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Pharmacokinetic and pharmacodynamic studies with 4′-epi-doxorubicin in nasopharyngeal carcinoma patients

Oliver Yoa-Pu Hu[1], Shiu-Pei Chang[1, 2], Jer-Min Jame[2], and Kuang-Yao Chen[2]

[1] School of Pharmacy, National Defense Medical Center, Taipei, Taiwan, Republic of China
[2] Cancer Therapy Center, Veterans General Hospital, Taipei, Taiwan, Republic of China

Summary. The plasma pharmacokinetic profile of 4′-epi-doxorubicin (epirubicin) was investigated in 28 patients with nasopharyngeal carcinoma (NPC) after single i.v. rapid infusions. All patients had normal liver and renal functions. Plasma concentrations of the parent compound were specifically determined by a high-performance liquid chromatographic (HPLC) method, with UV detection at 254 nm. Plasma levels of the compound were fitted to a three-compartment open model; a triexponential decrease in plasma concentrations with a long terminal plasma half-life (44.8 ± 21.2 h) was observed in 27 patients. The respective mean (± SD) serum concentration at 72 h and the AUC, plasma clearance, and terminal elimination rate constant in complete responders were 7.67 ± 1.98 ng/ml, 4,002 ± 3,080 ng · h/ml, 26.6 ± 12.9 l/h · m^2, and 0.009 ± 0.007 l/h, whereas those in nonresponders were 4.96 ± 1.8 ng/ml, 1,88 ± 652.8 ng · h/ml, 44.4 ± 15 l/h · m^2, and 0.017 ± 0.006 l/h, respectively; these differences were significant ($P < 0.05$). Epirubicin produced a 52% response rate, including 6 patients with a complete response, 8 with a partial response, 11 with no change, and 2 with progressive disease. No relationship could be found between the various pharmacokinetic parameters and either leukopenia, age, or sex. These observations strongly suggest that plasma clearance may be one of the determining factors affecting the response or nonresponse of NPC patients to epirubicin, and a dose adjustment according to plasma clearance would probably increase the response rate.

Introduction

4′-Epi-doxorubicin (epirubicin) is one of the new doxorubicin analogs with antitumor activity that are synthesized in the Farmitalia Carlo Erba Laboratories [1, 2, 9]. Epirubicin is an epimer of doxorubicin, with a different configuration of the hydroxyl substituent in the 4′-C position of the amino sugar moiety (Fig. 1).

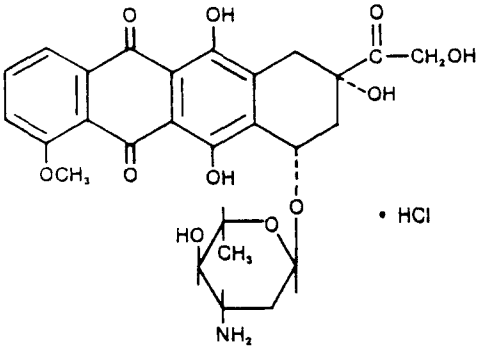
The mechanism of epirubicin's antitumor activity is similar to that of its stereoisomer doxorubicin, which intercalates into DNA and blocks protein synthesis. From in vitro experiments, Hill and Whelan [13] have emphasized the similarities in the cytotoxic and kinetic effects of doxorubicin and epirubicin in several human and murine cell lines [4]. Phase II clinical studies [14, 15, 21] have suggested that epirubicin was as effective as doxorubicin against a broad spectrum of human neoplasms with less hematologic or cardiac toxicity at comparable doses; moreover, the use of doxorubicin is limited by dose-related cardiomyopathy. Many pharmacokinetic studies of epirubicin have been done in animals [3] and human beings with a variety of cancers [4, 5, 7, 10, 12, 23, 24]. However, there have been no reports on the pharmacokinetics of epirubicin in patients with nasopharyngeal carcinoma (NPC). The incidence of NPC is rather high (4.82/million) in the Republic of China, and the prognosis is relatively poor (5-year survival, 34%) [6, 8]. We carried out a pharmacokinetic study in 28 NPC patients with normal liver and renal functions who received rapid i.v. infusions of epirubicin; the clinical response and eventual side effects were also monitored.

