Pharmacokinetics of idarubicin (4-demethoxydaunorubicin; IMI-30; NSC 256439) following intravenous and oral administration in patients with advanced cancer

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1 The plasma pharmacokinetics of idarubicin (4-demethoxydaunorubicin) were studied in 20 patients with advanced malignant disease after intravenous (21 occasions) and oral (14 occasions) administration. Idarubicin plasma concentrations were measured by high performance liquid chromatography with fluorescence detection.

2 Pharmacokinetic parameters calculated for the intravenous plasma drug concentration, time data revealed a terminal half-life of 12.9 ± 6.0 h (mean $\pm$ s.d.), clearance 98.7 ± 47.3 l h⁻¹ m⁻² and volume of distribution 1533 ± 536 l m⁻². A bi-exponential equation corresponding to a two compartment open model best fitted the data.

3 Half-life and clearance were not significantly different following oral administration.

4 Bioavailability of oral idarubicin was 0.29 ± 0.20 (mean $\pm$ s.d.). There was a wide range of bioavailability between and within subjects.

5 Plasma concentrations of idarubicinol (the only metabolite detected) rapidly exceeded those of the parent drug, and exposure to this metabolite was greater than to the parent drug. The mean half-life of idarubicinol was not significantly different after i.v. (63.1 ± 28.2 h) and oral (45.8 ± 16.0 h) administration. Much larger amounts of this metabolite were formed following the oral route of administration. This may have implications for the clinical use of this drug as idarubicinol may have appreciable cytotoxic activity.

Keywords pharmacokinetics idarubicin

Introduction

Idarubicin (IMI-30, NSC 256439; 4-demethoxydaunorubicin) is a derivative of daunorubicin in which the methoxy group at the C-4 position of the aglycone is replaced by hydrogen (Arcamone *et al.*, 1976). It has shown superior activity to daunorubicin and doxorubicin in a number of experimental animal tumour systems including P388, L1210 and gross leukaemias (Casazza *et al.*, 1980), T-cell lymphoma EL-4 (Broggini *et al.*, 1984) and solid sarcoma S180 (Arcamone *et al.*, 1976). In addition, idarubicin has less cardio-

toxicity than daunorubicin or doxorubicin in chronic studies carried out in several species including the mouse (Casazza *et al.*, 1979) and dog (Di Marco *et al.*, 1978). In mice the therapeutic ratios (cardiotoxic dose relative to dose producing tumour regression) were idarubicin 3.1, doxorubicin 0.7, daunorubicin 1.1 (Casazza *et al.*, 1979). Pre-clinical studies therefore have suggested that idarubicin has an extremely promising therapeutic profile relative to anthracyclines presently in clinical use.

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Early clinical studies in man have so far revealed good efficacy in acute leukaemias (Daghestani *et al.*, 1985; Carella *et al.*, 1985) with activity in patients previously resistant to anthracycline therapy. There is also evidence for activity in breast cancer (Arcamone, 1985) but little or no effect in melanoma (Stanton *et al.*, 1985), non-small cell lung cancer (Joss *et al.*, 1984) or upper gastro-intestinal adenocarcinoma (Einzig *et al.*, 1984).

The principal metabolite of idarubicin is the 13-dihydro derivative, idarubicinol (4-demethoxy-13-dihydrodaunorubicin), which by analogy with doxorubicin is probably rapidly formed by the action of a cytoplasmic aldoketoreductase. It is analogous to doxorubicinol and daunorubicinol, the metabolites of doxorubicin and daunorubicin respectively. Idarubicinol has been shown to be as active as idarubicin both *in vitro*, in the Hela cell colony inhibition test, and in the P388 murine leukaemia model (Casazza *et al.*, 1983).

