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Pharmacokinetics of mitoxantrone in humans following single-agent infusion or intra-arterial injection therapy or combined-agent infusion therapy

S. J. P. Van Belle[1], M. M. de Planque[2], I. E. Smith[3], A. T. van Oosterom[4], T. J. Schoemaker[5], W. Deneve[1], and J. G. McVie[2]

[1] Academic Hospital Vrije Universiteit Brussel, B-1090 Brussels, Belgium
[2] Nederlands Kanker Instituut, 1066 CX Amsterdam, The Netherlands
[3] Royal Marsden Hospital, London 9W36JJ, England
[4] Academisch Ziekenhuis, Leiden, The Netherlands
[5] Slotervaart Ziekenhuis, 1066 EC Amsterdam, The Netherlands

Summary. This study describes the pharmacokinetics of mitoxantrone determined by a sensitive and specific HPLC-method.

The time-concentration curves of i.v.-treated patients (15 mg/m^2 over 30 min) correspond to a three-compartment model with a T1/2α of 12 min, a T1/2β of 93 min, and a slow elimination phase of 36 h.

The central compartment volume was 26.22 and the distribution volume, 1381.9. The mean urinary excretion was 4.9% of the total dose.

The pharmacokinetic parameters were also defined in five patients who were treated with combination chemotherapy (mitoxantrone 12 mg/m^2, methotrexate 30 mg/m^2 and vincristine 2 mg). These results were not different from those with the single-drug treatment, except for the volume of the central compartment, which was significantly decreased. The peak levels after hepatic arterial infusion of mitoxantrone were three times lower than those after the identical dose given i.v. to the same patient. Pleural fluid sampling showed a six-fold increase compared with the plasma level (12 ng/ml versus 2 ng/ml).

A multiple linear regression analysis of the data revealed correlations between the pharmacokinetic results and some of the baseline parameters. It is possible to predict changes in the kinetic behaviour of mitoxantrone on the basis of these relations but on the other hand toxicity is less predictable from the baseline parameters or from the pharmacokinetic results.

Introduction

Mitoxantrone (NSC-301739) or 1,4-dihydroxy-5,8-bis ((2-((2-hydroxyethyl)amino)-ethyl)amino)-9,10-anthracenedione dihydrochloride (DHAD) (Fig. 1) is an anthracenedione derivative, which has shown substantial antitumour activity in phase I and II trials [1, 10, 19, 24]. It has proved to be active in breast cancer [21, 26] acute leukaemia [5, 8, 23], and malignant lymphoma [6].

Mitoxantrone (MX) inhibits RNA and DNA synthesis [6], and its antitumour activity is believed to be based on DNA intercalation [6], although other mechanisms may be of importance [3].

Offprint requests to: S. J. P. Van Belle, Department of Medical Oncology, Academic Hospital Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium

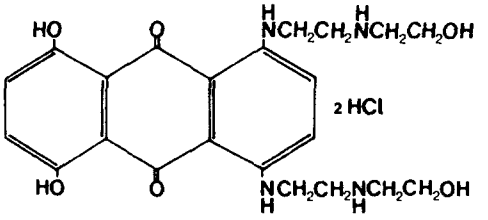

Fig. 1. Chemical structure of mitoxantrone.

Pharmacokinetics (PK) of this drug have been studied by several authors, but most have been hampered by the lack of a sensitive and specific assay to determine MX. We have developed an HPLC method [22] which is very specific and highly sensitive. Based on this assay we will describe the pharmacokinetic behaviour of MX in patients treated with MX administered as a single drug or in combination by the i.v. route and in patients treated with MX by the intra-arterial route.

The data from the i.v.-treated patients were analysed with a multiple linear regression program. This provided new information about the disposition of this cytotoxic drug in cancer patients.

Materials and methods

Patients. Eighteen patients with histologically proven cancer (eleven with breast cancer, six with renal carcinoma and one with lung cancer) were treated i.v. with MX 15 mg/m^2. The infusion was given over 30 min and the drug was dissolved in 150–250 ml 5% dextrose in water. The mean age of these patients was 58 ± 12 years, and the female-to-male ratio was 17 : 2. All the patients had normal renal and hepatic function, except for six who had hepatic involvement that was due to malignancy but not severe enough to cause jaundice. No patient had received prior therapy with MX, and all were studied during the first administration of the drug. In one patient a sample of pleural fluid was taken 72 h after the MX infusion.

