Regional Pharmacokinetics of Doxorubicin following Hepatic Arterial and Portal Venous Administration: Evaluation with Hepatic Venous Isolation and Charcoal Hemoperfusion

Takeshi Iwasaki, Yonson Ku, Nobuya Kusunoki, Masahiro Tominaga, Takumi Fukumoto, Sanshiro Muramatsu, and Yoshikazu Kuroda

First Department of Surgery, Kobe University School of Medicine, Chuo-ku, Kobe 650, Japan

ABSTRACT

We evaluated the regional pharmacokinetics of doxorubicin after hepatic arterial infusion (HAI) and portal venous infusion (PVI) using a novel system for hepatic venous isolation and charcoal hemoperfusion (HVI-CHP). The HVI-CHP system was used to determine directly the doxorubicin plasma concentration in the hepatic veins and the hepatic venous flow rate, and simultaneously, to eliminate hepatic re-entry of the drug. Beagles received doxorubicin (1 mg/kg) through either the hepatic artery (HAI group, n = 6) or the portal vein (PVI group, n = 6). In both groups, hepatic venous blood was completely isolated and directed to the CHP filter. The filtered blood was returned through the left jugular vein. During HVI-CHP, the hepatic venous flow rate was monitored and plasma doxorubicin concentrations were serially measured in prefilter (= hepatic venous), postfilter, and systemic blood. The hepatic tissue uptake of doxorubicin was determined based on the blood flow rate and doxorubicin level in the hepatic vein. The hepatic extraction ratio of doxorubicin was defined as the percentage hepatic tissue uptake to the amount of drug administered. During drug infusion, similarly in either group, HVI-CHP produced a 66–87% reduction of the postfilter doxorubicin level as compared with the prefilter level. The prefilter drug level was significantly lower in the HAI group than in PVI group (P < 0.01). Thus, the area under the time concentration curve for the prefilter drug level in the HAI group (6.90 ± 0.96 μg min/ml) was significantly lower than that in the PVI group (18.10 ± 2.90 μg min/ml, P < 0.01). Conversely, the hepatic extraction ratio in the HAI group (84.6 ± 2.9%) was significantly higher than that in the PVI group (58.1 ± 3.4%, P < 0.01). We conclude that in the beagle, doxorubicin is more effectively extracted by the liver when administered via the hepatic artery than when administered via the portal vein. These results indicate that HAI of doxorubicin is superior to PVI in terms of reduction of systemic drug exposure and systemic toxicity.

INTRODUCTION

Regional chemotherapy has been used frequently for both primary and secondary hepatic malignancies. The rationale of regional chemotherapy lies in attempts to increase drug delivery to the cancer-bearing region with reduction of systemic toxicity (1–3). The theoretical basis is that the increase in local drug concentration after regional infusion of any drug depends on the blood flow rate of the infused vessel and the rate of drug elimination by the rest of the body, whereas the reduction of systemic drug exposure depends largely on the ability of the infused organ to extract and metabolize the drug. Thus, the first-pass HER 3 of the drug is one major factor that governs the delivery advantage of regional chemotherapy of the liver.

The dual blood supply to the liver by the hepatic artery and the portal vein raises the question of which of these two access routes should be used in regional chemotherapy for hepatic tumors. Although infrequently, PVI is employed in specific situations such as early adjuvant chemotherapy after resection of primary colorectal carcinomas (4, 5). However, based on a vast number of studies regarding tumor blood supply (6–8) and pharmacological studies in patients or tumor-bearing animals (9–12), HAI is predominantly employed in clinical practice. Accordingly, doxorubicin has been administered via the hepatic artery, exhibiting activity against hepatocellular carcinoma and a number of metastatic hepatic tumors (13–16). The general belief is that this drug has a low first-pass HER. Some investigators have reported that the HER of doxorubicin ranged between 5% and 50% (17) or was less than 24% (18), whereas others have reported that the ratio is probably close to 60% (19). Thus, the reported data for HER vary widely, and little is known regarding the first-pass HER of doxorubicin administered via various routes of administration.

