Cancer Chemother Pharmacol (1992) 29: 391–395

Cancer Chemotherapy and Pharmacology

Variability in the pharmacokinetics of epirubucin: a population analysis

Janet R. Wade[1], Andrew W. Kelman[2], David J. Kerr[3], Jacques Robert[4], and Brian Whiting[1]

[1] Department of Medicine and Therapeutics, University of Glasgow, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT, UK
[2] Department of Clinical Physics and Bioengineering, West of Scotland Health Boards, 11 West Graham Street, Glasgow, G4 9LF, UK
[3] CRC Department of Medical Oncology, University of Glasgow, Alexander Stone Building, Garscube Estate, Glasgow, G61 1BD, UK
[4] Fondation Bergonié, 180, Rue de Saint Gènes, 33 076 Bordeaux Cedex, France

Received 9 March 1991/Accepted 27 September 1991

Summary. Population pharmacokinetic analysis of the anticancer agent epirubicin was carried out using the program NONMEM. Data were available from 36 patients aged 20–73 years, of whom 23 were women. All subjects exhibited normal liver and renal function. Epirubicin was given as a short-term i.v. infusion over the dose range of 25–100 mg/m^2, and an average of 11 plasma samples/subject were taken for a period of up to 72 h after each dose. A Two compartment model was fitted to the data, characterised by the parameters clearance, volume of the central compartment, alpha and beta. Clearance was tested as a linear function of various demographic and/or biochemical features. A significant proportion of the variability in clearance could be attributed to sex, and also to age in women. For example, a 25-year-old man would display an average clearance of 95 l/h, whereas a 70-year-old woman would exhibit an average clearance of 64 l/h. Such differences in clearance might be important in the selection of epirubicin dose regimens.

Introduction

In common with other anticancer drugs [6, 10, 15], epirubicin shows a large degree of pharmacokinetic variability that may have extremely serious consequences in cancer chemotherapy. For example, Eksborg [4] reported an almost 10-fold intersubject variability in plasma epirubicin area under the curve (AUC) values when these had been normalised for dose.

Epirubicin is a stereoisomer of doxorubicin and exerts its antitumour activity via a similar mechanism. Previous work has revealed an identifiable relationship between dose and response, and clinical studies have shown epirubicin to be as effective as doxorubicin but to exhibit less toxicity at comparable doses [3]. The reduced cardiotoxicity observed for epirubicin has been attributed to differences in its metabolic degradation [14]. A study of the treatment of nasopharyngeal carcinoma found that responders exhibited lower epirubicin clearance values than did non-responders, emphasising the clinical importance of pharmacokinetic variability. However, further analysis failed to show any relationship between clearance and any other identifiable factor in the 28 patients studied [8].

The aim of the present study was to explore further and characterise the pharmacokinetic variability of epirubicin. The population pharmacokinetic data-analysis program NONMEM [1] was used. This program enables the quantification of the relationships between pharmacokinetic parameters and several pathophysiological features exhibited by a group of patients receiving this drug.

Patients and methods

Patients

Data on plasma drug concentrations were available from 36 patients, including 23 women and 13 men. All subjects had received epirubicin in a short infusion as part of a combined chemotherapy course, with the epirubicin being given at 1–2 h prior to initiation of the remaining therapy. Nine of the women had breast cancer and received 50 mg/m^2. Of the patients who suffered from Hodgkin's lymphoma, five received 35 mg/m^2 and five were given 25 mg/m^2. Among the 17 subjects who exhibited a sarcoma, 16 received 100 mg/m^2 and the remaining patient was given 50 mg/m^2. All infusions were given over 3–20 min, the median duration of administration being 5 min. For measurements of epirubicin concentration, blood samples were drawn at the end of the infusion and for a further 48 h. Five patients were also sampled at 72 h. A total of 10–12 samples were obtained from each patient, giving a total of 419 concentration-time data points for the population analysis.

Demographic and biochemical data included those on sex, age, weight and serum levels of creatinine and bilirubin. The distribution of weight and age for men and women is shown in Fig. 1. The age ranged from 20 to 73 years and the weight, from 49 to 90 kg. The ranges for serum creatinine and bilirubin were 40–119 and 2–19 μmol/l, respectively; all patients showed values within the normal ranges.

