Cancer Chemother Pharmacol (1989) 24: 225–229

Cancer Chemotherapy and Pharmacology

Comparison of the intracellular pharmacokinetics of doxorubicin and 4'-epi-doxorubicin in patients with acute leukemia

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Summary. A direct comparison of the intracellular pharmacokinetics of 4'-epi-doxorubicin and doxorubicin was carried out in five patients with leukemia who were given weekly low doses of a combination of these drugs at 20 mg each in an i.v. injection. Blood samples were collected for 48 h after administration and the drug concentrations in leukemic cells were determined by high-performance liquid chromatography (HPLC). The intracellular peak concentrations of 4'-epi-doxorubicin were higher than those of doxorubicin in all patients. The AUC for the intracellular drug concentration vs time curve was significantly higher for 4'-epi-doxorubicin. The intracellular uptake and retention were also studied in vitro after incubation of isolated leukemic blast cells with the two drugs; they showed the same pattern observed in vivo. We conclude that 4'-epi-doxorubicin and doxorubicin exhibit different pharmacokinetics in malignant cells. The therapeutic significance of this finding requires further evaluation.

Introduction

Anthracycline antibiotics are effective in the treatment of leukemia and many solid tumors. Their clinical use is restricted by acute bone marrow toxicity and chronic cumulative cardiotoxicity [8]. A number of analogues of daunorubicin and its 14-hydroxy derivative doxorubicin have been synthetized with the aim of reducing toxicity and thereby increasing the therapeutic index. One of these analogues, 4'-epi-doxorubicin, is an epimer of doxorubicin in which the hydroxyl group at position 4 of the amino sugar has been rotated from the L-*lyxo* configuration of doxorubicin to the L-*arabino* configuration.

Plasma pharmacokinetic studies [4, 5, 17, 21] have shown a similar pattern but suggest a higher distribution volume and faster elimination for 4'-epi-doxorubicin than for doxorubicin. Another difference is that higher concentrations of glucuronides of 4'-epi-doxorubicin and its 13-dihydro metabolite are found in plasma and urine compared with doxorubicin concentrations [5, 17, 21]. From studies in animals [6] and patients [3, 6, 7, 20], there are indications of lower myelotoxicity and chronic cardiotoxicity for 4'-epi-doxorubicin than for doxorubicin. It has also been reported that 4'-epi-doxorubicin may have clinical activity in a wider spectrum of solid tumors [3, 7]. Clinical phase I-II studies have shown activity for 4'-epi-doxorubicin against acute leukemias [18], but there have been no randomized studies comparing the antileukemic effect of this drug to that of doxorubicin. The effect of 4'-epi-doxorubicin on solid tumors appears to be comparable to that of doxorubicin, but some reports [3, 7] have indicated an effect for the former on doxorubicin-resistant tumors as well.

In previous studies [13] we have found that there is no simple relationship between the concentration of anthracyclines in plasma and that in tumor cells. The uptake and retention of cytostatic drugs in the malignant cells are probably decisive for the clinical effects. The objective of this study was therefore to compare simultaneously the intracellular pharmacokinetics of doxorubicin and 4'-epi-doxorubicin in tumor cells from patients with acute leukemia to investigate as to whether differences could be found that might be important for the clinical effects of the two drugs.

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Patients and methods

Patients. After informed consent had been obtained, pharmacokinetic studies were carried out in five patients, four of whom had acute nonlymphoblastic leukemias that were not considered suitable for standard intensive chemotherapy. Two patients had undergone relapses after previous therapy that had included anthracyclines, one had leukemia secondary to alkylating agents, and one had a blast crisis of chronic myeloid leukemia. An additional patient was initially diagnosed as having acute lymphocytic leukemia, but after reevaluation the diagnosis was changed to chronic lymphocytic leukemia. The latter three patients had not previously received anthracyclines. No obvious hepatic or renal dysfunction was observed in any of the patients; mean serum alanine aminotransferase was 0.33 μK/l (range, 0.19–0.60 μK/l; ref: <0.70 μK/l), and mean serum creatinine was 96 μmol/l (range, 49–136 μmol/l; ref: <115 μmol/l).

