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Bayesian estimation of doxorubicin pharmacokinetic parameters

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Summary. Doxorubicin was given by brief i.v. infusion (doses ranging from 25 to 72 mg/m^2) to 28 patients for 2–7 successive courses of chemotherapy (68 courses studied in all). A Bayesian approach was developed to determine the individual pharmacokinetic parameters of doxorubicin. Statistical characteristics of the population pharmacokinetic parameters were first evaluated for 19 patients and a total of 30 courses, which, when combined with 4 individual plasma concentrations of drug, led to a Bayesian estimation of individual pharmacokinetic parameters for the remaining 38 courses. The estimated parameters for the elimination phase (A_3/V_1 and $t_{1/2}$ elimination) and the residual plasma level at 48 h as computed by Bayesian estimation on this reduced sub-optimal sampling protocol were compared with a maximal likelihood estimation of these parameters. No statistically significant differences were found. Performance of the developed methodology was evaluated by computing bias and precision. The mean errors were -0.0315×10^{-4} l^{-1} for A_3/V_1, 0.0839 h for $t_{1/2}$ elimination, and –0.22 ng/ml for $c_{(48\ h)}$. The precision of the prediction of these three parameters (0.304×10^{-5} l^{-1}, 3.34 h, and 0.659 ng/ml, respectively) remained lower than the interindividual standard deviation (1.42×10^{-4} l^{-1}, 14.9 h, and 4.54 ng/ml, respectively). This procedure enables the estimation of individual pharmacokinetic parameters for doxorubicin at minimal cost and minimal disturbance of the patient.

Introduction

Doxorubicin (DOX) is one of the major antineoplasic agents used in the treatment of non-Hodgkin's lymphoma and diverse solid tumors and is usually given as a bolus injection. The DOX plasma concentration-time curve after an intravenous bolus has been described as biphasic, showing a distribution half-life of <5–10 min and a terminal elimination half-life of 27–39 h [6, 9, 15, 31], or, more generally, as triphasic, displaying a distribution half-life of 5 min (range, 3–12 min), an initial elimination half-life of 1.5 h (range, 0.5–3 h), and a terminal elimination half-life of 28 h (range, 13–50 h) [15, 20, 31].

Experimental studies have suggested that the DOX concentration-time product (area under the curve) is a determinant factor for tumor cell lethality [5, 21]. Robert et al. [23] have observed a correlation between the pharmacokinetic parameters and the short-term clinical response. In searching for a pharmacokinetic parameter that might correlate with clinical toxicity, Ackland et al. [1] have identified a pharmacodynamic relationship between white blood cells (w.b.c.) and the temporally related steady-state plasma concentration of DOX. The use of DOX as a bolus injection is accompanied by the usual toxic effects (i.e. myelosuppression, nausea, vomiting, and alopecia, as well as its specific toxicity, cardiomyopathy [10, 19, 33]). Furthermore, continuous infusion of DOX is associated with clinical efficacy in malignant hemopathies, including multiple myeloma, and leads to a significant reduction in the toxic effects and cardiotoxicity of the drug [2].

The purpose of the present study was to define a Bayesian estimation (BE) procedure enabling the estimation of individual DOX pharmacokinetic parameters so as to minimize the number of samples collected and optimize the decision-making process as to the best therapeutic dose regimen for each patient. The Bayesian approach, proposed by Sheiner et al. [29] to individualize the dosage of drug regimens, combines individual information with the knowledge of an a priori probability density function containing the statistical properties of the parameters to be estimated. The basic feature of BE is that it combines population characteristics of the parameters to be estimated with drug concentrations measured in the individual concerned [29] such that the individual pharmacokinetic parameters can be estimated. The outcome obtained using the classic maximal likelihood estimation (MLE) along with extended least-squares nonlinear regression and that obtained using the Bayesian approach have been compared

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for parameter estimation under adaptive control for several drugs; the Bayesian method seemed to produce better results [3, 8, 11, 14, 17, 18, 30, 32].

The population characteristics of DOX have been calculated by Launay et al. [18] based on a sampling schedule ranging from 5 min to 24 h and according to an open two-compartment model. Validation was obtained by comparing the clearance values computed using MLE estimation and those computed by BE. We found that the mean terminal half-live for the population that has been proposed by Launay et al. [18], 12.4 h, was very short as compared with the values reported in the literature [15, 31]; this population did not enable the proper estimation of individual half-life values, whereas the clearance values were correct.