A potentially important property of idarubicin is its activity when given orally. It therefore differs from most anthracyclines like doxorubicin or daunorubicin which do not show useful activity by this route. It is not however entirely unique as carminomycin, an anthracycline developed in the USSR, is also absorbed after oral administration (Crooke, 1977). Oral absorption of idarubicin has been demonstrated both in the mouse (Di Marco *et al.*, 1977a; Broggin *et al.*, 1984) and in women with advanced breast cancer (Bastholt *et al.*, 1985). It is possible that these differences in systemic availability among the anthracyclines are related to different lipid solubilities, as revealed by their partition coefficients. These have been determined in a 1-butanol/Tris HCl (pH 7.4) buffer system at 37°C (Di Marco *et al.*, 1977b), and a value of 32.3 was found for idarubicin (compare 17.8 for daunorubicin and 6.3 for doxorubicin).

There are few comprehensive published studies of idarubicin pharmacokinetics. In a study of idarubicin and daunorubicin given to mice bearing the EL-4 T-cell lymphoma (Broggin *et al.*, 1984) the serum and tissue distributions of these drugs and their 13-OH metabolites were studied. Idarubicin was found to have a half-life after i.v. treatment of 23 h compared to 4.6 h for daunorubicin, and levels of idarubicinol accumulated to a much greater extent in tissues, and particularly in tumour tissue. Oral administration resulted in even higher accumulation of these compounds in tumour tissue.

In man, a pharmacokinetic study in four subjects (Kaplan *et al.*, 1982) suggested a triphasic decline in plasma drug concentration after intra-

venous administration of 18 mg m⁻² over 3–5 min. However, plasma sampling was terminated at 24 h, so only limited conclusions could be drawn from this study. In a Phase I study (Berman *et al.*, 1983) in which plasma drug concentrations were measured up to 48 h, triphasic decay curves were found in two of three patients after i.v. administration of 12.5 mg m⁻² but the half-life of the terminal phase could not be determined. However, an oral bioavailability of 32–35% was suggested. There was a marked difference in the amounts of idarubicinol formed by the two routes of administration, with the AUC for the metabolite after i.v. and oral administration being respectively 1.5 and 3.2 times that of the parent drug. Pacciarini *et al.* (1983) found a biphasic decline in plasma drug concentration after i.v. administration, with a terminal half-life of around 70 h, and confirmed an oral bioavailability of around 30%. A recent study (Pannuti *et al.*, 1986) has confirmed the formation of large amounts of idarubicinol after oral administration to seven patients with breast cancer.

We have studied patients with advanced malignant disease who have been given idarubicin both intravenously and orally to determine the definitive pharmacokinetics of this drug and its principal metabolite, further to guide its use in the treatment of malignant disease.

Methods

Patients and drug administration

Twenty patients (13 male, seven female, mean age 60 years) were enrolled: all had advanced, malignant disease (Table 1), refractory to standard treatments or which was without treatment of established efficacy. All patients gave informed consent to the study, the protocol of which was approved by the Guy's Hospital Committee on Ethical Practice.

Parameters evaluated prior to entry into the trial included hepatic and renal function, full blood count, electrocardiogram and cardiac ejection fraction (determined by gated cardiac scan). Patients with severe impairment of liver or kidney function or evidence of cardiac failure were excluded from the study. No patient had received chemotherapy or radiotherapy treatment in the 3 weeks preceding the study.

All 20 patients received an intravenous dose of idarubicin first. Idarubicin was supplied by Farmitalia Carlo Erba, Italy: drug for i.v. use was supplied as an orange powder in 5 mg vials each of which was reconstituted with 5 ml sterile

Table 1 Demographic details of patients studied

Initials	Age (years)	Sex	Weight (kg)	BSA (m^2)	Diagnosis
MR	47	F	50	1.62	Non-Hodgkins lymphoma
SS	22	M	66	1.85	Non-Hodgkins lymphoma
JH	55	M	70	1.80	Non-Hodgkins lymphoma
HD	72	F	42	1.35	Non-Hodgkins lymphoma
VH	76	F	48	1.37	Non-Hodgkins lymphoma
HS	73	M	66	1.80	Non-Hodgkins lymphoma
AT	51	M	60	1.75	Non-Hodgkins lymphoma
WB	63	M	76	1.80	Non-Hodgkins lymphoma
JW	56	M	70	1.80	Anaplastic carcinoma
EL	56	M	76	1.85	Non-Hodgkins lymphoma
IJ	73	F	56	1.54	Transitional cell carcinoma of bladder
KP	65	F	75	1.85	Hodgkins disease
BH	63	F	55	1.60	Non-Hodgkins lymphoma
Hy D	65	M	65	1.80	Non-Hodgkins lymphoma
BR	67	M	78	1.85	Salivary carcinoma
DM	65	F	52	1.54	Non-Hodgkins lymphoma
KR	28	M	75	2.00	Hodgkins disease
AC	71	M	72	1.80	Adenocarcinoma of gall bladder
LG	66	M	70	1.86	Non-Hodgkins lymphoma
HH	65	M	75	1.90	Carcinoma of pancreas
Mean	60	13 M 7 F	65	1.74	

