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ORIGINAL ARTICLE

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Pharmacokinetics and pharmacodynamics of MX2 hydrochloride in patients with advanced malignant disease

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Abstract The purpose of the present study was to investigate the pharmacokinetics and pharmacodynamics of the new morpholino anthracycline drug MX2. A total of 27 patients with advanced cancer participated in a dose-escalation study in the first cycle of treatment with drug given i.v. at doses of 10–50 mg/m^2 (total dose 16.8–107.5 mg). The mean total systemic plasma clearance (CL) of MX2 was 2.98 ± 1.68 l/min, the mean volume of distribution at steady state was 1460 ± 749 l and mean elimination half-life was 10.8 ± 5.1 h. The area under the plasma concentration-time curve (AUC) of MX2 was linearly related to the dose per kilogram and the dose per body surface area ($r^2 = 0.43$, $P < 0.01$ and $r^2 = 0.44$, $P < 0.01$, respectively). CL did not correlate with total body weight, lean body mass or body surface area. The mean elimination half-lives of the metabolites M1, M2, M3 and M4 were 11.8 ± 5.0, 21.9 ± 11.8, 19.0 ± 11.3 and 12.3 ± 6.3 h, respectively. The fractional E_{max} model produced a much better fit to the relative nadir neutrophil count versus dose data ($r^2 = 0.42$) than to the relative nadir neutrophil count versus AUC or peak concentration (C_{max}) data ($r^2 = 0.15$ and 0.09, respectively). There seemed to be a threshold dose of about 65 mg of MX2 at or above which a large proportion of patients had a nadir neutrophil count of less than 0.5×10^9/l. This study shows that the pharmacokinetics of MX2 are similar to those of other anthracyclines. With other anthracyclines the degree of myelosuppression seems to depend more on the AUC and C_{max} than on the delivered dose; however, with MX2 the degree of myelosuppression depends more on the dose given than on drug exposure expressed as the AUC or C_{max}.

Key words MX2 · Pharmacokinetics · Pharmacodynamics · Anthracyclines

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Introduction

KRN8602 is the hydrochloride salt of MX2 (3′-deamino-3′-morpholino-13-deoxo-10-hydroxycarminomycin; Fig. 1), a new morpholino anthracycline that in vitro has cytotoxicity comparable with or superior to that of doxorubicin (Adriamycin), including activity against doxorubicin-resistant cell lines [28, 29]. In preclinical studies its toxicity profile, in particular its cardiotoxicity, has been more favourable than those of other anthracyclines [23]. Two preliminary phase I studies have been completed in Japan using differing dose schedules [13, 25]. The maximum tolerated dose defined by these studies was between 30 and 54 mg/m^2. Four metabolites

