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Hepatic arterial infusion chemotherapy with complete hepatic venous isolation and extracorporeal chemofiltration: a feasibility study of a novel system

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When chemotherapeutic drugs with low liver extraction are used for hepatic arterial infusion (HAI), dosage limits are usually determined by systemic rather than hepatic toxicity. If such agents could be administered by HAI at dosages limited by hepatic toxicity, regional drug exposure and therapeutic efficacy might be significantly enhanced. We report herein a novel system that achieves complete hepatic venous isolation using a dual-balloon vena cava catheter that can be inserted percutaneously. This catheter is connected to a carbon filter in an extracorporeal venous bypass circuit to recover drug that is not absorbed by the liver after HAI. The hemodynamic response to this system was evaluated in six pigs. When the animals were placed on the extracorporeal circuit, we observed a 22% decrease in cardiac output that was well tolerated without significant change in blood pressure. When the filter was incorporated into the circuit, cardiac output was significantly reduced (50%); however, continuous infusion of phenylephrine rapidly normalized blood pressure, heart rate, cardiac output, and left ventricular filling pressures. Initial testing of chemofiltration efficacy was performed in four of the six animals, the remaining two animals being used only to assess hemodynamic response. One each of the four tested animals received either doxorubicin (3 or 9 mg/kg), mitomycin C (1 mg/kg), or cisplatin (1 mg/kg) by HAI. The filter removed over 90% of hepatic venous doxorubicin and mitomycin C and 65% of hepatic venous cisplatin. This feasibility study confirms that hepatic venous isolation with chemofiltration can significantly reduce systemic exposure to high-dose chemotherapeutic agents given by HAI.

Key words: Intra-arterial chemotherapy, chemofiltration, hepatic venous isolation.

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Introduction

Hepatic arterial infusion (HAI) of chemotherapeutic agents is an attractive option in the treatment of primary and metastatic liver cancers since the tumors receive the majority of their blood supply from the hepatic artery. Fluoropyrimidines, such as 5-fluorouracil (5-FU) and 5-fluoro-2-deoxyuridine (FUDR), have a high first-pass hepatic clearance that allows high-dose HAI with little systemic toxicity. Many other potentially useful chemotherapeutic drugs do not have high hepatic clearance; when such agents are given by HAI at conventional doses, dose-limiting systemic toxicity occurs. Thus, the utility of agents such as doxorubicin (DOX), mitomycin C (MMC), and cisplatin (CDDP) when administered by HAI is limited by systemic toxicity.

Numerous techniques have been devised to limit systemic exposure following regional infusion of chemotherapeutic drugs. These include complete surgical isolation perfusion of the liver[1] and extremities,[2] and use of venous catheters placed surgically or percutaneously for non-isolated drug extraction by membrane or carbon filtration.[3–6] However, the utility of these techniques is limited either by the requirement for an extensive operative procedure with associated morbidity and mortality or by insufficient drug extraction which does not allow major increases in dosage levels.

We report herein our feasibility studies and hemodynamic data using a novel system employing a double-balloon vena cava catheter. The catheter is designed to achieve complete hepatic venous isolation. Following HAI of chemotherapeutic drugs, systemic exposure to drug is significantly reduced by passing the hepatic venous blood through an extracorporeal bypass circuit and carbon filter prior to its return to the systemic circulation.

Materials and methods

Chemotherapeutic agents

DOX was purchased from Cetus Corp. (Emeryville, CA). MMC and CDDP were purchased from Bristol-Meyers (Evansville, IN).

Procedures

Six adult domestic pigs (35–40 kg) were anesthetized with ketamine (20 mg/kg), acepromazine (0.5 mg/kg) and atropine (1.2 mg), all given by intramuscular injection. General anesthesia was maintained with isoflurane (1.5%) following endotracheal intubation of the animals. The femoral arteries, femoral veins, and external jugular veins were exposed on both sides through small cut-down incisions. A 16-French silastic catheter was placed into the left femoral artery for continuous blood pressure monitoring. A 7.5-French arterial introducer sheath was placed in the right femoral artery. Cordis introducer sheaths 8.5-French in diameter were placed into each of the external jugular veins. The right external jugular vein catheter was used to complete the extracorporeal pump circuit as the systemic blood return site. To provide continuous hemodynamic monitoring, a Swan-Ganz catheter (Baxter Healthcare Corp., Irvine, CA) was introduced through the Cordis sheath in the left external jugular vein; positioned in the pulmonary artery so that, with the balloon inflated, the left ventricular filling pressures could be measured and, with the balloon deflated, the pulmonary artery pressure could be measured. Following placement of these catheters, systemic anticoagulation was achieved by administering heparan sulfate (150 mg/kg) as an intravenous bolus. Systemic anticoagulation was maintained throughout the duration of the procedure by administering heparan sulfate (75 mg/kg) by intravenous bolus every hour.

