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Multiple-dose pharmacokinetics of epirubicin at four different dose levels: studies in patients with metastatic breast cancer*

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Summary. Pharmacokinetic analysis of epirubicin and its metabolites epirubicinol and 7-deoxy-13-dihydro-epirubicinol aglycone during the first and the fourth courses of treatment was performed in 78 patients with metastatic breast cancer. The patients were treated every 3 weeks with epirubicin given as 10-min i.v. infusions at four different dose levels: 40, 60, 90 and 135 mg/m^2. In most cases (76 of 78 cases), plasma concentration-time curves fitted to a three-compartmental pharmacokinetic model. The terminal half-life of epirubicin was independent of dose and duration of treatment. Large interindividual differences were demonstrated (mean $t_{1/2\gamma}$, 21.6±7.9 h; range, 10.6–69 h; n = 110). In two subjects, extremely long half-lives and high serum bilirubin concentrations indicated impaired liver function. No correlation was found between the half-life and levels of liver alanine aminotransferase (ALAT) or serum creatinine. The metabolite epirubicinol appeared quickly after epirubicin administration and its half-lives were shorter than that of the parent compound (mean $t_{1/2\gamma}$, 18.1±4.8 h; range, 8.2–38.4 h; n = 105). Formation of the aglycone metabolite was delayed and the half-life of this metabolite was shorter than that of epirubicin (mean $t_{1/2\gamma}$, 13±4.6 h; range, 2.7–29 h; n = 104). The AUC of epirubicin and the total AUC (drug and metabolites) were linearly proportional to the dose, with the former value constituting two-thirds of the latter. A correlation was found between AUC and the plasma concentration of epirubicin at two time points (2 and 24 h after administration). The proposed model was AUC = 9.44 × c_2 + 62.5 × c_{24} + 157.7 (r = 0.953).

Introduction

Epirubicin (4′-epidoxorubicin) is a doxorubicin analog in which the OH group in the 4′ position of the amino sugar has been epimerized. When given in equimolar doses to patients with metastatic breast cancer, this anthracycline possesses antitumor activity comparable with that of doxorubicin and supposedly produces less toxicity, particularly cardio toxicity [2, 12].

Before a possible relationship between the dose or dose intensity of epirubicin and its antitumor effect can be investigated, the pharmacokinetics of the drug must be elucidated. Previous studies [11, 17] have suggested that the pharmacokinetics of doxorubicin is dose-dependent and that plasma clearance is increased after multiple administration; however, these studies involved only a few patients. Vrignaud et al. [18] have studied the pharmacokinetics of epirubicin in ten patients after repeated and escalated administration. These authors found a tendency towards increased plasma clearance after repeated courses of treatment given at approximately the same dose (25–35 mg/m^2). No change in terminal half-life was found.

The present study reports the pharmacokinetic parameters of epirubicin in 78 patients with metastatic breast cancer who were randomized to receive repetitive treatment at four different doses. In a subsequent paper the relationship between pharmacokinetic parameters, antitumor activity and toxic effects will be evaluated.

Patients and methods

Patients and blood sampling. The present investigation is part of a randomized phase II study of epirubicin in metastatic breast cancer. The study was accepted by the Danish Health Authorities and the Ethical Committee. After they had given informed consent to partipate, the patients were randomly allocated to receive either 40, 60, 90 or 135 mg/m^2 i.v. every 3rd week. In phase II studies in previously untreated patients, epirubicin could safely be given as a single agent at doses of up to 135 mg/m^2 [4, 13]. A total of 78 patients were included in the present pharmacokinetic study.

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Doses were given i.v. over 10 min using a multiplum of 5-mg vials. During the first treatment course, blood samples were drawn from all 78 patients both before the infusion and at 5, 30 and 60 min as well as at 2, 4, 6, 7, 9, 11, 24 and 30 h after drug administration. In 31 of these subjects the blood sampling was repeated during the fourth course of treatment. Blood samples (5 ml) were drawn into heparinized test tubes. The samples were kept on ice and immediately centrifuged at 4° C and 3,000 *g*. The plasma was separated and stored at –70° C.

Chemicals. Epirubicin, its metabolites and doxorubicin were kindly provided by Farmitalia Carlo Erba (Milan, Italy). All solvents and other chemicals were at least of analytical grades.

