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Doxorubicin and doxorubicinol: intra- and inter-individual variations of pharmacokinetic parameters

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Summary. Doxorubicin was given by short i.v. infusion (dose range 25–72 mg/m^2) to 18 patients who underwent three to seven successive courses of chemotherapy (total, 57 courses). Plasma levels of doxorubicin and its major metabolite doxorubicinol were determined by high-performance liquid chromatography over a 48-h period after the infusion. Pharmacokinetic parameters for the parent drug and its metabolite were calculated for each course of treatment. The results show considerable inter- and intra-individual variations for most parameters. The coefficients of variation (CV) ranged from 37% to 93% (inter-individual) and from 6% to 59% (intra- individual). Nevertheless, we observed a good stability over successive courses for terminal half-life in six patients (CV, 6%–25%) and for clearance and AUC in four subjects (CV, 10%–22%). The ratio of the AUCs for doxorubicinol : doxorubicin averaged 0.514. The pharmacokinetic pattern of doxorubicinol was biphasic in plasma of the majority of patients. We propose a model for curve-fitting of these metabolite plasma concentrations that is based on two successive releases of the compound in the plasma compartment, separated by a lag time.

Introduction

Doxorubicin (DOX) is one of the major antineoplastic agents used in the treatment of non-Hodgkin's lymphoma and diverse solid tumours. Therapeutic schedules include bolus i.v. injection either every 3–4 weeks or every week and protracted infusion over a period lasting from 4 days to 1 month. The pharmacokinetics of DOX are linear [7]; all of these schedules result in approximately the same monthly injected dose, which ranges from 25 to 80 mg/m^2. Thus far, only empirical methods have been used to determine the amount of drug to be given. The monitoring of individual doses requires a knowledge of the pharmacokinetic characteristics of the drug and more especially, the way in which these characteristics vary in a given patient over successive courses. Few studies involving the administration of two to three successive courses to the same patient [8, 11, 21] have been carried out in this field, and the investigators reported large individual fluctuations of pharmacokinetic parameters without a well-defined direction of variation.

The aim of this work was to determine intra-individual variations of the pharmacokinetic parameters of DOX over a maximal number of successive courses and to include a sufficient number of patients to constitute an adequate population for ulterior Bayesian estimation of pharmacokinetic parameters.

Patients and methods

Patient population. A total of 18 patients were included in the study. All of the subjects had not previously been treated with DOX or radiotherapy regimens and all were investigated for biological and clinical evaluation of renal and liver function. Cardiac function (ECG, echocardiogram and/or angioscintigraphy) was also checked. None of the patients showed signs of renal or hepatic dysfunction. Informed consent was obtained from each patient for every treatment course. Patient characteristics and prior chemotherapy regimens are summarized in Table 1.

Drug administration and doses. DOX was infused in a peripheral vein by brief infusion (range, 5–15 min); in six cases the duration of infusion was longer (0.42 h: patient GON, four courses; patients TIX and VAS, one course). The delivered dose varied from 25 to 72 mg/m^2 and was invariable for each patient over the treatment period. Courses were repeated every 4 weeks.

Blood sampling. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-coated tubes at the end of each infusion and at 10, 20 and 40 min as well as 1, 2, 4, 6, 12, 24, 36 and 48 h post-infusion. One sample was taken from each patient prior to the injection for the calculation of calibration curves using plasma. Plasma was rapidly centrifuged and frozen at –20° C before testing, and plasma analysis was performed during the subsequent 2 weeks.