The novel system of HVI-CHP, described by us elsewhere, seems well suited for the determination of the HER of anticancer drugs with a high charcoal affinity (20–23). The HVI-CHP system profoundly reduces hepatic re-entry of the drug after the first-pass and, thus, enables us to compare more precisely the influence of different administration routes. Moreover, the actual amount of drug recovered from the hepatic vein can be quantified as the product of the blood flow rate and the drug concentration in the completely isolated hepatic vein. The purpose of this study was to determine the effects of two different administration routes on the first-pass HER of doxorubicin and to provide a pharmacologic basis for their use in regional chemotherapy of the liver.

MATERIALS AND METHODS

Animals. A total of 14 beagles of both genders from the same large colony were used. The use of animals in this study conformed to the guidelines of the NIH and was approved by our institutional Animal Care Committee. Food was withheld for 12 h preoperatively. Each beagle was anesthetized with sodium pentobarbital (25 mg/kg) and pancuronium bromide (0.1 mg/kg) i.v. The dog was then intubated and ventilated mechanically throughout the experiment. The left carotid artery was cannulated for blood sampling as well as for continuous monitoring of blood pressure and heart rate.

Experimental Groups and Surgical Procedure. After a midline laparotomy and complete freeing of the liver from all ligaments around it, the dogs were randomly assigned to two groups. In the HAI group (n = 7), the gastroduodenal artery was divided and cannulated with a catheter (3F) for hepatic arterial administration of doxorubicin. In the PVI group (n = 7), the pancreaticoduodenal vein was divided and a catheter (3F) was placed into the portal vein for portal venous administration of the drug. For one set of experiments the HVI-CHP system was established in six dogs each in the HAI and PVI groups, weighing 8.5 ± 0.5 and 8.6 ± 0.6 kg (mean ± SE), respectively, according to the method described previously, with minor modifications (19). In brief, a 12F Trocar catheter was introduced into the retrohepatic IVC through the right femoral vein for collection of hepatic venous outflow, and was connected to an extracorporeal unit containing the CHP filter (DHP-I; Kuraray Co., Ltd., Osaka, Japan) and a centrifugal pump (Biopump-
Fig. 1. Experimental design of HVI-CHP system (A) and HVI alone (B). Catheters were introduced into the retrohepatic IVC and infrahepatic IVC from the right and left femoral veins, respectively. A catheter placed in the retrohepatic IVC was connected to a CHP filter and pumped to the left jugular vein together with infrahepatic IVC blood. HVI was achieved by clamping the suprahepatic and infrahepatic IVC. Hepatic venous blood flow rate was measured by an electromagnetic flow probe placed in the extracorporeal circuit. Blood samples were drawn at inlet side (a) and outlet side (b) of the CHP filter in the extracorporeal circuit and the carotid artery. The experimental design of HVI alone (B) is similar with A except that the circuit contains no CHP filter. Blood samples were collected from the hepatic venous line (a) and the carotid artery.

A catheter placed in the retrohepatic IVC was connected to a CHP filter and pumped to the left jugular vein together with infrahepatic IVC blood. HVI was achieved by clamping the suprahepatic and infrahepatic IVC. Hepatic venous blood flow rate was measured by an electromagnetic flow probe placed in the extracorporeal circuit. Blood samples were drawn at inlet side (a) and outlet side (b) of the CHP filter in the extracorporeal circuit and the carotid artery. The experimental design of HVI alone (B) is similar with A except that the circuit contains no CHP filter. Blood samples were collected from the hepatic venous line (a) and the carotid artery.

In the second set of experiments, in one dog weighing 11 kg in each group, we evaluated the influence of hepatic re-entry of the drug on pharmacokinetic indices including HER. In these experiments, the design was essentially the same as that described above except that the CHP filter was excluded from the extracorporeal circuit (Fig. 1B). Therefore, the isolated hepatic venous blood was simply returned to the systemic circulation in both dogs.

