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Pharmacokinetics and Metabolism of Epirubicin during Repetitive Courses of Administration in Hodgkin's Patients

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Abstract—*We studied the pharmacokinetics and metabolism of epirubicin (4'-epidoxorubicin) in ten patients suffering from Hodgkin's disease and receiving three successive injections of epirubicin at 15-day intervals in a combined chemotherapy regimen. Doses were either constant (35 mg/m²) or escalated from 25 to 35 and 50 mg/m². Epirubicin metabolism was characterized by the presence of high levels of epirubicin glucuronide in plasma and urine. The area under the time-concentration plasma curve of epirubicin glucuronide reached almost that of unchanged epirubicin (mean ratio = 0.7-0.85), whereas the cumulative urinary excretion of epirubicin glucuronide was one-half of that of epirubicin (mean ratio = 0.45-0.51). Repeating or escalating the doses did not change the levels of the glucuronide significantly. Only a trend towards higher relative levels of glucuronide could be noticed at the lowest dose. The pharmacokinetic parameters of epirubicin were characterized by a high total plasma clearance (mean value: 70-85 l/hr) and a mean elimination half-life of 25-35 hr. Repeating or escalating the doses was followed by a slight increase of the total plasma clearance in most patients, without changes of the elimination half-life. The cumulative urinary excretion was 11-12% of the dose administered and did not vary significantly as a function of time or dose.*

INTRODUCTION

EPIRUBICIN (4'-epidoxorubicin) is an anthracycline antibiotic derived from doxorubicin, with a different configuration of the hydroxyl substituent in the 4' position of daunosamine. It is active against a broad spectrum of animal tumors [1, 2] and has been selected in clinics because of its reduced cardiac toxicity [3, 4]. As compared to doxorubicin, this molecule is active in therapeutics at similar doses, but the same toxicity is observed for 1.5-2 times higher doses [5]. Pharmacokinetic studies have been conducted in animals [6] and in humans [3, 7-10]. A glucuronidation pathway, which is unique in the anthracycline series, has been recognized first by Weenen *et al.* [9, 11] and high levels of epirubicin glucuronides have been found in plasma [10]. Distribution and elimination of epirubicin are comparable to those of doxorubicin; however, epirubicin is characterized by an increase of the total volume of distribution and therefore by an increase of the total plasma clearance [9, 10].

It is now established that doxorubicin follows a time-dependent and dose-dependent kinetics [12-14]. In view of the important level of glucuronides which are formed from epirubicin, the question raises whether this metabolic pathway is time and/or dose-dependent, i.e. whether the plasma levels and plasma clearance of epirubicin are subjected to important variations during the successive courses of treatment, due to differences in the metabolic transformations of the drug. The aim of the present study was to evaluate the pharmacokinetic and metabolic parameters in patients receiving three successive courses of treatment either at the same dosage (35 mg/m², five patients) or at escalating doses (25, 35, 50 mg/m², five patients). Our results showed no change in the metabolic trans-

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formation of epirubicin during the three courses of treatment, in the whole range of doses studied. Only a trend towards an increase of the total plasma clearance of the drug was noticed between the first and second courses of treatment; this trend had also been noticed for doxorubicin [14].

MATERIALS AND METHODS

Patients

Ten patients were included in the study. All of them had Hodgkin's disease, type 1-4, stage I-IIIA. They were included in a pilot study organized by the French "Groupe Pierre & Marie Curie". The scheme derived from the ABVD regimen of Bonadonna *et al.* [15]. Patients each received epirubicin (25-50 mg/m^2), bleomycin (10 mg/m^2) and vinblastine (6 mg/m^2) for 15 days and prednisone (40 mg/m^2/day) for 7 days. Preliminary clinical results have been reported recently [16].

Epirubicin was injected first; the duration of the perfusion was 3-6 min and was exactly measured. The remainder of the chemotherapy was injected 2 hr after epirubicin. Blood samplings were made at selected times after the end of epirubicin infusion, generally close to 3, 6, 12, 20 and 40 min, and 1, 2, 4, 8, 24, 32 and 48 hr. The blood was collected on EDTA-coated Vacutainer tubes and immediately centrifuged. The plasma was frozen until analysis. Urine specimens were collected cumulatively as fractions representing the following periods after drug injection: 0-4 hr, 4-8 hr, 8-24 hr and 24-48 hr. Urine was extracted and analyzed immediately after collection.

