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Effect of tumor presence on cisplatin and carboplatin: disposition in the isolated, perfused tumor and skin flap*

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Abstract. The purpose of this study was to evaluate the disposition of elemental platinum (Pt) derived from cisplatin (CDDP) or carboplatin (CBDCA) in the isolated, perfused tumor and skin flap (IPTSF). Flaps were perfused with either 3.0 μg CDDP/ml perfusion medium ($n = 4$ tumor, $n = 4$ control) or 15 μg CBDCA/ml ($n = 4$ tumor, $n = 3$ control) at a rate of 1 ml/min for 3 h. A 2-h (CDDP experiments) or 3-h (CBDCA experiments) washout phase using undosed medium was then performed. The disposition kinetics of free (ultrafilterable) Pt were characterized using a four-compartment physiologically relevant pharmacokinetic model. A tumor effect on the disposition of Pt was noted in that the Pt mass from CDDP in the central and mobile tissue compartments was greater in tumor flaps than in control flaps ($P < 0.05$). Similar trends were noted in CBDCA-treated flaps, but these were not significant. The Pt mass in the fixed tumor and non-tumor tissue compartments was significantly greater when Pt was derived from CDDP than when it was derived from CBDCA ($P < 0.05$). A linear relationship existed between the estimated micrograms of Pt in the flaps from both CDDP and CBDCA and the cross-sectional vascular resistance of the flaps at 30 (CDDP, $r = 0.78$; CBDCA, $r = 0.89$) and 60 min (CDDP, $r = 0.65$; CBDCA, $r = 0.85$) of perfusion. We conclude that the IPTSF is a useful model for evaluating the disposition of Pt drugs in tumor and non-tumor tissue and that tumor presence alters the disposition of CDDP.

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Introduction

The use of regional drug delivery for localized cancer chemotherapy is theoretically advantageous to systemic delivery because increased local and decreased systemic drug concentrations might allow for enhanced efficacy and reduced systemic toxicity [1, 7]. The increase in local drug concentrations, with the potential advantage of increasing tumor response, is largely dependent on the relative rate of blood perfusion into the target region and the rate of systemic drug elimination. The reduction in systemic toxicity is dependent on the ability of the target organ to eliminate the drug and thereby decrease systemic exposure [1].

cis-Diamminedichloroplatinum(II) (cisplatin, CDDP) and diammine-(1,1-cyclobutanedicarboxylato)platinum-(II) (carboplatin, CBDCA) are important drugs in the treatment of many forms of cancer [11]. These drugs exhibit different pharmacokinetics and dose-limiting toxicities. Preclinical and clinical studies have shown favorable responses to platinum (Pt) drugs given regionally [5, 8, 11]. The systemic toxicity of Pt compounds is often dose-limiting, making regional delivery of these drugs even more attractive. However, in one study the therapeutic advantage of local intraarterial administration was small because increased intratumoral Pt concentrations after intraarterial administration were not statistically increased relative to the concentrations attained following systemic administration of Pt [4]. Studies are needed that critically evaluate the regional disposition of Pt compounds to determine factors that may affect the preferential uptake of drugs into tumors.

We have developed a model system in which the regional pharmacokinetics of a drug in tumor and non-tumor tissue can be evaluated under a variety of physiological conditions [14]. This model is unique in that it consists of a tumor surrounded by normal tissue, both of which are supplied by the same isolated vascular system. The pharmacokinetic parameters derived from this model can describe drug distribution and binding within the tumor compartment under a variety of conditions without the effects of eliminating or metabolizing organ systems. The purpose