Drug treatment. One patient (number 2 in Table 1) received doxorubicin and 4'-epi-doxorubicin at 30 mg/m^2 each as the starting dose in a reinduction therapy following relapse. The other four patients were treated with weekly injections of 20 mg doxorubicin (Adriamycin) mixed with 20 mg 4'-epi-doxorubicin (Farmorubicin;

Farmitalia, Carlo Erba, Milan, Italy) followed by a flush with physiologic saline. All patients received at least two consecutive courses.

Blood sampling. Peripheral blood was collected in heparinized vacuum tubes before, immediately after, and at ½, 1, 2, 4, 12, 24, and 48 h after the injections. The samples were immediately put in an ice bath and thereafter handled at 4° C. Leukemic cells (80%–90% pure; >90% trypan blue-excluding) were separated (400 *g* for 20 min) on Lymphoprep (Nyegaard & Co; Oslo, Norway: specific weight, 1.067) and then washed twice in phosphate-buffered saline [PBS (pH 7.4); 1000 *g* for 10 min). The plasma and the leukemic cells were frozen and stored at −20° C until analyzed.

In vivo anthracycline assay. Plasma and intracellular concentrations of doxorubicin and 4'-epi-doxorubicin were determined by high-performance liquid chromatography (HPLC) [2]. Cell samples were thawed and sonicated for 20 s at 50 W with a Branson B-12 sonicator (Branson Sonic Power Company; Danbury, Conn). A 0.4-ml aliquot of cell sample or plasma was added to 0.2 ml 0.1 *M* borate buffer (pH 9.3) containing 0.2 μ*M* daunorubicin as an internal standard. The anthracyclines were extracted with 1.8 ml chloroform/methanol (4:1 vol/vol). A 200- to 500-μl aliquot of the organic phase was injected into the model U6-K injector (Waters Associates; Milford, Mass). The Lichrosorb Si-60 column (Hibar, 25 cm × 4 mm; E. Merck, Darmstadt, FRG) was eluted by a mixture of chloroform, methanol, glacial acetic acid, and 0.3 m*M* $MgCl_2$ (720:210:20:30 by vol.) at a flow rate of 1.5 ml/min. The flow rate was maintained with a Waters Associates chromatography pump. The column outlet was connected to a Gilson model FL-1B fluorometer (Gilson Medical Electronics; Middleton, Wis) and the fluorescence (excitation and emission wavelengths, 480 and 560 nm; respectively) signal, integrated by a Chromatopac data processor (Shimadzu Seisakusho Ltd; Kyoto, Japan). The retention times were 3.3 min for daunorubicin, 3.9 min for 4'-epi-doxorubicin, and 4.3 min for doxorubicin. The detection limit of the system is about 0.2 pmol, corresponding to a sample concentration of 0.5 n*M*. Intracellular drug concentrations were related to the amount of cell protein in the sample, determined according to Lowry et al. [11].

In vitro incubation. After separation and washing, leukemic cells from three patients were separated and resuspended to 5×10^5 cells/ml in RPMI 1640 supplemented with 10% fetal calf serum and 1% glutamine. Doxorubicin and 4'-epi-doxorubicin were diluted in PBS to 10 times the incubation concentrations. Then 1.8 ml cell suspension was incubated at 37° C with 0.2 ml anthracyclines to final concentrations of 0.5 μ*M* (cells from three patients) and 1.0 μ*M* (cells from two patients) in a gently shaking bath. After 3 h incubation, when steady-state concentrations were achieved, the cells were centrifuged (400 *g* for 10 min) and resuspended in the same (but fresh) culture medium. The cells were cultured in a humidified incubator at 37° C and 5% CO_2 (ASSAB, T-303); 2-ml samples were taken daily up to 3 days after incubation, washed twice in ice-cold PBS, and frozen until analyzed. All incubations were carried out in duplicate.

