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Extracorporeal hemofiltration: a model for decreasing systemic drug exposure with intra-arterial chemotherapy*

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Summary. Cisplatin (3 mg/kg) was infused through the hepatic artery in nine mongrel dogs. Four of these dogs underwent simultaneous extracorporeal hemofiltration (ECH) of the hepatic venous effluent using a high-flow, dual-lumen catheter placed in the vena cava at the level of the hepatic veins. Platinum levels were measured in the plasma, urine, and ultrafiltrate and in kidney and liver tissue. ECH significantly reduced systemic drug exposure as measured by the AUC for free and total platinum, by urinary excretion, and by 24-h kidney levels. Regional liver levels were minimally affected. Recovery of platinum in the ultrafiltrate was 40% ± 14%. ECH resulted in efficient extraction of platinum and reduced systemic drug exposure with relative preservation of regional hepatic drug exposure.

Introduction

A basic principle of cancer chemotherapy is that increasing the dose intensity enhances tumor cell kill [13, 27]; however, that approach is limited by the narrow therapeutic index of most chemotherapeutic agents. Several techniques have been used to target drug delivery so as to minimize systemic drug exposure and toxicity, including regional drug administration, monoclonal antibody targeting, coadministration of drug and particles (chemoembolization), and the use of carrier systems such as liposomes [2, 5, 11, 12, 23, 28, 29].

Regional chemotherapy has been used clinically for many years in an attempt to increase the therapeutic ratio; however, systemic toxicity remains the dose-limiting factor for many agents. The relative advantage of intra-arterial drug delivery is a composite of increased target exposure (R_T) and decreased systemic exposure (R_S). Overall regional benefit (the ratio of the target site concentration to the systemic concentration) is denoted by R_D. Thus,

$$R^D = \frac{R_T}{R_S} = 1 + \frac{Cl_{TB}}{Q(1-E)},$$

where Cl_{TB} is the total body clearance of the drug, Q is the blood flow through the infused artery, and E is the rate of drug extraction [6, 7, 17].

This experiment was designed to increase the advantage of regional hepatic chemotherapy (R_D) by increasing Cl_{TB}, thereby decreasing the fraction of injected drug that reaches the venous circulation. This was accomplished by combining extracorporeal hemofiltration (ECH) of the hepatic venous drainage with hepatic arterial delivery of cisplatin (CDDP). The liver was chosen as the regional circuit because of the high incidence of primary and secondary malignancies in this organ and the established interest in hepatic regional treatments. CDDP was chosen as a model compound for determination of the efficacy of hemofiltration because of its limited hepatic extraction and its demonstrated activity against certain liver tumors [18].

Materials and methods

Operative procedure. Nine adult mongrel dogs (19–26 kg) were anesthetized with sodium pentobarbital (15–20 mg/kg). In each dog, a leg vein was cannulated for the collection of blood samples and the abdomen was opened through a midline incision. Both ureters were ligated distally and cannulated proximally with a 10-F silastic catheter. Urine was collected hourly for 4 h, after which the catheters were connected to a 1-l collection bag, which was left in the dog's abdomen and retrieved at 24 h when the dog was killed. The gastroduodenal artery was ligated and the common hepatic artery was cannulated with a 22-gauge, 3/4-in. angiocath.

Four dogs underwent ECH of the hepatic venous drainage. A cytostatic filtration set was provided by Plastik für die Medizin GmbH (FRG). The double-lumen catheter was inserted through a suprarenal venotomy and positioned immediately cephalad to the hepatic veins; placement was determined by direct palpation. Both lumens were flushed

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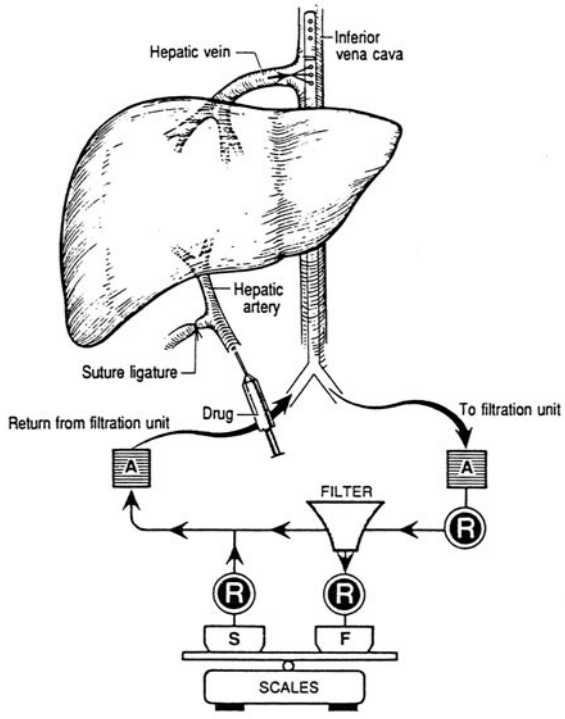

