

Pharmacokinetic and Pharmacodynamic Advantages of Pirarubicin over Adriamycin after Intraarterial Hepatic Administration in the Rabbit VX2 Tumor Model¹

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ABSTRACT

Intraarterial chemotherapy with Adriamycin (ADM) has shown limited advantages over i.v. administration, with no reduction in systemic toxicities and modest decrease in peripheral plasma levels. In an effort to improve the selectivity of i.a. anthracycline chemotherapy, we compared pirarubicin (4'-*O*-tetrahydropyranyladriamycin, THP) and ADM in the surgically implanted VX2 rabbit tumor model. Both drugs were administered at the same dose (0.5 mg/kg) either by the intraarterial hepatic route (i.a.h.) or by the i.v. route. Anthracycline plasma and tissue levels were determined by high-performance liquid chromatography with fluorescence detection. ADM peak plasma concentration and area under the curve were not significantly reduced after i.a.h. administration compared to the i.v. route; however, ADM tumor concentration was 1.9-fold higher following i.a.h. administration compared to the i.v. infusion. After THP administration by the i.a.h. route, systemic exposure (area under the curve) was markedly reduced (8-fold) compared to the same dose administered i.v. These findings correlated well with the very low concentration of the drug in heart tissue following i.a.h. infusion. After i.a.h. administration, tumor THP concentrations were 10.5 times higher compared to the i.v. route. The pharmacokinetic advantage of i.a.h. administration of THP also led to a better antitumoral effect, as shown by a significantly lower tumor growth rate [$3 \pm 2\%$ (SD)] in the i.a.h.-treated animals compared to the i.v.-treated groups ($58 \pm 9\%$). Administration of ADM by the i.a.h. route was also inferior to i.a.h. THP. Taken together, our results suggest a clear-cut advantage of THP over ADM for i.a.h. locoregional chemotherapy, because of higher local tumor concentrations, greater antitumoral effect, and lower systemic exposure following the i.a.h. administration of THP. This anthracycline analogue could also be of therapeutic advantage in tumors partially resistant to anthracyclines that would become vulnerable to the high local concentrations achieved with i.a.h. administration. Based on these encouraging results, clinical trials using THP administered by the i.a.h. route were initiated.

INTRODUCTION

Intraarterial cancer chemotherapy can provide a double advantage over systemic administration by increasing local drug delivery to the tumor and also by reducing systemic toxicity because of lower concentrations of the drug outside the targeted organ (1-3). Drug administration via the hepatic arterial route offers a specific advantage because of the dual vascularization of the liver, which is predominantly portal in normal tissue, but mostly arterial in developed tumors (2-4). Another advantage of the hepatic arterial route is the high capacity of the liver to metabolize numerous xenobiotics, thus reducing systemic exposure to the parent drug.

To date, clinical trials evaluating i.a.h.³ chemotherapy have mostly used pyrimidines, probably because of their activity in gastrointestinal

cancers and of their important hepatic extraction. Higher response rates after i.a.h. chemotherapy compared to i.v. administration are obtained (1, 3), but with significant and limiting hepatic and biliary toxicities (5, 6). These side effects may partly explain why, in patients with metastases from colorectal origin confined to the liver, a survival advantage has been shown in only one trial (7). Thus, to improve i.a.h. chemotherapy, better schedules of administration of fluoropyrimidines have to be explored, or other anticancer agents fulfilling efficacy and toxicity criterias for locoregional administration have to be selected.

The criteria for the selection of drugs useful for i.a.h. chemotherapy are a high local extraction rate, a high hepatic metabolism, and limited vascular, hepatic, or biliary toxicities. A limited number of cytotoxic drugs fulfilling the above conditions for i.a.h. chemotherapy are under experimental and clinical studies. In the anthracycline family, one of the most active class of cytotoxic drugs used in systemic therapy, investigations have been limited almost exclusively to ADM. However, i.a.h. chemotherapy with ADM does not lead to a clear therapeutic advantage over i.v. administration (8, 9). As a matter of fact, studies in both experimental models and humans do not support an important ADM hepatic extraction (10, 11). For example, studies comparing the administration of identical doses after i.a.h. or i.v. infusions have shown a limited decrease in ADM plasma levels after i.a.h. administration, with no reduction in systemic toxicities (8, 9, 12). Also, the clinical evaluation of i.a.h. administration of 4'-epiadriamycin has not shown any advantage over ADM (13).