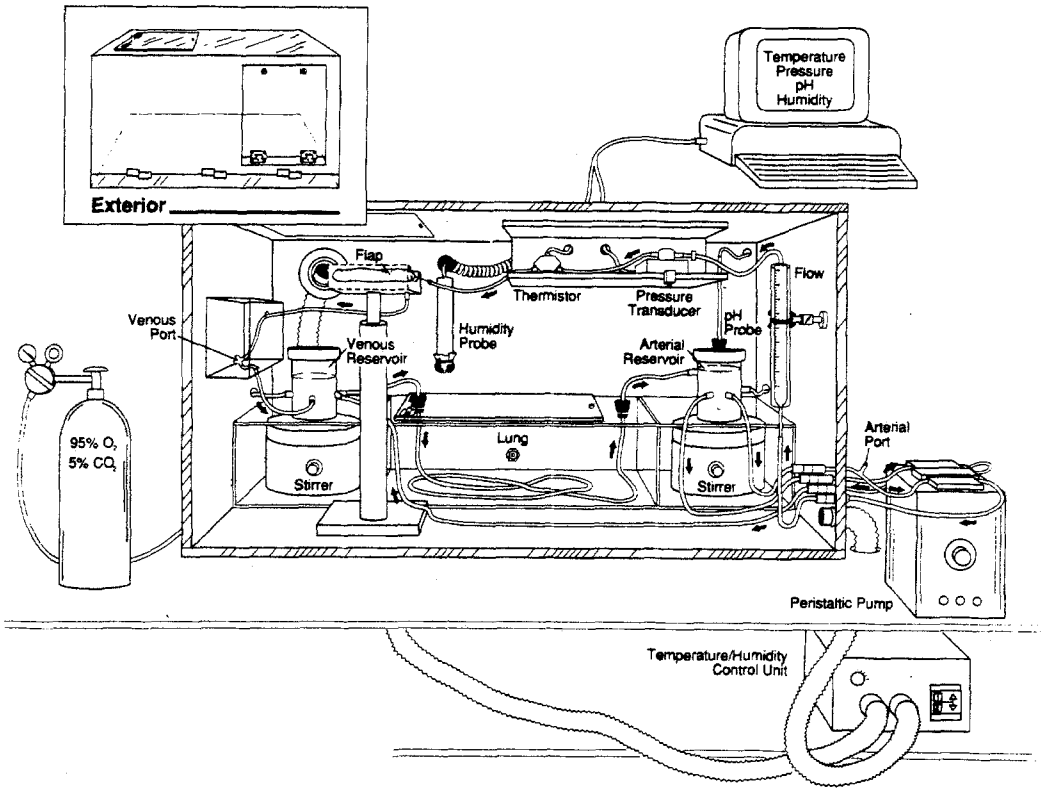

Fig. 1. Schematic illustration of the perfusion chamber and apparatus used in the experiments

of this study was to evaluate the disposition of CDDP and CBDCA in the isolated, perfused tumor and skin flap.

Materials and methods

Eight weanling Yorkshire pigs weighing approximately 15 kg (range, 12–21 kg) were used for this study. The administration of 25 mg/kg cyclosporine q24 h p. o. was initiated at least 7 days prior to the creation of skin flaps and was continued until harvesting of the flaps [13].

Skin flaps were created and harvested as previously described [12, 14]. Briefly, two 12- × 4-cm^2 skin regions perfused primarily by the caudal superficial epigastric arteries and associated paired venae comitantes were marked and incised. Two single pedicle, axial-pattern, tubed flaps were then created that encompassed these areas. A cell suspension containing approximately 3 million human choriocarcinoma cells (JAR) and 1 million normal human fibroblasts was injected s.c. into the midsection of one flap. The other flap served as the non-tumor control. A second surgical procedure was used 11 days later to cannulate the caudal superficial epigastric artery and harvest each of the flaps.

Each isolated flap was immediately transferred to a perfusion apparatus enclosed in a Plexiglas chamber (Fig. 1). The perfusion techniques, morphological and biochemical assessment of skin physiology, and viability of the flaps have been reported previously [12, 14]. The perfusion medium used in these experiments contained a Kreb's-Ringer's bicarbonate buffer, glucose, bovine serum albumin (4.5 g/dl), amikacin (0.03 mg/ml), penicillin G (10 IU/ml), and heparin (5 USP units/ml). The medium was gassed with a mixture of 95% oxygen and 5% carbon dioxide. The pH of the media was maintained at 7.44 ± 0.01 (mean ± SE) by the addition of 0.5 *N* hydrochloric acid or 1.0 *N* sodium hydroxide as needed. Concentrated dextrose (45 mg/ml) was infused to maintain perfusate glucose concentrations of 90–120 mg/dl (actual value, 112.9 ± 2.3 mg/dl). Glucose utilization represents the product of glucose extraction (in milligrams per deciliter) and flow rate (in milliliters per hour) at each observation time.

Commercially available forms of cisplatin (Platinol; Bristol-Myers Squibb Co., Evansville, Ind.) and carboplatin (Paraplatin; Bristol-Myers Co., Syracuse, N. Y.) were diluted on the day of use with sterile water to final concentrations of 1 and 10 mg/ml, respectively. Cisplatin and CBDCA were further diluted in 300 ml perfusion medium to final concentrations of 3 and 15 μg/ml, respectively. These concentrations were selected to approximate the concentrations used therapeutically [9, 16].

All flaps were perfused for at least 60 min with undosed medium to ensure viability (glucose utilization of greater than 10 mg/h) prior to dosing [12]. Afterwards, flaps were moved to another chamber containing medium that had been dosed with either CDDP or CBDCA. An infusion pressure of 43.2 ± 23.6 mmHg (mean ± SE) was applied to maintain a flow rate of 1.00 ± 0.06 ml/min (parameters were measured every 30 min). Vascular resistance (in millimeters of mercury times minutes per milliliter per gram) represents the ratio of infusion pressure (in millimeters of mercury) to flow rate (in milliliters per minute) per gram of tissue. The perfusate temperature was maintained at 35.9 ± 0.5°C by adjusting the temperature of the input air. The relative humidity of the chamber was $40.1\% \pm 9.3\%$.

