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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 50-778

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	21-010
Submission Date:	November 5, 1998
Drug Name:	**Epirubicin Hydrochloride**
Formulation:	10, 20, 50, 150, and 200 mg (2 mg/ml) in Single-Dose Vials for Intravenous Administration
Sponsor:	Pharmacia & Upjohn, Kalamazoo, MI
Reviewer:	Safaa Ibrahim, Ph.D.
Submission Type:	Review of New Drug Application (1P)

1. SYNOPSIS

This New Drug Application seeks approval to market epirubicin for the treatment of node-positive early breast cancer and advanced/recurrent breast cancer in the United States. The proposed recommended doses are 100-120 mg/m^2 as an adjuvant therapy. .
Epirubicin is given intravenously (IV) in repeated 3- to 4-week cycles. The total epirubicin dose may be given on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle.

Epirubicin, an anthracycline cytotoxic agent, has been commercially available in several countries for fifteen years for the treatment of patients with a variety of malignancies (e.g., breast, ovarian, lung, stomach, liver, lung, pancreatic, and bladder carcinomas). Epirubicin is structurally related to doxorubicin. It differs from doxorubicin in the epimerization of the OH group in position 4'- of the amino sugar moiety.

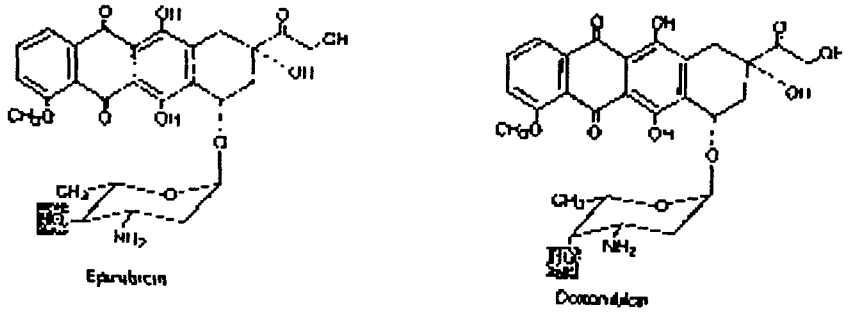

Fig. 1: Structure Formula of Epirubicin and Doxorubicin

Epirubicin was shown to be effective as doxorubicin, but with less cardiac toxicity at comparable doses (Cersosimo and Hong 1986, Attachment 2, pp.1). The clinical pharmacokinetics of epirubicin and its metabolites have been reported in many publications. These publications describe the basic characteristics of the drug's pharmacokinetics and address the specific factors that affect the pharmacokinetics behavior (e.g., age, gender, disease state). A summary of the results of these published data is presented below.

Clinical Pharmacology and Metabolism

In most studies, epirubicin and its metabolites were measured in biological fluids using a high performance reversed-phase liquid chromatography (HPLC) with fluorescence detection.

Distribution: Epirubicin is extensively distributed throughout the body with a mean±SD steady-state volume of distribution of 21±7 L/kg, following 150 mg/m^2 IV dose to 6 cancer patients. It is about 77% bound to human plasma proteins, mainly to albumin. Epirubicin appears to concentrate in red blood cells; drug concentrations in whole blood are about 2-fold higher than those in plasma. Epirubicin and doxorubicin have similar distribution and binding properties.

Metabolism: Epirubicin is extensively metabolized mainly by the liver to 13-dihydro metabolite, epirubicinol, by aldoketoreductase. Both epirubicin and epirubicinol undergo glucuronidation. They also undergo hydrolysis to aglycones and hydrolysis followed by reduction to 7-deoxy aglycones. Cytochrome P450 oxidative system does not play a role in the metabolic conversion of epirubicin. Plasma concentrations of epirubicinol are lower than that of the parent drug; mean metabolite/parent AUC ratio is about 30%. Epirubicin glucuronide is the major metabolite found in plasma, accounting for about 50% of the epirubicin AUC. The other metabolites were found at low concentrations. Epirubicinol has an *in vitro* cytotoxic activity about 10-fold lower than that of epirubicin. Other metabolites are pharmacologically inactive.

Excretion: Based on mass-balance data from only one patient, it is shown that about 61% of total radioactive dose was excreted in urine (27%) and feces (34%) over 10 days. This means that about 40% of radioactivity has not been accounted. Literature data indicated that urinary excretion is about 11% over the period of 2-7 days. Unchanged drug accounts for about 6 % of the dose excreted in urine. Biliary excretion, evaluated in only 3 patients, was about 35%. These excretion data are considered incomplete and a mass balance study of epirubicin is recommended (See Comment 1, Section A).

Dose- and Time Dependency: The pharmacokinetics of epirubicin are linear over the therapeutic dosage range (60-150 mg/m^2) and are neither affected by the duration of infusion nor administration schedule.

Pharmacokinetics: Plasma concentrations of epirubicin decline triexponentially with half-lives for the initial ($t_{1/2,\alpha}$), intermediate ($t_{1/2,\beta}$), and terminal ($t_{1/2,\gamma}$) elimination phases of approximately 3 minutes, 1.0 hour, and 30 hours, respectively. Mean±SD plasma clearance is 68±13 L/h following 150 mg/m^2 IV dose to 6 cancer patients.

Epirubicin is eliminated faster than doxorubicin; mean plasma clearance is 1.3-fold higher and mean terminal half-life is 1.5-fold shorter than that of doxorubicin.

Mean AUC is 1.3-fold lower for epirubicin than doxorubicin, 1495 ng.h/ml versus 1974 ng.h/ml, respectively, following intravenous administration of 60 mg/m^2 of both drugs to 8 cancer patients. The mean metabolite/parent AUC ratio of epirubicin is 2.5-fold lower than that of doxorubicin, 0.27±0.21 versus 0.69±0.08, respectively.

Special Populations:

Age: A population analysis of plasma data from 36 cancer patients (13 males and 23 females, 20 to 73 years) showed that age is a significant factor affecting the plasma clearance of epirubicin in female patients but not in male patients. The predicted plasma clearance for a female patient of 70 years of age was about 35% lower than that for a female patient of 25 years of age; 64 L/h versus 98 L/h, respectively. Clinical experience of epirubicin in patients above 70 years is limited. Caution should be exercised when epirubicin is administered to female patients of 70 years of age and above.

Gender: No gender related differences were observed in the pharmacokinetics of epirubicin.

Race: The effect of race on the pharmacokinetics of epirubicin has not been evaluated.

Hepatic Patients: Mean plasma clearance decreased by 60% in patients with hepatic metastases but with normal liver biochemistry (n=8) compared to patients with normal hepatic function (n=14). Mean AUC metabolite/parent ratio was comparable in both groups. Dosage adjustment is not necessary in patients with hepatic metastases and normal liver biochemistry.

In another study, the median plasma clearance of epirubicin decreased by about 30% in patients with mild hepatic impairment (n=22) and by 50% in patients with moderate hepatic impairment (n=8) compared to patients with normal hepatic function (n=22). In hepatically impaired groups, there was a significant correlation between plasma clearance of epirubicin and log serum AST (r=-0.72). Dosage adjustment is necessary in patients with abnormal liver biochemistry. Epirubicin dose should be reduced by one-third in patients with mild hepatic impairment (median serum AST value of 93 units/l and normal bilirubin value) and by one

half in patients with moderate hepatic impairment (median serum AST value of 175 units/l and median bilirubin value of 47 μmol/l).

