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PLASMA PHARMACOKINETICS OF IDARUBICIN AND ITS 13-HYDROXYMETABOLITE AFTER INTRAVENOUS AND ORAL ADMINISTRATION UNDER FASTING AND NON-FASTING CONDITIONS

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Abstract

The plasma pharmacokinetics of Idarubicin and its 13-hydroxymetabolite have been studied in 10 patients with solid tumours after intravenous and oral administration under fasting and non-fasting conditions in a randomized cross-over design. The plasma concentration time curves of Idarubicin after intravenous administration could be described by the open two or three compartment models. No pharmacokinetic modelling of Idarubicin was possible after oral administration. After oral administration of Idarubicin, the amount of intact drug was higher under non-fasting conditions. The extensive and long-lasting appearance of Idarubicinol suggests that this cytotoxic metabolite is of major clinical importance in i.v. and oral therapy with Idarubicin. The pharmacokinetics of Idarubicinol was not affected by food intake.

Key words: Idarubicin, intravenous, oral, pharmacokinetics.

Anthracycline glycosides have been successfully used for the treatment of a variety of neoplastic diseases, mostly after intravenous administration. In general the anthracyclines are poorly absorbed when administered orally, but recently a few new derivatives have shown cytostatic activity after oral administration (1, 2). Idarubicin (4-demethoxy-daunorubicin) is at present the clinically most important anthracycline used orally. Idarubicin is active in acute leukemia and various solid tumours (3–5). In preclinical studies, Idarubicin has demonstrated several potential advantages over daunorubicin, including reduced cardiotoxicity (6, 7), a dose-limiting factor in anthracycline therapy.

The anthraquinone glycosides are strong complexing agents (8). It is therefore not unlikely that the amount of Idarubicin absorbed after oral administration might be influenced by the simultaneous intake of food. In the present study the plasma pharmacokinetics of Idarubicin and its main metabolite, the 13-hydroxy derivative, shown to be as active as the unchanged drug in vivo and in vitro (5, 9, 10), were investigated in 10 patients with solid tumours after intravenous and oral administration under fasting and non-fasting conditions.

Material and Methods

Patients. Ten patients, 5 females and 5 males, median age 62 years (range 45–76 years) participated in the study. Seven patients with cancer in the colon or rectum, two with soft tissue sarcoma and one with breast cancer were included. All patients had advanced disease not responding to conventional chemotherapy. Three patients had received prior doxorubicin therapy, with accumulated doses not exceeding 300 mg. Six patients, all with colorectal tumours, had liver metastases. No patient had impaired liver function tests.

All patients were informed of the purpose of the study and gave their consent to participate.

Treatment schedules. The patients were randomized for the sequence of the three treatment schedules, i.e. intravenous administration (10 mg/m^2), oral administration (35 mg/m^2) after a 'standard breakfast' (150 ml of low fat milk, 100 ml of orange juice, 1 egg, 2 pieces of bread, 5 g of butter, 20 g of cheese and 20 g of orange marmalade) (11) and under fasting conditions respectively (Table 1). Under the fasting conditions no food intake was allowed 9 h prior to and 3 h after treatment. Oral administration of Idarubicin were in all instances supervised by a nurse, in order to assure drug compliance. In all cases the drug was

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Table 1

Patients

Patient No.	Age (years)	Sex	Dose of Idarubicin					
			Intravenous		Oral, non-fasting		Oral, fasting	
			mg	mg/m^2	mg	mg/m^2	mg	mg/m^2
1	69	M	18	9.93	65	35.9	65	35.9
2	45	M	–[1]	–[1]	70	35.5	–[1]	–[1]
3	58	M	18	9.64	65	34.8	65	34.8
4	63	M	15	8.10	65	35.1	65	35.1
5	76	F	15	9.46	55	34.7	55	34.7
6	68	M	20	9.37	75	35.1	75	35.1
7	58	F	15	9.45	55	34.6	55	34.6
8	60	F	20	9.67	70	33.8	70	33.8
9	60	F	15[2]	9.72[2]	50	32.4	55	35.6
10	65	F	17	9.54	60	33.7	60	33.7

[1] Not treated (early death)
[2] No pharmacokinetic study performed

given at 9 a.m. The time interval between the various treatments was 1 month.

Idarubicin was intravenously administrated as short time (1–7 min) infusions, the exact infusion time being used in the pharmacokinetic calculations. The drug was dissolved in sterile water (1 mg/ml). For oral use gelatin capsules containing 5 and 10 mg Idarubicin were used. The drug was supplied by Farmitalia Carlo Erba, Milano (Italy).

