Cancer Chemother Pharmacol (1994) 33: 450–454

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis

Hiroshi Yoshida[1], Mitsuyoshi Goto[1], Atsuko Honda[1], Toshitaka Nabeshima[2], Takao Kumazawa[3], Jiro Inagaki[3], Naoki Yamanaka[3], Kazuo Ota[3]

[1] Department of Hospital Pharmacy, Nagoya Memorial Hospital, Hirabari, Tenpaku-ku, Nagoya 468, Japan
[2] Department of Hospital Pharmacy, Nagoya University Hospital, Tsurumai, Showa-ku 466, Japan
[3] Department of Clinical Oncology, Nagoya Memorial Hospital, Hirabari, Tenpaku-ku, Nagoya 468, Japan

Received: 9 June 1993/Accepted: 27 October 1993

Abstract. The comparative pharmacokinetics of doxorubicin (DOX) were investigated in five hemodialysis (HD) and eight non-hemodialysis (non-HD) patients who were infused with a 40- to 60-mg dose of DOX at a constant rate over 30 min. A significant difference was observed in the total body clearance (Cl tot) of DOX between HD and non-HD patients. The area under the curve (AUC) for both DOX and doxorubicinol (DOXol), an active metabolite, showed increases of approximately 1.5 and 3 times in HD patients as compared with non-HD patients. Although these differences were not statistically significant ($P < 0.1$), the mean residence time (MRT) of DOX and DOXol in HD patients showed a 2-fold increase in comparison with those in non-HD patients. Compartmental analysis indicated that the greater AUC values and longer MRT of DOX and DOXol in HD patients resulted from the lesser DOXol formation and disappearance of rate constants. As a consequence of the decrease in Cl tot for DOX and the marginal hemodialysis clearance of both DOX and DOXol, the present study suggests that the exposure to DOX and DOXol obtained in HD patients greater that achieved in non-HD patients. Careful attention should therefore be paid to HD patients receiving DOX.

Introduction

Amid recent increases in the numbers of patients undergoing dialysis, advances in hemodialysis technology and supporting therapies have given rise to longer life spans. Due to this lengthened life span and an immunocompromised situation, which is caused by renal failure, the occurrence of malignant tumors in these patients is also increasing [1]. Little is known, however, on the pharmacokinetics of anticancer drugs in hemodialysis (HD) patients.

It has recently been reported that significant differences have been observed in the area under the curve (AUC) of doxorubicin (DOX), one of the drugs used in the treatment of tumors [2], and doxorubicinol (DOXol), an active metabolite [3], between non-hemodialysis (non-HD) patients and HD patients [4]. However, no report has been published regarding compartmental kinetic analysis, including the metabolic pathway from DOX to DOXol in HD and non-HD patients.

This study was therefore conducted to compare the pharmacokinetic profiles of DOX and DOXol in non-HD and HD patients with cancer and to elucidate the mechanism of change in DOX kinetics.

Patients and methods

Patients. Informed consent was obtained from the five HD and eight non-HD patients who participated in this study. The serum creatinine levels of the eight non-HD patients were within normal ranges. The patients' characteristics and laboratory values are summarized in Table 1.

Protocol. DOX (Adriacin, Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) was dissolved in 100 ml of 0.9% saline and infused at a constant rate over 30 min. The delivered dose ranged from 40 to 60 mg/subject. In HD patients, DOX was given immediately after the end of the first HD of the week. Heparinized blood specimens were drawn at 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, 24, and 43 h after the initial DOX infusion had been completed. Samples were always drawn from the arm contralateral to that used for infusion. In three HD cases, blood was also drawn from the catheter of an arteriovenous (AV) shunt at the midpoint of subsequent HD. The HD membrane was made of cupraammonium rayon (Benberg, Asahi Medical, Tokyo, Japan). In the five non-HD patients, urine samples were collected from 0 to 43.5 h after administration of the prescribed dose. Blood samples were immediately centrifuged. The separated plasma and collected urine were frozen at –70° C until assayed.

