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Bioavailability and pharmacology of oral idarubicin

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Summary. A total of 9 patients entered in a phase I trial who received oral idarubicin daily for 3 days took part in pharmacokinetic studies, and bioavailability studies were performed on 13 additional patients receiving single doses of oral idarubicin alternating with i.v. treatment. The data were best fit by a two-compartment model (distribution and elimination compartments for i.v. drug and absorption and single-phase elimination for oral drug). For different idarubicin doses in the phase I and bioavailability studies, the median values for the terminal half-life of idarubicin varied from 5.6 to 11.6 h. High concentrations of the active metabolite idarubicinol were formed. Idarubicinol was eliminated more slowly than was the parent compound, with median half-lives for different dose levels varying from 8 to 32.7 h. Although most pharmacokinetic parameters were similar in plasma and whole blood, peak concentrations and AUCs in whole blood were about 3–4 times those calculated in plasma for idarubicin and about 1.5–2 times those determined in plasma for idarubicinol, indicating fairly extensive uptake into erythrocytes. Oral bioavailability was determined by comparing oral idarubicin to i.v. drug with respect to the combined idarubicin and idarubicinol plasma AUCs, and it varied from 12%–49% (median, 29%). Bioavailability was essentially the same (30%) when whole-blood values were used. Urinary excretion of the drug was <5% of the delivered dose by 96 h. Granulocytopenia correlated with plasma idarubicinol "estimated" clearance and steady-state volume of distribution, with whole-blood idarubicinol AUC, area under the moment curve (AuMC), and "estimated" clearance and volume of distribution, and with whole-blood combined idarubicin and idarubicinol AUCs. This suggests that drug contained in erythrocytes plays a major role in toxicity and that idarubicinol may play a larger role in toxicity than does the parent compound.

Introduction

Idarubicin (4-demethoxydaunorubicin), a new anthracycline, has shown excellent antitumor activity against a variety of animal tumors. Its potency is greater and its efficacy comparable with that of daunorubicin in the treatment of ascitic P388 leukemia [1]. It displays activity against sarcoma 180 but is less active than doxorubicin against murine C3H mammary carcinoma [1]. Unlike daunorubicin and doxorubicin, idarubicin is also active in murine tumor systems when given orally [1]. In most animal species tested, i.v. idarubicin has caused less cardiotoxicity than doxorubicin, and oral idarubicin has caused no cardiotoxicity whatsoever [1].

Cellular uptake of idarubicin has been significantly higher than that of daunorubicin in in vitro studies in mouse embryo fibroblasts [1]. Tissue concentrations following i.v. idarubicin have been higher than those for daunorubicin in all organs except the heart and have been similar for the two drugs in the heart [1].

The Pharmacokinetic studies of idarubicin published to date have indicated that high concentrations of the cytotoxic metabolite idarubicinol are formed [2, 3, 5, 10]. The pharmacokinetics of the parent compound have been described as best being fit by a two-compartment model in some studies [2, 5, 10] and by a three-compartment model in others [9, 15]. The metabolite idarubicinol persists in the plasma for far longer intervals than does the parent compound, and in studies of oral idarubicin it has been reported to be present at higher concentrations than the parent compound at all times tested [5]. The bioavailability of oral idarubicin has been reported to be approximately 30% [2, 5, 9].

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We have recently completed a phase I study of oral idarubicin given daily for 3 days [13]. We conducted pharmacokinetic studies of idarubicin as part of this phase I study, and we also conducted a formal bioavailability study of idarubicin given on a single day.

Patients and methods

To be eligible for the study, patients had to have a microscopically confirmed diagnosis of cancer, and the cancer had to be incurable by and unlikely to respond to standard therapeutic measures. Only subjects with solid tumors were eligible for this study. Patients were required to be ≥ 18 years of age and to have a life expectancy of at least 12 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better. They had to have been off previous chemotherapy and radiotherapy for at least 3 weeks (6 weeks for nitrosoureas or mitomycin C) and must have recovered from reversible toxic effects of prior treatment. Patients had to be capable of ingesting oral medication.

