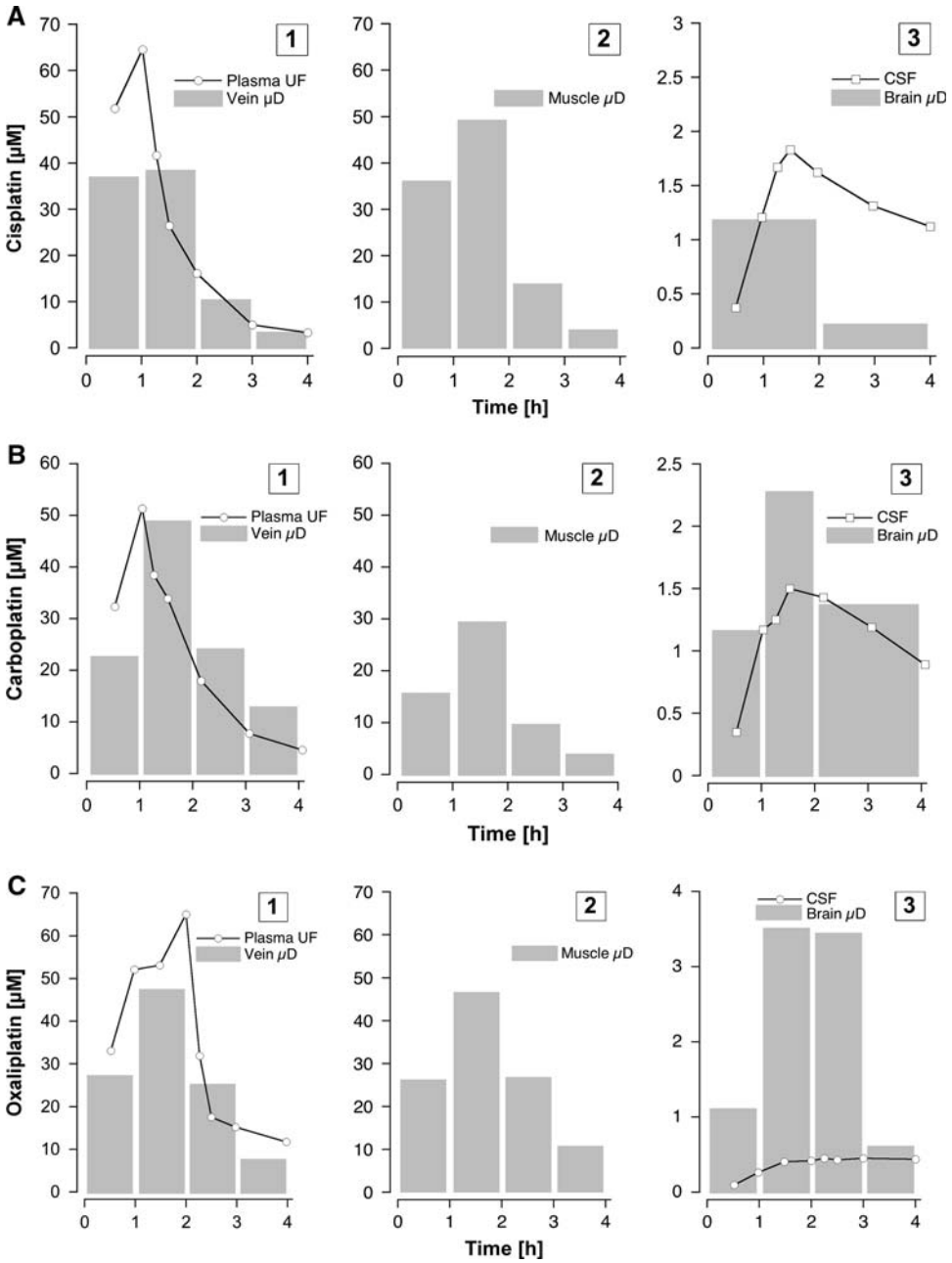

Fig. 1 Representative concentration–time curves for cisplatin **a**, carboplatin **b**, and oxaliplatin **c**. *Solid lines* are the platinum concentrations in plasma UF or CSF using standard sampling. *Bars* are the concentrations measured using microdialysis sampling over each time interval. For each drug, *panel 1* is plasma UF and vein microdialysis, *panel 2* is the muscle concentration using microdialysis, and *panel 3* is CSF and brain microdialysis

Microdialysis is a sampling method that can be used to continuously monitor free drug concentrations in blood or tissue ECF. To accurately quantify drug concentration in tissue ECF from a microdialysis sample, the probe recovery, which is the proportionality factor that measures the efficiency of the probe in collecting drug from tissue ECF, must be determined. There are several methods for estimating recovery, but we have found that retrodialysis performed prior to drug administration is an efficient and accurate method of estimating probe recovery for pharmacokinetic studies.