Because of the recognized efficacy and the widespread use of anthracyclines in clinical cancer therapy, it was of interest to evaluate an analogue with pharmacological properties that could offer a better local selectivity than ADM when administered i.a.h. THP, a novel ADM analogue, was selected based on its faster cellular uptake *in vitro* as well as *in vivo*, when compared to ADM (14, 15). This high cellular uptake is responsible for its very short initial half-life and its extensive total body clearance values in the range of those found for 5-fluorouracil and 5-fluorodeoxyuridine (16, 17). THP has also shown a clinical antitumor activity similar to that of ADM, but with less cardiotoxicity (18).

In the present study, we compared the pharmacokinetics of THP and ADM after i.v. or i.a.h. administration in the rabbit model. We also assessed the antitumor activity of THP and ADM when injected via the i.v. or the i.a.h. routes in the rabbit VX2 tumor model. This model was selected because of its relevance for clinical regional chemotherapy (19-22).

The data presented here show that THP offers a pharmacokinetic advantage of THP over ADM because of the lower systemic exposure, and the higher tumor concentrations achieved after its i.a.h. administration. In addition, these higher tumoral concentrations translated into a pharmacodynamic advantage, inasmuch as a greater antitumoral

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³ The abbreviations used are: i.a.h., intraarterial hepatic; i.a., intraarterial; ADM,

Adriamycin; THP, 4'-*O*-tetrahydropyranyladriamycin or pirarubicin; HPLC, high-performance liquid chromatography; DMSO, dimethyl sulfoxide; AUC, area under the curve.

effect was observed after the i.a.h. infusion of THP compared to its i.v. administration and to i.a.h. ADM.

MATERIALS AND METHODS

Drugs and Chemicals. ADM hydrochloride, THP hydrochloride, daunorubicin, adriamycinol, THP-adriamycinol, and adriamycinone were provided by Laboratoire Roger Bellon (Neuilly-sur-Seine, France). Solvents used for extraction and HPLC analyses were of HPLC grade or of the highest available purity.

VX2 Tumor Implantation and Surgical Procedures for i.a.h. Infusion. White female New Zealand rabbits weighing 2.5–3 kg were used for these studies (Elevage Scientifique des Dombes, Romans, France). The VX2 tumor was provided by Dr. Orth (U190 INSERM, Institut Pasteur, Paris, France) and was maintained by serial passage in carrier rabbits. From one single animal, a VX2 tumor was removed, minced in NCTC 109 medium (Eurobio, Paris, France), and filtered through four layers of cotton gauze. The filtrate was adjusted to 10^7 cells/ml with the above medium containing 10% DMSO and 20% fetal calf serum (Gibco, Paris, France) to constitute a homogenous stock that was frozen in liquid nitrogen in 1-ml aliquots and used throughout this study. This procedure minimized intersubject variations in tumor growth rate.

Hepatic implantation of the VX2 carcinoma was accomplished under general i.v. anesthesia using ketamine hydrochloride (50 mg/kg; Ketamine; Parke Davis) and xylazine 2% (0.1 ml/kg; Rompun; Bayer) through a small median subxyphoid incision. The 1-ml frozen sample of VX2 cells was quickly thawed and centrifuged to sediment the cells. The cell pellet was adjusted to 0.2 ml (NCTC 109 medium) and injected with a 25-gauge needle in the median hepatic lobe. Three weeks later, under general anesthesia (same as mentioned above), a 24-gauge catheter (Verelcath, Vermed, Neuilly-en-Thelle, France) was inserted into the gastroduodenal artery, with its distal extremity at the confluence with the hepatic artery. The collateral duodeno-pancreatic arteries were ligated. Fluorescein was injected through the catheter to ensure proper perfusion of the liver. At that time a tumor could be visualized at the liver surface. In the present study, the frozen samples gave a engrafting rate at day 21 greater than 80%. The mean product of length and width was 33 ± 18 (SD) mm^2 , and no variation in engraftment as well as in kinetics of growth was noted throughout the study.