Required pretreatment hematological criteria included a granulocyte count of $>1.5\times10^9$/l, a platelet count of $>100\times10^9$/l and a hemoglobin value of >80 g/l. Patients also had to have a bilirubin level of ≤ 30 µmol/l, with values for transaminases and alkaline phosphatase being <2 times the upper limit of normal, and a normal prothrombin time. Subjects with higher alkaline phosphatase values were accepted on study if these were due to bony metastases rather than to hepatic dysfunction. Patients with elevated prothrombin times were accepted if they were being anticoagulated therapeutically. Pretreatment serum creatinine levels had to be <200 µmol/l.

Subjects were required to have adequate cardiac function, with no electrocardiographic evidence of acute ischemia, recent myocardial infarct, multifocal premature ventricular contractions, or major heart block. Patients with a history of congestive heart failure or life-threatening arrhythmias and those who had had a myocardial infarct within the previous 6 months were excluded. Subjects who had previously been treated with anthracyclines or anthracenes were accepted on study, provided that the total cumulative dose of previous treatment was <350 mg/m^2 for doxorubicin, <100 mg/m^2 for mitoxantrone, and <600 mg/m^2 for epirubicin. Patients were not eligible if they had previously been treated with idarubicin. Patients previously exposed to anthracyclines were also requried to have a pretreatment left ventricular ejection fraction of >45% as determined by gated radionuclide scan.

Individuals who had received >4,000 cGy radiation to the lower mediastinal region and subjects who had received radiation to >25% of their red bone marrow were ineligible, as were women at risk of becoming pregnant and patients who were taking other experimental drugs. All patients gave written, informed consent for participation in this study.

Treatment during the phase I part of the study consisted of oral idarubicin taken daily for 3 days on an empty stomach. Treatments were repeated at three-week intervals, provided that the patient had not shown evidence of tumor progression and that the granulocyte count had recovered to $>1\times10^9$/l (and was clearly rising), the platelet count had recovered to a value of $>100\times10^9$/l, and other toxicity had resolved.

Treatment doses were adjusted to the nearest 5 mg, the size of the smallest available idarubicin capsule. When necessary, different drug doses were given on each of the 3 days so as to bring the cumulative 3-day dose as close to the total planned dose as possible. The details of the phase I study have been reported elsewhere [13]. Doses at which pharmacokinetic studies were done included 15, 20, and 25 mg/m^2. Patients took nothing by mouth for at least 4 h prior to treatment, with the exception of essential oral medications along with a small amount of fluid. Blood samples were obtained before treatment and after the 1st day's treatment at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 24, 48, 72, and 96 h. The 24- and 48-h samples were drawn immediately before the 2nd and 3rd days treatments, respectively. Urine samples were also collected for 96 h after the 1st day of treatment.

In the bioavailability part of the study, patients were randomized to receive idarubicin either by mouth or by i.v. infusion. After a 3-week interval (or upon recovery from toxicity), patients received the drug by the alternate route. For this bioavailability study, idarubicin was given on a single day at an oral dose of 45 mg/m^2 and an i.v. dose of 15 mg/m^2. Blood sampling times were the same as those for pharmacology studies done during the phase I trial.

Idarubicin, idarubicinol, and doxorubicin used as standards during assay procedures were supplied by Adria Laboratories. Idarubicin and doxorubicin were clinical formulations and were made up to 2 and 1 mg/ml, respectively, in mobile phase (described below). Idarubicinol was dissolved in mobile phase to 0.5 mg/ml. All compounds dissolved readily and were stored at 4° C. These solutions were further diluted to appropriate concentrations with mobile phase containing desipramine at 10 ug/ml [6].

To 1 ml plasma containing 10 µl of 10 µg/ml (100 ng) doxorubicin (internal standard), 3 ml methanol was added with vortexing. The samples were kept on ice for 5 min and then vortexed for 1 min. The tubes were centrifuged at 12,500 *g* (av) for 15 min at 4° C, and the supernatant was removed and diluted with 25 ml water in a Labconic 50-ml copolymer centrifuge tube. For the analysis of urine, 50 or 100 µl urine was diluted with 1 ml water; 30 µl of 10 µg/ml (300 ng) doxorubicin was then added as an internal standard. The samples were then diluted with an additional 25 ml water.

