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Idarubicin metabolism and pharmacokinetics after intravenous and oral administration in cancer patients: a crossover study

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Summary. The pharmacokinetics and metabolism of 4-demethoxydaunorubicin (idarubicin, IDA) were studied in 21 patients with advanced cancer after i.v. (12 mg/m^2) and oral (30–35 mg/m^2) treatment according to a balanced crossover design. Patients were divided into four groups: subjects who showed normal liver and kidney function (group N), those who presented with normal kidney function and liver metastases (group L), those with kidney dysfunction (creatinine clearance, $\leq$60 l/h; group R), and those with both liver and kidney dysfunction (group LR). Five patients showed variations in liver or kidney function after the first treatment and were considered to be non-evaluable for the crossover study but evaluable for the liver/kidney function study; some of them appeared in different groups for the i.v. as opposed to p.o. treatments. After i.v. administration, IDA plasma levels followed a triphasic decay pattern. The main metabolite observed in all patients was the 13C-reduced compound (IDAol), which attained plasma levels 2–12 times higher than those of the parent compound. IDA pharmacokinetics was not dependent on the presence of liver metastases but was related to the integrity of kidney function. Analysis of variance indicated a significant correlation between IDA plasma clearance and creatinine clearance; it was also found that IDA plasma clearance was lower in patients whose creatinine clearance was <60 ml/min [group N, 122.8$\pm$44.0 l/h; group L, 104.4$\pm$27.7 l/h (P = 0.58) vs group R, 83.4$\pm$18.3 l/h (P = 0.037)]. The IDAol terminal half-life and mean residence time (MRT) were significantly increased in patients with impaired kidney function [MRT: group N, 63.6$\pm$10.8 h; group L, 69.9$\pm$10.2 h (P = 0.27) vs group R, 83.2$\pm$10.9 h (P = 0.025) and $t_{1/2\gamma}$: group N, 41.3$\pm$10.1 h; group L, 47.0$\pm$7.4 h (P = 0.31) vs group R, 55.8$\pm$8.2 h (P = 0.025)]. After oral treatment, drug absorption occurred during in the first 2–4 h after IDA administration; a biphasic decay pattern was observed thereafter. The main metabolite observed in all patients was again IDAol. The AUC of IDAol was greater after oral administration than after i.v. treatment in proportion to the AUC of IDA (i.v.: AUC-IDAol/AUC-IDA, 2.4–18.9; p.o.: AUC-IDAol/AUC-IDA, 4.1–21.4). Following oral dosing, a substantial amount of 4-demethoxydaunomycinone (AG1) was found in 11/21 patients. No AG1 was detected after i.v. treatment, nor was the corresponding aglycone derived from IDAol found after p.o. or i.v. administration. IDA bioavailability, computed as the ratio of the dose-corrected AUC after p.o. and i.v. treatments in the same patient, was in the 25.2%–35.7% range for groups N, L, and R. Group LR showed a significantly reduced IDA bioavailability (15.7%$\pm$5.2%). However, a better description of the actual bioavailability was obtained by taking into account the AUCs of both IDA and IDAol after i.v. and p.o. administration and the relative potency of the two compounds.

Introduction

Idarubicin (4-demethoxydaunorubicin, IDA) is a new daunorubicin analogue endowed with higher biological activity and lower cardiotoxicity than the parent compound. Antitumor activity has been observed in clinical trials following both i.v. and oral administration [2, 9, 14, 25]. Its main metabolite, idarubicinol (4-demethoxy-13-dihydrodaunorubicin, IDAol) also exhibits antineoplastic activity in experimental models [7]. We report the results of a pharmacokinetics study in which 21 patients were treated both i.v. (12 mg/m^2) and orally (30–35 mg/m^2) according to a balanced crossover design. The plasma pharmacokinetics of IDA after i.v. treatment and its bioavailability following p.o. administration have been the subject of several reports [2, 16, 19, 21, 25]. The aim of the present study was to obtain a more accurate evaluation of these topics and to assess the possible dependence of pharmacokinetic and metabolic parameters on the presence of liver metastases or renal impairment.

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Table 1. Characteristics of the patients before IDA administration

Patient number	Liver metastases	1st/2nd treatment, Group		Creatinine clearance (ml/min)		Creatinine (mg%)		BUN (mg%)		Bilirubin (mg%)		SGOT (mIU/ml)		SGPT (mIU/ml)		Alkaline phosphatase (mIU/ml)	
		i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.
79	No	1,N	2,LR	88.5	88.5	0.9	0.8	21	12	0.5	0.3	17	198	17	431	69	244
80	No	2,N	1,N	104.8	104.8	1.1	1.2	22	22	0.5	0.4	22	14	19	23	57	57
81	No	1,N	2,LR	85.2	85.2	0.8	0.6	13	10	0.4	0.4	18	39	37	154	108	225
105	No	2,N	1,N	106.6	118.5	1.0	0.9	20	21	0.5	0.6	15	17	26	19	89	80
106	No	1,N	2,R	86.0	43.6	1.0	1.1	19	42	0.5	0.5	11	11	9	9	103	78
107	No	2,N	1,N	121.9	104.5	0.6	0.7	24	20	1.0	0.4	22	25	34	48	110	95
78	Yes	1,L	2,L	95.3	91.5	1.1	1.1	15	17	0.9	0.9	6	18	12	13	71	69
82	Yes	1,L	2,L	86.7	77.0	0.8	0.9	16	15	0.1	0.2	47	83	60	68	163	163
87	Yes	1,L	2,L	102.9	121.6	0.6	0.6	15	10	0.3	0.3	79	31	28	57	101	103
88	Yes	2,L	1,L	74.8	65.5	0.7	0.8	14	17	0.4	0.6	54	51	24	35	147	109
97	Yes	2,L	1,L	108.9	118.8	0.6	0.5	21	17	0.3	0.3	44	99	117	251	75	95
76	No	1,R	2,R	24.5	29.0	2.9	2.5	34	32	0.3	0.3	12	10	14	7	68	66
85	No	2,R	1,N	53.0	70.7	1.3	0.9	22	16	0.3	0.2	30	8	32	11	222	72
95	No	1,R	2,R	38.9	33.8	2.0	2.3	30	26	0.2	0.3	6	26	17	43	82	72
98	No	1,R	2,R	60.0	60.0	1.0	1.0	22	20	0.8	0.4	8	6	14	8	74	82
101	No	2,R	1,R	23.5	46.5	2.6	1.5	54	24	0.2	0.4	13	35	6	11	53	115
102	No	2,R	1,R	43.7	35.4	1.7	2.1	16	25	0.3	0.5	8	26	13	23	66	73
86	Yes	1,LR	2,LR	32.4	43.6	1.2	1.1	26	22	0.3	0.3	30	9	11	8	62	91
91	No	2,LR	1,LR	42.0	45.5	1.3	1.2	25	26	0.6	0.4	55	52	65	77	143	145
92	Yes	2,LR	1,LR	40.3	34.6	1.5	1.5	24	27	0.3	0.4	42	27	55	28	203	111
94	Yes	2,LR	1,LR	42.7	49.1	2.3	2.2	28	21	0.4	0.9	18	11	10	9	158	101