Drug Administration and Biological Sample Collection. For pharmacokinetic studies, 4 groups of 8 rabbits each were randomly assigned to receive either ADM (0.5 mg/kg) or THP (0.5 mg/kg) i.v. or i.a.h. Drugs were diluted in 5 ml 0.9% NaCl solution and infused over 5 min with a pump (MS 16 A Graseby; Michel Frères, Montreuil, France) either through the i.a. catheter for the i.a.h. administration or through the right auricular vein for the i.v. administration. Heparinized systemic blood samples (2 ml) were collected prior to injection and at 0.5, 2, 5, 15, 30, and 60 min thereafter. Blood samples were centrifuged ($2000 \times g$, 10 min) and the plasma samples were frozen at -20°C until HPLC analysis.

Four additional groups of 4 rabbits implanted with VX2 tumors were sacrificed for tissue collection 30 min after the end of infusion. ADM or THP were administered as mentioned above via the i.v. or the i.a.h. route. Tissue samples were obtained from normal liver, VX2 tumor, and heart. These samples were immediately frozen at -20°C until HPLC analysis.

Plasma and Tissue Anthracycline Concentration Determination. Plasma concentrations were determined using reversed-phase HPLC. Daunorubicin was added as the internal standard (100 ng/ml). Plasma (0.5 ml) was extracted on 100 mg octadecyl (C_{18}) columns (1 ml Bakerbond spe; Baker, Phillipsburg, NJ) preconditioned with 1 ml of methanol, followed by 1 ml of water. After air drying, elution was accomplished with 1 ml of methanol:dichloromethane (1:1, v/v) following the addition of 200 μl of DMSO. The volume was then reduced to approximately 200 μl under a nitrogen stream before HPLC injection. This procedure allowed a 95% recovery of THP, ADM, internal standard, and metabolites. The HPLC system consisted of a C_{18} column (Nucleosil C, 10 μm , 3.9 x 300 mm; SFCC, Neuilly-sur-Seine, France), a Wisp automatic injector (710B; Waters Associated, Milford, MA), a 6000A pump (Waters), and a fluorescence detector (Shoefel FS 970) set at 251 nm (excitation) and 550 nm (emission). The mobile phase consisted of water (adjusted to pH 2.4 with phosphoric acid) and acetonitrile (68:32, v/v) at a flow rate of 1.75 ml/min. Under these conditions, the retention times of adriamycinol, ADM, THP-adriamycinol, daunorubicin, and THP were 3.59, 4.48, 5.94,

6.90, and 9.65 min, respectively. Two peaks corresponding to adriamycinol and ADM were observed in plasma after ADM injection, whereas four peaks could be detected following THP infusion. These peaks coeluted with adriamycinol, ADM, THP-adriamycinol, and THP.

Tissue concentrations were determined using our previously described procedure (14, 15). Briefly, the samples were homogenized with 25 μl of alkaline buffer (100 mM $\text{Na}_2\text{HPO}_4/30$ mM heptasulfonic acid, pH 8.5) in DMSO (1 ml of DMSO/100 mg of tissue, wet weight), and after centrifugation the supernatant was directly injected onto the HPLC system described above. This DMSO extraction has been compared to other published techniques (chloroform/isopropyl alcohol or chloroform/methanol) and was found to be at least equivalent in terms of amount of anthracyclines extracted from cells previously exposed to the drugs as well as from nuclear preparations. Moreover tissular pellets submitted to classical procedures of extraction after prior extraction with DMSO did not yield detectable amounts of anthracyclines. The DMSO technique was also chosen because it allowed direct injection onto the HPLC system.

Pharmacokinetic Analysis. Plasma concentrations were best fitted to a two-compartment model with first-order elimination using a 5-min i.v. infusion input. Curve fitting was accomplished with the PC-NONLIN nonlinear regression program (Statistical Consultants, Inc., Lexington, KY) using a data weight of the reciprocal of the concentration. The total AUC was determined using the trapezoidal method. The other pharmacokinetic parameters were calculated according to standard methods (23). Briefly, α and β half-lives were calculated as 0.693 divided by α or β , respectively; the volume of distribution β was calculated as the dose divided by $\beta \times \text{AUC}$; total plasma clearance was calculated as the dose divided by total AUC.