Offprint requests to: J. R. Wade, Dept. Biopharm. Pharmacokin., BMC Box 580, Uppsala, S-75123, Sweden

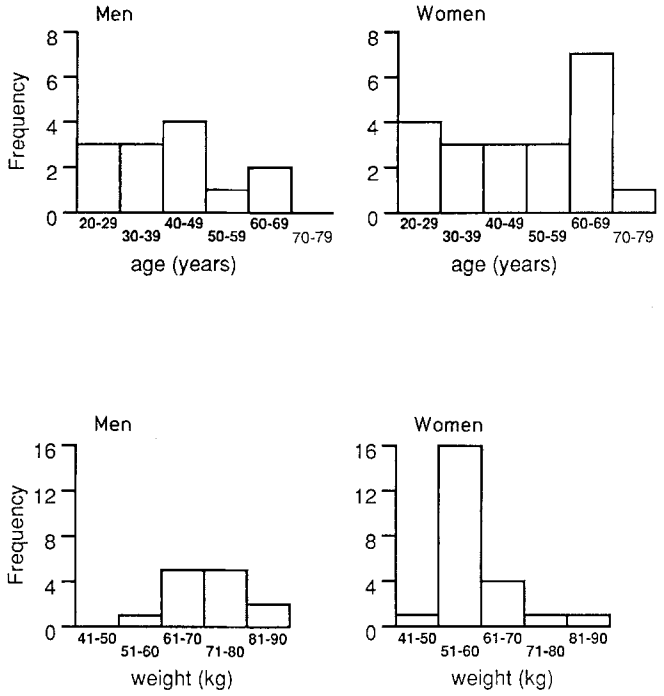

Fig. 1. Distribution of age (*upper panels*) and weight (*lower panels*) for men and women

Epirubicin analysis

Blood samples were drawn into ethylenediaminetetraacetic acid (EDTA)-coated Vacutainer tubes, immediately centrifuged and stored frozen until required for analysis. Epirubicin was extracted by a solid-phase extraction technique and quantified by HPLC using fluorescence detection as previously described [9, 13]. The limit of sensitivity of the assay was 2 ng/ml.

Population pharmacokinetic analysis

Average values for pharmacokinetic model parameters. The concentration-time data obtained from all subjects were analysed using the NONMEM program [1], which enables the pharmacokinetic parameters of a model to be estimated and the relationships between those parameters and the pathophysiological features of a group of patients to be quantified in a single step. This contrasts with traditional pharmacokinetic analysis, which is conducted in two stages: (1) the different individuals' pharmacokinetic parameters are characterised and (2) relationships between the pharmacokinetic parameters and the pathophysiological data are sought, usually via simple or multiple linear regression.

Previous pharmacokinetic analysis of these and other epirubicin data have almost always used a three-compartment model [3, 14, 18]. However, visual inspection of the pooled concentration-time data for all subjects indicated that a two-compartment model might be alternatively applied. Using NONMEM, both models were tested. As the three-compartment model could not be justified statistically, the two-compartment model was used as the basis for investigating the influence of various demographic factors on the pharmacokinetics of epirubicin. The parameters of this model were clearance (*Cl*), the volume of the central compartment (V_c) and the rate constants associated with the distribution and elimination phases, termed alpha and beta, respectively.

We tested the influence of the available demographic and biochemical factors by relating them to the pharmacokinetic parameters using linear models of the type

$$Pk = \Theta_1 \cdot Fac_1 + \Theta_2 \cdot Fac_2 + ,\ldots, + \Theta_n \cdot Fac_n, \quad (1)$$

$$C = \frac{Ro}{(\alpha-\beta)}\left[\frac{\beta}{Cl} - \frac{1}{Vc}\right](e^{-\alpha\tau} - 1)\ e^{-\alpha t'} + \frac{Ro}{(\alpha-\beta)}\left[\frac{1}{Vc} - \frac{\alpha}{Cl}\right](e^{-\beta\tau} - 1)\ e^{-\beta t'}$$

$$Cl = \Theta_1 \cdot Fac_1 + \Theta_2 \cdot Fac_2 + ... + \Theta_n \cdot Fac_n$$

where Ro is the infusion rate, Cl is clearance, Vc is the volume of the central compartment, α and β are hybrid rate constants, τ is the length of the infusion, t' is the time elapsed since the end of the infusion, Fac_1, Fac_2 etc are identifiable patient factors (eg, age, weight, etc) and Θ_1, Θ_2 etc are a series of regression coefficients