Due to differences in the binding characteristics of CDDP and CBDCA, the duration of experiments differed as based on a previous study evaluating the disposition of these drugs in the isolated and perfused porcine skin flap [17]. CDDP experiments were carried out over a 5-h period (3-h dosing, 2-h washout), whereas CBDCA experiments took 6 h (3-h dosing, 3-h washout). Washout phases were accomplished by returning flaps for perfusion in the original chambers that contained undosed medium. This regimen ensured that model parameters were estimated on the basis of both uptake and washout kinetics, which implies that model predictions would apply to both phases.

Venous effluent samples were collected at 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 185, 190, 195, 200, 205, 210, 220, 230, 240, 255, 270, and 300 min from flaps perfused with CDDP. Additional venous samples were collected at 330 and 360 min from flaps perfused

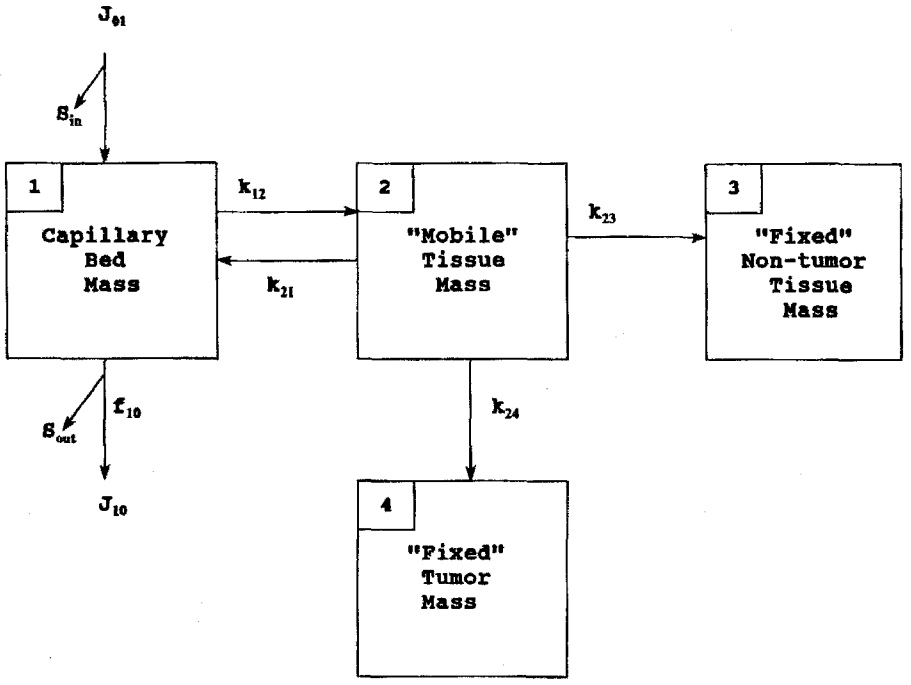

Fig. 2. Structure of the proposed model for drug disposition in the isolated and perfused tumor and skin flap. k_{12}, k_{21}, k_{23}, and k_{24} are transfer rate constants; J_{01} is the arterial input flux; J_{10} is the flux from the capillary bed to the venous drainage; f_{10} is a rate function dictating output from compartment 1 to the venous drainage; and S_{in} and S_{out} represent the experiment sample ports

with CBDCA. For all experiments, arterial perfusate samples were collected at 5 min and then hourly thereafter. An aliquot of each sample was immediately ultracentrifuged through 30,000-Da cutoff filters for the determination of free (ultrafilterable) Pt. Platinum concentrations were assayed by atomic absorption spectroscopy (AAS) [10].

At the completion of each experiment, skin flaps were quick-frozen in liquid nitrogen. Each control, non-tumor-bearing flap was cut transversely such that three sections (one each from the proximal, middle, and distal aspects of the flap) of approximately equal mass were obtained. Two transverse sections were taken from each tumor flap: one each from the proximal and distal aspects of the flap, away from the tumor. The skin was separated from the underlying tissue for separate analysis. In each tumor flap, a third section was taken from the skin surrounding the tumor. The tumor was dissected from the remaining tissue. One sample was taken from each end; one, from the periphery of the midsection; and another, from the central area of the tumor. Remaining non-tumor and tumor tissues were separated from each other and handled as one (non-tumor tissue) or two (non-tumor and tumor tissues) samples to provide constraints in the parameter-estimation process so as to facilitate the physiologic relevance for Pt in the kinetic model. Each tissue sample was weighed, digested in 2 *M* HNO_3, diluted with water and Triton-X, and assayed for Pt by AAS [10].

Tissue uptake of a compound of interest in the tumor and control flaps can be assessed by perfusing the flaps with dosed media and sampling arterial and venous concentrations while monitoring the perfusate flow. Figure 2 outlines the model used to characterize the disposition kinetics based on these measurements.

