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Pharmacokinetics of Adriamycin and cisplatin for anhepatic chemotherapy during liver transplantation

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Abstract We investigated the pharmacokinetics of cytotoxic anticancer agents administered under anhepatic conditions. Beagle dogs underwent either a sham operation consisting of laparotomy only (control group, $n = 11$) or a laparotomy and total hepatectomy under venovenous bypass (anhepatic group, $n = 12$). Each dog received a bolus intravenous injection of either Adriamycin (1 mg/kg) or cisplatin (1 mg/kg). The plasma and urine concentrations of each drug were measured at intervals for up to 2 h after drug injection. The dogs given Adriamycin were then sacrificed to determine tissue drug concentrations in the liver (controls only), spleen, kidney, heart, lung, skeletal muscle and small intestine. The control and anhepatic groups showed similar Adriamycin profiles during the initial 5 min after drug injection. However, subsequently, the plasma Adriamycin concentrations remained persistently higher in the anhepatic dogs than in the controls, yielding a two-fold elevation of the mean area under the concentration-time curve in the anhepatic group ($P < 0.01$ vs controls). The renal clearance values did not significantly differ between the two groups. The tissue Adriamycin concentrations in all measured organs, excluding the liver, were higher in the anhepatic group than in the controls. In a second set of experiments with cisplatin, the plasma platinum concentrations did not significantly differ between the two groups throughout the time course. However, the renal clearance of platinum in the anhepatic dogs showed a fourfold increase compared with that in the controls ($P < 0.01$). These pharmacokinetic data suggest that Adriamycin carries the risk of increased systemic toxicities, while cisplatin may be associated with increased renal toxicity when administered during the anhepatic period of liver transplantation.

Key words Anhepatic chemotherapy · Liver transplantation · Hepatocellular carcinoma · Adriamycin · Cisplatin

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the Far East and occurs frequently in men with cirrhosis associated mainly with hepatitis B or C infection [14]. Surgical removal is the only chance for cure. However, curative resection is often hampered by the extent of tumor involvement, or by the underlying cirrhosis, and early tumor recurrence is frequently noted in the remnant liver [2, 10, 20]. Orthotopic liver transplantation (OLT) is, theoretically, the ultimate treatment in patients with HCC not amenable to surgical resection, since it eliminates both the HCC and the cirrhosis. Despite the early enthusiasm for this procedure, however, OLT has also been plagued by a high rate of tumor recurrence, either in the allograft or at extrahepatic sites [7, 15].

The high rate of HCC recurrence after OLT may be explained by inappropriate patient selection [7, 17], the presence of circulating HCC cells and micrometastases at the time of liver replacement, and rapid tumor growth caused by immunosuppressive therapy [13, 25]. Thus, many transplant centers have recently been excluding patients at high risk of HCC recurrence, such as those with large tumors, bilobar involvement, and vascular invasion. In addition, these centers have incorporated some form of perioperative adjuvant

chemotherapy to control tumor recurrence after OLT [4, 5, 16, 18, 23]. However, the chemotherapy protocols in these trials vary greatly, and they raise the additional questions as to which chemotherapeutic regimen is optimum, and how and when the chemotherapy should be performed.

As to the timing of the adjuvant chemotherapy, some investigators have designed a protocol consisting of only a postoperative regimen [16, 18], while others have combined preoperative and postoperative regimens [4, 5]. Furthermore, the use of an intraoperative dose of Adriamycin in an attempt to increase the effect on micrometastatic disease has recently been proposed by Stone et al. [23]. In their study, Adriamycin was given after the induction of general anesthesia, but before manipulation of the liver. However, the anhepatic period during OLT would appear to be an even more suitable time for the administration of anticancer agents not only for the agents to exert an impact on micrometastases present before surgery or shed as a result of manipulation of the tumor at the time of hepatectomy, but also to minimize drug toxicity on the liver allograft. The objectives of this study were to experimentally illustrate the pharmacokinetics of two major cytotoxic agents, Adriamycin and cisplatin, under anhepatic conditions and to provide a pharmacologic basis for their use in anhepatic chemotherapy during OLT.