The diluted samples were fractionated on Bond Elut C18 columns (100 mg) fitted with 8-ml reservoirs placed in a Vac Elut apparatus (Analytichem International). The columns were first preconditioned by washing with 4 ml 0.25 M HCl in methanol (prepared by the addition of 5.2 ml 12 N HCl to 250 ml methanol), 4 ml methanol, and 25 ml water. The diluted supernatant was applied to the columns and drawn through under a low vacuum. The columns were then washed with 25 ml water. Nitrogen was blown through to remove as much residual water as possible. The columns were placed in 15-ml conical centrifuge tubes, and doxorubicin, idarubicin and idarubicinol were eluted with 300 µl 0.25 M HCl in methanol containing 10 µg/ml desipramine. Nitrogen was again used to remove as much of the eluate as possible. In all, 110 µl eluate was placed in inserts in autosampler vials, and 75 µl of this was analyzed by high-performance liquid chromatography (HPLC).

The HPLC system consisted of a Shimadzu LC6A pump, an SCL6A programmer, an SIL6A autosampler, and a Kratos FS 950 fluorescence detector. Compounds were separated on a Waters µBondapak phenyl column (300×3.9 mm) coupled with a Guard-Pak Resolve CN precolumn-insert guard column. Mobile phase consisted of 700 ml 0.4 M ammonium formate (pH 4.0; prepared with 12.2 ml 88% formic acid and 12.9 g 28% ammonium hydroxide made up to 700 ml with water) and 300 ml acetonitrile; the flow rate was 1.5 ml/min. Fluorescence was detected with excitation at 254 nm and emission at 550 nm. Peak heights were quantitated with a Shimadzu C-R5A chromatography data processor. Typical elution times were 3.4, 4.5, and 6.3 min for doxorubicin (internal standard), idarubicin, and idarubicinol, respectively.

Standard curves were obtained daily by extracting 1-ml plasma samples that typically contained idarubicin and idarubicinol at 100, 25, 10, 5, and 1 ng/ml. In addition, for plasma, three seed control samples that contained idarubicin and idarubicinol at 3, 9, and 40 ng/ml were prepared at the beginning of the study, were stored at –20° C, and were analyzed daily. The peak-height ratios (i.e., the peak height for idarubicin or idarubicinol divided by the peak height for doxorubicin) were calculated. Regressions of the peak-height ratios vs concentrations of the standards were done using the ECSTAT program (Insight Software, Winchester, Mass.). The regression line was used to calculate the concentrations of idarubicin and idarubicinol in patient samples from the observed peak-height ratios.

Pharmacokinetic parameters were calculated using a computerized curve-stripping technique (PKCALC) [8] to arrive at initial estimates of parameters. Compartmental pharmacokinetic parameters were then calculated by nonlinear regression using the PCNONLIN program [11]. Noncompartmental parameters were calculated using the PKCALC program. For i.v. idarubicin, calculations were corrected for infusion duration [4]. Bioavailability was calculated by adding together the AUCs for idarubicin and idarubicinol, dividing the value obtained for the oral route by that obtained for the i.v. route, and correcting for route-specific differences in doses.

For calculation of dose-dependent pharmacokinetic parameters (clearance and volume of distribution), the oral dose was multiplied by

Table 1. Median (range) pharmacokinetic parameters (two-compartment model) in plasma and whole blood after day 1 of treatment for patients receiving idarubicin daily ×3 days[a]