Fig. 2. Example of the relationship between the pharmacokinetic model and the equation relating available demographic and biochemical factors to the pharmacokinetic parameters

where *Pk* is the expected value for the pharmacokinetic parameter (e.g. *Cl* or V_c) in any patient; Fac_1, Fac_2... are identifiable patient factors (e.g. age, weight); and Θ_1, Θ_2... are a series of regression coefficients.

Models that related age, weight, sex, and serum levels of creatinine and bilirubin to clearance were tested, as were those that related weight and sex to volume (Table 1). These models were embedded in the two-compartment pharmacokinetic model used (Fig. 2). NONMEM then estimated the Θ values (Eq. 1) and/or other kinetic parameters (if these were not specified as functions of demographic factors) simultaneously.

Variance parameters. The distribution of the pharmacokinetic parameters in the population may be characterised by either a normal or a log normal distribution. If the distribution of any pharmacokinetic parameter *Pk* is normal, the value for the *j*th individual may be described by

$$Pk_j = \overline{Pk} + \eta_{ij}, \quad (2)$$

where Pk_j is the value of the parameter (e.g. *Cl* or V_c) for the *j*th individual, Pk is the mean value of the parameter for the population and η_{ij} represents randomly, normally distributed errors exhibiting a mean value of zero and a variance of σ_{Pk}^2. If the Pk parameters are distributed log normally, the value for the *j*th individual is then given by

$$Ln(Pk_j) = Ln(\overline{Pk}) + \eta_{ij}. \quad (3)$$

Similarly, the residual (intrasubject) error in concentration may be described by either a normal or a log normal distribution. In the former case,

Table 1. List of models tested and log likelihood differences

Model number	cf.	LLD	*P*
Clearance models:			
1. $Cl = \Theta_1$		–	
2. $Cl = \Theta_1 + Wt \cdot \Theta_4$	1	0	NS
3. $Cl = \Theta_1 + Sex \cdot \Theta_4$	1	13.5	<0.005
4. $Cl = \Theta_1 + Age \cdot \Theta_4$	1	30.0	<0.005
5. $Cl = \Theta_1 + Bili \cdot \Theta_4$	1	0	NS
6. $Cl = \Theta_1 + Creat \cdot \Theta_4$	1	0	NS
7. $Cl = (\Theta_1 + Age \cdot \Theta_4)\ \sigma + (\Theta_5 + Age \cdot \Theta_6)\ ♀$	4	11.0	<0.005
8. $Cl = \Theta_1\ \sigma + (\Theta_4 + Age \cdot \Theta_5)\ ♀$	7	0	NS
9. $Cl = \Theta_1 + Dose \cdot \Theta_4$	1	0	NS
10. $Cl = \Theta_1 + SA \cdot \Theta_4$	1	0	NS
11. $Cl = \Theta_1 + Dose/m^2 \cdot \Theta_4$	1	0	NS
Volume models:			
12. $V_c = \Theta_2$		–	
13. $V_c = \Theta_2 \cdot Wt$	12	0	NA
14. $V_c = \Theta_2 \cdot Sex$	12	6.4	<0.025
15. $V_c = \Theta_2 \cdot Sex + \Theta_3 \cdot Wt$	14	0	NS

Bili, Bilirubin; cf., as compared with model number ...; Creat, creatinine; LLD, log likelihood difference; NA, not appropriate; NS, not significant; SA, surface area (m^2); Wt, weight