Materials and methods

Animals and experimental design

Beagle dogs of either sex weighing 8.4 ± 2.6 kg (mean ± SD) were used in this study. The animal procedures used in this study conformed to the guidelines of the National Institutes of Health and were approved by our institutional Animal Care Committee. Food was withheld for 12 h preoperatively. Anesthesia was induced with the intravenous administration of sodium pentobarbital (25 mg/kg) and pancuronium bromide (0.1 mg/kg). Endotracheal intubation was performed, and the dogs were mechanically ventilated throughout the experiment. An arterial line was placed into the left carotid artery for blood pressure and heart rate monitoring and for blood sampling. Lactated Ringer's solution was administered intravenously at 30 ml/kg per h, during the procedure. A midline laparotomy was performed, and the bilateral ureters were exposed and cannulated to collect urine. The dogs were then allocated to either of two groups: control group ($n = 7$ for Adriamycin, and $n = 4$ for cisplatin) and anhepatic group ($n = 8$ for Adriamycin, and $n = 4$ for cisplatin).

In the anhepatic group, the liver was mobilized and isolated by dividing all of its peritoneal attachments. Subsequently, a pump-assisted venovenous bypass from the inferior vena cava and the portal vein to the left jugular vein was instituted, as described elsewhere [8]. During the venovenous bypass, the portal vein and the supra- and infrahepatic inferior vena cava were clamped and the anticancer agents were administered immediately after removing the liver.

Anticancer agents and mode of administration

Adriamycin and cisplatin were dissolved in sterile physiologic saline at concentrations of 1 mg/ml and 0.5 mg/ml, respectively. Each animal received a bolus injection of Adriamycin (1 mg/kg) or cisplatin (1 mg/kg) through the left antecubital vein.

Adriamycin measurements

Blood samples were collected in heparinized tubes from the carotid artery just before and 1, 3, 5, 10, 30, 60, and 120 min after drug injection. For a 2-h period after drug injection, urine was collected every 30 min and urine samples were obtained from each group to determine the urinary excretion of the drug. The dogs were then sacrificed to determine tissue Adriamycin concentrations in the liver (control dogs only), spleen, kidney, heart, lung, skeletal muscle, and small intestine. The plasma and urinary concentrations of Adriamycin were determined by high-performance liquid chromatography (HPLC), using a method described previously [19]. In brief, aliquots of plasma or urine were placed on minicolumns (Nucleosil 5C18, Chemco Co., Hirakata, Japan) and, after being washed, the drug was eluted and the eluent was dried under vacuum. Samples were then redissolved in the mobile phase before injection onto the HPLC column. A standard curve was obtained with samples dissolved in control canine plasma.

Tissue Adriamycin concentrations were determined by homogenizing the tissue and then performing chloroform–methanol centrifugation extraction of Adriamycin from the homogenate. The phase containing the extracted Adriamycin was washed and eluted and the eluent was dried under nitrogen. Samples were then redissolved in the HPLC mobile phase, and Adriamycin concentrations were measured by routine HPLC. The mean recoveries of Adriamycin were 93% from plasma, and 61% to 96% from various control tissues. The actual concentrations of Adriamycin were calculated based on these percentage recoveries.