After anticoagulation was achieved, the 16-French dual-balloon vena cava catheter (Bodden catheter; Delcath Systems, New York, NY) was introduced through the left femoral vein and advanced under fluoroscopic control until the tip was above the hepatic veins. The cephalad balloon was then inflated with 3 ml of 25% iodinated contrast dye (Omnipaque; Winthrop Pharmaceuticals, New York, NY). The catheter was gently withdrawn until indentation of the balloon occurred at the diaphragmatic hiatus. The caudal balloon was inflated with 15 ml of iodinated contrast dye, and then contrast was injected through the central fenestrations between the balloons of the vena cava catheter. Radiographs taken during this injection demonstrated (1) complete retrograde filling of the entire hepatic venous system and (2) confirmed absence of contrast leak around the isolation balloons. If complete capture of all hepatic veins was not demonstrated, the catheter was repositioned until this was achieved. With the cephalad balloon on the vena cava catheter deflated, the arterial introducer sheath placed in the right femoral artery was used to introduce a 4-French catheter for cannulation of the celiac artery. The catheter tip was advanced under fluoroscopy until only the hepatic artery was being infused. An arteriogram was then performed to confirm liver perfusion and absence of extrahepatic flow.

A capacitance pump (model BP50; Biomedicus Inc., Minneapolis, MN) was used for the extracorporeal pump circuit. The vena cava catheter and the systemic return catheter were connected to the saline-primed pump tubing, and the circuit was initiated with the caudal balloon on the caval catheter inflated and the cephalad balloon deflated. The cephalad balloon was then inflated slowly, and hemodynamic stability of the animals was assessed as complete hepatic venous isolation was achieved (Figures 1 and 2). Arterial blood pressure, heart rate, pulmonary artery pressure, and left heart filling

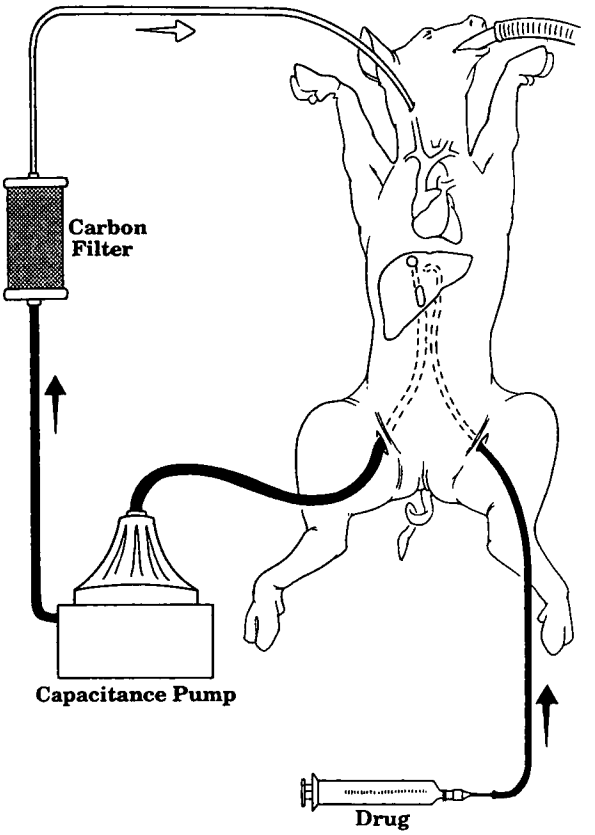

Figure 1. Extracorporeal pump and filter circuit used in experiments with pigs. Chemotherapeutic drugs are administered in the hepatic artery through a catheter advanced through the left femoral artery. The double-balloon vena cava catheter is introduced through the right femoral vein, and the outflow is pumped through a carbon filter prior to blood being returned to the right external jugular vein.