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Table 1. Patients' characteristics

Patient	Sex (M/F)	Age (years)	Diagnosis/histology	Treatment	Doxorubicin (mg)	Courses (*n*)
AUJ	M	61	NHL-DSCC	m-BACOD	75	3
BOU	M	70	Lung carcinoma-SC	VAC-VP16	75	6
COM	F	55	NHL-DLSCC	CHOP-Bleo	80	6
GAR	F	66	Breast cancer	AVCF	70	3
GON	M	68	NHL	CHOP-Bleo	75	6
IZA	M	65	NHL-DLC	AVCB	130	3
QUA	M	48	Lung carcinoma-SC	VAC-Cis-VP	90	4
TIX	M	66	CLL	CHOP	40	5
VAS	M	51	NHL-DLCC	CHOP-Bleo	70	6
BAB	F	51	Breast cancer	AVCF	60	1
DEG	F	65	NHL-DMC	m-BACOD	40	1
DEN	F	60	Ovarian carcinoma	AVEC	70	4
DUR	F	63	NHL-DLC	m-BACOD	70	2
JAR	F	55	Breast cancer	AVCF	70	1
LOP	M	61	Lung carcinoma-SC	VAC	80	1
MOR	F	43	Breast cancer	FAC	80	2
PUI	M	69	Hodgkin's disease	ABVD	48	1
ROB	M	31	Hodgkin's disease	ABVD	45	1

NHL, Non-Hodgkin's lymphoma; DSCC, diffuse small-cell, cleaved; SC, small-cell; DLSCC, diffuse, large small-cell, cleaved; DLC, diffuse large-cell; CLL, chronic lymphocytic leukemia; DLCC, diffuse large-cell, cleaved; DMC, diffuse mixed-cell. m-BACOD: Methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; VAC-VP16: vincristine, doxorubicin, cyclophosphamide, etoposide; CHOP-Bleo: cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; AVCF: doxorubicin, vindesine, cyclophosphamide, 5-fluorouracil; AVCB: doxorubicin, vindesine, cyclophosphamide, bleomycin, methyl prednisolone; Cis, cisplatin; AVEC: doxorubicin, teniposide, cyclophosphamide, cisplatin; FAC: 5-fluorouracil, doxorubicin, cyclophosphamide; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine

Analytical method. Concentrations of DOX and its major metabolite doxorubicinol (DOXOL) were determined in all samples by high-pressure liquid chromatography (HPLC) with fluorescence detection, using a previously described method [19] modified as follows.

DOX, DOXOL, and daunorubicin (internal standard) were extracted from plasma (0.5 ml) with acetonitrile (3 ml) in the presence of sodium chloride. The organic phase was evaporated to dryness. The column was a spherisorb phenyl (inside diameter, 25 cm ×4.6 mm; particle size, 5 μm). The mobile phase (acetonitrile : 0.03 M citrate buffer adjusted to pH 4 with formic acid; 30 : 70, vol/vol) was used isocratically at a flow rate of 1.5 ml/min. Drugs were detected with a Perkin Elmer fluorometer (model LS-1; excitation wavelength, 480 nm; emission wavelength, 590 nm). The detection limit was 0.5 ng/ml for both DOX and DOXOL. Within-day and between-day variabilities of the assay were 4.5% and 8.9%, respectively.

Pharmacokinetic analysis. The plasma concentration of DOX and DOXOL vs time followed a tri- or bicompartmental exponential decay. The coefficients (C_1, C_2, C_3) and exponents (α_1, α_2, α_3) of the exponential terms were estimated with the SIPHAR computer program [12] (zero-order input) using the extended least-squares method for DOX and the weighted $[1/Ycalc)^2]$ least-squares method for DOXOL. Elimination half-life was determined from the slope of the log-linear portion of the curve.

The AUC was calculated using the equation $AUC = AUC_{0\to T} + AUC_{T\to th} + Cth/\alpha$ (T = infusion time); $AUC_{0\to T}$ was calculated by the integral of the fitted model between 0 and T; $AUC_{T\to th}$ was calculated by the trapezoidal rule, with Cth representing the concentration at the last sampling time and α the rate of the terminal log-linear phase. The total body clearance (Cl_T) was calculated from the ratio of the DOX dose to AUC, and the volume of distribution in equilibrated tissues was evaluated by $V_d = Cl_T/\alpha$.

The model used to fit the variation of plasma DOXOL concentration vs time, which takes into account a re-increase in DOXOL plasma levels during the terminal phase, was expressed as follows.

