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Time Dependency of Adriamycin and Adriamycinol Kinetics

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Summary. *Adriamycin was administered by IV injection to seven patients with various solid tumors at a dose of 30 mg/m² during successive courses. Extraction was carried out by the SEP-PAK method for plasma and by solvents for urine. Plasma and urinary levels of adriamycin and adriamycinol were determined by high-performance liquid chromatography over 72-h period after injection. Pharmacokinetic parameters for adriamycin and adriamycinol were calculated for each course of treatment. The results show significant inter- and intra-individual variations in the kinetics and elimination of both compounds. The analysis of pharmacokinetic data reveals a wide variability in the fluctuations observed during the successive courses in different patients. This study confirms the time-dependency of ADR kinetics.*

Introduction

Adriamycin (ADR) is a glycosidic antibiotic of the anthracycline group, which possesses a wide spectrum of activity, essentially in the treatment of solid tumors and hematologic malignancies [3, 5, 6, 14, 19, 22]. The most commonly used dosage schedule for ADR involves a rapid IV injection every 21 days [6].

Ehninger et al. have reported fluctuations in ADR kinetics [10]. Their sampling procedure was insufficient to detect the different phases of the concentration-time curves. Moreover, they calculated only half-lives, and parameters such as clearance or areas under curves were not presented. Piazza et al. [15] have studied ADR kinetics but only during the early distributive phase, over a period of 4 h after drug administration. In these two studies, no urinary data were reported.

In the analysis of pharmacokinetic data, Thron has reported the existence of time-dependent processes (i.e., processes in which the rate coefficients or other parameters are functions of time) [20].

In a preliminary study, we recently described a possible time-dependent relationship of the kinetics of ADR after successive courses [12]. In this paper we report complete kinetic and metabolic studies in seven patients receiving successive courses of ADR at the same dose by rapid IV injection. The unmetabolized drug and its major metabolite adriamycinol (ADR-OH) were measured in the plasma and urine of patients by a high-performance liquid chromatography (HPLC) assay.

This study indicates important inter- and intra-individual variations in the kinetics and metabolism of ADR and hence a detailed knowledge of the time-dependency of ADR appears essential for the design of effective therapeutic regimens.

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Materials and Methods

Patient Protocol. Seven patients with various solid tumors were studied (Table 1). ADR, provided in lyophilized form, was dissolved in physiological saline and then injected by IV bolus to all patients at a dose of 30 mg/m² every 10 or 21 days. No patients had received ADR previously. All received the concomitant therapy detailed in Table 1 in the successive courses, 2–4 days after ADR administration to avoid any drug interference. In addition, hepatic and renal functions during the observation period were studied. The biological parameters included transaminases, alkaline phosphatase, lactic dehydrogenase, gamma glutamyl transferase, bilirubin and creatinin data (Table 2). Pathological values were observed in patients 2 and 4, who presented hepatic metastasis; patient 2 also had high levels of creatinin after unilateral nephrectomy.

Reagents. Adriblastine, a commercial form of ADR, was provided by Roger Bellon Laboratories (Neuilly sur Seine, France). Pure standard ADR-OH hydrochloride, ADR hydrochloride, and daunorubicin (DNR) hydrochloride were kindly supplied by Rhône-Poulenc (Vitry, France). All other biochemicals were of analytical grade and were purchased from Farmitalia Carlo Erba (Milan, Italy) and Merck (Darmstadt, FRG).

Blood and Urine Sampling. Venous blood specimens (approximately 10 ml) were taken and collected into 10 ml heparinized tubes at specified times: 0.083 h, 0.166 h, 0.333 h, 0.5 h, 0.75 h, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, 36 h, 60 h, and 72 h after the end of the injection. A pretreatment plasma sample was also processed for each patient to verify the absence of endogenous compounds interfering with the chromatographic procedure. The blood samples were immediately centrifuged for 15 min at 3,000 rpm. The plasma was removed, frozen, and kept at −20° C in the dark until analysis.

Fractions of urine were collected until 96 h; the volume of each fraction was determined and analysis was carried out immediately.