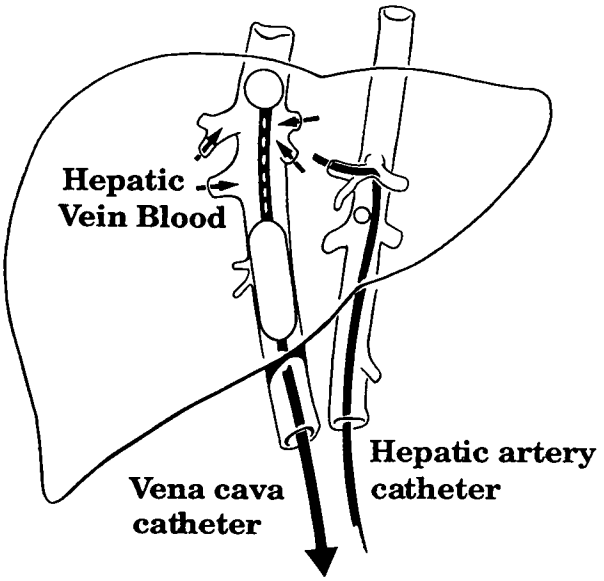

Figure 2. Detail of dual-balloon vena cava catheter, which functions to capture all hepatic venous outflow and exclude the systemic circulation from the hepatic venous outflow. The chemotherapy is administered through a catheter advanced from the left femoral artery into the hepatic artery. Arteriograms are performed to confirm that there is flow only to the liver with no extrahepatic perfusion.

pressures were measured every 5 min during the procedure. After a flow of 1–1.5 l/min was established on the extracorporeal pump circuit, the carbon filter (Hemokart 01-6004-4; National Medical Corp., Rockleigh, NJ) was opened to the circuit. Cardiac output was measured by cold caloric hemodilution through the Swan-Ganz catheter prior to initiating the pump circuit, immediately after the carbon filter was added to the pump circuit, and every 20 min thereafter during the procedure. The hepatic artery catheter was then used to deliver a 10-min infusion of drug (either DOX, 3 or 9 mg/kg; MMC, 1 mg/kg; or CDDP, 1 mg/kg) in each of the four tested animals, the other two animals being used to assess only hemodynamic response to the isolation circuit. Systemic, pre-filter (hepatic venous outflow), and post-filter blood samples were drawn at 5-min intervals for 30 min after the initiation of drug infusion and then at 10-min intervals up to 60 min. Blood samples were centrifuged (1500 ***g***) for 10 min; the resulting plasma was aspirated and frozen for drug analysis. Animals were killed at the conclusion of the procedure by intravenous sodium pentobarbital overdose (150 mg/kg).

Drug analysis

To determine plasma CDDP levels, 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 platinum levels. Total platinum levels were measured in the remaining plasma. Platinum levels were determined using a Varian (model AA1475) flameless atomic absorption spectrophotometer as previously described.[7]

DOX levels in plasma were determined by high performance liquid chromatography (HPLC) using the method of Robert.[8] Aliquots of plasma were placed on mini-columns (Sep-Paks; WATERS Assoc., New York, NY); after washing, drug was

eluted, and the eluant was dried under nitrogen. Samples were then redissolved in HPLC mobile phase. A routine internal standard was used to account for assay variability.

MMC levels in plasma were measured by a reverse-phase, isocratic elution HPLC procedure modified after that of Buice *et al.*[9] MMC is detected at 365 nm and the mobile phase (65% methanol, 35% water) is pumped at 1.2 ml/min. Peak heights were compared to a standard curve generated on the same day as the sample analysis.