Antitumoral Effects of THP. The antitumoral activity of THP was evaluated after i.v. or i.a.h. administration. Rabbits were randomly assigned to a control group, an ADM i.v. group, an i.a.h. ADM group, an i.v. THP group, and an i.a.h. THP group (6 animals/group). Tumor was implanted on day 0 as described above. A laparotomy was performed on day 21 and THP or ADM were injected at 0.5 mg/kg/dose under the same conditions described above. In control and i.v. treated groups, 5 ml of 0.9% NaCl solution were also injected in the hepatic artery to compensate for possible effects of the i.a.h. administration procedure. The animals were sacrificed 14 days later (on day 35) for tumor measurements and histopathological evaluation. The tumor growth rate was evaluated by comparing the size of the tumor at the beginning of chemotherapy (day 21) and at the time of the last measurement (day 35). The percentage growth rates were calculated as (24):

$$\frac{a_{35}b_{35} - a_{21}b_{21}}{a_{21}b_{21}} \times 100$$

where a and b are, respectively, the length (mm) and the width (mm) of the tumor determined on day 21 (day of chemotherapy) and on day 35 (day of evaluation).

Statistical Analysis. Data are presented as means \pm SD. The Student t test was used to assess differences between means. For tumor growth inhibition comparisons, the nonparametric Wilcoxon test was used. $P \leq 0.05$ was considered significant.

RESULTS

Pharmacokinetics. ADM and THP plasma concentrations following either i.v. or i.a.h. administration are depicted in Fig. 1. In all cases, plasma decay was biphasic and could be fitted to a two-compartment model. For ADM, no statistically significant difference was observed between the i.v. and the i.a.h. routes with regard to either the maximal concentrations achieved at completion of the 5-min infusion or the total AUC (Table 1). Other ADM pharmacokinetic parameters were also similar after i.v. or i.a.h. administration (Table 1). Contrary to ADM, THP administration by the i.a.h. route led to a significant decrease in both THP peak plasma levels and AUC, compared to the i.v. route (Fig. 1; Table 1). The i.a.h. administration led to a 7-fold decrease in estimated peak plasma concentration of THP and to an 8-fold reduction in systemic exposure (AUC), compared to the i.v. route.

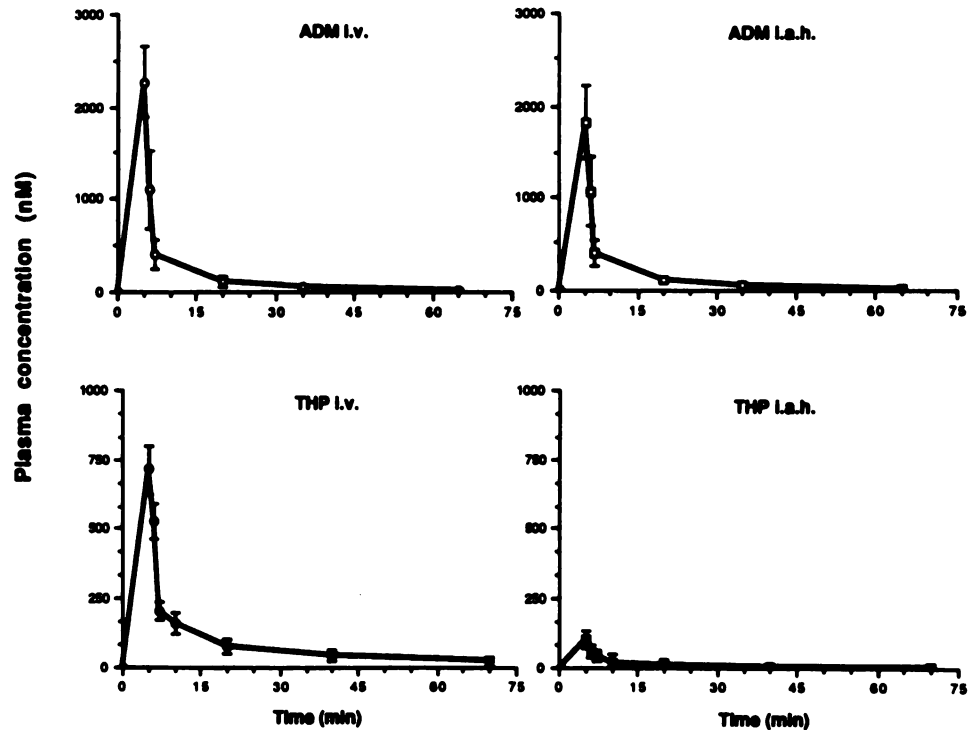


Fig. 1. Plasma concentrations of ADM and THP in rabbits following i.v. or i.a.h. administration of a 0.5-mg/kg dose. Concentrations were determined by HPLC. ○, i.v. ADM; □, i.a.h. ADM; ●, i.v. THP; ■, i.a.h. THP. Each point represents the mean of 8 rabbits; bars, SD.