Five women (all with breast cancer) were treated with a combination of MX (12 mg/m^2), methotrexate (30 mg/m^2) and vincristine (1.4 mg/m^2). Mitoxantrone was given i.v. over 30 min dissolved in 150–250 ml 5% dextrose in water. Methotrexate and vincristine were injected directly i.v. immediately before MX administration. One of these patients presented with jaundice because of liver metastases.

A 28-year-old male patient with a primary hepatoma was treated with MX (15 mg/m^2) infused by way of a catheter placed in the hepatic artery. The first infusion was given over 1 h, and 3 weeks later the same dose was given over 6 h. Six weeks later he received the same dose i.v. over 1 h.

Blood and urine were sampled during all these three cycles.

Drugs. Mitoxantrone was provided by American Cyanamid (Louvain-La-Neuve, Belgium) and ametantrone by the Drug Synthesis and Chemistry Branch of the National Cancer Institute, Bethesda, Md, USA (Dr J. P. Davignon).

Plasma and urine collection in heparinized tubes. Blood samples were collected at the beginning of the infusion and at 15, 30, 40, 45, 60, 90 and 120 min and 4, 8, 12, 24, 36, 48 h after, and then daily up to 6 days after infusion in some patients.

After centrifugation at 1500 *g* and separation, the plasma was immediately frozen and stored in plastic tubes at −20 °C. All urine was collected in 6-h portions in plastic bottles for 3 days, and a 100-ml aliquot from each portion was stored at −20 °C.

The pleural fluid samples were treated in the same way as the plasma specimens.

Extraction procedure and HPLC analysis. We developed an extraction procedure and an HPLC-method to determine mitoxantrone in physiological fluids, based on an ion-paired system [22]. The extraction procedure can be summarized as follows:

Plasma (1 ml) was added to a solution (1 ml) containing hexane sulphonic acid (0.01 mg/ml), ascorbic acid (0.5 mg/ml) and ametantrone (1.2 mg/ml). Hexane sulphonic acid acts as an ion-pair former; ascorbic acid is used as an antioxidant; and ametantrone, as the internal standard.

After vortexing, 1 ml 0.1 *M* borax buffer (pH 9.5) was added. Extraction was then performed with 5 ml dichloromethane. After centrifugation at 1500 *g* the organic layer was separated off and dried under nitrogen. The dry residue was reconstituted with the mobile phase of the HPLC system, which consisted of a mixture of acetonitrile (30%) and 0.16 *M* ammonium formate buffer pH 2.7 (70%). Hexane sulphonic acid was added to the mobile phase in a concentration of 0.025 *M*.

The system used a 30 × 0.39 cm μBondapak C_{18} column. Detection was performed at 658 nm, which is highly selective. The detection limit of this technique is about 1 ng/ml extracted plasma or urine.

Urine samples need not be extracted; after addition of the internal standard urine can be injected into the HPLC system.

All assays were done in duplicate and all glassware was siliconized to prevent attachment of the drug to the glass tubes.

Pharmacokinetic data handling. The curves were obtained from plasma results using a computerized program with three exponential terms.

The parameters derived from the curves were correlated for the infusion time according to Loo and Riegelman [14].

In summary the equations are:

For the intercepts: $Ai' = \dfrac{Ai * ki * \tau}{(1 - e^{-ki*\tau})}$

For the $AUC^0{}_{corr}{}^{to\ oo}$: $AUC^{0\ to\ oo} = \dfrac{Al' + A2' + A3'}{kl \quad k2 \quad k3}$