Analytical method. A reverse-phase HPLC technique based on the method described by Deesen and Leyland-Jones [8], with minor modifications, was chosen for the analysis of epirubicin and its 13-dihydro- and circulating aglycone metabolites. No attempt was made to determine the levels of circulating glucuronide metabolites. Duplicate 0.5-ml plasma samples containing doxorubicin (100 ng/ml) as the internal standard were extracted with 5 ml chloroform : isopropanol (4 : 1, v/v). After centrifugation at 3,000 *g* for 5 min, the organic phase was separated and evaporated to dryness under nitrogen at 30° C in a dark environment. The residue was redissolved in 100 µl of the chromatographic eluent, of which 25 µl was analyzed in an HPLC system consisting of a stainless steel column (length, 12.5 cm; inside diameter, 4 mm) slurry-packed with Nucleosil 100-5 C18 (Machery-Nagel, Düren, FRG). The eluent consisted of 30% acetonitrile (HPLC grade S, Rathburn; Walkerburn, Scotland) in 10 mM ammonium formate buffer adjusted to a pH of 4; it was pumped through the column at a flow rate of 1.5 ml/min by a Shimadzu LC-6A pump. The fluorescent drug and metabolites were detected with a Hitachi F-1000 fluorescence spectrophotometer using an excitation wavelength of 480 nm and an emission wavelength of 560 nm. HPLC peaks were recorded on a strip chart recorder. An automatic sampler (Promis II, Spark Holland) was used for the injection of samples.

Retention times for epirubicinol, epirubicin and 7-deoxy-13-dihydro-doxorubicinol aglycone were 3.5, 5.6 and 6.9 min, respectively. The internal standard, doxorubicin, had a retention time of 4.5 min. Other possible metabolites of epirubicin, such as the aglycone and 7-deoxy-aglycone of epirubicin and the aglycone of epirubicinol, were chromatographically separated from the compounds mentioned above. These potential metabolites were never found in significant amounts in the plasma samples. The minimal detectable concentration was 1 ng/ml for both the parent drug and its two metabolites. The interassay coefficient of variation determined in plasma samples containing 50 ng/ml of each compound was 6.2% for the parent drug, 5.1% for epirubicinol and 8.3% for the aglycone metabolite.

Pharmacokinetic analysis. The plasma decay curves for epirubicin were fitted to a polyexponential function by means of a computer program for iterative nonlinear least-squares analysis using a personal computer:

$$C(t') = \sum_{i=1}^{n} Q'_i \times \exp(-k_i \times t).$$

The nonlinear least-squares fit of the experimental data for two patients fitted to a two-exponential equation, whereas all other data required a three-exponential equation. The number of exponential terms (n) were estimated by application of Akaike's information criterion (AIC) [1] using minimization of residual sums of squares. Q'_i represents the intercepts on the ordinate, and t' is the time measured from the end of infusion. When T is the time of constant infusion, Q'_i is given by the following equation [10]:

$$Q'_i = \frac{Q_i}{k_i T} (1 - e^{-k_i \times T}).$$

For the triple decay curves, half-lives, AUCs, early plasma clearance (C_{EA}) and total plasma clearance (C_{tot}), mean residence time (MRT) and steady-state volume of distribution (V_{ss}) were calculated from:

$t_{1/2\alpha} = \ln 2/\alpha$, $t_{1/2\beta} = \ln 2/\beta$, $t_{1/2\gamma} = \ln 2/\gamma$

$AUC = A/\alpha + B/\beta + C/\gamma$

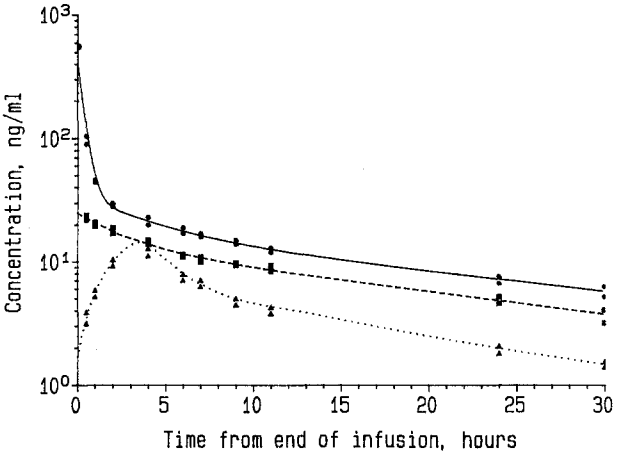

Fig. 1. Plasma concentrations of epirubicin (●) and the two metabolites epirubicinol (■) and 7-deoxy-13-dihydro-doxorubicinol aglycone (▲) in patient 9. The *solid line* represents the best least-squares fit to the triexponential function: $c = 3{,}501 \times e^{-9 \times t} + 54.1 \times e^{-0.58 \times t} + 16.8 \times e^{-0.030 \times t}$