An accurate error analysis was carried out to distinguish between experimental accuracy and physiological interpatient variability. A pharmacokinetic trial can be considered to be a *nonrepeatable* experiment because it is not possible a priori to be certain that the experimental conditions will not change in subsequent trials. If the same study is carried out several times on the same patient and the experimental accuracy is not estimated, there is no way of telling whether variations in pharmacokinetic parameters depend on actual changes in the metabolism (or the rate of absorption) of a drug or on experimental uncertainties. Surprisingly enough although regulatory institutions and editorial boards require accuracy or precision data relative to the analytical assay of a drug, they are not particularly concerned about the knowledge as to how analytical errors influence the precision and accuracy of pharmacokinetic parameters, which are the real objects of a study. In this report, when *mean* data are discussed, the errors reported are the standard deviations computed in the usual way and represent a measure of interpatient variability; when pharmacokinetic data relative to *individual* patients are reported, the error represents the accuracy of the experiment.

Patients and methods

Patients. A total of 21 inpatients with advanced cancer (Table 1) were included in this study (Division of Oncology, M. Malpighi Hospital, Bologna, Italy). The eligibility criteria included (a) progressive neoplastic disease; (b) a life expectancy of >3 months; (c) a WHO performance status of 0, 1, or 2; (d) a WBC of >4,000/mm^3 and a platelet count of >120,000/mm^3; (e) no other antitumor treatment within 30 days prior to the beginning of the study; and (f) written informed consent. The exclusion criteria were (a) previous treatment with anthracyclines at a cumulative dose of >350 mg/m^2 and (b) the presence of cardiac disorders.

Patients were divided into four groups according to kidney and liver function:

1. Group 1 consisted of individuals with normal renal and liver function who displayed (a) a creatinine clearance of ≥70 ml/min; (b) total bilirubin levels of <1.2 mg/100 ml, SGOT and SGPT values of <45 mIU/ml, and alkaline phosphatase levels of <130 mIU/ml (patients exhibiting an increase of <30% in only one of these parameters were nonetheless considered to be eligible for this group); and (c) the absence of liver metastases.
2. Group 2 comprised subjects who exhibited (a) a creatinine clearance of ≥70 ml/min and (b) documented evidence of liver metastases.
3. Group 3 consisted of patients with impaired renal function who displayed (a) a creatinine clearance of ≤60 ml/min; (b) total bilirubin levels of <1.2 mg/100 ml, SGOT and SGPT values of <45 mIU/ml, and alkaline phosphatase levels of <130 mIU/ml (patients exhibiting an increase of <30% in only one of these parameters were nonetheless considered to be eligible for this group); and (c) the absence of liver metastases.
4. Group 4 comprised all patients who were not eligible for groups 1, 2, or 3.

For the sake of brevity in the Discussion and in Tables 1–8, data relative to the different groups of patients are labeled N (group 1), L (group 2), R (group 3), and LR (group 4). Patients 79, 81, 85, 88, and 106 showed variations in liver and/or kidney function after the first treatment. These individuals were considered to be nonevaluable for the crossover study but evaluable for the liver-/kidney-function study, in which some of them appeared in different groups for the i.v. versus p.o. treatments.

IDA was supplied by Farmitalia-Carlo Erba (Milan, Italy) and was given either as a rapid i.v. infusion over 3–5 min at a dose of 12 mg/m^2 (freeze-dried, injectable 5-mg vials) or orally (30–35 mg/m^2; 5-, 10-, or 25-mg capsules). The sequence of oral and i.v. treatments was allocated according to a randomization table. Blood samples were drawn prior to treatment, at time zero (i.e., immediately after the i.v. infusion), and at 5, 15, 30, and 60 min and 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h after drug administration. Plasma samples, which were separated after centrifugation, were kept frozen at –20° C in light-protected tubes; drug and metabolite analysis was performed at no later than 48 h after sampling.

Analytical methods. A novel HPLC assay with fluorimetric detection was applied for the quantitative determination of IDA, its main metabolite IDAol, and 4-demethoxydaunomycinone (AG1) in plasma and urine at concentrations of as low as 0.1–0.3 ng/ml. A detailed description of this method has been reported elsewhere [6]. Batch-to-batch and concentration-dependent variations in the analytical accuracy were taken into account in the pharmacokinetic procedures by weighting of the data points according to the experimental standard deviations (SD_{IDA} and SD_{IDAol}; see below) measured in the calibration run for each IDA and IDAol concentration.

Pharmacokinetic analysis. The experimental data were analyzed according to statistical moment theory [15], which requires the evaluation of both the area under the concentration-time curve (AUC) and the area under the first-moment curve (AUMC). Experimental IDA and IDAol concentrations were computer-fitted using a linear combination of exponential terms:

$$c = \sum_{i=1}^{n} A_i \times \exp(-a_i \times t).$$

When a time lag for the appearance of the unchanged drug (as observed after p.o. administration) or of the reduced metabolite occurred, the t-axis origin was translated to the last $c = 0$ data point. The selection of the number of exponential terms describing the drug and metabolite concentration-time course was performed according to the Akaike Information Criterion [1, 27].

Interpolation was carried out using a specifically designed double-precision FORTRAN program based on the CERN MINUIT package [17], which was run on a Digital μVAX GPX workstation. At each iteration of the nonlinear fitting, the theoretical concentration of IDA or IDAol [$IDA(i)_{calc}$ and $IDAol(i)_{calc}$] was computed for the proposed model. A chi-square error function (F) was then computed (and minimized) as:

$$F = \sum_{i=1}^{n} \frac{(IDA(i)_{calc} - IDA(i)_{exp})^2}{SD(i)^2_{IDA}} \text{ or as}$$

$$F = \sum_{i=1}^{n} \frac{(IDAol(i)_{calc} - IDAol(i)_{exp})^2}{SD(i)^2_{IDAol}},$$

where $SD(i)_{IDA}$ and $SD(i)_{IDAol}$ represent the experimental standard deviations measured at each $IDA(i)_{exp}$ and $IDAol(i)_{exp}$ experimental concentration. Due to the proper normalization described above, the parameter errors presented in this report represent 1 SD, including the effects of correlation with the other parameters [12, 13].