Our study was undertaken in a group of 28 patients who received between 1 and 7 brief infusions of DOX, and blood samples were obtained on each occasion. Successive courses were repeated every 3 or 4 weeks, and the total number of courses was 68. In all, 30 courses were used to estimate the population characteristics of DOX according to an open three-compartment model and to determine a limited sampling schedule [4, 7, 17]. The remaining courses were used to validate this methodology; for this purpose, the values obtained for the computed elimination-phase parameters and for the residual plasma level at 48 h using either MLE or BE on a limited sampling protocol were compared.

Materials and methods

Patient population

A total of 28 patients were included in the study. None of the subjects had previously been treated with DOX or with radiotherapy. Their renal and liver functions were investigated by biological and clinical evaluation, and their cardiac function (ECG, echocardiogram, and/or angioscintigraphy) was also checked. None of the patients showed signs of renal or hepatic disfunction. Informed consent was obtained from each patient for every treatment course. The patients' characteristics and prior chemotherapy regimens are summarized in Table 1.

Drug administration and doses

DOX was infused in a peripheral vein by brief infusion over a period ranging from 5 to 15 min; in six courses the duration of infusion was 25 min (patient GON, four courses; patients TIX and VAS, one course each). The delivered dose varied from 25 to 75 mg/m^2 and remained the same for each patient over the treatment period. Courses were repeated every 4 weeks. Administration of the other drugs given was carried out at least 18 h after the DOX infusion.

Blood sampling

Blood samples were collected in tubes coated with ethylenediaminetetraacetic acid (EDTA) at the end of each infusion and at 10, 20 and 40 min and 1, 2, 4, 6, 12, 24, 36 and 48 h afterwards. 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 until its use; plasma analysis was performed during the subsequent 2 weeks.

Analytical method

Concentrations of DOX were determined in all samples by high-pressure liquid chromatography (HPLC) with fluorescence detection using a previously described method [22], with modifications as follows. DOX 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 used was a spherisorb phenyl (25 cm × 4.6 mm inside diameter; particle size, 5 μm) column. The mobile phase (acetonitrile: 0.03 M citrate buffer adjusted to pH 4 with formic acid; 30:70, v/v) was run isocratically at a flow rate of 1.5 ml/min. Drugs were detected using a Perkin-Elmer fluorometer (model LS-1; excitation wavelength, 480 nm; emission wavelength, 590 nm). The detection limit was 0.5 ng/ml for DOX. The within-day and between-day variation of the assay was 4.5% and 8.9%, respectively.

Pharmacokinetic analysis

Estimation of individual pharmacokinetic parameters by MLE. For 62 courses, the plasma concentration of DOX versus time followed a tri-compartmental exponential decay ($n = 3$) expressed as:

$$c(t) = \Sigma \frac{D \times A_i}{\lambda_i \times T \times V_1} (e^{\lambda_i T} - 1) \times e^{-\lambda_i t} \text{ when } t > T, \quad (1)$$

where D is the infused dose, V_1 is the volume of the central compartment, T is the duration of infusion, A_i is the macrocoefficient, and λ_i is the rate constant;

$$c(t) = \Sigma c_i \times e^{-\lambda_i t}, \text{ and} \quad (2)$$

$$c_i = \frac{A_i}{V_1} \times \frac{D}{T} \times \frac{(e^{\lambda_i T} - 1)}{\lambda_i}. \quad (3)$$

For the six remaining courses, the results were consistent with an open two-compartment body model ($n = 2$); comparison of competing models was done using the Fisher test. On these six occasions, the venous access was difficult and blood samples obtained from this patient between 1 and 12 h were inadequate (four instead of five). In this case, when the data were analyzed according to a three-compartment model, the coefficients of variation of the coefficient and the exponent of the initial elimination phase were very high, and the model that minimized the Fisher test was the two-compartment body model.

With zero-order input, the pharmacokinetic parameters were estimated by the MLE method using an error model proportional to $c(t)$ [weight (w) = $1/c(t)$] [28]. A maximal likelihood estimator chooses the set of estimates of model parameters for which the probability of the data is highest [25].