In vitro anthracycline assay. After thawing, the cells were sonicated as described above and the drugs were extracted with trichloroacetic acid (TCA) (27%). The drugs were assayed by photofluorometry using a Shimadzu spectrofluorometer model RF-510 (excitation and emission wavelengths, 485 and 560 nm, respectively). Anthracycline concentrations in each sample were determined by comparison with identically treated standard solutions and related to the amount of cell protein.

Drug interaction study. Cells from two patients were incubated in duplicate as described above with doxorubicin and 4'-epi-doxorubicin at a concentration of 0.5 μ*M* separately and in combination. The intracellular drug concentrations were determined by HPLC in samples taken immediately after the incubation. With cells from one of the patients, samples were also taken after 23 h further cultivation in drug-free medium.

Pharmacokinetic evaluation. The $t_{1/2}$ for intracellular drug concentrations was obtained by least-squares linear regression analysis of the terminal log intracellular concentration vs time curves. The AUC for intracellular drug concentrations vs time was calculated using the trapezoidal rule.

Statistical evaluation. For statistical comparison of $t_{1/2}$, peak concentrations, and AUC, Student's *t*-test for paired data was used.

Results

Pharmacokinetics. The pharmacokinetics of doxorubicin and 4'-epi-doxorubicin in leukemic cells are shown as the mean for all patients in Fig. 1 and for each patient in Table 1. No reduced metabolites were detected intracellularly. The mean intracellular peak concentration for all patients was 0.042 nmol/mg cell protein for doxorubicin, compared with 0.065 nmol/mg cell protein for 4'-epi-doxorubicin. This difference was not statistically significant ($P \leq 0.1$), although the maximal uptake of 4'-epi-doxorubicin was consistently higher in all patients. Mean $t_{1/2}$ values for the decline in intracellular drug concentration were shorter for 4'-epi-doxorubicin than for doxorubicin, being

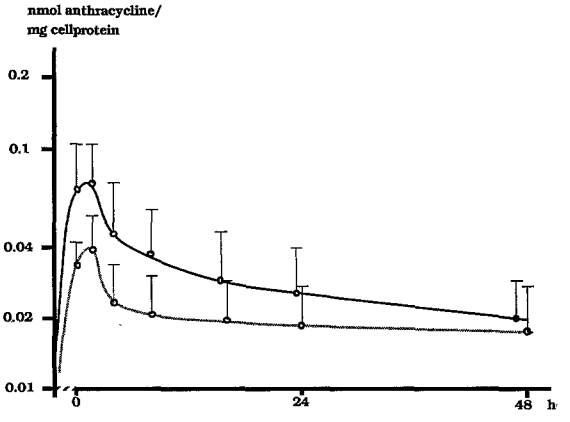

Fig. 1. Intracellular uptake and retention of doxorubicin (*dox, lower curve*) and 4'-epi-doxorubicin (*epi, upper curve*) in vivo (mean ± SD of five patients)

Table 1. Intracellular in vivo pharmacokinetics of doxorubicin (dox) and 4'-epi-doxorubicin (epi) in five patients with leukemia

Patient	Peak concentration (nmol/mg protein)		AUC/48 h (nmol/mg per hour)	
	dox	epi	dox	epi
1	0.026	0.044	0.671	1.306
2	0.038	0.054	0.944	1.612
3	0.060	0.077	0.688	0.638
4	0.050	0.068	1.078	1.736
5	0.041	0.139	1.872	2.552

51 and 115 h, respectively ($P \leq 0.1$). Since 4'-epi-doxorubicin exhibits higher peak concentrations, the intracellular concentrations of that drug remained consistently higher than those of doxorubicin in three patients throughout the 48-h study. In the remaining two patients the concentrations of doxorubicin exceeded those of 4'-epi-doxorubicin within 8 and 20 h, respectively.