The AUC and AUMC values were computed for unchanged drug and metabolites according to the trapezoidal rule and by analytical integration of the exponential equation (zero-to-infinity interval). The two integration methods gave consistent results. The infusion time was taken into account by adding the area of the triangle [(infusion time × initial concentration)/2] to the zero-to-infinity AUC. The initial concentration was considered to be the experimental one (t = 0; plasma sample taken in the controlateral arm immediately after the end of the i.v. infusion) for the trapezoidal-rule area and was computed as the sum of the preexponential terms A_i (for the interpolated area).

After oral administration of IDA, the time to peak and the peak concentration of unchanged drug and reduced metabolite were computed by equating the first derivative of the exponential equation to zero (without forgetting the time lag). The drug bioavailability following oral administration (IDA systemic bioavailability [15]) was computed as the ratio of the dose-corrected AUC values obtained after oral and i.v. administration:

$$\%\ \text{Bioavailability} = \frac{AUC_{IDA\ (p.o.)} \times Dose_{IDA\ (i.v.)}}{AUC_{IDA\ (i.v.)} \times Dose_{IDA\ (p.o.)}} \times 100.$$

Errors in pharmacokinetic parameters were computed according to standard error-propagation rules [26],

$$\delta q = \sqrt{\left(\frac{\delta q}{\delta x} \times \delta x\right)^2 + ... + \left(\frac{\delta q}{\delta z} \times \delta z\right)^2},$$

starting from the parameter errors computed in the interpolation procedure, and represent 1 SD.

Statistical analysis. Statistical analysis of the results was carried out using the BMDP Statistical Software package [11], which was run on a Digital VAX GPX workstation. The Mann-Whitney rank-sum test and the Kruskal-Wallis one-way analysis of variance were used unless otherwise specified. A z-test [26] was performed to check whether the corresponding parameters were identical within the experimental error ($P = 0.05$) when measured after i.v. and p.o. treatment in the same patient. Asterisk-flagged values for MRT, $t_{1/2\gamma}$, and AUC(IDAol)/AUC(IDA) indicate a significant difference in the pharmacokinetic parameter.

Results

IDA pharmacokinetics after i.v. treatment

In each patient, the IDA plasma-concentration decay curve was well described by a triexponential equation. Our selection is based on the Akaike Information Criterion (AIC) [27]. In the worst case (patient 106), the AIC value calculated for a biexponential equation was 1.1-fold that computed for the triexponential case; typically, the AIC value for a biexponential interpolation is 1.3-fold that for triexponential decay. A simple comparison of the total interpolation error would have been even more favorable for triexponential decay (F value for biexponential decay is typically 2–4 times the corresponding value for the triexponential fitting).

As shown in Table 2, the experimental uncertainities for *each* $t_{1/2\gamma}$ value were quite low, generally falling within the ±2%–5% range. The coefficients of variation in the *mean* $t_{1/2\gamma}$ value (range, 19%–24%) are true measures of interpatient variability. On the other hand, the experimental errors in $t_{1/2\alpha}$ and $t_{1/2\beta}$ values were definitely larger (±10%–30%). However, as shown in Table 3, these uncertainties do not significantly influence the AUC error, which is more important in the model-independent analysis.

Influence of kidney function and liver metastases on IDA pharmacokinetics

Mean IDA MRT and $t_{1/2\gamma}$ values were slightly higher in patients with impaired renal function or liver metastases, but this difference did not reach statistical significance when nonparametric group comparisons were done [MRT: N, 15.3±2.1 h; L, 18.1±4.1 h ($P = 0.31$) vs R, 19.2±6.2 h ($P = 0.20$) and $t_{1/2\gamma}$: N, 15.2±3.7 h; L, 15.8±3.0 h ($P = 0.86$) vs R, 19.0±4.5 h ($P = 0.20$)].

Analysis of variance indicated a significant correlation between IDA plasma clearance and creatinine clearance (Fig. 1, $P = 0.0144$; 46.6% of the variability in plasma clearance was explained by the linear association with creatinine clearance). Using a different statistical ap-

Table 2. IDA half-lives for the three decay phases following i. v. administration

Patient number	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)
79	0.070±0.013	2.47±1.52	14.45±1.23
80	0.018±0.005	0.26±0.04	10.79±0.37
81	0.059±0.008	1.96±0.32	14.99±0.97
105	0.064±0.011	0.74±0.11	14.82±0.49*
106	0.252±0.038	1.18±0.54	22.04±0.83*
107	0.039±0.013	0.86±0.17	14.34±0.58*
Mean, N	0.084	1.24	15.24
SD	0.085	0.82	3.68
78	0.030±0.004	0.78±0.18	14.97±0.39*
82	0.038±0.011	0.48±0.07	15.86±0.56*
87	0.024±0.004	0.82±0.14	14.28±0.71
88	0.025±0.004	0.83±0.20	12.99±0.51*
97	0.024±0.003	0.61±0.10	20.88±1.49
Mean, L	0.028	0.70	15.80
SD	0.006	0.15	3.03
76	0.028±0.003	0.66±0.11	18.19±0.60
85	0.034±0.006	0.44±0.11	13.83±0.47*
95	0.028±0.004	0.53±0.12	18.89±0.74*
98	0.021±0.002	0.80±0.16	14.81±0.71
101	0.007±0.001	0.70±0.08	23.80±0.68
102	0.209±0.018	2.85±0.54	24.68±1.87
Mean, R	0.054	1.00	19.03
SD	0.076	0.92	4.48
86	0.037±0.004	0.68±0.14	10.73±0.33
91	0.021±0.003	0.77±0.12	17.42±0.46
92	0.029±0.006	0.75±0.15	11.92±0.57*
94	0.019±0.002	0.53±0.11	15.64±0.65
Mean, LR	0.027	0.68	13.93
SD	0.008	0.11	3.13

* Data significantly different when measured after i. v. and p. o. treatment in the same patient

proach, we also found that IDA plasma clearance was lower in patients whose creatinine clearance was <60 ml/min [plasma clearance: N, 122.8±44.0 l/h; L, 104.4±27.7 l/h (P = 0.58) vs R, 83.4±18.3 l/h (P = 0.037)]. The volume of distribution at steady state (V_{ss}) was not significantly dependent on kidney or liver function [V_{ss}: N, 24.7±5.9 l/kg; L, 28.5±5.2 l/kg (P = 0.27) vs R, 23.3±7.4 l/kg (P = 0.87)].

IDAol plasma concentration-time course. IDAol was the only fluorescent compound detectable in plasma at 72–96 h after IDA administration. Plasma concentrations of the (active) metabolite IDAol increased rapidly, exceeding IDA levels at 2–8 h after administration. In all patients, the metabolite's terminal half-life was significantly longer than that of the parent drug (Table 4).