Anticancer Drug and Routes of Administration. Doxorubicin (Kyowa Hakko Co., Ltd., Osaka, Japan) at a dose of 1 mg/kg was dissolved in 20 ml of sterile physiologic saline and administered continuously through either the hepatic artery (HAI group) or the portal vein (PVI group) for 10 min using a syringe infusion pump (Terufusion Model STC-523, Terumo Co., Ltd., Tokyo, Japan). The HVI-CHP system was maintained for 20 min after the initiation of drug infusion.

Doxorubicin Measurement. In the HVI-CHP setting, blood samples were obtained from the left carotid artery (= systemic blood), pre-CHP filter extracorporeal circuit line (= hepatic venous blood), and post-CHP filter line just before and 2, 4, 6, 8, 10, 15 and 20 min after the initiation of drug administration. In the setting of HVI alone, blood samples were collected from the hepatic venous line and the left carotid artery at the same interval as in the HVI-CHP setting. The plasma concentrations of doxorubicin were determined by HPLC as described previously (24). In brief, aliquots of plasma were placed on minicolumns (Nucleosil SC18; Chemo Co., Ltd., Takatsuki, Japan). After washing, the drug was eluted and the eluent was evaporated in vacuo. The residual samples were redissolved in the HPLC mobile phase, and doxorubicin concentrations were measured by routine HPLC. A standard curve was obtained with samples dissolved in control canine plasma.

Flow Measurement and Pharmacokinetic Evaluation. Hepatic venous blood flow rate was monitored continuously with an electromagnetic flow probe (Bioprobe TX40; Bio-Medicus, Inc.) placed at the pre-CHP filter circuit line (Fig. 1). Based on the blood flow rate (Q) and doxorubicin concentrations in the hepatic vein (C), the amount of the drug in the hepatic effluent was determined as the product of Q and C (20, 21, 25). The hepatic tissue uptake was calculated using the following equation:

Hepatic tissue uptake\(_{i,j}\) = \(\frac{Dose_{i,j} - AUC_{i,j}Q_i}{AUC_{i,j}Q_i}\)

where \(Dose_{i,j}\) = the amount of drug administered between the times \(i\) and \(j\), \(AUC_{i,j} = \text{area under the time-concentration curve between times } i \text{ and } j\), \(Q_i\) (ml/min) = the average blood flow rate between the times \(i\) and \(j\), and \(Q_i\) (ml/min) = the average blood flow rate between the times \(i\) and \(j\). The HER of doxorubicin was defined as the percent hepatic tissue uptake to the amount of drug administered. The drug extraction ratio of the CHP filter at each sampling time was calculated as the percent filter extraction (%) at sampling time \(i\) as follows: \((C_i-C_i')/C_i \times 100\), where \(C_i\) and \(C_i'\) = the prefiler and the postfilter drug concentration at the sampling time of \(i\). The AUC was calculated by the trapezoidal method.

Statistical Analysis. All values are presented as mean ± SE. The significance of difference was analyzed using the unpaired Student’s \(t\)-test, and a \(P\) value of <0.05 was considered statistically significant.

RESULTS

Hemodynamic Effects of HVI-CHP. In both groups, the mean arterial pressure showed a slight decrease after the initiation of HVI-CHP. However, all dogs had stable systolic blood pressures over 90 mmHg throughout the course, and no significant difference was noted between the two groups. The two groups also had similar hepatic venous flow rates in the range from 240–390 ml/min during HVI-CHP, which were markedly stable in each dog. The hepatic venous blood flow rates of the HAI and PVI groups averaged 268.3 ± 16.4 and 267.5 ± 16.5 ml/min, respectively.

