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ORIGINAL ARTICLE

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A population model of epirubicin pharmacokinetics and application to dosage guidelines

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Abstract *Purpose*: To use a population approach to identify readily available clinical or biochemical characteristics that influence the pharmacokinetics of epirubicin and to develop new dosage guidelines based on these results. *Methods*: Data were available from 109 patients with advanced breast cancer, 72 of whom were known to have liver metastases. They were treated with single-agent epirubicin 12.5 to 120 mg/m^2. Analysis was performed using the software package NONMEM and a three-compartment model was fitted to the data. *Results*: Individual clearance (CL) estimates ranged from 4 to 86 l/h and the final model included CL as a function of aspartate aminotransferase (AST): CL (l/h) = 72.9−(72.9×0.135×lnAST). Inclusion of this factor reduced the interindividual variability in CL from 49% to 39%. Using a target AUC of 4000 ng·h/ml, the following doses were predicted to achieve this exposure with the greatest precision: AST < 150 IU/l 125 mg; AST 150–250 IU/l 90 mg; AST 250–500 IU/l 60 mg; AST > 500 IU/l 30 mg. These new guidelines were compared with three other guidelines based on serum bilirubin or AST concentrations and body surface area (BSA). The new guidelines achieved the target with greater precision (root mean squared error, rmse, 39.0%) than the current UK guidelines, current USA guidelines or an earlier equation based on AST (rmse 63%, 62% and 59%, respectively). *Conclusions*: The proposed dosing guidelines should reduce variability in systemic exposure to epirubicin more effectively than traditional approaches. In addition, as they do not require adjustment according to BSA, they could reduce dosage preparation time and the potential for prescribing and dispensing errors.

Keywords Epirubicin · Population pharmacokinetics · Liver dysfunction

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Introduction

Epirubicin is a cytotoxic anticancer agent of the anthracycline group that is structurally identical to that of its prototype, doxorubicin, except for the spatial orientation of the hydroxyl group at the 4′ position of the daunosamine sugar [17]. Epirubicin is active against a range of tumours [15] and is widely used in the treatment of women with early or advanced breast cancer, administered either alone or in combination with other anticancer agents [4].

The plasma concentration-time profile of epirubicin is best described by a triexponential equation [2, 22]. Although plasma clearance (CL) of epirubicin is rapid (50 l/h/m^2), the terminal half-life is relatively long (30 h) due to the large volume of distribution of epirubicin (1000 l/m^2) [16].

As epirubicin is predominantly cleared by the liver, patients with hepatic metastases and impaired liver function may have reduced clearance [2]. The current product label recommends a reduction in the dose of epirubicin for patients with liver dysfunction based primarily on bilirubin concentration [8]. In addition,

epirubicin doses are routinely adjusted according to body surface area (BSA), although Gurney et al. [12] did not find any relationship between BSA and any pharmacokinetic parameter. Twelves et al. [21] identified aspartate aminotransferase (AST) as a more sensitive and reliable marker of epirubicin clearance than bilirubin in 52 women with advanced breast cancer. Their studies suggested that the current guidelines may not be optimal for patients with hepatic disease and they proposed a dosage equation based on AST and BSA [7]. In the present study, the data set previously evaluated by Twelves et al. [7, 21] was extended to include a total of 109 patients. The pharmacokinetics of epirubicin were then assessed using a population approach to identify the clinical and biochemical factors that best described epirubicin clearance and would consequently influence dosage requirements.

Methods

Patient data

Data were collated from three trials that were performed at Guys Hospital, London. There were 109 patients in total, some of whom were included in studies described previously [7, 21]. The studies were approved by the local ethics committee and all patients gave written informed consent. Epirubicin was given as a single agent administered as a rapid intravenous infusion (median 3 min, range 0.4 to 19 min) to women with advanced or metastatic breast cancer. Trial 1 comprised 50 women with liver biochemistry tests that were either normal or minimally disturbed (AST not more than 2.5 times above the upper limit of the reference range and bilirubin within the reference range); epirubicin 12.5–120 mg/m^2 was given once every 3 weeks. In trial 2, a total of 23 women with radiologically proven liver metastases received weekly epirubicin at a dose of 25 mg/m^2. The 36 women in trial 3 had liver metastases and received epirubicin at doses of 20 to 75 mg/m^2 every 3 weeks, according to their serum AST and performance status.