Influence of kidney function and liver metastases on the IDAol plasma concentration-time course. As observed for IDA disposition, the IDAol plasma concentration-time course was not significantly altered in group 2 (L) patients. The mean dose-corrected IDAol AUC (expressed as IDAol AUC units per milligram of IDA received) was higher in patients with impaired renal function [N, 36.1±10.5 ng h ml^{-1} mg^{-1}; L, 39.8±16.3 ng h ml^{-1} mg^{-1} (P = 0.86) vs

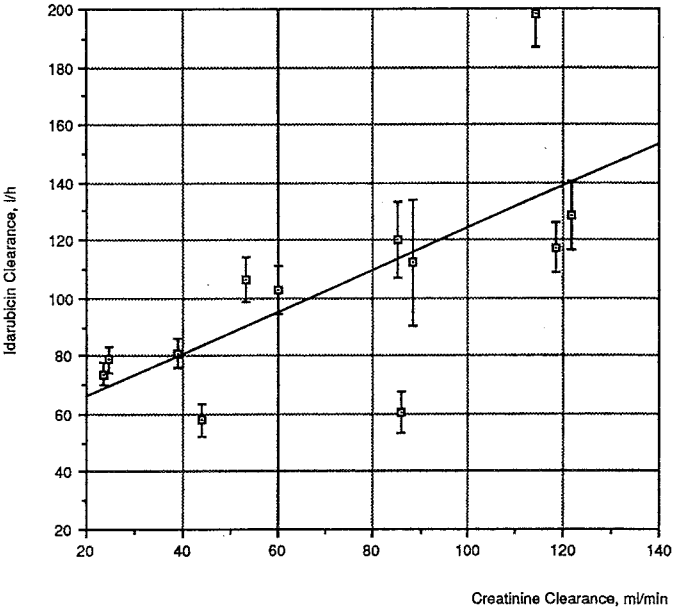

Fig. 1. IDA plasma and creatinine clearance ($y = 51.093+0.72752\,x$, $r^2 = 0.466$)

Table 3. IDA model-independent parameters following i. v. administration

Patient number	AUC (ng h ml^{-1})	c (l/h)	MRT (h)	V_{ss} (l/kg)
79	169.3±32.9	112.2±21.8	16.2±5.0	30.9±15.4
80	126.3± 7.1	197.9±11.2	12.6±1.1	20.7± 3.0
81	158.2±17.5	120.1±13.3	14.7±2.9	29.6± 9.0
105	212.9±15.2	117.4± 8.4	14.3±1.5	16.6± 3.0
106	296.2±35.0	60.8± 7.2	19.0±3.1	21.4± 6.0
107	155.9±14.4	128.3±11.8	14.9±2.1	29.4± 6.8
Mean, N	186.5	122.8	15.3	24.7
SD	60.7	44.0	2.1	5.9
78	178.1±10.6	140.4± 8.3	18.5±1.7	28.3± 4.2
82	187.1±11.3	106.9± 6.5	18.6±1.8	30.3± 4.7
87	157.3±12.6	120.8± 9.7	14.9±2.0	31.1± 6.7
88	241.2±19.8	74.6± 6.1	14.0±1.7	19.7± 4.0
97	239.1±19.4	79.5± 6.4	24.4±3.5	32.9± 7.4
Mean, L	200.6	104.4	18.1	28.5
SD	37.7	27.7	4.1	5.2
76	254.1±15.3	78.7± 4.7	21.4±2.0	23.4± 3.6
85	188.0±13.3	106.4± 7.5	15.1±1.6	27.7± 4.9
95	296.6±18.3	80.9± 5.0	22.8±2.1	21.1± 3.3
98	194.5±15.4	102.8± 8.1	15.5±2.0	25.3± 5.2
101	271.0±14.0	73.8± 3.8	28.6±2.3	32.0± 4.3
102	345.3±32.7	57.9± 5.5	11.8±2.5	10.3± 3.2
Mean, R	258.2	83.4	19.2	23.3
SD	60.4	18.3	6.2	7.4
86	179.3±12.1	100.4± 6.8	10.8±1.1	21.7± 3.7
91	416.9±25.9	43.2± 2.7	19.2±1.7	15.3± 2.3
92	196.3±18.2	96.8± 9.0	12.1±1.7	20.7± 4.8
94	257.8±17.1	93.1± 6.2	17.7±1.8	17.9± 3.0
Mean, LR	262.6	83.4	14.9	18.9
SD	108.3	27.0	4.1	2.9

c, Plasma clearance

Table 4. IDAol model-indepent parameters following i. v. administration of IDA

Patient number	AUC (ng h ml^{-1})	AUC/dose (ng h ml^{-1} mg^{-1})	IDAol/IDA	MRT (h)	Terminal half-life (h)
79	724.3±110.1	38.1± 5.8	4.26±1.05*	53.8±16.4	32.8±1.5*
80	453.3± 27.5	18.1± 1.1	3.57±0.30*	63.8± 9.1	42.9±1.4
81	831.5± 87.2	43.8± 4.6	5.24±0.80	71.4±18.3	48.5±3.1
105	997.5±498.3	39.9±19.9	4.67±2.35	54.1±48.3	28.3±2.4*
106	843.4± 40.4	46.9± 2.2	2.84±0.36*	81.0±10.0	56.0±1.9*
107	599.1± 43.8	30.0± 2.2	3.83±0.45	57.7± 9.9	39.4±1.6
Mean, N	741.5	36.1	4.07	63.6	41.3
SD	193.7	10.5	0.8	10.8	10.1
78	535.1± 54.1	21.4± 2.2	2.99±0.35*	66.2±14.7	42.9±1.9
82	899.5± 71.1	45.0± 3.6	4.79±0.48*	63.3±12.2	45.3±2.1
87	722.6± 87.1	38.0± 4.6	4.57±0.66*	60.0±15.4	38.2±1.8
88	1,156.0± 92.2	64.2± 5.1	4.77±0.55*	85.2±17.0	57.3±3.0*
97	572.5± 47.5	30.1± 2.5	2.39±0.28*	74.9±15.9	51.3±3.0
Mean, L	777.2	39.8	3.90	69.9	47.0
SD	255.9	16.3	1.1	10.2	7.4
76	4,815.9±536.9	240.8±26.8	18.88±2.39	75.8±19.1	48.9±2.7
85	764.8± 76.6±	38.2± 3.8	4.05±0.50*	93.7±23.5	63.8±4.2
95	1,104.5±114.1	46.0± 4.8	3.71±0.45*	75.5±18.0	48.9±2.7
98	974.6± 83.7	48.7± 4.2	4.99±0.58*	99.9±22.2	68.0±4.2*
101	1,460.7±146.3	73.0± 7.3	5.37±0.61	80.3±19.2	53.6±3.1
102	699.6± 29.8±	35.0± 1.5	2.02±0.21*	74.0± 8.7	51.3±1.8
Mean, R	1,636.7	80.3	6.50	83.2	55.8
SD	1,581.0	79.8	6.2	10.9	8.2
86	753.9± 57.9	41.9± 3.2	4.19±0.43*	67.7±12.7	46.8±2.2*
91	1,703.2±161.7	94.6± 9.0	4.07±0.46*	59.2±12.7	39.4±1.8
92	1,117.0± 69.1	58.8± 3.6	5.67±0.63*	76.1±11.7	52.2±2.1
94	1,283.6±180.8	13.7± 1.9	4.96±0.77*	102.5±35.3	67.7±6.0
Mean, LR	1,214.4	52.2	4.72	76.4	51.6
SD	393.8	33.8	0.7	18.7	12.0