$C_{EA} = \text{Dose} \times \alpha/A$, $C_{tot} = \text{Dose}/AUC$

$$MRT = \frac{\frac{A}{\alpha^2} + \frac{B}{\beta^2} + \frac{C}{\gamma^2}}{AUC}$$

$V_{ss} = \text{Dose} \times MRT/AUC$

For the metabolites a model-independent approach was used. The terminal half-lives for the metabolites ($t_{1/2elim}$) were calculated by linear regression analysis of the logarithms of the late experimental data, and the AUCs were calculated by the trapezoidal method and extrapolated to infinity using the formula:

$$AUC = AUC_{trap\ 0-30\ h} + \frac{c\,(30\ h) \times t_{1/2elim}}{\ln 2}.$$

Statistical evaluation. Statistical packages for the IBM PC, SPSS and Statgraphics, were used. One-way analysis of variance (ANOVA) was used to detect differences among the four sub-groups receiving the different doses of epirubicin. When ANOVA indicated differences, a multiple-comparison procedure (Student-Neuman-Keuls) was used to assess them. For multiple regression analysis with stepwise variable selection, the computer program Statgraphics was used.

Results

The plasma concentrations of epirubicin after i.v. administration described either a three- (76 patients) or a two-compartmental (2 subjects, 1st course of treatment) open pharmacokinetic model. Figure 1 shows the plasma concentrations of epirubicin and the metabolites in one patient. The pharmacokinetic parameters calculated after the first and fourth courses of treatment for epirubicin are presented as means ± SD and ranges in Table 1 and as AUCs in Table 2. Kinetic data on two patients with very high serum bilirubin levels are not included in the tables.

During the first treatment course, statistical analysis showed a significantly ($P < 0.05$) longer terminal half-life for epirubicin in the group of patients receiving the lowest dose as compared with the groups receiving 60 and 135 mg/m². The same statistical differences were found for the derived parameters MRT and C_{tot}. No significant

Table 1. Pharmacokinetic parameters at the first and fourth courses of treatment

Dose (mg/m^2)		$t_{1/2\gamma}$ (h)		MRT (h)		C_{EA} ($ml\ min^{-1}\ m^{-2}$)		C_{tot} ($ml\ min^{-1}\ m^{-2}$)		V_{ss} (l/m^2)	
		1st course	4th course	1st course	4th course	1st course	4th course	1st course	4th course	1st course	4th course
40	Mean	23.1	23.2	20.3	22.6	2,301	2,934	799	769	974	1,016
	± SD	4.8	7.5	5.9	12	982	1,716	204	131	358	502
	Range	14.8–33.4	17 –40.9	8.6–35.4	12.3–54	996–4,066	1,442–6,863	463–1,408	612–1,107	281–1,784	579–2,332
	n	25	9	25	9	25	9	25	9	25	9
60	Mean	19.3	17.5	17.2	16.4	2,828	3,334	838	784	866	760
	± SD	4.9	4.3	6.3	5.7	1,609	2,142	286	215	378	310
	Range	11.4–27.5	11.9–24.3	5.9–29.4	8.5–24.6	780–7,042	1,348–7,846	303–1,616	553–1,112	108–1,881	306–1,399
	n	15	7	15	7	15	7	15	7	15	7
90	Mean	20.6	20.6	19.4	19.5	4,048	3,273	891	881	1,047	985
	± SD	4.6	4.2	4.7	4	2,734	972	264	253	456	223
	Range	11.8–26.7	14.3–25.9	11.7–29	13.2–26.8	1,631–9,406	1,988–4,605	503–1,479	493–1,293	492–2,128	761–1,527
	n	18	8	18	8	18	8	18	8	18	8
135	Mean	17.4	22.4	15.2	20.5	2,962	3,517	898	911	808	1,076
	± SD	3.3	6.3	3.9	5.8	1,154	1,050	137	212	188	173
	Range	10.6–24.1	14.7–30.7	9 –25.5	10.7–28	1,376–5,769	2,553–5,681	683–1,164	674–1,337	444–1,183	856–1,413
	n	18	7	18	7	18	7	18	7	18	7
Total[a]:											
	Mean	20.6		18.7		3,148		848		838	
	± SD	5.2		6.5		1,623		225		266	
	Range	10.5–40.9		5.9–54		780–9,406		303–1,616		108–2,128	
	n	107		107		105[b]		107		107	