For the Vd_{AREA}: $Vd_{AREA} = \dfrac{Dose\ (\mu g/ml)}{Area * k3}$

For the $v_{central}$: $V_c = \dfrac{Dose\ (\mu g/ml)}{A1 + A2 + A3}$

For the half-lives: $t_{1/2}i = -\ln(0.5)/ki$

where

A1	: intercept first phase
A2	: intercept second phase
A3	: intercept third phase
A1'	: corrected intercept first phase
A2'	: corrected intercept second phase
A3'	: corrected intercept third phase
k1	: coefficient first phase (h^{-1})
k2	: coefficient second phase (h^{-1})
k3	: coefficient third phase (h^{-1})
$t_{½}1$	: half-life first phase (h)
$t_{½}2$	: half-life second phase (h)
$t_{½}3$	: half-life third phase (h)
AUC	: area under the curve (to infinity)
$AUC^0{}_{corr}{}^{to\ oo}$	: corrected area under the curve (to infinity)
DOSE	: total administered dose (mg)
Vd_{AREA}	: distribution volume (l)
Vd_{AREA}corr	: corrected distribution volume (l)
V_c	: volume central compartment (l)
$V_c$corr	: corrected volume central compartment (l)

Statistical correlation analysis. A multiple linear regression analysis [13] (least squares) was performed on a VAX 11/785 computer (Digital Equipment Corporation) running under a UNIX V (Bell Telephone). The correlation coefficients between the independent variables (age, weight, dose per square metre of body surface area, time lapse between sampling and determination, haemoglobin concentration, white blood cell count, platelet count, alkaline phosphatase and albumin level in serum) and each of the dependent variables (plasma peak concentration, $T_{1/2\alpha}$, $T_{1/2\beta}$, $T_{1/2\gamma}$; AUC/mg, Vd, VC and urinary excretion) were calculated for 14 patients from whom we had all these parameters in detail.

The same was then done with the toxicity scores (WHO scores for nausea and vomiting, and for mucositis and haematological toxicity) and the variables mentioned above [25].

An analogous analysis was also performed between the logarithmic values of the parameters which were not normally distributed (weight dose per square metre of body

Table 1. Pharmacokinetic data of i.v.-treated patients (mitoxantrone mg/m² over 30 min)

	Mean value	Range
Peak	683 ng/ml	180.3 – 1474
T1/2 α	0.206 h	0.082 – 1.95
T1/2 β	1.55 h	0.32 – 11.95
T1/2 γ	36.14 h	7.22 – 138.6
AUC/mg	36.64 ng ml⁻¹ mg⁻¹	13.5 – 62.76
V central	26.22 l	11.09 – 114
V distribution	1381.9 l	30 – 3373
Urinary excretion	4.92% of total dose/24 h	0.8 – 12.1

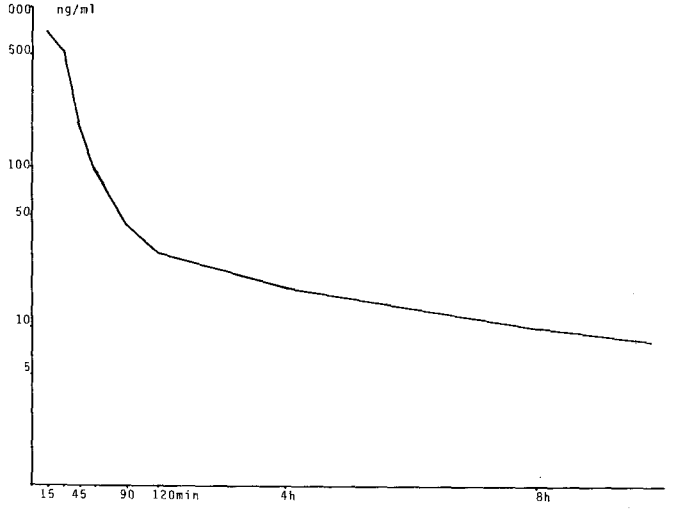

Fig. 2. Time-concentration curve representing the mean values from 18 patients treated with MX 15 mg/m² i.v. over 30 min

surface areas, time lapse between sampling and determination) and the logarithmic values of the dependent variables. A correlation was accepted as being meaningful if the correlation coefficient *(r)* was above 0.7 and if this coefficient was statistically significant (F ratio $\leqslant 0.05$) [9].

Results

The results of the pharmacokinetic data from 18 patients treated i.v. with MX alone are summarized in Table 1. In 16 of the 18 the curves fitted very well with a three-compartment model, while in two others they were more in favour of a two-compartment model.

The level of MX in pleural fluid removed 72 h after treatment with this drug was 12.0 ng/ml, while the concentration in plasma at the same moment was 2.0 ng/ml.

A typical plasma elimination curve is shown in Fig. 2 and is plotted from the mean values from 18 patients treated i.v. over 30 min.