For $t < T$, zero-order process,

$$C = \frac{P_1}{P_2 T}\ [1-\exp^{-P2\ t}] + \frac{P_3}{P_4 T}\ [1-\exp^{-P4\ t}];$$

for $t \geq T$, first-order process,

$$C_1 = \frac{P_1}{P_2 T}\ [1-\exp^{-P2\ T}]\exp^{-P2\ (t-T)} + \frac{P_3}{P_4 T}\ [1-\exp^{-P4\ T}]\exp^{-P4\ (t-T)};$$

for $t_1 = t - P_7$, first-order process,

$-t_1 <= 0$, $C_2 = 0$

$-t_1 >> 0$

$C_2 = P_5\ [\exp^{-P4\ t1} - \exp^{-P6\ t1}]$;

for $t \geq T$,

$C = C_1 + C_2$;

where P_1 is coefficient 1 (distribution phase), P_2 is exponent 1 (distribution phase), P_3 is coefficient 2 (elimination phase), P_4 is exponent 2 (elimination phase), P_5 is the coefficient of second release, P_6 is the exponent of second release and P_7 is the lag time between the two biphasic phenomena.

Results

After the end of the infusion, the distribution of DOX to peripheral tissues was followed by an apparent biexponential decline in plasma concentration as a function of time in 52 analyses. The plasma results of these patients were fitted to a three-compartment open model. Five sets of plasma profiles did not show the two characteristic distributive phases and were fitted to a two-compartment open model. The goodness of fit as described by r^2 was typically ≥ 0.998 in 81% of the analyses. The main metabolite detected was DOXOL; although other metabolites were present, they occurred in very small amounts and were not quantified. For DOXOL, the results were consistent with an open two-compartment model.

The individual pharmacokinetic parameters determined for each patient after the first course are shown in Tables 2 and 3. For DOX, the terminal half-life varied

Table 2. Individual pharmacokinetic parameters of DOX after the first course

Subject	Dose (mg/m^2)	Infusion time (h)	AUC[a] ($\mu g\ l^{-1}\ h$)	k_{el} (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{13} (h^{-1})	k_{31} (h^{-1})	$t^1/_2\alpha_3$ (h)	Vd (l)	Cl_T[b] (l/h)
AUJ	44.12	0.17	70.5	5.18	0.79	1.22	5.09	0.06	22.42	779.9	24.5
BOU	51.12	0.25	74.9	3.32	2.14	1.28	3.71	0.06	25.74	728.1	23.1
COM	48.6	0.17	39.6	1.13	2.47	0.22	1.57	0.08	27.34	1,637.8	43.7
GAR	41.18	0.17	33	6.68	0.4	0.98	2.61	0.06	16.53	1,230.7	52.5
GON	51.37	0.17	21.2	3.27	0.9	0.66	3.36	0.06	24.56	2,444.2	81.7
IZA	72.2	0.17	36.5	1.59	0.87	0.76	3.57	0.11	21.75	1,545.7	21.8
QUA	45.9	0.25	26	1.68	3.03	1.03	4.53	0.13	20.92	2,760.5	75.6
TIX	23.1	0.25	25	3.15	1.7	1.17	4.17	0.05	34.13	3,416.7	69.3
VAS	35.35	0.25	35.2	3.24	2.39	0.3	3.01	0.03	36.63	2,974.3	49.1
BAB	37.5	0.17	44.1	3.19	1.69	0.39	4.6	0.03	51.81	2,709.2	39.2
DEG	27.59	0.17	34.8	0.96	3.76	0.95	3.61	0.23	17.38	1,044.3	49.7
DEN	49.3	0.083	43.4	4.56	0.73	0.55	3.5	0.03	32.64	1,542.4	39.8
DUR	42.4	0.17	57.3	3.06	2.37	0.21	2.53	0.03	51.17	2,133.7	30.2
JAR[c]	50	0.17	29.1	1.58	3.01	0.171	–	–	12.08	838.8	59.5
LOP	48.19	0.23	55.2	0.94	2.79	0.5	1.7	0.08	27.89	1,212.3	31.3
MOR	50	0.17	35.1	7.19	0.83	0.58	4.46	0.03	37.45	2,460.9	49.2
PUI	30	0.17	47.8	3.22	1.01	0.69	3.39	0.05	27.3	1,316.8	36.2
ROB	28.1	0.17	69.2	5.66	0.92	3.7	7.52	0.06	26.01	870.4	25
Mean			43.2	3.31	1.77	0.85	3.7	0.07	28.54	1,758.2	44.5
SD			16.2	1.9	1	0.79	1.38	0.05	10.74	850	18.1
CV (%)			37.5	57.5	56.9	93	37.4	72.3	37.6	48.3	40.7

