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Epirubicin
Clinical Pharmacology and Dose-Effect Relationship

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Summary The pharmacokinetic properties of epirubicin are characterised by a triphasic plasma clearance, with half-lives for the initial (α), intermediate (β) and terminal (γ) elimination phases of approximately 3 minutes, 1 hour and 30 hours, respectively. These values are similar to or slightly shorter than the corresponding half-lives of doxorubicin. The total plasma clearance of epirubicin is approximately 50 L/h/m^2, which is almost 2-fold higher than that of doxorubicin. This difference is mainly due to the relatively high volume of distribution of epirubicin, and the unique glucuronidation metabolic pathway of epirubicin and epirubicinol, which is not available to doxorubicin or doxorubicinol. Glucuronide metabolites of epirubicin and epirubicinol are not active *per se,* but could divert epirubicin from free radical formation, which may induce cardiotoxic effects. This may explain, at least in part, the lower cardiotoxicity of this new anthracycline relative to that of the parent compound. There is a linear relationship between the dose administered and area under the plasma concentration-time curve (AUC) values of both unchanged drug and metabolites, so that the total plasma clearance of epirubicin is constant with epirubicin doses ranging from 40 to 140 mg/m^2. No variation in total plasma clearance as a function of age in the range of 31 to 74 years has been observed, and this parameter is unaffected by subsequent courses of treatment. Hepatic dysfunction causes an increase in the terminal elimination half-life of epirubicin, which is well correlated with serum bilirubin levels and which necessitates a reduction in epirubicin dosage.

Epirubicin is responsible for a dose-dependent neutropenia, which is clearly related to drug exposure as established in pharmacodynamic studies. The maximum tolerated dose (MTD) of epirubicin was first established to be approximately 90 mg/m^2 but this was re-examined recently and is now deemed to be approximately 150 mg/m^2, which is about 2-fold higher than the MTD of doxorubicin. Cumulative cardiac toxicity occurs for both epirubicin and doxorubicin, but the dose ratio for equal risk is about 1.8 in favour of epirubicin (500 to 550 mg/m^2 for doxorubicin *vs* 900 to 1000 mg/m^2 for epirubicin). Consequently, there is not a higher risk of developing cardiotoxicity after administration of high dose epirubicin, since this adverse effect is associated with total cumulative anthracycline dose. In several controlled trials, epirubicin exhibited the same anticancer activity as doxorubicin when administered at equimolar doses to patients with advanced breast cancer. When used in high dose regimens, either as a single agent or in combination with other cytotoxic drugs, response rates were significantly increased in most studies, with acceptable immediate toxicity and no increase in cardiac risk. Together, these factors justify the use of epirubicin as adjuvant therapy in patients with breast cancer of poor prognosis.

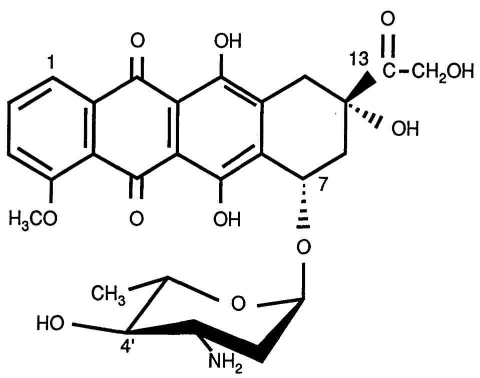


Fig. 1. Structural formula of epirubicin. The ketone moiety of C-13 is reduced in epirubicinol; the hydroxyl group of C-4′ is axial in doxorubicin and equatorial in epirubicin, which allows conjugation of epirubicin with glucuronic acid.