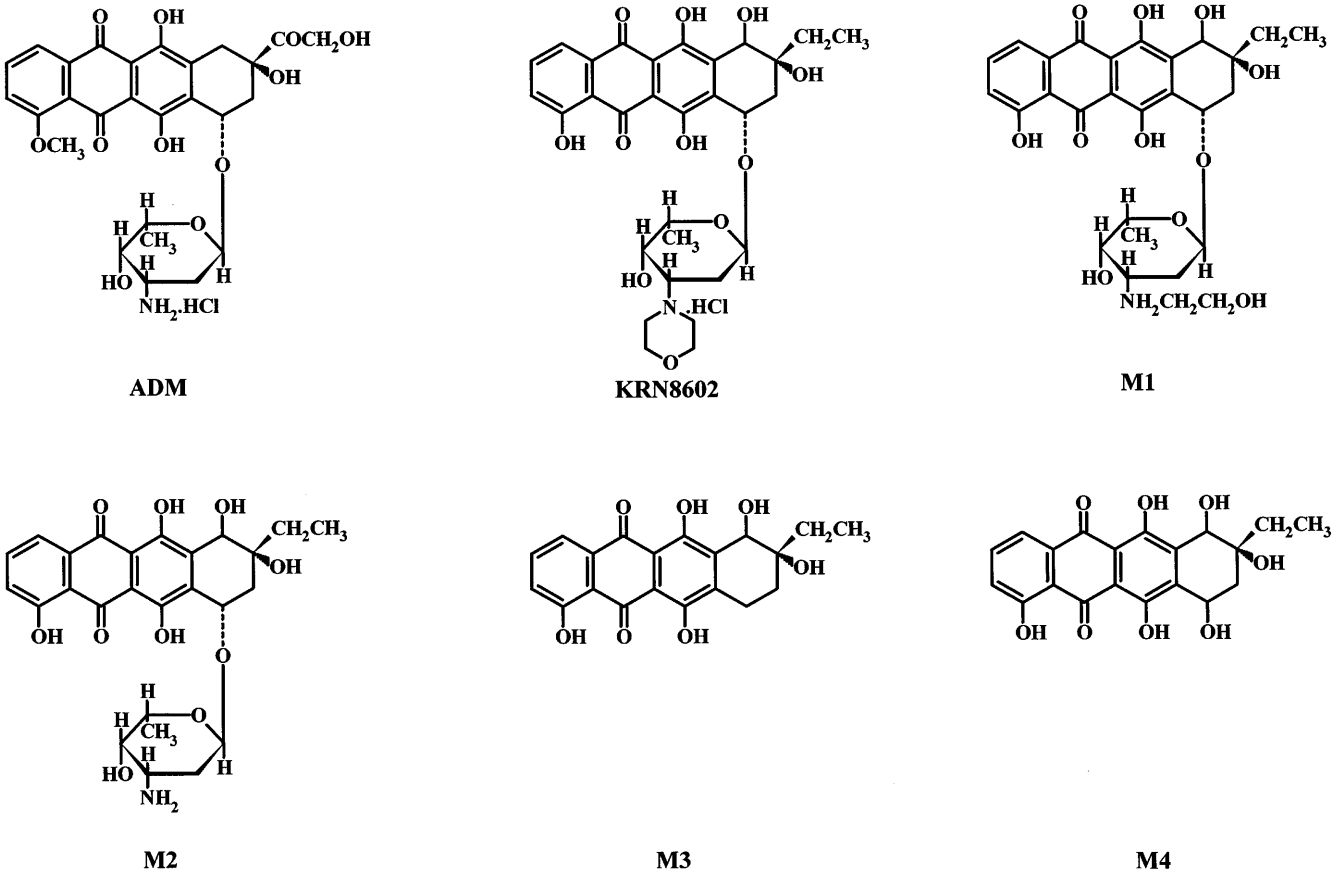

Fig. 1 Structures of doxorubicin (*ADM*), MX2-HCl (*KRN8602*), the two glycoside metabolites of MX2, (*M1*, *M2*) and the two aglycone metabolites of MX2 (*M3*, *M4*)

of MX2 have been identified and these have been named M1, M2, M3 and M4 [24] (Fig. 1).

This study was part of a phase I study to investigate the safety of MX2 after i.v. bolus administration and to determine the maximal dose that can be tolerated using a 21-day cycle. We report on the pharmacokinetics of the parent drug and several metabolites after the first dose of treatment. Dose rates were increased by increments from 10 mg/m^2 until the dose limited by toxicity was reached. The effect of the drug on haematological parameters was also measured.

Patients and methods

Patients

A total of 27 patients participated in this study. Patients had histologically proven locally advanced or metastatic cancer along with a life expectancy of at least 2 months, an Eastern Cooperative Oncology Group (ECOG) performance of 2 or better, a neutrophil count of greater than 1.5×10^9/l, a platelet count of greater than 100×10^9/l, a serum creatinine value of less than 0.2 mmol/l and liver-enzyme values (AST, ALT) of less than 3 times the upper limit of normal. Patients had not received prior anthracycline therapy, chemotherapy or radiotherapy in the previous 6 weeks and did not have significant non-malignant disease (e.g. pulmonary or cardiac). All patients gave written informed consent prior to their involvement and the study was approved by the institutional ethics committee. A summary of the patients' details is shown in Table 1.

Dosing and sampling

This was an open label phase I dose-escalation study. The starting dose was 10 mg/m^2 and doses were increased in increments of 10 to 50 mg/m^2. On day 7 of the first cycle of treatment, patients received an i.v. dose of MX2-HCl over 1 min. A blood sample (10 ml) was collected from each patient into a heparinised tube immediately prior to the injection and at 5, 15, 30, 60, 120 and 240 min and 6, 8, 24, and 48 h after MX2-HCl administration. From the last three patients a blood sample was taken at 2 min, and the 120-min sample was not collected. Plasma was separated from the blood cells and stored at −20 °C until analysis. Blood samples were also collected for full blood examination and differential white cell count on days 3, 5, 8, 10, 12, 15, 17 and 19 after drug administration.