Time Course of Drug Extraction Ratio of the CHP Filter. During a 10-min drug infusion, the drug extraction ratios by the CHP filter were similar in the two groups; the mean values at 2 and 10 min were 84.5 ± 3.2 and 66.4 ± 4.5% for the HAI group, and 87.8 ± 2.6 and 79.5 ± 4.9% for the PVI group, respectively. Regardless of the route of administration, HVI-CHP profoundly reduced the postfilter and the systemic drug concentrations compared with the prefiler drug concentration.
HEPATIC EXTRACTION OF ARTERIAL VS. PORTAL DOXORUBICIN

Fig. 2B shows the time courses of the postfilter and systemic doxorubicin concentrations. Despite the similar extraction ratios of the CHP filter in the two groups, the postfilter plasma doxorubicin levels in the PVI group tended to be higher than those in the HAI group, resulting from the consistently higher prefilter drug concentrations in the PVI group. The mean AUC was 1.94 ± 0.28 in the HAI group and 3.30 ± 0.53 µg min/ml in the PVI group (P < 0.05; Table 1). On the other hand, the peak systemic concentration of doxorubicin in the HAI group was 140.8 ± 21.7 ng/ml, and that in the PVI group was 249.2 ± 49.4 ng/ml, showing no significant differences in the two groups at any measurement time point. Consequently, there was no significant difference in the mean AUC of systemic plasma between the two groups.

HER of Doxorubicin. Fig. 3 illustrates the HER of doxorubicin at the discrete time intervals during drug infusion. The ratio for the interval from 0–2 min after the start of drug infusion was 92.5 ± 2.7 and 83.9 ± 2.4% in the HAI and PVI groups, respectively. For all of the subsequent time intervals, the HER in the HAI group exceeded 80%, whereas it decreased to as low as 47.5 ± 6.7% in the PVI group. The overall (0- to 10-min) HER in the HAI group (84.6 ± 2.9%) was significantly higher than that in the PVI group (58.1 ± 3.4%, P < 0.01).

Pharmacokinetic Comparison with and without CHP. Fig. 4 illustrates the time courses of hepatic venous and systemic doxorubicin concentrations after each HAI and PVI with HVI-CHP or HVI alone. After HAI, the mean hepatic venous (= prefilter) and systemic concentrations of doxorubicin in the six dogs with CHP were markedly lower at all measurement time points than those in the dog without CHP (Fig. 4A). Exclusion of the CHP filter from the extracorporeal circuit produced a 2- and 7-fold increase in the AUC of doxorubicin for hepatic venous and for systemic plasma, respectively, as compared with the corresponding mean values in the six dogs with CHP. This difference was similarly observed after portal venous administration (Fig. 4B). The dog receiving intraportal doxorubicin without CHP exhibited a 1.7- and 10-fold increase in the AUC for the hepatic venous and for the systemic plasma, respectively, compared with the corresponding mean values in the six dogs with CHP. The HER during the 10-min infusion with and without CHP was 84.6% (mean value for six dogs) and 41.9%, respectively, after HAI, and 58.1% (mean value for six dogs) and 19.2%, respectively, after PVI.

Fig. 2. Plasma doxorubicin concentration in the prefilter (A) and postfilter and systemic (B) blood samples. These data represent the means ± SE. Bars are not shown when they are smaller than the symbols. Significant differences between HAI and PVI are indicated by asterisks (*P < 0.05, **P < 0.01).

Table 1 AUC of plasma doxorubicin and HER during the 10-min drug infusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Prefilter</th>
<th>Postfilter</th>
<th>Systemic</th>
<th>HER (0–10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAI</td>
<td>6.90 ± 0.96$^b$</td>
<td>1.94 ± 0.28$^c$</td>
<td>1.71 ± 0.24</td>
<td>84.6 ± 2.9%$^d$</td>
</tr>
<tr>
<td>PVI</td>
<td>18.10 ± 1.72</td>
<td>3.30 ± 0.53</td>
<td>2.76 ± 0.54</td>
<td>58.1 ± 3.4%</td>
</tr>
</tbody>
</table>

$^a$ Each value represents mean ± SE.
$^b$ P < 0.01 compared with the PVI group.
$^c$ P < 0.05 compared with the PVI group.
$^d$ P < 0.01 compared with the PVI group.