Idarubicin (mg/m^2/day)	Patients (*n*)	T_{lag} (h)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2\ abs}$ (h)	$t_{1/2\ elim}$ (h)	AUC (ng h/ml)	AUMC (ng h^2/ml)	MRT (h)	Cl ($l/h/m^2$)	VD_{SS} (l/m^2)
Plasma idarubicin:											
15	5	0	2.2	3.6	1.5	11.5	37	544	17.3	122	1,561
		(0–0.41)	(1.4–4.3)	(1–9.1)	0.5–3.8	(3.7–87.7)	(30–532)	(234–64,308)	(7.8–120.9)	(8–144)	(990–2,401)
20	3	0.26	2.5	3.6	1.7	11.2	58	1,092	19	99	1,889
		(0.12–0.26)	(2.5–3.2)	(3.5–5.9)	(0.6–1.8)	(3.3–32.8)	(30–128)	(229–6,185)	(7.5–48.3)	(46–197)	(1,489–2,235)
25	1	(0.41)	5.4	3.5	1	5.6	64	645	10.1	120	1,214
Plasma idarubicinol:											
15	5	0.40	4.1	5.4	1.6	11.6	103	1,875	19.3	38	998
		(0–0.51)	(1.7–6.6)	(0.7–9.2)	(0.5–4.8)	(2.7–18.1)	(12–203)	(57–5,196)	(4.9–27.5)	(22–372)	(570–1,816)
20	3	0.32	6.5	4.1	0.8	18.2	190	8,113	27.5	30	688
		(0.30–0.36)	(2.9–9.7)	(3.9–10.1)	(0.6–4.3)	(11.2–42.7)	(189–292)	(4,279–11,950)	(22.7–62.8)	(20–32)	563–1,980
25	1	0.51	11	3.6	0.9	8	163	2,180	13.4	47	631
Whole-blood idarubicin:											
15	4[b]	0.33	8.8	5.4	1.8	6.1	162	2,054	12.6	28	414
		(0.16–0.70)	(3.3–11.8)	(3.3–7.9)	(1.7–2.8)	(2.4–37.1)	(66–204)	(421–11,416)	(6.4–56)	(21–66)	(284–1,198)
20	3	0.22	8.3	4	1.2	6.2	176	3,213	13.4	34	588
		(0.20–0.23)	(4.9–12.7)	(3.4–6.5)	(0.8–3.3)	(4.7–22.2)	(88–232)	(773–5,871)	(8.8–33.4)	(25–67)	(342–1,137)
25	1	0.46	21	3.7	0.9	7.4	301	3,800	12.6	26	322
Whole blood idarubicinol:											
15	5	0.43	6.1	9.1	4.4	8.3	150	3,678	19	14	483
		(0.33–0.49)	(3.8–18.9)	(3.9–10.8)	(0.7–6.3)	(7.2–17.6)	(108–399)	(2,310–6,716)	(16.8–27)	(11–40)	(184–867)
20	3	0.33	11.7	5.1	1	19.4	383	14,293	30	15	460
		(0.30–0.35)	(4–17.9)	(4.8–11.7)	(0.8–5.7)	(11.1–54.7)	(337–579)	(11,388–27,100)	(24.7–80.3)	(10–18)	(243–1,429)
25	1	0.52	15.4	4	0.9	11.8	321	6,072	18.9	24	454

[a] Calculations were somewhat inaccurate since the period of sample collection (24 h) was <3 times the length of the elimination half-life. In addition, since bioavailability was not determined for patients in this part of the study, the dose term used to calculate Cl and Vd_{SS} was estimated using the average bioavailability of 30%. There was a further intrinsic "error" in estimating these terms for idarubicinol, since it was not possible to determine what proportion of the total idarubicin dose was converted to idarubicinol. Hence, Cl and VD_{SS} values for idarubicinol are actually lower than those indicated. Abbreviations: T_{lag}, lag time; C_{max}, maximal concentration; T_{max}, time to maximal concentration; $T_{1/2\ abs}$, absorption half-life (or production half-life for idarubicinol); $t_{1/2\ elim}$, elimination half-life; AUC, area under the concentration-time curve; AUMC, area under the moment curve; MRT, mean residence time; Cl, clearance (plasma or whole blood); VD_{SS}, volume of distribution at steady state

[b] Values could not be fit to a two -compartment model for one patient

the bioavailability for an individual patient. For patients in the phase I part of the study and for the two patients entered in the bioavailability study who ended up receiving the drug p. o. only, the average bioavailability was used in determining a dose term for calculation of clearance and volume of distribution, recognizing that this would introduce an error factor for these patients, the size of which would depend on the degree to which the individual patient's absorption of oral idarubicin differed from the average. "Estimated" clearances and volumes of distribution for idarubicinol were calculated using the dose that was applied for idarubicin calculations, recognizing that a further error would be introduced, the size of which would depend both on the proportion of absorbed idarubicin that was not converted to idarubicinol and on the rate at which the parent drug was converted to its metabolite.