The AUC for intracellular drug concentration vs time for the 48 h after injection was significantly higher for 4'-epi-doxorubicin than for doxorubicin ($P \leq 0.025$). The mean values for the AUC during 48 h were 1.05 and 1.57 nmol/mg cell protein per hour for doxorubicin and 4'-epi-doxorubicin, respectively; when extrapolated to infinity, this difference was eliminated. The mean values for total AUC were 3.49 and 2.86 nmol/mg cell protein per hour for doxorubicin and 4'-epi-doxorubicin, respectively (not significant). However, due to the very long $t_{1/2}$ of the drugs, such extrapolation is hazardous, resulting in 62% of the total area for doxorubicin and 37% for 4'-epi-doxorubicin being under the extrapolated (not studied) curve. The plasma peak concentration was 0.36 ± 0.34 μ*M* (mean ± SD) for doxorubicin and 0.39 ± 0.29 μ*M* for 4'-epi-doxorubicin; both drugs showed biphasic elimination kinetics. Due to the low drug concentrations in plasma, it was impossible to make an accurate calculation of the β-slope and thus of other plasma pharmacokinetic parameters.

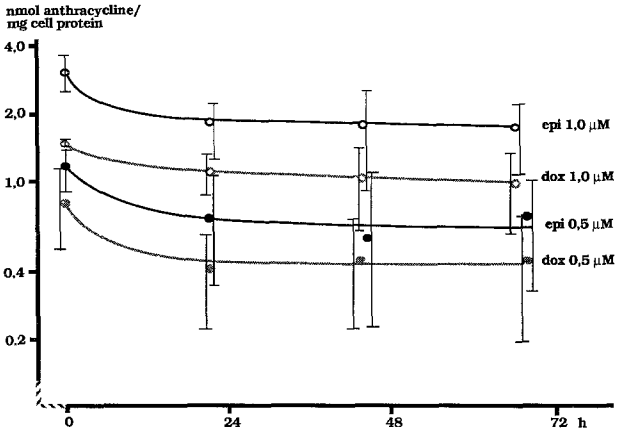

Fig. 2. Intracellular uptake and retention of doxorubicin (*dox*) and 4'-epi-doxorubicin (*epi*) in vitro [mean and range in cells from three (*0.5* μ*M*) and two patients (*1.0* μ*M*)]

In vitro drug uptake and retention

The accumulation and retention of doxorubicin and 4'-epi-doxorubicin by leukemic cells incubated with either 0.2 μ*M* or 0.5 μ*M* drug is shown in Fig. 2 and Table 2. Intracellular peak concentrations of 4'-epi-doxorubicin exceeded those of doxorubicin. The mean uptake was 0.82 nmol/mg cell protein for doxorubicin compared with 1.23 nmol/mg cell protein for 4'-epi-doxorubicin at an incubation concentration of 0.5 μ*M* and 1.46 compared with 3.05 nmol/mg cell protein at 1.0 μ*M*. Both anthracycline derivatives exhibited the same retention pattern in vitro as in vivo. The AUC for intracellular drug concentration vs time was 65% higher for 4'-epi-doxorubicin than for doxorubicin at both concentrations.

Drug interaction

The intracellular concentrations of doxorubicin in cells from two patients were 0.73 and 0.76 nmol/mg protein at the end of the cells' incubation with doxorubicin alone, compared with 0.72 and 0.76 nmol/mg protein after incubation with both drugs in combination. For 4'-epi-doxorubicin the corresponding values were 1.05 and 1.09 nmol/mg protein when the cells were incubated with that drug alone, compared with 0.97 and 0.93 nmol/mg protein after incubation in combination with doxorubicin. After 23 h further cultivation in drug-free medium, the intracellular concentrations of doxorubicin and 4'-epi-doxorubicin were 0.33 and 0.64 nmol/mg protein, respectively, after incubation with the single drugs compared with 0.33 and 0.53 nmol/mg cell protein after incubation with the drugs in combination.