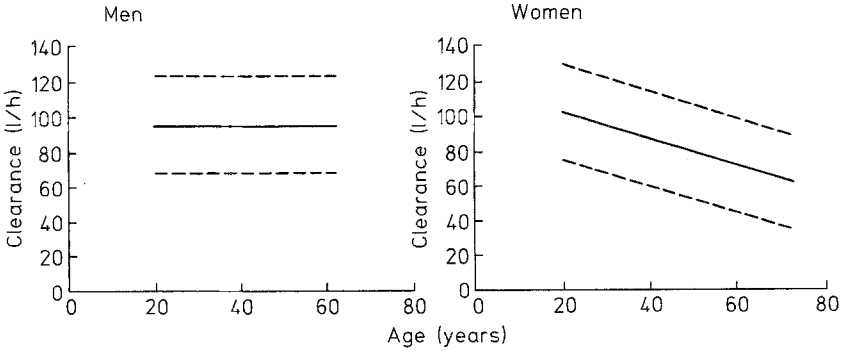

Fig. 3. Model predictions for the relationship of clearance to age (*solid line*) in men (*left panel*) and women (*right panel*) together with the intersubject variability (*dashed lines*)

Table 2. Parameter estimates and variability from NONMEM as related to models 8 and 14

Parameter estimates:						
Men		Women			Alpha (/h)	Beta (/h)
Cl (l/h)	V_c (l)	*Cl* (l/h) Slope	Intercept	V_c (l)		
95.2 (13.4)	37.7 (5.1)	–0.773 (0.19)	118 (13.5)	26.9 (3.1)	6.78 (0.82)	0.04 (0.003)
Variability estimates:						
		Cl (l/h)		V_c (l)	Beta (/h)	
Interindividual variability		27.4 (24.5)		7.4 (9.8)	0.016 (0.010)	
Intraindividual variability (%)			42.0 (17.0)			

Numbers in parentheses represent the standard error

$$c_{ij} = \hat{c}_{ij} + \varepsilon_{ij}, \quad (4)$$

where c_{ij} is the ith observed concentration for the jth subject; $\hat{c}_{ij}$ is the corresponding concentration expected, given the delivered dose and the subject's pharmacokinetic parameter values; and ε_{ij} is the residual error exhibiting a mean value of zero and a variance of σ_ε^2. The residual error incorporates true intrasubject variability, assay error, model misspecification and any remaining unexplained error.

The latter case, i. e. log normal error, may be described by

$$\mathrm{Ln}(c_{ij}) = \mathrm{Ln}(\hat{c}_{ij}) + \varepsilon_{ij}, \quad (5)$$

where the error increases in proportion to the measured concentration, as occurs with most assays.

In summary, NONMEM estimates (1) each Pk parameter or the regression coefficients (Θ in Eq. 1) linking the Pk parameters to the various factors under test, (2) the variance terms specified in Eqs. 2–5, and (3) the standard errors of all parameters.

Model selection

Because a series of models of the type specified by Eq. 1 are tested, model selection is an important part of the data analysis process. This is performed by using plots of weighted residuals and comparison of the log likelihood values. Both the residual plots and the log likelihood values are part of the NONMEM output. Hierarchical models (such as the initial comparison of the two- and three-compartment models) were compared by chisquare test ($P < 0.01$) of the difference between the log likelihood values obtained from fitting the full (three-compartment) vs the reduced (two-compartment) models [16]. This procedure was also applied to other hierarchical models such as (a) a model that incorporated clearance as a function of age and (b) a model that incorporated clearance without any explanatory factors. Non-hierarchical models (e. g. two different models for clearance, each of which includes a different single explanatory factor) were assessed by direct comparison of the log likelihood values. Different models for intersubject variability (Eqs. 2 and 3) and intrasubject variability (Eqs. 4 and 5) were also assessed by direct comparison of the log likelihood values.

Results

Comparison of the different variance models indicated that the additive model for intersubject variability (Eq. 2) and the proportional model for intrasubject variability (Eq. 5) were most appropriate for these data. The inclusion of sex as a factor in the model for clearance produced a significant reduction in variability (model 3). The same held true for age (model 4), and although the combination of age and sex (model 7) led to a further reduction in variability, age was a significant factor only in women (model 8). Relating clearance to total dose, surface area (m^2) or dose/m^2 did not help to explain the variability in clearance (models 9, 10 and 11, respectively). Sex significantly influenced volume (model 14), but neither weight (models 2 and 13) nor biochemical factors (bilirubin and creatinine; models 5 and 6, respectively) had any explanatory power.