[a] Normalized for dose ($1\ mg/m^2$)
[b] Expressed for $1.73\ m^2$ body area
[c] A two-compartment model was used for this subject
SD, Standard deviation; CV, coefficient of variation

Table 3. Individual pharmacokinetic parameters of DOXOL after the first course

Subject	AUC[a] ($\mu g\ l^{-1}\ h$)	$t_{1/2elim}$ (h)	R(AUC)[b]
AUJ	19.1	38.13	0.271
BOU	36	28.9	0.481
COM	23.8	27.54	0.601
GAR	18	24.89	0.545
GON	7.88	30.47	0.372
IZA	17.3	30.24	0.474
QUA	13.2	22.35	0.508
TIX	16.2	57.7	0.648
VAS	12.3	31.55	0.349
BAB	19.2	36.07	0.435
DEG	Not measurable		–
DEN	15.4	47.95	0.355
DUR	25	34.98	0.436
JAR	8.88	22.57	0.305
LOP	44.9	43.32	0.813
MOR	15.9	40.01	0.453
PUI	31.1	42.01	0.65
ROB	95.8	26.08	1.38
Mean	26.4	34.4	0.534
SD	22.3	9.6	0.259
CV (%)	84.6	27.9	48.5

[a] Normalized for dose ($1\ mg/m^2$)
[b] R = AUC DOXOL/AUC DOX
CV, Coefficient of variation

between 12 and 52 h, and extreme values for distribution volume and normalized total clearance ranged between 728 and 3,417 l and 22 and 82 l/h, respectively. For DOXOL, the terminal half-life varied between 22 and 58 h and was higher than that for DOX in all but five cases. The proportion of drug metabolized, given by the ratio of the AUCs for DOXOL: DOX, averaged 0.534, with extreme values of 0.271 and 1.38.

A total of 12 patients were evaluated for intra-individual variation; each subject was monitored over two to seven successive courses. The results are shown in Tables 4 and 5 for DOX and DOXOL, respectively.

Illustrations of plasma elimination of unchanged drug over successive courses are presented in Figs. 1 and 2. Patient GON displayed very close elimination half-lives over six courses; in contrast, a lengthening of the same parameter over the last four courses was observed in patient BOU.

Discussion

The inter-individual variations in the pharmacokinetic parameters of DOX and DOXOL were considerable, with the coefficient of variation (CV) ranging from 37% to 93% according to the parameter considered. High variations were observed for the microscopic rate constants, particularly k_{21}, whereas lower variations were found for terminal half-life and AUC. The pharmacokinetic parameters calculated in the present study are in agreement with those determined in previous studies [1, 2, 11, 13, 16, 17, 20–23] (Table 6).