Materials and methods

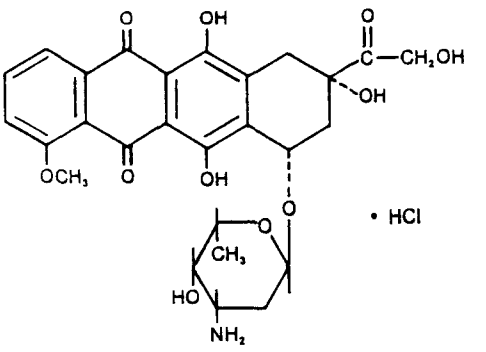
Patient selection. A total of 28 patients (8 women and 20 men) aged from 18 to 64 years (mean, 42.9 years), with a body surface of between 1.27 and 1.95 m^2 (mean, 1.6 m^2) and pathologically proven NPC were selected. All patients were evaluated by physical examination and laboratory evaluation, including blood chemistry [WBC count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count] and SMAC-25 [serum creatinine, SGOT, SGPT, blood urea nitrogen (BUN), alkaline phosphatase, bilirubin, total protein, blood sugar, and cholesterol]. All patients had normal laboratory data and none had third-space fluid accumulation. The clinical staging of these 28 patients according to Union International Contra le Cancrum (UICC) criteria was N2a-3b without distant metastasis. None had received chemotherapy and/or radiotherapy prior to epirubicin administration.

Chemicals. Epirubicin for clinical use, the pure analytic standard of epirubucin and daunorubicin (as internal standard), was kindly supplied by Farmitalia Carlo Erba (Taiwan branch); 1-heptanesulfonic acid, methanol (LC grade), chloroform, 1-heptanol, glacial acetic acid, and n-hexane were purchased from Merck and were of analytical grade.

Offprint requests to: Oliver Yoa-Pu Hu, P. O. Box 8244-14, School of Pharmacy, National Defense Medical Center, Taipei, Taiwan, Republic of China



Epirubicin hydrochloride



Adriamycin hydrochloride

Fig. 1. Chemical structures of epirubicin and adriamycin

Drug administration and blood sampling. The dose regimen was 75 mg/m^2 every 3 weeks. Epirubicin was dissolved in 100 ml normal saline and given as a rapid i.v. infusion for 10 min. Blood samples were drawn from a forearm vein without anticoagulant prior to drug administration and 0, 30, and 60 min as well as 3, 6, 24, 48, and 72 h after drug administration in the first cycle of treatment. Plasma was separated by centrifugation immediately after collection and the samples were frozen at −80° C until analysis. All patients underwent drug administration and blood withdrawal in an outpatient clinic.

Sample analysis. The epirubicin plasma concentration was determined by a modified high-performance liquid chromatographic (HPLC) method [20]. A 100-ng daunorubicin hydrochloride stock solution (internal standard) and 1 ml phosphate buffer (pH 8.4) were added to plasma and extracted with 8 ml chloroform:1-heptanol (9:1 vol/vol) by mechanical shaking for 30 min, then centrifuged at 3,500 rpm for 10 min. Following centrifugation, the upper aqueous layer was removed by aspiration to facilitate the transfer of the lower organic layer to another test tube and evaporated under nitrogen to a 2-ml volume, which was re-extracted with 0.2 ml 0.3 *M* phosphoric acid in a vortex mixer. The aqueous phase was again transferred into a centrifuge tube containing 2 ml n-hexane, vortexed, and centrifuged to remove nonpolar contaminants. A portion of 100- to 150-µl aliquot of the aqueous phase was injected directly into the chromatograph.

Chromatographic analysis was carried out on a Hewlett-Packard 1084B liquid chromatographic system with a model 450 variable wavelength detector (Waters Associates), Lichrosorb RP-18 column (7 µm, 25 cm × 4 mm internal diameter) (E. Merck; Darmstadt, FRG) and Hewlett-Packard recorder (79850B). The peak area was integrated and recorded. The mobile phase was methanol: water (7:3 vol/vol) plus 0.5% acetic acid and 2.5 m*M* sodium heptanesulfonic acid; the flow rate was 1.2 ml/min. The standard curve was constructed by adding epirubicin standard solution to pooled plasma from healthy donors. The detection wavelength was 254 nm, and the lowest limit of detection was 4 ng.