Results

Hemodynamic effects

The results from measurement of hemodynamic parameters using the bypass circuit are summarized in Table 1. When the animals were first placed on the extracorporeal bypass pump without the filter in the circuit, there was no significant change in systolic and diastolic blood pressure. An 18% increase in heart rate and a 20% decrease in cardiac output were noted. Immediately after adding the filter to the circuit, there was a drop in systolic and diastolic blood pressure and a 50% reduction in cardiac output compared to baseline levels ($p < 0.01$, Student's two-tailed t-test). There was a concomitant rapid decrease in left heart filling pressures ($p < 0.01$). The addition of the filter to the circuit produced no change in the pressure required to maintain flow in the bypass circuit, and there was no drop in the rate of flow across the filter. The rapid decline in blood pressure, cardiac output and left heart filling pressures was rapidly reversed by continuous intravenous infusion of phenylephrine (2–5 μg/kg/min) (Elkins Sinn Corp., Cherry Hill, NJ). The phenylephrine drip was required only for the first 22–40 min of the filtration run; blood pressure and other hemodynamic parameters returned to normal without the pressor infusion after that time. There was no significant difference in blood pressure, heart rate, cardiac output, or filling pressures by the end of the 60-min pump procedure when compared to baseline values. Animals received a total of 1.2–2 liters of sterile normal saline intravenously during the anesthetic course.

Drug clearance by filter

Protection of the systemic circulation from chemotherapeutic agents after HAI utilizing this system requires two key components. First, the double-balloon vena cava catheter must capture all hepatic venous effluent and pass it through the extracorporeal bypass pump without any leak into the systemic circulation around the balloons. Second, the extracorporeal carbon filter must bind a significant fraction of the drug in the hepatic venous effluent prior to return of this blood to the systemic circulation. To evaluate the ability of this system to fulfil these aims, blood was drawn from the pre-filter (hepatic venous outflow), post-filter, and systemic circulation at regular intervals to confirm that minimal amounts of drug were entering the systemic circulation.

DOX infused at 3 mg/kg produced a pre-filter (hepatic vein) level of almost 2700 ng/ml at 10 min, which coincided with the end of the 10-min drug infusion. The post-filter and systemic drug levels of DOX at the same 10-min interval were 68 and 61 ng/ml, respectively (Figure 3). Thus, there was a 97.5% reduction in post-filter and systemic level of drug compared with the hepatic venous outflow level at 10 min. The pre-filter level of drug rapidly

Table 1. Hemodynamic effects of complete hepatic venous isolation and extracorporeal chemofiltration

	BP syst	BP dias	HR	CO	PCWP
Pre-pump run	93.00 ± 8.51	50.00 ± 8.32	91.67 ± 5.01	5.74 ± 1.36	6.67 ± 3.88
On pump w/o filter in circuit	87.17 ± 16.52	48.67 ± 10.63	112.67 ± 20.82	4.47 ± 0.97	4.00 ± 2.19
On pump with filter in circuit	50.50 ± 6.98[a]	27.17 ± 5.31[a]	93.33 ± 5.72	2.80 ± 0.40[a]	0.67 ± 0.82[a]
End of pump run	91.67 ± 19.08	48.33 ± 12.08	107.67 ± 21.40	5.24 ± 1.60	6.00 ± 2.83

All numbers are mean ± SEM, $n = 6$.
[a] $p < 0.01$ Student's t-test pre-pump run vs on pump with filter in circuit.
BP syst, systolic blood pressure; BP dias, diastolic blood pressure; HR, heart rate; CO, cardiac output; PCWP, pulmonary capillary wedge pressure.