Our results indicate that the value for terminal half-life depends on the extension of the sampling period after the infusion. The mean value for this parameter was 28.5 ± 10.7 h for DOX (n = 18) and 34.4 ± 9.6 h for DOXOL (n = 17). For patients GAR, DEG and JAR, whose last sampling time was 24 h, the terminal half-life was short (<20 h for DOX and <25 h for DOXOL) as

Table 4. Intra-individual variations of DOX: mean pharmacokinetic parameters ± standard deviation

Patient	Dose (mg)	Compartments (*n*)	Courses (*n*)	Infusion time (h)	AUC[a] (μg l^{-1} h)	$t_{1/2elim}$ (h)	V_d (l)	Cl[b] (l/h)
AUJ	75	3	3	0.17	62.6 ±6.9	24.59 ±8.84	970.3 ±412.9	27.9 ±2.9
BOU	75	3	4	0.25	49.7 ±20.9	45.83 ±19.19	2,279.6 ±1,292.1	40.9 ±18
			3	0.17				
COM	80	3	4	0.17	40.5 ±11.3	25.96 ±6.37	1,574.9 ±437.1	45.7 ±13.4
		3	1	0.25				
		2	1	0.25				
GAR	70	3	3	0.17	27.5 ±7.17	13.1 ±2.96	1,201.8 ±284.8	66.3 ±19.9
GON	75	3	2	0.17	41.8 ±24.9	24.41 ±2.24	1,551 ±708.5	52.35 ±23.47
		3	4	0.42				
IZA	130	3	3	0.17	32.9 ±6.45	22.12 ±1.42	1,843.6 ±421.3	54.2 ±12
QUA	90	3	2	0.25	26 ±10.6	23.76 ±5.95	2,760.5 ±714.3	75.6 ±31.3
		2	2	0.25				
TIX	40	3	4	0.25	25 ±4.53	50.21 ±18.31	5,238.5 ±1,919.8	73 ±11.8
		3	1	0.42				
VAS	70	3	5	0.25	54.9 ±20.4	41.23 ±5.92	2,364.3 ±749.3	35.5 ±13.1
		3	1	0.42				
DEN	70	3	3	0.17	44.8 ±9.82	29.2 ±10.1	1,324.7 ±314.7	40 ±7.64
		2	1	0.17				
DUR	70	3	2	0.17	50.2 ±10	39.7 ±16.2	1,847.8 ±404.3	35.2 ±7
MOR	80	3	2	0.17	56.6 ±30.4	52.3 ±21	2,225.3 ±332.2	35.7 ±19.1

[a] Normalized for dose (1 mg/m^2)
[b] Expressed for 1.73 m^2 body area

Table 5. Intra-individual variations of DOXOL: mean pharmacokinetic parameters ± standard deviations

Patient	Dose (mg)	Courses (*n*)	$t_{1/2elim}$ (h)	AUC[a] (μg l^{-1} h)	AUC DOXOL/ AUC DOX
AUJ	75	3	40.54 ±8.78	23.2 ±3.81	0.377 ±0.0946
BOU	75	7	83.7 ±29.6	28.4 ±13	0.564 ±0.181
COM	80	6	27.43 ±2.26	20.3 ±4.16	0.534 ±0.17
GAR	70	3	26.13 ±8.4	17.4 ±0.503	0.668 ±0.205
GON	75	6	42.34 ±13.89	11.4 ±5.35	0.311 ±0.153
IZA	130	3	42.47 ±14.14	17.4 ±0.627	0.517 ±0.0559
QUA	90	4	41.29 ±18.32	16.2 ±5.96	0.665 ±0.227
TIX	40	5	60.37 ±10.11	13.5 ±4.36	0.534 ±0.151
VAS	70	6	48.58 ±15.87	23.2 ±8.64	0.438 ±0.148
DEN	70	4	42.14 ±6.7	16.52 ±1.8	0.383 ±0.0958
DUR	70	2	30.1 ±7.21	27.02 ±2.86	0.554 ±0.168

[a] Normalized for dose (1 mg/m^2)

compared with the value obtained for other subjects, who were submitted to sampling over 48 h. This phenomenon seems to be quite common as reported in the literature [6–9], the only exception being the value of 40.8 h obtained by Natale [17] over a sampling period of 24 h (Table 6). A minimum of 48 h sampling time seems to be necessary for acceptable estimation of elimination half-life. The CV of our estimated pharmacokinetic parameters also showed values that agree with the extent of inter-individual variability reported in the studies cited above.