In all cases, blood samples were collected for the measurement of epirubicin concentration following the first cycle of treatment. The mean number of blood samples collected from each patient was 12 (range 8 to 18). Typical blood sampling times were predose then 6, 10, 15 and 30 min and 1, 2, 4, 6, 12, 24 and 48 h after dosing. The plasma was separated and stored at −20°C until analysis. Epirubicin plasma concentrations were then determined by HPLC as previously described [6].

Population analysis

Data were analysed with NONMEM version V using the first-order conditional estimation method with interaction (FOCE-INTER) [1], although some exploratory analyses were performed with the first-order method (FO). Two- and three-compartment models with zero order input were fitted to the data. NONMEM was used to estimate the pharmacokinetic parameters of the structural model and the random effects models, i.e. interpatient variability and residual variability. Interpatient variability (η) of the pharmacokinetic (PK) parameter estimates was assumed to correspond to a log-normal distribution, described as follows:

$$PK_i = P_k \times \exp(\eta_{ik})$$

where PK_i represents the kth pharmacokinetic parameter for the ith individual and P_k is the typical population estimate of parameter (e.g. CL or V_1) and η_{ik} is the individual deviation from the population parameter (P_k). A full variance-covariance (Ω) matrix was used. The following residual error models were compared:

- Additive: $c_{ij} = pred_{ij} + \varepsilon_{ij}$
- Proportional: $c_{ij} = pred_{ij} + pred_{ij}\varepsilon_{ij}$
- Combined: $c_{ij} = pred_{ij} + pred_{ij}.\varepsilon_{ij} + \varepsilon_{2ij}$

where c_{ij} is the measured concentration at the jth sampling time in the ith individual, $pred_{ij}$ is the predicted concentration at the jth sampling time in the ith individual and ϵ_{ij} and ϵ_{2ij} are residual error terms. The models were compared by examining the objective function values (OFV) and plots of weighted residuals against time.

Potential relationships between pharmacokinetic parameters and covariates were investigated by visual inspection of scatter plots and statistical analysis by Generalized Additive Modelling (GAM) using the software packages Xpose version 3.0 [14] and S-plus 2000 (MathSoft International, Bagshot, UK). In the GAM analysis each covariate was included as a linear regression model in a stepwise manner, and if found to be statistically significant was then included as a natural cubic spline with one internal breakpoint. Individuals who had any missing covariate information were excluded from the GAM analysis. Individuals with high leverage and/or Cook's values were removed from the data set and the GAM analysis was repeated [3]. Covariates identified from the scatter plots and from the top three models of the GAM analysis as influencing epirubicin CL were investigated using NONMEM. Subjects with missing covariates were excluded. Covariates were added as linear or nonlinear functions as judged appropriate from the scatter plots. Following the addition of a covariate to the model, a fall in OFV associated with a value of $P < 0.05$ was required (3.84, one degree of freedom) [1]. The covariate with the greatest influence on CL, as judged by the largest fall in OFV, was retained in the model and the other covariates were then added into the model singly, again retaining the covariate combination with the lowest OFV. This was repeated until all identified covariates were added into the model or until there was no further statistically significant reduction in OFV. Covariates were then included in the models for other pharmacokinetic parameters using the same approach. Changes in interindividual variability were also examined and covariates that produced a negligible improvement in interpatient variability were removed from the model. If the final model for a PK parameter included a covariate, the prediction errors (P_{ei}) of the PK parameter estimates in the basic and final model were calculated as follows:

$$P_{ei}(\%) = (P_{ki} - PK_i)/P_{ki} \times 100$$

where P_{ki} is the population estimate of the PK parameter for the ith individual and PK_i is the empirical Bayesian estimate of the PK parameter for the ith individual. The root mean squared prediction error (rmse), which describes the imprecision of the population PK parameter estimates, was calculated from the square-root of the mean squared P_{ei} (%) (mse) values [20], that is:

$$mse = \frac{1}{N}\sum_{i=1}^{N} pei^2 \quad rmse = \sqrt{mse}$$

The mean prediction error (me), which describes the bias of the estimates, was calculated from the average of the P_{ei} (%) values.