Epirubicin pharmacokinetics have not been evaluated in patients with severe hepatic impairment, therefore, the drug should not be used in this patient population. An alternative therapy should be recommended.

Renal Patients: Both mean plasma clearance and AUC metabolite/parent ratio decreased by 50% in patients with severe renal impairment (n=4) compared to patients with normal renal function (n=14). Epirubicin dose should be reduced by one-half when it is administered to patients with severe renal impairment. Patients with mild-to-moderate renal impairment and patients under dialysis have not been studied.

Drug Interactions:

In Vitro:

No *in vitro* studies have been conducted to examine the potential for inhibition or induction by epirubicin on the oxidative cytochrome P450 isoenzymes.

Epirubicin is a substrate of the efflux transporter, P-glycoprotein. Drugs that are known to modulate the P-glycoprotein function (e.g., cyclosporines, verapamil, dipyridamole, metronidazole, quinine, and quinidine) may increase the cellular uptake of epirubicin and enhance its cytotoxicity.

In Vivo:

Paclitaxel: Coadministration of paclitaxel (175 mg/m^2 as a 3-hour infusion) did not affect the pharmacokinetics of epirubicin (90 mg/m^2 as an intravenous bolus) but significantly affected its metabolism. AUC of epirubicinol and 7-deoxy aglycone increased by 2.2-fold and 1.7-fold, respectively, when epirubicin was coadministered with paclitaxel. Epirubicin and epirubicinol glucuronidation increased by 273% and 194%, respectively, in the presence of paclitaxel.

Docetaxel: Coadministration of docetaxel (70 mg/m^2 as a 1-hour infusion) had no effect on the pharmacokinetics of epirubicin (90 mg/m^2 as an intravenous bolus), but affected its metabolism. AUC of epirubicinol and 7-deoxy aglycone increased by 1.2-fold and 1.9-fold, respectively, when epirubicin was coadministered with docetaxel. Epirubicin and epirubicinol glucuronidation increased by 174% and 89%, respectively, in the presence of docetaxel.

As epirubicin metabolites are pharmacologically inactive, no dosage adjustment for epirubicin is necessary when it is coadministered with either paclitaxel or docetaxel.

Dexverapamil: Coadministration of dexverapamil (428 mg/daily p.o. for 4 consecutive days) increased the mean AUCs of epirubicin (40 mg/m^2 in a daily i.v. bolus for 3 consecutive days) and epirubicinol by 17% and 45%, respectively. No dosage adjustment is necessary for epirubicin when it is coadministered with dexverapamil.

Dexrazoxane (ADR-529): Coadministration of 600 mg/m^2 dexrazoxane (ADR-529), a protective agent against the cardiac toxicity of anthracyclines, decreased the mean plasma clearance of epirubicin (60 mg/m^2) by 25% and epirubicinol/ epirubicin AUC ratio by 12%. No significant difference was observed in the other pharmacokinetic parameters of epirubicin when it was coadministered with dexrazoxane.

In another study, pretreatment with dexrazoxane (600 mg/m^2) decreased plasma clearance of epirubicin (120 mg/m^2) by 35%, when compared with epirubicin alone (n=6). Other dosing schedules of dexrazoxane/epirubicin of 900/120, 900/135, 900/150, and 1200/135 mg/m^2 (n=6 patients/schedule) resulted in an increase in plasma clearance of epirubicin of about 1.8-, 3.6-, and 6.1-fold, respectively, when compared to epirubicin treatment alone. From clinical point of view, dexrazoxane should not be coadministered with epirubicin.

Cimetidine: Coadministration of cimetidine (400 mg b.i.d. for 7 days starting 5 days before chemotherapy) increased mean AUC of epirubicin (100 mg/m^2) by 50% and decreased its clearance by 30%. Cimetidine should not be coadministered with epirubicin and an alternative therapy should be recommended.

Quinine: Quinine accelerated the distribution of epirubicin; mean initial distribution half-life decreased from 6 to 3 minutes when epirubicin was coadministered with quinine. The mean initial serum concentration of epirubicin reduced from 7359±506 ng/ml to 4351±1682 ng/ml (40%) when epirubicin was coadministered with quinine. Furthermore, quinine caused a reduction in exposure to epirubicin; mean $AUC_{0\text{-}24h}$ decreased from 3404±1008 ng.h/ml to 2359±1073 ng.h/ml (30%). No dosage adjustment is recommended at this time.

Interferon-alpha-2b: Epirubicin was injected as an intravenous bolus at a dose of 60 mg/m^2 over 2 minutes. Interferon-alpha-2b (IFN) was pre-administered as a subcutaneous injection at a dose of 5x10^6 IU 3 times a week. IFN reduced the mean plasma clearance of epirubicin from 72 ml/min to 48 ml/min (33%) and increased its AUC from 2004 ng.hr/ml to 2582 ng/.hr/ml (28%). INF showed no significant interference with the metabolism of epirubicin. No dosage adjustment is recommended at this time.

Pharmacokinetic/Pharmacodynamic Relationships:

There was a positive correlation between AUC values and the myelosuppression induced by epirubicin at doses of 40-135 mg/m^2, indicating that AUC is a good predictor of toxicity. The logarithm of the surviving fraction of white blood cells was significantly correlated with the AUC of epirubicin ($r=-0.55$, $p < 0.0001$). There was a significant relationship between the proportion of complete responders/nonresponder and several pharmacokinetic parameters (e.g., AUC, plasma clearance, terminal rate constant, elimination rate constant from central compartment). Peak plasma concentration (Cmax) of epirubicin is not a good indicator of toxicity ($r=0.033$, $p > 0.05$).

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2. COMMENTS

A. To be sent to the firm

1. Based on data from one patient (Reports IMI28/616i and IMI28/614I), the total excretion of radioactivity is about 60% of the administered dose in urine and feces. This means that about 40% of radioactivity is not accounted for. The submitted literature data do not also adequately reflect the excretion of epirubicin. Therefore, the sponsor is recommended to conduct a mass-balance study using at least 6 cancer patients to fully describe the excretion of epirubicin and its metabolites.

2. *In vitro* studies with human liver microsomes to evaluate the potential for the inhibition or induction by epirubicin on the oxidative cytochrome P450 isoenzymes should be performed and submitted to the Agency for review and for incorporating proper information in the package insert.

3. Pharmackinetic/pharmacodynamic relationships indicated that exposure (expressed as AUC) is a good indicator of efficacy (Hu et al. 1989) and toxicity of epirubicin (Jakobsen et al. 1991). The sponsor is encouraged to further explore the relationship between AUC and efficacy in patients with breast cancer.

4. The sponsor is requested to incorporate the OCPB's pharmacokinetic labeling in their package insert as outlined in pages # 7-13.

B. To the Medical Reviewer

1. In the published population analysis report by Wade et al. 1992, it was found that age was a significant factor affecting epirubicin clearance only in females but not in males. It is predicated that a 70-year female patient had a 35% lower clearance than a 25-year female. Although dosage adjustment may not

be necessary in elderly patients, caution should be exercised when epirubicin is administered to female patients of 70 years of age and above.

2. Epirubicin pharmacokinetics have not been evaluated in patients with severe hepatic impairment, therefore, epirubicin should not be used in this patient population. An alternative therapy should be recommended.