Compartment 1 (C_1) represents the central (vascular) compartment. C_2 represents the mobile (transitional), nonvascular, viable tissue-space compartment, whereas C_3 is the fixed (slowly equilibrating), non-tumor, nonvascular, viable tissue-space compartment and C_4 is the fixed, nonvascular, tumor tissue-space compartment. The term "mobile" is used in reference to ultrafilterable Pt that is spatially nonvascular and temporarily awaiting either binding by tissue (fixation) or absorption into the vascular space. A Pt-containing molecule in C_2 is thus defined as retaining the ability to traverse cell membranes and enter vascular and/or nonvascular compartments. The term "fixed" implies Pt that is irreversibly bound to any macromolecule (proteins and other tissue components). In this state, Pt is no longer ultrafilterable and, by definition, permanently associated with C_3 and C_4. These definitions are roughly equivalent to the "mobile" and "fixed" components of other physiological pharmacokinetic (PPK) models of CDDP in rats and other species [2, 6].

The model presented herein could be related to skin and/or tumor components of the larger PPK models, albeit the present model includes the specific metabolic aquation reaction in the mass-transfer rates k_{23} and k_{24}.

The arterial input flux (J_{01}) is sampled (S_{in}) on the afferent or proximal side of the flap. J_{10}, the flux from the capillary bed to the venous drainage, is sampled (S_{out}) on the efferent or distal side of the flaps. The terms k_{12}, k_{21}, k_{23}, and k_{24} are intercompartmental first-order rate constants that are estimated on the basis of the observed J_{01} and J_{10} profiles; f_{10} is a rate function dictating output from C_1 to the venous drainage. Rate constants for each infusion were estimated with the aid of the CONSAM computer program [3]. An automated iterative curve-fitting (to the venous Pt-flux profile) procedure producing a minimal sum-of-squares error was applied in each case. Before fitting, concentration profiles were normalized to percentages of the dose and divided by the initial flap mass (in grams), then multiplied by the respective flow-rate profile to produce the normalized flux profile. This normalization was effected to minimize biases due to flap size and dose variation. allowing for direct comparisons between different experiments and drugs. The dose is defined as the area under the curve of the arterial Pt-flux profile during the experiment. Only free Pt profiles were used for parameter estimation since this is the active form of CDDP and CBDCA [11].

Realistic treatment of experiments using the isolated perfused porcine skin flap (IPPSF) or IPTSF model requires consideration of a limited vascular volume (and hence the drug mass in the vascular space). Thus, as was effected in a previous three-compartment IPPSF model [17], a mass constraint in C_1 was forced. In the previous model, the mass in C_1 was assumed to be unchanging (after a brief initial internal equilibrating time) throughout a constant-input infusion (i.e., forcing a realistic mass in the vascular compartment). The present model differs from the previous one because the assumption of constant mass (i.e., that $dA/dt = 0$) has been relaxed to force constant volume (i.e., $dV_1/dt = 0$) only. An additional modification is that C_4 (tumor drug mass) has been added. For the present model, the development of the solution for drug mass in C_1 is as follows: the concentration of drug in C_1 is

$$C_1(t) = \frac{J_{01}(t)+k_{21}A_2(t)-k_{12}A_1(t)}{Q(t)}, \quad (1)$$

where $Q(t)$ represents the perfusate flow. Since the mass $[A_1(t)]$ in C_1 is the product of concentration and volume, we can write

$$A_1(t) = \frac{V_1}{Q(t)} \times [J_{01}(t)+k_{21}A_2(t)-k_{12}A_1(t)], \quad (2)$$

Table 1. Measured Pt concentrations in tumor and non-tumor tissue

	Tumor flaps (μg/g)		Control flaps, non-tumor (μg/g)
	Tumor	Non-tumor	
CDDP	0.67[a] (0.06)	1.11 (0.09)	0.98 (0.07)
CBDCA	0.39[a] (0.04)	0.66 (0.08)	0.72 (0.14)

Data represent mean values (SE)

[a] $P < 0.05$ for tumor vs non-tumor tissue in both control and tumor flaps

where V_1 is the vascular volume. Solving for $A_1(t)$ gives

$$A_1(t) = \frac{\tau(t)[J_{01}(t)+k_{21}A_2(t)]}{1+k_{12}\tau(t)}, \quad (3)$$

where $\tau(t) = V_1/Q(t)$ = the vascular transit time. V_1 (in milliliters) was assumed constant and estimated as 0.08 M_i, where M_i is equal to the initial flap mass in grams. The factor of 0.08 has previously been validated for the IPPSF model [18].