Fig. 1. Extracorporeal hemofiltration circuit. *A*, air trap; *R*, roller pump; *F*, filtrate; *S*, solution (Ringer's lactate), which is returned to the dog to replace the filtrate in equivolume amounts

with heparinized saline, clamped, and connected to a roller pump and Gambro hemofilter (Gambro Dialysatoren KG, FRG) (Fig. 1).

Drug administration and hemofiltration. cis-Diamminedichloroplatinum (CDDP) was purchased from the Bristol-Myers Oncology Division (Syracuse, NY) and given through the hepatic artery (3 mg/kg in D_5W) as a 3-min bolus (four dogs) or 60-min infusion (five dogs). Venous blood samples for free and total platinum (Pt) were collected at time 0 and at 5, 10, 20, 30, 45, 60, and 90 min and at 2, 3, 4, 5, 6, 7, and 24 h after CDDP administration was completed. Urine was collected at 1, 2, 3, 4, and 24 h. For the dogs undergoing 1-h CDDP infusion, blood was also sampled at 30 and 60 min during the infusion and an additional urine sample was collected at 60 min.

For animals undergoing ECH, heparin (150 units/kg) was given i. v. and, 5 min later, CDDP administration and ECH were started. Heparin was readministered (75 units/kg) at 45 min. ECH was continued for 60 (CDDP bolus) or 90 min (CDDP infusion). Flow rates were maintained at 300–500 ml/min, and fluid equilibrium was achieved using an electronic balance, replacing ultrafiltrate with an equal volume of Ringer's lactate solution. Following completion of ECH, the double-lumen catheter was removed and the heparin was reversed with i. v. protamine (25 mg). The hepatic arterial catheter was removed and the midline incision was closed. All dogs were killed by exsanguination at 24 h. At that time, liver biopsies were carried out to measure CDDP concentrations of the target site, and kidney cortex biopsies (the primary organ for CDDP toxicity) were taken to measure systemic tissue concentrations of the drug.

Platinum analysis. To determine plasma Pt levels, 1 ml venous blood was mixed with 10 µl heparin (1,000 unti/ml) and microcentrifuged for 30 s. A 0.25 ml-aliquot of plasma was mixed with 1 ml trichloroacetic acid (10% in distilled water), placed in ice for 15 min, and microcentrifuged for 30 s. The supernatant was collected to determine free Pt levels. Total Pt levels were measured in the remaining plasma and in urine, ultrafiltrate, kidney cortex, and liver parenchyma. Samples were stored at 4° C, and all Pt levels were determined using a Varian (model AA1475) flameless atomic absorption spectrophotometer as previously described [25]. Protein in tissue homogenates was measured by the standard Lowry technique. Data are presented as means ± standard deviations. When bolus and infusional CDDP administration were compared, independent of ECH, there were no apparent differences in plasma, urine, or tissue Pt levels (data not presented). Therefore, the results of the bolus and infusion experiments were combined to analyze the effect of ECH (Table 1).

Pharmacokinetic and statistical analysis. A two-compartment open model was used to fit the postinjection or postinfusion data for free Pt in plasma. A nonlinear least-squares regression program was used for this purpose as previously reported [26]. The biphasic decay constants were not corrected for the infusion time. Areas under the plasma PT concentration × time curve were calculated by the standard trapezoidal method and used to determine clearances by the method of Gibaldi and Perrier [14]. Statistical significance was determined by Student's *t*-test analyses.

Results

Systemic exposure

Pt levels measured in the plasma, urine, and kidney cortex are presented in Figs. 2–4 and summarized in Table 1. All three of these indicators of systemic exposure were significantly reduced by ECH (48%–58%). This reduction in systemic exposure is consistent with the amount of Pt recovered in the ultrafiltrate (40% ± 14%; Fig. 5). Free (filterable) Pt levels were negligible at 30–60 min after ECH, indicating that additional ECH would be of no benefit. During continuous infusion, Pt recovery in the ultrafiltrate was constant over time, indicating that filtration efficiency was maintained.