3. In an article by Murray et al. 1998, it was shown that coadministration of cimetidine (400 mg b.i.d. for 7 days starting 5 days before chemotherapy) increased mean AUC of epirubicin (100 mg/m^2) by 50% and decreased its plasma clearance by 30%. Therefore, cimetidine should not be coadministered with epirubicin and an alternative therapy should be recommended.

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3. OCPB's PHARMACOKINETIC LABELING

[Note: Statements added are in bold and italic. Statements deleted are strikeout]

CLINICAL PHARMACOLOGY

Pharmacokinetics

Draft

6 pages redacted from this section of the approval package consisted of draft labeling

4. RECOMMENDATION

The NDA submitted for Epirubicin For Injection has adequately addressed the Office of Clinical Pharmacology and Biopharmaceutics' requirements. The sponsor is requested to address Comments 1-3, and to incorporate the OCPB's pharmacokinetic labeling as outlined in Comment 4.

Please forward the above Recommendation, Comments in section A, and the OCPB's pharmacokinetic labeling (pages 7-13) to the firm.

Comments in Section B should be forward to the Medical Reviewer.

/S/

Reviewer: Safaa Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

ClinPharm/Biopharm Briefing on June 3rd, 1999: [Attendees: Drs.: M. Mehta, A. Rahman, S. Honig, P. Andrews, J. Hunt, J. Lazor, B. Booth, J. Gobburu, and S. Ibrahim]

RD/FT_____
Division Director: Mehul Mehta, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 21-010 (Orig.)
HFD-150/Division file
HFD-150/Guinn, Williams, Honig
HFD-850/Lesko
HFD-860/Mehta, Rahman, Ibrahim
HFD-205/FOI
CDR (Biopharm)

5. TABLE OF CONTENTS

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6. Background

Epirubicin (4'-epi-doxorubicin hydrochloride) is a cytotoxic alkylating agent related to a series of anthracyclines. It is a red-orange, hygroscopic powder, sparingly soluble in water, methyl alcohol, and NaCl solution. It is insoluble in acetonitrile and tetrahydrofuran. The pKa value is 8.0 at 25°C. The partition coefficient between n-octanol/pH 7 buffer is 2.5 at room temperature.

The chemical name of epirubicin is (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphtacenedione hydrochloride. It has an empirical formula of $C_{27}H_{29}NO_{11}$.HCl and a molecular weight of 579.95. The structural formula is shown in Fig.1.

It is proposed that the cytotoxic activity of epirubicin is due to the formation of a complex with DNA by intercalation with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals.

Epirubicin for Injection is supplied as a sterile, clear, ready-to-use solution in polypropylene vials which contain 10, 20, 50, 150, and 200 mg of epirubicin hydrochloride (2 mg/ml). Epirubicin for Injection will be manufactured by Pharmacia & Upjohn at Bentley, Western Australia.

7. Summary of Clinical Pharmacology and Metabolism

7.1 Distribution and Protein Binding

In Vivo:

Epirubicin is extensively distributed throughout the body with a mean ±SD steady-state volume of distribution (Vss) of 21 ±7 L/kg, determined in 6 patients with advanced cancer after an intravenous dose of 150 mg/m^2 (Camaggi et al. 1993, Attachment 2, pp. 16).

The distribution of epirubicin into human tissues was examined in cancer patients undergoing surgery 2 to 4 hours after administration of 10 mg/m^2 and 20 mg/m^2 of epirubicin (Italia et al. 1983, Attachment 2, pp. 25). Epirubicin concentrations in normal tissues ranged from 67 ng/g in subcutaneous fat to 973 ng/g in lung following the 20 mg/m^2 dose. Epirubicin concentrations tended to be higher in tumor cells than those in normal cells. However, these concentrations were determined at much lower doses (10 mg/m^2 and 20 mg/m^2) than therapeutic doses of epirubicin (60-135 mg/m^2).

Epirubicin appears to concentrate in red blood cells; drug concentrations in whole blood are about 2-fold higher than those in plasma 4 to 10 hours after 50 mg/m^2 dose to a cancer patient (Camaggi et al. 1985, Attachment 2, pp. 28)

In Vitro:

Epirubicin is about 77% bound to human plasma proteins (Report I/28/812i, Attachment 2, pp. 38). Binding is independent of concentrations over the range of 20-1000 ng/ml which cover the therapeutic concentration range for the drug.

Distribution of Epirubicin Versus Doxorubicin:

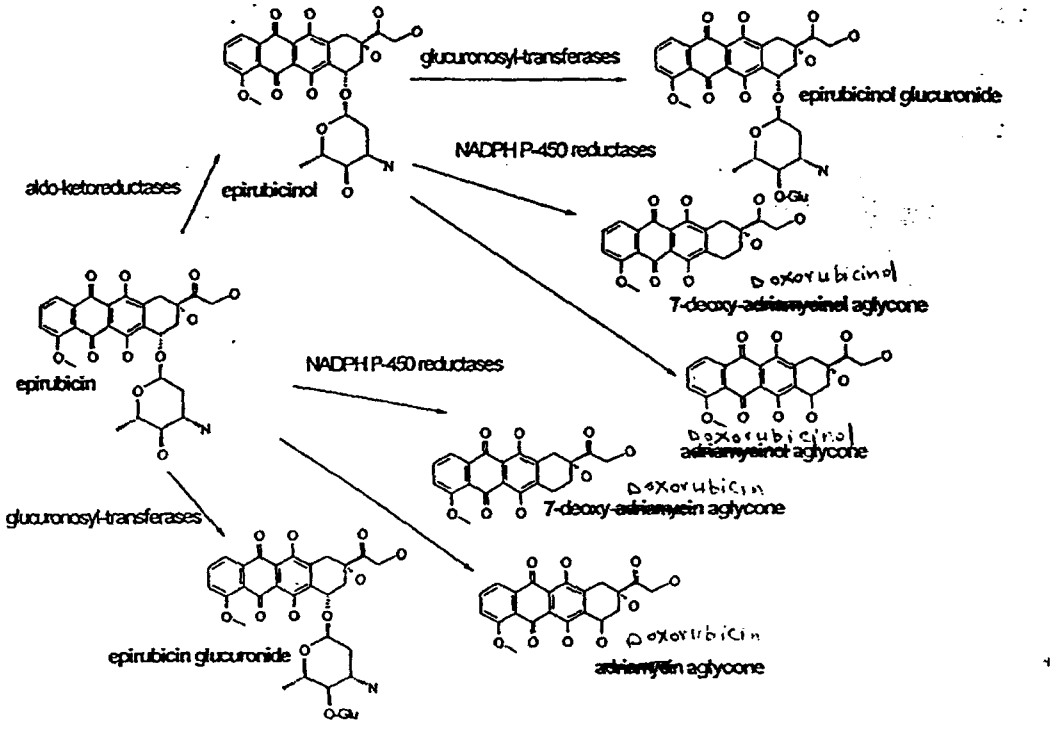
Epirubicin and doxorubicin have comparable volume of distribution, Vss=32 ±7.4 L/kg versus 33±5.6 L/kg, respectively, determined in 8 cancer patients who received 60 mg/m^2 of both drugs in a crossover study by Camaggi et al. 1988 (Attachment 2, pp. 49).

The protein binding of epirubicin is similar to that observed for doxorubicin, 75% and 71%, respectively (Eksborg et al. 1982, Attachment 2, pp. 57). Both epirubicin and doxorubicin are bound mainly to albumin, 57% and 62%, respectively (Eksborg et al. 1982, Attachment 2, pp. 57).