Table 1 ADM and THP pharmacokinetic parameters following an i.v. or an i.a.h. administration in rabbits^a

Drugs (route)	Maximal concentration ^b (μM)	Area under the curve (μM·min)	α half-life (min)	β half-life (min)	Volume of distribution β (liters/kg)	Plasma clearance (ml/min)
ADM (i.v.)	3.17 ± 0.7 ^c	14.7 ± 2.0	1.1 ± 0.4	37 ± 13	3.35 ± 1.84	180 ± 25
ADM (i.a.h.)	2.42 ± 0.94	12.3 ± 2.4	1.8 ± 0.8	33 ± 17	3.01 ± 1.82	190 ± 26
THP (i.v.)	0.66 ± 0.19	6.3 ± 0.5	1.2 ± 0.7	52 ± 16	7.99 ± 3.34	355 ± 53
THP (i.a.h.)	0.09 ± 0.04 ^d	0.8 ± 0.3 ^d	1.9 ± 1.4	44 ± 20	40.04 ± 18.93 ^d	3096 ± 772 ^e

^a Rabbits weighing 2.5–3 kg received the indicated drug (0.5 mg/kg) as a 5-min infusion by i.v. or i.a.h. administration. Plasma concentrations were determined by HPLC.

^b Estimated maximal concentration at the end of infusion.

^c Mean ± SD of 8 rabbits/group.

^d Statistically different from the THP i.v. group ($P < 0.001$).

^e Statistically different from the THP i.v. group ($P < 0.05$).

Circulating levels of metabolites (Adriamycin, adriamycinol, THP-adriamycinol) remained constantly low following either THP or ADM administration, and no significant difference was observed between the i.v. and the i.a.h. routes of administration for both drugs (Table 2).

Tissue Drug Levels. Liver, tumor, and heart drug anthracycline levels after i.v. or i.a.h. administration are presented in Fig. 2.

For ADM, tumor concentrations were 1.9 times higher after i.a.h. infusion (7.8 ± 2.3 nmol/g) compared to the i.v. route (4.1 ± 1.2 nmol/g) ($P < 0.05$). However, cardiac ADM concentrations were similar after i.v. or i.a.h. injection (3.3 ± 1.2 versus 2.8 ± 0.6 nmol/g,

respectively). In normal liver, no significant difference in drug uptake was observed between either the i.a.h. or the i.v. infusion (3.7 ± 1.3 and 3.4 ± 1.1 nmol/g, respectively).

For THP the tumor uptake was greatly enhanced after i.a.h. administration compared to the i.v. route (Fig. 2). The intratumoral concentrations of THP were 10-fold higher ($P < 0.005$) after the i.a.h. infusion compared to the i.v. administration (34.6 ± 11.6 versus 3.5 ± 1.5 nmol/g, respectively). When THP was compared to ADM, for the i.a.h. route, the THP/ADM ratio for tumor concentration was 4.4 in favor of THP ($P < 0.01$). However, THP uptake in heart was significantly reduced ($P < 0.01$) after the i.a.h. administration (0.2 ± 0.2 nmol/g), while it was in the range of the values found for ADM (4.1 ± 1.9 nmol/g) after i.v. administration of THP. In normal liver, there was no significant difference in THP concentrations for the i.v. or the i.a.h. route (3.6 ± 0.9 versus 8 ± 6.2 nmol/g, respectively). This contrasted with high levels of metabolites such as Adriamycin (10.9 ± 3.6 nmol/g), adriamycinol (14.5 ± 6.2 nmol/g), adriamycinone (30.4 ± 14 nmol/g), and THP-adriamycinol (10.6 ± 3.2 nmol/g) after i.a.h. administration, while these metabolites were at the limit of detection after i.v. administration. Thus, the lack of significant increase in THP concentration in normal liver after an i.a.h. injection was probably due to its extensive local metabolism. Since ADM is one of the major cytotoxic metabolites of THP, its relative content was also assayed in heart and in tumor after THP administration. In tumor, the ADM/THP

Table 2 Plasma metabolites levels of Adriamycin (ADM) and pirarubicin (THP) following an i.v. or an i.a.h. administration in rabbits^a

	Maximal concentration (μM)			
	ADM i.v.	ADM i.a.h.	THP i.v.	THP i.a.h.
Adriamycinol	0.116 ± 0.04 ^b (2 min)	0.095 ± 0.05 (2 min)	0.007 ± 0.004 (5 min)	0.005 ± 0.003 (5 min)
Adriamycin	n.a. ^c	n.a.	0.032 ± 0.016 (5 min)	0.023 ± 0.007 (2 min)
THP-adriamycinol	n.a.	n.a.	0.035 ± 0.029 (2 min)	0.042 ± 0.031 (5 min)

^a Metabolites levels were determined by HPLC using standard metabolites as reference.