Correspondence to: Mitsuyoshi Goto, Ph.D., Department of Hospital Pharmacy, Nagoya Memorial Hospital, Hirabari, Tenpaku-ku, Nagoya 468, Japan

Table 1. Patients' characteristics

Patient	Age (years)	Weight (kg)	Sex	Diagnosis	GOT (IU/l)	GPT (IU/l)	Hematocrit (%)	Serum albumin (g/dl)	Total bilirubin (mg/dl)	Direct bilirubin (mg/dl)	Duration of hemo-dialysis	Treatment
Non-HD group:												
1	69	50.2	M	Malignant lymphoma	26	20	42.4	3.6	0.8	0.3		CPA, VCR
2	54	55.5	F	Breast cancer	12	6	40.6	3.6	0.3	0.2		CPA, 5-FU, Tamo
3	47	70.0	M	Bone tumor	13	12	36.5	3.6	0.4	0.2		CDDP
4	53	43.1	F	Malignant lymphoma	25	4	38.3	3.5	0.6	0.3		VCR, CPA, PSL
5	62	63.0	M	Gastric cancer	41	18	34.6	3.8	0.7	0.2		5-FU
6	52	48.0	F	Breast cancer	26	36	28.1	3.8	0.2	0.1		CPA, 5-FU
7	73	74.0	M	Prostate cancer	22	8	31.0	3.6	0.4	0.3		CDDP, 5-FU
8	66	39.8	F	Breast cancer	19	6	33.7	3.7	0.4	0.1		CPA, 5-FU
HD group:												
9	52	68.0	M	Hepatoma	51	97	23.2	3.3	0.6	0.3	2 years	5-FU
10	47	65.0	M	Malignant lymphoma	42	15	30.0	3.0	0.4	0.1	6 years	VCR, CPA, PSL
11	64	50.0	M	Lung cancer	16	7	21.6	3.7	0.4	0.3	6 months	5-FU
12	72	57.2	M	Malignant lymphoma	19	3	27.5	3.1	0.3	0.2	19 years	CPA, VCR, PSL
13	47	42.0	F	Lung cancer	22	7	30.0	3.8	0.5	0.2	14 years	VCR, CPA

CPA, Cyclophosphamide; VCR, vincristine; 5-FU, 5-fluorouracil; Tamo, tamoxifene; CDDP, cisplatin; PSL, predonisolone

Drug analysis. DOX and DOXol in plasma were specifically determined by the high-performance liquid chromatography (HPLC) method of Ohtsubo and Aoyama [5]. Briefly, the plasma containing internal standard (daunorubicin) was passed though a Toyopak ODS-M cartridge (Tosoh, Tokyo, Japan). DOX and DOXol were eluted from the cartridge with acetonitrile/100 m*M* sodium citrate buffer (pH 3.5; 30:70, v/v). The eluate was injected into an HPLC apparatus (LC-6A system; Shimadzu Co., Ltd., Kyoto, Japan) equipped with an RF-530 fluorescence detector (excitation wavelength, 470 nm; emission wavelength, 560 nm) and a Cosmosil-packed ODS column (25 cm × 4.6 mm inside diameter; Nacalai Tesque Co., Ltd., Kyoto, Japan). The coefficients of variation found at concentrations of 10 and 100 ng/ml ($n = 5$) for DOX were 6.7% and 3.9%, respectively, and those found at concentrations of 10 and 50 ng/ml ($n = 3$) for DOXol were 2.8% and 1.1%, respectively. The sensitivity limits observed by this method were as low as 1 ng/ml.

Pharmacokinetic analyses. Statistical moment theory was applied in the pharmacokinetic analysis [6]. The AUC was calculated by the trapezoidal rule with extrapolation to infinity. Total body clearance was determined as follows:

$$\text{Cl tot} = \text{dose/AUC}. \quad (1)$$

The mean residence time (MRT) was calculated by the following equation:

$$\text{MRT} = \text{AUMC/AUC}, \quad (2)$$

where *AUMC* represents the area under the first moment curve.

Renal clearance was determined as follows:

$$\text{Cl renal} = \frac{[\text{Xu}]_0^{43.5}}{[\text{AUC}]_0^{43.5}}, \quad (3)$$

where $[xu]_0^{43.5}$ is the urinary recovery from the initiation of the drug administration to 43.5 h and $[AUC]_0^{43.5}$ is the AUC from 0 to 43.5 h.