7.2 Metabolism

Epirubicin undergoes extensive metabolism primarily in the liver, but also in other organs and cells including red blood cells. Fig. 2 presents the proposed metabolic pathways for epirubicin.

Fig 2: Proposed metabolic pathways for epirubicin.



As common with most anthracyclines, the metabolic pathways identified for epirubicin are the followings (Camaggi et al. 1993, Attachment 2, pp. 16):

(1) reduction of the C-13 keto-group with the formation of the 13(S)-dihydro metabolite, epirubicinol. The enzyme responsible for this metabolic pathway is an aldoketoreductase;

(2) conjugation of both the unchanged drug and epirubicinol with glucuronic acid acid by glucuronosyl transferases;

(3) loss of the amino sugar moiety through a hydrolytic process with the formation of the doxorubicin and doxorubicinol aglycones; and

(4) loss of the amino sugar moiety through a redox process with the formation of the 7-deoxy-doxorubicin aglycone and 7-deoxy-doxorubicinol aglycone; this process is catalyzed by cytochrome P450 reductase.

Conjugation with glucuroic acid is a unique metabolite pathway for epirubicin (Weenen 1984, Attachment 2, pp. 61). Glucuronide formation was not observed in doxorubicin metabolism (Mross et al. 1988, Attachment 2, pp. 69). This is due to the more available equatorial position of the 4'-hydroxy group in epirubicin molecule. Cytochrome P450 oxidative system does not play a role in the metabolic conversion of epirubicin.

Plasma concentration of 13-dihydro metabolite, epirubicinol, is lower than that of the parent drug. Mean epirubicinol/epirubicin AUC ratio is about 30% (Camaggi et al. 1993, Attachment 2, pp. 16). Epirubicin glucuronide is the major metabolite found in plasma, accounting for about 50% of the epirubicin AUC (molecular-weight corrected). The other metabolites were found at low concentraions. The mean metabolite/parent AUC ratio is about 20% for epirubicin glucuronide, 25% for epirubicinol glucuronide, 15% for doxorubicin aglycone, 15% doxorubicinol aglycone, 25% for 7-deoxy-doxorubicin aglycone and 4% for 7-deoxy-doxorubicinol aglycone (Camaggi et al. 1993, Attachment 2, pp. 16).

Epirubicinol has an *in vitro* cytotoxic activity about 10-fold lower than that of epirubicin; GIC_{50} (C6 cells)= 1.05 μg/ml versus 0.123 μg/ml, respectviely (Scott and Robert, 1989, Attachment 2, pp. 79 and 85). Glucuronides of epirubicin and epirubicinol have no cytotoxic activity (Haisma et al. 1992, Attachment 2, pp. 91).

7.3 Excretion

Epirubicin and its metabolites are eliminated mainly through biliary excretion and, to a minor extent, by urinary excretion:

7.3 1 Mass-Balance

Excretion of radioactivity was evaluated in one study following a single intravenous dose of 75 mg/m^2 of ^{14}C-epirubicin (33 μCi/vial) to 2 cancer patients (Reports IMI28/616i and IMI28/614i, Attachment 2, pp. 96 and 121). Patient #1 (52 years) had a small cell lung-carcinoma with hepatic metastases and mild renal insufficiency. Patient #2 (36 years) had a lung carcinosarcoma with bone and cutaneous metastases and normal hepatic and renal function. The results showed that over 10 days, the urinary and fecal excretion of radioactivity accounted for 16% and 24% of administered dose in Patients #1, respectively, and 27% and 34% of administered dose in Patient #2, respectively. Unchanged drug in urine accounted for about 4% in Patient #1 and 7% in Patient #2 over 48 hours. Major metabolites excreted in urine are those known as "other polar metabolites", represented 6% and 7% in Patients #1 and #2, respectively. In general, urinary excretion of unchanged drug and metabolites was lower in

Patient #1 (had hepatic metastases and mild renal insufficiency) than in Patient #2 (had normal hepatic and renal function). Based on data from Patient #2, the total excretion of radioactivity is about 60% of administered dose in urine and feces. This means that about 40% of radioactivity has not been accounted for. These results are considered inadequate and a mass-balance study should be conducted using at least 6 patients to fully describe the excretion of epirubicin and its metabolites (see Comment #1, Section A).

Urinary excretion of epirubicin and its metabolites was evaluated by Camaggi et al. 1991, Camaggi et al. 1986, Mross et al. 1988, Camaggi et al. 1988, and Weenen et al. 1984. Biliary excretion was evaluated in 3 patients by Camaggi et al. 1986 (Attachment 2, pp. 139). The results are summerized in Table 1:

Table 1 Cumulative biliary and urinary excretion of epirubicin and its metabolites expressed as percentage of dose.

Fluid	Reference	No. pts	Dose (mg/m^2)	Period (h)	Biliary and urinary excretion (% of Administered Dose)				
					Cumulative	EPI	EPIOL	EPI-GLU	EPIOL-GLU
Urine	Camaggi 1991	12	60-150	0-168	5.9-9.2	3.2-5.6	0.5-0.8	1.3-2.0	0.3-0.6
	Camaggi, 1986	3	50	0-96	20.0	9.6	4.1	4.6	1.7
	Mross, 1988	8	50	0-48	10.5	6.2	0.6	3.3	0.4
	Camaggi 1988	8	60	0-168	11.3	6.4	0.9	3.2	0.8
	Weenen, 1984	7	75-90	0-48	10.7	5.9	0.8	3.2	0.8
Bile	Camaggi, 1986	3	50	0-96	34.9	21.9	6.5	4.6	1.9

GLU: glucuronide

From this table, it is seen that the cumulative urinary excretion is about 11% over the period of 2-7 days. Unchanged drug accounts for about 6 % of the dose excreted in urine. In Camaggi et al.1986 study, only 3 patients were used. The results obtained may not adequately reflect the cumulative urinary excretion (20%) or the excretion of unchanged drug in urine (9.6%).

Biliary excretion is about 35%; this was also evaluated in 3 patients who had extrahepatic obstruction and percutaneous drainage. It is known that during extraheptic obstruction, a decrease in bile flow is expected. Therefore, the extent of biliary elimination of parent drug and metabolites reported by Camaggi et al. 1986 may likely to be an underestimate.

Excretion of Epirubicin Versus Doxorubicin:

In a crossover study by Camaggi et al. 1988 (Attachment 2, pp. 49), the percent of drug excreted unchanged in urine over 7 days was found to be lower for epirubicin than for doxorubicin, 6.4±3.3% versus 9.0±3.5%, respectively. Renal clearance values are similar, 4.3±2.1 L/h and 4.6±2.1 L/h for epirubicin and doxorubicin, respectively. These results were obtained from 8 cancer patients who received 60 mg/m^2 of both drugs.

7.3.2 Plasma Clearance and Elimination Half-Life

Mean±SD plasma clearance (CLp) and terminal half-life ($t_{1/2\gamma}$) of epirubicin are 68±13 L/h and 30±6 hours, respectively, determined in 6 patients with advanced cancer after an intravenous dose of 150 mg/m^2 (Camaggi et al. 1993, Attachment 2, pp. 16). Epirubicin CLp is about 70% of hepatic blood flow (Q_H=90 L/h).