In this study, in vivo recovery was highly dependent on the tissue in which the probe was inserted. Recovery in brain (32–46%) was lower than in blood (75–82%). This tissue dependence of recovery is consistent with our prior experience with microdialysis in sampling brain ECF, muscle ECF, and blood concentrations of zidovudine [8], and is also similar to the experiences of other investigators using microdialysis [11]. The variation in recovery among tissue types emphasizes the importance of measuring recovery in vivo in each probe to accurately quantify tissue drug concentration from the microdialysate. Measurement

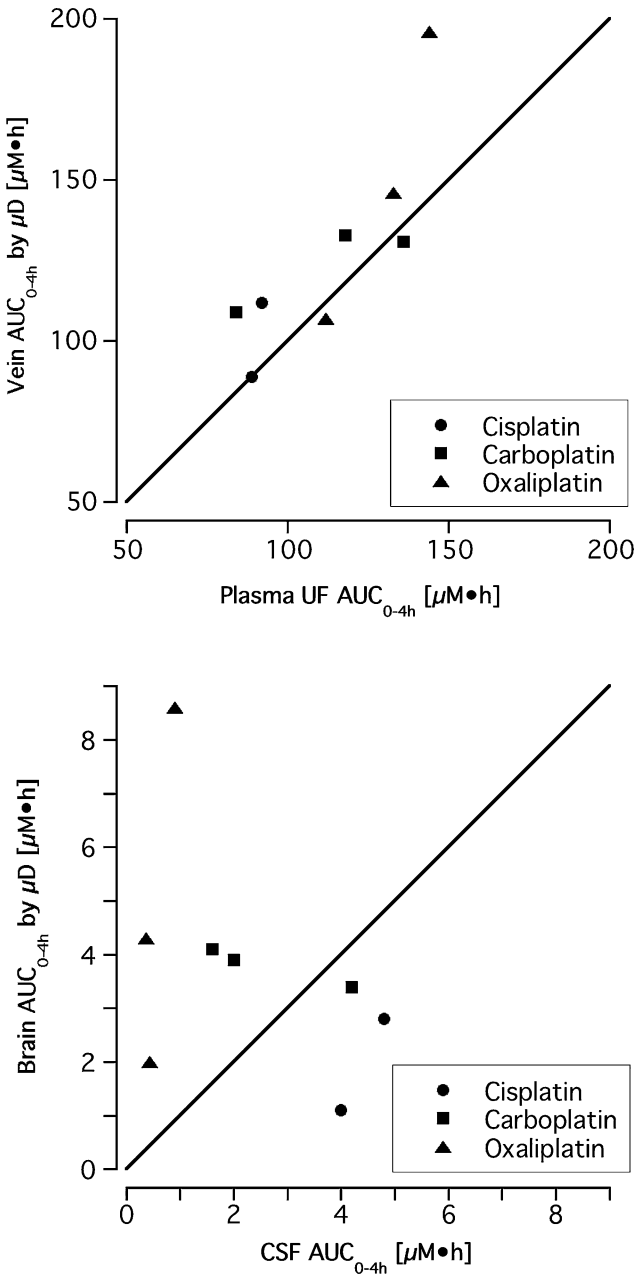

Fig. 2 Comparison of standard and microdialysis sampling methods in: **a** blood (plasma UF vs. vein microdialysis sampling) and **b** the central nervous system (CSF vs. brain ECF microdialysis sampling). *Line* represents the line of unity. Data from animal T68 that had undetectable cisplatin concentrations in the brain ECF are not included

of in vitro recovery overestimates in vivo recovery for most tissues because it does not account for tissue factors that influence recovery.

Microdialysis offers several advantages for measuring tissue drug concentrations over conventional sampling techniques, but there are still limitations, particularly for chemotherapeutic drugs. Plasma concentrations have been found to correlate poorly with intratumoral concentrations,

Table 3 Penetration of the platinum analogs into the CNS (CSF standard sampling or brain measured using microdialysis) expressed as a percentage of drug systemic exposure (AUC in plasma UF by standard sampling or vein by microdialysis)

	$AUC^{CNS}_{0\text{-}4h}$:$AUC^{Blood}_{0\text{-}4h}$ (%)	
	CSF:Plasma UF	Brain:Vein
Cisplatin	4.4, 5.4[a]	1.0, 3.1[a]
Carboplatin	1.5 (1.4–5.0)	3.1 (3.0–3.1)
Oxaliplatin	0.3 (0.3–0.8)	2.2 (1.4–8.0)

Values represent the median (range)

[a] Data from two animals receiving the 10 mg/kg dose

normal tissue ECF concentrations are not necessarily reflective of concentrations in tumors, and intratumoral concentrations are often difficult to measure due to variability [16, 21, 30]. Tokunaga et al. reported that normal brain ECF platinum concentrations and brain tumor ECF platinum concentrations were markedly different after intravenous injection of a cisplatin derivative in rats (AUC of 311 ± 62 vs. 11 ± 3 min μg/ml), with very different distribution coefficients (0.85 compared to 0.03) [28]. Their group found similar results for cisplatin [22]. This is likely to be related to the increased BBB permeability within brain tumors compared with normal brain tissue.

In conclusion, penetration of platinum analogs into CSF and brain of nonhuman primates is low. The differences in the CNS penetrations of the three platinum analogs are not clinically significant. For cisplatin and carboplatin, CSF penetration appears to be a surrogate for brain extracellular free drug exposure.

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