Pharmacokinetic analysis. By means of computer programs CSTRIP [25] and PCNONLIN [19], the epirubicin plasma concentration-time data were fitted to a three-compartment open model (scheme 1) with a triexponential equation:

$$C(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} + C \cdot e^{-\gamma t}$$

$$\boxed{A_3} \underset{k_{31}}{\overset{k_{13}}{\rightleftharpoons}} \boxed{A_1} \underset{k_{12}}{\overset{k_{21}}{\rightleftharpoons}} \boxed{A_2}, \quad \downarrow k_{10}$$

(scheme 1)

where $C(t)$ is the drug concentration in nanograms per milliliter at time t after an intravenous dose of the drug. *A*, *B*, and *C* are intercepts on the *y* axis for each exponential segment of the curve in units of concentration, and α, β, and γ are the first-order rate constants for two distribution phases and the elimination phase, respectively, per unit of reciprocal time. The weighted residual sum of squares, correlations, and residual plots were used to obtain the best estimate of *A*, *B*, *C* and α, β, γ.

The AUC was calculated by the trapezoidal rule and included a terminal slope correction factor Cp^n/γ, where Cp^n is the last measured concentration-time point. The total body clearance (Cl) was determined by dose/AUC. The apparent volume of distribution (V_d) and the volume of the central compartment (V_c) were calculated from:

V_d = dose/(AUC · γ) and
V_c = dose/(A + B + C).

Other pharmacokinetic microconstants were calculated for each patient using standard formulas [11]:

$k_{10} = \alpha\beta\gamma/(k_{21} \cdot k_{31})$
$k_{12} = [(\alpha\beta + \alpha\gamma + \beta\gamma) - k_{21}(\alpha + \beta + \gamma) - k_{31} \cdot k_{10} + k_{21}^2]/(k_{31} - k_{21})$
$k_{13} = (\alpha + \beta + \gamma) - (k_{10} + k_{21} + k_{31} + k_{12})$
$k_{21} = \beta + [B(\alpha-\beta)(\beta - \gamma)/(A + B + C)(\beta - k_{31})]$
$k_{31} = \gamma + [C(\alpha - \gamma)(\beta - \gamma)/(A + B + C)(k_{21} - \gamma)]$,

where k_{10} is the first-order elimination rate constant out of the central compartment, k_{12} and k_{21} are intercompartmental transfer rate constants between the tissue compartment and central compartment in scheme 1, and k_{13} and k_{31} are intercompartmental transfer rate constants between the deep tissue compartment and central compartment in scheme 1. Analysis of variance (ANOVA) and Student's *t*-test were used for the statistical evaluation of these data.

Clinical response evaluation. The clinical responses were classified as complete response (CR), partial response (PR), no change (NC), and progressive disease (PD).

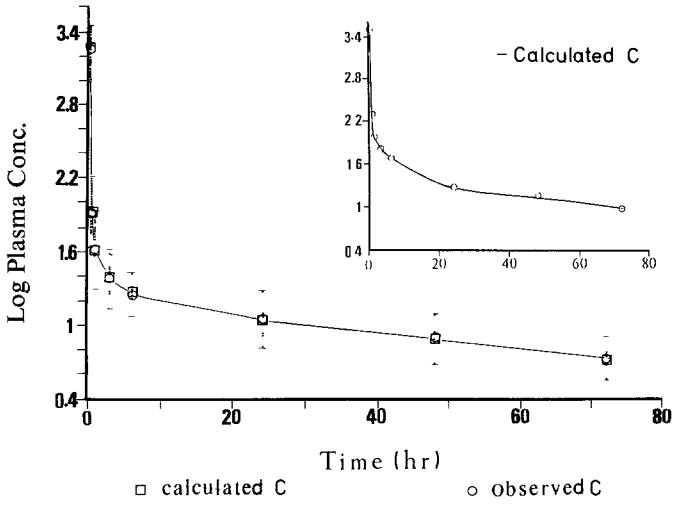


Fig. 2. Mean (± SD) concentration-time curve of epirubicin in 27 patients after 75 mg/m^2 was given as a rapid i.v. infusion. □, calculated; ○, observed. *Insert*: concentration-time curve from a typical patient. –, calculated C; ○, observed C

A CR was defined as the complete disappearance of all evidence of the tumor (X-ray, physical examination). A PR was defined as a reduction in measurable tumor mass of >50% lasting longer than 1 month. NC was defined as any decrease in tumor size short of a PR or the lack of any evidence of PD. PD was defined as an increase in tumor size of >25%, measured in a similar fashion, or the appearance of new lesions. The clinical response evaluation was done after three cycles of treatment. The nonresponders included patients in the NC and PD groups. Toxicity was evaluated beginning at the first cycle of treatment according to WHO criteria.