Table 1 Summary of patients' details[a] (*BSA* Body surface area, *LBM* lean body mass)

Patients (*n*)	M/F	Age (years)	Weight (kg)	Height (cm)	BSA (m^2)	LBM (kg)
27	23/4	54.0 29–74	69.0 49–98	170 146–188	1.78 1.50–2.20	54.2 38.7–71.2

[a]Median and range

Drug analysis

The plasma concentrations of MX2 and its four metabolites were assayed by a previously published high-performance liquid chromatography method [24]. The method used solid-phase extraction followed by chromatography on a C-18 reverse-phase column and fluorescence detection as previously described. On each day of analysis a standard curve was prepared using pooled plasma from normal volunteers. The standard curves were linear from the limit of quantitation to 500 ng/ml for MX2 and its four metabolites. The limits of quantitation for MX2, M1, M2, M3 and M4 were 0.2, 0.3, 0.2, 0.1 and 0.1 ng/ml, respectively. The within-day coefficient of variation at the limit of quantitation was less than 10% for each compound.

Pharmacokinetic and statistical analysis

Plasma concentrations of MX2 were fitted with a triexponential function by nonlinear least-squares regression using Sigmaplot for Windows 2.0 (Jandel Scientific, San Rafael, Calif., USA). The area under the plasma concentration versus time curve to infinite time (AUC) was calculated using the coefficients and exponents of the triexponential equation [9]. The theoretical peak plasma concentration occurring at the end of the bolus injection (C_{max}) was calculated as the sum of the polyexponential coefficients, and the volume of the central compartment was calculated as $dose/C_{max}$ [9]. The volume of distribution at steady state (V_{SS}) was calculated by the method by Benet and Galeazzi [2], and the total systemic plasma clearance (CL) was calculated as $dose/AUC$ [9].

The elimination half-life of each of the four metabolites was determined by linear regression of the terminal log-linear portion of the plasma metabolite concentration versus time curve. The AUC for each metabolite was determined by the trapezoidal rule with extrapolation to infinity.

The relationship between the duration of neutropenia and the drug dose (D) was examined using the Hill equation [10]:

$$E = \frac{E_{max} \cdot D^n}{(ED_{50})^n + D^n}, \quad (1)$$

where E is the drug effect (duration of neutropenia), E_{max} is the maximal drug effect, ED_{50} is the dose that causes half of the maximal effect and n is a parameter influencing the slope of the relationship. The relationship between the dose, AUC or C_{max} and the relative nadir neutrophil count (E/E_0) was examined using the fractional E_{max} model [10]:

$$\frac{E}{E_0} = \left[1 - \frac{C}{(IC_{50} + C)}\right], \quad (2)$$

where E is the nadir neutrophil count, E_0 is the baseline neutrophil count, C is the dose, AUC or C_{max} of MX2 and IC_{50} is the dose, AUC or C_{max} that causes a half-maximal reduction in neutrophil count.

Comparisons between groups were made using the unpaired t-test or, for non-normally distributed data, the rank-sum test. Correlations between variables were performed by linear regression and correlations between more than two variables were performed by forward stepwise linear multiple regression. Statistical analyses were carried out with Sigmastat for Windows (Jandel Scientific). A probability value of <0.05 was considered statistically significant.

Results

Pharmacokinetics of MX2

Plasma concentrations of MX2 and its four metabolites after i.v. bolus administration are shown for a typical patient in Fig. 2. The pharmacokinetic parameters of MX2 are summarised in Table 2. The best fit for the nonlinear least-squares regression was obtained with a weighing factor of 1 in seven subjects, a weighing factor of $1/C$ in ten patients and a weighing factor of $1/C^2$ in ten patients. In the last three patients, in whom the first plasma sample was collected at 2 min rather than 5 min, omission of the 2-min data point in the curve fitting gave an estimate of C_{max} similar to that obtained when the 2-min data point was included. This indicates that the estimates of C_{max} for the other 24 patients, in whom the first plasma sample was collected at 5 min, were reliable. The doses given in this study ranged from 10 to 50 mg/m^2, and this corresponded to total doses of 16.8–107.5 mg. Over this dose range the AUC of MX2 was linearly related to the dose per kilogram of body weight ($r^2 = 0.43$, $P < 0.01$; Fig. 3), to the absolute dose ($r^2 = 0.37$, $P < 0.01$) and to the dose per body surface area ($r^2 = 0.44, P < 0.01$; Fig. 3), indicating constant CL.