Cisplatin measurements

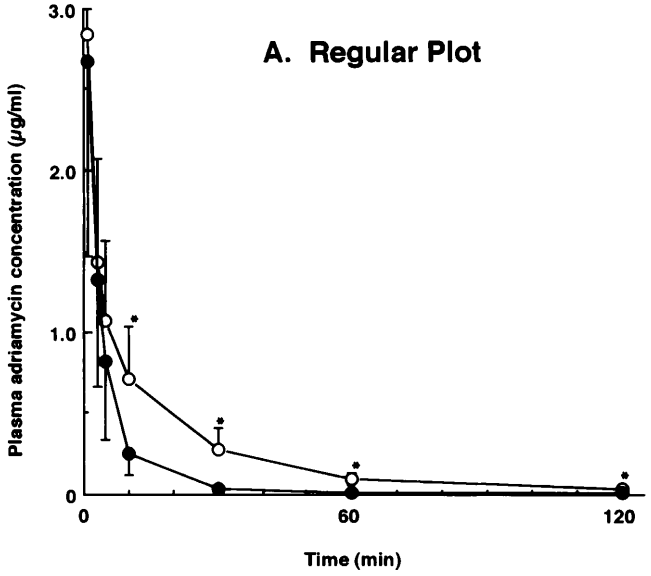
Blood samples were collected in heparinized tubes from the carotid artery 5, 30, 60, and 120 min after drug injection, placed immediately on ice, and centrifuged at 1000 *g* at 4 °C for 10 min. Approximately 1 ml of plasma was transferred to an ultrafiltration YMT membrane system (Centrifree MPS-3, Amicon, Beverly, Mass.) and centrifuged at 1000 *g* at 4 °C for 20 min. Urine samples were collected to determine the platinum concentration every 30 min. The ultrafiltrates, plasma and urine samples were analyzed directly by flameless atomic absorption spectroscopy to determine the free and total platinum concentrations, as described previously [11].

Estimation of pharmacokinetic parameters

A pharmacokinetic analysis program, MULTI [24], for a microcomputer was used to estimate the values of pharmacokinetic parameters from the concentration–time data for Adriamycin and cisplatin. A two-compartment model was used to describe the time course of Adriamycin, and a single-compartment model was used for cisplatin. A nonlinear least squares algorithm of the damping Gauss-Newton method was employed for the calculations of pharmacokinetic parameters in MULTI.

Statistical analysis

Values are presented as means ± SD. Statistical analysis was performed with a one-way analysis of variance (ANOVA) and Student's *t*-test with $P = 0.05$ as the minimal level of significance.



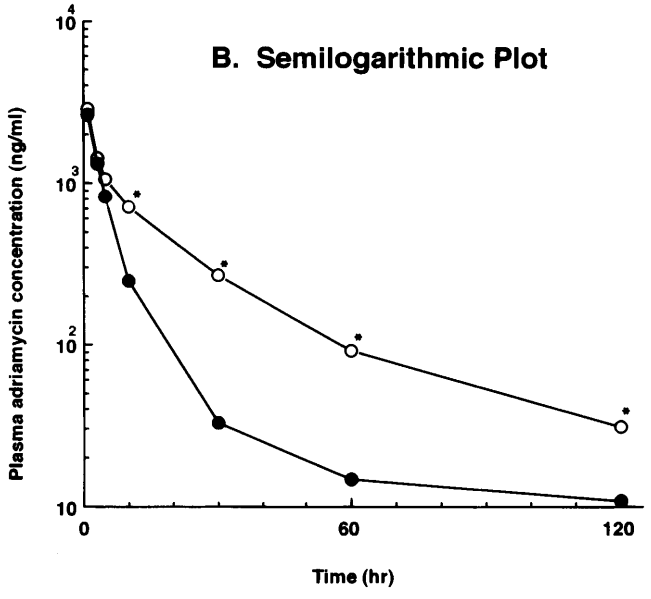


Fig. 1A,B Time course of plasma Adriamycin concentration: **A** linear plot **B** semilogarithmic plot (● control dogs, ○ anhepatic dogs). Values are means ± SD. *$P < 0.05$ vs controls

Results

Hemodynamic changes

In both groups, a bolus injection of Adriamycin produced a transient decrease in the mean arterial pressure, while cisplatin injection had no significant effect on mean arterial pressure. The mean arterial pressure in the Adriamycin-injected dogs promptly returned to baseline levels. Thereafter, regardless of the drug administered, the mean arterial pressure remained essentially unchanged in each group, and no significant difference was observed between the two groups throughout the 2-h observation. Heart rates were stable, and similar in both groups throughout the experiment.