Equation 3 implies that the drug mass in C_1 is a function of the rate of intraarterial input, the drug mass in C_2, and the vascular transit time. Thus, there is no need to write a differential equation for $A_1(t)$ because Eq. 3 is its solution. The treatment of C_1 in the present model improves on that of the previous model [13] by allowing the vascular space to accommodate dynamic changes in Pt concentration (and hence mass) while remaining physiologically relevant [classic compartmental methods would allow the mass (and/or volume) of C_1 to increase or decrease without bound, abdicating physical reality]. True in vivo PPK models such as those previously proposed [2, 6] enjoy an inarguable advantage over classic compartmental models in that physiological reality is possible, assuming that the correct perfusion and partitioning parameters are available. The use of a completely isolated system such as the IPTSF model simply corresponds to one or two modules (i.e., skin and/or tumor) in a complete in vivo physiological model. The motivation to study such a module in greater detail as reported herein could ultimately be construed to provide more appropriate skin and/or tumor components in the "next generation" of PPK models.

The differential equations for C_2, C_3, and C_4, respectively, are

$$\frac{dA_2(t)}{dt} = \frac{k_{12}\tau(t)J_{01}(t)}{1+k_{12}\tau(t)} + A_2(t)\left[\frac{k_{12}k_{21}\tau(t)}{1+k_{12}\tau(t)} - k\right], \quad (4)$$

where $k = k_{21}+k_{23}+k_{24}$;

$$\frac{dA_3(t)}{dt} = k_{23}A_2(t); \text{ and} \quad (5)$$

$$\frac{dA_4(t)}{dt} = k_{24}A_2(t). \quad (6)$$

The solution of Eqs. 4–6 is straightforward using Laplace transforms (not shown) and was implemented in a computer program that was written by us for execution on a DEC VAX station for effecting the simulations.

Parameter estimations were based on least-squares fitting of simulated-to-observed venous flux profiles. Venous flux $[J_{10}(t)]$ is simply $C_1(t)Q(t)$, or Eq. 1 multiplied by the flow rate. The rate function $f_{10}(t)$ describing the mass transfer from the vascular space to the exterior (i.e., venous efflux) is only an incidental parameter since its estimation is not required for model validation, but its assumed value is $\tau^{-1}(t)$, which is consistent with the notion that molecules not taken up by extravascular tissue will be effluxed in bulk flow. Note that

$$J_{10}(t) = C_1(t)Q(t) = A_1(t)f_{10}(t) \quad (7)$$

and that solving for $f_{10}(t)$, we get

$$f_{10}(t) = Q(t)/V_1 = \tau^{-1}(t). \quad (8)$$

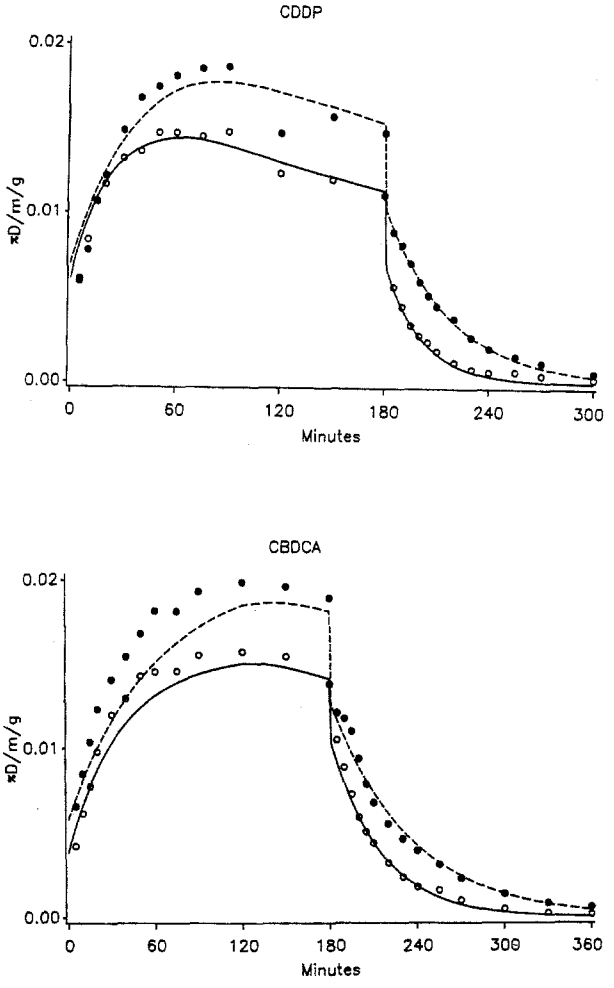

Fig. 3. Mean normalized [divided by dose × 100 and by initial flap mass (g)] predicted and observed venous ultrafilterable Pt flux determined from control (*filled circles*) and tumor (*open circles*) CBDCA and CDDP infusions

Student's *t*-test was used to test differences between means; *P* values of <0.05 were considered to be significant. Strengths of linear associations were determined by simple correlations; *r* values are reported. The k_{12} data were not amenable to statistical analysis because they were constrained between 0 and 1 and some estimates for k_{12} were 1.