Plasma samples. Blood samples (ca. 5 ml) were collected in glass test tubes (Vacutainer) containing 250 IU heparin (freeze-dried). The samples were immediately centrifuged to separate the plasma fractions, which were stored at −70°C until analysis. The blood samples were withdrawn 10 min prior to and 1, 5, 15, 30, 45 min and 1, 2, 3, 6, 12, 18, 24, 36, 48, 72, 96 h after drug administration.

Analytical procedure. Idarubicin and Idarubicinol were assayed by an analytical method based on liquid-liquid extraction and reversed-phase liquid chromatography with photometric detection at 484 nm (12). The limit of determination was about 1 ng/ml plasma.

Pharmacokinetic evaluation. After intravenous administration pharmacokinetic modelling of Idarubicin was performed by a non-linear estimation program using a Gauss-Newton-Hartley agorithm, with initial estimates from a stripping procedure (13). The maximum plasma concentration of Idarubicin was obtained by extrapolation to the end of the infusion period. The area under the plasma concentration time curves (AUC) from start of the administration to 96 h postadministration was obtained by the trapezoidal rule.

Statistics. Mann-Whitney U-test was used for the comparison of two independent samples.

Results

Plasma concentration time curves of Idarubicin and Idarubicinol after intravenous and oral drug administration under fasting and non-fasting conditions are exemplified in Fig. 1.

After i.v. administration of Idarubicin the plasma concentration time curves were characterized by an initial (distribution) phase with a very short half-life ($t_{1/2\alpha}$ = 1.34 min; median value). The median half-life of the β-phase was 1.32 h (Table 2).

In five of the patients more than two exponential terms were needed to characterize the plasma concentration time curves. The slopes of the γ-phase, however, could only be evaluated in patients No. 3 and 10, giving half-lives of 25 and 22 h respectively, which is of the same order of magnitude as previously reported (14).

The dose corrected area under the plasma concentration time curves (AUC/mg/m^2) and the maximum plasma concentration ($C_{p,max}$) of Idarubicin after i.v. administration, were 0.50 $\mu g \cdot min \cdot ml^{-1}$ and 189 ng/ml respectively (median values) (Table 2).

The time for maximum plasma concentration of Idarubicinol showed very large interindividual variation, and was obtained 2–18 h after i.v. administration of Idarubicin. The maximum plasma concentration of Idarubicinol did not exceed 11 ng/ml in any of the patients (Table 2). The concentration of Idarubicinol decayed with a half-life of 53 h (median value). The AUC values of Idarubicinol was 5.1 times (median value) higher than the AUC values of the intact drug.

After oral administration of Idarubicin, only trace amounts of the intact drug were found in plasma. The