[a] All determinations except those from patients with extremely high bilirubin levels
[b] The two plasma concentration-time curves that fitted a two-exponential function were excepted

Table 2. AUC curves

Dose (mg/m^2)		AUC_{epi} ($ng\ ml^{-1}\ h$)		AUC_{tot} ($ng\ ml^{-1}\ h$)		AUC_{epi}/AUC_{tot} (%)	
		1st course	4th course	1st course	4th course	1st course	4th course
40	Mean	890	791	1,248	1,268	72	67
	± SD	273	321	273	681	10	14
	Range	472–1453	611–1,089	730–1,710	853–2,552	48–98	36–84
	n	25	9	25	9	25	9
60	Mean	1,377	1,294	1,857	1,893	71	69
	± SD	651	331	658	530	12	6
	Range	619–3,314	902–1,675	916–3,615	1,183–2,591	48–100	58–78
	n	15	7	15	7	15	7
90	Mean	1,800	1,874	2,707	2,682	68	69
	± SD	576	607	828	707	12	7
	Range	1,027–2,998	1,164–3,068	1,528–5,295	1,656–3,950	49–99	55–79
	n	18	8	18	8	18	8
135	Mean	2,569	2,682	3,694	4,110	71	63
	± SD	404	677	794	1,100	10	9
	Range	1,928–3,298	1,680–3,361	2,908–6,277	2,748–5,525	52–95	48–76
	n	18	7	18	7	18	7

differences in kinetic parameters were found among the groups receiving the three highest doses. During the fourth treatment course, no differences in half-life, MRT or clearance were found among the groups and no changes were observed between the two treatment courses.

Figure 2 shows plots of AUCs versus the doses of epirubicin delivered during the first (Fig. 2a) and fourth (Fig. 2b) courses of treatment. Total AUCs (epirubicin and the two metabolites) versus dose are plotted in Fig. 2c and d. Linear regression analysis gave the equations for the four regression lines listed in Table 3. No significant differences were found between the two courses of treatment.

Table 4 shows the half-lives of epirubicin and the two metabolites, with all determinations being included. In Fig. 3, corresponding values for serum bilirubin levels are plotted against the terminal half-life of epirubicin. In the two patients who had high levels of serum bilirubin, the terminal half-lives were very long. No correlation between serum creatinine or alanine aminotransferase could be demonstrated. No correlation between the early-phase