Estimation of population characteristics. Population characteristics were evaluated using the standard two-stage method [26]. This technique consists of estimating individual pharmacokinetic parameters for 30 selected courses in 18 patients and then computing the mean parameters, the covariance matrix describing the interindividual variability, and the coefficient of variation of the residual error. The 30 data sets selected included those from all 18 first courses and those from 12 other randomly selected courses (1 course for 6 of these subjects and 2 different courses for subjects 4 and 7). The 30 courses evaluated for these patients represented the number beyond which the introduction of another course would not have significantly changed the pharmacokinetic parameters obtained for the population.

Estimation of individual pharmacokinetic parameters by BE. The other courses ($n = 38$) were used to estimate the performance of BE associated with a limited sampling protocol.

Numerical calculation. MLE and BE calculations were performed by means of a general software package named APIS [12]; it is written in C language and is supported by an IBM PS computer.

Table 1. Patients' characteristics

Patients/sex	Age (years)	Diagnosis	Treatment[a]	Courses (*n*)	DOX (mg)	Infusion time[b] (h)
1 QUA/M	48	Lung carcinoma-SC	VAC-CIS-VP	4	90	0.25
2 LOP/M	61	Lung carcinoma-SC	VAC	1	80	0.23
3 GON/M	68	NHL	CHOP-Bleo	6	75	0.17 (2) 0.42 (4)
4 BOU/M	70	Lung carcinoma-SC	VAC-VP16	7	75	0.25 (3) 0.17 (4)
5 TIX/M	66	CLL	CHOP	5	40	0.25 (4) 0.42 (1)
6 COM/F	55	NHL-DLSCC	CHOP-Bleo	6	80	0.17 (4) 0.25 (2)
7 VAS/M	51	NHL-DLCC	CHOP-Bleo	6	70	0.25 (5) 0.42 (1)
8 IZA/M	65	NHL-DLC	AVCB	3	130	0.17
9 JAR/F	55	Breast cancer	AVCF	1	70	0.17
10 MOR/F	43	Breast cancer	FAC	2	80	0.17
11 ROB/M	31	Hodgkin's disease	ABVD	1	45	0.17
12 DUR/F	63	NHL-DLC	m-BACOD	2	70	0.17
13 DEN/F	60	Ovarian carcinoma	AVEC	4	70	0.083
14 BAB/F	51	Breast cancer	AVCF	1	60	0.17
15 AUJ/M	61	NHL-DSCC	m-BACOD	3	75	0.17
16 PUI/M	69	Hodgkin's disease	ABVD	1	48	0.17
17 GAR/F	66	Breast cancer	AVCF	3	70	0.17
18 DEG/F	65	NHL-DMC	m-BACOD	1	40	0.17
19 WAR/M	60	Liver cancer	DOX	1	70	0.17
20 SALA/M	58	Liver cancer	DOX	1	70	0.17
21 CAZ/M	68	Liver cancer	DOX	1	70	0.17
22 TEI/M	57	Liver cancer	DOX	1	70	0.17
23 MAR/M	55	Liver cancer	DOX	1	70	0.17
24 LAV/M	69	Liver cancer	DOX	2	70	0.17
25 PUP/F	59	Liver cancer	DOX	1	50	0.17
26 LOP/M	53	Liver cancer	DOX	1	70	0.17
27 SAL/F	31	Liver cancer	DOX	1	70	0.17
28 GAU/F	78	Liver cancer	DOX	1	70	0.17

[a] The different coadministered drugs were given at least 18 h after DOX infusion

[b] Values in parentheses represent the number of courses

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-cells; m-BACOD, methotrexate/bleomycin/doxorubicin/cyclophosphamide/vincristine/dexamethasone; VAC-VP16, vincristine/doxorubicin/cyclophosphamide/VP16; CHOP-Bleo, cyclophosphamide/doxorubicin/vincristine/prednisone/bleomycin; AVCF, doxorubicin/vindesine/cyclophosphamide/5-fluorouracil; AVCB, doxorubicin/vindesine/cyclophosphamide/bleomycin/methyl-prednisolone; Cis, cisplatin; AVEC, doxorubicin/VM26/cyclophosphamide/cisplatin; FAC, 5-fluorouracil/doxorubicin/cyclophosphamide; ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; VP16, etoposide; VM26, teniposide

Sampling time. The population data enabled us to choose sampling times so as to study the variation of the observation function with respect to the variation of a given parameter. The study of the parameter sensitivity function consisted of:

1. Computing the partial derivative of the observation function with respect to each value for λ_i and A_i/V_1 (i = 1,2,3):

$$U = \frac{d\,c(t)}{d\,\lambda_i} \quad \text{and} \tag{4}$$

$$W = \frac{d\,c(t)}{d\,A_i/V_1} \tag{5}$$

where $c(t)$ is given by Eq. 1, and

$$U = \frac{D \times A_i}{T \times V_1 \times \lambda_i^2}\, e^{-\lambda i t} \{e^{\lambda i T} [\lambda_i (T - t) - 1] + \lambda_i t + 1\} \quad \text{and} \tag{6}$$

$$W = \frac{D}{T \times \lambda_i} (e^{\lambda i T} - 1)\, e^{-\lambda i t} \tag{7}$$

2. Computing the partial derivatives of U and W with respect to time:

$$V = \frac{dU}{dt} \tag{8}$$

with a constant experimental error (w = 1),

$$V = \frac{D \times A_i}{\lambda_i \times T \times V_1}\, e^{-\lambda i t} (-t + t \times e^{\lambda i T} - T \times e^{\lambda i T}), \tag{9}$$

$$Z = \frac{dW}{dt}, \tag{10}$$

with a constant experimental error (w = 1),

$$Z = -\frac{D}{T} (e^{\lambda i T} - 1)\, e^{-\lambda i t} \tag{11}$$

The sampling times are those for which the equations for V and Z become equal to zero [4, 7, 17]. In the present study, we also computed an experimental error proportional to $c(t)$ [w = $1/c(t)$].

Statistical analysis

Choice of the pharmacokinetic parameters used to evaluate the performance of MLE and BE estimations. In a preliminary study, the individual pharmacokinetic parameters computed using the BE procedure along with the population characteristics published by Launay et al. [18] and a reduced sampling protocol (two blood samples) were compared for each course with those computed using the MLE method. The total body clearance values computed by BE and MLE for DOX were in the same range, showing a variation of 5.6%–20%, but the elimination-phase parameters differed markedly, showing a variation of 56%–70%. For example, for the seventh course of subject 7, the total body clearance was found to be 37.3 and 35.4 l/h by BE and MLE, respectively; the $t_{1/2}$ elimination value was 11.5 h as determined by BE, whereas that found using the MLE method was 35.7 h. We decided to use the A_3/V_1, the terminal elimination half-life, and the concentration at 48 h instead of total body clearance to compare the performance of MLE and BE estimations.

Evaluation of the results. The performance of BE in parameter prediction was assayed by computing:

1. The coefficient of variation (CV):

$$\frac{|P_{MLE} - P_{BE}|}{P_{MLE}} \times 100,$$

where P_{MLE} is the parameter determined by MLE and P_{BE} is that determined by the BE procedure

2. The estimation of bias or mean prediction error (ME):

$$\text{Bias} = \frac{1}{N} \sum_{i=1}^{i=n} [P_{BE}(i) - P_{MLE}(i)] \quad (12)$$

3. The estimation of precision or root mean square error (RMSE) according to Sheiner and Beal [26, 27]:

$$\text{Precision} = \sqrt{\frac{1}{N} \sum_{i=1}^{i=n} [P_{BE}(i) - P_{MLE}(i)]^2} \quad (13)$$

(In these expressions, the index i refers to the individual patient number, and N is the total number of patients involved in the study. Confidence intervals for bias and precision were also computed).

4. Statistical comparisons between the MLE and the BE analyses of the pharmacokinetic parameters (A_3/V_1, $t_{1/2}$ elimination, and $c_{48\,h}$) were performed using Student's paired t-test.

Results

Population characteristics

Population characteristics computed for the population group from the 30 concentration-time curves are summarized in Table 2. From these characteristics, it can be seen that λ_1 was the parameter exhibiting the lowest coefficient of variation (CV, 19.5%) and A_2/V_1 was that displaying the highest one (CV, 99.8%). The mean and standard deviation (SD) for the parameters of the terminal log-linear phase were $A_3/V_1 = 3.458 \times 10^{-4} \pm 1.73 \times 10^{-4}$ l^{-1} (CV, 50%) and $t_{1/2} = 33.62 \pm 12.3$ h (range, 22.1–82.2 h; CV, 36.5%).