Results

One patient was excluded from the study due to insufficient blood sampling. The mean plasma concentration-time curve for epirubicin after a rapid i.v. infusion of

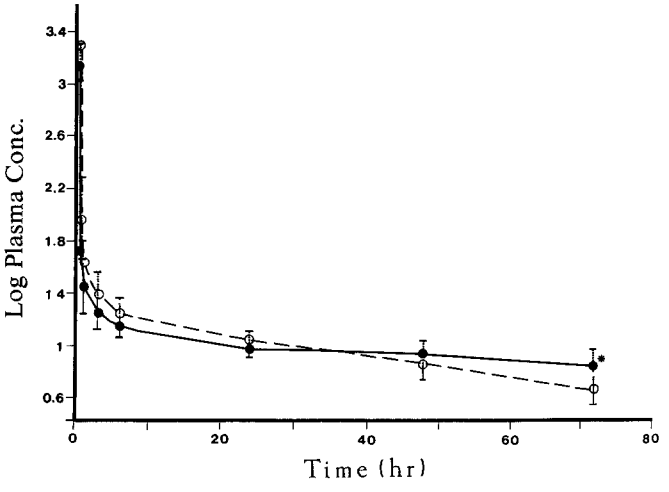


Fig. 3. Comparison of plasma concentrations of epirubicin (mean ± SD) in complete responders (●; $n = 6$) vs nonresponders (○; $n = 13$); *$p < 0.05$

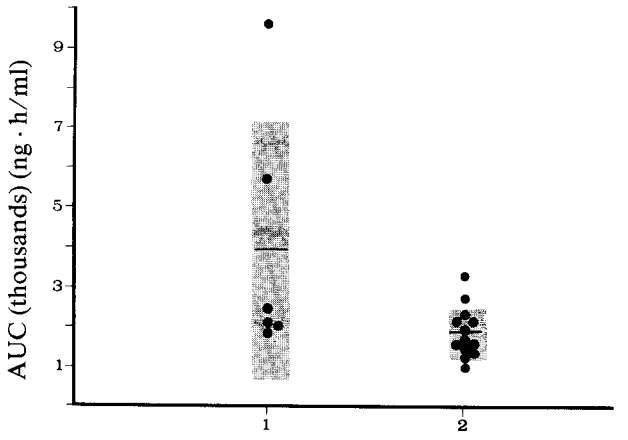


Fig. 4. The AUC of epirubicin in patients, showing the significant difference between complete responders (*1*) and nonresponders (*2*). $p < 0.05$

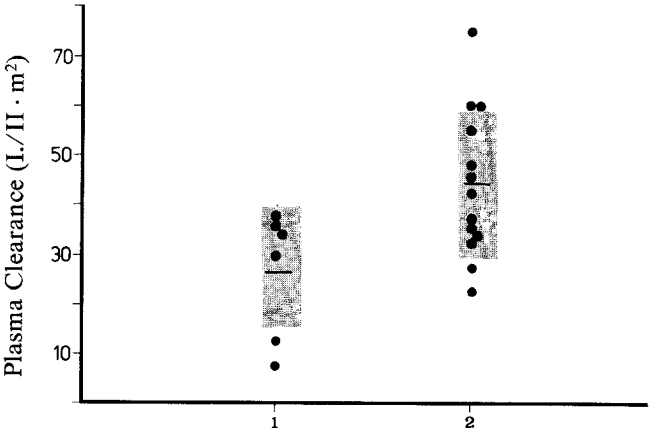


Fig. 5. The plasma clearance of epirubicin in patients, showing the significant difference between complete responders (*1*) and nonresponders (*2*). $p < 0.05$