* Data significantly different when measured after i. v. and p. o. treatment in the same patient

R, 80.3±79.8 ng h ml^{-1} mg^{-1} (P = 0.11)], but the difference did not reach statistical significance, mainly due to the sole excessively high AUC value noted for patient 76 (Table 4). The mean value calculated for the remaining five group 3 (R) patients was 48.2 ng h ml^{-1} mg^{-1}. IDAol terminal half-life and MRT values were significantly increased in patients with impaired renal function [MRT: N, 63.6±10.8 h; L, 69.9±10.2 h (P = 0.27) vs R, 83.2±10.9 h (P = 0.025) and $t_{1/2\gamma}$: N, 41.3±10.1 h; L, 47.0±7.4 (P = 0.31) vs R, 55.8±8.2 (P = 0.025)].

IDA pharmacokinetics after p. o. treatment

IDA plasma concentration-time course. After oral administration, IDA appeared in the plasma of subjects after a time lag of 0.08–0.25 h; in one patient the delay was 3 h and in five others, between 0.5 and 1 h. In normal (group N) patients, a peak concentration of 6.9±0.12 ng/ml was reached at 5.4±2.4 h after administration (group L, 9.0±3.2 ng/ml at 2.6±0.7 h; group R, 10.5±3.2 ng/ml at 3.0±0.8 h; group LR, 8.65±5.5 ng/ml at 2.7±0.3 h). A biphasic decay then followed; within the experimental error (P = 0.05), the IDA terminal half-life calculated after oral dosing was identical to that determined following i. v. administration of IDA in 12/21 patients. Four of the remaining patients showed a slightly longer half-life after i. v. treatment and five were characterized by a longer half-life after p. o. treatment (Table 5). A significantly longer IDA MRT value was observed after p. o. treatment in 2/21 patients. The remaining subjects did not significantly differ in respect to this parameter.

Influence of kidney function and liver metastases on IDA pharmacokinetics. As observed after i. v. treatment, following oral administration, both the MRT and the terminal half-life of IDA showed a slight increase in patients with impaired renal function or liver metastases. However, the variation did not reach statistical significance in this limited patient sample [MRT: N, 19.8±5.8 h; L, 19.8±2.4 h (P = 0.78) vs R, 26.4±5.7 h (P = 0.09) and $t_{1/2\gamma}$: N, 14.3±3.7 h; L, 16.4±2.2 h (P = 0.19) vs R, 21.7±5.0 h (P = 0.055)].

IDAol plasma concentration-time course. IDAol appeared in the plasma of 18/21 patients after a time lag of 0.17–0.5 h; in the remaining 3 subjects the time lag was 1.0, 1.0, and 2.0 h. A peak concentration of 21.7±4.0 ng/ml was reached after 7.9±2.3 h in group N patients (group L, 21.5±3.0 ng/ml after 4.5±2.5 h; group R, 41.4±25.1 ng/ml after 4.6±0.9 h; group LR, 22.5±9.5 ng/ml after 4.4±1.5 h). IDAol terminal half-life

Table 5. IDA model-independent parameters following oral administration

Patient number	AUC (ng h ml^{-1})	AUC/dose (ng h ml^{-1} mg^{-1})	MRT (h)	Terminal half-life (h)
80	76.3±10.8	1.3±0.2	13.9±3.6	12.10±0.96
85	186.0±41.5	3.7±0.8	27.7±7.1	19.78±0.08*
105	160.0±32.1	2.3±0.5	19.7±5.4	12.67±0.80*
107	130.1±19.9	2.6±0.4	18.1±4.0	12.47±0.74*
Mean, N	138.1	2.5	19.8	14.26
SD	47.1	1.0	5.8	3.69
78	150.9± 9.9	2.5±0.2	23.0±2.4	16.55±0.61*
82	100.4±14.2	2.9±0.4	16.3±3.9	13.40±0.95*
87	118.5±13.3	2.6±0.3	18.1±3.5	15.28±0.96
88	85.5±13.2	1.9±0.3	19.1±6.6	17.89±2.27*
97	203.7±20.4	4.1±0.4	22.3±3.7	18.90±1.27
Mean, L	131.8	2.8	19.8	16.41
SD	47.0	0.8	2.8	2.17
76	271.7±29.9	4.5±0.5	23.6±3.9	17.64±1.36
95	202.9±28.7	3.4±0.5	31.1±8.4	26.84±3.13*
98	127.8±25.3	2.6±0.5	22.8±7.4	16.78±1.89
101	187.0±17.9	3.7±0.4	25.2±4.1	21.41±1.24
102	273.0±27.3	5.0±0.5	35.4±5.9	28.69±1.90
106	119.5±12.4	2.7±0.3	20.3±4.1	18.67±1.28*
Mean, R	197.0	3.6	26.4	21.67
SD	66.8	1.0	5.7	5.00
79	126.1±14.3	2.5±0.3	20.6±3.6	14.82±0.78
81	164.3±17.9	4.7±0.5	18.9±3.1	14.39±0.69
86	71.7±12.8	1.6±0.3	13.3±3.8	10.36±0.80
91	238.7±17.8	5.3±0.4	22.9±2.6	18.71±0.67
92	56.1± 1.7	1.2±0.0	16.5±0.9	14.33±0.17*
94	75.2± 7.3	1.3±0.1	13.8±2.8	13.79±0.88
Mean, LR	122.0	2.8	17.7	14.40
SD	70.0	1.8	3.8	2.66

* Data significantly different when measured after i. v. and p. o. treatment in the same patient

values calculated after oral and i. v. treatment were equivalent within the experimental error in 15/21 patients; 4 of the remaining subjects showed a slightly longer half-life after i. v. treatment and 2 were characterized by a longer half-life after p. o. treatment.