In Table 2 the data recorded with combination therapy are displayed and compared with those obtained with single-drug treatment. There is no significant difference except for the Vc (Mann-Whitney Test). The peak levels and the kinetic data recorded in the jaundiced patient did not differ from the results in other patients. Neither the terminal half-life nor the AUC was altered.

The peak levels of the hepatic arterial treatment (15 mg/m² over 60 min) was three times lower than after the same dose given i.v. (120 ng/ml versus 351.6 ng/ml at 1 h, but the shape of the curve was identical. The threefold decrease persisted throughout the course of the curve. The maximum level reached at the end of the 6-h intra-arterial infusion was 45.6 ng/ml.

The time-concentration curves for this patient are shown in Fig. 3.

The multiple linear regression analysis showed statistically significant correlations between some independent variables and the pharmacokinetic data; the most reliable are listed in Table 3.

If a positive correlation was found, this meant that an elevation of the pharmacokinetic parameter could be predicted by an increase of the independent variable. Some correlations were not statistically significant, but nevertheless might be of importance if further investigated in a larger series of patients.

There was no clear correlation between toxicity scores for gastrointestinal side effects, mucositis, nadir of white blood cell count, platelet nadir, fall in WBC, or fall in platelet count (initial count minus nadir) (Table 4).

Discussion

This study describes the pharmacokinetics of MX, assessed by a sensitive and specific HPLC-method.

Table 2. Single-agent therapy versus combination therapy[a]

	$T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	$T_{1/2\gamma}$ (h)	AUC/mg	VC (L)	VD (L)	Urinary excretion (% total dose)
Single $n = 16$	0.206	1.81	38.43	30.76	28.71*	1562	4.92
Combination $n = 5$	0.208	0.74	28.85	55.46	18.28*	805.6	4.66
Mean $n = 21$	0.206	0.55	36.14	36.64	26.22	1382	4.85

[a] Combination: Mitoxantrone 12 mg/m²; methotrexate 30 mg/m²; vincristine 2 mg. Single agent: Mitoxantrone 15 mg/m²
* $0.02 < P < 0.05$ (Mann–Whitney test)
Pharmacokinetic data were corrected for dose

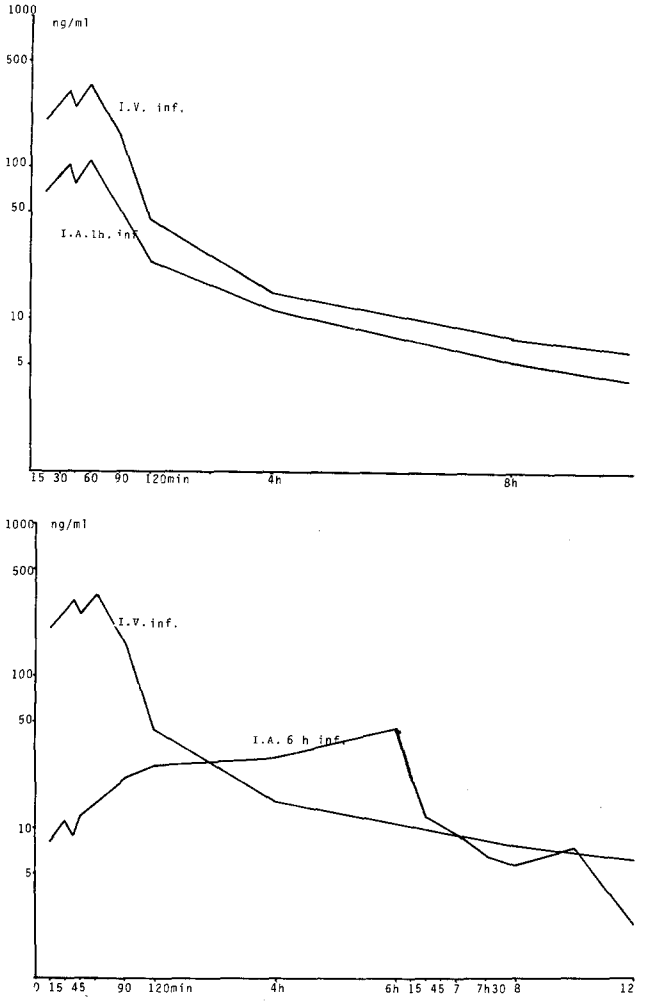

Fig. 3. Plasma elimination curves of a patient treated with MX i.v. over 1 h *(I. V. inf.)*, intra-arterially over 1 h *(I. A. 1 h inf.)* and over 6 h *(I. A. 6 h inf.)*

The plasma disappearance curve could be best fitted to an open three-compartment model (in 16 out of 18 patients).