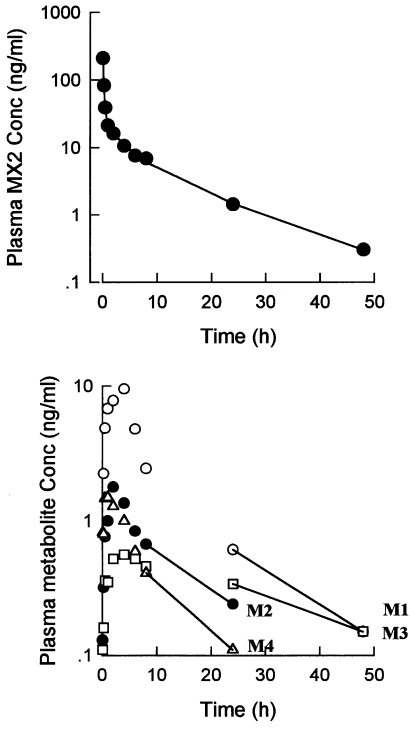

Fig. 2 *Upper panel*: Plasma concentrations of MX2 (●) and fit of the triexponential equation (—) in patient 8 following an i.v. bolus injection of 32 mg. *Lower panel*: Plasma concentrations of metabolites in patient 8, showing the terminal log-linear portion used for half-life calculation (——)

A significant inverse correlation was found between CL of MX2 and age ($r^2 = 0.27$, $P < 0.01$; Fig. 4). There was no significant correlation between CL and total body weight ($r^2 = 0.025$, $P > 0.05$), body surface area (BSA; $r^2 = 0.064$, $P > 0.05$) or lean body mass ($r^2 = 0.095$, $P > 0.05$).

Pharmacodynamic-pharmacokinetic relationships

There was a weak linear correlation between the relative nadir neutrophil count and the AUC ($r^2 = 0.20$, $P > 0.05$; Fig. 5). The fit of the fractional E_{max} model to

Table 2 Pharmacokinetics of MX2 and its metabolites (*AUC* Area under the time × concentration curve from the start of the injection to infinity)

Parameter	Mean	SD
MX2:		
Fast distribution half-life (min)	3.6	2.2
Slow distribution half-life (h)	1.31	1.28
Elimination half-life (h)	10.8	5.1
Volume of the central compartment (l)	95.7	87.3
Steady-state volume of distribution (l)	1460	749
Total plasma clearance (l/min)	2.98	1.68
Metabolites:		
Elimination half-life of M1 (h)	11.8	5.0
Percentage of the M1 AUC extrapolated	11.3	8.0
Elimination half-life of M2 (h)	21.9	11.8
Percentage of the M2 AUC extrapolated	28.9	11.9
Elimination half-life of M3 (h)	19.0	11.3
Percentage of the M3 AUC extrapolated	16.0	11.7
Elimination half-life of M4 (h)	12.3	6.3
Percentage of the M4 AUC extrapolated	10.5	10.3
AUC_{M1}/AUC_{MX2}	0.36	0.17
AUC_{M2}/AUC_{MX2}	0.24	0.20
AUC_{M3}/AUC_{MX2}	0.23	0.19
AUC_{M4}/AUC_{MX2}	0.10	0.04

these data was also poor ($r^2 = 0.15$, Fig. 5). The EC_{50} value produced by this fit was 216 ng h ml^{-1}. There was no significant linear correlation between the relative nadir neutrophil count and C_{max} ($r^2 = 0.12$, $P > 0.05$; Fig. 5), and the fit of the inhibitory E_{max} model to these data was poor ($r^2 = 0.09$, Fig. 5). However, there was a stronger linear correlation between the relative nadir neutrophil count and the total dose delivered ($r^2 = 0.53, P < 0.01$; Fig. 6). Furthermore, the fractional E_{max} model produced a better fit to the relative nadir neutrophil count versus dose data than to the relative nadir neutrophil versus AUC or C_{max} data ($r^2 = 0.42$, Fig. 6). The fractional E_{max} model gave an IC_{50} value of 34.9 mg. The fractional E_{max} model produced a similar fit to the relative nadir neutrophil count versus *dose/BSA* data ($r^2 = 0.43$).