Patients were monitored with twice-weekly complete blood counts (CBC) and differential and platelet counts and by weekly prothrombin times, partial thromboplastin times, urinalyses, and serum chemistry studies. Both an electrocardiogram and a chest X-ray were planned every 3 weeks.

Pearson correlation coefficients were used to correlate granulocyte nadirs with pharmacokinetic parameters of patients entered in the bioavailability study. For these calculations, pharmacokinetic parameters and granulocyte nadirs from both oral and i. v. idarubicin treatments were used.

Results

Nine patients from the phase I study of oral idarubicin underwent pharmacokinetic studies. The results are presented in Table 1. The data were best fit by a two-compartment model (an absorption phase followed by a single elimination phase). Peak plasma concentrations of idarubicin were achieved approximately 3.5 h after ingestion of the drug. Both peak plasma concentration and AUC tended to increase with increasing drug dose. It could not be determined with certainty whether pharmacokinetics were linear with dose, since only a single patient was treated at the highest dose level; however, there was nothing to suggest that pharmacokinetics were not linear.

Idarubicinol appeared rapidly and exceeded concentrations of the parent compound at most time points. Elimination half-life, mean residence time, AUC, and area under the moment curve (AUMC) values were generally higher for idarubicinol than for idarubicin. Concentrations of both idarubicin and idarubicinol were generally higher in whole blood than in plasma (Table 1), with peak concentrations, AUCs, and AUMCs being higher in whole blood as compared with plasma. Peak concentrations and AUCs in whole blood were approximately 3–4 times those found in plasma for idarubicin and approximately 1.5–2 times those determined in plasma for idarubicinol. Elimination of idarubicin and idarubicinol from whole blood occurred at a rate that was comparable with that seen in plasma.

With successive days of treatment, there was evidence of accumulation of both idarubicin and idarubicinol in

Table 2. Median (range) idarubicin and idarubicinol plasma concentrations after oral idarubicin

Time (h) from		Plasma concentration (ng/ml)	
First dose	Third dose	Idarubicin	Idarubicinol
24		0.7 (0–55.1)	2.5 (0–5.3)
48		0.7 (0–42.1)	3.6 (0–7.3)
72	24	1.6 (0–77)	5 (0–11.9)
96	48	0.4 (0–260)	3.2 (0–6.7)

Patients were given 15–25 mg/m^2 oral idarubicin daily ×3 days

Table 3. Urinary excretion of idarubcin and idarubicinol after oral administration of idarubicin

Time (h)	Cumulative % of total idarubicin dose recovered in urine to each time point[a]	
	Idarubicin	Idarubicinol
24	0.24	1.37
48	0.32	1.12
72	0.86	1.41
96	2.25	2.08

Patients were given 15–25 mg/m^2 idarubicin daily ×3 days

[a] Decreased with time in some instances within the first 3 days as the total dose increased

plasma (Table 2). Urinary excretion was very low (Table 3); by 96 h after treatment, a median of 2.25% of the drug had been excreted as unchanged idarubicin and 2% had been excreted as idarubicinol.

For the bioavailability study, a total of 16 patients were studied. Blood was drawn from three patients after only a single course of treatment because of excessive toxicity or tumor progression after the first course. Hence, bioavailability data are available for only 13 of the patients, although pharmacokinetic data obtained for at least one administration route were available for all 16. The results of i.v. administration of idarubicin were best fit by a two-compartment model (Table 4). The median elimination half-life was quite short (4.5 h) according to the two-compartment model, but it was considerably longer (15.5 h) when noncompartmental parameters were considered.