Dialysis clearance in three HD patients was estimated by the usual procedure [6]:

$$\text{Cl}_{\text{HD}} = \text{Qb}(1 - \text{H}) \times (\text{Cap} - \text{Cvp})/\text{Cap}, \quad (4)$$

where *Qb* is the blood flow through the dialyzer, *H* is the hematocrit, and *Cap* and *Cvp* are the arterial and venous plasma concentrations of drugs, respectively.

In elucidating the mechanism of the change in Cl tot and MRT for DOX and DOXol, we created a two-compartment model with DOXol formation and elimination as shown in Fig. 1 (see Appendix). It has been reported that the K_m values of aldo-keto reductase in the human liver and kidney that can metabolize DOX to DOXol are 0.275 ± 0.070 and 0.539 ± 0.113 m*M*, respectively [7]. Since these values are greater than the concentrations observed in the present study, we used the first-order metabolite-formation rate constant. Estimates of kinetic parameters in this model were calculated via MULTI [RUNGE] [8] applying the Runge-Kutta-Gill method. The data are weighted by unity (weight = $1/C^2$) in all calculations for the present study. All analysis was performed using an FMR-70 personal computer (Fujitsu Co., Ltd., Tokyo, Japan).

Statistical analysis. Statistical differences between the two groups were calculated using the Mann-Whitney *U*-test. Statistical significance was defined as $P < 0.05$.

Results

The time courses of DOX and DOXol plasma levels observed after the administration of DOX to HD and non-HD patients are shown in Fig. 2. The postinfusion peak levels of DOX in HD and non-HD patients were 1539 and 1336 ng/ml, respectively. At 43 h after cessation of the infusion, the levels were 10.0 and 4.3 ng/ml, respectively. The maximal observed concentrations of DOXol in HD and non-HD patients were 14.0 and 18.0 ng/ml, respectively. At the final sampling, the levels were 8.5 and 3.9 ng/ml in HD and non-HD patients, respectively. In contrast to the earliest appearance of peak concentrations of DOXol in non-HD patients, the peak time of mean observed levels in HD patients was 0.25 h after cessation of the infusion. Thus, the levels of DOX and DOXol measured in HD patients were higher than those determined in non-HD patients throughout the sampling period.

Table 2 summarizes the pharmacokinetic parameters of DOX and DOXol in HD and non-HD patients as analyzed by moment theory. A significant difference was observed in the Cl tot of DOX between HD and non-HD patients ($P < 0.05$). The AUC values obtained for DOX and DOXol in HD patients were approximately 1.5 and 3 times those determined for non-HD patients, respectively. Although these differences were not statistically significant ($P < 0.1$), the MRT of DOX and DOXol showed a 2-fold increase in