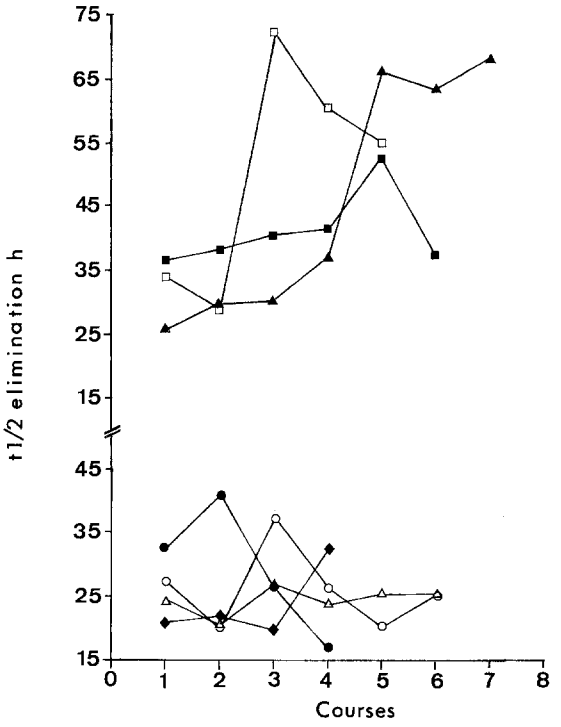

Fig. 1. Intraindividual variation of DOX $t_{1/2\ elim.}$ from course to course for patients TIX ($n = 5$, □), VAS ($n = 6$, ■), BOU ($n = 7$, ▲), COM ($n = 6$, ○), DEN ($n = 4$, ●), GON ($n = 6$, △), and QUA ($n = 4$, ◆). n, Number of successive courses

Intraindividual variation of the pharmacokinetic parameters

Large intraindividual variations in DOX kinetics were observed. All of the pharmacokinetic parameters increased or decreased at ramdom, showing CV values ranging from 6% to 57% [15]. Figure 1 shows the variation of DOX $t_{1/2}$ elimination ($t_{1/2\ elim.}$) obtained for the seven patients who received at least four successive courses.

Table 2. Population characteristics computed from 30 concentration-time curves

A_1/V_1 (l^{-1})	7.148×10^{-2}	2.035×10^{-3}				
A_2/V_1 (l^{-1})	9.68×10^{-4}	2.195×10^{-5}	9.3415×10^{-7}			
A_3/V_1 (l^{-1})	3.458×10^{-4}	1.473×10^{-6}	8.743×10^{-8}	2.99×10^{-8}		
λ_1 (h^{-1})	7.604	4.325×10^{-2}	4.336×10^{-4}	1.602×10^{-5}	2.205	
λ_2 (h^{-1})	5.262×10^{-1}	2.77×10^{-3}	1.189×10^{-4}	1.753×10^{-5}	1.361×10^{-1}	5.842×10^{-2}
λ_3 (h^{-1})	2.061×10^{-2}	-1.585×10^{-5}	1.453×10^{-6}	9.048×10^{-7}	1.347×10^{-3}	9.215×10^{-4}, 5.651×10^{-5}

Residual error: 1.199×10^{-1}

The mean value for each parameter is shown in the first column. The variance-covariance matrix follows; the variance of each parameter (squared standard deviation) is presented on the diagonal of the matrix and the covariances are shown in the lower triangle

Table 3. Bias, precision, and coefficient of variation after Bayesian estimation using t_1, t_2, and t_4

	Bias (ME)	Precision (RMSE)	CV %
A_3/V_1 (l^{-1})	-0.408×10^{-4} (-0.832×10^{-4}; 0.0164×10^{-4})	1.34×10^{-5} (0.477×10^{-5}; 2.2×10^{-5})	32.53 ± 26.8
$t_{1/2}$ elim. (h)	1.77 (0.34; 3.2)	17.45 (11.97; 22.99)	36.62 ± 31
$c_{48\ h}$ (ng/ml)	−1.33 (−2.33; −0.317)	2.31 (0.363; 4.26)	21.6 ± 16.69

The values in parentheses represent the 95% confidence intervals

Sampling times

For each course, the corresponding reduced sampling times were computed using Eqs. 6 and 7 as corrected for the weight factor $[1/c(t)]$ and taking into account the true infusion time. For example, for T = 0.17 h, the sampling times were 0.17, 0.55, 1.4, and 3.2 h (+ ∞). To check the consistency of the results obtained based on the assumption of a variance of experimental error proportional to $c(t)$ $[w = 1/c(t)]$, the previous calculation was repeated assuming a constant experimental error ($w = 1$); in this case, for T = 0.17 h, the sampling times computed were 0.17, 0.23, 1.98, and 48.6 h (+ ∞). Due to practical reasons of feasibility and compliance, BE was performed using only three points (t_1 = 0.17 h, t_2 = 1.5 h, and t_4 = 48 h, when T = 0.17 h); for each course, the closest points among the available observations were taken. Due to the large interval between t_2 and t_4, we decided to apply the alternative four-point sampling protocol, by which an additional sample is taken at t_3 = 24 h. This strategy was used for kinetic reasons so as to identify better the kinetic parameters of the terminal elimination curve.