water. The i.v. dose of 15 mg m^{-2} was given over exactly 1 min into a fast running 0.9% saline infusion. Eleven patients were subsequently studied after receiving oral doses of idarubicin 3 weeks after the initial i.v. dose. Nine of the 11 patients were studied on one occasion only, and the doses given were 40 mg m^{-2} (one patient) and 50 mg m^{-2} (eight patients). Two patients were studied on more than one occasion, one (HD) was studied twice after i.v. administration and twice after oral administration of 30 and 50 mg m^{-2} respectively. The other patient (WB) was studied after one i.v. administration and three sequential oral doses at 3 week intervals of 40, 40 and 70 mg m^{-2} respectively. For oral use the drug was supplied as 5 and 10 mg capsules and the entire dose was administered with 100 ml of water in the early morning. A light breakfast was taken 1–2 h after drug administration. Where necessary metoclopramide was used as antiemetic.

Blood sampling and drug analysis

Whole blood samples (7 ml) were taken into lithium heparin tubes from an indwelling venous cannula before drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 7, 10 and 24, and then at approximately 50, 72 and 96 h following dosing. The plasma was rapidly separated by centrifuga-

tion and stored at -20°C pending analysis by high performance liquid chromatography.

Idarubicin and idarubicinol were estimated as described briefly below: plasma was extracted after the addition of daunorubicin as the internal standard using chloroform/isopropanol (1:1, v/v) after deproteinisation using solid ammonium sulphate. The upper phase was removed, evaporated to dryness and then reconstituted with the same solvent prior to injection into the chromatograph. Idarubicin, idarubicinol and the internal standard were separated on a $3.9 \text{ mm} \times 30 \text{ cm}$ phenyl μ -Bondapak (Waters Associates, Milford, Mass.) column using a 31:69, v/v mixture of acetonitrile/ammonium formate buffer (pH4) at a flow rate of 1.5 ml min^{-1} . Detection was by fluorescence spectrometry with excitation at 470 nm and emission at 545 nm. Quantitation was by peak height measurements with a lower limit of detection of 2 nmol l^{-1} , for both compounds. The within assay coefficients of variation for idarubicin and idarubicinol were 9% and 7% respectively at 20 nmol l^{-1} . Assay specificity was ascertained by retention time measurement and peak enhancement. All samples from one subject were analysed simultaneously concurrently with several standard curves.

Pure samples of idarubicin, idarubicinol and daunorubicin were kindly donated by Farmitalia Carlo Erba.

Pharmacokinetic analysis

Plasma drug concentration-time data after intravenous administration were fitted by both two and three compartment open models using an iterative non-linear least squares regression programme (Yamaoka *et al.*, 1981) with unweighted ($w_i = 1$) and weighted, $1/y$ or $1/y^2$, data. It was invariably found that the latter weight produced the best fit of model to data. Minimisation of the residual sum of squares and Akaike's information criterion (Yamaoka *et al.*, 1978) were used to define the best choice of model to fit the data.

The plasma drug concentration-time data after oral administration were best described by an open one compartment model with first order absorption and elimination. Area under the plasma drug concentration-time curve was determined from the linear trapezoidal approximation with extrapolation for the infinite portion of the curve.

Total body clearance (CL) and apparent volume of distribution in the elimination phase (V_{area}) were calculated by standard methods (Gibaldi & Perrier, 1975).

The bioavailability fraction (F) of oral idarubicin was calculated with appropriate correction for dose (Gibaldi & Perrier, 1975).