Large intra-individual variations in DOX pharmacokinetics were observed (6%–59%). These variations were mostly due to the increase in elimination half-life after the second course. In spite of this variability, it is noteworthy that in some patients, some parameters were rather reproducible over successive courses. The CV for $t^1/_2\alpha_3$ was 6%–14% in patients GON, IZA and VAS and was 25% in subjects COM, GAR and QUA. Cl_T and AUC also showed little variation in patients AUJ, TIX, IZA, DEN and DUR ranging from 18% (AUJ) to 22% (DEN), as shown in Table 7.

For DOXOL, $t_{1/2\alpha 2}$ showed a CV of 8% in patient COM, 16% in subject DEN, 17% in patient TIX, 22% in subject AUJ and 24% in patient DUR. For the other subjects, the CV was >30%. The proportion of drug metabolized showed equally large variations: from 11% in patient IZA to 49% in subject GON (Table 7).

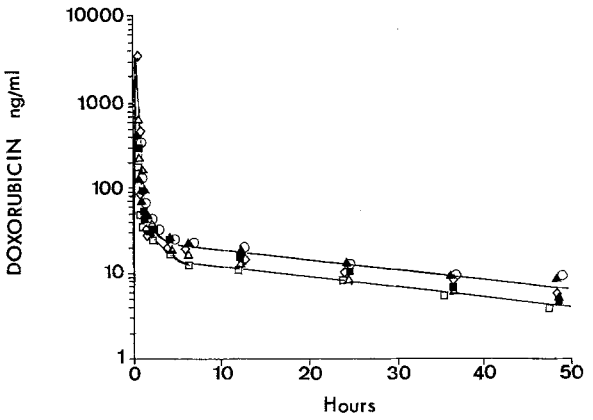

Fig. 1. Plasma concentrations of DOX following the administration of six courses of 75 mg doxorubicin to patient GON. □, First course; ■, second course; △, third course; ▲, fourth course; ○, fifth course; ◇, sixth course

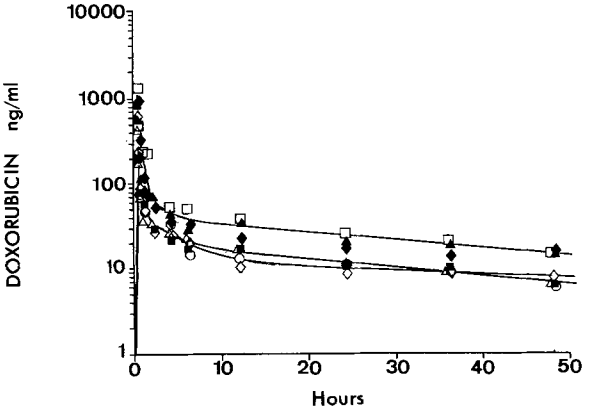

Fig. 2. Plasma concentrations of DOX following the administration of seven courses of 75 mg doxorubicin to patient BOU. □, First course; ■, second course; △, third course; ▲, fourth course; ○, fifth course; ◇, sixth course; ◆, seventh course

Table 6. Mean pharmacokinetic parameters of DOX as compared with data in the literature [27]