Parameter estimates are shown in Table 2. No value is shown for the intersubject variability in alpha since the

data set did not contain sufficient information for the estimation of this parameter. For example, a 25-year-old man would show an average clearance of 95 l/h, whereas a 70-year-old women would exhibit an average clearance of 64 l/h [=118+(–0.773 × 70)]. The model predictions for the relationship of clearance to age in men and women together with the intersubject variability are shown in Fig. 3. Intrasubject/residual variability was reduced from 50% for the simplest model (models 1 and 12) to 42% for the best models (models 8 and 14).

Discussion

Variability in the pharmacokinetics of epirubicin was investigated in a population of patients exhibiting breast cancer, Hodgkin's lymphoma and sarcoma. In the 36 patients studied, age and sex contributed significantly to the explanation of variability in clearance. The age influence was significant only in women, probably due to the difference in the distribution of age for men vs women (Fig. 1). In all, 11/23 women were older than 50 years, whereas only 3/13 men were in this category. Therefore, there was insufficient information on an age-related effect in the group of men.

When no factors were included in considerations of clearance (model 1), the intersubject variability in this parameter (as a standard deviation) was 59 l/h. The inclusion of age and sex as factors in the clearance model reduced the intersubject variability from 59 to 27 l/h. Thus, a significant part of the variability in clearance was attributable to these factors.

The intrasubject variability was reduced from 50% for the simplest model to 42% for the final model. Nevertheless, the value of 42% is fairly high, which implies that other demographic and biochemical factors that were not included in the present analysis may also have contributed to the variability in epirubicin pharmacokinetics. However, it is not surprising that neither bilirubin nor creatinine influenced this variability; although epirubicin is eliminated principally by the hepatobiliary system [2], bilirubin levels proved to be normal. Previous work [2] showed that the plasma clearance of epirubicin was significantly reduced in patients displaying liver metastases, and the authors suggested that dose modification is required in such patients. The pharmacokinetics of epirubicin in five patients exhibiting impaired renal function has been studied by the same authors, who found a nonsignificant reduction in mean plasma clearance of epirubicin as compared with that observed in patients whose renal function was normal. However, this finding was attributable to a single patient; the four others showed values lying within the same range observed in the group with normal renal function.

The inclusion of dose (either as the total delivered dose or as the dose/m^2) in the model for clearance did not help to explain the variability in epirubicin pharmacokinetics. Vrignaud et al. [18] reported that they observed no dose dependency in the pharmacokinetics of epirubicin over the dose range of 25–50 mg/m^2. However, dose dependency has been reported for the dose range of 90–150 mg/m^2 by Tjuljandin et al. [17]. The results of the present study indicate that epirubicin pharmacokinetics are linear over the range of 25–100 mg/m^2.

Assay variability (interassay variability, 6%) is also included in the value of 42% but is obviously not the major cause of the high residual variability. This highlights the need for accuracy in the recording of all data – demographic, biochemical and pharmacokinetic (e.g. dose, timing of administration, times of sampling).

All patients received concomitant chemotherapy that included combinations of bleomycin, vinblastine, prednisone, 5-fluorouracil and cyclophosphamide. Remarkably few reports have dealt with a potential interaction between epirubicin and any of these drugs in man. Hartman et al. [7] have shown that cyclophosphamide pretreatment modifies the disposition of doxorubicin in rats. Natale et al. [11] have reported that doxorubicin and epirubicin seem to accelerate the excretion of cyclophosphamide. In the present study, all patients were given epirubicin at 1–2 h prior to initiation of the remaining therapy; however, this certainly does not rule out the possibility of an interaction that may have contributed to the observed variability in epirubicin pharmacokinetics.