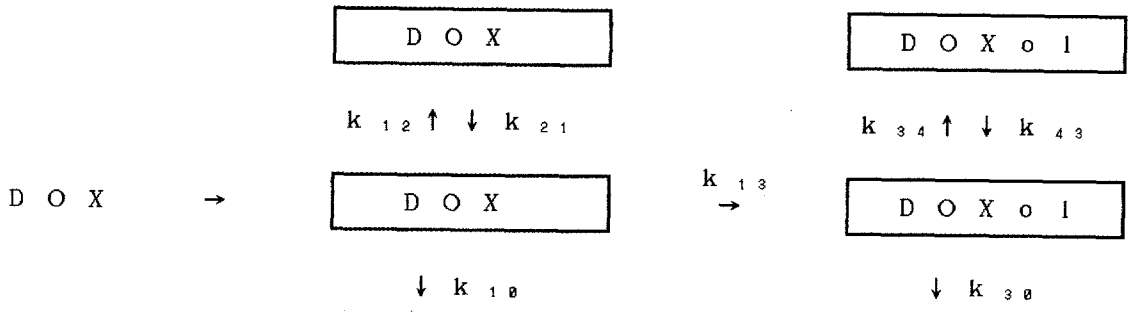

Fig. 1. Proposed compartment model

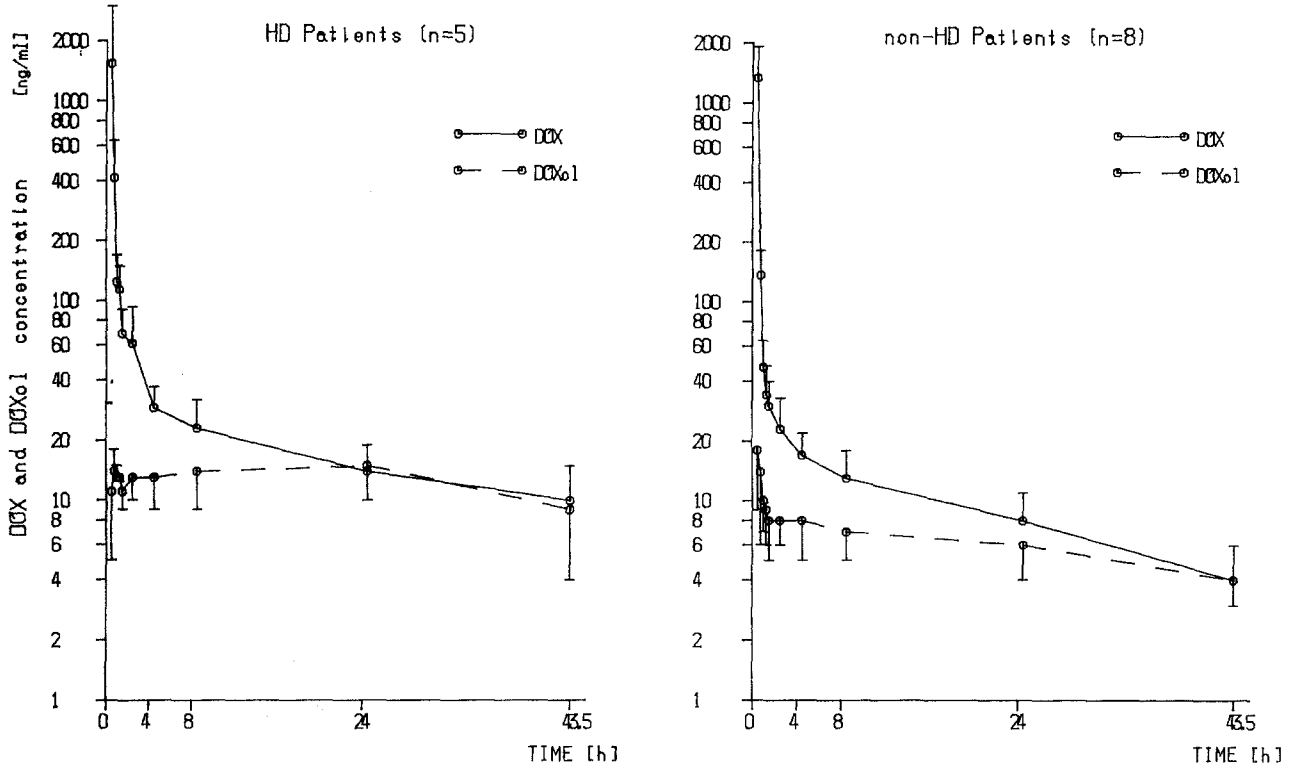

Fig. 2. Plasma DOX and DOXol concentration after a 30-min infusion of DOX to 5 HD patients and 8 non-HD patients. Data represent mean values ± SD

Table 2. Pharmacokinetic parameters of DOX and DOXol in HD and non-HD patients

Parameter	DOX		DOXol	
	HD (n = 5)	Non-HD (n = 8)	HD (n = 5)	Non-HD (n = 8)
Dose (mg/kg)	0.92 ±0.22	0.90 ±0.25		
Cl total (l h^{-1} kg^{-1})	0.520 ±0.210**	0.894 ±0.308		
AUC ([μg/ml] h kg^{-1})	0.0360±0.0185**	0.0210±0.0111	0.0285±0.0094*	0.0090±0.0039
MRT (h)	30.9 ±22.8	14.0 ±6.1	117.6 ±59.5	55.6 ±26.9
Cl_{HD} (l h^{-1} kg^{-1})	0.018 ±0.024 (n = 3)		0.052 ±0.018 (n = 3)	
Cl renal (l h^{-1} kg^{-1})		0.152 ±0.110 (n = 5)		0.0822±0.0640 (n = 5)