Course number	$t^1/_2\alpha_1$ (min)	$t^1/_2\alpha_2$ (h)	$t^1/_2\alpha_3$ (h)	V_d (l/kg)	Cl (l/h)	Assay method	Metabolites observed	DOXOL/ DOX AUC ratio	References
13	12	3	30		66[b]	TLC	DOXOL, DOXONE		Benjamin et al. [1]
23	9	1.5	26			TLC	DOXOL, DOXONE		Chan et al. [3, 4]
20	11	3	27			TLC	DOXOL, DOXONE		Lee [15]
15	9	[a]	35			TLC	DOXOL, DOXONE	0.8	Ehninger et al. [5]
24	47	[a]	35			HPLC	DOXOL	0.3	Evans et al. [10]
16	4.4	1.6	41		53	HPLC	DOXOL		Natale et al. [17]
11	5	2.5	50	24	24	HPLC	DOXOL	0.4	Oosterbaan et al. [18]
10	9	[a]	27	25	52[b]	HPLC	DOXOL, DOXONE	0.5	Greene et al. [13]
7	4	1.6	37		73	HPLC	DOXOL	0.9	Gil et al. [11]
12	4.8	0.8	19		49	HPLC	DOXOL		Robert et al. [20]
9	4	1.2	29		55	HPLC			Robert et al. [21]
26	4	1.6	35	22	52[b]	HPLC	DOXOL	0.3	Robert et al. [23]
21	[a]	[a]	37	39	66[b]	HPLC	DOXOL, DOXONE	0.9	Brenner et al. [2]
16	4	0.5	13		66	HPLC	DOXOL	0.5	Eksborg et al. [6]
21	4	0.7	14		60	HPLC	DOXOL	0.3	Eksborg et al. [7]
6	4.3	0.85	16		83	HPLC			Eksborg et al. [8]
18	3	[a]	39	25	54	HPLC	DOXOL	0.3	Speth et al. [25, 26]
26	3.8	0.9	19		55[b]	HPLC			Erttmann et al. [9]
8	3	0.8	26	24	60[b]	HPLC	DOXOL	0.4	Mross et al. [16]
57	5.1	1.53	33	30	48[b]	HPLC	DOXOL	0.51	Present study

[a] No intermediate half-life
[b] Expressed for 1.73 m^2 body area
TLC, Thin-layer chromatography; DOXONE, doxorubicinone

Intra-individual variations of pharmacokinetic parameters appeared to be a slightly lower than inter-individual variations (Table 7). The stability we noted in some parameters in certain patients has not been observed in prior studies. Nevertheless, the intra-individual variations observed confirm the general conclusions of studies carried out by Gil et al. [11] and Robert et al. [21]. The CV values calculated in this study are very close to those reported by Gil et al., especially those for $t_{1/2\alpha 1}$, $t_{1/2\alpha 2}$ and Cl_T. However, $t_{1/2\alpha 3}$ displayed minor variations in the present study (6%–42%) in relation to the results of Gil et al. [11].

In 27 of the analysed curves, we observed a re-increase in plasma DOXOL values at between 1 and 6 h after an initially steep decrease. The pattern of DOXOL plasma concentration differed among patients, and the second-release phenomenon was very pronounced in some patients and only slight in others; in some cases it was very reproducible over successive courses (Fig. 3). This biphasic phenomenon has previously been noted by Gil et al. [11] who attributed this transient increase to an initial sequestration of the metabolite in a peripheral compartment, followed by its release at 2 or 4 h after drug administration. Delayed metabolism of DOX to DOXOL (hepatic?) could also be an explanation for this phenomenon. An initially steep decrease in the plasma concentration of DOXOL would reflect only its early production by blood cells and the distribution of the parent drug. In the present study, for fitting of the variation of DOXOL plasma concentration vs time we used a two-compartment model that makes allowance for this pattern. The goodness of fit as

Table 7. Comparison of intra- and inter-individual variations of DOX and DOXOL pharmacokinetic parameters

Parameters	Intra-individual variations (CV %): Subjects												Mean value	Inter-individual variations (CV %)
	AUJ	BOU	COM	GAR	GON	IZA	QUA	TIX	VAS	DEN	DUR	MOR		
DOX:														
AUC ($\mu g\ l^{-1}\ h$)	11	42	28	30	59	20	41	18	37	22	20	54	32	37
$t_{1/2\alpha 3}$ (h)	36	42	24	23	9	6	25	36	14	34	41	40	26	37
V_d (l)	42	57	28	24	46	23	26	36	31	24	22	15	31	48
Cl_T (l/h)	10	44	29	30	45	22	41	16	37	19	20	53	30	41
DOXOL:														
$t_{1/2\alpha 2}$ (h)	22	35	8	32	33	33	44	17	33	16	24		27	28
AUC DOXOL/AUC DOX	25	32	32	31	49	11	34	28	34	25	30		30	48