Table 1. Patient characteristics

Patient	Sex	Diagnosis	Weight (kg)	Age (years)	Adriamycin total dose for each course (day 0)	Concomitant therapy for each course		
1	F	Hodgkin	60	28	50 mg	Bleomycin	8.5 mg	Day 2 and day 8
						Vinblastine	8.5 mg	
						Procarbazine	170 mg	Day 2 and day 14
						Prednisolone	65 mg	
2	M	Liposarcoma	70	62	60 mg	VM_{26}	50 mg	Day 2
						Cyclophosphamide	1,500 mg	
						Prednisolone	80 mg	Day 2 to day 10
3	F	Ovarian adenocarcinoma	55	71	50 mg	Cisplatin	150 mg 1 course	Day 2
							20 mg 2 course	
							3 course	
						Acenocoumarin		Associated drugs
						Clorazepate dipotassium		
						Clomipramine		
						Pentaerythritol tetranitrate		
						Nifedipine		
4	F	Parotid carcinoma	53	52	50 mg	5-Fu	750 mg	Day 2
						Mitomycin	16 mg	
5	M	Esophageal carcinoma	53	60	50 mg	5-Fu	1,200 mg	Day 4
						Mitomycin	16 mg	
						Gentamicin		Associated drugs
						Indomethacine		
6	M	Rectal adenocarcinoma	55	34	50 mg	5-Fu	830 mg	Day 2
						Mitomycin	17 mg	
7	M	Epidermoid carcinoma	49	50	50 mg		–	

Table 2. Biological parameters during the observation period

Subject	SGOT (IU/l)	SGPT (IU/l)	Alkaline phosphatase (IU/l)	LDH (IU/l)	γ GT (IU/l)	Total bilirubin (μmole/l)	Creatinin (μmole/l)
1	10	8	133	187	12	11	72
2	63	50	699	275	140	22	156
3	10	7	108	175	10	6	70
4	24	28	248	370	86	13.7	82
5	–	7	126	145	30	8	101
6	9	10	139	150	15	6	78
7	8	7	100	180	20	12.5	75

Extraction Procedure

Plasma: Unmetabolized ADR and its metabolite ADR-OH were extracted from plasma utilizing polyethylene cartridges filled with C_{18}-bonded silica (C_{18} SEP-PAK, Waters Associates, Milford, Mass., USA). Then 3 ml methanol, 3 ml methanol/water mixture (1/1), 10 ml Na_2HPO_4 0.05 *M* pH 8.5, and 0.1–3 ml plasma containing known amounts of DNR hydrochloride (internal standard) were applied to the C_{18} mini-column using a 10-ml glass syringe. The column was then washed with 3 ml Na_2HPO_4 0.05 *M* pH 8.5 and the compounds were eluted with 4 ml chloroform/methanol mixture (2/1). The collected organic phase was concentrated to dryness at 45° C under a stream of nitrogen. The residue was resuspended in 120 μl of the mobile phase and centrifuged; aliquots of the supernatant (50 μl) were injected into the chromatograph. This technique has been described in detail previously [17]. Plasma volumes and internal standard amounts were adjusted according to the anticipated ADR and ADR-OH quantities to be determined in the sample. The percentage recoveries for ADR and ADR-OH were 94 ± 1.3 and 100 ± 1.1, respectively.

Urine: Attempts to use the plasma extraction procedure were unsuccessful because of the endogenous impurities which interfered with the chromatographic profile. In this case, urine samples (0.1–3 ml) containing DNR hydrochloride (internal standard) were adjusted to pH 8.5 with phosphate buffer 0.05

M and extracted with 10 ml chloroform/methanol mixture 4/1 (v/v). After agitation for 5 mn and centrifugation, the organic phase was collected and evaporated at 45° C under a stream of nitrogen. The residue was redissolved in 120 µl of the mobile phase, and 50 µl was analyzed by liquid chromatography (described below).

Under these conditions, the extraction percentages for ADR and ADR-OH were 97.4 ± 3.9 and 96.7 ± 3.8, respectively.

HPLC Methodology. The quantitation of ADR and ADR-OH in plasma and in urine was achieved by a modification of the method of Israel et al. [13]. All analyses were performed on a high-performance liquid chromatograph equipped with a Model 6000 A pump (Waters Associates, Milford, Mass.), a U_6K injector (Waters Associates, Milford, Mass.), and a Spectra Glo fluorimeter (Gilson Medical Electronics, Middleton, Wis.). A 10 µm microbondapak column (4 × 300 mm; Waters Associates, Milford, Mass.) was isocratically eluted with an acetonitrile/formate buffer pH 4 mixture (32/68) at 2 ml/min. The formate buffer consisted of a solution of 0.1% ammonia in distilled water, adjusted to pH 4 with formic acid. Absorbance was monitored at 480 nm for excitation wavelength and 560 nm for emission wavelength. The ADR-OH, ADR, and DNR (internal standard) chromatographic peaks occurred regularly at 3.0 min, 4.0 min, and 8.0 min, respectively. Peak areas were determined on a model 3390 A computing and recording integrator (Hewlett-Packard, Palo Alto, Calif.) and used for quantitation. The limit of quantitation of the assay was 5 ng/ml, with a coefficient of variation of 8.7%.