Evaluation of BE pharmacokinetic parameter prediction

The 38 concentration-time curves that were not used to estimate the population characteristics were applied to compute the A_3/V_1, $t_{1/2}$ elimination, and $c_{48\ h}$ values according to the BE procedure.

Results obtained using t_1, t_2, and t_4. Using the population characteristics and the three theoretical sampling times, the mean pharmacokinetic parameters computed by BE were $A_3/V_1 = 2.74 \times 10^{-4} \pm 1.28 \times 10^{-4}$ l^{-1} (range, $0.609 \times 10^{-4} - 5.36 \times 10^{-4}$ l^{-1}), $t_{1/2}$ elimination = 40.1 ± 8.65 h (range, 23.7–58.5 h), and $c_{48\ h}$ = 5.2 ± 3.84 ng/ml (range, 1.26–15.72 ng/ml). These values were close to those determined using MLE: $3.1 \times 10^{-4} \pm 1.42 \times 10^{-4}$ l^{-1} (range, $0.852 \times 10^{-4} - 6.29 \times 10^{-4}$ l^{-1}), 34.03 ± 14.9 h (range, 17.1–95.9 h), and 6.52 ± 4.54 ng/ml (range, 0.83–19.35 ng/ml), respectively.

Using Student's paired t-test, slightly statistically significant differences (P <0.05) were found between the MLE and the BE estimates of DOX $t_{1/2}$ elimination (t = −2.155) and $c_{48\ h}$ (t = 0.549). No significant difference was found for A_3/V_1. The performance of BE in pharmacokinetic parameter prediction as expressed by bias and precision are given in Table 3. The analysis of mean error (ME) did not reveal a significant bias for A_3/V_1. The DOX elimination half-life was overestimated by BE (ME, 1.77 h), and the plasma concentrations at t = 48 h were underestimated (ME, −1.33 ng/ml); the confidence intervals confirmed that bias was slightly significant (P <0.05).

Table 4. Percentage of error between MLE and BE estimates of the parameters

CV %	Number of cases					
	A_3/V_1		$t_{1/2}$ elim.		$c_{48\ h}$	
	3 points	4 points	3 points	4 points	3 points	4 points
<10	9	29	12	29	15	27
10–25	13	9	11	9	15	9
25–50	13	0	8	0	6	2
50–80	3	0	4	0	2	0
>90	0	0	3	0	0	0

Using these three points, the Bayesian procedure enabled a good estimation of individual pharmacokinetic parameters for subjects whose $t_{1/2}$ elimination ranged from 26 to 50 h. In the other cases ($t_{1/2}$, <26 or >50 h), the BE estimates were not correct (CV, >50%).

Analysis of the individual data revealed that for the terminal half-life, for A_3/V_1 and for $c_{48\ h}$, the percentage of error (CV) between the MLE and the BE estimates ranged from <10% to 90% (n = 3 cases; Table 4).

Results obtained using t_1, t_2, t_3, and t_4. Using the population characteristics and four individual plasma DOX determinations, the mean pharmacokinetic parameters computed by BE were $A_3/V_1 = 3.11 \times 10^{-4} \pm 1.35 \times 10^{-4}$ l^{-1} (range, $0.904 \times 10^{-4} - 6.55 \times 10^{-4}$ l^{-1}), $t_{1/2}$ elimination = 34.4 ± 13.4 h (range, 17.9–86.9 h), and $c_{48\ h}$ = 6.3 ± 4.38 ng/ml (range, 0.843–18.76 ng/ml). For all these parameters, the mean values obtained using BE were close to those determined by MLE.