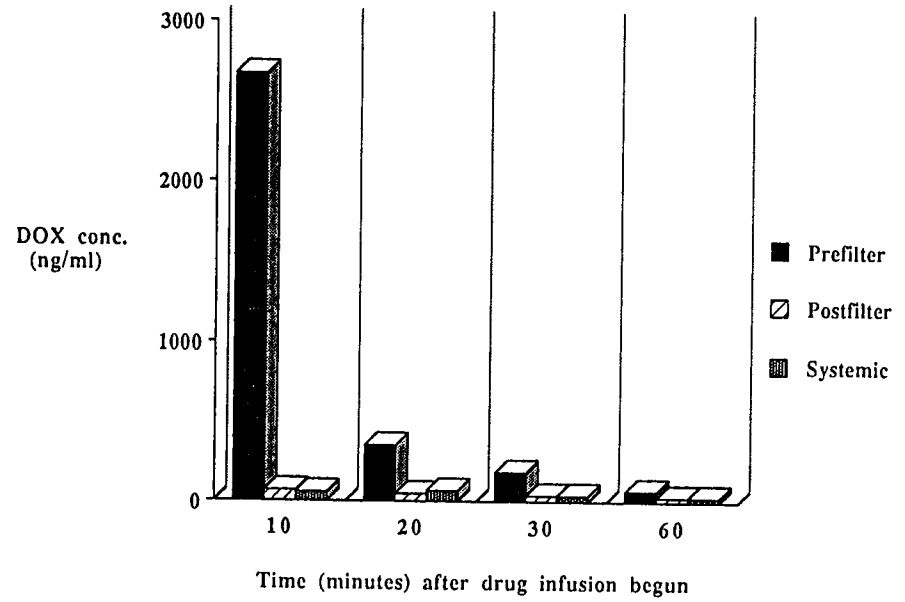

Figure 3. Doxorubicin (DOX; 3 mg/kg) administered by hepatic arterial infusion over 10 min. Prefilter levels of DOX represent the hepatic vein outflow levels of the drug prior to passage through the carbon filter. The values at 10 min represent the end of the 10-min hepatic arterial infusion of drug. The data represent a single animal experiment.

declined over the subsequent 50 min of the extracorporeal pump run and by 60 min, the pre-filter level of drug was similar to the post-filter and systemic levels. Similarly, administration of DOX at 9 mg/kg resulted in a 10-min pre-filter level of >6200 ng/ml while the post-filter and systemic levels at 10 min were 92% lower than the pre-filter level (Figure 4). There was a similar pattern of decline in the pre-filter level of drug following completion of the drug infusion during the remainder of the 60-min extracorporeal pump run.

MMC infused over 10 min at a dose of 1 mg/kg produced a pre-filter level of 1040 ng/ml while the associated post-filter and systemic levels at 10 min

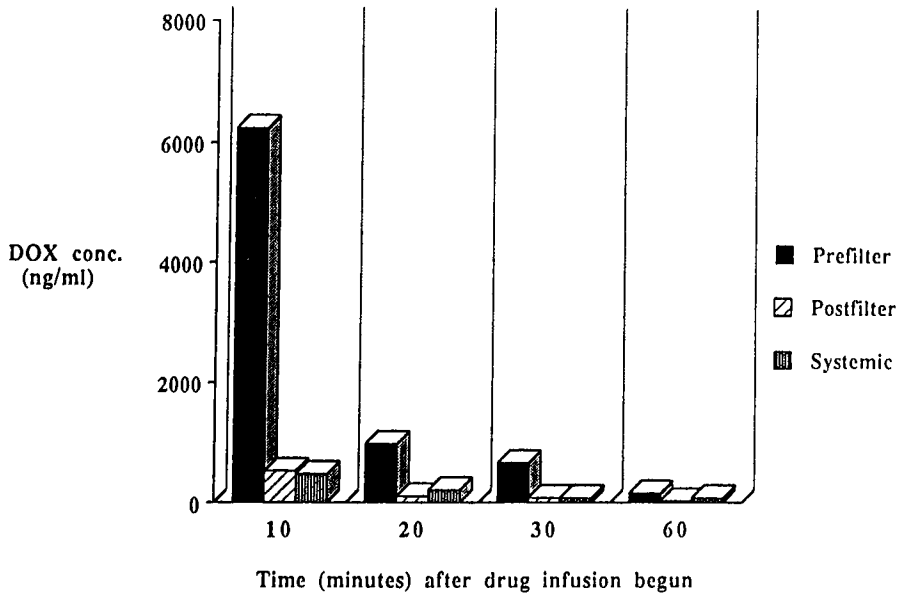

Figure 4. Doxorubicin (DOX; 9 mg/kg) administered by hepatic arterial infusion over 10 min. Data represent a single animal experiment.