MX has a very fast distribution phase (T1/2α: 12 min), an intermediate phase with a T1/2β of 93 min, and a very slow elimination phase of about 36 h.

The terminal half-life has always been a point of discussion since, as presented in Table 5, the published values range from 8.9 h to 212 h.

Our study concerns the largest number of patients (21), which means that the mean values are probably more reliable than those in smaller series. Some authors claim that shorter terminal half-live values probably reflect the limitations of the assay, but our sensitivity level of 1 ng/ml is equal to those of Alberts et al. [2] and Ehninger et al. [7], who found values for T1/2γ of 42.6 h and 212 h, respectively.

These latter controversial results probably only reflect the great variability in values, as even in our own series we observed a range of 7.2–138 h.

The accumulation of MX in blood cells is well known [2, 16], and we also confirmed a 6- to 8-fold concentration of MX in haemolysed blood samples compared with serum samples.

The blood cells are probably part of the third space, from which MX is slowly released into circulation, a fact that is reflected in the prolonged terminal half-time.

This observation is supported by the results of the linear regression analysis which shows that the peak concentration and AUC increased but the central compartment decreased as the haemoglobin level declined. This could be

Table 4. Correlation between toxicity parameters and independent or dependent variables

	Independent variables		Dependent variables
Nausea/vomiting	None[a]		None[a]
Mucositis	None[a]		None[a]
Nadir WBC	None		None
Nadir platelets	None		T1/2γ (P: 0.06)
Fall in WBC	None		None
Fall in platelets	Platelets, Age, Hb	(P: 0.046)	None

[a] The frequency of these events was too low to be correlated with the variables

Table 3. Correlation between independent variables and dependent variables

Variables	Positively correlated	Negatively correlated	F-Ratio
Dependent	Independent		
Peak	WBC	Hb, AP	0.017
T1/2 α	–	weight, dose/m², A.P.	0.039
T1/2 β	age, platelets	–	0.01
T1/2 γ	WBC, platelets	–	0.14
AUC	–	Hb	0.053
Vc	AP, Hb	–	0.095
Vd	age, dose/m²	WBC	0.02
Log T1/2 α	–	weight, dose/m², A.P.	0.017
	–	log. weight, dose/m², A.F.	0.0026
Log AUC	AP	Hb	0.035

Note: correlation is meaningful if $F \leq 0.05$; $0.05 \leq F \leq 0.15$ is not statistically significant but is a definite indication
Abbreviations: WBC, white blood cell count; Hb, haemoglobin; AP, alkaline phosphatase. Abbreviations for pharmacokinetic parameters are given in the text

Table 5. Comparison of mitoxantrone pharmacokinetics published by various authors

Author [Ref.]	Number of patients	Dose/m² (mg)	$T_{1/2\gamma}$ (h)	Vd (l)	Number of metabolites
Stewart et al. [20]	6	–	17	–	–
Savaraj et al. [17]	–	1–3	37.4	13.8	–
McPherson et al. [12]	6	–	17.0	–	2
Hulhoven et al. [11]	5	24	8.9	317	0
Alberts et al. [2]	8 (5)[a]	12	42.6	1875	3
Ehninger et al. [7]	7	14	212	3790	4
Van Belle et al. [22]	21	12–15	36.14	1382	1