Extraction and analysis of epirubicin and its metabolites

Plasma or urine samples were supplemented with a known amount of daunorubicin as an internal standard. Anthracyclines and metabolites were extracted on C18 Sep-pak cartridges as already described [17]. This extraction technique allows a quantitative recovery of the glycosides, of the aglycones and of the glucuronoconjugates. The extracts were injected in a Waters high-performance liquid chromatograph equipped with a Microbondapak phenyl column. The solvent (3 ml/min) was a mixture of 0.1% ammonium formate buffer, pH 4, and acetonitrile (68/32) [18]. The detection was done by a Perkin-Elmer LS 1 spectrofluorometer with an excitation wavelength of 470 nm and an emission wavelength of 560 nm. Epirubicin and all its metabolites could be separated with this technique in less than 10 min, with a sensitivity of 2×10^{-9} g of compound. Identification of the peaks was obtained by comparison with authentic standards provided by Farmitalia-Carlo Erba. Glucuronides had been positively identified in our system in a previous work [11]. Their structure has been definitively proved by several authors [11, 19].

Mathematical processing of the data

The epirubicin data were analyzed by fitting a three-compartment model to the observed plasma concentrations, taking into account the duration T of the infusion of the dose injected D. The epirubicin concentration is computed at each time t, for $t \geqslant T$, as follows:

$$y(t) = \frac{D}{T} \sum_{j=1}^{3} \frac{A_j}{\alpha_j} (e^{\alpha_j T} - 1)\ e^{-\alpha_j t}$$

We have used, as already described [10, 20], a weighted least squares method to estimate the unknown parameters A_j and α_j. This method consists in the minimization of the expression

$$J = \sum_{i=1}^{m} \frac{1}{Yi^2} [Yi - y(ti)]^2$$

with respect to A_j and $\alpha_j s$. In the above expression Yi are the experimental values, $y(ti)$ the values generated from the model and $1/Y_i^2$ the weights taking into account the reproducibility of the analytical method.

Minimization of J has been done by using an iterative algorithm from the non-linear programming technique. This algorithm is based on the BFGS formula implemented in the VA 13A subroutine of the Harwell Subroutine Library [21].

Estimated values of the microconstants α_j and A_j enable the computation of most relevant pharmacokinetic parameters, the total plasma clearance Cl, the successive half-lives $T_{1/2}$ and the total volume of distribution of the drug, V_T.

Concerning the metabolites, a model-independent approach was used. Only terminal half-lives and areas under the concentration-time curves were evaluated, the former by linear regression analysis, the latter by the trapezoidal rule. We have computed for each metabolite the ratio of the area under the time-concentration curve to that of the parent compound.

RESULTS

The pharmacokinetic parameters obtained for the first course of treatment in the 10 patients are presented in Table 1. The results have been pooled for the two initial dosages, 25 and 35 mg/m^2, since no difference could be evidenced between the two groups. The mean half-lives of

Table 1. Pharmacokinetic parameters of epirubicin obtained from the mathematical modeling of analytical data (all parameters concern only the unchanged drug and the first course of treatment)

Patients	Sex, age	A	B	C	α	β	γ	Cl	V_T
		($l^{-1} \times 10^{-3}$)				(hr^{-1})		(l/h)	(l)
				dose: 35 mg/m²					
CRO	M, 45	72.8	0.460	0.208	14.8	0.533	0.0132	46.6	2577
BUI	M, 46	65.9	0.470	0.186	10.2	0.792	0.0194	60.1	1791
DES	M, 26	75.1	1.05	0.247	16.7	1.86	0.0308	77.0	1530
TIN	M, 26	88.3	1.04	0.211	18.6	1.75	0.0276	77.1	1644
DEZ	M, 34	75.3	0.828	0.167	17.3	1.06	0.0304	94.1	1609
				dose: 25 mg/m²					
DAS	F, 31	59.7	0.618	0.182	15.6	0.841	0.0294	93.1	1828
DUB	M, 38	108	1.25	0.233	23.0	2.72	0.0460	97.9	1061
BAU	F, 20	135	0.756	0.204	21.9	0.654	0.0304	71.4	1129
JEG	F, 58	106	0.581	0.179	14.6	0.172	0.0139	42.4	1711
DSI	M, 21	129	0.901	0.300	20.7	1.139	0.0304	59.0	1137
Mean		91.6	0.795	0.212	17.34	1.152	0.0272	71.9	1602
S.D.		26.6	0.267	0.039	3.86	0.756	0.0096	19.7	446