Data represent mean values ± SD
*P <0.01, **P <0.05 vs non-HD group (Mann-Whitney U-test)

Table 3. DOX and DOXol disposition rate constants in HD and non-HD patients

Patients	k_{10} (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{13} (h^{-1})	k_{30} (h^{-1})	k_{34} (h^{-1})	k_{43} (h^{-1})	Vd (l/kg)
Non-HD group	1.967 ±0.557	4.204 ±0.539	0.114 ±0.0227	0.183 ±0.122	0.325 ±0.183	3.139 ±1.621	0.765 ±0.423	0.577 ±0.203
HD group	1.559 ±0.741	3.106** ±0.770	0.0925 ±0.0278	0.0510* ±0.0180	0.0882* ±0.0553	2.343 ±2.391	1.331 ±0.484	0.437 ±0.287

Data represent mean values ± SD. Vd, Distribution volume of DOX in the central compartment
*P <0.02, **P <0.05 vs non-HD group (Mann-Whitney U-test)

HD patients in comparison with non-HD patients. The renal contributions to DOX and DOXol elimination were approximately 15%, a finding that concurs with previous research [9]. This indicates that the neither higher nor longer exposure to DOX and DOXol resulted from the absence of renal function for excretion of the drug.

DOX is present in red blood cells (RBC) and equilibrates with plasma [10, 11]. Therefore, Eq. 4 as described above may underestimate the amount of drug removal by dialysis [12]. In truth, however, the Cl_{HD} in the present study was negligible as compared with the Cl tot. This finding implies that the removal of DOX and DOXol from the body by HD is minimal.

The DOX and DOXol disposition rate constants as analyzed by the compartment model (Fig. 1) are listed in Table 3. Significant differences were observed between the groups in k_{12}, k_{13}, and k_{30}. These findings indicate that the patterns of distribution of DOX to the peripheral compartment and of DOXol formation and disappearance in HD patients differ from those in non-HD patients. Decreased DOXol formation and disappearance were responsible for the prolongation of MRT and the increases in the AUC of DOX and DOXol.

Discussion

Previous reports on the pharmacokinetics of DOX were described according to two- or three-compartment model analyses [13, 14]. However, the half-life of the alpha phase in the three-compartment model was merely 10 min [13]. No apparent objection seems to exist to the estimation of significant kinetic parameters of DOX using the two-compartment model.

It is known that cyclophosphamide (CPA) can delay DOX clearance in children [15], but further kinetic interactions with DOX have been not reported. Since CPA was given to five non-HD and three HD patients, its influence on DOX kinetics in both groups can be considered equal.

In rabbit models in which the pharmacokinetics of DOX have been found to be closest to those in humans [16], the highest tissue levels of DOX and DOXol were shown in the kidneys [17]. Although aldo-keto reductase, which can convert DOX to DOXol, was found in all tissues, the greatest amount of activity took place in the kidneys [18]. In humans, it has been also reported that the activity of aldo-keto reductase is greater in the kidneys than in the liver [7]. Furthermore, one of the five HD patients was dialyzed for only 6 months. Because the mean daily urine volume of this patient was approximately 250 ml, it is likely that the patient, whose Cl tot was 0.870 l h^{-1}, kg^{-1}, had residual renal enzyme activity, although the other HD patients were anuric. On the exclusion of this patient, the mean values found for the Cl tot and MRT of DOX in HD patients were 0.433±0.088 l h^{-1}, kg^{-1} and 34.8±24.3 h, respectively, and the mean MRT of DOXol was 138.3±43.1 h. Further significant differences were observed in the MRT of DOX and DOXol between the non-HD and HD groups, excluding the above-described patient. Such findings suggest that the kidneys play a large part in DOX metabolism and may be responsible for the increases in DOX AUC and decreases in k_{13} observed in HD patients.

The blood flow in the kidneys is great in humans [19], and DOX uptake into the kidneys is higher than that into other rabbit tissues [17]. Moreover, a larger fraction of DOX is quite rapidly distributed from the plasma to RBC [10, 11], which can result in a smaller k_{12} in HD patients with lower hematocrit values. Unfortunately, our pharmacokinetics studies were not performed using blood concentrations. It has been reported, however, that most of the DOX in RBC was unavailable for metabolic elimination after equilibration between plasma and RBC had occurred [10].