Regional exposure

Pt levels were measured in the liver parenchyma to determine regional drug exposure (Fig. 4). Initially, in each of three dogs, five different liver samples were taken to assess regional differences in drug concentration due to arterial

Table 1. Effect of ECH on the hepatic arterial administration of CDDP

	Plasma AUC(free) (µg · min/ml)	Plasma AUC(total) (µg · min/ml)	UE (% dose)	Tissue concentration (µg Pt/g protein)	
				Kidney	Liver
Without ECH	290 ± 49	1,921 ± 518	35 ± 8	123 ± 59	57 ± 10
With ECH	152 ± 37	800 ± 154	17 ± 3	63 ± 18	48 ± 3
Percentage of change	–48%	–58%	–51%	–49%	–16%
P values	0.001	0.002	0.002	0.046	0.062

Values are presented as means ± SD; UE, cumulative urinary excretion in 24 h

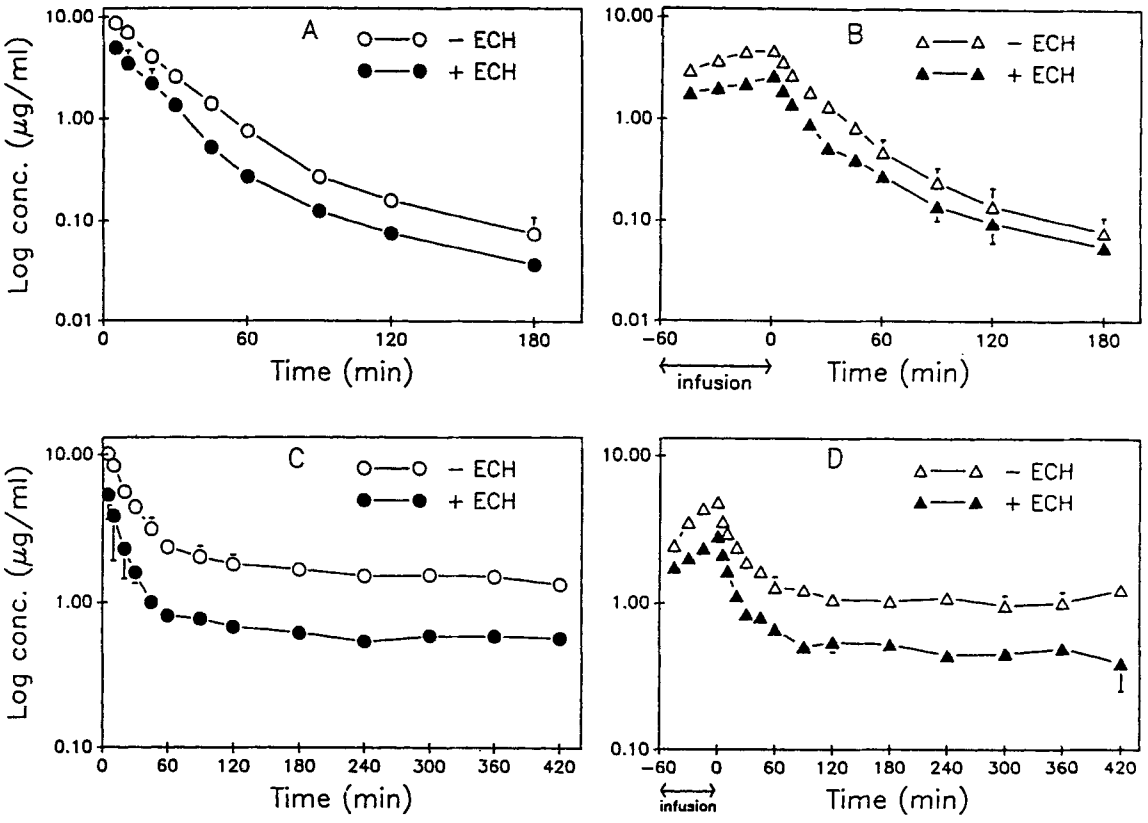

Fig. 2 A–D. Plasma concentrations of A free Pt, bolus; B free Pt, infusion; C total Pt, bolus; and D total Pt, infusion. Each data point represents a mean of values from 2–3 dogs