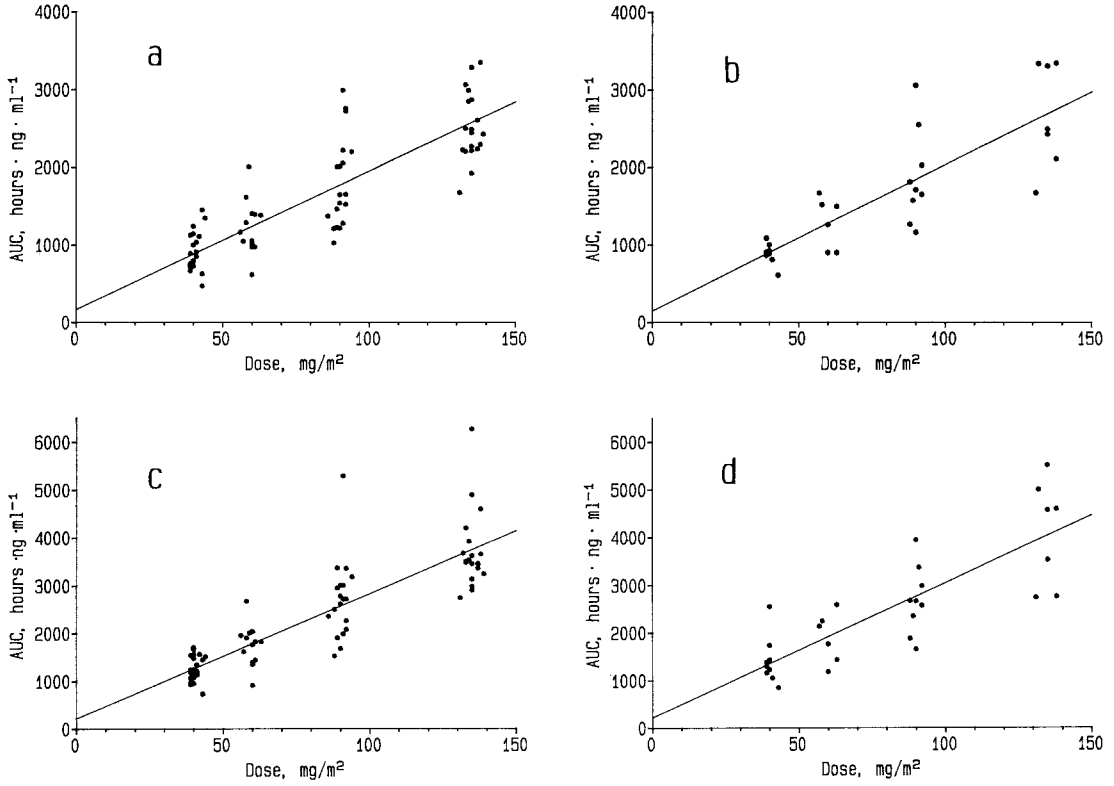

Fig. 2 a – d. AUCs for epirubicin alone versus dose during **a** the first and **b** the fourth course of treatment and for epirubicin and the two metabolites during **c** the first and **d** the fourth course of treatment. Linear regression lines are shown. Formulae for the straight lines are given in Table 3

Table 3. Linear regression lines for AUC versus dose according to the formula $y = (a \pm SD) \times X + (b \pm SD)$

	a	± SD	b	± SD	r	n
Epirubicin:						
1st treatment	17.9	1.3	169	113	0.8536	76
4th treatment	18.4	2.4	180	210	0.8196	30
Epirubicin + metabolite:						
1st treatment	26	1.9	228	171	0.8442	76
4th treatment	27.5	3.7	276	322	0.8125	30

Table 4. Half-lives of epirubicin and metabolites

	$t_{1/2elim}$ ± SD (h)	Range (h)	n
Epirubicin	21.6±7.9	10.6–69	110
Epirubicinol	18.1±4.8	8.2–38.4	105
Aglycone	13 ±4.6	2.7–29	104

pharmacokinetic parameter C_{EA} and patient age was found.

Correlations between the AUC and the concentration of epirubicin at different time points (1, 2, 4, 6, 7, 9, 11 and 24 h) as determined using linear regression analysis are given in Table 5. Results from the first as well as the fourth course of treatment are included. Multiple linear regression analysis with forward stepwise selection of the independent variables incorporated two concentrations, c_2 and c_{24}, resulting in the model:

$$AUC = 9.44 \times c_2 + 62.5 \times c_{24} + 157.7 \quad r = 0.953$$

Figure 4 illustrates the relationship between the AUCs calculated from the complete pharmacokinetic analysis and those estimated by the model.

Discussion

For all but two patients, the plasma concentrations fitted to a three-compartmental open model. The half-lives determined for the three phases are in accordance with values described in the literature [5, 6, 9, 14, 16, 18]. A minor disrepancy between the results we obtained for the early-phase half-life and those previously reported may be due to the rather limited number of blood samples we collected early after the infusion. The metabolite epirubicinol was detectable in the blood at 5 min after the administration of epirubicin and showed a terminal half-life that was close to but never larger than that of the parent compound. Plasma concentration-time curves for the aglycone metabolite could not be model-fitted. The appearance of this metabolite was delayed and its terminal half-life was always shorter than that of epirubicin. The aglycone was not found in substantial amounts by Camaggi et al. [6], but Mross et al. [14] also reported the presence of this metabolite. Glucuronides, which play a significant role in the elimination of epirubicin [7], were not determined in this study.

The slightly longer terminal half-life found for epirubicin in the group of patients receiving the low dose cannot

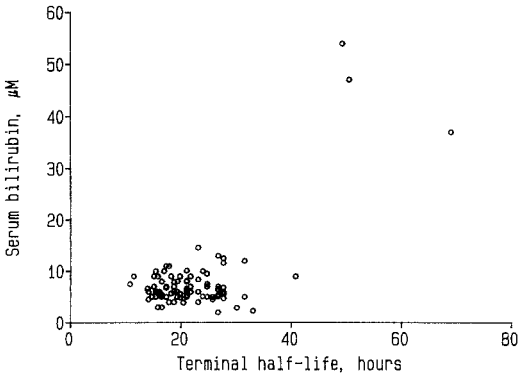

Fig. 3. Relationship between the terminal half-life of epirubicin and serum bilirubin levels