[a] Results calculated for five of eight patients

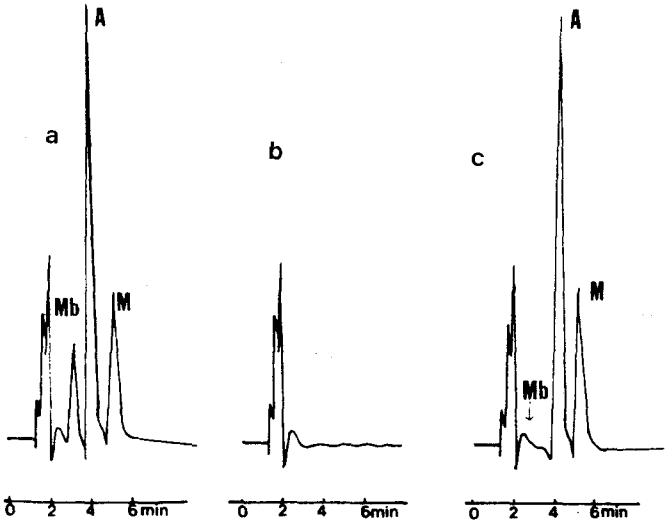

Fig. 4a–c. Urinary chromatogram of a treated patient **(a)**, blank urine **(b)** and spiked urine **(c)**. The metabolite *(Mb)* elutes before ametantrone *(A)* and mitoxantrone *(M)*

of importance, since cancer patients often present with anaemia.

Other correlations, especially between the alkaline phosphatase and the peak concentration, the T1/2α and the Vc, might suggest that metabolism occurs mostly in the liver. This was suggested by Lu et al. [15], who found an excretion of 1.0% of unchanged MX in bile, a low urinary excretion and a high clearance rate.

They also found almost 50% of the administered drug in the liver of dogs autopsied 5 h after an infusion of 5 mg/kg over 15 min. The amount of drug retained by the liver declined after 24 h to 10.6%. In contrast to the level of mitoxantrone excreted by dogs in bile, other authors detected about 40% excreted over 24 h in the bile of rats [4].

All these data support the hypotheses that the drug is metabolized by the liver, that a very low amount is excreted in the urine and that a variable quantity is excreted in bile.

Further controversy centres round the detection of metabolites in urine or bile. Table 5 summarises the pharmacokinetic results of some authors and also shows the number of metabolites found in urine [2, 7, 11, 12, 17, 22].

We visualized at least one metabolite (Fig. 4) which is still unidentified. Ehninger [7] identified two as the dicarboxylic acid and the monocarboxylic acid of MX.

The concentration of MX in pleural fluid was six times higher than that in blood when sampled at a random time (72 h). This observation might be of importance especially in patients presenting with pleural or ascites fluid collections. Such a "third space" might give rise to a "depot effect" and increased toxicity, as is known for methotrexate [18], and perhaps removal of the fluid collection before administration of MX should be considered. On the other hand, the high concentration of the drug in these collections might be better for the patient in terms of response. There are several anecdotal reports of responses in pleural mesothelioma (EORTC Lung Cancer Cooperative Group, protocol 08852).

The data recorded with combination therapy were not very different from those observed with single-drug treatment except for the central compartment, which was significantly smaller with the combination therapy. This could mean that the three drugs (MX, methotrexate and vincristine) had the same central compartment. The significance of this reduced central compartment is difficult to estimate, but it could influence the supply of drug to the target.

One of the patients treated in the combination-therapy group presented with jaundice. Her data were not different from others. Hulhoven et al. [11] also studied a patient recovering from hepatitis, with elevated transaminases but without cholestasis, and found no difference in pharmacokinetics parameters. These two cases illustrate the contradiction between the assumed liver metabolism and the unaffected kinetics of the drug in liver dysfunction. This could mean that dose reduction was not necessary in the case of liver impairment.

Intra-arterial treatment via a catheter in the hepatic artery is a modality often used in the treatment of liver tumours. We followed the kinetic behaviour of MX in this setting. As already pointed out, the peak levels of MX were three times higher after i.v. than after intra-arterial administration. As toxicity was minimal after both treatments it is not possible to draw any conclusions about the relation between decreased levels and toxicity. Except for the level of the peak, the time-concentration curves are comparable.

As summarized in Table 4, toxicity cannot be predicted from the pharmacokinetic data, except for the nadir of platelets; there is an almost significant correlation between platelet nadir and the terminal plasma half-life of MX. On the other hand, the fall in platelet count (initial count minus nadir of platelets) is related not only to the initial platelet count but also to the age of the patient and the

haemoglobin level. In other words, older patients will have a more pronounced decrease in platelets following the same standard dose of drug, and a state of anaemia will enhance this fall of platelets.

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