Development and assessment of new dosage guidelines

In clinical practice, a nadir total white blood cell (WBC) count of 1–2×10^9/l would be typical in women receiving palliative chemotherapy for metastatic breast cancer. Applying the relationship between WBC and AUC previously described by Jakobsen et al. [13], a target epirubicin AUC of 4000 ng·h/ml was calculated to produce this nadir. Dosage guidelines to achieve this target AUC were subsequently developed from the population model. The standard dose for patients with normal liver function was set at 125 mg, calculated from the current recommended dose of 75 mg/m^2 multiplied by the median BSA of the patients (1.65 m^2). Using the relationship CL = dose/AUC, the CL estimates that would require 100%, 75%, 50% and 25% of this standard dose (i.e. 125, 90, 60 and 30 mg) to attain the target AUC of 4000 ng·h/ml were calculated. These CL estimates were found to be 32, 22.5, 15 and 7.5 l/h. CL

values in the middle of these ranges, i.e. 27.25, 18.75 and 11.25 l/h, together with the population model for CL, were used to determine the AST concentrations required for dosage alteration.

Using the proposed new dosage guidelines, the expected AUC values (AUC_i) for patients in the current data set were then calculated using the following formula:

$$AUC_i = Dose/CL_i$$

where dose was entered according to the proposed dosage scheme and CL_i is the individual Bayesian estimate for CL estimated from the NONMEM analysis.

The expected AUC values were estimated in a similar manner using doses suggested by the current UK guidelines for epirubicin [8], current USA guidelines [9] and according to the dosage scheme previously developed by Dobbs et al. [7]. All current guidelines recommend adjusting dose according to BSA. In addition, the UK guidelines state that the standard dose of 75 mg/m^2 should be reduced by 50% if the bilirubin concentration is 24–51 μmol/l and by 75% if the bilirubin concentration is >51 μmol/l. The USA guidelines suggest a standard dose of 110 mg/m^2 with a 50% reduction if bilirubin concentrations are 20–51 μmol/l or AST concentrations are 86 to 172 IU/l. A 75% dose reduction is recommended if bilirubin concentrations are >51 μmol/l or AST concentrations are >172 IU/l. The dosage equation developed by Dobbs et al. [7] was intended for patients with abnormal liver biochemistry and is also based on AST: dose (mg/m^2) = target AUC (97.5−34.2×$\log_{10}$AST).

The percentage prediction error (P_{ei}) of the AUC_i estimates relative to the target AUC was calculated as follows:

$$P_{ei}(\%) = (AUC_i - \text{targetAUC}) \times 100/\text{targetAUC}$$

where AUC_i is the individual estimate of AUC for the ith individual, given each set of dosage guidelines. The rmse and me of the AUC estimates, relative to the target AUC, were calculated as described previously. A paired two-sided *t*-test was performed to test if the difference in rmse between the new proposed guidelines and the other guidelines was statistically significant ($P < 0.05$). The 95% confidence intervals (CI) were calculated for me [20]. The predicted AUC values were considered significantly biased if the 95% CI excluded zero.

Results

Patient data

Summary statistics of patient demographics and clinical characteristics are displayed in Table 1. Of the 109 patients, 21% had bilirubin levels above the reference range, 69% had AST levels above the reference range and 69% had alkaline phosphatase levels above the reference range. Creatinine and albumin levels were generally within the reference range; only 6% of patients had albumin concentrations below the reference range and 7% had creatinine concentrations above the reference range.

Population analysis

The two-compartment model did not converge successfully using FOCE-INTER, so the structural component of the model was assessed using FO only. Plots of the weighted residuals versus time showed a more symmetrical pattern about the *x*-axis for the three-compartment model compared to the two-compartment model. The residual error was best described by a proportional model and interindividual variability could only be estimated on CL, intercompartmental CL between compartments 1 and 3 (Q_3) and volume of compartment 3 (V_3). Individual concentration measurements adjusted for a dose of 75 mg/m^2, and a typical concentration-time profile simulated using the basic population pharmacokinetic parameters, are illustrated in Fig. 1. Figure 2 shows the population and individual predicted concentrations that were obtained using the selected model plotted against the observed concentration measurements. Individual Bayesian estimates of CL ranged from 4 to 86 l/h.