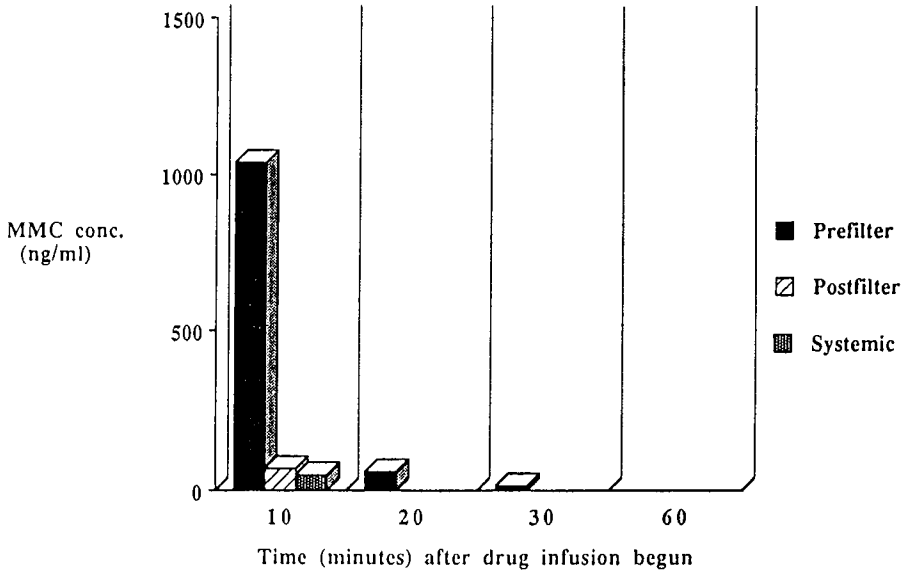

Figure 5. Mitomycin C (MMC; 1 mg/kg) administered by hepatic arterial infusion over 10 min. Data represent a single animal experiment.

were reduced by 93.5% (Figure 5). Interestingly, at all time periods after 15 min, post-filter and systemic levels of MMC were undetectable, and there was no detectable drug in the system after 30 min.

The clearance of CDDP administered at 1 mg/kg was less efficient than that of DOX or MMC. At the completion of the 10-min infusion, the pre-filter level was approximately 2000 ng/ml while the post-filter level was 700 ng/ml, producing a 65% reduction in the drug level (Figure 6). At 20, 30, and 60 min, the pre-filter, post-filter and systemic levels were nearly equal and showed minimal decline over the duration of the bypass run.

Discussion

Drugs used for cancer chemotherapy generally have a narrow therapeutic index. Thus, systemic toxicity

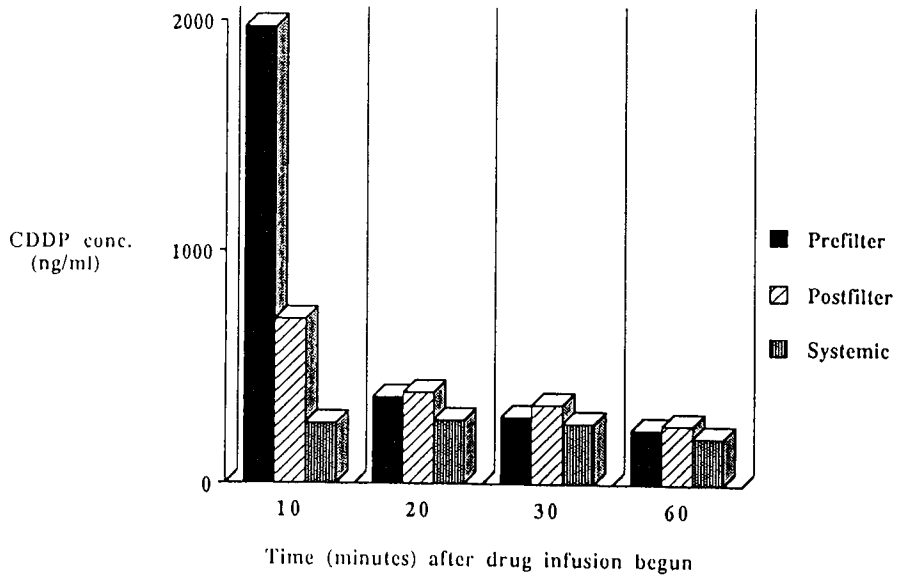

Figure 6. Cisplatin (CDDP; 1 mg/kg) administered by hepatic arterial infusion over 10 min. Data represent a single animal experiment.