Using Student's paired t-test, we found no statistically significant differences between the MLE and the BE analyses. The performance of BE in pharmacokinetic parameter prediction as expressed by bias and precision are given in Table 5. No significant bias was found, and the precision was much better than that obtained using the three-point

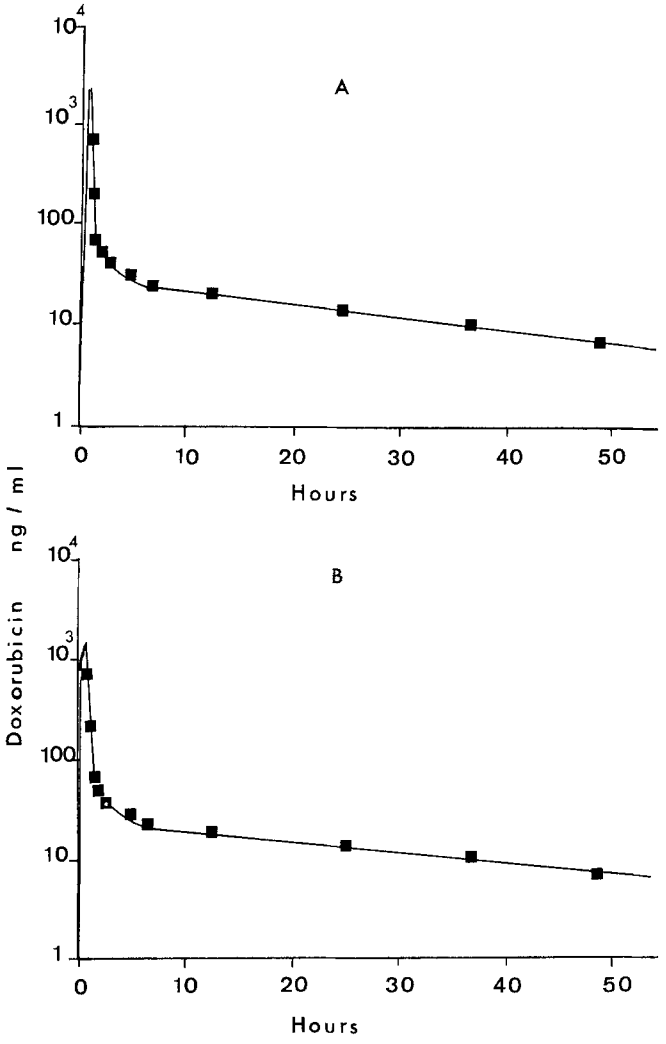

Fig. 2 A, B. Plasma DOX levels observed in patient COM at a dose of 80 mg (sixth course). **A** MLE procedure; the data were fitted to a three-compartment model. **B** BE procedure

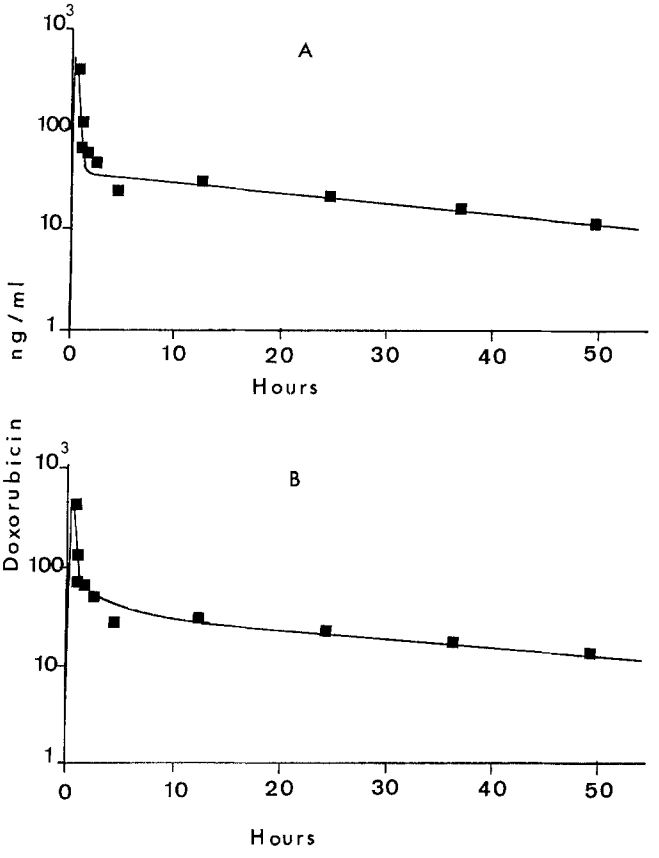

Fig. 3 A, B. Plasma DOX levels observed in patient COM at a dose of 80 mg (third course). **A** MLE procedure; the data were fitted to a two-compartment model. **B** BE procedure

sampling strategy. Analysis of the individual data revealed that for the terminal half-life, for A_3/V_1 and for $c_{48\ h}$, the percentage of error (CV) between the MLE and the BE estimates ranged from <10% to 50% ($n = 2$ cases; Table 4).