Influence of kidney function and liver metastases on the IDAol plasma concentration-time course. No statistically significant difference was observed among the first three groups of patients in IDAol MRT value [N, 59.7±19.7 h; L, 56.1±6.4 h ($P = 0.45$) vs R, 66.1±8.8 h ($P = 0.20$)], in IDAol terminal half-life [N, 47.3±11.3 h; L, 45.7±3.1 h ($P = 0.34$) vs R, 48.9±5.3 h ($P = 0.29$)], or in the IDAol/IDA AUC ratio [N, 7.9±1.5; L, 6.7±1.6 ($P = 0.57$) vs R, 10.9±5.2 ($P = 0.16$); Table 6].

Deglycosylated products. A substantial amount of 4-demethoxydaunomycinone (AG1) was found after oral IDA administration in 11/21 patients (Table 7). Of eight subjects with liver metastases, six were characterized by high plasma AG1 levels. Of the remaining five individuals showing appreciable AG1 plasma concentrations, patient 81 was characterized by high pretreatment SGPT values (154 mIU/ml) and patient 91 by high glutamic transaminase levels (SGOT, 71 mIU/ml, SGPT, 71 mIU/ml). Patients 76, 101 and 102 showed normal liver function (but low creatinine clearance).

IDA and IDAol bioavailability. After oral administration, IDA bioavailability, computed as the ratio of the dose-corrected AUC after i.v. and p.o. treatment in the same patient, lay within the 25.2%–35.7% range for group 1–3 (mean: N, 28.5%±4.3%; L, 32.5%±2.0%; R, 29.1%±3.8%; Table 7). Group 4 patients showed significantly lower IDA bioavailability (LR, 15.7%±5.2%). Experimental standard deviations in individual values were of the same order as those in mean values.

Side effects

Table 8 shows the toxicity data recorded according to WHO grade in the patients after i.v. and p.o. treatments. The main toxicity observed during this study was leukopenia. Two subjects developed grade 4 leukopenia after i.v. treatment and one, after oral administration: patient 81 (first treatment, i.v., WBC nadir: 650 mm^3; second treatment, p.o., 25% dose reduction, WBC nadir: 2,210/mm^3, grade 2), patient 101 (first treatment, p.o., grade 0 leukopenia; second treatment, i.v., WBC nadir: 600/mm^3), and patient 76 (first treatment, i.v., WBC nadir: 1,340/mm^3, grade 3; second treatment, p.o., WBC nadir: 360/mm^3). Grade 3 leukopenia was observed in four patients after i.v. treatment and in one subject after oral administration. A statistically significant difference (Wilcoxon signed-rank test, $P = 0.041$) was found between the incidence and gravity of this side effect after p.o. and i.v. treatments, in favor of the oral treatment. Interestingly, the IDA AUC calculated after oral administration was almost always *lower* than that determined after i.v. treatment (18/21 patients, mean AUC: i.v., 224.8±71.3 ng h ml^{-1}; p.o., 148.8±64.2 ng h ml^{-1}). In contrast, the IDAol AUC was generally *higher* after oral treatment (14/21 patients, mean AUC: i.v., 1,095.8±907.9 ng h ml^{-1}; p.o., 1,352.1±112.1 ng h ml^{-1}).

Anemia was also more frequently observed after i.v. treatment; the difference was not of statistical significance due to the rather high proportion of nonevaluable patients (6/21; in these subjects, anemia corresponding to a hemoglobin count of <10.9 g/100 ml was evident prior to IDA treatment). Nausea and vomiting were more frequently encountered after oral administration (Wilcoxon signed-rank test, $P = 0.015$). Notwithstanding the significant reduction observed in IDA plasma clearance, we found no evidence for a higher incidence of side effects in patients with impaired renal function (or liver metastases).

Discussion

IDA plasma concentration after i.v. administration is well described by a triexponential equation. This behavior has previously been described in the literature [9, 18, 19, 25], although the reasons for the selection of a triexponential equation were never stated. Biexponential decay has been

Table 6. IDAol model-independent parameters following oral administration of IDA

Patient number	AUC (ng h ml^{-1})	AUC/dose (ng h ml^{-1} mg^{-1})	IDAol/IDA	MRT (h)	Terminal half-life (h)
80	686.5 ± 71.9	11.4 ± 1.2	8.97 ± 1.58*	48.8 ± 7.4	39.3 ± 2.1
85	1,723.6 ± 43.0	34.5 ± 0.9	9.23 ± 2.07*	89.1 ± 2.7	64.0 ± 0.6
105	1,206.2 ± 170.1	17.2 ± 2.4	7.51 ± 1.84	52.2 ± 10.0	41.7 ± 2.8*
107	782.6 ± 228.9	15.7 ± 4.6	5.99 ± 1.98	48.6 ± 20.9	44.1 ± 6.6
Mean, N	1,099.7	19.7	7.9	59.7	47.3
SD	473.2	10.1	1.5	19.7	11.3
78	985.7 ± 59.0	16.4 ± 1.0	6.50 ± 0.58*	63.2 ± 5.2	44.6 ± 1.6
82	736.4 ± 66.8	21.0 ± 1.9	7.31 ± 1.23*	59.8 ± 8.6	51.0 ± 3.1
87	963.6 ± 124.8	21.4 ± 2.8	8.10 ± 1.39*	53.5 ± 10.0	44.7 ± 3.3
88	653.7 ± 54.3	14.5 ± 1.2	7.62 ± 1.33*	57.7 ± 7.0	42.8 ± 2.0*
97	841.1 ± 88.0	16.8 ± 1.8	4.11 ± 0.60*	46.5 ± 7.8	45.5 ± 3.2
Mean, L	836.1	18.0	6.7	56.1	45.7
SD	143.1	3.0	1.6	6.4	3.1
76	5,823.0 ± 481.8	97.0 ± 8.0	21.35 ± 2.94	66.3 ± 6.3	45.8 ± 2.1
95	1,975.3 ± 160.8	32.9 ± 2.7	9.70 ± 1.58*	64.7 ± 6.6	45.2 ± 2.1
98	1,265.5 ± 134.4	25.3 ± 2.7	9.86 ± 2.22*	74.0 ± 11.0	54.8 ± 3.7*
101	1,409.1 ± 300.1	28.2 ± 6.0	7.51 ± 1.75	52.9 ± 15.6	43.2 ± 6.3
102	2,120.6 ± 255.3	38.6 ± 4.6	7.74 ± 1.21*	77.5 ± 12.1	56.0 ± 4.2
106	1,096.9 ± 90.1	24.4 ± 2.0	9.14 ± 1.21*	61.4 ± 7.2	48.4 ± 2.5*
Mean, R	2,281.7	41.1	10.88	66.1	48.9
SD	1,780.9	27.9	5.2	8.8	5.3
79	1,434.9 ± 122.1	28.7 ± 2.4	11.33 ± 1.61*	61.3 ± 6.7	42.8 ± 1.9*
81	1,074.4 ± 94.3	30.7 ± 2.7	6.51 ± 0.91	69.2 ± 8.4	49.0 ± 2.6
86	723.4 ± 15.9	16.1 ± 0.4	10.05 ± 1.81*	53.0 ± 1.6	40.9 ± 0.4*
91	1,452.4 ± 109.5	32.3 ± 2.4	6.06 ± 0.64*	55.6 ± 5.3	39.4 ± 1.5
92	544.3 ± 54.0	12.1 ± 1.2	9.67 ± 1.00*	68.4 ± 10.8	51.2 ± 3.2
94	895.7 ± 83.5	14.9 ± 1.4	11.87 ± 1.60*	64.3 ± 9.8	57.8 ± 4.1
Mean, LR	1,020.9	22.5	9.25	62.0	46.8
SD	372.0	9.0	2.4	6.6	7.1