Idarubicinol could not be fit well by either a two- or three-compartment model following i.v. administration. Noncompartmental calculations indicated that elimination half-life, mean residence time, AUC, and AUMC values were considerably higher for idarubicinol than for idarubicin. Idarubicinol levels surpassed idarubicin levels in plasma between 2 and 27 (median, 7) h after i.v. drug administration, except in a single patient who showed prolonged elevation of concentrations of the parent compound. This subject experienced very prolonged myelosuppression during treatment.

Results in patients receiving oral drug as part of the bioavailability study were comparable with those seen in the phase I study (Table 5). One patient showed an unusually long time to peak plasma concentration (19.3 h) as well as a very large AUC and AUMC; he did not develop any unusual degree of toxicity, but bioavailability could not be calculated in this case.

Based on comparisons of dose-corrected oral vs i.v. AUCs for idarubicin plus idarubicinol, the median bioavailability for idarubicin was 29% (range, 12%–49%; Table 6). The bioavailability was <21% for only one patient and >43% for only two subjects. For both oral and i.v. idarubicin, of the total AUC used for the calculation of bioavailability, a higher proportion was accounted for by idarubicinol than by idarubicin. This was particularly true for the oral route. The median dose-corrected idarubicin AUC value after oral administration of idarubicin was only 21% of that seen after i.v. administration, whereas the median dose-corrected idarubicinol AUC after oral idarubicin was 40% of that calculated for i.v. idarubicin (Table 5). The biovailability was essentially the same (median, 30%; range, 23%–54%) when calculated using whole-blood values as when plasma values were used.

Pearson correlation coefficients for granulocyte nadirs vs plasma and whole-blood pharmacokinetic parameters are presented in Table 7. Correlations of granulocyte nadirs with idarubicin parameters did not achieve statisti-

Table 4. Median (range) plasma pharmacokinetic parameters for patients treated with 15 mg/m^2 i.v. idarubicin

C_{max} (ng/ml)	$t_{1/2\ dist}$ (h)	$t_{1/2\ elim}$ (h)	AUC (ng h/ml)	AUMC (ng h^2/ml)	MRT (h)	Cl (l/h/m^2)	VD_{SS} (l/m^2)
Idarubicin:							
Two-compartment model[a]:							
96 (30–191)	0.09 (0.06–0.85)	4.5 (2.5–120)	171 (97–5,669)	613 (260–978,544)	4.8 (2.4–172.6)	91 (3–156)	478 (231–1303)
Noncompartmental parameters:							
		15.5 (3.2–110.7)	278 (89–5,324)	5,154 (333–861,895)	22.5 (3.6–161.7)	56 (3–169)	1,138 (602–2,220)
Idarubicinol: noncompartmental parameters[b]:							
		51.4 (31.2–138.6)	834 (461–2,426)	67,762 (25,980–279,006)	74.1 (50.6–203.2)	20 (7–33)	1,596 (434–2,919)

[a] For the three-compartment model, the standard deviations were excessively high in many patients when calculated using nonlinear regression

[b] The data did not fit a two- or three-compartmental model very well. See footnote to Table 1 regarding calculation of Cl and VD_{SS} and for abbreviations

Table 5. Median (range) plasma pharmacokinetic parameters for patients treated with 45 mg/m^2 oral idarubicin

T_{lag} (h)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2\ abs}$ (h)	$t_{1/2\ elim}$ (h)	AUC (ng h/ml)	AUMC (ng h^2/ml)	MRT (h)	Cl (l/h/m^2)	VDss (l/m^2)
Idarubicin: Two-Compartment model[a]:									
0.20 (0–0.70)	10.1 (4.7–47.3)	3 (1.8–19.3)	0.93 (0.43–5.43)	7.3 (2–42.9)	105 (33–3,940)	1,495 (180–277,743)	12.5 (4.1–70.5)	77 (20–155)	1,249 (115–1,950)
Noncompartmental parameters:									
				11.7 (3.2–62)	154 (34–4,598)	2,228 (213–427,819)	15.4 (4.1–85.2)	68 (20–167)	1,458 (147–14,216)
Idarubicinol[b]: Two compartment model:									
0.34 (0–0.70)	20.9 (10.2–49.4)	4 (2.3–20.2)	0.68 (0.28–5.77)	26.7 (8.6–43.7)	753 (458–4,235)	32,900 (7,672–305,109)	39.8 (16.7–72.1)	21 (7–50)	686 (182–2,677)
Noncompartmental parameters:									
				32.7 (17.7–64.1)	874 (563–4,898)	42,678 (14,349–468,732)	46.6 (21.6–87.4)	15 (7–33)	710 (381–1,973)