of chemotherapeutic agents is the principal impediment to achieving enhanced tumor cell kill by increasing dose intensity.[10] Intra-arterial infusion of chemotherapeutic drugs has been a frequently used strategy in attempts to increase regional exposure to the drugs. However, systemic toxicity remains the dose-limiting factor for many agents. The relative pharmacokinetic advantage, R_d, for arterial infusion of drug can be expressed as

$$R_d = \frac{R_t}{R_s} = 1 + \frac{Cl_{TB}}{Q(1 - E)},$$

where R_t is the increased target exposure, R_s is decreased systemic exposure, 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.[11–13]

It can be seen from the equation that the three parameters (Q, E, Cl_{TB}) that affect the pharmacokinetic advantage of the intra-arterial drug infusion can be manipulated to improve drug exposure at the target site. Blood flow (Q) has been reduced using vasoconstrictors such as angiotensin II[14] or by combining arterial infusion with mechanical occlusion of the artery.[15] Fluoropyrimidines such as FUDR have a high first-pass hepatic extraction (E) rate and have been used extensively for the intra-arterial treatment of primary and metastatic liver tumors.[16,17] Predictably, systemic drug exposure is limited, but hepatobiliary toxicity has been the dose-limiting factor, particularly with FUDR.[18–21]

Increasing the total body clearance (Cl_{TB}) of drug is the parameter we are manipulating with our system. Two criteria guided our choice of DOX, MMC and CDDP for testing our system. First, these drugs, when given by HAI, do not undergo high first-pass hepatic extraction, so that systemic toxicity limits the dose that can be administered. Second, these three agents have demonstrated activity against primary and/or metastatic tumors in the liver.[22–27] There is substantial interest in attempting to improve treatment response in liver tumors by intensifying drug dose while reducing risk of systemic toxicity. The carbon filter in our system achieves the equivalent of a pharmacologic first-pass effect by binding drug that was not extracted by the liver. It has been previously demonstrated that chemotherapeutic agents can be removed from the circulation by adsorption onto sorbents, particularly activated charcoal.[28] Regional arterial infusion of chemotherapeutic drugs has been combined with non-isolated venous hemoperfusion utilizing carbon filters or with hemodialysis of regional or systemic venous drainage. A variety of systems that employ some type of hemoperfusion or hemodialysis have been used in conjunction with infusion of DOX,[28,29] MMC,[29–31] CDDP,[32] bleomycin,[29] or 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU).[33] Hemoperfusion or hemodialysis reduced systemic exposure between 48 and 87%.

Although we performed HAI of three chemotherapeutic agents in only four animals, it is interesting to note that systemic exposure to DOX and MMC was reduced by >90% while CDDP exposure was reduced by 65%. CDDP is highly protein-bound, and this may in part account for the less efficient binding by the filter. Obviously, further experiments with this system are necessary to establish the exact magnitude of the reduction in systemic drug exposure. These preliminary results support further investigation of extracorporeal chemofiltration associated with complete hepatic venous isolation. It must be stressed that the dual-balloon vena cava catheter used to achieve complete hepatic venous isolation can be placed percutaneously or through a small cut-down incision and does not require an extensive operative procedure.

The hemodynamic alterations that occurred when the carbon filter was added to the extracorporeal bypass circuit were profound, but quickly reversed by addition of an alpha adrenergic agonist (phenylephrine). The animals tolerated the brief period of hypotension and showed no untoward effect at the end of the procedure. The hypotension resulting from placing the filter in the circuit was not due to changes in the blood flow rate or the pressure gradient across the filter. Since it is possible that binding of plasma catecholamines by the filter is responsible for the transient hypotension, this is currently under investigation.

Conclusion

We report herein the initial feasibility studies of a novel HAI system using DOX, MMC and CDDP given by HAI in association with complete hepatic venous isolation employing a dual-balloon vena cava catheter combined with extracorporeal chemofiltration. The filter removed >90% of the DOX and MMC and reduced systemic exposure to CDDP by 65%. Additionally, we demonstrated that

the 1-h venovenous bypass run was well-tolerated, with transient hypotension and decreased cardiac output occurring when the carbon filter was placed in the circuit. The period of hypotension was not associated with a drop in blood flow or increase in pressure across the filter, and the hypotension resolved immediately with an intravenous phenylephrine drip. These results indicate that this novel system may allow dose intensification of these chemotherapeutic agents when administered by HAI. Our goal is to attain improved tumor cell kill while minimizing systemic exposure to drug.

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