A, B and C and α, β and γ are the parameters A_i and α_i in the equation presented in Materials and Methods; Cl is the total plasma clearance and V_T the total volume of distribution of the drug.

the α, β and γ phases are successively 2.53 ± 0.66 min, 1.04 ± 1.10 hr and 29.3 ± 12.6 hr. The metabolites are presented in Table 2. Two parameters only have been considered: the elimination half-life and the ratio of the area under the curve of the metabolite and that of the unchanged drug. The patients receiving the lower dose show slightly higher glucuronide plasma levels ($P < 0.05$).

The urinary excretion of the drug and its metabolites has been studied over 48 hr. The cumulative excretions are presented in Table 3 and the rate of excretion, expressed per hour, is presented in Fig. 1. The mean cumulative urinary excretion is about 11% of the dose injected, and the glucuronides account for one-third of the total. About 70% of the urinary excretion of epirubicin occurs during the first 4 hr, whereas during the same period only 23% of the urinary excretion of epirubicinol and 55% of the urinary excretion of

Table 2. Pharmacokinetic parameters obtained for the metabolites of epirubicin by a model-independent analysis (first course of treatment only)

Patient	$T_{1/2}$ (hr)			R		
	epi ol	glc-epi	glc-epi ol	epi ol	glc-epi	glc-epi ol
			dose: 35 mg/m²			
CRO	24.3	19.0	10.5	0.201	0.594	0.159
BUI	17.1	12.3	11.3	0.227	0.683	0.286
DES	13.6	8.2	10.4	0.158	0.547	0.161
TIN	25.6	21.4	N.E.	0.178	0.848	0.112
DEZ	39.5	12.1	N.E.	0.326	0.471	0.144
			dose: 25 mg/m²			
DAS	17.4	5.3	N.E.	0.343	1.495	0.405
DUB	11.1	14.4	N.E.	0.398	1.207	0.438
DUB	20.8	N.E.	N.E.	0.308	0.788	0.328
JEG	18.4	23.0	19.6	0.256	1.007	0.507
DSI	23.1	N.E.	N.E.	0.188	0.888	0.213
Mean	21.1	14.5	13.0	0.258	0.854	0.275
S.D.	7.9	6.3	4.4	0.081	0.317	0.139

Abbreviations: $T_{1/2}$: elimination half-life; R: ratio of the area under the curve of the metabolite and that of the unchanged drug; epi ol: 1,3-dihydroepirubicin (epirubicinol); glc-epi: epirubicin glucuronide; glc-epi ol: epirubicinol glucuronide; N.E.: not evaluable.

Table 3. Urinary excretion of epirubicin and its metabolites after 48 hr from the first injection

Patient	% of dose recovered in urine	R epi ol	R glc-epi	R glc-epi ol
	dose: 35 mg/m²			
CRO	12.0	0.114	0.502	0.128
BUI	11.6	0.127	0.442	0.167
DES	13.6	0.187	0.476	0.049
TIN	11.5	0.135	0.581	0.184
DEZ	8.1	0.113	0.312	0.102
	dose: 25 mg/m²			
DAS	11.8	0.130	0.441	0.135
DUB	10.9	0.179	0.605	0.182
BAN	12.8	0.190	0.560	0.236
JEG	10.8	0.144	0.634	0.164
DSI	7.1	0.073	0.528	0.134
Mean	11.0	0.139	0.513	0.148
S.D.	2.0	0.037	0.100	0.051

R = ratio of cumulative urinary excretions: (metabolite)/(unchanged drug).
The abbreviations used are the same as in Table 2.