Discussion

4'-Epi-doxorubicin is an anthracycline analogue that differs from doxorubicin by an altered stereoisomeric configuration of a hydroxyl group in the amino sugar moiety.

Table 2. Intracellular in vitro pharmacokinetics of doxorubicin (dox) and 4'-epi-doxorubicin (epi) in cells from three patients with acute leukemia

Patient	Incubation concentration (μ*M*)	Peak concentration (nmol/mg protein)		AUC/72 h (nmol/mg per hour)	
		dox	epi	dox	epi
6	0.5	1.25	1.40	24.1	32.9
7	0.5	0.49	0.85	17.5	31.2
8	0.5	0.73	1.45	49.0	81.7
6	1.0	1.50	3.60	54.1	94.9
8	1.0	1.42	2.50	103.0	166.0

There are no conclusive results about the clinical effects of 4'-epi-doxorubicin compared with doxorubicin in the treatment of acute leukemias [18]. In a previous study [10], a comparison of the plasma pharmacokinetics after simultaneous injections of doxorubicin and 4'-epi-doxorubicin showed a reduced AUC and slightly reduced peak concentrations for 4'-epi-doxorubicin. Other studies [4, 5, 17, 21] have also indicated differences between the two drugs, with a somewhat shorter terminal half-life and a higher apparent volume of distribution for 4'-epi-doxorubicin.

The aim of the present study was to compare pharmacokinetically the uptake and retention of 4'-epi-doxorubicin and doxorubicin by malignant cells. After mixtures of 4'-epi-doxorubicin and doxorubicin had been injected into patients, blood samples were taken and the two drugs were separated and quantitated by HPLC. With this technique it was possible to offset interindividual as well as time-to-time variations, thus making full use of a limited patient material. On the other hand, there is a possibility that the results could be influenced by drug interaction. Because of the close similarity of the molecular structure of the two drugs, it is likely that they are transported in and out of cells by the same mechanisms. As the cellular uptake of anthracyclines in relation to surrounding concentration is linear within a wide range of concentrations [12], interaction of drug uptake is unlikely; this was supported by our in vitro uptake study.

The intracellular drug concentrations in leukemic cells were around 200 times higher than plasma concentrations, which is in accordance with our previous findings for daunorubicin, assuming that a cell volume of 5 µl corresponds to 1 mg cell protein [15]. In leukemic cells 4'-epi-doxorubicin and doxorubicin appeared to differ in terms of their pharmacokinetic properties. The area under the intracellular drug concentration vs time curve during the 48 h after drug administration was significantly higher for 4'-epi-doxorubicin. We observed a tendency for cells to accumulate 4'-epi-doxorubicin at higher concentrations ($P < 0.1$), and the intracellular retention time was shorter for this drug than for doxorubicin.

To evaluate whether these in vivo findings were mainly due to differences in liver metabolism and excretion of the drugs, the accumulation and retention of 4'-epi-doxorubicin and doxorubicin in leukemic cells derived from two additional patients were studied in vitro. The retention curves obtained with cultured cells showed patterns similar to the in vivo curves. These results indicate that the observed differences are most likely manifested at the cellular level. The pK_a of the amino group of doxorubicin is 8.34 compared with 8.08 for 4'-epi-doxorubicin [9]; this can affect the membrane binding. 4'-Epi-doxorubicin has a higher lipid solubility (relative lipophilicity, 0.19, compared with 0.16 for doxorubicin [19], which can increase its transport across membranes. The affinity to DNA is somewhat lower for 4'-epi-doxorubicin than for doxorubicin [9]. Altogether, these factors cause a higher initial uptake and a lower intracellular retention of drug; our results indicate that this is also the case under in vivo conditions.