As an example, the DOX concentration versus time curves obtained when the data of one subject were fitted using either the MLE or the BE procedure are shown in Fig. 2.

For six courses, the pharmacokinetic parameters were estimated by MLE using a two-compartment model that minimized the Fisher test, although the goodness of the fit seemed to be better for the three-compartment model. The Bayesian approach together with the same population characteristics found for the other courses was a good predictor of parameter estimation for these six courses (Fig. 3).

Discussion

In many clinical situations, including hepatic impairment and obesity of patients associated with difficult venous

Table 5. Bias, precision, and coefficient of variation after Bayesian estimation using t_1, t_2, t_3 and t_4

	Bias (ME)	Precision (RMSE)	CV %
A_3/V_1 (l^{-1})	-0.0315×10^{-4} (-0.132×10^{-4}; 0.0695×10^{-4})	0.304×10^{-5} (0.245×10^{-5}; 0.363×10^{-5})	7.78±6.01
$t_{1/2\ elim.}$ (h)	0.0839 (−1.03; 1.19)	3.34 (0.52; 6.16)	7.41±5.83
$c_{48\ h}$ (ng/ml)	−0.22 (−0.480; 0.04)	0.659 (0.437; 0.882)	8.69±6.34

The values in parentheses represent the 95% confidence intervals

access, the determination of DOX pharmacokinetic parameters may be relevant [16, 24]. The BE procedure is of great clinical interest because it minimizes the number of blood samples required. DOX population characteristics were estimated according to an open three-compartment model in the present study. The evaluated population was representative enough to exhibit interindividual variability.

The present report describes a method for the estimation of individual pharmacokinetic parameters for each patient using the BE procedure following a brief infusion of DOX. BE was compared with the classic MLE procedure, and the coefficient A_3/V_1, the half-life of elimination, and the residual plasma level at 48 h were chosen so as to evaluate the performance of the Bayesian procedure. The main reason for the choice of these three parameters, all of which are related to the elimination of DOX, was that the terminal phase of DOX elimination is the most critical aspect of this drug's pharmacokinetics, since it controls the drug accumulation process and is more sensitive to assay. The precision of the prediction of these three parameters (0.304×10^{-5} l^{-1}, 3.34 h, and 0.659 ng/ml, respectively) remained lower than the interindividual standard deviation (1.42×10^{-4} l^{-1}, 14.9 h, and 4.54 ng/ml, respectively). The ratios of precision/standard deviation were 0.0214, 0.224, and 0.145, respectively.

These low values showed that the Bayesian procedure is a good predictor of estimated pharmacokinetic parameters in very different subjects belonging to the same population. The total clearance value found using the proposed BE procedure was always very close (46.95 ± 15.64 l/h) to that determined by the reference procedure (46.52 ± 13.94 l/h). The sampling times used were either exactly those computed for the study of the sensitivity function (three points) or those in addition to an extra sampling point at 24 h. The application of the three-sample strategy, with only one point lying in the terminal phase, yielded enough information that we could compute the elimination half-life using the BE procedure for subjects whose pharmacokinetic parameters lay within the range of population characteristics computed in this study. This procedure did not enable the accurate determination of this parameter for subjects exhibiting $t_{1/2}$ elimination values that were lower (<26 h) or higher (>50 h) than the range established for the overall population. The four-sample strategy, which included two points in the terminal elimination phase, gave better results in all cases.

Conclusions

This approach is a good method for the efficient estimation of pharmacokinetic parameters at a minimal clinical cost and for subsequent determination of the optimal dosage required to achieve the desired plasma concentrations in a given patient. When DOX is given by brief i.v. infusion, the population characteristics obtained in the present study can also be used for the adaptive control of the drug dosage during a long-term continuous infusion of DOX so as to obtain a given steady-state plasma level, as has previously been done by Iliadis et al. using methotrexate [13, 14] and cisplatin [13].

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