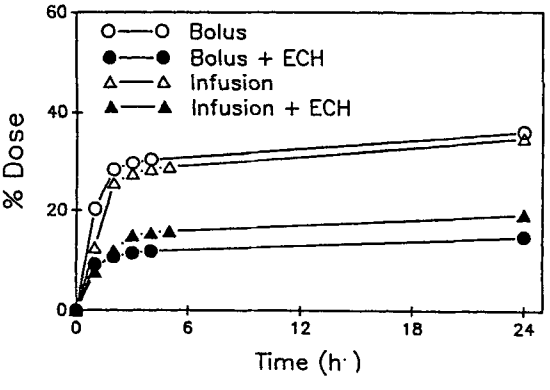

Fig. 3. Percentage of the cumulative dose of cisplatin in urine collected over 24 h. Each data point represents a mean of values from 2–3 dogs

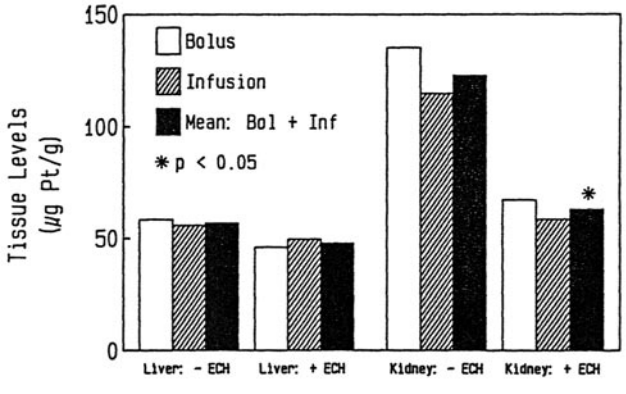

Fig. 4. Tissue levels of cisplatin in the liver and kidney, collected at 24 h. The bolus or infusion data represent a mean of values from 2–3 dogs

anomolies or streaming of infused drug [9]. No regional differences were noted. Liver-tissue Pt levels were nearly identical in both groups of dogs (with and without ECH) (Table 1).

Pharmacokinetic analysis

Pharmacokinetic parameters for free CDDP were determined for each dog and are presented in Table 2. ECH substantially increased the plasma clearance of free CDDP. For bolus CDDP delivery, it increased the plasma clearance from 7.83 and 7.39 to 12.21 and 19.56 ml min^{-1} kg^{-1}. For infusional CDDP delivery, the plasma clearance was enhanced by ECH from 7.82, 5.59, and 5.79 to 11.85 and 10.55 ml min^{-1} kg^{-1}. ECH did not affect the renal clearance of free CDDP for either method of administration.

Discussion

Intra-arterial chemotherapy is used to maximize drug concentration at the target site and to minimize systemic exposure. Each of the parameters affecting pharmacokinetic

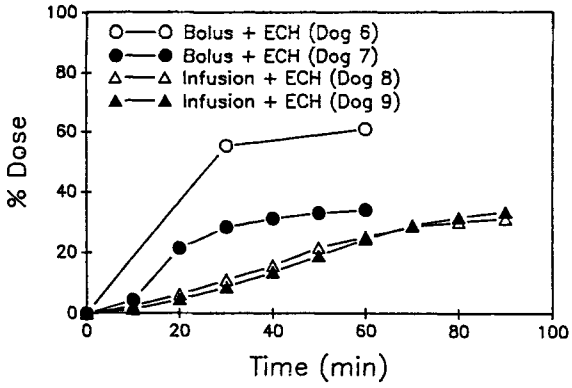

Fig. 5. Percentage of the dose of CDDP in the ultrafiltrate, collected over 60 (*Bolus*) or 90 (*Infusion*) min

advantage (Q, E, Cl_{TB}) can be manipulated to improve drug exposure at the target site. Sasaki et al. [24] used angiotensin II, a potent vasoconstrictor, to alter blood flow (Q) within the liver and increase tumor drug concentration. Given as a continuous intra-arterial infusion, angiotensin II decreased overall hepatic blood flow, redirected intrahepatic flow to the tumor, and increased the tumor: nontumor drug concentration by a factor of 3.3.