The initial uptake of 4'-epi-doxorubicin and doxorubicin in tumor cells was recently studied in patients with gastrointestinal cancer who, prior to laparatomy, received 10 mg doxorubicin immediately followed by the same amount of 4'-epi-doxorubicin [16]. Despite the intracellular concentration of 4'-epi-doxorubicin being higher than that of doxorubicin in five of six biopsies, the authors did not conclude that there was a difference in accumulation between the two drugs. In contrast to the present study, their results were based on single biopsies and no conclusions about the retention or the AUC could be made.

In a previous study we found pronounced differences in the in vivo pharmacokinetics of daunorubicin and doxorubicin in leukemic cells [15]. Daunorubicin had a much higher initial uptake and a quicker elimination from the tumor cells than doxorubicin. We proposed that these differences might be important for their differences in clinical spectrum. The long intracellular retention of doxorubicin might be a prerequisite for its activity against solid tumors; in this respect 4'-epi-doxorubicin behaves more like doxorubicin. Although there was a tendency toward a more rapid elimination of 4'-epi-doxorubicin during the first 48 h, the AUC for intracellular drug concentrations vs time was higher for 4'-epi-doxorubicin than for doxorubicin during this period. The therapeutic significance of this is not clear, but in vitro studies indicate that the cell-killing capacity of an anthracycline is proportional to the product of the drug concentration and time [1]. Furthermore, in a recent study [14] we showed that, compared with free doxorubicin, complex binding of doxorubicin to DNA gave higher intracellular concentrations and that this was correlated to significantly improved survival in patients with acute leukemia. However, it is feasible that the higher initial AUC for 4'-epi-doxorubicin is offset by the tendency to a more rapid elimination of the drug from the leukemic cells. Due to the pronounced intracellular retention of both 4'-epi-doxorubicin and doxorubicin, it was impossible to make an accurate estimation of the infinite area for the drugs.

Our results suggest that there are differences in the pharmacokinetics of doxorubicin and its stereoisomer 4'-epi-doxorubicin in malignant cells. The significance of this finding for the toxic and antitumor effects of 4'-epi-doxorubicin should be further evaluated.

Acknowledgements. This study was supported by grants from the Swedish Medical Research Council (B 85-04X-07156-01A), the Swedish Fund for Scientific Research without animal Experiments, and the Swedish Medical Association. We gratefully acknowledge the skillful technical assistance of Miss Kerstin Jönsson and the revision of English grammar by Miss Ann-Sofie Ljungdahl.

References

1. Andersson B, Beran M, Peterson C, Tribukait B (1982) Significance of cellular pharmacokinetics for the cytotoxic effects of daunorubicin. Cancer Res 42: 178
2. Baurain R, Masquelier M, Peterson C, Deprez-De Campenere D, Trouet A (1978) Quantitive determination of intracellular concentrations of daunorubicin and Adriamycin and their main metabolites by high-pressure liquid chromatography. In: Current Chemotherapy. Proceedings of the 10th International Congress of Chemotherapy, vol 2, p 1130
3. Bonfante V, Villani F, Bonadonna G (1982) Toxic and therapeutic activity of 4'-epi-doxorubicin. Tumori 68: 105
4. Camaggi CM, Strocchi E, Tamassia V, Martoni A, Giovannini M, Iafelice G, Canova N, Marraro D, Martini A, Pannuti F (1982) Pharmacokinetic studies of 4'-epi-doxorubicin in cancer patients with normal and impaired renal function and with hepatic metastases. Cancer Treat Rep 66: 1819