Elimination of Epirubicin Versus Doxorubicin:

Epirubicin is eliminated faster than doxorubicin. The mean plasma clearance of epirubicin is 1.3-fold higher than that of doxorubicin, 75±30 L/h versus 57±29 L/h, respectively. The mean terminal half-life is 1.5-fold shorter than that of doxorubicin, 31±9 hours versus 48±15 hours, respectively. This was determined in 8 cancer patients receiving 60 mg/m^2 of both drugs (Camaggi et al. 1988, Attachment 2, pp. 49).

Mean AUC is 1.3-fold lower for epirubicin than doxorubicin, 1495 ng.h/ml versus 1974 ng.h/ml, respectively (Camaggi et al. 1988, Attachment 2, pp. 49). The mean metabolite/parent AUC ratio of epirubicin is 2.5-fold lower than that of doxorubicin, 0.27±0.21 versus 0.69±0.08, respectively (Camaggi et al. 1985, Attachment 2, pp. 28). The higher plasma clearance and lower metabolic ratio of epirubicin compared to doxorubicin may be explained either by the difference in glucuronidation processes between the two drugs or by the higher lipophilicity of epirubicin than doxorubicin (partition coefficient =1.15 versus 0.52, respectively).

7.4 Pharmacokinetics

Many studies have reported the human pharmacokinetic of epirubicin. In these studies, patients with various types of cancer (e.g., soft tissue sarcoma, solid tumors advanced cancer, metastatic breast carcinoma, ovarian carcinoma, nasopharyngeal carcinoma, and Hodgkin's disease) have been used. The pharmacokinetic parameters are summarized by Robert, 1993 (Attachment 2, pp. 143) and presented in Table 2. Typical plasma concentration/time curves for epirubicin and its metabolites and epirubicin and doxorubicin are shown in Fig. 3 and Fig. 4, respectively.

Table 2. Pharmacokinetic parameters of epirubicin

Reference	No. of courses	Dose (mg/m²)	$t_{½\alpha}$ (min)	$t_{½\beta}$ (h)	$t_{½\gamma}$ (h)	CL (L/h/m²)	Vd_{ss} (L/m²)	$t_{½\ metab}$ (h)	AUC_{metab} : AUC_{drug}
Camaggi et al. (1982)	11	60-90			40.0	30.5	1844		0.25
Camaggi et al. (1985)	14	30-90			39.4	48.0	1856	32.2	0.37
Camaggi et al. (1988)	8	60	2.92	1.08	31.4	43.1	1272		0.35
Eksborg et al. (1986a)	6	20	3.40	0.89	13.9	71.5			0.18
Hu et al. (1989)	27	75	5.4	1.7	44.8	29.0	2964		
Jakobsen et al. (1991a)	107	40-135			20.6	50.9	838	18.1	
Martini et al. (1984)	8	70	3.15	1.25	30.1	84.2	2332		
Mross et al. (1988)	8	40-60	1.80	0.49	15.3	50.1	592	31.5	0.20
Robert et al. (1985)	9	50	3.44	1.12	18.3	37.0	583	21.1	0.62
Tjulandin et al. (1990)	52	90-150	10		42.0	46-111			
Vrignaud et al. (1985)	10	25-35	2.53	1.04	29.3	41.5	925	21.1	0.26
Weenen et al. (1983)	8	75-90	4.8	2.6	38.0	94.9	1432		0.64

Abbreviations: $t_{½\alpha}$ = half-life of initial phase; $t_{½\beta}$ = half-life of intermediate phase; $t_{½\gamma}$ = half-life of terminal elimination phase; $t_{½\ metab}$ = elimination half-life of epirubicinol; CL = total plasma clearance; Vd_{ss} = volume of distribution at steady-state; AUC_{metab} : AUC_{drug} = area under the concentration-time curve ratio of epirubicinol to epirubicin.

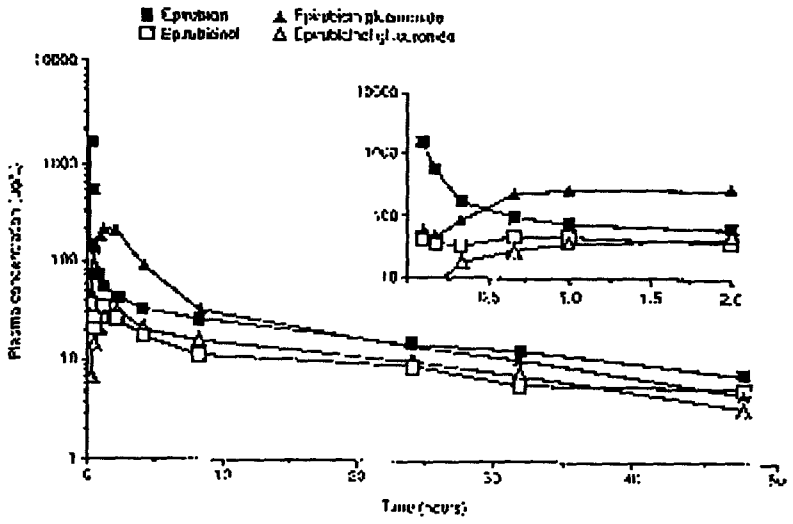


Fig. 3. Plasma concentration/time curves of epirubicin and its metabolites derived from mean values in 9 patients following intravenous administration of 50 mg/m².

Fig. 3 Plasma concentration/time curves of epirubicin and its metabolites derived from mean values in 9 patients following intravenous administration of 50 mg/m².

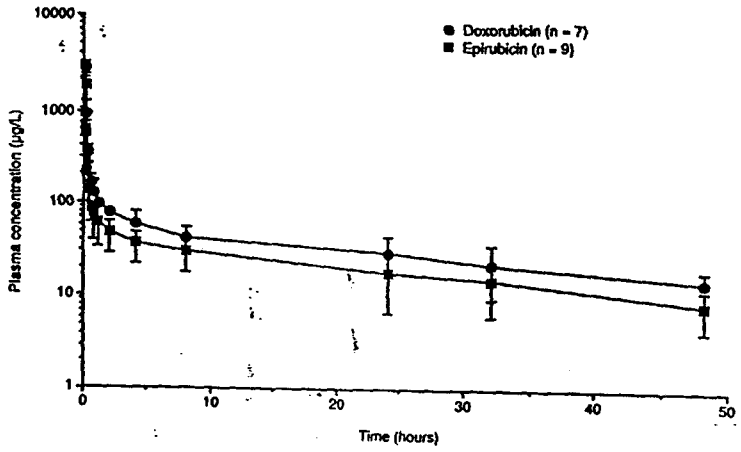


Fig. 4. Comparative plasma decay curves of doxorubicin and epirubicin after intravenous bolus administration of 50 mg/m² in patients with breast cancer (mean ± SD).

Like doxorubicin, epirubicin pharmacokinetics are characterized by a three-compartment open model with half-lives for the initial ($t_{1/2,\alpha}$), intermediate ($t_{1/2,\beta}$), and terminal ($t_{1/2,\gamma}$) elimination phases of approximately 3 minutes, 1.0 hour, and 30 hours, respectively.

7.5 Dose- and Time Dependency

Epirubicin exhibits linear kinetics over the dosing range of 60-150 mg/m^2, which covers the therapeutic range of the drug (Camaggi et al. 1993, Attachment 2, pp. 16).