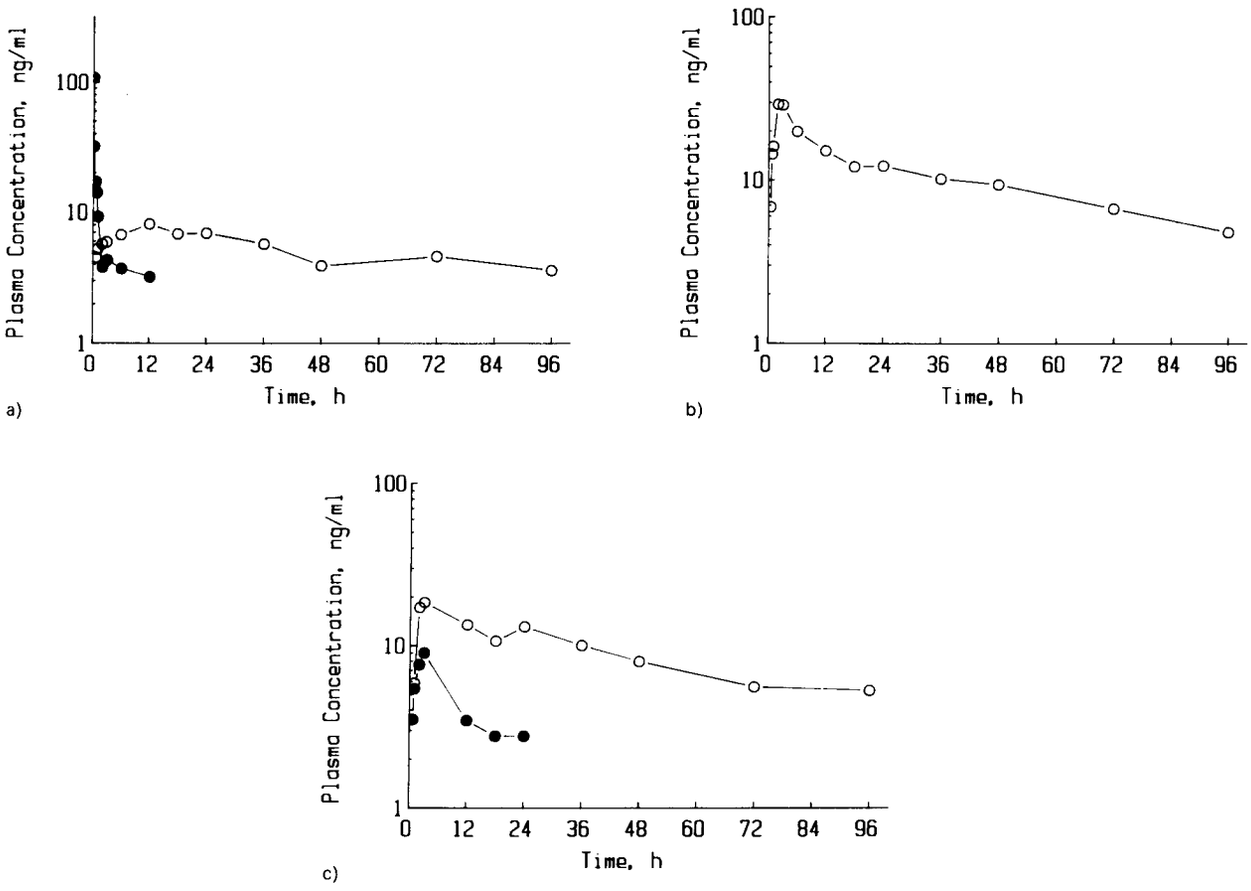

Fig. 1. Plasma concentration time curves. Data from patient No. 10 obtained after a) intravenous (dose 17 mg) and b) oral administration under fasting conditions (dose 60 mg), and c) non-fasting conditions (dose 60 mg) respectively. (●) = Idarubicin, (○) = Idarubicinol.

maximum plasma concentration did not exceed 20 ng/ml in any patient. In 2 of the 10 patients treated under non-fasting conditions and in 6 of the 9 patients treated under fasting conditions, all the plasma samples contained less than 1 ng/ml, i.e. were below the determination limit. Pharmacokinetic modelling of Idarubicin after oral administration was unsuccessful.

The maximum plasma concentration of Idarubicinol after oral administration of Idarubicin was higher under fasting conditions in 7 out of the 8 patients treated during non-fasting as well as fasting conditions (Table 3). The maximum plasma concentration was obtained within 2–6 h after the drug administration, and was 16 ng/ml and 20 ng/ml (median values) under non-fasting and fasting

Table 2

Plasma pharmacokinetics after intravenous administration of Idarubicin

Patient No.	Idarubicin			Idarubicinol			
	AUC/mg/m² $\mu g \cdot min \cdot ml^{-1}$	$C_{p,max}$ $ng \cdot ml^{-1}$	$t_{\frac{1}{2}\beta}$ h	AUC/mg/m² $\mu g \cdot min \cdot ml^{-1}$	$C_{p,max}$ $ng \cdot ml^{-1}$	t_{max} h	$t_{\frac{1}{2}}$ h
1	0.38	217	1.39	1.59	5	12	>80
3	0.66	390	1.59	3.09	7	18	55
4	0.34	142	1.36	2.38	11	2	50
5	0.59	671	1.13	3.33	8	12	33
6	0.56	679	1.33	1.48	7	6	47
7	0.43	160	1.31	2.35	8	6	37
8	0.86	91	0.94	2.82	7	9	56
10	0.44	108	0.73	3.12	8	12	77
Median	0.50	189	1.32	2.60	8	9	53