^b Mean ± SD of 8 rabbits/group. Numbers in parentheses, time after end of administration of the parent drug.

^c n.a., not applicable.

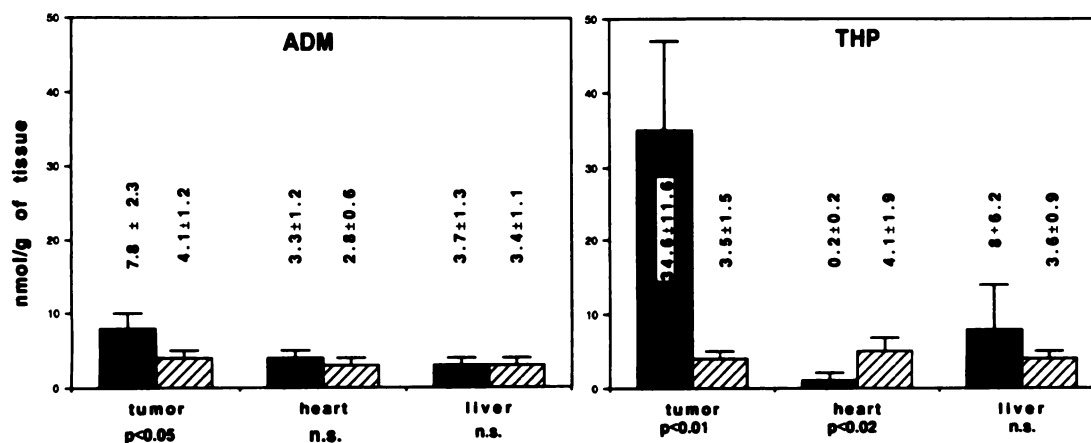


Fig. 2. Tissue concentrations (liver, tumor, and heart) of ADM and THP in rabbits following i.v. or i.a.h. administration of a 0.5-mg/kg dose. Tissues were sampled 30 min after injection, and drug concentrations were determined by HPLC. ■, i.a.h. route; ▨, i.v. route. Values are the mean ± SD (bars) of 4 rabbits.

ratios were 0.6 ± 0.2 and 0.13 ± 0.06 after i.v. and i.a.h. administration, respectively. In heart, the ratio was 0.35 ± 0.12 after i.v., while levels of ADM were too low to be quantified with the i.a.h. route.

Antitumoral Effects of THP. In view of the pharmacokinetic advantages observed above for the i.a.h. administration of THP, we then evaluated if the increased local concentrations and decreased systemic exposure were leading to a greater antitumoral effect. The antitumoral effects of THP or ADM administered by the i.v. or the i.a.h. route are presented in Table 3. For this rapidly growing and aggressive tumor, no tumoral reduction could be obtained with single drug injection, and only rates of growth inhibition were compared. The i.v. route for both drugs did not lead to a significant reduction of the tumor growth rate compared to control tumors. However, the i.a.h. route with THP led to a significant reduction in tumor growth rate compared to either the control group, the i.v. groups, or the ADM i.a.h. group. Thus, the antitumoral effects of i.a.h. administration of THP correlated well with the pharmacokinetic advantages observed above for the i.a.h. administration.

DISCUSSION

Despite theoretical advantages (1–4) of using i.a.h. administration of ADM, previous clinical (10–12) and experimental studies (25, 26) have found little difference in systemic levels when comparing the i.a.h. to the i.v. route. Consistent with this lack of a clear pharmaco-

kinetic advantage in using the i.a.h. route, no reduction in systemic toxicity and no greater antitumoral efficacy have been clearly demonstrated with the i.a.h. administration of ADM (8, 9, 12).