Plasma concentration–time data of Adriamycin and cisplatin

Figure 1 shows the time course of plasma Adriamycin concentrations. As shown by a linear plot (Fig. 1A), the plasma concentrations showed a rapid exponential decline from the mean peak values of 2.7 ± 1.2 μg/ml and 2.8 ± 1.2 μg/ml at 1 min in the control and anhepatic groups, respectively. During the initial 5 min after drug injection, no significant difference was noted between the two groups. However, subsequently, the anhepatic dogs had significantly higher plasma Adriamycin concentrations at all measured time points from 10 to 120 min ($P < 0.05$ vs controls). Figure 1B shows a semilogarithmic plot of the plasma concentration-time data for Adriamycin.

Two distinct phases were identified in each dog. Table 1 shows the estimated pharmacokinetic parameters. During the first phase, the mean plasma half lives were 2.76 ± 0.85 min and 4.10 ± 0.65 min, respectively, in the control and anhepatic groups. The mean area under the concentration-time curve (AUC) in the control and anhepatic groups were 14.4 ± 5.9 μg min/ml and 31.0 ± 11.4 μg min/ml, respectively, representing a two-fold elevation in the anhepatic dogs compared with the controls ($P < 0.01$). Conversely, the mean total body clearance of Adriamycin showed a reduction of approximately 50% in the anhepatic group. The volume of distribution at steady-state was not significantly different between the anhepatic and control groups.

Table 1 Plasma disposition characteristics of Adriamycin (AUC area under the time–concentration curve, CL_T total body clearance, V_{SS} volume of distribution, $T_{1/2\,\alpha}$ distribution half-life, $T_{1/2\,\beta}$, elimination half-life). Values are means ± SD * $P < 0.01$ vs control group

Treatment group	AUC (μg min/ml)	CL_T (ml/min/kg)	V_{SS} (l/kg)	Plasma half-life of Adriamycin (min)	
				$T_{1/2\,\alpha}$	$T_{1/2\,\beta}$
Control dogs ($n = 7$)	14.4 ± 5.9	79.0 ± 30.1	1.68 ± 0.87	2.76 ± 0.85	59.8 ± 13.5
Anhepatic dogs ($n = 8$)	31.0 ± 11.4*	37.5 ± 17.4*	1.49 ± 1.15	4.10 ± 0.65	43.0 ± 16.4