The kinetics of epirubicin are also time-independent. Plasma clearance is not affected either by the duration of administration (53 versus 47 L/h/m^2 after bolus and 48-h infusion, respectively) (Robert & Bui. 1992, Attachment 2, pp. 154), or by repeated doses every 3 weeks (54 and 55 L/h/m^2 after the 1st and 4th course of the 135 mg/m^2 dose, respectively, Jakobsen et al. 1991, Attachment 2, pp. 160), or every 2 weeks (41, 48, and 50 L/h/m^2 after the 1st, 2nd, and 3rd course of the 35 mg/m^2 dose, respectively, Vrignaud et al. 1985, Attachment 2, pp. 166).

7.6 Special Populations

7.6.1 Age

A population analysis of plasma data from 36 cancer patients (13 males and 23 females, 20-73 years) who administered 25-100 mg/m^2 doses indicated that age is a significant factor affecting the plasma clearance of epirubicin only in female patients, but not in male patients (Wade et al. 1992, Attachment 2, pp. 173). The

predicted plasma clearance in a female patient of 70 years of age is about 35% lower than that in a female patient of 25 years of age; 64 L/h versus 98 L/h, respectively. Clinical experience of epirubicin in patients above 70 years is limited. Caution should be exercised when epirubicin is adminsitered to elderly female patients of 70 years of age and above.

7.6.2 Gender

The population analysis by Wade et al. 1992 showed that males (n=13) and females (n=23) have comparable plasma clearance values for epirubicin, 95 L/h versus 98 L/hr, respectively (Wade et al. 1992, Attachment 2, pp. 173).

In a study by Hu et al. 1989 (Attachment 2, pp. 178), gender was also found to have no effect on the pharmacokinetics of epirubicin after administration of 75 mg/m^2 dose to 28 patients (20 males and 8 females, 18-64 years).

7.6.3 Race

The effect of race on the pharmacokinetics of epirubicin has not been evaluated.

7.6.4 Hepatic Impairment

In a study by Camaggi et al. 1985 (Attachment 2, pp. 28), it was found that mean plasma clearance decreased by 60% in patients with hepatic metastases but with normal liver biochemistry (n=8) compared to patients with normal hepatic function (n=14). Mean AUC metabolite/parent ratio was comparable in both groups. Dosage adjustment is not necessary in patients with hepatic metastases and normal liver biochemistry.

Twelves et al. 1992 (attachment 2, pp. 184) studied the effect of hepatic impairment on the pharmacokinetics of epirubicin in 52 women with advanced breast cancer. Patients were divided into three separate groups according to their serum aspartate transaminase (AST) and bilirubin: normal group with serum AST and bilirubin both within normal limits (n=22), mild group with serum AST above the upper limit of normal but a normal serum bilirubin (n=22), and moderate group with raised serum AST and bilirubin above the upper limit of normal (n=8). Doses administered ranged from 12.5 to 120 mg/m^2.

The results indicated that the median plasma clearance of epirubicin decreased by about 30% in patients with mild hepatic impairment (n=22) and by 50% in patients with moderate hepatic impairment (n=8) compared to patients with normal hepatic function (n=22). In hepatically impaired groups, there was a significant correlation between plasma clearance of epirubicin and log serum AST (r=-0.72). Epirubicin clearance was not significantly correlated with log serum bilirubin (r=0.37), alkaline phosphatase (r=0.47), albumin (r=0.06), or creatinine (r=0.16).

Based on these results, dosage adjustment is necessary in patients with abnormal liver biochemistry. Epirubicin dose should be reduced by one-third in patients with mild hepatic impairment (median serum AST value of 93 units/l and normal bilirubin value) and by one half in patients with moderate hepatic impairment (median serum AST value of 175 units/l and median bilirubin value of 47 µmol/l).

Epirubicin pharmacokinetics have not been evaluated in patients with severe hepatic impairment and therefore, epirubicin should not be used in this patient population. An alternative therapy should be recommended.

7.6.5 Renal Impairment

In a study by Camaggi et al. 1985 (Attachment 2, pp. 28), it was found Both mean plasma clearance and AUC metabolite/parent ratio decreased by 50% in patients with severe renal impairment (n=4) compared to patients with normal renal function (n=14). Epirubicin dose should be reduced by one-half when it is administered to patients with severe renal impairment. Patients with mild-to-moderate renal impairment and patients under dialysis have not been studied.

7.6.6 Cancer Type

Mean pharmacokinetic parameters obtained for epirubicin in patients with a variety of cancers are comparable (Hu et al. 1989, Attachment 2, pp. 178). Lowest values for plasma clearance (CLp=4.3 L/min), volume of distribution (Vd=3.2 L/kg), and terminal half-life ((t½γ=8.3 h) were obtained in patients with solid tumors; but this may be due to the small sample size used in the study (n=3).

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

Disease (number of patients)	$t_{1/\alpha}$ (min)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	Clp (l/min)	V_d (l/kg)	AUC
Ovarian cancer (6)	3.4	0.9	15.9	2.26		
Solid tumor:						
normal liver and renal function (11)			40.0 ± 19.0	0.882 ± 0.25	46.1 ± 24.9	2,977
impaired renal function (5)			39.1	0.687	38.6	3,275
liver metastasis (6)			31.9	0.910	27.1	3,031
Soft tissue sarcoma (14)			38.0 ± 14.0			1,041
Lung, ovarian, larynx cancer (15)	3.2	1.25	30.1	1.4	62	1,305
Metastatic breast cancer (16)	3.1	1.1	18.3 ± 2.4	1.0 ± 0.49	928 ± 639*	
Solid tumors (3)			9.3 ± 2.3	4.3 ± 1.0*	3.2 ± 1.5	
Nasopharyngeal carcinoma (17)	5.4	1.2	44.5 ± 31.2	0.66 ± 0.28	34.1 ± 10.8	2,58

7.7 Drug Interactions

7.7.1 *In Vitro* Drug Interaction Studies

Cytochrome P450: No *in vitro* studies have been conducted to examine the potential for inhibition or induction by epirubicin on the oxidative cytochrome P450 isoenzymes.

P-Glycoprotein: Epirubicin is a substrate of the efflux transporter, P-glycoprotein (Mulder et al. 1995, Attachment 2, pp. 189). Drugs that are known to modulate the P-glycoprotein function (e.g., cyclosporines, verapamil, dipyridamole, metronidazole, quinine, and quinidine) may increase the cellular uptake of epirubicin and enhance its cytotoxicity.

7.7.2 *In Vivo* Drug Interaction Studies

Paclitaxel:

In a study by Esposito et al. 1998 (Manuscript, Attachment 2, pp. 197), 4 patients with breast cancer received epirubicin 90 mg/m^2 as an intravenous bolus alone and 8 patients received epirubicin 90 mg/m^2 as an intravenous bolus followed immediately by paclitaxel 175 mg/m^2 as 3-hour infusion as an adjuvant therapy No significant differences were observed in the pharmacokinetic parameters of epirubicin when it was coadministered with paclitaxel. However, the metabolism of epirubicin is significantly affected by coadministration of paclitaxel. AUC of epirubicinol and 7-deoxy aglycone increased by 2.2-fold and 1.7-fold, respectively, when epirubicin was coadministered with paclitaxel. Epirubicin and epirubicinol glucuronidation increased by 273% and 194%, respectively, in the presence of paclitaxel. As epirubicin metabolites are pharmacologically inactive, no dosage adjustment for epirubicin is necessary when it is coadministered with paclitaxel.