Pharmacokinetic Analysis. Statistical considerations lead us to choose a three-compartment model to describe ADR pharmacokinetics. Thus, the experimental kinetic data are fitted by a sum of three exponential functions of time, parameters of which are estimated using a weighted least-square procedure.

Half-lives and clearance are computed, respectively, from: $t_{1/2}$ (i) = $0.693/\alpha_i$, where α_i is the estimated exponent of the i term in the sum of exponentials; and Cl = DOSE/AUC, where areas under curves were determined from experimental points using the trapezoidal rule.

Results

Figures 1 and 2 show the plasma disappearance versus time curves for ADR and its metabolite ADR-OH in patient 5 after the three successive courses. The limit of the sensitivity of the HPLC method allowed measurement over 60 h for ADR and 72 h for ADR-OH. ADR and ADR-OH plasma concentration-time profiles were quite parallel by 8 h after injection, suggesting an equilibrium between the two compounds. ADR disappearance was triphasic, with an extremely rapid first phase ($t_{1/2}\alpha$ = 0.072 h), indicating a wide distribution of the drug in the tissues. After a initial decrease, ADR-OH concentrations increased slightly between 2 h and 4 h and then decreased exponentially. This metabolite appeared very rapidly in plasma, and wide individual variations in plasma levels of this metabolite were observed 5 min after ADR administration (11–125 ng/ml).

Table 3 illustrates plasma pharmacokinetic parameters of ADR calculated for each patient during the different cycles of

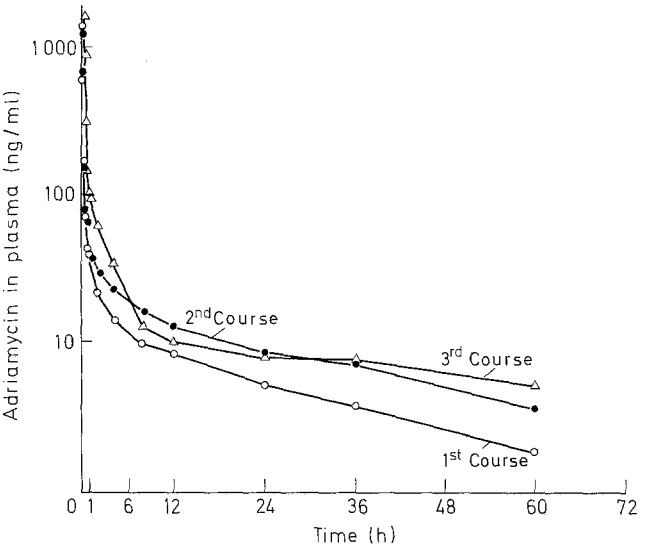

Fig. 1. Plasma ADR levels in patient 5 during three successive courses of adriamycin (50 mg IV)

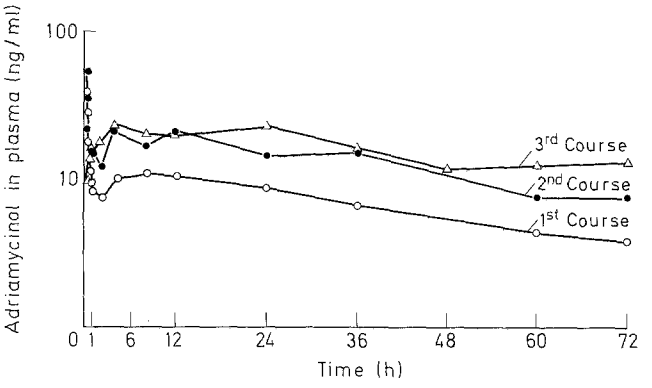

Fig. 2. Plasma ADR-OH levels in patient 5 during three successive courses of adriamycin (50 mg IV)