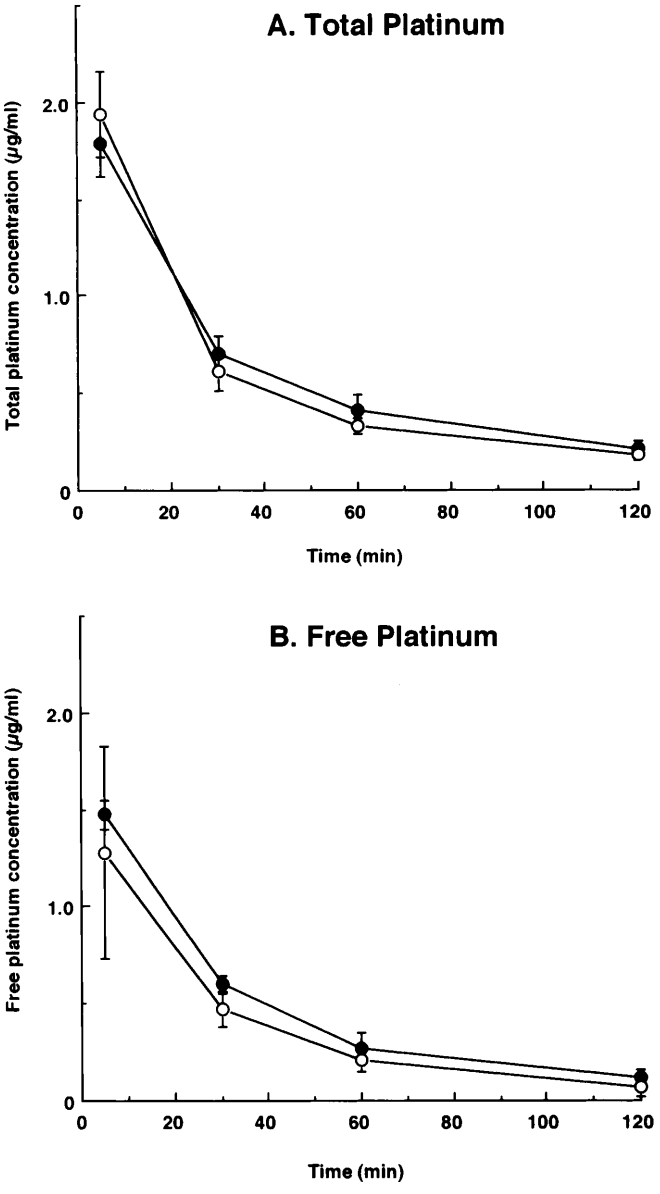


Fig. 2A,B Time course of plasma platinum concentration: **A** total platinum **B** free platinum (● control dogs, ○ anhepatic dogs). Values are means ± SD

The changes in total and free plasma platinum concentrations are presented in Fig. 2. During the initial 30 min in both groups, from 74% to 95% of plasma platinum was in its free, unbound form. However, thereafter, the percentage of platinum in the unbound form was reduced to from 16% to 48% 2 h after drug injection. Regardless of the form of platinum, there was no significant difference in plasma concentrations between the two groups throughout the time course. The estimated pharmacokinetic parameters for cisplatin are summarized in Table 2. In contrast to the pharmacokinetic parameters for Adriamycin, for cisplatin the two groups showed no significant difference in either the mean AUC or the total body clearance.

Urine data

Urine data are summarized in Table 3. The mean cumulative amount of Adriamycin excreted in the urine during the time interval from 0 to 120 min was higher in the anhepatic dogs than in the controls, although the difference was not significant. The two groups did not differ significantly in the renal clearance of Adriamycin. The ratio of renal clearance to total body clearance tended to be higher in the anhepatic dogs compared with the controls, reflecting the significantly lower total body clearance in the anhepatic group. However, renal elimination was still a minor component in both the control and anhepatic groups, constituting only 2.7% and 4.3% of total body clearance, respectively.

On the other hand, the mean cumulative amounts of platinum excreted in urine were markedly different in the two groups (anhepatic 163.8 ± 27.0 μg/kg, control 41.4 ± 6.6 μg/kg; $P < 0.01$). Similarly, there was a significant difference in renal clearance of platinum between the anhepatic and control groups (anhepatic 3.5 ± 1.0 ml/min per kg, control 0.7 ± 0.2 ml/min per kg; $P < 0.01$). Renal elimination of platinum in the control and anhepatic groups constituted 4.1 ± 0.7% and 16.4 ± 2.7% of total body clearance, respectively, representing a significant compensatory increase under anhepatic conditions.

Tissue data of Adriamycin

As shown in Fig. 3, in both groups, the kidney had the highest tissue Adriamycin concentration, and skeletal muscle had the lowest. In all tissues measured except for the liver, Adriamycin concentrations in the anhepatic group were higher than those in the control group; the tissue distribution profiles of Adriamycin were analogous in the two groups.