The GAM analysis identified AST, dose, creatinine clearance, BSA and weight as influencing CL. Bilirubin was not selected in the top three or even the top ten GAM models as a statistically significant covariate influencing CL. Liver metastases, dose and albumin were identified as influencing Q_3 and AST, albumin, bilirubin and height were identified as influencing V_3. Four patients with missing covariates were excluded, leaving a total of 105 patients whose data were analysed using NONMEM. A summary of the OFVs obtained for the principal models tested is given in Table 2. The largest fall in OFV (56.4) was observed following inclusion of the natural log of AST into the model for CL. Including bilirubin as a covariate in the CL model resulted in a fall in the OFV of 12.1, and there was no statistically significant fall in the OFV when creatinine clearance was included in the CL model. The full model included CL as a function of lnAST, dose, BSA and liver metastases, Q_3 as a function of ln dose and liver metastases and V_3 as a function of bilirubin, albumin and height. AST accounted for approximately 10% of the interindividual variability in CL, whereas other covariates each accounted for less than 2% of the inter-

Table 1 Summary of demographics and clinical characteristics of patients

	No. of patients	Reference range	Median	Range	*n*
Dose (mg)			78	20–228	109
Age (years)			57	35–79	109
Height (cm)			157	132–175	108
BSA (m^2)			1.65	1.25–2.2	108
Weight (kg)			62.8	37–89	108
Percent of ideal body weight			110	71–157	108
Bilirubin (μmol/l)		<23	10	1–282	109
AST (IU/l)		<43	90	7–815	109
Creatinine (μmol/l)		50–130	82	47–167	104
Albumin (g/l)		30–46	36.5	25–54	106
Alkaline phosphatase (IU/l)		<255	403	61–2972	108
WHO performance status					
0	11				
1	47				
2	41				
3	10				
Liver metastases present	72				109

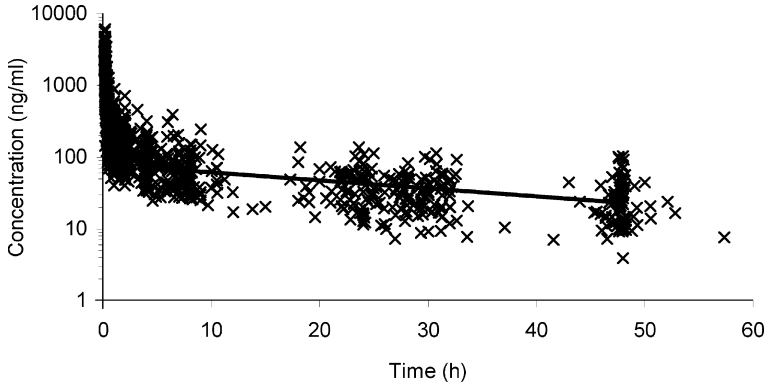

Fig. 1 Measured concentration data adjusted for a dose of 75 mg/m^2 plotted versus time. The *solid line* represents a typical concentration-time profile following a dose of 75 mg/m^2 assuming the population parameters estimated using the basic model

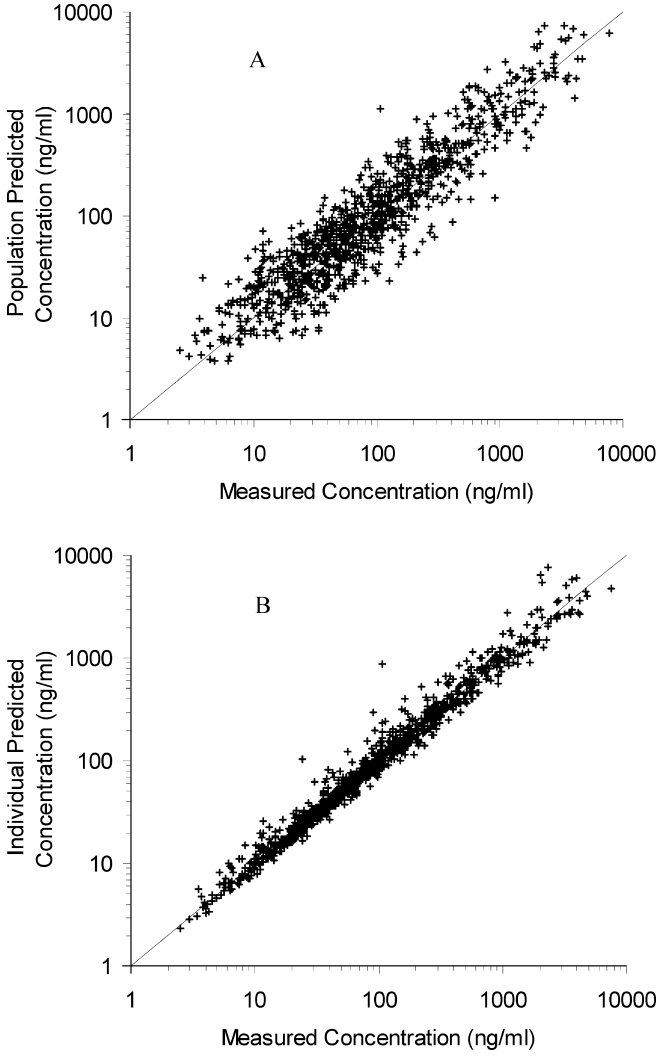

Fig. 2A, B Model-predicted epirubicin concentrations against observed concentrations: **A** population predicted vs observed concentrations; **B** individual predicted versus observed concentrations