Table 3. ADR pharmacokinetic parameters during successive courses

Subject	Courses	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	$t_{1/2}\gamma$ (h)	AUC ∞ (ng/ml/h)	Cl (l/h)
1	I	0.102		43.9	950.5	52.6
	II	0.034	0.325	41.7	687	72.7
	III	0.042	2.880	22.4	864	57.8
2	I	0.068	1.296	37.8	793.9	75.5
	II	0.076	1.773	50.07	891.5	67.2
	III	0.049	0.882	42.3	1,016	59.0
3	I	0.053	0.400	22.4	539	92.7
	II	0.091	2.452	24.6	462	108.2
	III	0.072	1.168	19.5	484	103.3
4	I	0.084	1.529	52.3	807	61.9
	II	0.083	0.495	19.3	523	95.6
5	I	0.072	0.949	21.3	668	74.8
	II	0.075	1.249	24.9	948	52.7
	III	0.081	1.818	60.8	1,660	30.1
6	I	0.097	3.80	72.7	604	82.8
	II	0.072	2.61	42.7	619	80.7
7	I	0.086	2.28	28.3	682	73.3
	II	0.067	0.84	32.1	642	77.9

Table 4. ADR-OH pharmacokinetic parameters

Subject	Course	AUC ∞ (ng/ml/h)	$t_{1/2}$ (h)	AUC ∞ ADR-OH / AUC ∞ ADR
1	I	433	25.9	0.455
	II	426	30.2	0.620
	III	382	16.4	0.442
2	I	912.7	30.3	1.148
	II	2,259	82	2.533
	III	1,454	33.4	1.431
3	I	275	27.6	0.510
	II	256	21.9	0.554
	III	464	39.9	0.958
4	I	748	35.4	0.927
	II	422	26.9	0.807
5	I	739	42.3	1.106
	II	1,462	42.4	1.542
	III	2,058	57.5	1.239
6	I	Not measurable	Not measurable	–
	II	257	39.9	0.415
7	I	414	25.3	0.607
	II	350.8	31.2	0.546

Table 5. Cumulative urinary excretion of ADR and ADR-OH (percentages of administered dose)

Subject	Course	Adriamycin	Adriamycinol	Adriamycin + adriamycinol
1	I	10.82	1.09	11.91
	II	14.70	1.86	15.56
	III	15.30	1.87	17.17
2	I	5.10	0.60	5.70
	II	13.68	1.97	15.65
3	I	11.3	1.8	13.1
	II	10.7	1.6	12.3
	III	8.1	1.9	10.0
4	I	5.8	1.4	7.2
	II	4.8	1	5.8
5	I	4.1	0.6	4.7
	II	3.9	0.5	4.4
	III	6.2	1.1	7.3
6	I	2.4	0.8	3.2
	II	1.4	0.5	1.9
7	I	5.5	0.6	6.1
	II	4.8	0.6	5.4

therapy. These data show considerable fluctuations in the values of Cl and $t_{1/2}$ when the different courses are compared in the same patient. We have observed a decrease of the clearance in patients 2, 5, and 6, an increase in patients 4 and 7, and an increase followed by a decrease in patients 1 and 3. At the same patient. We have observed a decrease of the clearance in patients 2, 5, and 6, an increase in patients 4 and 7, and an increase followed by a decrease in patients 1 and 3. At the same time, we have noted a decrease of $t_{1/2}\gamma$ in patients 1, 4, and 6, an increase in patients 5 and 7, and an increase followed by a decrease in patients 2 and 3. Comparison of Cl, $t_{1/2}$ and AUC values recorded in different patients shows significant inter-individual differences. ADR-OH pharmacokinetic parameters are reported in Table 4; the AUC ∞ values, and particularly the ratio AUC ∞ (ADR-OH)/AUC ∞ (ADR), suggest variations in the metabolism process between subjects and courses. In patients 2 and 5 the ratio is > 1, indicating an intensive metabolism of ADR, whereas in patients 1, 3, 4, 6, and 7 the ratio is < 1. In three cases (patients 1, 2, and 5) the ratio is noted to increase with the second course and then return to the initial value with the third. This ratio increases successively in each of the three courses in patient 3, and decreases in patients 4 and 7. These data suggest the existence of a very wide individual variability in the metabolism processes.

ADR and ADR-OH levels were determined in urine, and the cumulative excretion for each compound was calculated. The data, expressed as percentages of the administered dose, are summarized in Table 5. The occurrence of ADR-OH was very early, from the first fraction (35 min after injection in patient 3), and though the concentrations found in the first samples were significant, they were lower than ADR concentrations. The cumulative elimination of ADR-OH after 96 h did not exceed 2% of the administered dose, whereas ADR excretion reached 15.3%, the major part of the drug being eliminated via the biliary route. These results show significant variations in the excretion of ADR + ADR-OH among subjects with normal renal function.