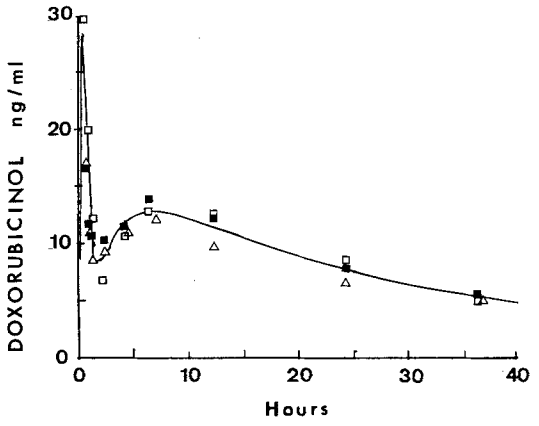

Fig. 3. Plasma concentrations of DOXOL following the administration of the three first courses of 90 mg doxorubicin to patient QUA. □, First course; ■, second course; △, third course

Table 8. Pharmacokinetic parameters of DOXOL for patient QUA after the first three courses

	Course		
	1	2	3
Rebound matched fitting:			
Lag time (h)	0.916	2.02	1.28
$t_{1/2}$ distribution (h)	0.408	0.695	0.583
$t_{1/2}$ second process (h)	2.41	1.7	1.08
$t_{1/2}$ elimination (h)	19.74	19.25	21
AUC ($\mu g\ l^{-1}\ h$)	523.61	524.48	443.79
Log-linear analysis of terminal points:			
$t_{1/2}$ elimination (h)	22.35	20.06	21.09
AUC ($\mu g\ l^{-1}\ h$)	544.70	529.04	444.68

described by r^2 was typically ≥ 0.98 in 74% of the analyses. The terminal half-life value obtained by rebound matched fitting (35.7 ± 20.3 h, $n = 27$) was in the same range as that estimated by log-linear analysis of terminal points (39.8 ± 23.1 h, $n = 27$). For example, the pharmacokinetic parameters obtained for patient QUA are shown in Table 8.

Conclusions

First, this study enabled us to determine the amplitude of the inter-individual (37%–93%) and intra-individual (6%–59%) variabilities of the pharmacokinetic parameters of DOX and to ascertain its great extent by the pharmacokinetic study of the drug's elimination from plasma over the maximal number of successive courses (from two to seven) in patients. Second, we proposed a satisfying model for DOXOL data that takes into account a reincrease in DOXOL plasma concentrations at between 1 and 6 h after an initially steep decrease. This model adequately describes the plasma-concentration profile of DOXOL in 27 analyses. To explain this biphasic phenomenon, a sequestration of the metabolite in a peripheral compartment has been proposed by Gil et al. [11]. Another explanation could be a delay in the metabolism of DOX to DOXOL. This working hypothesis may be further verified, for example, using a more sophisticated physiological modeling technique. However, this approach requires additional information and knowledge that are not presently available.

The pharmacokinetic parameters calculated in the present study will be used for a determination of population characteristics in which inter- and intra-individual variations will be represented and for validation of the use of such a method in the individualisation of pharmacokinetic parameters. Such an approach has been proposed by Launay et al. [14]; however, the mean terminal half-life of 12.4 h calculated in this study was too short to enable a proper estimation of this half-life in comparison with the data in the literature; thus, it cannot be used for the estimation of individual pharmacokinetic parameters. The use of an adequate population would enable this estimation to be made with minimal blood sampling. This point is very important in terms of patient comfort and precautions related to sample processing in clinical practice (immediate centrifugation and freezing). Moreover, since the Cl_T value for DOX is lower in obese patients [24], its determination may be justified in this category of patients; a limited sampling procedure can be very useful, as venous access is often difficult in these patients. The Bayesian approach would be efficient for drug monitoring in studies investigating the toxicity or efficiency of DOX given by continu-

ous infusion over several days in relation to a target value for plasma concentration.

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