5. Camaggi CM, Strocchi E, Martoni A, Angelelli B, Comparsi R, Pannuti F (1985) Epirubicin plasma and blood pharmacokinetics after single i.v. bolus in advanced cancer patients. Drugs Exp Clin Res XI(4): 285
6. Casazza AM, Di Marco A, Bonadonna G, Bonfante V, Bertazzoli C, Bellini O, Pratesi G, Sala L, Ballerini L (1980) Effects of modification in position 4 of the chromophore or in position 4' of the aminosugar, on the antitumor activity and toxicity of daunorubicin and doxorubicin. In: Crooke ST, Reich ST (eds) Anthracyclines; current status and new developments. Academic, New York, p 403
7. Cersosimo RJ, Hong WK (1986) Epirubicin: a review of the pharmacology, clinical activity and reverse effects of an Adriamycin analogue. J Clin Oncol 4: 425
8. Davis HL, Davis TE (1979) Daunorubicin and Adriamycin in cancer treatment: an analysis of their roles and limitations. Cancer Treat Rep 63: 809
9. Di Marco A, Casazza AM, Dasdia T, Necco A, Pratesi G, Rivolta P, Velcich A, Zaccara A, Zunino F (1977) Changes of activity of daunorubicin, Adriamycin and stereoisomers following the introduction or removal of hydroxyl groups in the amino sugar moiety. Chem Biol Interact 19: 291
10. Eksborg S, Stendahl U, Lönroth U (1986) Comparative pharmacokinetic study of Adriamycin and 4'-Epi-adriamycin after their simultaneous intravenous administration. Eur J Clin Pharmacol 30: 629
11. Lowry OM, Rosebrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the folin phenol reagent. Biol Chem 193: 265
12. Paul C, Peterson C, Gahrton G, Lockner D (1979) Uptake of free and DNA-bound daunorubicin and doxorubicin in human leukemic cells. Cancer Chemother Pharmacol 2: 49
13. Paul C, Baurain R, Gahrton G, Peterson C (1980) Determination of daunorubicin and its main metabolites in plasma, urine and leukemic cells in patients with acute myeloblastic leukemia. Cancer Lett 9: 263
14. Paul C, Björkholm M, Christenson I, Engstedt L, Gahrton G (1987) Induction and intensive consolidation in acute non-lymphoblastic leukemia (ANL) with combinations containing doxorubicin-DNA. Prolonged remission duration and survival. In: Lapsis K, Eckhardt S (eds) Lectures and Symposia of the 14th International Cancer Congress, Budapest 1986, vol 10. Karger, Basel/Akadémiai Kiado, Budapest, p 101
15. Peterson C, Paul C, Gahrton G (1983) Studies on the cellular pharmacology of daunorubicin and doxorubicin in experimental systems and human leukemia. In: Mathé G, Maral R, Jager R de (eds) Anthracyclines; current status and future development. Masson, New York, p 85
16. Peterson C, Gunvén P, Theve N-O (1986) Comparative pharmacokinetics of doxorubicin and epirubicin in patients with gastrointestinal cancer. Cancer Treat Rep 70: 947
17. Robert J, Vrignaud P, Nguyen-Ngoc T, Iliadis A, Mauriac L, Hurteloup P (1985) Comparative pharmacokinetics and metabolism of doxorubicin and epirubicin in patients with metastatic breast cancer. Cancer Treat Rep 69: 633
18. Sampi K, Masaoka T, Shirakawa S, Shirai T, Abe T, Shibata H, Umeda M, Kobayashi T, Sugiyama H, Toki H, Kozuru M, Tamura K, Ogura M, Hirota Y (1987) A phase II study of epirubicin in acute leukemia: a cooperative group study. Anticancer Res 7: 29
19. Schwartz H, Kanter P (1979) Biochemical parameters of growth inhibition of human leukemia cells by antitumor anthracycline agents. Cancer Treat Rep 63: 821
20. Torti FM, Bristow MR, Howes AE, Aston D, Kohler M, Mitchell EP, Billingham ME (1984) Preliminary observations of the cardiotoxicity of 4'-epi-doxorubicin: an evaluation by endomyocardial biopsy. Proc Am Assoc Cancer Res 25: 179
21. Weenen H, Lankelma J, Penders PGM, McVie JG, Ten Bokkel Huinink WW, Planque MM de, Pinedo HM (1983) Pharmacokinetics of 4'-epi-doxorubicin in man. Invest New Drugs 1: 59

Received June 3, 1988/Accepted December 12, 1988