When the duration of grade IV neutropenia (i.e. the period during which the neutrophil count was less than 0.5×10^9/l) was plotted against the AUC and C_{max}, no relationship was apparent (Fig. 7). However, when the duration of grade IV neutropenia was plotted against the dose given there appeared to be a threshold for the development of neutropenia of approximately 65 mg (Fig. 7). The neutrophil nadir did not fall below 0.5×10^9/l at doses that were lower than this threshold, but at doses greater than 65 mg the nadir neutrophil was below 0.5×10^9/l in 8 of 13 patients. Attempts to fit the

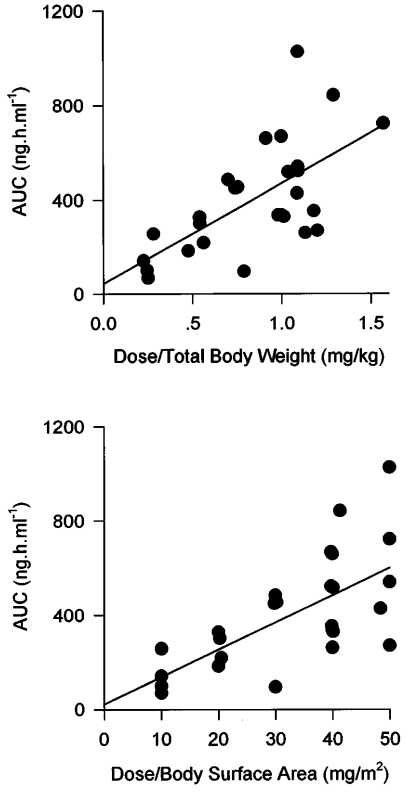

Fig. 3 *Upper panel*: Relationship between the AUC and the dose/kg body weight ($r^2 = 0.43, P < 0.01$). *Lower panel*: Relationship between the AUC and the dose/m^2 body surface area ($r^2 = 0.44$, $P < 0.01$)

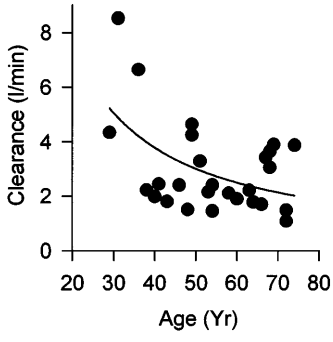

Fig. 4 Relationship between the clearance of MX2 and age, showing an inverse correlation ($r^2 = 0.27$, $P < 0.01$)

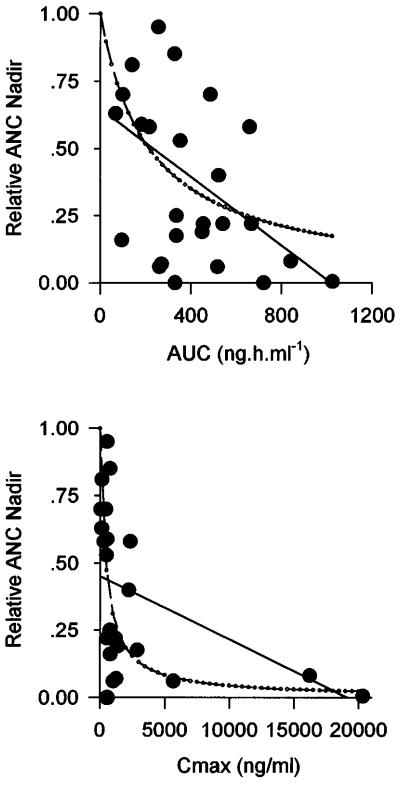

Fig. 5 *Upper panel*: Relationship between the relative nadir neutrophil count and the AUC, showing a linear correlation (—— $r^2 = 0.20$, $P < 0.05$) and fit of the fractional E_{max} model (· · · · · · · · · $r^2 = 0.15$). *Lower panel*: Relationship between the relative nadir neutrophil count and C_{max}, showing a linear correlation (—— $r^2 = 0.12$, $P > 0.05$) and fit of the fractional E_{max} model (· · · · · · · · · $r^2 = 0.09$)

Hill equation (Eq. 1) to these data gave a very poor fit. When examined in terms of the dose/BSA, nadir neutrophils did not fall below 0.5×10^9/l in any patient who received 10, 20 or 30 mg/m^2. However, nadir neutrophil counts of less than 0.5×10^9/l were observed in four of the ten patients who received 40 mg/m^2 and in four of the five patients who received 50 mg/m^2.