Time Course of Plasma Doxorubicin Concentrations during HVI-CHP. The peak hepatic venous concentration (prefilter level) of doxorubicin in the HAI group (600.6 ± 88.1 ng/ml) was significantly lower than that in the PVI group (1880.0 ± 145.4 ng/ml; P < 0.01; Fig. 2A). In addition, at all measurement time points during the 10-min drug infusion, the prefilter concentrations in the six dogs in the PVI group were consistently higher than those in the HAI group. Consequently, as listed in Table 1, the mean AUC for the prefilter plasma in the HAI group was significantly lower than that in the PVI group (6.90 ± 0.96 and 18.10 ± 1.72 µg min/ml, respectively, P < 0.01).

Fig. 3. HER was calculated as percentage hepatic tissue uptake to the amount of drug administered. Each column represents the mean ± SE of each time interval. Significant differences between the HAI group and PVI group are indicated by asterisks (*P < 0.05, **P < 0.01).
represent the mean values of six dogs with HAI and PVI, respectively. CHP) under HAI; (A) and PVI; (B). Data of HVI-CHP (•and •¿) in panels A and B effective in preventing hepatic re-entry of doxorubicin after the first-extraction ratios. Thus HVI-CHP in this canine model was highly doxorubicin in HAI and in PVI, respectively, as assessed by the filter regional administration via two different routes. We also evaluated the after HAI of a drug which, like doxorubicin, has high charcoal affinity has been shown that HVI-CHP profoundly reduces hepatic re-entry metabolism and degradation directly as the product of drug concen- tribution (20-23). In this study, we compared the HER of doxorubicin after DISCUSSION

Direct measurement of HER has been technically elusive, since the concentration and flow rate must be measured at three sites: the hepatic artery, portal vein, and hepatic vein (25, 26). We used the HVI-CHP system for determining the HER of doxorubicin because the system allows us to quantify the amount of drug escaping hepatic metabolism and degradation directly as the product of drug concentrations and blood flow rates in the hepatic circulation. In addition, it has been shown that HVI-CHP profoundly reduces hepatic re-entry after HAI of a drug which, like doxorubicin, has high charcoal affinity (20-23). In this study, we compared the HER of doxorubicin after regional administration via two different routes. We also evaluated the influence of drug recirculation in regional pharmacokinetics using HVI-CHP and using HVI alone.

The first set of experiments with HVI-CHP revealed that the system provided 66–85% and 80–88% reduction in systemic exposure to doxorubicin in HAI and in PVI, respectively, as assessed by the filter extraction ratios. Thus HVI-CHP in this canine model was highly effective in preventing hepatic re-entry of doxorubicin after the first-pass irrespective of the route of hepatic infusion. Under conditions of drug elimination by HVI-CHP, the HER of doxorubicin averaged 84% with HAI and 58% with PVI. These findings indicate that doxorubicin is more efficiently extracted by the normal liver when administered via the hepatic artery compared with the portal vein. Thus, HAI of doxorubicin seems to be more beneficial than PVI for reducing systemic drug exposure. However, since HER, per se, does not predict tumor drug uptake, it should be noted that tumor blood supply is still the primary determinant of the vessel to be selected for hepatic drug infusion.

The published data for the HER of doxorubicin vary greatly, ranging from 10–60% (17-19, 28). In the rabbit model, Harris and Gross (19) found that the HER of doxorubicin was 60% by comparing the AUC for lung concentrations following 30-min PVI at 3 mg/kg and after i.v. infusion at the same dose rate. In human subjects, Ballet et al. (28) found a very low HER of less than 10% using temporary placement of hepatic venous catheters with i.v. administration of doxorubicin. On the other hand, Garnick et al. (17) reported that the HER ranged from 5–50% in five patients with metastatic liver tumors and two patients with bile duct tumors during i.v. infusion of the drug at a dose of 40 mg/m². Although the species, dose rates, and routes of infusions used were different in these studies, these published values for the HER of doxorubicin are somewhat lower compared with the data obtained under HVI-CHP. There are at least two possible reasons for this. First, in the previous studies by others, HER was calculated according to the following equation: \[ \text{HER} = \frac{(C_{v})_{A}}{(C_{v})_{A}} \] where \( (C_{v})_{A} \) is the hepatic venous concentration of doxorubicin measured after the first pass, as assumed by the systemic AUC. HVI