Results

Flaps that were considered to be viable after 1 h of perfusion with undosed media and were therefore perfused with dosed media included four CDDP tumor, four CDDP control, four CBDCA tumor, and three CBDCA control flaps. The measured tissue Pt concentrations are listed in Table 1. Figure 3 shows the model-predicted and observed normalized venous flux profiles, and Fig. 4 gives the predicted Pt accumulations in each compartment. The profiles in Figs. 3 and 4 are shown as normalized (divided) by the initial flap mass (in grams) and converted to percentages of the dose, where the dose is the estimated amount of Pt infused during the experiment. The estimated model rate constants and the Pt masses in each compartment are listed in

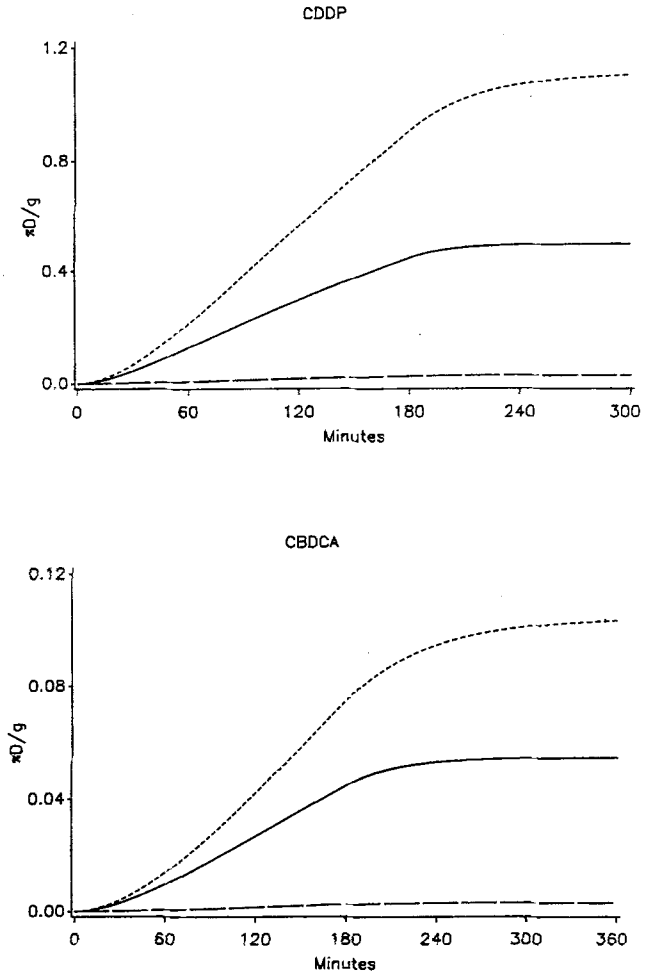

Fig. 4. Predicted mean fixed non-tumor (compartment 3) and tumor (compartment 4) tissue Pt mass during CDDP and CBDCA infusions. *Solid line:* tumor flaps, C3; *dashed line:* tumor flaps, C4; *dotted line:* control flaps, C3. Profiles were normalized as in Fig. 3

Table 2. The estimated mass of Pt from CDDP in C_1 and C_2 and the estimated residual Pt mass from CDDP after dosing in control flaps were significantly greater than those in tumor flaps ($P < 0.05$). A similar trend was noted for the estimated mass in C_2 in CBDCA flaps, although this was not significant. The estimated mass of Pt from both CDDP and CBDCA in C_3 tended to be greater in control flaps. The estimated residual Pt mass (ResW) from both CDDP and CBDCA after washout also tended to be greater in control flaps than in tumor flaps. Therefore, the model suggests that control flaps tended to accumulate more Pt than did tumor flaps.

In tumor flaps, the mass of Pt from CDDP in C_3 and C_4 and the rate constant describing the movement of Pt between C_2 and C_3 were significantly different from those parameters derived in tumor flaps treated with CBDCA. Likewise, the mass of Pt from CDDP versus CBDCA in C_3 was significantly different in control flaps. These differences, attributable to dissimilar binding characteristics of CDDP and CBDCA, were further reflected in the significant differences that existed between the residual Pt from CDDP versus CBDCA in both tumor and control flaps after washout.

The flap weights and mean vascular resistance values are listed in Table 3. Figure 5 demonstrates that strong linear relationships existed between the estimated mass of Pt in the flaps from CBDCA or CDDP and the vascular resistance of the flaps at 30 or 60 min of perfusion.

Discussion

This paper describes the use of an isolated, perfused tumor and skin flap to develop a physiologically relevant regional pharmacokinetic model. This model was used to evaluate the disposition of Pt derived from CDDP and CBDCA within tumor and non-tumor tissues without the effects of an eliminating or metabolizing organ system. Furthermore, factors that have the potential to affect tissue uptake (e.g., flow rate, temperature) were controlled.