Table 4. Time- and dose-dependence of the plasma pharmacokinetic parameters of epirubicin during three courses of treatment

Patient	Total plasma clearance (l/hr) 1st	2nd	3rd	Elimination half-life (hr) 1st	2nd	3rd
			dose: 3 × 35 mg/m²			
CRO	46.6	65.8	58.0	52.4	40.8	33.8
BUI	60.0	81.2	108.5	35.8	43.3	23.5
DES	77.0	91.3	77.8	22.5	27.6	21.5
TIN	77.1	86.3	95.7	25.1	32.9	31.1
DEZ	94.1	93.3	93.7	22.8	26.4	44.2
Mean	71.0	83.6	86.7	31.7	34.2	30.8
S.D.	18.2	11.0	19.4	12.8	7.6	9.1
			dose: 25, 35, 50 mg/m²			
DAS	93.1	72.9	82.3	23.5	18.5	20.2
DUB	97.9	90.9	65.8	15.1	30.3	47.1
BAU	71.4	84.7	109.3	22.0	33.4	25.6
JEG	42.4	67.2	74.3	50.0	28.5	30.1
DSI	59.0	73.6	84.6	22.8	24.4	20.9
Mean	72.8	77.9	83.5	26.8	27.0	28.4
S.D.	23.2	9.7	18.8	13.4	5.8	6.9

epirubicin glucuronide have occurred. It should be noticed that the plasma ratio of the areas under the curve (metabolite/unchanged drug) is significantly higher than the corresponding ratios of urinary cumulative excretions.

When repeating the courses of treatment at the same dose, one can observe in four patients an increase of the total plasma clearance of the drug between the two first injections; in two cases the clearance comes back to its initial value between the second and third injections of the drug. The differences observed between the means show a trend towards an increase of the clearance, whereas no change at all of the elimination half-life is seen (Table 4). Increasing the doses from course to course shows an increase in the clearance of three patients and irregular modifications in two other patients. No change of the elimination half-life can be seen.

We present in Table 5 the evolution of the plasma parameters concerning the main metabolite, epirubicin glucuronide, during the successive courses of treatment. No significant changes were exhibited either in the patients receiving the same dosage or in the patients receiving escalating doses. In some patients, however, we observed a decrease of glucuronide levels when increasing the dose.

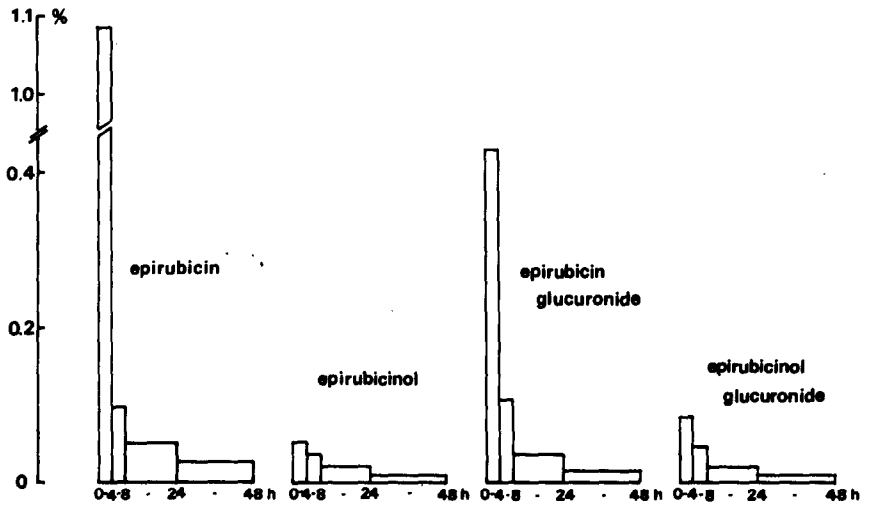

Fig. 1. Rate of urinary excretion of epirubicin and its metabolites during the first course of treatment of the ten patients of the study. Columns represent the mean percentages of the total dose injected excreted in urine per hour during the periods considered.

Table 5. Time- and dose-dependence of the plasma pharmacokinetic parameters of epirubicin during three courses of treatment

Patient	Elimination half-life (hr) 1st	2nd	3rd	*R* 1st	2nd	3rd
		dose: 3 × 35 mg/m²				
CRO	19.0	15.7	14.5	0.594	0.538	0.446
BUI	12.3	9.9	11.1	0.683	0.676	0.805
DES	8.2	10.1	20.1	0.547	0.568	0.779
TIN	21.4	N.E.	16.0	0.848	0.553	0.739
DEZ	12.1	10.7	6.8	0.471	0.355	0.514
		dose: 25, 35, 50 mg/m²				
DAS	5.3	25.3	15.4	1.495	0.660	0.647
DUB	14.4	12.8	24.0	1.207	0.545	0.695
BAU	N.E.	N.E.	N.E.	0.788	0.181	0.925
JEG	23.0	12.0	18.8	1.007	1.075	0.624
DSI	N.E.	N.E.	N.E.	0.888	1.069	1.193
Mean	14.5	13.8	15.8	0.853	0.722	0.737
S.D.	6.3	5.5	5.3	0.317	0.282	0.213

The abbreviations used are the same as in Table 2.