Table 3

Plasma pharmacokinetics after oral administration of Idarubicin

Patient No.		Idarubicin			Idarubicinol			
		AUC/mg/m^2 $\mu g \cdot min \cdot ml^{-1}$	$C_{p,max}$ $ng \cdot ml^{-1}$	t_{max} h	AUC/mg/m^2 $\mu g \cdot min \cdot ml^{-1}$	$C_{p,max}$ $ng \cdot ml^{-1}$	t_{max} h	$t_{\frac{1}{2}}$ h
1	F	0.052	9	3	0.57	19	3	32
1	NF	0.023	3	3	0.62	8	3	21
2	NF	0.223	5	6	0.84	14	6	47
3	F	0.025	6	3	1.29	33	3	40
3	NF	0.099	10	2	1.52	22	6	43
4	F	–	<1	–	0.79	11	6	35
4	NF	0.294	20	3	1.32	19	3	43
5	F	0.055	8	3	2.08	36	3	58
5	NF	0.128	11	3	1.35	19	3	39
6	F	–	<1	–	1.12	18	6	48
6	NF	0.064	9	2	1.03	16	6	51
8	F	–	<1	–	1.40	20	6	50
8	NF	0.067	5	6	1.02	10	6	56
9	F	–	<1	–	0.41	12	3	28
9	NF	–	<1	–	0.75	11	6	52
10	F	–	<1	–	1.74	29	2	50
10	NF	0.192	9	3	1.52	18	3	52

F = fasting; NF = non-fasting

All plasma samples from patient 7 contained less than 1 ng/ml of Idarubicin and Idarubicinol

conditions respectively. The plasma concentration of Idarubicinol decayed with a terminal half-life of 47 h (median value) (Table 3).

Clinical observations. One patient with soft tissue sarcoma had stable disease after three initial courses and continued Idarubicin treatment another three months. All other patients had progression of the disease during the Idarubicin treatment. No severe side-effects were recorded during treatment. Despite antiemetic treatment, mild to moderate nausea was observed, especially after oral intake of the drug. In most patients this appeared during late evening or night. No hematological toxicity was registered, probably due to the low doses of Idarubicin.

Discussion

The results in the present study confirm earlier findings that the i.v. pharmacokinetics of Idarubicin could not be defined by one single pharmacokinetic model for all patients, (cf. 3, 14, 15).

The AUC/mg/m^2 values of Idarubicin were significantly lower ($p < 0.01$) than previously observed for epidoxorubicin and doxorubicin, the currently most frequently used anthracyclines (16, 17).

Also the $C_{p,max}$ values of Idarubicin were lower than previously observed for epidoxorubicin and doxorubicin after 3.0 min i.v. infusions (17). The large interindividual variation observed (Table 2) can, at least partly, be explained by the varying infusion time used.

The results in the present study show that simultaneous food intake has an impact on the pharmacokinetics of intact Idarubicin in the systemic circulation. Formation of complexes with Idarubicin and calcium and other metal ions present in the food might affect bioavailability, since the anthracyclines are strong complexing agents (8). Such effects have previously been observed for tetracycline antibiotics (18), which are related chemically to the anthracyclines.

The AUC values of Idarubicinol after oral administration were about one-third of the AUC values obtained after i.v. administration, and were not systematically affected by the food intake. This metabolite has a high cytostatic activity in several test systems (9, 10), and it is likely that it has a major role in the Idarubicin therapy. Since only trace amounts, if any, of the intact drug were detected in peripheral plasma samples from treated patients after oral administration, the clinical importance of Idarubicinol seems to be even more pronounced after oral administration of Idarubicin than after i.v. administration.

The amount of 13 hydroxymetabolites formed from the anthracyclines in clinical use seems to be correlated with the hydrophobic character of the drug. Pharmacokinetic studies of the hydrophilic anthracyclines doxorubicin and epidoxorubicin (16, 17) showed that AUC of the 13 hydroxymetabolites were approximatively 23% of the AUC of the intact drug. In contrast, AUC of daunorubicinol exceeded the AUC of daunorubicin, which is almost as hydrophobic as Idarubicin (19). An increasing degree of daunorubicinol formation has been associated with an increase in therapeutic efficacy (20).

Our study indicates that oral administration of Idarubicin with food might be beneficial, as the amount of intact drug reaching the systemic circulation is greater than under fasting conditions. However, an increased pharmacokinetic variability has been reported for Idarubicin administered under non-fasting conditions (21). The extensive and long-lasting appearance of Idarubicinol suggests than this active metabolite might be of a major clinical importance in i.v. and oral therapy with Idarubicin.

In a recently published study (22) a correlation between AUC of Idarubicin and its 13-hydroxymetabolite and the antitumor effect/hematologic toxicity was observed, underlining the importance of pharmacokinetic studies of this drug.

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