* Data significantly different when measured after i. v. and p. o. treatment in the same patient

reported in nine patients by Lu et al. [19], who did not give their reasons for this selection, and in 20 subjects by Gillies et al. [16], who applied the Akaike Information Criterion (AIC), as we did in the present study. The AIC selects not the "real" equation but the simplest one consistent with the available data. If the sampling of the concentration-time course is sparse, information contained in the true decay is missed. In the study of Gillies et al. [16], early-phase plasma samples were taken at 0.25, 0.5, 0.75, and 1 h after drug administration, and the fast α-half-life was probably lost. Lu and co-workers [19] did not report sampling times.

A compartmental analysis of plasma IDA decay has been attempted [25], but the investigators used a structurally nonidentifiable model (the so-called "first-pass" three-compartmental open model with elimination from a peripheral compartment). As shown by systems theory [20], only the volume of the central compartment is identifiable in such a model; the single kinetic microconstants cannot be uniquely identified. It should also be noted that the "kinetic constants" reported by Smith et al. [25] are not internally consistent with the half-lives reported in the same paper (i. e., the half-lives that can be computed from the kinetic constants are different from the reported half-lives).

The triexponential disposition of IDA after i. v. treatment is qualitatively similar to doxorubicin (DX) or epidoxorubicin (epiDX) disposition; nevertheless, IDA plasma disappearance is faster. Hereafter, we discuss (when relevant) IDA pharmacokinetics in comparison with our published data on DX and epiDX, which were obtained using the same technology in a similar patient population [3–5]. A proper statistical comparison can be carried out, as no *experimental* bias is present among these data. In contrast, the sampling times reported in other pharmacokinetics studies on anthracyclines are often inadequate; decay processes must be followed for at least two to three half-lives if reasonable estimates of kinetic parameters are to be obtained.

In the patients with normal liver and renal function (group N), the half-lives found for the first two decay phases ($t_{1/2\alpha}$, 5.0 ± 5.1 min; $t_{1/2\beta}$, 1.24 ± 0.82 h) were close to both the epiDX and the DX initial half-lives we had previously determined under similar experimental conditions. However, the rather large experimental error (Table 2) in these half-lives suggests that any fine comparison should be avoided.

The terminal half-life of IDA (15.2 ± 3.7 h) was significantly shorter than the corresponding DX (44.8 ± 14.0 h, $P = 0.0027$) and epiDX (29.0 ± 7.4 h, $P = 0.0067$) values. As a consequence, the IDA plasma concentration was not measurable under the present experimental conditions (minimal measurable concentration, <0.1 ng/ml) at

Table 7. Bioavailability of IDA and IDAol following oral administration of IDA

Patient number	IDA systemic availability (%)	IDA+IDAol systemic availability (%)	AUC AG1 (ng h ml^{-1})
80	25.2±3.8	54.8± 3.5	0.0
105	26.9±5.7	40.3±16.7	0.0
107	33.4±6.0	48.4± 5.7	0.0
Mean, N	28.5	47.8	0.0
SD	4.3	7.3	0.0
78	35.3±3.1	66.4± 5.3	310.4
82	30.7±4.7	44.0± 3.6	456.3
87	31.8±4.4	51.9± 5.8	118.1
97	32.4±4.2	48.9± 3.5	0.0
Mean, L	32.5	52.8	221.2
SD	2.0	9.6	202.3
76	35.7±4.5	40.1± 4.4	855.9
95	27.4±4.2	62.2± 5.5	0.0
98	26.3±5.6	47.7± 3.9	0.0
101	27.6±3.0	36.9± 4.2	198.3
102	28.8±4.0	83.2± 4.8	513.9
Mean, R	29.1	54.0	313.6
SD	3.8	19.0	368.8
86	16.0±3.1	34.1± 2.2	360.6
91	22.9±2.2	31.9± 2.6	845.9
92	12.1±1.2	19.3± 1.3	426.8
94	11.7±1.4	25.2± 3.1	0.0
Mean, LR	15.7	27.6	408.3
SD	5.2	6.7	346.8
79[a]			0.0
81[a]			91.8
85[a]			0.0
88[a]			319.6
106[a]			0.0
Mean			82.3
SD			138.5

[a] Patients showing variations in liver or renal function after the first treatment and not considered to be evaluable for the crossover study

72–120 h after administration; in contrast, appreciable concentrations of DX and epiDX were previously measured at 144 h after standard-dose (60 and 90 mg/m^2, respectively) treatment.

In patients with normal liver and kidney function, IDA plasma clearance (122.8±44 l/h) was significantly higher than the previously determined DX clearance (61.4±28.1 l/h, $P = 0.015$) and was closer to the corresponding epiDX value (80.6±28.1 l/h, $P = 0.12$). The high IDA clearance was probably related to the efficient metabolism of the parent drug to IDAol, as the rapid clearance of epiDX is attributable to glucuronide formation.

The volume of distribution at steady state (V_{ss}) indicates the typical extraplasmatic distribution of anthracycline drugs. As expected, the experimental uncertainties in this second-order parameter (it depends on both the AUC and the AUMC) are generally rather large (±10%–±50%). Care must be taken in reporting V_{ss} values if experimental errors are unknown.

The only fluorescent metabolite observed after i.v. treatment was IDAol. The ratio between IDAol and IDA AUC values (N, 4.07±0.8) was greater than the corresponding epirubicinol/epirubicin (0.34±0.13, $P = 0.0027$) and doxorubicinol/doxorubicin (0.54±0.25, $P = 0.0027$) ratios. Similar behavior has been reported for the reduced metabolites of daunorubicin [10] and carminomycin [8].