The pharmacokinetics of epirubicin in combination with paclitaxel was also evaluated in another study by Rischin et al. (Manuscript, Attachment 2, pp. 220). This study is considered inadequate because of small sample size used; data were available only for 4 patients.

Docetaxel:

In the previous study, another 8 patients with breast cancer received epirubicin 90 mg/m^2 as an intravenous bolus followed immediately by docetaxel 70 mg/m^2 as 1-hour infusion as first line chemotherapy. No significant differences were observed in the pharmacokinetic parameters of epirubicin when it was coadministered with docetaxel. However, the metabolism of epirubicin is significantly affected by coadministration of docetaxel. AUC of epirubicinol and 7-deoxy aglycone increased by 1.2-fold and 1.9-fold, respectively, when epirubicin was coadministered with docetaxel. Epirubicin and epirubicinol

glucuronidation increased by 174% and 89%, respectively, in the presence of docetaxel. As epirubicin metabolites are pharmacologically inactive, no dosage adjustment for epirubicin is necessary when it is coadministered with docetaxel.

Dexverapamil:

The effects of dexverapamil, R-enantiomer of verapamil on the pharmacokinetics and metabolism of epirubicin were evaluated by Mross et al. 1993 (Attachment 2, pp. 245). Ten patients with advanced breast cancer received epirubicin (40 mg/m^2 in a daily i.v. bolus for 3 consecutive days) and five of them also received dexverapamil (480 mg/daily p.o. for 4 consecutive days). AUCs of epirubicin and epirubicinol increased by 17% and 45%, respectively, when epirubicin was coadministered with dexverapamil. Dexverapamil is a vasodilator that has been shown to increase the liver blood flow in humans. This effect may have contributed to the observed alterations in epirubicin metabolism. No dosage adjustment is necessary for epirubicin when it is coadministered with dexverapamil.

Dexrazoxane (ADR-529):

A crossover study was conducted in 16 patients with metastatic breast carcinoma by Jakobsen et al 1994 (Attachment 2, pp. 252) to determine whether the pharmacokinetics of epirubicin (60 mg/m^2, treatment A), as part of a combination including, cyclophophamide (600 mg/m^2), 5-fluorouracil (600 mg/m^2), and tamoxifen (30 mg/day), are affected by ADR-529 (600 mg/m^2, treatment B). ADR-529 has a protective action against the cardiac toxicity of anthracyclines. Total clearance and AUC ratio of epirubicinol/epirubicin decreased by 25% and 12%, respectively, with concomitant administration of ADR-529. No significant difference was observed in the other pharmacokinetic parameters of epirubicin when was coadministered with ADR-529.

In another crossover study, the toxicity and pharmacokinetics of the combination of dexrazoxane (ADR-529) and epirubicin were evaluated in 26 patients with advanced malignancy by Basser et al. 1994 (Attachment 2, pp. 260). Patients received 5 combinations of dexrazoxane and epirubicin at dose levels of 600/120 mg/m^2 (n=6), 900/120 mg/m^2 (n=6), 900/135 mg/m^2 (n=6), 900/150 mg/m^2 (n=2), and 1200/135 mg/m^2 (n=6), respectively. The maximum tolerated doses of dexrazoxane and epirubicin in combination were 1200 mg/m^2 and 135 mg/m^2, respectively. The dose-limiting toxicities of grade 4 neuropenia (2 patients) and stomatitis (1 patient) occurred at doses of 900 mg/m^2 dexrazoxane and 150 mg/m^2 epirubicin. There was no increase in the grade of neuropenia or thrombocytopenia with the addition of dexrazoxane to epirubicin at any dosing level. There were three episodes of grade 3 and one of grade 4 nausea and vomiting, and two episodes of grade 3 stomatitis. These severe toxicities occurred more often following administration of epirubicin alone when compared with dexrazoxane/epirubicin combination. Pretreatment with dexrazoxane

decreased plasma clearance of epirubicin by 35%, at 600/120 mg/m^2 level, and increased plasma clearance of epirubicin by 1.8-, 3.6-, and 6.1-fold at dosing levels of 900/120 mg/m^2, 900/135 mg/m^2, and 1200/135 mg/m^2, respectively, when compared with epirubicin treatment alone. Changes in volume of distribution and terminal half-life are not conclusive because of the high variability observed in these two parameters. From clinical point of view, dexrazoxane should not be coadministered with epirubicin.

Cimetidine:

In a study by Murray et al. 1998 (Attachment 2, pp. 268), epirubicin 100 mg/m^2 was administered intravenously every 3 weeks to 7 patients who also received oral cimetidine (400 mg b.i.d. for 7 days starting 5 days before chemotherapy) with either the first or second cycles. AUC of epirubicin increased by 50% and its plasma clearance decreased by 30%, with the coadministration of cimetidine. Therefore, cimetidine should not be coadministered with epirubicin and an alternative therapy should be recommended.

Quinine:

The serum and red blood cell disposition of epirubicin after intravenous bolus injection alone and with quinine was investigated in patients undergoing a cyclic chemotherapy with epirubicin (Czejka et al. 1995, Attachment 2, pp. 272). Quinine accelerated the distribution of epirubicin; mean half-life of initial distribution phase for epirubicin decreased from 6 to 3 minutes when it was coadministered with quinine. The mean initial serum concentration was reduced by quinine from 7359±506 mg/ml to 4351±1682 ng/ml (40%). Furthermore, quinine caused a reduction in exposure to epirubicin; $AUC_{0\text{-}24h}$ decreased from 3404±1008 ng.h/ml to 2359±1073 ng.h/ml (30%). No dosage adjustment is recommended at the present time.

Interferon-Alpha-2b:

The influence of interferon-alpha-2b (IFN) on the pharmacokinetics of epirubicin was investigated in 10 patients (4 males and 6 females) by Bandak et al. 1995 (Attachment 2, pp. 273). Epirubicin was injected as an intravenous bolus at a dose of 60 mg/m^2 over 2 minutes. IFN was pre-administered as a subcutaneous injection at a dose of 5x10^6 IU three times a week. IFN reduced the mean plasma clearance of epirubicin from 72 ml/min to 48 ml/min (33%) and increased its AUC from 2004 ng.hr/ml to 2582 ng.hr/ml (28%). INF showed no significant interference with the metabolism of epirubicin. No dosage adjustment is recommended at the present time.

Pharmacokinetic/Pharmacodynamic Relationships

The major dose-limiting toxicity of epirubicin therapy is myelosuppression, predominantly leukopenia, with nadir white blood cell counts (WBC) usually occurring between 10 to 14 days after drug administration.

A study was performed by Jakobsen et al. 1991 (Attachment 2, pp. 277) in 55 patients with breast cancer who had been randomized to 4 different doses of epirubicin (40, 60, 90 or 135 mg/m^2 given intravenously every 3 weeks). The results showed that there is a positive correlation between AUC values and the myelosuppression induced by epirubicin at doses of 40-135 mg/m^2 indicating that AUC is a good predictor of epirubicin toxicity. The logarithm of the surviving fraction of white blood cells was significantly correlated with the AUC of epirubicin (r=-0.55, p<0.0001, Fig. 5).