The relationship between the nadir neutrophil count and the AUC of MX2 and its four metabolites was analysed by forward stepwise multiple linear regression. This showed that the only parameter that was a covariate of the nadir neutrophil count was the AUC of MX2. This suggests that the metabolites of MX2 do not contribute significantly to the neutropenic effect of the drug.

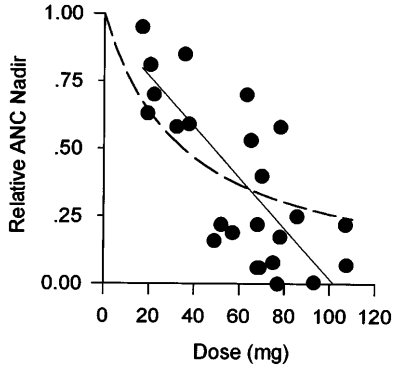

Fig. 6 Relationship between the relative nadir neutrophil count and the dose, showing a linear correlation (—— $r^2 = 0.53$, $P < 0.01$) and fit of the fractional E_{max} model (· · · · · · · · · $r^2 = 0.42$)

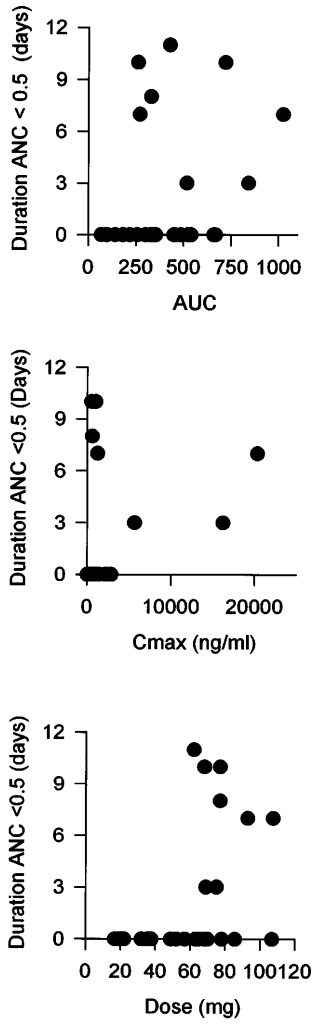

Fig. 7 Relationship between the duration of neutropenia (number of days during which the neutrophil count was less than 0.5×10^9/l) and the AUC (*upper panel*), C_{max} (*middle panel*) and dose (*lower panel*)

Discussion

The mean total systemic plasma CL of MX2 (2.98 l/min, Table 2) and the mean V_{ss} (1458 l, Table 2) were relatively high, but this is typical of the anthracycline cytotoxics [3, 12, 15, 17]. The mean elimination half-life (10.8 h, Table 2), however, was somewhat lower than that of other anthracyclines, which have elimination half-lives that tend to be as high as 20–60 h [3, 7, 12, 15, 17]. The pharmacokinetic parameter values obtained for MX2 in this study were similar to those reported previously [14]. As MX2 is extensively metabolised, presumably in the liver, this high CL value points to

extremely efficient hepatic metabolism. Although plasma CL exceeds the hepatic plasma flow rate (about 800 ml/min), this does not necessarily suggest the presence of extrahepatic elimination. Only if total systemic blood CL exceeds the hepatic blood-flow rate, can the presence of extrahepatic elimination be invoked [30]. Whole blood concentrations of MX2 were reported to be greatly in excess of plasma concentrations, and this resulted in a blood CL of MX2 of approximately 400 ml/min [14], which is lower than the usually accepted value for the hepatic blood-flow rate of 1500 ml/min.

Over the range of doses used, i.e. 10–50 mg/m^2 or 16.8–107.5 mg, the AUC was linearly related to the total dose given and to the dose adjusted for body weight. Whereas a previous study found that the AUC of epirubicin was not linearly related to the dose [26], other studies have confirmed that the AUC of epirubicin and other anthracyclines is linearly related to the dose over a wide range of doses [3, 12, 17, 27]. The elimination half-lives of the two metabolites M1 and M4 were similar to that of the parent drug (Table 2), suggesting that the rate of elimination of these metabolites is dependent on their rate of formation from the parent drug. The elimination half-lives of metabolites M2 and M3 were greater than that of the parent drug (Table 2), which suggests that the elimination rates of these two metabolites are slower than their rate of formation from the parent drug. The mean AUC of each of the metabolites was a significant proportion of the mean AUC of the parent drug, ranging from 10%–36% among the four metabolites (Table 2). This could be of clinical significance if these metabolites have antitumour activity.