[a] An absorption and an elimination compartment. A three-compartment model fit the data poorly
[b] See footnotes to Table 1 regarding calculation of Cl and VDss and for abbreviations

Table 6. Bioavailability of oral idarubicin based on AUCs for idarubicin plus idarubicinol, derived from noncompartmental calculations using plasma idarubicin and idarubicinol concentrations

Patient Number	Intravenous idarubicin			Oral idarubicin			Bioavailability (%)
	Idarubicin AUC	Idarubicinol AUC	Total AUC	Idarubicin AUC	Idarubicinol AUC	Total AUC	
1	229	456	685	132	563	695	34
2	286	2,426	2,712	104	853	957	12
3	292	1,988	2,280	262	1,947	2,209	32
4	119	602	721	176	846	1,022	47
5	269	633	902	205	961	1,339	49
6	343	1,068	1,411	71	926	997	24
7	129	1,338	1,467	145	1,122	1,267	29
8	753	1,034	1,787	147	1,283	1,430	27
9	520	543	1,063	160	762	922	29
10	209	512	721	129	798	927	43
11	331	1,372	1,704	202	894	1,096	21
12	323	594	917	34	659	693	25
13	129	461	590	107	644	751	42
Median							29%

cal significance, whereas granulocyte nadirs did correlate significantly with a number of idarubicinol parameters. Correlation with granulocyte nadirs achieved statistical significance for "estimated" plasma clearance and steady-state volume of distribution of idarubicinol in both plasma and whole blood, whereas correlations of AUCs and AUMCs with granulocyte nadirs achieved statistical significance only for whole-blood idarubicinol pharmacokinetic parameters. Adding idarubicin AUCs and AUMCs to those of idarubicinol did not increase the degree of correlation.

It should be stressed that the clearance and volume of distribution values used in these calculations are not real for the metabolite idarubicinol, since the idarubicin dose was used in the calculation of these parameters. The idarubicinol "dose" was unknown since it was not possible to determine accurately the proportion of parent drug that was converted to its metabolite. Nevertheless, it seemed reasonable to study the relationship between these "estimated" parameters and drug toxicity. Too few patients responded to idarubicin to enable a correlation of pharmacokinetic parameters with response.

Discussion

Our study agrees with previously published data indicating that the bioavailability of oral idarubicin is about 30% [2, 5, 9]. Our data also agree with other studies indicating that the metabolite idarubicinol reaches high concentra-

Table 7. Correlation of granulocyte nadirs with plasma and blood idarubicin and idarubicinol noncompartmental pharmacokinetic parameters (based on combined i.v. and oral data) for patients participating in the idarubicin bioavailability study

Pharmacokinetic parameter	Pearson correlation coefficient
Plasma idarubicin:	
AUC	–0.14
AUMC	–0.09
MRT	0.02
Cl	0.14
VD_{SS}	0.30
$t_{1/2\ elim}$	0.04
Plasma idarubicinol:	
AUC	–0.32
AUMC	–0.18
MRT	–0.04
Cl[a]	0.60*
VD_{SS}[a]	0.51*
$t_{1/2\ elim}$	–0.02
Plasma idarubicin plus idarubicinol[b]:	
AUC	–0.24
AUMC	–0.06
Whole-blood idarubicin:	
AUC	–0.20
AUMC	–0.02
MRT	0.27
Cl	0.18
VD_{SS}	0.37
$t_{1/2\ elim}$	0.28
Whole-blood idarubicinol:	
AUC	–0.45*
AUMC	–0.40*
MRT	0.05
Cl[a]	0.44*
VD_{SS}[a]	0.41*
$t_{1/2\ elim}$	0.05
Whole-blood idarubicin plus idarubicinol[b]:	
AUC	–0.43*
AUMC	–0.30