Discussion

Previous studies have reported fluctuations in ADR kinetics. Ehninger et al. [10] have utilized thin-layer chromatography and fluorescence spectrophotometry, and reported only half-lives as pharmacokinetic parameters. Piazza et al. [15], using spectrofluorimetry and thin-layer chromatography, have presented ADR kinetic data only from the early distributive phase.

This study presents further information on the variation of kinetics and metabolism of ADR during successive courses of treatment and on the urinary excretion of the parent drug and its metabolite.

The plasma concentration-time curves obtained are triphasic, except for the first course in patient 1. The mean half-life of ADR (± SD) is calculated for each phase of the curve. The short half-life is 0.072 h (± 0.018 h), the intermediate half-life is 1.573 h (± 0.967 h), and the apparent elimination half-life 36.6 h (± 15.46 h). This long half-life is in agreement with reports in the literature, which give elimination half-lives ranging from 11 to 53 h [1, 2, 4, 7, 8, 16, 23, 24]. Our α half-life is very close to the values of Piazza et al. [15], but is shorter than reported by several other authors [4, 8, 10, 24]. These authors used an inadequate initial sampling schedule, which did not allow precise calculation of $t_{1/2}\alpha$. High levels of ADR-OH were generated very rapidly in these patients. After a initial decrease, the ADR-OH levels increased slightly between 2 and 4 h and then decreased exponentially with a mean half-life of 35.8 h (± 15.28 h). The cause of this transient increase could be the initial sequestration of this metabolite in a peripheral compartment, followed by a release 2 or 4 h after drug administration.

If we compare the kinetics of patients 2 and 4, in whom hepatic metastases were observed, with those of the other patients, we do not observe significant differences in the values for $t_{1/2}$, Cl, or AUC, except a prolonged half-life of ADR-OH during the second course in patient 2. These results are close to the observations of Chan et al. [7], who reported no alterations in the ADR kinetics in hepatoma patients.

Urinary excretion of ADR and ADR-OH is very variable according to different authors [2, 8, 9, 18, 24]. In our study, during a 96-h period the cumulative excretion for ADR ranged from 1.4% to 15.3% of administered dose. Excretion of ADR-OH remained lower and did not exceed 2%, a value similar to that of 3.3% reported by Riggs et al. for a 7-day period [16]. The data obtained in different subjects during several courses of treatment show individual fluctuations in the excretion of the parent drug and its metabolite. It was noticed that ADR-OH elimination is exactly parallel to that of ADR over the collection period, so these data suggest that renal elimination cannot be correlated with the time-dependency of ADR and ADR-OH kinetics. Individual variations of ADR pharmacokinetic parameters have been observed by several authors [10, 15], but in a non-homogenous group of patients. Our study was performed in patients with various types of cancer, who received the same dose of ADR (30 mg/m^2) during all the courses. Analysis of the pharmacokinetic parameters reveals significant variability and two major aspects can be pointed out. First, we observe inter-individual variations; the terminal half-life ranges from 19.3 h to 72.7 h, the total plasma clearance from 30.1 l/h to 108.2 l/h and the AUC ∞ from 462 ng/ml/h to 1,660 ng/ml/h. Second, we observe striking intra-individual variations in ADR kinetics; for instance, in patient 5 $t_{1/2}\gamma$ ranges from 21.3 h to 60.8 h, total clearance from 74.8 l/h to 30.1 l/h and AUC ∞ from 668 ng/ml/h to 1,660 ng/ml/h. It is important to notice the irregularity of the fluctuations of AUC ∞, Cl, and $t_{1/2}$ increasing or decreasing with the successive courses according to the patient. These observations disagree with those of Tipping et al. [21], who reported an accelerated disappearance of ADR from plasma during four courses of treatment in eight patients. The occurrence of a decrease in ADR plasma levels after a prior treatment cannot be ruled out [11, 21], since our study shows it is not a general rule. The cause of the time-dependency remains to be found and a possible hypothesis is a connection with the fluctuations of ADR disposition and metabolism. ADR-OH parameters exhibit the same inter- and intra-individual variations as the parent drug, and the differences in the ratio of AUC ∞ show that the metabolism processes are also time-dependent.

The aim of our study was to obtain further information on the kinetics of ADR during successive courses of treatment in patients with different types of cancer but receiving the same doses of drug. These results demonstrate the existence of wide variability in the disposition and metabolism of the drug and the time-dependency of ADR and ADR-OH pharmacokinetic parameters. Further studies are needed to determine the cause of this phenomenon, and metabolic studies in the form of the development of a mathematical model taking into account plasma and urinary levels of ADR and ADR-OH are currently being considered.

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