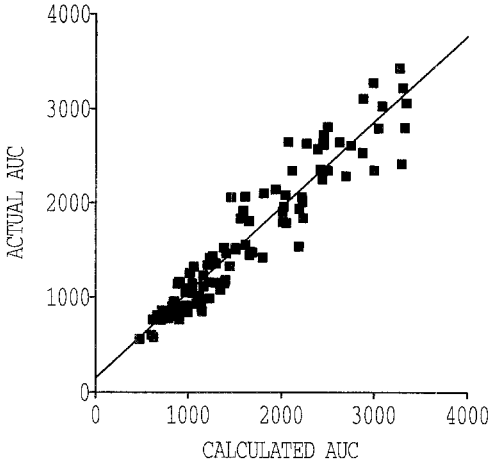

Fig. 4. Relationship between the actual AUC determined from complete pharmacokinetic analysis and the AUC calculated from the model AUC = 9.44 × c(2 h) + 62.5 × c(24 h) + 157.7; AUC is expressed in ng h ml^{-1} and concentration, in ng/ml

Table 5. Linear regression lines for AUC versus the concentration of epirubicin at selected time points (c_i)

Time (h)	$AUC_{epi} = a \times c_i + b$			
	a	b	r	n^a
1	9	817	0.715	107
2	19.6	479	0.869	107
4	31	343	0.922	107
6	39.5	302	0.924	107
7	42.9	297	0.921	107
9	49.1	292	0.917	107
11	55.5	263	0.917	107
24	96.9	212	0.914	107
Model[b]	$AUC_{epi} = 9.44 \times c_2 + 62.5 \times c_{24} + 157.7$			$r = 0.953$

[a] When exact time points were missing, concentrations were estimated by extrapolation

[b] From multiple regression analysis

be explained and the clinical importance of this observation is questionable. One plausible reason would be that patient plasma samples containing the lowest concentrations might have been slightly overestimated, maybe because of the presence of small amounts of interfering compounds.

As shown in Fig. 2 and Table 3, AUCs for epirubicin and its metabolites were linearly proportional to the delivered dose; however, during the first course of treatment the regression line intercepts the ordinate at a value that is significantly different from zero ($P < 0.05$), which is in agreement with the longer half-life found in patients receiving the low dose. The regression line for AUCs calculated during the fourth course of treatment intercepts the ordinate at a value that is not statistically different from zero.

Figure 3 demonstrates a correlation between very high serum bilirubin concentrations and extremely high terminal epirubicin half-lives. In one patient receiving 63 mg/m^2, a terminal half-life of 69 h and a correspondingly high AUC (bilirubin, 37.2 µM) was found during the first course of treatment. After the fourth treatment course the terminal half-life had decreased to 17.7 h (bilirubin, 11 µM), and the AUC demonstrated a similar reduction. In a second patient receiving 62 mg/m^2 epirubicin, we found an abnormally high terminal half-life of 49.3 h and an extremely high AUC (bilirubin, 53.9 µM), which did not decrease after repeated treatments ($t_{1/2}$, 50.5 h; bilirubin, 62 µM; fourth treatment course). These extremely long half-lives might be due to liver insufficiency in these two patients. In patients with hepatic metastasis and elevated bilirubin levels, it has been shown, that the plasma disposition of doxorubicin was reduced and the toxicity, increased [3]. Mross et al. [14] and Camaggi et al. [6] reported a high terminal half-life in one patient with elevated serum bilirubin values who had been treated with epirubicin.

Robert and Hoerni [15] have found a highly significant correlation between the early-phase pharmacokinetics of doxorubicin and patient age (17–74 years). No such correlation could be demonstrated for epirubicin in our subjects, who showed a similar age distribution (31–74 years). Moreover, we could not find a significant difference between the total plasma clearance during the first course of epirubicin treatment and the values determined for subsequent courses in contrast to the suggestion of Vrignaud et al. [18].

The present study demonstrated large interindividual variations in terminal half-life, AUCs and total plasma clearance after the i.v. administration of epirubicin. The terminal half-life was independent of both the delivered dose and the number of previous treatments. Our data also indicated that very high serum bilirubin levels are likely to decrease the clearance of epirubicin.

The AUCs for epirubicin correlated well (Table 5) with the plasma concentration of epirubicin obtained at different time points after the administration of epirubicin. A better correlation was obtained when the concentrations found at both 2 and 24 h were incorporated into the model (Fig. 5). These correlations might be useful in therapeutical monitoring of patients, provided that a correlation is established between the epirubicin AUC and the clinical effect. In a subsequent publication correlations between the pharma-

cokinetic parameters of epirubicin and the pharmacodynamic response, side effects and antitumor effects of the drug in these patients will be presented.

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