Table 2 Plasma disposition characteristics of cisplatin (*AUC* area under the time–concentration curve, *Pt* platinum, CL_T total body clearance, V_{SS} volume of distribution, $T_{1/2}$ half-life). Values are means ± SD

Treatment group	AUC (μg min/ml)		CL_T (ml/min/kg)		V_{SS} (l/kg)		$T_{1/2}$ (min)	
	Total Pt	Free Pt	Total Pt	Free Pt	Total Pt	Free Pt	Total Pt	Free Pt
Control dogs (n = 4)	74.4 ± 12.0	57.7 ± 8.6	13.7 ± 2.2	17.6 ± 2.7	5.03 ± 0.63	5.64 ± 1.22	29.4 ± 2.0	24.5 ± 5.4
Anhepatic dogs (n = 4)	63.4 ± 9.5	47.8 ± 7.9	16.1 ± 2.4	21.4 ± 3.7	4.94 ± 2.29	5.06 ± 3.03	26.6 ± 11.0	21.4 ± 7.5

Table 3 Urine data (CL_R renal clearance, CL_T total body clearance). Values are means ± SD. *$P < 0.01$ vs control group

Treatment group	Cumulative amount (0–2 h) excreted from urine (μg/kg)		CL_R (ml/min/kg)		CL_R/CL_T (%)	
	Adriamycin	Platinum	Adriamycin	Platinum	Adriamycin	Platinum
Control dogs	24.2 ± 16.0	41.4 ± 6.6	1.8 ± 1.1	0.7 ±0.2	2.7 ± 1.9	4.1 ± 0.7
Anhepatic dogs	41.4 ± 20.9	163.8 ± 27.0*	1.1 ± 0.6	3.5 ± 1.0*	4.3 ± 2.2	16.4 ± 2.7*

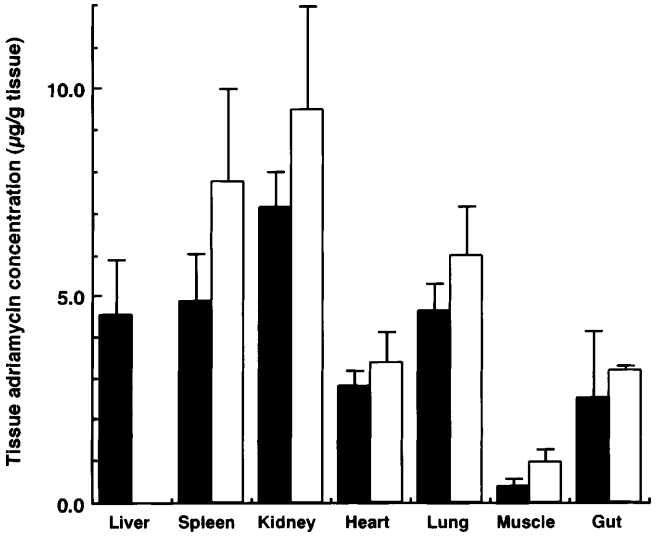


Fig. 3 Tissue Adriamycin concentration in various organs. Tissue specimens were taken 2 h after an i.v. bolus injection of Adriamycin (■ control dogs, □ anhepatic dogs). Values are means ± SD

Discussion

In order to maximize oncologic and toxicologic advantages in anhepatic chemotherapy, the agents used should have a demonstrated activity against HCC, have a short biological half-life, and be able to be eliminated through extrahepatic pathways. Adriamycin is mainly metabolized by the liver and is eliminated via the biliary route [1]. Benjamin et al. have reported that the cumulative 5-day urinary excretion of Adriamycin and its metabolites is only 5.7% of the administered dose [3]. Under anhepatic conditions one would expect an increased drug elimination through extrahepatic pathways, primarily by renal excretion. However, the current study clearly demonstrated that anhepatic conditions did not affect the renal clearance of this drug. The plasma disposition characteristics showed that anhepatic conditions resulted in approximately a twofold increase in systemic Adriamycin exposure, as assessed by the AUC. Considering the small difference in the volume of distribution between the two groups, the higher plasma levels of Adriamycin in the anhepatic dogs may primarily be explained by the lack of hepatic metabolism of the drug. Indeed, these Adriamycin pharmacokinetics under anhepatic conditions may produce more favorable effects on extrahepatic micrometastatic disease, if compared with an identical dose under physiologic conditions. On the other hand, however, tissue Adriamycin concentrations in six organs excluding the liver were uniformly higher in the anhepatic dogs. These results indicate that Adriamycin at any given dose may be associated with increased systemic toxicities under anhepatic conditions compared with physiologic conditions.