A constant percentage of the dose injected was recovered in the urine as unchanged drug and metabolites after 48 hr in most patients (Table 6). In one patient, however, escalating the dose was followed by an increase of the urinary excretion. The urinary excretion of the main metabolite was slightly higher in patients receiving 25 mg/m² than in patients receiving 35 mg/m², whatever the course of treatment (Table 6).

DISCUSSION

Epirubicin metabolism is characterized by the existence of glucuronoconjugates, which are unique in the anthracycline series. Those metabolites are present at high levels in plasma as already mentioned [10], and their area under the time-concentration curve is almost as high as that of the unchanged drug. It must be underlined that the ratio of the cumulative urinary excretions of both compounds is lower than the ratio of their plasma area under the curve; which means that glucuronides are not a preferential urinary mode of excretion.

Whether glucuronides are mainly excreted through bile or further transformed in the organism is at present not known. The meaning of this original pathway is not clearly understood; these metabolites are probably not active, but the use of epirubicin as a substrate for glucuronyltransferases may play an important role in the tissue distribution of this drug and its bioavailability. Moreover, the further transformations of these glucuronides are not known; they can serve as precursors for active epirubicin through tissue glucuronidases, for instance. Further work is actually required for the complete understanding of this pathway and its possible role on the clinical activity of epirubicin as compared to that of doxorubicin. This metabolic pathway is not dramatically modified by previous injections of epirubicin; this could be of importance in view of possible hepatic induction of glucuronyltransferases. Only a trend towards a decrease in the relative amounts of glucuronides in plasma and urine could be noticed when the dose administered was increased; this could indicate a saturation of the metabolic transformation.

The pharmacokinetics of epirubicin is characterized by a very high volume of distribution, as compared to that of doxorubicin. This had

Table 6. Time- and dose-dependence of the urinary parameters of epirubicin and its metabolites

Patient	% of dose recovered in urine after 48 hr 1st	2nd	3rd	Cumulative urinary excretion: (glucuronide)/(epirubicin) 1st	2nd	3rd
			dose: 3 × 35 mg/m²			
CRO	12.0	14.8	14.3	0.502	0.338	0.425
BUI	11.6	11.8	9.9	0.442	0.455	0.362
DES	13.6	13.4	11.5	0.476	0.433	0.557
TIN	11.5	10.6	9.2	0.581	0.424	0.392
DEZ	8.1	8.2	11.6	0.312	0.209	0.360
			dose: 25, 35, 50 mg/m²			
DAS	11.8	12.9	9.3	0.441	0.514	0.407
DUB	10.9	11.9	11.2	0.605	0.379	0.296
BAU	12.8	11.5	13.8	0.560	0.552	0.529
JEG	10.8	11.3	13.2	0.684	0.616	0.521
DSI	7.1	10.2	18.4	0.528	0.698	0.602
Mean	11.0	11.7	12.2	0.513	0.476	0.445
S.D.	2.0	1.8	2.8	0.100	0.137	0.101

already been noticed in previous studies [9, 10]. As a consequence, the total plasma clearance of the drug is higher than that of doxorubicin. It can be hypothesized that the kinetic differences between epirubicin and doxorubicin are due to the original biotransformation of epirubicin. Epirubicin is eliminated from the plasma 1.5–2 times faster than doxorubicin [7, 9, 11]; a toxicity comparable to that of doxorubicin is obtained only for doses 1.5–2 times higher [3–5]. However, the clinical efficacy of doxorubicin is maintained at the same doses, as indicated by the results of a randomized phase III study [22]. In most patients the successive courses of treatment are characterized by an increase of the total plasma clearance, as already noticed for doxorubicin [12, 14]. Escalating the dose did not cause further modification of this parameter. No change of the elimination half-lives was noticed during the successive courses of treatment. No change of the urinary elimination was noticed either. In summary, only slight changes are exhibited in epirubicin disposition from one course to another.

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