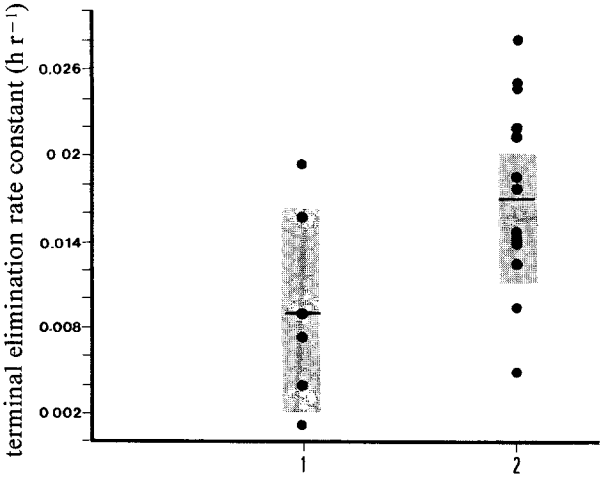


Fig. 6. The terminal elimination rate constant in patients, showing the significant difference between complete responders (*1*) and nonresponders (*2*). $p < 0.05$

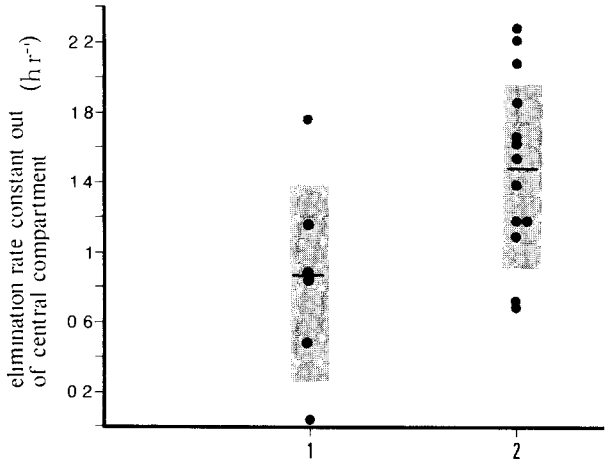


Fig. 7. The elimination rate constant out of the central compartment, showing the significant difference between complete responders (*1*) and nonresponders (*2*)

75 mg/m^2 to the remaining 27 patients is shown in Fig. 2. Following drug administration, the mean (± SD) peak serum concentration was 1,860 ± 828.4 ng/ml. The serum data of each patient were fitted to a three-compartment open model. Pharmacokinetic parameters were estimated using computer programs CSTRIP and PCNONLIN. The results of a comparison of plasma concentrations at each time point in complete responders vs nonresponders are shown in Fig. 3.

The pharmacokinetic parameters in patients according to different tumor response, sex, and age are listed in Tables 1–3. There were significant differences ($P < 0.05$) in the serum level at 72 h, as well as the AUC (Fig. 4), plasma clearance (Fig. 5), terminal elimination rate constant (γ) (Fig. 6), and elimination rate constant out of the central compartment (Fig. 7) in a comparison of these parameters in complete responders vs nonresponders. No significant difference was observed between the pharmacokinetic parameters and age or sex.

Epirubicin produced a 52% response rate (six patients had CRs and eight had PRs; 13 patients were in the PD or NC groups). The major dose-limiting toxicity of epirubicin therapy was myelosuppression, predominantly leukopenia, with nadirs usually occuring at 10–14 days after drug administration. We correlated various pharmacokinetic parameters with the nadir and maximal difference in WBC counts (variation between the pretreatment and nadir counts). The correlations of the peak serum concentration, AUC, and plasma clearance with these WBC values were not significant; no obvious relationship could be found between these parameters and leukopenia (Fig. 8).

Table 1. Pharmacokinetic parameters among patients with different tumor responses after the administration of 75 mg/m^2 epirubicin as a rapid i.v. infusion

	CR (mean ± SD)	PR (mean ± SD)	NC + PD (mean ± SD)	Statistics (CR, NC + PD)
Mean peak plasma concentration (ng/ml)	1,664.7 ± 850.74	1,568.6 ± 702.82	2,138.7 ± 856.91	NS[b]
$t_{1/2}$ (h)	62.6 ± 37.9	41.2 ± 20.3	40.9 ± 17.6	NS[b]
AUC (ng · h/ml)	4,002 ± 3,081	2,568 ± 2,214	1,881 ± 652.8	S[a]
V_d (l/m^2)	3,762 ± 1,557	3,674 ± 2,764	2,842 ± 1,135	NS[b]
V_c (l/m^2)	73.2 ± 75.4	55.3 ± 20.0	43.3 ± 26.3	NS[b]
Cl (l/h · m^2)	26.6 ± 12.9	40.6 ± 19.7	44.4 ± 15.0	S[a]
α (per h)	8.62 ± 4.93	8.02 ± 2.38	9.61 ± 4.81	NS[b]
β (per h)	0.45 ± 0.34	0.77 ± 0.44	0.69 ± 0.59	NS[b]
γ (per h)	0.009 ± 0.007	0.017 ± 0.008	0.017 ± 0.006	S[a]
k_{10} (per h)	0.868 ± 0.588	1.271 ± 0.796	1.51 ± 0.52	S[a]