It has been shown that the kidney functions as the major organ of both excretion and concentration of platinum [6, 12]. Previous studies in dogs have demonstrated that, although cisplatin is partially excreted via the liver, the proportion of the drug found in the bile is less than 1% and the platinum recovery in urine ranges from 50% to 60% of the administered dose within the first 4 h [12]. In our study, the cumulative platinum recovery in urine in the first 2 h was approximately 16% of the administered dose under anhepatic conditions, which was fourfold higher than that under physiologic conditions, resulting from a significant increase in the renal clearance of platinum. These urinary data could account for the similarities between the anhepatic and the control groups in the plasma disposition characteristics of cisplatin including the AUC. This renal compensatory mechanism under anhepatic conditions appears to be beneficial from the point of view of systemic toxicity. However, more importantly, this apparently increases the exposure of the kidneys to platinum. Thus, nephrotoxicity may still remain as the dose-limiting factor of this agent, when used during the anhepatic period of liver transplantation.

Another important factor to be considered for selection of a drug and its dose in anhepatic chemotherapy is the potential risk of drug toxicity on the liver allograft after reperfusion. Administration of chemotherapeutic agents during the anhepatic phase might have longlasting negative effects. It has been reported by several investigators that plasma levels of platinum decay in a biphasic mode with an initial half-life of 25 to 49 min and a secondary phase ranging from 2 to 3 days after a single intravenous administration of cisplatin [6, 9, 12]. Regardless of the presence or absence of the liver, our results for plasma platinum decay in the first phase were essentially consistent with these previous findings. Adriamycin, on the other hand, showed a relatively rapid fall in plasma concentration, yielding an initial half-life of less than 5 min in both groups. Thus, in terms of the distribution half-life, Adriamycin appears to be more suitable than cisplatin for anhepatic chemotherapy. As shown by the concentration–time curve, the tissue distribution of Adriamycin reached near steady-state by 60 min even in

the anhepatic dogs and the AUC during the initial 60 min constituted more than 90% of the total AUC.

Assuming that the anhepatic period averages 60 min in OLT, it is reasonable to assume that a bolus injection of this drug, if given as a conventional dosage at the beginning of the anhepatic period, may exhibit only a marginal toxic effect on the liver allograft. In contrast, because of the more protracted decay of plasma platinum concentrations, the AUC during the initial 60 min was in the range 70% to 80% of the total AUC, which was clearly lower compared with the proportion for Adriamycin. Furthermore, in the clinical situation, patients with cirrhosis already have a markedly decreased liver and probably kidney function prior to OLT. Taken together, we feel that Adriamycin, although potentially more hepatotoxic, is better suited than cisplatin for anhepatic chemotherapy to maximize the theoretic advantages of this form of chemotherapy.

It should also be kept in mind that, for adjuvant chemotherapy with OLT, cyclosporine enhances drug transport into cells [21, 22]. Thus any given dose may be more effective, but also more toxic, under immunosuppressive treatments after OLT. Stone et al. designed a protocol using 50% of the standard dose of Adriamycin, yet they encountered leukopenia in 70% of their patients, and reported that substantially higher perioperative doses of Adriamycin could not be tolerated [23]. This should also be taken into account in determining the optimal dose of either drug for anhepatic chemotherapy.

In conclusion, this study showed that anhepatic conditions do not affect the renal clearance of Adriamycin, leading to a significant increase in systemic exposure to this agent. On the other hand, cisplatin exhibited a marked increase in renal clearance when administered under anhepatic conditions. This compensatory increase in renal elimination of cisplatin may account for the similar plasma disposition characteristics under anhepatic and physiologic conditions. These findings suggest that Adriamycin may carry the risk of increased systemic toxicities, while cisplatin may be associated with increased renal toxicity, when administered during the anhepatic period of OLT.

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