The AUC of DOXol was greater in HD patients than in non-HD patients, whereas a smaller k_{30} was seen in HD patients. DOXol is primarily metabolized to nonactive aglycone by reduced nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome P-450 reductase in the liver [20]. However, this enzyme also exists in the kidneys [21]. Moreover, it is known that the loss of renal function decreases the hepatic clearance of some drugs [22]. Bianchetti et al. [23] reported a significant increase in the fraction of the dose available to the systemic circulation in chronic renal failure after oral dosage of propranolol. Bateman et al. [24] found that the Cl tot of metoclopramide determined in patients with chronic renal failure was approximately 30% of that found in healthy volunteers. Kirch et al. [25] compared the pharmacokinetics of nimodipine in patients with renal dysfunction with that of healthy volunteers. The mean AUC was significantly higher in the renal failure group and the mean elimination half-life was also significantly greater in subjects with renal dysfunction than in healthy volunteers. These reports indicate that renal dysfunction may result in a decrease in the Cl tot of drug metabolized mainly in the liver. In view of these observations, it seems likely that the accumulation of DOXol is induced by delays in its metabolism.

As a consequence of the decrease in the Cl tot of DOX and the low Cl_{HD} of DOX and DOXol observed in HD patients (Table 2), the present study suggests that the exposure to DOX and DOXol in HD patients was greater than that in non-HD patients. Careful attention should be paid to long-term HD patients receiving DOX.

Acknowledgements. The authors wish to thank Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan), for the donation of doxorubicin and Farmitalia Carlo Erba K.K. (Tokyo, Japan) for the donation of doxorubicinol. We also thank Mrs. K. Ito and Ms. T. Sekine for their assistance in preparing this manuscript.

Appendix. Four simultaneous differential equations for kinetic parameters

$T \leqq 0.5$:

$$\frac{dC_1}{dt} = \text{Dose}/0.5/Vd + C_2 \times k_{21} - C_1 \times (k_{10} + k_{12} + k_{13}),$$

$$\frac{dC_3}{dt} = C_1 \times k_{13} - C_3 \times (k_{30} + k_{34}) + C_4 \times k_{43},$$

$$\frac{dC_2}{dt} = C_1 \times k_{12} - C_2 \times k_{21}, \text{ and}$$

$$\frac{dC_4}{dt} = C_3 \times k_{34} - C_4 \times k_{43};$$

$T > 0.5$:

$$\frac{dC_1}{dt} = C_2 \times k_{21} - C_1 \times (k_{10} + k_{12} + k_{13}),$$

$$\frac{dC_3}{dt} = C_1 \times k_{13} - C_3 \times (k_{30} + k_{34}) + C_4 \times k_{43},$$

$$\frac{dC_2}{dt} = C_1 \times k_{12} - C_2 \times k_{21}, \text{ and}$$

$$\frac{dC_4}{dt} = C_3 \times k_{34} - C_4 \times k_{43},$$

where C_1 and C_2 are the concentrations of DOX in the central and the peripheral compartment, respectively, C_3 and C_4 are the concentrations of DOXol in the central and the peripheral compartment, respectively, and Vd is the distribution volume of DOX in the central compartment. The initial condition is as follows:

$C_1 = 0$, $C_2 = 0$, $C_3 = 0$, and $C_4 = 0$

References

1. Sotherland Ga, Glass J, Gabriel R (1977) Increased incidence of malignancy in chronic renal failure. Nephron 18: 182
2. Balis FM, Holcenberg JS, Bleyer WA (1983) Clinical pharmacokinetics of commonly used anticancer drugs. Clin Pharmacokinet 8: 202
3. Bachur NR (1979) Anthracycline antibiotic pharmacology and metabolism. Cancer Treat Rep 63: 817
4. Goto M, Yoshida H, Honda A, Kumazawa T, Ohbayashi T, Inagaki J, Yamanaka N, Ota K (1993) Delayed disposition of Adriamycin and its active metabolite in hemodialysis patients. Eur J Clin Pharmacol 44: 301
5. Ohtsubo K, Aoyama T (1988) High sensitive assay method of DOX in blood by HPLC (abstract, in Japanese). Proc Annu Meet Jpn Pharm Soc 108: 507
6. Gibaldi M, Perrier D (1982) Application of pharmacokinetic principles and noncompartmental analysis based on statistical moment theory. In: (eds) Pharmacokinetics, 2nd edn. Marcel Dekker, New York, pp 385, 409
7. Loveless H, Arena E, Felsted RL, Bachur NR (1978) Comparative mammalian metabolism of Adriamycin and daunorubicin. Cancer Res 38: 593
8. Yamaoka K, Nakagawa T (1983) A nonlinear least squares program based on differential equations, MULTI [RUNGE], for microcomputers. J Pharmacobiodyn 6: 596
9. Riggs CE, Benjamin RS, Serpick AA, Bachur NR (1977) Biliary disposition of Adriamycin. Clin Pharmacol Ther 22: 234
10. Lee HJ, Chiou WL (1989) Erythrocytes as for drug elimination in the isolated rat liver. I. Doxorubicin. Pharm Res 6: 833
11. Terasaki T, Iga T, Sugiyama Y, Hanano M (1984) Pharmacokinetic study on the mechanism of tissue distribution of doxorubicin: interorgan and interspecies variation of tissue-to-plasma partition coefficients in rats, rabbits, and guinea pigs. J Pharm Sci 73: 1359
12. Matzke GR, Millikin SP (1992) Influence of renal function and dialysis on drug disposition. In: (eds) Applied pharmacokinetics, 3rd edn. Applied Therapeutics, Inc., Vancouver, Washington, p 8-1
13. Benjamin RS, Riggs CE, Bachur NR (1977) Plasma pharmacokinetics of Adriamycin and its metabolites in humans with normal and hepatic renal function. Cancer Res 37: 1416
14. Wilkinson PM (1978) Clinical pharmacology of Adriamycin. In: Pinedo HM (ed) Clinical pharmacology of anti-neoplastic drugs. Elsevier/North-Holland, Amsterdam, p 209
15. Evans WE, Crom WR, Yee GC, Green AA, Hayes FA, Pratt CB, Avery TL (1980) Adriamycin pharmacokinetics. Proc Am Assoc Cancer Res 21: 176
16. Koren G, Beaty K, Seto A, Einarson TR, Lishner M (1992) The effects of impaired liver function on the elimination of anti-neoplastic agents. Ann Pharmacother 26: 363
17. Bachur NR (1975) Adriamycin(NCS-123127) pharmacology. Cancer Treat Rep 6: 153
18. Bachur NR, Hildebrand RC, Jaenke RS (1974) Adriamycin and daunorubicin disposition in the rabbit. J Pharmacol Exp Ther 191: 331
19. Chan KK, Cohen JL, Gross JF, Himmelstein KJ, Bateman JR, Tsu-Lee Y, Maris AS (1978) Prediction of Adriamycin disposition in cancer patients using a physiologic, pharmacokinetic model. Cancer Treat Rep 62: 1161
20. Mross K, Maessen P, Vijgh WJF, Gall H, Boven E, Pinedo HM (1988) Pharmacokinetics and metabolism of epidoxorubicin and doxorubicin in humans. J Clin Oncol 6: 517
21. Anders MW (1980) Metabolism of drugs by kidney. Kidney Int 18: 636
22. Touchette MA, Slaughter RL (1991) The effect of renal failure on hepatic drug clearance. Ann Pharmacother 25: 1214
23. Bianchetti G, Graziani G, Brancaccino D, Morganti A, Leonetti G, Manfrin M, Sega R, Gomeni R, Ponticelli C, Morselli PL (1976) Pharmacokinetics and effects of propranolol in terminal uraemic patients and inpatients undergoing regular dialysis treatment. Clin Pharmacokinet 1: 373
24. Bateman D, Gokal R, Dodd TRP, Blain PG (1981) The pharmacokinetics of single doses of metoclopramide in renal failure. Eur J Clin Pharmacol 19: 437
25. Kirch W, Ramsch KD, Duhrsen U, Ohnhaus EE (1984) Clinical pharmacokinetics of nimodipine in normal and impaired renal function. Int J Clin Pharmacol Res 4: 381