In previous studies, we have found that epirubicin disposition is significantly dependent on the presence of liver metastases (even if no alteration is apparent in the liver-function tests) and only marginally influenced by renal impairment [3–5]. The pharmacokinetics of IDA was not significantly dependent on the presence of liver metastases but was somewhat related to the integrity of renal function. Although IDA terminal half-life and MRT values were only marginally affected in patients showing creatinine clearance of <60 ml/min, IDA plasma clearance was reduced by 30%, whereas IDAol terminal half-life and MRT values were significantly increased in such patients.

The profile of IDA metabolism and pharmacokinetics after oral treatment determined in this study is in qualitative agreement with the findings of other authors [2, 16, 19, 21, 25]. In all patients, the relative bioavailability of IDAol (as indicated in terms of the molecular-weight-corrected AUC ratio of IDAol/IDA) found after p.o. dosing was higher than that observed following i.v. administration; statistical significance ($P < 0.05$) was reached in 16/21 patients. This finding can be attributed to the liver metabolic first-pass effect after p.o. treatment. IDAol itself is active against experimental tumors. A substantial amount of 4-demethoxydaunomycinone (AG1) was also found after oral treatment in 11/21 patients. No AG1 was detected after i.v. treatment, nor was the corresponding aglycone derived from IDAol apparent after p.o. or i.v. administration. It can therefore be suggested that AG1 is formed not by systemic metabolism but during drug absorption from the gastrointestinal tract.

After oral administration, IDA bioavailability lay within the 25.2%–35.7% range for patients in groups N, R and L. Group LR patients showed a significant reduction in IDA bioavailability (15.7%±5.2%). Our mean data are in agreement with the findings of Gillies et al. [16], Smith et al. [25], Robert et al. [23], and Zanette et al. [28], but the interpatient spread in drug bioavailability was less pronounced in the present study. Unfortunately, there is no way of determining whether the larger spread observed by other authors is attributable to actual interpatient variations in drug absorption or to experimental uncertainities (not reported in the above-mentioned papers). The estimation of systemic availability is particularly subject to experimental uncertainties. Its determination depends on the assumption that the patients' conditions do not change in crossover experiments; for this reason, five subjects (patients 79, 81, 85, 88, and 106) showing variations in liver or renal function after the first treatment were not considered to be evaluable for the crossover study. In addition, the uncertainty in the AUC value after both oral and i.lv. treatment contributed to the experimental error in drug bioavailability. These factors are sometimes overlooked, and experimental errors or changes in metabolism are interpreted as interpatient variations in drug absorption.

The usual assessment of the efficiency of drug absorption (systemic bioavailability) must be reconsidered in the case of IDA, whereby an active metabolite – IDAol – is

Table 8. Side effects encountered according to WHO grade

Patient number	Leukopenia		Thrombocytopenia		Anemia		Vomiting		Diarrhea		Hepatic toxicity	
	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.
79	3	1	0	0	1	0	0	2	0	0	0	0
80	0	1	0	0	0	0	0	0	0	0	0	0
81	4	2	0	0	1	0	0	2	0	0	0	0
105	0	1	0	0	0	0	0	0	0	0	0	0
106	2	2	0	0	0	0	1	0	0	0	0	0
107	3	3	0	0	NE	NE	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
82	1	0	0	0	2	0	1	2	0	0	0	0
87	0	0	0	0	1	2	0	0	0	0	0	0
88	1	0	0	0	0	0	1	2	0	0	0	0
97	0	0	0	0	2	1	0	0	0	0	0	0
76	3	4	0	2	NE	NE	0	2	0	0	0	0
85	2	1	0	0	NE	NE	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	2
98	0	0	0	0	0	0	0	2	0	0	0	0
101	4	0	0	0	NE	1	0	2	0	0	0	0
102	0	1	0	0	NE	NE	0	0	0	0	0	0
86	3	0	1	0	2	0	0	0	0	2	0	0
91	1	0	0	0	0	1	0	0	0	0	0	0
92	2	0	0	0	2	2	2	2	0	0	0	0
94	1	0	0	0	NE	NE	0	2	0	0	0	0

NE, Not evaluable

efficiently formed in the liver following first pass through the portal system. A straightforward comparison of the IDA AUC after i.v. and p.o. administration in this case would lead to a significant underestimation of the *active* circulating species in 16/21 patients, which can be proven by examining the IDAol/IDA ratios after i.v. and p.o. treatment. A better description of the actual bioavailability could be obtained by taking into account the AUCs of both IDA and IDAol after i.v. and p.o. administration. The pharmacokinetic literature does not currently report any generally accepted way of quantitatively coping with this situation. Using a pharmacodynamic approach, Rowland [24] proposed the concept of "actual bioavailability", defined as the ratio of the dosing rates (oral to i.v.) required to produce the same therapeutic response at steady state. Following a pharmacokinetic approach, and estimation of the actual availability could in our opinion be obtained by the straightforward addition of IDA and IDAol dose-corrected AUC values. Indeed, Rowland showed that the sum of the AUC of the parent drug and that of the metabolite is somewhat related to the area under the *response* curve, even if many assumptions must thereby be made.

According to this approach, only three patients showed an active bioavailability (IDA+IDAol) of <30% (Table 7). These subjects experienced grade 2 (WHO) vomiting after IDA oral administration and before the peak plasma drug concentration had been reached. In addition, two of these individuals (patients 92 and 88) were characterized by appreciable amounts of circulating AG1, which accounted for an additional 18% and 12% of the delivered dose. Overall IDA+IDAol availability was 53.0% in patients who did not experience vomiting and 40.6% in subjects exhibiting grade 2 vomiting. Although the difference in bioavailability did not reach statistical significance, it is noteworthy that the bioavailability coefficient of variation (CV) was 47% after vomiting episodes and only 30% when vomiting did not occur. The bioavailability of IDA alone was 28.0% in patients who did not experience vomiting and 24.0% in subjects exhibiting grade 2 vomiting. The bioavailability CV was 41% after vomiting episodes and only 21% when vomiting did not occur.

We have previously reported on a pharmacokinetics study in which cumulative oral doses of 30 and 45 mg/m^2 IDA were given to 12 cancer patients over 3 consecutive days to circumvent gastric toxicity [22]. When the dose was divided, a mean AUC(IDA)/dose of 4.6 ± 1.6 ng h ml^{-1} mg^{-1} and a mean AUC(IDAol)/dose of 30.6 ± 19.8 ng h ml^{-1} mg^{-1} were found. The corresponding mean values determined in the present study were 2.5 ± 1.0 and 19.7 ± 10.1 ng h ml^{-1} mg^{-1}, respectively. A historical comparison of dose-corrected AUC values therefore indicates that better availability is achieved when the cumulative oral dose is given over 3 consecutive days.

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