Recently, August et al. (29) studied the HER of doxorubicin after HAI for 90 min with use of the HVI-CHP in a swine model. Although they carried out HVI without laparotomy using a specially designed double-balloon catheter, their model and ours are based on the same concept that the system aims at circumventing an extensive operation but feasible in our HVI-CHP model.

In the rabbit model, Harris and Gross (19) found that the HER of doxorubicin was 60% by comparing the AUC for lung concentrations following 30-min PVI at 3 mg/kg and after i.v. infusion at the same dose rate. In human subjects, Ballet et al. (28) found a very low HER of less than 10% using temporary placement of hepatic venous catheters with i.v. administration of doxorubicin. On the other hand, Garnick et al. (17) reported that the HER ranged from 5–50% in five patients with metastatic liver tumors and two patients with bile duct tumors during i.v. infusion of the drug at a dose of 40 mg/m². Although the species, dose rates, and routes of infusions used were different in these studies, these published values for the HER of doxorubicin are somewhat lower compared with the data obtained under HVI-CHP. There are at least two possible reasons for this. First, in the previous studies by others, HER was calculated according to the following equation: \[ \text{HER} = \frac{(C_{v})_{A}}{(C_{v})_{A}} \] where \( (C_{v})_{A} \) is the hepatic venous concentration of doxorubicin measured after the first pass, as assumed by the systemic AUC. HVI

In the rabbit model, Harris and Gross (19) found that the HER of doxorubicin was 60% by comparing the AUC for lung concentrations following 30-min PVI at 3 mg/kg and after i.v. infusion at the same dose rate. In human subjects, Ballet et al. (28) found a very low HER of less than 10% using temporary placement of hepatic venous catheters with i.v. administration of doxorubicin. On the other hand, Garnick et al. (17) reported that the HER ranged from 5–50% in five patients with metastatic liver tumors and two patients with bile duct tumors during i.v. infusion of the drug at a dose of 40 mg/m². Although the species, dose rates, and routes of infusions used were different in these studies, these published values for the HER of doxorubicin are somewhat lower compared with the data obtained under HVI-CHP. There are at least two possible reasons for this. First, in the previous studies by others, HER was calculated according to the following equation: \[ \text{HER} = \frac{(C_{v})_{A}}{(C_{v})_{A}} \] where \( (C_{v})_{A} \) is the hepatic venous concentration of doxorubicin measured after the first pass, as assumed by the systemic AUC. HVI

In the rabbit model, Harris and Gross (19) found that the HER of doxorubicin was 60% by comparing the AUC for lung concentrations following 30-min PVI at 3 mg/kg and after i.v. infusion at the same dose rate. In human subjects, Ballet et al. (28) found a very low HER of less than 10% using temporary placement of hepatic venous catheters with i.v. administration of doxorubicin. On the other hand, Garnick et al. (17) reported that the HER ranged from 5–50% in five patients with metastatic liver tumors and two patients with bile duct tumors during i.v. infusion of the drug at a dose of 40 mg/m². Although the species, dose rates, and routes of infusions used were different in these studies, these published values for the HER of doxorubicin are somewhat lower compared with the data obtained under HVI-CHP. There are at least two possible reasons for this. First, in the previous studies by others, HER was calculated according to the following equation: \[ \text{HER} = \frac{(C_{v})_{A}}{(C_{v})_{A}} \] where \( (C_{v})_{A} \) is the hepatic venous concentration of doxorubicin measured after the first pass, as assumed by the systemic AUC. HVI