The difference in the Pt mass in the central compartment noted between tumor and control flaps treated with CDDP may reflect true differences in the capillary Pt mass between tumor and non-tumor flaps. However, the significant difference in the Pt mass in the mobile tissue compartment observed in CDDP flaps, the similar trend noted in CBDCA flaps, as well as the apparent differences in Pt accumulation in the fixed non-tumor tissue compartment observed in both CDDP and CBDCA flaps suggest an effect of tumor presence on Pt disposition in the flap. These differences cannot be explained as a normalization bias since the magnitude of difference in compartmental masses is greater than that attributable to flap mass alone.

The differences between the tissue accumulation of Pt from the highly reactive compound CDDP versus the less reactive CBDCA were expected, considering the differences in binding characteristics noted between these two compounds [17]. These differences become even more pronounced when consideration is given to the observations that the data were normalized and that a higher dose of Pt was actually applied to the CBDCA-infused flaps. The normalization is valid because the mass of Pt from CBDCA or CDDP in the central compartment proved to be similar in tumor and control flaps. The lack of a significant difference in the residual Pt in flaps at the end of the dosing phase is not surprising because this takes into consideration the mass of Pt in all compartments and there was no difference in Pt accumulation in the central and mobile tissue compartments when the Pt was derived from either CDDP or CBDCA. The dissimilar binding characteristics of CDDP and CBDCA are also reflected in k_{23}, the rate constant describing the movement of Pt between the mobile and the fixed non-tumor tissue compartments.

The finding of a greater Pt mass in the non-tumor versus tumor fixed-tissue compartments can be explained in part by the observation that skin is a major site of CDDP and CBDCA deposition [15, 16]. This difference is further magnified by normalization of the data by weight of the flap, since the majority of the flap weight is due to non-tumor tissue. Actual Pt concentrations in tumor tissue were approximately one-half of the Pt concentrations in non-

Table 2. Estimated compartmental masses and model parameters following CDDP and CBDCA infusions

	CDDP Tumor	CDDP Control	CBDCA Tumor	CBDCA Control
C_1[a]	0.0377[b] (0.0036)	0.0500[c] (0.0064)	0.0414 (0.0103)	0.0463 (0.0220)
C_2	0.221 (0.023)	0.698[c] (0.219)	0.494 (0.380)	0.910 (0.576)
C_3	0.460 (0.201)	0.898[d] (0.431)	0.0403[e] (0.0035)	0.0764[e, f] (0.0272)
C_4	0.0270 (0.0142)		0.00255[e] (0.00235)	
k_{12}[g, h]	0.714 (0.210)	1.000 (0.00)	0.985 (0.031)	0.818 (0.120)
k_{21}	0.111 (0.031)	0.0927 (0.0429)	0.112 (0.046)	0.0591[i] (0.0217)
k_{23}	0.0117 (0.0058)	0.00912 (0.00657)	0.00078[e] (0.00041)	0.00072[j] (0.00025)
k_{24}	0.000675 (0.000330)		0.00045 (0.00005)	
ResD[k]	0.711 (0.185)	1.57[c] (0.39)	0.559 (0.377)	1.01 (0.58)
ResW	0.520 (0.210)	1.10[l] (0.47)	0.0806[e] (0.0608)	0.186[e] (0.127)

[a] C represents simulated μg Pt/g tissue in compartments 1–4 at the end of the dosing phase (3 h)
[b] Data represent mean values (SD)
[c] $P < 0.05$ for CDDP tumor vs control experiments
[d] $P = 0.12$ for CDDP tumor vs control experiments
[e] $P < 0.05$ for CDDP vs CBDCA experiments
[f] $P = 0.15$ for CBDCA tumor vs control experiments
[g] Rate constants are expressed in min^{-1}
[h] $k12$ data not amenable to statistical analysis
[i] $P = 0.10$ for CBDCA tumor vs control experiments
[j] $P = 0.08$ for CDDP vs CBDCA experiments
[k] ResD and ResW represent predicted mass (μg) of Pt in flaps/g tissue at the end of dosing (3 h) and washout phases (CDDP, 5 h; CBDCA, 6 h), respectively
[l] $P = 0.07$ for CDDP tumor vs control experiments

Table 3. Physiologic data for tumor and control CDDP and CBDCA infusions

	CDDP Tumor	CDDP Control	CBDCA Tumor	CBDCA Control
M_i[a]	34.1 (4.9)	23.3 (2.6)	38.3 (8.6)	28.2 (7.2)
M_m[a]	43.4 (9.3)	36.6 (5.4)	45.9 (7.1)	38.9 (4.9)
M_f[a]	52.6 (15.8)	49.8 (9.2)	53.4 (8.5)	49.5 (6.5)
M_t[a]	5.9 (1.1)		6.4 (0.5)	
$VRes_d$[b]	1.21 (0.44)	2.09 (0.44)	0.63 (0.11)	1.16 (0.23)
$Vres_w$[b]	1.75 (0.97)	2.59 (0.45)	0.93 (0.21)	1.48 (0.52)
$VRes_m$[b]	1.52 (0.68)	2.33 (0.42)	0.79 (0.16)	1.32 (0.38)