CR, complete response; PR, partial response; NC, no change; PD, progressive disease
[a] Significant according to Student's *t*-test ($P < 0.05$)
[b] Not significant according to Student's *t*-test ($P < 0.05$)

Table 2. Lack of correlation between pharmacokinetic parameters and sex

	Female (mean ± SD)	Male (mean ± SD)	Statistics (Student's *t*-test)
Mean peak plasma concentration (ng/ml)	2,264 ± 564.3	1,711 ± 806.2	NS[a]
$t_{1/2}$ (h)	50.5 ± 23.3	42.9 ± 21.8	NS[a]
AUC (ng · h/ml)	2,043 ± 468.6	2,185 ± 1,331	NS[a]
V_d (l/m^2)	2,742 ± 1,115	3,301 ± 1,124	NS[a]
V_c (l/m^2)	34.8 ± 7.9	53.4 ± 25.6	NS[a]
Cl (l/h · m^2)	38.6 ± 9.4	43.8 ± 19.1	NS[a]
α (per h)	10.00 ± 6.34	8.83 ± 3.04	NS[a]
β (per h)	0.40 ± 0.25	0.83 ± 0.60	NS[a]
γ (per h)	0.016 ± 0.0072	0.015 ± 0.006	NS[a]
k_{10} (per h)	1.54 ± 0.42	1.20 ± 0.67	NS[a]

[a] $P > 0.05$

Table 3. Lack of correlation between pharmacokinetic parameters and age

	⩾55 years (n = 7) (mean ± SD)	⩽40 years (n = 13) (mean ± SD)	Statistics (Student's t-test)
Mean peak plasma concentration (ng/ml)	1,520±972.8	1,913±685.1	NS[a]
$t_{1/2}$ (h)	48.5 ±29.7	46.0 ±23.6	NS[a]
AUC (ng · h/ml)	4,176±3,166	2,261±1,262	NS[a]
V_d (l/m^2)	4,151±3,061	3,038±1,115	NS[a]
V_c (l/m^2)	77.3 ±67.9	46.1 ±25.3	NS[a]
Cl (l/h · m^2)	26.6 ±14.0	40.4 ±16.9	NS[a]
α (per h)	8.87±4.56	7.95±2.08	NS[a]
β (per h)	0.46±0.22	0.73±0.64	NS[a]
γ (per h)	0.014±0.010	0.016±0.008	NS[a]
k_{10} (per h)	0.94±0.69	1.30±0.53	NS[a]

[a] $P > 0.05$

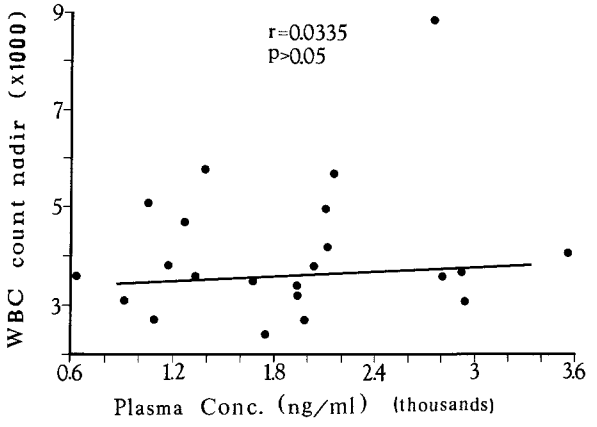


Fig. 8. The peak plasma concentration of epirubicin vs the WBC count nadir in patients, showing the lack of correlation between these parameters

Other toxicities were observed, including nausea or vomiting (88.8%), alopecia (92.6%), and general malaise (100%). Three patients did not experience nausea or vomiting: one was in the CR group, one was in the PR group, and one was a nonresponder. Two patients experienced no alopecia: one was in the PD group and the other was in the NC group. These observations suggest the lack of a relationship between these toxicities and the clinical response to epirubicin therapy.