Epirubicin (4′-epidoxorubicin) is a new anthracycline that is commercially available in several countries; it was selected on the basis of its activity against a broad range of tumours (Arcamone et al. 1975; Casazza 1979) and reduced cardiac toxicity (Bertazzoli et al. 1985; Casazza 1979) in experimental models. Epirubicin differs from doxorubicin only in the spatial orientation of the 4′ hydroxyl moiety (fig. 1). Epirubicin behaves like doxorubicin in several *in vitro* systems (Hill & Whelan 1982; Plumbridge & Brown 1978), but has a higher cellular uptake than doxorubicin, probably because of its lower pKa and higher lipophilicity. In addition, from a metabolic and pharmacokinetic perspective, epirubicin exhibits some unique features. This paper reviews its clinical pharmacology, with special emphasis on the high dose protocols that have recently been developed for the treatment of advanced breast cancer.

1. Clinical Pharmacology

1.1 Pharmacokinetic Properties

A number of studies have evaluated the pharmacokinetic properties of epirubicin after intravenous administration of doses ranging between 20 and 150 mg/m^2. An overview of the main phar- is presented in table I. Figure 2 demonstrates representative triphasic plasma decay of epirubicin and doxorubicin in patients with breast cancer after administration of an intravenous bolus of 50 mg/m^2. Successive half-lives of epirubicin were approximately 3 minutes, 1 hour and 30 hours, which were slightly shorter than those observed for doxorubicin in crossover studies (Camaggi et al. 1988; Eksborg et al. 1986a; Mross et al. 1988). Furthermore, as illustrated in figure 2, plasma levels achieved after epirubicin administration were consistently lower than those obtained after doxorubicin administration. As a result, the total plasma clearance of epirubicin was approximately 50 to 100% higher than that of doxorubicin (50 *vs* 30 L/h/m^2), which reflects both a major supplementary metabolic pathway for epirubicin and substantial tissue penetration, as shown by the high volume of distribution of epirubicin compared with that of doxorubicin (1000 *vs* 500 L/m^2).

When epirubicin was administered as a prolonged infusion, the pharmacokinetic parameters remained unchanged (de Vries et al. 1987; Robert & Bui 1992; Workman 1992). The main characteristic of this type of administration is the relatively short time required to achieve steady-state plasma concentrations (< 24 hours), despite the protracted half-life of the drug. There is a good linear relationship between the dose administered and the values for area under the plasma concentration-time curve (AUC) of both unchanged drug and metabolites, so that the total plasma clearance of epirubicin is constant over the dosage range of 40 to 140 mg/m^2 (Jakobsen et al. 1991a). No significant variation in total plasma clearance as a function of age in the range of 31 to 74 years has been observed, and this parameter remains unchanged after subsequent courses of treatment (Jakobsen et al. 1991a). Hepatic dysfunction causes an increase in the terminal elimination half-life of epirubicin, which is well correlated with serum bilirubin levels and which necessitates epirubicin dosage reduction (Camaggi et al. 1982; Jakobsen et al. 1991a). Several investigators have studied intrahepatic administration of epirubicin through the hepatic artery;

Table I. Pharmacokinetic parameters of epirubicin

Reference	No. of courses	Dose (mg/m^2)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	CL ($L/h/m^2$)	Vd_{ss} (L/m^2)	$t_{1/2}$ 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
Tjuljandin 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: $t_{1/2\alpha}$ = half-life of initial phase; $t_{1/2\beta}$ = half-life of intermediate phase; $t_{1/2\gamma}$ = half-life of terminal elimination phase; $t_{1/2\ metab}$ = 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.

et al. 1985). The elimination curves obtained under these conditions are similar to those obtained after intravenous administration, but systemic plasma drug concentrations were lower and total plasma clearance was 1.5- to 2-fold higher with intrahepatic administration. Other routes of epirubicin administration have been tested, such as intraperitoneal (Strocchi et al. 1985) and intravesical instillations (Mross et al. 1987), but have not yet become routine clinical practice.

1.2 Metabolism and Elimination

Epirubicin undergoes extensive metabolism, including conversion to a 13-dihydro metabolite, epirubicinol. The enzyme responsible for this

able to reduce most anthracyclines, with different rates and affinities for the specific agents (Loveless et al. 1978). As with doxorubicinol, epirubicinol remains quantitatively less important than the parent drug, and displays only minimal cytotoxic activity (Schott & Robert 1989). 7-Deoxyaglycone metabolites of epirubicin are also generally found in plasma after epirubicin administration; however, concentrations are low and are not detectable in all patients.