A second strategy for increasing tumor cell kill is the use of chemotherapeutic agents with high regional extraction (E). 5-Fluoro-2′-deoxyuridine (FUDR) has been used extensively for the intra-arterial treatment of colorectal metastases to the liver. First-pass hepatic extraction removes 97% of the delivered dose, such that systemic exposure is minimal and local hepatobiliary toxicity represents the dose-limiting factor [3, 15, 16, 20].

A third method that enables dose intensification is to increase the total body clearance (Cl_{TB}) of a given drug. This is best accomplished with total isolation and perfusion of a regional circuit and has been used for both hepatic and extremity neoplasms [4, 8, 19]. However, vascular isolation of most regional circuits is technically difficult and is associated with significant morbidity. Alternatives are therefore being explored, such as the application of ECH or hemodialysis to the venous drainage of the infused region. This achieves the equivalent of a pharmacologic first-pass effect and simulates an isolated-perfusion model.

Oldfield et al. [21] combined intra-carotid 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) with hemodialysis of the ipsilateral jugular venous drainage. Systemic exposure was reduced by 56%–87%, with a calculated pharmacokinetic advantage (brain: body ratio) of between 21:1 and 51:1. Similarly, intra-carotid infusion of CDDP together with extracorporeal hemodialysis resulted in a reduction of 51%–61% in systemic exposure and a pharmacokinetic advantage of 15:1 [22]. Aigner et al. [1] infused intra-arterial mitomycin C into the hepatic artery and used ECH on the hepatic venous drainage, achieving a 50% reduction in systemic exposure.

Our present data confirm these early results, as ECH of the hepatic venous drainage reduced systemic CDDP exposure by 48%–58%. Theoretically, this should enable us to double the intra-arterial CDDP dose without major increases in the drug's systemic concentration. To achieve greater dose escalations will require modification of the extracorporeal circuit's design. Dedrick et al. [10] derived an equation that describes the pharmacokinetics of drug removal from the venous blood draining the infused region during chemotherapy:

$$R_D = \frac{1 + \frac{EQ_S + k_2v_2}{Q}}{1-fE},$$

where E is the rate of drug extraction by the extracorporeal device, Q_S is the systemic blood flow that dilutes the drug entering the device, k_2v_2 is the total body clearance (Cl_{TB}) of the drug, and f is the fraction of blood flow (Q) that exits the regional circuit and enters the extracorporeal device. As Dedrick et al. stated, if all of the venous drainage (f=1) can be directed through an extracorporeal circuit with complete extraction of the drug (E=1), then the pharmacokinetic advantage (R_D) is limitless. Hence, a further reduction of systemic exposure and enhancement of the therapeutic advantage of hepatic intra-arterial CDDP will require improved isolation of the hepatic venous return (i.e., using balloon-cuffed catheters) and more efficient extraction of CDDP.

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Table 2. Pharmacokinetics of free CDDP

Dog	Cisplatin	A (μg Pt/ml)	α (min^{-1})	$t_{1/2\alpha}$ (min)	B (μg Pt/ml)	β (min^{-1})	$t_{1/2\beta}$ (min)	$AUC_{0-\infty}$ (μg·min/ml)	Plasma clearance (ml min^{-1} kg^{-1})	Renal clearance (ml min^{-1} kg^{-1})	Ultrafiltrate clearance (ml min^{-1} kg^{-1})
1	Bolus	10.50	0.0560	12.38	0.88	0.0174	39.8	249.2	7.83	3.67	–
2	Bolus	10.49	0.0490	14.14	0.32	0.0059	117.5	263.9	7.39	1.86	–
3	Bolus+ECH	8.53	0.0682	10.16	0.33	0.0125	55.4	159.7	12.21	1.48	8.34
4	Bolus+ECH	4.31	0.0561	12.35	0.19	0.0089	77.9	99.7	19.56	3.40	6.65
5	Infusion	3.14	0.0454	15.26	0.16	0.0066	105.0	249.4	7.82	2.49	–
6	Infusion	3.17	0.0413	16.78	0.97	0.0109	63.6	348.6	5.59	1.88	–
7	Infusion	5.08	0.0485	14.29	0.27	0.0147	47.1	336.6	5.79	2.26	–
8	Infusion+ECH	1.95	0.1940	3.57	1.19	0.0258	26.9	164.6	11.85	2.39	4.27
9	Infusion+ECH	2.47	0.0880	7.88	0.59	0.0127	54.6	184.9	10.55	1.93	3.52

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