In the rabbit model, Harris and Gross (19) found that the HER of doxorubicin was 60% by comparing the AUC for lung concentrations following 30-min PVI at 3 mg/kg and after i.v. infusion at the same dose rate. In human subjects, Ballet et al. (28) found a very low HER of less than 10% using temporary placement of hepatic venous catheters with i.v. administration of doxorubicin. On the other hand, Garnick et al. (17) reported that the HER ranged from 5–50% in five patients with metastatic liver tumors and two patients with bile duct tumors during i.v. infusion of the drug at a dose of 40 mg/m². Although the species, dose rates, and routes of infusions used were different in these studies, these published values for the HER of doxorubicin are somewhat lower compared with the data obtained under HVI-CHP. There are at least two possible reasons for this. First, in the previous studies by others, HER was calculated according to the following equation: \[ \text{HER} = \frac{(C_{v})_{A}}{(C_{v})_{A}} \] where \( (C_{v})_{A} \) is the hepatic venous concentration of doxorubicin measured after the first pass, as assumed by the systemic AUC. HVI
alone showed 7- and 10-fold increases in systemic exposure to doxorubicin with HAI and PVI, respectively, compared with HVI-CHP. Thus, we consider that mainly hepatic recirculation of the drug accounts for the marked decrease in HER with HVI alone compared with that with HVI-CHP with either HAI or PVI.

Another factor that might cause overestimation of the HER of doxorubicin with HVI-CHP is the delayed washout of the drug from the liver after the end of drug infusion. As shown in the prefilter time concentration curve, the AUC fraction between 10 and 20 min constituted approximately one-fourth of the AUC during 20 min. This was also supported by the observation by August et al. (29) in a swine model of HVI-CHP that unmetabolized doxorubicin is washed out of the liver after the end of drug infusion at a higher concentration than drug entering the liver. Thus, they noted, the liver acts as a net source of doxorubicin during this washout phase. Indeed, previous studies have shown that doxorubicin is highly tissue bound and its systemic pharmacokinetics are characterized by a rapid distribution phase (half-life of 8–11 min) followed by a prolonged elimination phase (half-life of 25–30 h) (30, 31). The major portion of the total AUC is under the terminal portion of the elimination curve, which was not quantified in our study. Moreover, a portion of the hepatic tissue uptake estimated with HVI-CHP may simply be tissue-bound rather than metabolized or excreted in the bile, and this bound drug may return to the circulation at a later time. This would contribute to overestimation of the HER in the present experiments.

We are not able to account for the significantly higher HER of doxorubicin in HAI than in PVI. One possible explanation is the larger hepatic tissue uptake estimated with HVI-CHP due to the direct hemoperfusion. Either portal or hepatic arterial blood ultimately enters the hepatic sinusoids, where the drug is extracted by the hepatocytes. However, anatomic studies by others have shown that the vascular bed of the hepatic artery expands to the bile ducts, forming the peribiliary plexus, portal structures, and the capsule of the liver before entering the hepatic sinusoids (32). Thus it seems reasonable to assume that presinusoidal structures of the hepatic artery contribute to the higher HER of doxorubicin with HAI.

In summary, this pharmacokinetic study clearly demonstrated that the hepatic extraction of doxorubicin is significantly higher with HAI compared with PVI, thereby confirming the advantage of HAI over PVI in terms of reduction of systemic drug exposure and systemic toxicities. We believe that this canine model of HVI-CHP may be useful in determining the hepatic pharmacokinetics of other drugs with high affinity to CHP filters.

REFERENCES

Regional Pharmacokinetics of Doxorubicin following Hepatic Arterial and Portal Venous Administration: Evaluation with Hepatic Venous Isolation and Charcoal Hemoperfusion

Takeshi Iwasaki, Yonson Ku, Nobuya Kusunoki, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/58/15/3339

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.