C_{max} (maximum plasma concentration) and t_{max} (time at which maximum plasma concentration was reached) were taken from the observed data.

For idarubicinol, as infinite extrapolation was not always practicable, the area under the plasma concentration-time curve to a comparable time point for all patients, (50 h) was calculated. This allowed comparison with the corresponding 50 h AUC for its precursor idarubicin when the latter was given by i.v. and oral routes.

Results

Figures 1 and 2 show typical and contrasted plasma concentration-time curves for idarubicin and idarubicinol after intravenous and oral administration respectively to two patients. The wide differences in profile between these two patients will be noted. No other metabolite was detected in the plasma using the present technique.

Table 2 summarises the pharmacokinetic parameters for idarubicin following i.v. administration. All but one of the data sets was best described by a two-compartment model: this final set being best fitted by a triexponential function. The coefficients and exponents for the first and third compartments for this patient

Figure 1 Plasma concentrations of idarubicin (x) and idarubicinol (o) following i.v. (upper) and oral (lower) administration of idarubicin to patient S.S. (1 ng ml⁻¹ of idarubicin and idarubicinol = 2 nm).

Figure 2 Plasma concentrations of idarubicin (x) and idarubicinol (o) following i.v. (upper) and oral (lower) administration of idarubicin to patient HD.

were used in the calculations of mean and standard deviations of the data. Following oral administration only nine sets of plasma concentration-time data could be fitted by the one compartment pharmacokinetic model: a two compartment model was unable to describe these data (Table 3).

Table 2 Pharmacokinetic parameters for idarubicin following i.v. administration (21 occasions to 20 patients). All results presented as mean $\pm$ s.d.

C_1 (nmol l ⁻¹)	88.1 $\pm$ 41.4
C_2 (nmol l ⁻¹)	18.0 $\pm$ 5.6
λ_1 (h ⁻¹)	1.83 $\pm$ 0.94
λ_z (h ⁻¹)	0.082 $\pm$ 0.06
$t_{1/2_1}$ (h)	0.49 $\pm$ 0.26
$t_{1/2}$ (h)	12.7 $\pm$ 6.01
AUC (nmol l ⁻¹ h)	366.0 $\pm$ 72.0
CL (l h ⁻¹ m ⁻²)	98.7 $\pm$ 47.3
V_{area} (l m ⁻²)	1533.0 $\pm$ 536.0

C_1 , C_2 coefficients, and λ_1 , λ_z , exponents of two compartment open model

$t_{1/2_1}$ initial half-life

Other abbreviations as defined in Table 3

Table 3 Pharmacokinetic parameters for idarubicin following oral administration on nine occasions. All results presented as mean $\pm$ s.d.

k_a (h ⁻¹)	1.58 $\pm$ 0.91
k (h ⁻¹)	0.058 $\pm$ 0.023
Lag time (h)	0.51 $\pm$ 0.24
$t_{1/2_z}$	13.9 $\pm$ 5.9
C_{max} (nmol l ⁻¹)	23.7 $\pm$ 20.5*
t_{max} (h)	2.7 $\pm$ 1.6*
F	0.29 $\pm$ 0.2*
CL (l h ⁻¹ m ⁻²)	107.9 $\pm$ 51.7*
V_{area} (l m ⁻²)	1718.0 $\pm$ 1137.0*

*For all 14 sets of data following oral administration.

k_a apparent first order absorption rate constant
 k apparent first order elimination rate constant
 $t_{1/2_z}$ terminal elimination half-life
 F bioavailability fraction
 CL total body clearance
 V_{area} apparent volume of distribution during elimination phase

No significant differences were found between parameters (including half-life) following the two routes of administration.

Calculation of the absolute bioavailability of oral idarubicin gave an average of 0.29 with a wide range of values of 0.04–0.77 as may be seen by comparison of Figures 1 and 2.