In conclusion, future studies should include other demographic and biochemical indices such as smoking and concomitant drug therapy, and if there is a question about age-related changes in men, then more men in the older age groups should be included. This may enable some of the remaining 42% of variability to be explained. Patients exhibiting liver disease and renal impairment should also be studied to enable the quantification of any potential relationship between the disease state and the pharmacokinetics of epirubicin. Once a final model has been defined that satisfactorily explains the high variability in epirubicin pharmacokinetics, its validity should be checked in a separate group of patients; such a model may provide the basis for a more efficient approach to the selection of epirubicin dose regimens [5, 12].

References

1. Beal SL, Sheiner LB (1979, 1989) NONMEM (user's guide), parts I–VI. Technical report. Division of Clinical Pharmacology, 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 hepatic metastases. Cancer Treat Rep 66: 1819–1824
3. Cersosimo RJ, Hong WK (1986) Epirubicin: a review of the pharmacology, clinical activity, and adverse effects of an Adriamycin analogue. J Clin Oncol 4: 425–439
4. Eksborg S (1989) Pharmacokinetics of anthracyclines. Acta Oncol 28: 873–876
5. Evans WE, Relling MV (1989) Clinical pharmacokinetics-pharmacodynamics of anticancer drugs. Clin Pharmacokinet 16: 327–336
6. Evans WE, Crom WR, Abromowitch M, Dodge R, Look AT, Bowman P, George SL, Pui C-H (1986) Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. N Engl J Med 314: 471–477
7. Hartman N, Basseches PJ, Powis G (1982) Effect of cyclophosphamide pretreatment on the short-term disposition and biliary

excretion of Adriamycin metabolites in the rat. Cancer Chemother Pharmacol 10: 11
8. Hu OY-P, Chang S-P, Jame J-M, Chen K-Y (1989) Pharmacokinetic and pharmacodynamic studies with 4′-epi-doxorubicin in nasopharyngeal carcinoma patients. Cancer Chemother Pharmacol 24: 332–337
9. Israel M, Pegg WJ, Wilkinson PM, Garnick MB (1978) Liquid chromatographic analysis of Adriamycin and metabolites in biological fluids. J Liquid Chromatogr 1: 795–809
10. Milano G, Namer M, Boublil J-L, Khater R, Frenay M, Thyss A, Bourry J, Philip C, Renee N, Bruneton J-N (1987) Relationship between systemic 5-FU passage and response in colorectal patients treated with interhepatic chemotherapy. Cancer Chemother Pharmacol 20: 71–74
11. Natale N, Piazza E, Italia C, Trabattoni A, Luchini S (1983) The kinetics of anthracyclines in human plasma and tissues: daunomycin, doxorubicin and 4-′epidoxorubicin. Drugs Exp Clin Res IX: 775–779
12. Powis G (1985) Anticancer drug pharmacodynamics. Cancer Chemother Pharmacol 14: 177–183
13. Robert J (1980) Extraction of anthracyclines from biological fluids for HPLC evaluation. J Liquid Chromatogr 3: 1561–1572
14. Robert J, Vrignaud P, Nguyen-Ngoc T, Iliadis A, Mauriac L, Hurteloup P (1985) Comparative pharmacokinetics and metabolism of doxorubicin and epirubicin in patients with metastatic breast cancer. Cancer Treat Rep 69: 633–640
15. Rodman JH, Abromowitch M, Sinkule JA, Hayes A, Rivera GK, Evans WE (1987) Clinical pharmacodynamics of continuous infusion teniposide – systemic exposure as a determinant of response in a phase I trial. J Clin Oncol 5: 1007–1014
16. Sheiner LB, Rosenberg B, Marathe VV (1977) Estimation of population characteristics from routine clinical data. J Clin Oncol 5: 445–474
17. Tjuljandin SA, Doig RG, Sobol MM, Watson DM, Sheridan WP, Morstyn G, Mihaly G, Green MD (1990) Pharmacokinetics and toxicity of two schedules of high dose epirubicin. Cancer Res 50: 5095–5101
18. Vrignaud P, Eghball H, Hoerni B, Iliadis A, Robert J (1985) Pharmacokinetics and metabolism of epirubicin during repetitive courses of administration in Hodgkins' patients. Eur J Cancer Clin Oncol 21: 1307–1315