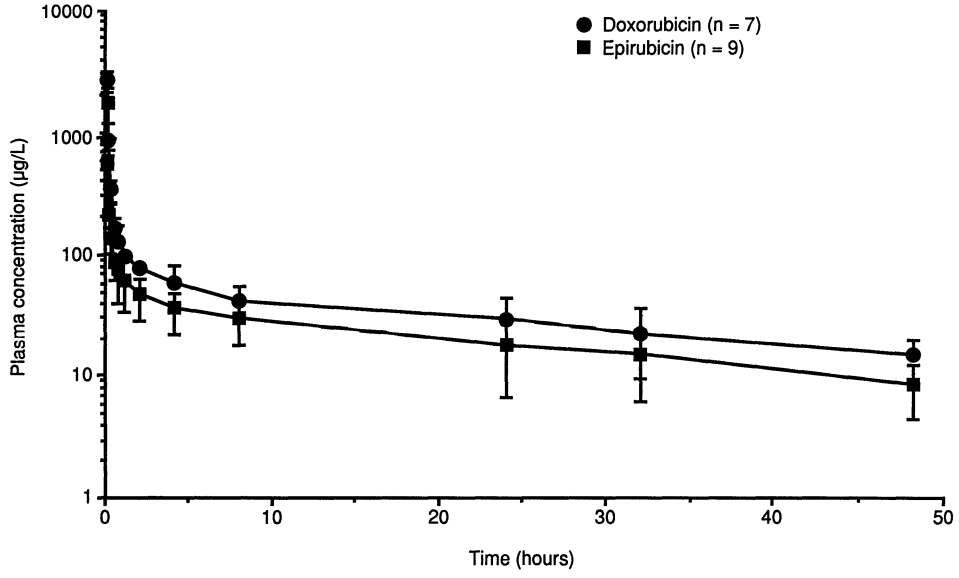
It was first recognised by Weenen et al. (1983, 1984) that, in humans, epirubicin could undergo conjugation with glucuronic acid as a result of the equatorial orientation of the hydroxyl moiety in the C-4′ position. High concentrations of glucu-

al. 1985) [fig. 3]. These glucuronide compounds display no cytotoxicity, but it has been suggested that they could divert epirubicin from the redox cycle, which leads to the formation of free radicals (activated oxygen species). These free radicals are thought to account, at least in part, for cardiac toxicity. Therefore, this metabolic pathway may result in the better cardiac tolerability of epirubicin. However, this is merely a hypothesis, and the possible roles of epirubicin conjugation have not been studied in detail. We have documented a bimodal distribution of patients with respect to metabolic transformation of epirubicin, and improved tolerability in patients having a low metabolite *vs* unchanged drug ratio (Robert et al. 1990).

As with other anthracyclines, urine remains a minor route of excretion, not exceeding 20% of an administered dose. Biliary excretion has been studied extensively by Camaggi et al. (1986), who found a cumulative excretion of approximately 40% over 3 days. Considered altogether, half of a doxorubicin dose is eliminated and accounted for in 7 days following administration, whereas half of an epirubicin dose is eliminated and accounted for in 4 days.

1.3 Pharmacokinetic-Pharmacodynamic Relationships

In a very detailed study performed in 55 patients, Jakobsen et al. (1991b) were able to show a positive correlation between the AUC and myelotoxicity of epirubicin in the dosage range of 40 to 135 mg/m^2. The logarithm of the surviving fraction of white blood cells (WBC) was strongly dependent upon the AUC of epirubicin, either unchanged or together with epirubicinol ($r = -0.55$). This correlation was clearly maintained when only 1 or 2 time-points were selected with a limited sampling model, and allowed good predictability of WBC nadirs after drug administration. It has been suggested that such plasma concentration evaluations could be used to determine whether the nadir expected falls below an acceptable limit, thus indicating the need for haemopoietic support with colony-stimulating factors (CSFs).