In an effort to increase the efficacy of locoregional chemotherapy in the anthracycline series, we investigated the potential advantage of using THP, a novel ADM analogue with clinical antitumor activity at least equivalent to ADM (18). This compound seemed a good candidate for locoregional chemotherapy, based on its faster cellular uptake than that of ADM (14), that could lead to a better intratumoral retention and a higher hepatic extraction. Also, the high hepatic metabolism of anthracyclines in general and of THP in particular was thought to possibly contribute to a reduction in systemic exposure. In this study, the i.a.h. modality of administration was chosen because of its clinical importance, and the rabbit VX2 tumor model was selected because of the similarity of its vascularization to the human liver metastases and primary tumors (27).

The results presented in this paper demonstrated both a pharmacokinetic and a pharmacodynamic advantage of using THP over ADM for locoregional i.a.h. chemotherapy. THP pharmacokinetics revealed a remarkable decrease in systemic as well as cardiac exposure and a 10-fold enhancement in tumor concentrations after the i.a.h. administration compared to the i.v. route. The high hepatic extraction ratio of THP was mainly due to extensive metabolism, as shown by the high metabolite concentrations. These results contrasted with ADM pharmacokinetics, since no clear advantage resulted from the i.a.h. administration, with the exception of a 2-fold increase in tumor concentration, probably due to the higher concentration in the arterial flow at first passage. Another consequence of the low local selectivity of ADM was the difficulty in reducing systemic exposure; indeed, not only was the systemic exposure similar after i.a.h. or i.v. administration of ADM but the cardiac concentrations were also similar.

Comparison of the pharmacokinetic data of ADM and THP after i.v. infusion in our animal model confirmed the larger volume of distribution and total body clearance of the latter over the former (15). This pharmacokinetic difference between the two anthracyclines and our results suggesting a more effective use of THP via the i.a.h. route are in agreement with pharmacological principles suggesting that drugs with a high total body clearance should be selected for intraarterial administration (1, 3).

These encouraging pharmacokinetic data obtained with THP led us to verify if the observed advantages were translating into a better antitumoral effect in the rabbit VX2 tumor model. Our results confirmed that the higher tumoral concentrations of THP achieved *in vivo* were also leading to a greater antitumoral effect, when the drug was

Table 3. Antitumoral effects of pirarubicin and Adriamycin administered either i.v. or i.a.h. in the VX2 tumor model^a

Treatment	Control (1) ^b	THP i.v. (2)	THP i.a.h. (3)	ADM i.v. (4)	ADM i.a.h. (5)
Tumor size (mm ²) on day 21	21 ± 10 ^c	24 ± 15	30 ± 8	36 ± 8	42 ± 14
Tumor size (mm ²) on day 35	1200 ± 490	890 ± 330	120 ± 90	1380 ± 610	760 ± 210
Growth rate (%)	73 ± 39	58 ± 42	2.9 ± 1.7	37 ± 18	18 ± 6

^a Three groups of 6 rabbits each were implanted in the median hepatic lobe with 10⁷ VX2 tumor cells on day 0. Treatments were administered on day 21. The two largest tumor diameters were measured on the day of treatment (a_{21} and b_{21}) and 14 days later (a_{35} and b_{35}). Growth rate was calculated as:

$$\frac{a_{35}b_{35} - a_{21}b_{21}}{a_{21}b_{21}} \times 100$$

Treatments consisted of THP (0.5 mg/kg) given either i.v. or i.a.h. To discriminate between drug and procedure effects, 5 ml of 0.9% NaCl solution were injected in the hepatic artery of both the control group and the i.v. group.

^b $P < 0.05$: 1 versus 3, 2 versus 3, 1 versus 5, 4 versus 5, 3 versus 5.

^c Mean ± SD.

administered into the hepatic artery. Correlations of the pharmacodynamic data with tumoral growth inhibition were also observed with ADM, since the i.a.h. route was significantly inferior to the THP i.a.h. route.

Taken together, these results suggest a potentially advantageous clinical application of this novel anthracycline when administered via the i.a.h. route. Based on these encouraging preclinical results, a clinical investigation using i.a.h. administration of THP has been initiated (28). Preliminary clinical observations indicated an absence of hepatotoxicity and an increased maximal tolerated dose following the i.a.h. administration of THP, compared to i.v. administration (29). These clinical data are therefore in agreement with the high local extraction of THP observed in the rabbit model after an i.a.h. administration.

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