Table 2 Summary of models tested in the population analysis (*CL* clearance, V_3 volume of compartment 3, Q_3 intercompartmental CL between compartments 1 and 3, *ALB* albumin, *AST* aspartate aminotransferase, *BILI* bilirubin, *BSA* body surface area, *HGT* height, *LMETS* liver metastases, *WHO* World Health Organization performance status, *OFV* objective function value)

Model no.	CL model	OFV	ΔOFV[a]	Compare with model no.
0	Base model	8035		
1	ln AST	7978	56.4	0
2	Dose	8007	27.1	0
3	LMETS	8016	18.5	0
4	BILI	8022	12.1	0
5	WHO	8026	9.0	0
6	ln AST + dose	7975	3.4	1
7	ln AST + LMETS	7973	5.5	1
8	ln AST + LMETS + dose	7967	5.9	7
9	ln AST + LMETS + dose + BSA V_3 model	7962	4.6	8
10	HGT	7958	4.0	9
11	BILI	7957	5.2	9
12	BILI + HGT	7953	3.9	11
13	BILI + HGT + ALB Q_3 model	7948	4.6	12
14	LMETS	7938	10.0	13
15	LMETS + ln dose	7931	7.8	14

[a]Fall in OFV of 3.84 is required for statistical significance ($P < 0.05$, one degree of freedom), except WHO performance status for which a fall in OFV of 7.81 is required for statistical significance ($P < 0.05$, three degrees of freedom)

individual variability and were, therefore, considered not clinically significant. Likewise, the covariates that were identified for Q_3 and V_3 each reduced interindividual variability on these parameters by less than 2%. Thus, the final model included CL as a function of lnAST only: CL (l/h) = 72.9−[72.9×0.135×lnAST (IU/l)]. The relationship between CL and AST is illustrated in Fig. 3, and population parameter estimates from the basic, full and final models are presented in Table 3. When the imprecision (rmse) of population CL estimates was calculated relative to Bayesian CL estimates, there was an improvement from 53% in the basic model to 44% following the inclusion of AST in the final model. The bias (me) in the estimates also improved from −13% in the basic model to −11% in the final model.

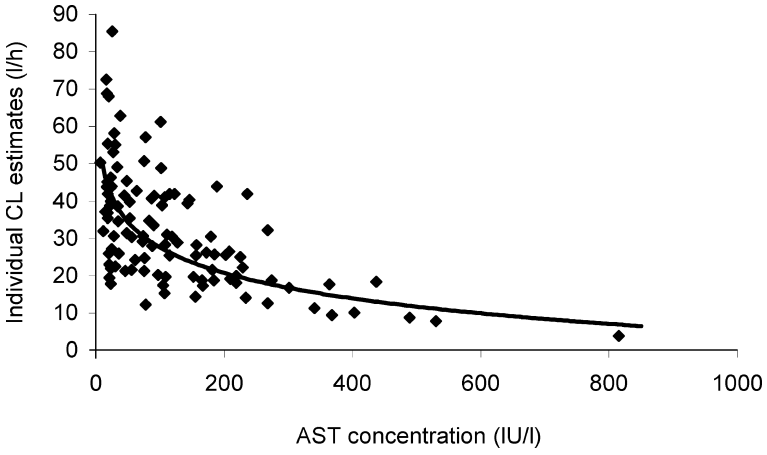

Fig. 3 Individual CL estimates (l/h) plotted against AST concentrations (IU/l) fitted with the population model equation for CL (*solid line*)

Development and assessment of new dosage guidelines

The AST concentrations associated with the mid-way CL values were determined from the population model for CL and used to define new dosage guidelines (Table 4). AUC could not be estimated using the earlier equation [7] for one patient with an AST level of 815 IU/l because the dose becomes negative at AST concentrations above 709 IU/l.