Even using sampling times in excess of 72 h characterisation of the pharmacokinetics of idarubicinol is difficult because of the long half-life of this metabolite and the data could not be adequately fitted by a simple model. It was possible (by regressive linear least squares regression to maximise the correlation coefficient) to estimate the half-life for 19 occasions following i.v. dosing and 10 occasions after oral administration. These estimates appear in Table 4. There were no statistically significant differences in half-life between routes of administration (Student's unpaired $t = 1.78$; $P > 0.05$ for 27 degrees of freedom). The higher C_{max} of idarubicinol after oral administration will be noted, which allowing for the higher idarubicin dose and its bioavailability, is disproportionate to that after i.v. administration. Calculation of the ratio of AUC to 50 h for idarubicinol to that of idarubicin shows that a significantly ($P < 0.05$) more extensive conversion to metabolite occurs after oral administration. These ratios are likely to be underestimates of the true ratio of total AUC for the metabolite to that of the parent drug, for even at 72 h, metabolite concentrations were still high and declining very slowly. However, it is important to note the wide interindividual variability of the idarubicin to idarubicinol conversion (compare for example Figures 1 and 2). Furthermore, following either route of administration the AUC of idarubicinol exceeds that of idarubicin.

Discussion

We have investigated the pharmacokinetics of idarubicin and have found no significant differ-

Table 4 Pharmacokinetic parameters for idarubicinol (13 OH-idarubicin) after intravenous (21 occasions) and oral (14 occasions) administration of idarubicin. All results presented as mean $\pm$ s.d.

	<i>i.v. administration</i>	<i>Oral administration</i>
$t_{1/2}$ (h)	63.1 ($\pm$ 28.2) ¹	45.8 ($\pm$ 16.0) ²
C_{max} (nmol l ⁻¹)	26.4 ($\pm$ 16.6)	56.5 ($\pm$ 32.2)
t_{max} (h)	6.7 ($\pm$ 7.8)	5.5 ($\pm$ 5.9)
AUC _{0-50 h} (nmol l ⁻¹ h)	917.0 ($\pm$ 575.00)	1391.0 ($\pm$ 971.0)
$\frac{AUC_{0-50 h}^{OH}}{AUC_{0-50 h}^{idarubicin}}$	3.0 ($\pm$ 1.69)	8.54 ($\pm$ 9.53)

1—determined for 19 occasions

2—determined for 10 occasions

ences in the disposition parameters calculated for i.v. as compared to oral administration for the parent drug. Our mean value for terminal half-life of 12.6 h is similar to that of 10.5 h found by Berman *et al.* (1983) though shorter than the median value of 24.8 h found by Daghestani *et al.* (1985) for five patients following three daily 15 min infusions and the mean of 21.6 (s.d. 9.0) h determined by Pannuti *et al.* (1986) in 11 patients receiving oral idarubicin. From the present study, idarubicin thus has a shorter terminal half-life than doxorubicin or daunorubicin which have half-lives of 25–35 h (Chan *et al.*, 1978; Gil *et al.*, 1983; Huffman *et al.*, 1977). Its pharmacokinetic behaviour is thus more analogous to carminomycin which has a half-life of 6–10 h (Comis *et al.*, 1982).

Idarubicin has a large volume of distribution of approximately $1,600 \text{ l.m}^{-2}$, which is larger than that found for doxorubicin of around 350 l.m^{-2} (Robert *et al.*, 1985) and presumably reflects extensive tissue binding.

We have found that our data following intravenous administration of idarubicin were best fitted by a two compartment open model, and only one patient's data required three compartments. This again resembles the findings of Comis *et al.* (1982) for carminomycin which was satisfactorily modelled by a two-compartment system, but differs from the results of Berman *et al.* (1983) and Daghestani *et al.* (1985) where a three compartment model was required for idarubicin kinetics. However, in concordance with these groups we have found the drug to be undetectable in plasma by 72 h after intravenous administration.