* $P < 0.05$ (two-tailed test)

[a] See footnote to Table 1 regarding calculations of these terms and for abbreviations

[b] For these calculations AUCs and AUMCs for idarubicin and idarubicinol were added together

tions and is eliminated from the blood more slowly than is the parent compound [2, 5, 10]. The high concentrations of idarubicin and idarubicinol that we found in whole blood suggest fairly extensive uptake by erythrocytes. This could potentially serve as a pool of drug that is released back into the plasma, as suggested by other investigators [7]. Our results also agree with studies showing that idarubicin pharmacokinetics conform best to a two-compartment model [5, 10] and that urinary excretion is low [5, 7].

We have no data on idarubicin biliary excretion, and none of our patients showed major abnormalities of hepatic function. However, other investigators have reported only minimal biliary excretion of idarubicin [7], suggesting that it would be reasonable to study the drug in patients with hepatic dysfunction. Since only a small proportion of the drug is found in either urine or bile and since its volume of distribution is quite large, one might speculate that the drug binds extensively to tissues. We have previously found that the related drugs doxorubicin [14] and mitoxantrone [12] persist in human tissues for several months after the last drug administration.

The oral: i.v. ratios for dose-corrected AUCs were higher for idarubicinol than for idarubicin (0.41 vs 0.20). This suggests that there is substantial first-pass conversion of idarubicin to idarubicinol during absorption from the gastrointestinal tract. Since granulocyte nadirs correlated with idarubicinol pharmacokinetic parameters to a far greater extent than with idarubicin parameters, one might speculate that idarubicinol accounted for toxicity to a greater extent than did the parent compound. This might be at least partially due to the longer persistence of idarubicinol in the circulation. When compared to i.v. idarubicin administration, a relatively greater proportion of the total AUC after oral administration was accounted for by idarubicinol than by idarubicin, and bioavailability was calculated based on this total AUC. Hence, one might further speculate that the bioavailability value of 29% may actually underestimate the biologic potential of oral idarubicin and that it might be safer to assume a bioavailability of close to 40% (based on our observed oral: i.v. ratio of 0.40 for idarubicinol).

However, in oppostion to this is the observation that the median granulocyte nadir seen after 45 mg/m^2 oral idarubicin (0.6×10^9/l) was identical to that observed after 15 mg/m^2 i.v. idarubicin. The greater degree of correlation of granulocyte nadir with whole-blood as compared with plasma pharmacokinetic parameters suggests that the large erythrocyte pools of drug readily exchange with plasma and tissue pools and thus retain full biologic potential.

Antineoplastic agents have a narrow therapeutic index. Hence, for oral antineoplastic agents, it is desirable that the bioavailability range be as narrow as possible. In our study, bioavailability was <21% in only one patient and >43% in only two subjects, i.e., essentially 29% ± 14%. Although this appears to be relatively narrow, it is important to recognize that patients at the top end of the scale receive at least twice as much drug as those at the bottom end. This could result in severe toxicity in patients at the high end of the scale or in serious undertreatment in those at the lower end.

However, it is very important that the range in AUCs for i.v. idarubicin (Table 6) was at least as great (if not greater) than the range in bioavailabilities. Hence, the degree of error in dosing as a result of variations in bioavailability would not likely be any worse than the degree of error in dosing that would result form interpatient variability in drug metabolism after i.v. administration. Thus, as with i.v. administration, it would be reasonable to give a particular dose of oral idarubicin (e.g. 45 mg/m^2 as a single dose or 15 mg/m^2 daily for 3 consecutive days) and then adjust the dose upwards or downwards for subsequent courses based on the degree of toxicity seen during the first course.

In summary, idarubicin is a new anthracycline that can be given orally. It is very possible that its suitability for oral administration could greatly increase its usefulness, particularly in studies of chronic administration or in investigations of the effect of the time of day of administration on the drug's toxicity and efficacy.

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