Clearance of MX2 correlated significantly with age (Fig. 4). Clearances of epirubicin and doxorubicin have also been found to correlate with age [21, 27]. However, this correlation (Fig. 4) seemed to depend heavily on the data from the three youngest patients. For patients over 40 years of age there appeared to be no clinically relevant correlation between clearance and age. No correlation was found between CL of MX2 and total body weight, lean body mass, or body surface area. This is consistent with the conclusions of several reviews that body weight and body surface area are not useful predictors of CL of cytotoxic drugs [5, 19, 20] but differs from reports on epirubicin, whose clearance does correlate with lean body mass [4].

There were very poor correlations between the relative nadir neutrophil count and the AUC and C_{max} ($r^2 = 0.20$ and 0.12, respectively; Fig. 5), and the use of the E_{max} model did not result in any improvement to the fit ($r^2 = 0.15$ and 0.09, respectively; Fig. 5). Likewise, there was no apparent relationship between the duration of neutropenia and the AUC and C_{max} (Fig. 7). Stepwise forward multiple linear regression was performed between the relative nadir neutrophil count and the AUC of MX2 and of each of the metabolites M1, M2, M3 and M4. The inclusion of the metabolites did not result in any significant improvement in the regression, suggesting that the metabolites may not contribute to the haematological toxicity of MX2. In contrast to the very poor relationships found between the relative nadir neutrophil count and the AUC and C_{max}, there was a strong correlation between the relative nadir neutrophil count and the total MX2 dose given ($r^2 = 0.53$, Fig. 6). The fit of the fractional E_{max} model to these data was also good ($r^2 = 0.42$, Fig. 6). According to this model, the dose causing a 50% reduction in neutrophils was 34.9 mg. A similar fit was obtained with the E_{max} model to the relative nadir neutrophil count versus the $dose/BSA$ ($r^2 = 0.43$). Thus, doses corrected and uncorrected for BSA would appear to result in similar degrees of predictabilty of haematological toxicity. There also seemed to be a threshold dose of approximately 65 mg above which the neutrophil count fell below 0.5×10^9/l in about half of the patients.

Our finding that haematological toxicity correlated better with the dose and the $dose/BSA$ than with the AUC is at odds with the findings reported for other anthracyclines. Studies with other anthracyclines consistently show a good correlation between myelosuppression and the AUC or steady-state plasma drug concentration [1, 3, 4, 6, 7, 11, 15, 17, 22]. Moreover, the literature for all classes of chemotherapeutic agents shows that the correlation between pharmacokinetic parameters, such as the AUC, C_{max} and steady-state plasma concentration, and toxicity is in many cases better than the relationship between the dose and toxicity [16]. The reason why the dose is a better predictor of haematological toxicity than are parameters based on plasma concentrations (e.g. AUC) is not known. Further studies with a larger patient population may clarify this.

We fitted the fractional E_{max} model (Eq. 2) to the data relating the relative nadir neutrophil count with the dose and with the AUC and C_{max}, but the dose, which gave the best correlation, nonetheless accounted for only a little less than half (42%) of the variability in the relative neutrophil count. Other investigators have used an exponential function to relate the white blood cell count with the AUC or steady-state plasma drug concentration, especially in cases where the dosing range is limited or maximal myelosuppression is not observed [17, 18], but the use of this function did not improve any of the correlations. For some drugs, such as methotrexate and taxol, the duration of exposure to a certain threshold plasma concentration is the main determinant of myelosuppression rather than the dose, AUC, C_{max}, or steady-state plasma concentration [8, 31]. We compared the plasma concentration versus time profiles of patients in whom the nadir neutrophil count was less than 0.5×10^9/l with those of patients whose nadir neutrophil count was greater than 4×10^9/l. There was no obvious difference in these profiles that would suggest that the nadir neutrophil count was a function of the duration of exposure to a threshold plasma concentration of MX2. Overall, these findings suggest that approximately 53% of the variability in nadir neutrophil count can be accounted for by the dose given (Fig. 6).

In conclusion, this study shows that the pharmacokinetic characteristics of MX2 are not dissimilar to those of other members of the anthracycline group of anticancer agents. With other anthracycline agents the degree of myelosuppression seems to depend more on the AUC and C_{max} than on the dose delivered; however, following administration of MX2 the degree of myelosuppression is more dependent on the dose given than on the AUC or C_{max}.

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