Following oral administration, idarubicin is rapidly absorbed with a lag-time of only 0.5 h (Table 3). We found the average bioavailability of oral idarubicin to be 29%, which confirms previously published data (Pacciarini *et al.*, 1983; Berman *et al.*, 1983). However, there was a very wide range in bioavailability from 0.035–0.77 on the 14 occasions (in 11 patients) investigated, and this variability might lead to difficulties in reliably treating patients with malignant disease by the oral route. Maximum plasma levels of idarubicin were similarly widely scattered ($7.4\text{--}89.4 \text{ nmol l}^{-1}$, median 20.6 nmol l^{-1}) and occurred between 1.5 and 8.0 h after ingestion. This variability in absorption occurred within subjects, thus for the two patients studied on more than one occasion, bioavailability for one (H.D.) was 0.035 and 0.04 on the two occasions studied, and for the other (W.B.) was 0.03, 0.37 and 0.40 on the three occasions studied. Nausea was occasionally reported by subjects after oral administration although vomiting was rare.

Antiemetics were given on 10 of the 14 occasions (metoclopramide was used on six occasions and a mixture of domperidone and prochlorperazine on the remaining four occasions). The average bioavailability in the group receiving antiemetics was 0.29 compared to 0.31 in those not given these drugs, thus antiemetic administration did not have any obvious effect on drug absorption.

After both oral and intravenous administration, the plasma concentrations of idarubicinol rapidly exceeded those of idarubicin and remained elevated for many hours. In fact, it was not possible accurately to calculate the terminal rate constant of this metabolite even though samples were taken to at least 72 h. Pannuti *et al.* (1986) found a plasma half-life of 57.1 (s.d. 15.1) for idarubicinol in 12 patients following oral idarubicin which is thus comparable with the present study. These authors found a mean AUC ratio of 6.7 over a period of 144 h during which three idarubicin doses of 10 mg m^{-2} were given. This is consonant with our finding of very high idarubicinol concentrations relative to the parent compound after oral dosing. Berman *et al.* (1983) in a pilot phase I study found that the AUC ratios of idarubicinol/idarubicin were 1.5 and 3.2 for the i.v. and oral routes respectively.

Idarubicin is similar to carminomycin (Comis *et al.*, 1982) and daunorubicin (De Gregorio *et al.*, 1982) in that exposure to the hydroxylated metabolite exceeds that to the parent anthracycline but unlike doxorubicin as doxorubicinol concentrations are usually 40–60% of those of doxorubicin (Benjamin *et al.*, 1977). As idarubicinol is believed to have appreciable cytotoxic activity in animals (Casazza *et al.*, 1983) its long half-life leads to greater exposure to the metabolite than to the parent drug, and this may be important for its clinical activity in malignant disease. Supino *et al.* (1977) have shown that exposure of HeLa cells to idarubicin concentrations of 2.0 nM for 8 h, or 0.3 nM for 24 h are required to produce 50% inhibition of colony formation. In our patients, levels of 2.0 nM were maintained for approximately 30 h after i.v. administration, and 16 h after oral administration (although there was wide interindividual variation after the latter). Levels of 0.3 nM idarubicinol were maintained throughout the period of sampling (usually 72 h) after both oral and i.v. administration.

The larger amounts of idarubicinol formed after oral administration might be an advantage for this route of administration. The cause of the increased conversion to idarubicinol after oral dosing is presently undetermined, although pre-systemic metabolism seems possible. Early fluctuations in plasma idarubicinol concentrations

occur after both routes of administration. This has been noted by others (C.W. Young—personal communication) and for adriamycinol (Gil *et al.*, 1983). Possible explanations include intermittent (possibly lytic) release from hepatic cells where it is synthesised, initial sequestration in a peripheral compartment followed by subsequent release or recycling.

In conclusion, our study has described the pharmacokinetics of idarubicin after both oral and intravenous administration. We have confirmed the bioavailability of the oral drug to be approximately 30% with the formation of the idarubicinol. However, consideration of the total cytotoxic bioavailability following oral administration suggests that a value of 50% of that following intravenous dosing would be

more appropriate. Nevertheless, our findings are consonant with the efficacy ratio of 15 mg m⁻² i.v. to 50 mg m⁻² oral dose found in phase I studies (Berman *et al.*, 1983). It is clear that the absorption of idarubicin shows wide variability between individuals. The cause of this variation is not determined and could even be related to formulation. Until the unpredictable bioavailability of idarubicin is controlled its use as an oral anthracycline, perhaps as a substitute for doxorubicin in regimens for leukaemia and lymphoma, must be carefully monitored.

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