The bias (me) with 95% CI of the AUC values calculated for the proposed new guidelines was −0.1% (−3.7, 7.4%), compared with 0.9% (−11.2, 13.0%), 4.9% (−7.0, 16.8%) and 18.9% (8.3, 29.5%) for the current UK guidelines, USA guidelines and the earlier equation [7] respectively. The imprecision (rmse) of the AUC values relative to the target was 39% for the new proposed guidelines compared with 63%, 62% and 59% for the current UK guidelines, USA guidelines and the earlier equation [7], respectively. A paired *t*-test indicated that the improvement in rmse observed with the new proposed guidelines compared to the UK guidelines, USA guidelines and the earlier equation was statistically significant, with *P*-values of 0.045, < 0.001 and < 0.001, respectively.

Discussion

The purpose of this analysis was to identify clinical characteristics that influence epirubicin clearance and to propose improved dosage guidelines. The most important findings of the current study are that a population-based approach has confirmed that AST has a significant impact on epirubicin pharmacokinetics but that BSA does not have an identifiable effect. These results have been used to develop a simplified epirubicin dose modification scheme based on serum AST alone.

The current UK epirubicin dosing guidelines recommend a reduction in dose of 50% in patients with moderately elevated serum bilirubin and 75% reduction in patients with severely elevated bilirubin [8]. In our study, however, bilirubin was not identified in the top ten models for CL by the GAM analysis. Moreover, inclusion of bilirubin level in the NONMEM analysis resulted in a fall in the OFV value that was smaller than that observed when AST or the presence of liver metastases were included in the model. Patients with liver metastases generally had bilirubin levels within the reference range but AST concentrations above the reference range. This indicates that AST may be a more sensitive marker of liver damage than bilirubin for such patients and that dosage adjustments based on bilirubin may not be ideal. It should be noted that patients with liver biochemistry within the reference range were not routinely scanned for liver metastases. Consequently, some women with normal liver biochemistry may have had unidentified liver metastases.

The comparison of the various dosage guidelines in this analysis assumes that the target AUC selected is appropriate. However, as the equation developed by Dobbs et al. [7] can be used for any AUC target and the UK and USA guidelines gave predicted AUC values that were not significantly biased relative to the target AUC, it would appear that this target is appropriate, at least for comparative purposes. The USA guidelines resulted in an average AUC that was approximately 5% greater than the target AUC. Since the standard epirubicin dose recommended in the USA is approximately 50% higher than in the UK, it is surprising that the USA guidelines produced an average AUC that was only 5% above the target. However, the USA guidelines tended to achieve AUC values above the target in patients with normal AST concentrations but below the target in patients with moderately elevated AST levels. This may have been due to the recommended dose reduction of 50% in patients with AST concentrations two to four times the upper limit of the reference range. As the present analysis suggests that a reduction of only 0–25% is required for such patients, it appears that the USA doses for patients with moderately elevated AST concentrations are too low. It should be noted that the evaluation of the dosage guidelines by their ability to minimize rmse assumes a linear relationship between AUC and response. Hence, for example, a 20% pre-

Table 3 Population pharmacokinetic parameter estimates for epirubicin from basic, full and final models [*RSE* relative standard error; *AST* aspartate aminotransferase; *BSA* body surface area; *LMETS* liver metastases; *BILI* bilirubin; *HGT* height; *ALB* albumin; ωCL, ωQ_3, ωV_3 interindividual variability (CV) for CL, V_3 and Q_3, respectively; σ residual variability (CV)]

		Basic		Full		Final	
		Estimate	RSE (%)	Estimate	RSE (%)	Estimate	RSE (%)
CL (l/h)	θ_1	29.0	5.1	81.0	19.3	72.9	8.0
V_1 (l)	θ_2	10.3	8.3	10.2	8.4	10.3	8.2
Q_2 (l/h)	θ_3	29.8	13.0	29.8	12.9	30.2	12.7
V_2 (l)	θ_4	34.9	16.6	35.5	16.4	35.7	16.1
Q_3 (l/h)	θ_5	61.5	6.3	22.0	60.0	61.5	6.1
V_3 (l)	θ_6	754	5.6	360	34.7	772	5.4
Ln AST (CL)	θ_7	–	–	0.139	5.4	0.135	4.5
DOSE (CL)	θ_8	–	–	0.00424	41.3	–	–
BSA (CL)	θ_9	–	–	0.276	20.3	–	–
LMETS (CL)	θ_{10}	–	–	1.45	10.3	–	–
BILI (V_3)	θ_{11}	–	–	−0.00193	17.4	–	–
HGT (V_3)	θ_{12}	–	–	−0.00381	21.4	–	–
ALB (V_3)	θ_{13}	–	–	0.0115	18.8	–	–
Ln DOSE (Q_3)	θ_{14}	–	–	0.317	101	–	–
LMETS (Q_3)	θ_{15}	–	–	1.29	6.8	–	–
ωCL (%)		49.5	15.5	34.4	16.1	39.4	14.3
ωQ_3(%)		34.6	18.4	31.4	18.6	34.4	17.8
ωV_3(%)		43.6	23.2	40.1	21.9	42.7	22.4
σ (%)		23.2	9.2	23.1	9.2	23.2	9.3