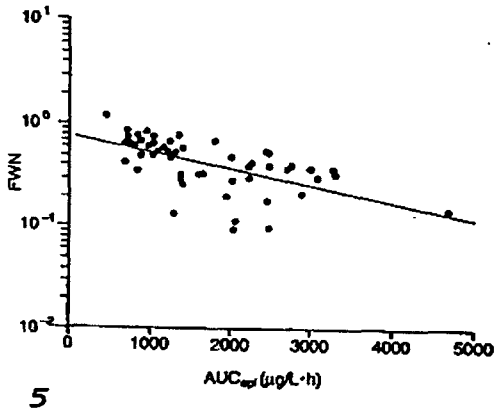


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Fig. 4. Relationship between the area under the plasma concentration-time curve for epirubicin (AUC_{epi}) and the logarithm of fractional white blood cell survival (FWN) at the nadir (r = –0.55, p < 0.0001) [from Jakobsen et al. 1991b, with permission].

In 27 patients with nasopharyngeal carcinoma who were administered 75 mg/m^2 epirubicin, it was found that epirubicin produced a 52% response rate; 6 patients had complete response (CR) and 8 patients with partial response (PR) (Hu et al. 1989, Attachment 2, pp.). Thirteen patients were in the progressive disease (PD) or no change (NC) groups. Mean exposure to epirubicin, as measured by AUC, was 4002±3081 ng.h/ml in CR, 2568±2214 ng.h/ml in PR, and 1881±653 ng.h/ml in NC+PD. There was a significant relationship between the proportion of complete responders/nonresponder and several pharmacokinetic parameters (e.g., AUC, plasma clearance, terminal rate constant, elimination rate constant from central compartment) (Fig. 6-9).

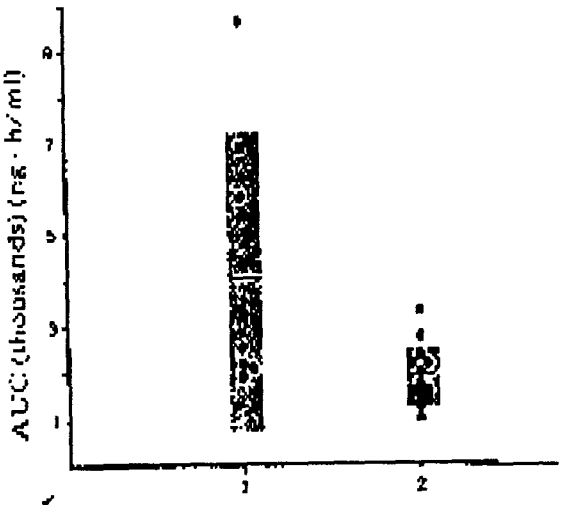

Fig. 6. The AUC of epirubicin in patients, showing the significant difference between complete responders (1) and nonresponders (2). $p < 0.05$

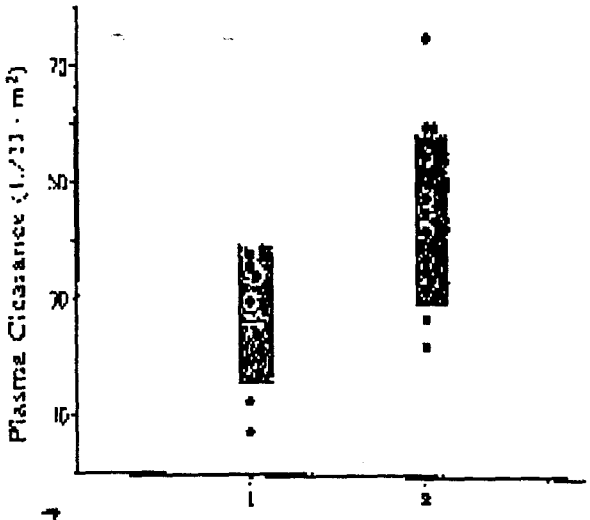

Fig. 7. The plasma clearance of epirubicin in patients, showing the significant difference between complete responders (1) and nonresponders (2). $p < 0.05$

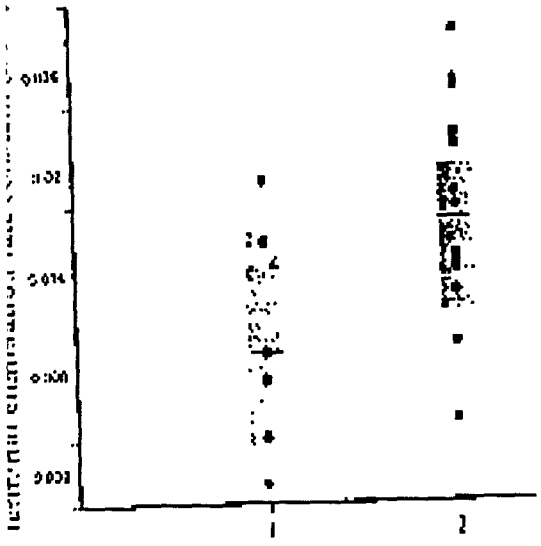

Fig. 8. The terminal elimination rate constants in patients, showing the significant difference between complete responders (1) and nonresponders (2). $p < 0.05$

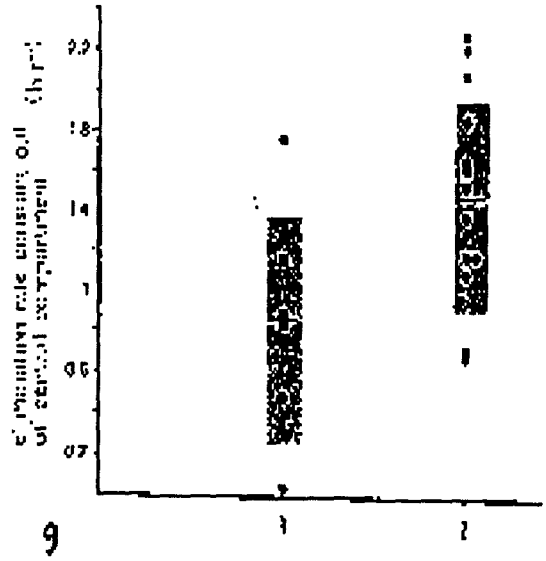

Fig. 9. The elimination rate constant out of the central compartment, showing the significant difference between complete responders (1) and nonresponders (2)

CR 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 CR were lower than those of non-responders ($p<0.05$). The correlation between peak plasma concentration of epirubicin (Cmax) and nadir WBC counts was not significant ($r=0.033$, $p>0.05$, Fig. 10). This suggests that Cmax is not a good indicator of toxicity.

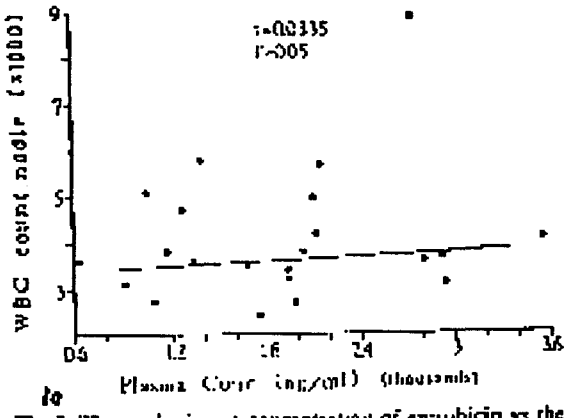

Fig. 8. The peak plasma concentration of epirubicin vs the WBC count nadir in patients, showing the lack of correlation between these parameters

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