Discussion

Human pharmacokinetic studies of epirubicin have been reported by several authors. Bonfante et al. [2] reported epirubicin plasma concentrations measured using a nonspecific fluorescence method. Camaggi et al. [4] conducted a pharmacokinetic study of epirubicin using an HPLC method in various cancer patients with normal or impaired renal function or liver metastases; they found that the terminal elimination half-lives were 40, 39, and 31.9 h in patients with normal liver and renal functions, impaired renal function, and liver metastases, respectively. Relatively high AUC and low plasma clearance were noted in patients with hepatic dysfunction. Weenen et al. [26] carried out another pharmacokinetic study in 14 patients (8 with soft tissue sarcoma, 5 with advanced breast carcinoma, and 1 with advanced colorectal carcinoma); the terminal half-lives obtained were similar to those reported by Camaggi et al. [4].

However, different pharmacokinetic parameters for epirubicin have been reported by Robert et al. [24] in 16 patients with metastatic breast cancer, by Eksborg et al. [16] in 6 ovarian cancer patients, by Libretti et al. [17] in

Table 4. Mean pharmacokinetic parameters of epirubicin in different cancer patients reported in the literature

Disease (number of patients)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	Clp (l/min)	V_d (l/kg)	AUC (ng · h/ml)	Reference
Ovarian cancer (6)	3.4	0.9	13.9	2.26			[10]
Solid tumor:							
normal liver and renal function (11)			40.0±19.0	0.882±0.25	46.1±24.9	2,977	[4]
impaired renal function (5)			39.1	0.687	38.6	2,279	
liver metastasis (6)			31.9	0.509	27.1	3,971	
Soft tissue sarcoma (14)			38.0±14.0			109±29[c]	[26]
Lung, ovarian, larynx cancer (15)	3.2	1.25	30.1	1.4	62	1,305	[17]
Metastatic breast cancer (16)	3.1	1.1	18.3±2.4	1.0 ±0.49	929±639[b]		[24]
Solid tumors (3)			8.3±3.0	4.3 ±1.0[a]	3.2±1.5		[16]
Nasopharyngeal carcinoma (27)	5.4	1.7	44.8±21.2	0.66±0.28	74.1±30.8	2,583±2,014	present study

[a] In ml/min per kg
[b] In l
[c] 10^{-8} mol · h/l

15 cancer patients, and by Leyland-Jones et al. [16] in 3 patients at different doses. In the latter report, the terminal half-life was rather short (499 min) and the values for the volume of distribution (3.2 l/kg) and the plasma clearance (4.3 ml/min per kg) were lower than those reported by other authors, possibly due to the small sample size and different doses.

Table 4 shows the mean pharmacokinetic parameters in patients with a variety of cancers as reported in the literature and in the present study. In the present study, the overall mean terminal half-life (44.8 ± 21.2 h) and the AUC ($2{,}583 \pm 2{,}014$ ng·h/ml) were similar to the findings of Camaggi et al. [4], whereas the plasma clearance was lower (0.66 ± 0.28 l/min) in our study. The pharmacokinetic values obtained in Chinese patients were comparable with those reported in the literature (Table 4).

The only metabolite of epirubicin, epirubicinol (13-dihydroepirubicin), was found in several studies using an HPLC method [4, 18, 22]. We also found an unidentified metabolite, which appeared very rapidly in the blood and followed a curve pattern similar to that of the unchanged drug, with consistently lower serum concentrations.

In this study we did not observe a relationship between the pharmacokinetic parameters and leukopenia, the major dose-limiting toxicity of epirubicin. Other toxicities such as gastrointestinal distress, alopecia, and general malaise were seen in most patients. This suggests that plasma concentration is not a good indicator for the clinical toxicities of this drug. Moreover, up to a maximal cumulative dose of 420 mg, none of our patients developed clinical evidence of congestive heart failure.

Complete responders had much higher AUC values and lower plasma clearance values than nonresponders ($P < 0.05$). Both the terminal rate constants (γ) and elimination rate constants from the central compartment (k_{10}) of complete responders were lower than those of nonresponders ($P < 0.05$). These phenomena may be one of the factors determining whether or not NPC patients respond to epirubicin. Moreover, at a concentration of 3,600 ng/ml, the bone marrow toxicity of epirubicin was independent of the peak plasma concentration. Therefore, a dose adjustment according to each patient's plasma clearance at the beginning of the second cycle of treatment would probably increase the response rate.

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