Full model: $TVCL = \theta_1*(1-\theta_7*(\text{lnAST})*(1+\theta_8*\text{DOSE})*(1-\theta_9*\text{BSA})$ if liver metastases present $*\theta_{10}$
$TVQ_3 = \theta_5*(1+\theta_{14}(\text{lnDOSE})$ if liver metastases present $*\theta_{15}$
$TVV_3 = \theta_6*(1+\theta_{11}*\text{BILI})*(1+\theta_{12}*\text{HGT})*(1-\theta_{13}*\text{ALB})$
Final model: $TVCL = \theta_1*(1-\theta_7*(\text{lnAST}))$

Table 4 New dosage guidelines for epirubicin based on AST concentration

AST (IU/l)	Dose (mg)	Dose (% normal)
< 150	125	100
150–250	90	75
250–500	60	50
> 500	30	25

diction error is twice as great as a 10% error, an assumption that may not be true if there is a non-linear relationship between AUC and response. Furthermore, as AUC values above and below the target AUC have been given equal weighting in this analysis, it does not account for the potentially different consequences of under and over dosing.

The variability in AUC, as measured by rmse relative to the target AUC, attained using the UK [8] and USA [9] guidelines and the earlier equation [7], was approximately 60%, but fell to less than 40% using the guidelines derived from the present analysis. This improvement was statistically significant. Of the 105 patients, the estimated AUC value evaluated with the new AST guidelines was between 3000 and 5000 ng·h/ml in 54 patients, compared to 39 patients with the current UK dosage guidelines, 37 patients with the USA dosage guidelines and 35 patients with the earlier equation.

The apparent improvement using the new guidelines compared to the earlier equation is likely to have been due to the larger number of patients used in their development (105 compared to 16) and the potential benefits of using a mixed effect model over the two-stage approach [19]. It is recognized that the apparent improvement in bias and precision following the inclusion of AST in the population model for CL, calculated using post-hoc CL estimates, may give an exaggerated sense of the model's validity as the same patient data were used for model development and validation. Further validation is required using an external dataset before definite conclusions can be drawn regarding the performance of this model. The dataset used in this study was derived from the first cycle of treatment only. It was not possible, therefore, to ascertain whether the pharmacokinetics and/or pharmacodynamics of epirubicin are affected by treatment period, nor to predict how well these guidelines would perform over several treatment cycles.

The difficulties in attaining the target AUC, even with the proposed new guidelines, reflect the high unexplained interindividual variability of CL. The basic model used in the current population analysis identified the interindividual variability in CL as 49%. In the final model that included an influence of AST on CL, interindividual variability only fell to 39%, indicating that a large amount of variability was not explained by the final model. However, inclusion of three additional covariates in the CL model only accounted for a further 5% of the interindividual variability in CL. It is possible that the data set used was too small to identify all the sources of variability, or that unknown factors, such as diet or genetic differences in metabolic enzymes, are also important. Consequently, it may not be feasible to consistently achieve the optimum systemic exposure

to epirubicin simply by using clinical characteristics to determine the dose. An alternative approach would be to explore an adaptive feedback dosing strategy. However, as there is currently resistance to adaptive feedback strategies due to the cost, time and impracticalities involved, it is important that dosage guidelines are practical and effective.

The earlier equation based on AST [7] along with the current UK and USA guidelines include dose adjustment according to BSA, as is the usual convention in oncology; however, adjustment for BSA is omitted from the proposed new guidelines. The scientific rationale for dose adjustment according to BSA is unclear for most cytotoxics [11] including epirubicin [5, 12]. Administration of a dose in milligrams rather than milligrams per metre squared, as proposed in this study, would be advantageous, as adjusting dose according to BSA is time-consuming and prone to prescribing and dispensing errors [10]. No positive relationship between BSA and CL of epirubicin was observed in this study, and this is consistent with the findings of previous studies [5, 12]. Indeed, a weak negative relationship was observed between CL and BSA. This is difficult to explain physiologically, although a negative relationship between CL and ideal body weight has previously been observed for doxorubicin [18].