[a] M_i, Initial flap mass (experiment start, g); M_m, mean flap mass $(M_i+M_f)/2$; M_f, final flap mass (experiment end); M_t, tumor mass (experiment end). Data represent mean values (SD)
[b] VRes, Mean vascular resistance (mmHg min ml^{-1} g^{-1}) during the dosing ($VRes_d$) and washout ($VRes_w$) phases and the entire experiment ($VRes_m$). Data represent mean values (SE)

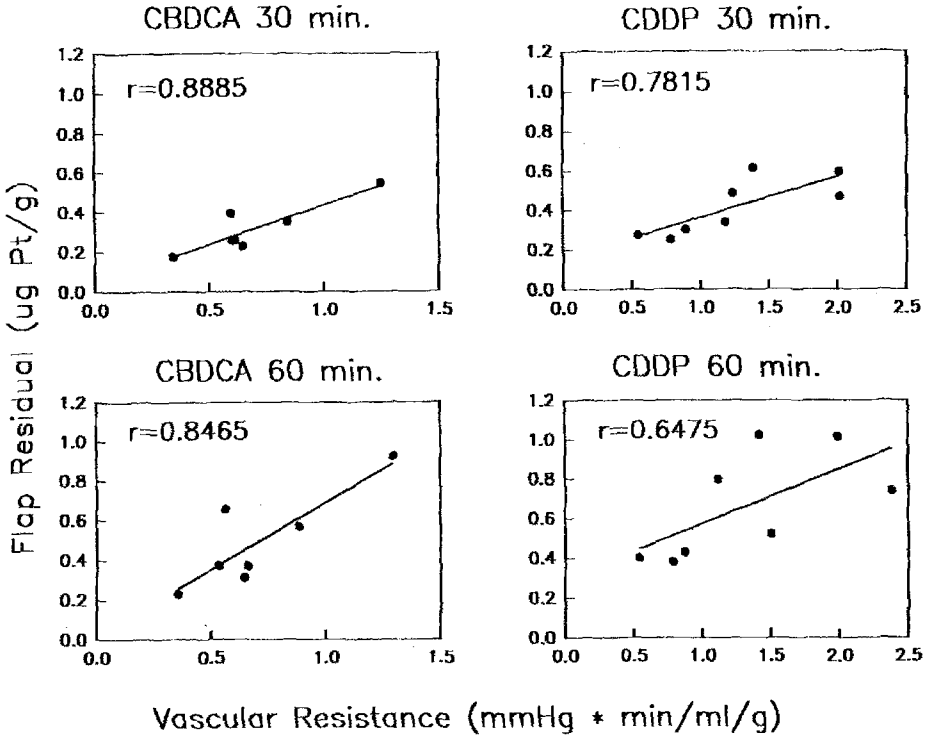

Fig. 5. Correlation between vascular resistance and estimated Pt mass at 30 and 60 min of infusion

tumor tissue. Differences in the affinity of Pt for tumor and non-tumor tissue may have accounted for the difference in tissue concentrations. Decreased intratumoral concentrations due to operative mechanisms of drug resistance cannot be discounted [11].

Although the difference was not significant, cross-sectional vascular resistance tended to be lower in tumor flaps than in control flaps. Significant differences in vascular resistance between tumor and control flaps have been noted in an initial report describing the development and viability of this model [14]. This tendency becomes important when consideration is given to the data represented in Fig. 5 that correlate vascular resistance to flap residual. This suggests that at least part of the difference in Pt accumulation noted between tumor and control flaps may be due to differences in vascular resistance.

The relationship between vascular resistance and estimated flap residual was evaluated at 30 and 60 min of perfusion because this is the period during which the mass of Pt in flaps is rapidly changing and is therefore more likely to be affected by the various parameters. Because the flow rate is kept constant, this putative relationship between vascular resistance and flap residual is probably not due to the inclusion of flow rate in the mathematical equations. Likewise, other parameters that are dependent on flow rate, such as the glucose utilization of the flap, did not consistently exhibit strong correlations with the estimated flap residual. Increased cross-sectional vascular resistance, leading to enhanced Pt uptake, may be due either to increased vascular permeability with increased extravascular pressure or to true increases in vascular tone. These results warrant further study in this area.

In conclusion, the present study demonstrates that this model can be used to estimate dispostion parameters of Pt from CDDP and CBDCA for tumor and non-tumor tissue. Although it was not done in this study, the model allows for the manipulation of physiological variables, thereby determining the effects of these variables on drug uptake. Future studies may allow for the identification of factors that favor the preferential uptake of drug into tumor versus normal tissue.

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