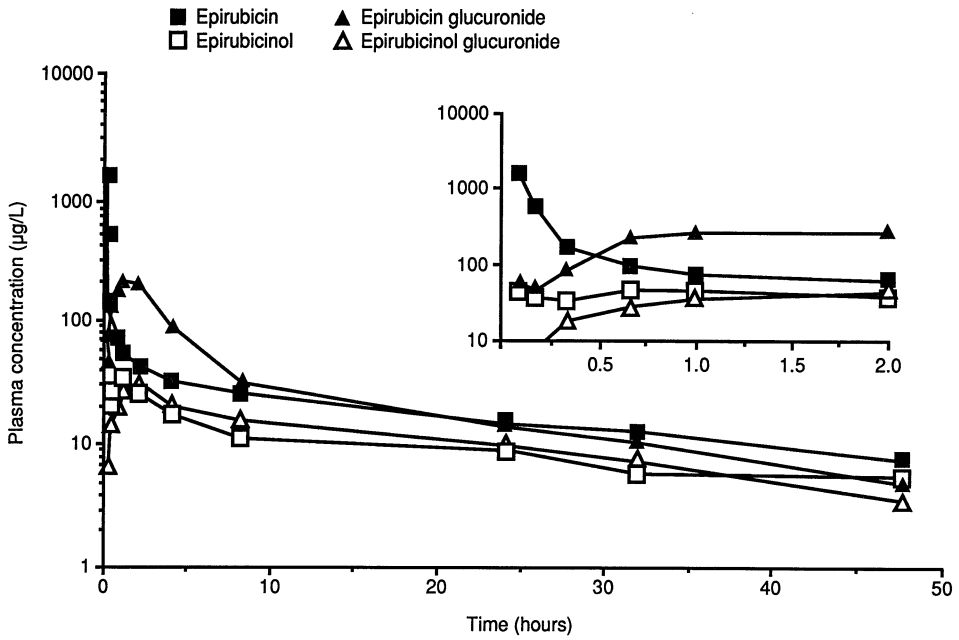


Fig. 3. Plasma concentration *vs* time curves of epirubicin and its metabolites derived from mean values in 9 patients following intravenous administration of 50 mg/m^2.

It is much more difficult to determine a relationship between pharmacokinetic parameters and drug efficacy. Hu et al. (1989) have observed that response to the drug occurred more frequently when the AUC of epirubicin was high.

2. Dose-Effect Relationships: Comparison with Doxorubicin

During the early development of epirubicin, the maximum recommended dose was between 75 and 90 mg/m^2, with leucopenia as the dose-limiting toxicity (Ganzina 1983). On this basis, a number of phase II and III studies have utilised doses in the range of 60 to 80 mg/m^2 administered every 3 weeks (see review by Mouridsen et al. 1990). Recently, the maximum tolerated dose has been reassessed, and is now estimated to be approximately 150 to 180 mg/m^2 in low risk patients and 105 to 120 mg/m^2 in previously treated patients (Case et al. 1987, 1988). In the following sections we have reviewed the efficacy and toxicity of epirubicin at compared with the efficacy and toxicity of doxorubicin, and the impact of using high dose (100 to 180 mg/m^2) regimens of epirubicin.

2.1 Efficacy and Toxicity of Epirubicin *vs* Doxorubicin with Single-Agent and Combination Regimens

Bone marrow toxicity is the dose-limiting acute toxicity associated with epirubicin and doxorubicin administration. Mouridsen (1990) evaluated several single-agent comparative randomised studies, and demonstrated slightly lower myelotoxicity with epirubicin. The dosage ratio of doxorubicin : epirubicin that achieved equivalent haematological toxicity was approximately 1 : 1.2. In another literature analysis, Hérait et al. (1992) observed grade 3 to 4 leucopenia in 40% of patients treated with 75 mg/m^2 doxorubicin and in 20% of patients treated with 85 to 90 mg/m^2 epirubicin. These results also demonstrated that epirubicin is less myelotoxic than doxorubicin. Potentially lethal cardio-

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