In conclusion, the dosage guidelines developed in the current study, which were based solely on serum AST, achieved AUC values that were closer to the target and with lower variability than current UK and USA dosage guidelines and a previous equation based on AST [7]. Dose administration in milligrams rather than milligrams per metre squared may be a further advantage of the proposed scheme as it could reduce dose preparation time and dosing errors. Prospective evaluation of these new dosage guidelines is warranted.

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References

1. Beal SL, Sheiner LB (1992) NONMEM (user's guide), parts 1-VII. Technical Report, University of California, San Francisco
2. Camaggi CM, Strocchi E, Tamassia V, Martoni A, Giovannini M, Iafelice G, Canova N, Marraro D, Martini A, Pannuti F (1982) Pharmacokinetic studies of 4′-epi-doxorubicin in cancer patients with normal and impaired renal function and with liver metastases. Cancer Treat Rep 66:1819
3. Cook RD (1977) Detection of influential observation in linear regression. Technometrics 19:15
4. Coukell AJ, Faulds D (1997) Epirubicin. An updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of breast cancer. Drugs 53:453
5. Dobbs NA, Twelves CJ (1998) What is the effect of adjusting epirubicin doses for body surface area? Br J Cancer 78:662
6. Dobbs NA, Twelves CJ (1991) Measurement of epidoxorubicin and its metabolites by high-performance liquid chromatography using an advanced automated sample processor. J Chromatogr 572:211
7. Dobbs NA, Twelves CJ, Gregory W, Cruickshanka C, Richards MA, Rubens RD (2003) Epirubicin in patients with liver dysfunction: development and evaluation of a novel dose modification scheme. Eur J Cancer 39:580–586
8. Epirubicin Product Label, UK (2003) http://emc.vhn.net
9. Epirubicin Product Label, USA (2003) www.fda.gov/cder/foi/label/1999/50778lbl.pdf
10. Favier M, deCazanove F, Saint Martin F, Bressolle F (1994) Preventing medication errors in antineoplastic therapy. Am J Hosp Pharm 51:832
11. Grochow LB, Baraldi C, Noe D (1990) Is dose normalization to weight or body surface area useful in adults? J Natl Cancer Inst 82:323
12. Gurney HP, Ackland S, Gebski V, Farrell G (1998) Factors affecting epirubicin pharmacokinetics and toxicity: evidence against using body-surface area for dose calculation. J Clin Oncol 16:2299
13. Jakobsen P, Basholt L, Dalmark M, Pfeiffer P, Petersen D, Gjedde SB, Sandberg E, Rose C, Nielsen OS, Mouridsen HT (1991) A randomised study of epirubicin at four different dose levels in advanced breast cancer. Feasibility of myelotoxicity prediction through single blood-sample measurement. Cancer Chemother Pharmacol 28:465
14. Jonsson EN, Karlsson MO (1999) Xpose—an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 58:51
15. Plosker GL, Faulds D (1993) Epirubicin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cancer chemotherapy. Drugs 45:788
16. Robert J (1994) Clinical pharmacokinetics of epirubicin. Clin Pharmacokinet 26:428
17. Robert J (1993) Epirubicin. Clinical pharmacology and dose-effect relationship. Drugs 45:20
18. Rodvold KA, Rushing DA, Tewksbury DA (1988) Doxorubicin clearance in the obese. J Clin Oncol 6:1321
19. Sheiner LB, Beal SL (1980) Evaluation of methods for estimating population pharmacokinetic parameters I. Michaelis-Menten model: routine clinical pharmacokinetic data. J Pharmacokinet Biopharm 8:553
20. Sheiner LB, Beal SL (1981) Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 9:503
21. Twelves CJ, Dobbs NA, Michael Y, Summers LA, Gregory W, Harper PG, Rubens RD, Richards MA (1992) Clinical pharmacokinetics of epirubicin: the importance of liver biochemistry tests. Br J Cancer 66:765
22. Weenan H, Lankelma H, Penders PGM, McVie JG, Ten Bokkel Huinink WW, de Planque MM, Pinedo HM (1983) Pharmacokinetics of 4′-epi-doxorubicin in man. Invest New Drugs 1:59