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One-Dose and Multiple-Dose Kinetics of Minocycline in Patients with Renal Disease[1]

by I. SKLENAR, P. SPRING and L. DETTLI
Clinic B, Department of Internal Medicine, University of Basel, Kantonsspital, 4031 Basel, Switzerland

Abstract

Kinetic analysis of minocycline concentrations in plasma and urine resulted in the following findings: In normal subjects the biological half-life is about 17 hours after the first dose and 21 hours after repeated administration. The renal drug clearance is only about 8% of the overall plasma clearance which is independent of renal function with a mean value of 47 ml/min. The fraction of the absorbed dose eliminated unchanged in the urine is only 9–19%. As a consequence the elimination rate of the drug is practically independent of renal function and decreases only 9–19% in anuric patients. The renal drug clearance depends linearly on renal function. The gastro-intestinal bio-availability of minocycline from the coated tablet preparation is incomplete. The cumulative behaviour of the drug corresponds to the kinetic parameters determined after repeated administration. It is suggested that the usual dosage regimen should be used in patients with renal disease.

Introduction

The influence of renal disease on the elimination of the tetracycline derivate minocycline (MC = 7-dimethylamino-6-deoxy-6-methyl-tetracycline) has been investigated experimentally by several authors in recent years [4, 11, 13, 18]. In our own experiments [14] we found that the elimination rate of the antibiotic is practically independent of kidney function because even in anuric patients the elimination was only about 15% slower than normal. These data suggest that the usual dosage regimen of MC should not be changed in patients with impaired kidney function. In contrast, BERNARD et al. [3] found a markedly lower elimination rate of MC in patients with renal disease. As a consequence these authors suggest that the dosage regimen of the drug in such patients should be modified accordingly. In view of these conflicting data we reinvestigated the problem based on the following considerations: In the experiments mentioned above the relationship between renal disease and the elimination of MC was characterized mainly by the influence of kidney disease on the elimination rate of the agent calculated from drug concentration measurements in the plasma. The same method was used in the experiments described in the present report. In addition, however, the fraction of the dose eliminated unchanged in the urine was analysed kinetically based on a recently developed theory [6, 7], i.e. the kinetic parameters were calculated from two different sets of experimental data analysed by essentially independent methods. The confidence in the kinetic interpretations will evidently increase when both methods result in similar values of the parameters.

Furthermore, DOLUISIO and DITTERT [8] have shown that the elimination rate of tetracyclines decreases with repeated administration. This phenomenon was investigated in a series of intrapatient comparisons.

The following symbols will be used in the present report [5, 6]: The subscript N signifies a normal mean value (e.g. Cl_{crN}, k_N). Renal function is characterized by the endogenous creatinine clearance, Cl_{cr}, with $Cl_{crN} = 100$ ml/min. The circumflex sign (^) denotes symbols related to individual patients with renal disease (e.g. $\hat{Cl}_{cr}$, $\hat{k}$). Symbols denoted by a prime (′) are related to experimental subjects (e.g. Cl'_{cr}, k'). Symbols without the above-mentioned subscripts or signs are of general validity, i.e. they denote both subjects with normal and with impaired kidney function. The superscripts U and P indicate whether a parameter was calculated from data measured in the plasma (e.g. Q_0^P) in the urine (Q_0^U)

[1]) Dedicated to K. Bucher on the occasion of his 65th birthday.

or by combined analysis of plasma and urine data (Q_0^{UP}).

Theoretical

The overall elimination rate constant, k, of many drugs depends linearly on the endogenous creatinine clearance, Cl_{cr}. The corresponding estimating equation reads as follows [5, 6]:

$$k = k_{nr} + \alpha \cdot Cl_{cr} \tag{1}$$

where k_{nr} signifies the extrarenal elimination rate constant and α is a constant relating the renal elimination rate constant, k_r, to the creatinine clearance, Cl_{cr}. The parameters k_{nr} and α are calculated by linear regression analysis from the elimination rate constants, k', determined in the plasma of a sample of patients with kidney disease of widely differing degrees of severity. Introducing $Cl_{cr} = 100$ ml/min in Eq. (1) results in the characteristic value k_N for patients with normal renal function.

On the other hand, the influence of renal disease on the elimination rate of a drug obviously depends on the fraction of the absorbed dose eliminated unchanged in the urine of patients with normal renal function, the so-called *normal renal dose fraction*, f_{rN}. WELLING et al. [17] demonstrated that approximate values of k_{nr} and α can be calculated from the values of k_N and f_{rN} determined in patients without kidney disease. Recently we developed a generalized theory which allows one to calculate these estimating parameters from the values of k' and f_r' determined in *any* subject with normal or with impaired kidney function [5, 6]. The theoretically exact relationships read as follows:

$$k_{nr}^{UP} = k' \cdot (1 - f_r') \tag{2}$$

$$\alpha^{UP} = k' \cdot \frac{f_r'}{Cl_{cr}'} \tag{3}$$

The introduction of Eqs. (2) and (3) in Eq. (1) yields the following estimating equation:

$$k = k'(1 - f_r') + k' \frac{f_r'}{Cl_{cr}'} \cdot Cl_{cr} \tag{4}$$

Introducing $Cl_{cr} = 100$ ml/min in Eq. (4) results in the characteristic value k_N for normal subjects.

In order to calculate the modified dosage regimen in patients with renal disease it is usually not necessary to know the absolute value of the individual drug elimination rate constant, $\hat{k}$, in the patient. Instead it is sufficient to know the so-called *elimination rate fraction*, $\hat{Q} = \hat{k}/k_N$ which describes the elimination rate constant in the patient as a fraction of the normal elimination rate constant [5, 15]. The linear relation between Q and Cl_{cr} is found by dividing Eq. (1) through k_N:

$$Q = \frac{k}{k_N} = \frac{k_{nr}}{k_N} + \frac{\alpha}{k_N} \cdot Cl_{cr} \tag{5}$$

In the anuric patient with $Cl_{cr} = 0$ one finds

$$Q = Q_0 = \frac{k_{nr}}{k_N} \tag{6}$$

The parameter Q_0 is called the *minimal elimination rate fraction*. In the normal subject with $Cl_{cr} = Cl_{crN}$ Eq. (5) results in $Q_N = 1$. It follows

$$\frac{\alpha}{k_N} = \frac{1 - Q_0}{Cl_{crN}} \tag{7}$$

Introducing Eq. (6) and Eq. (7) in Eq. (5) results in the following linear estimating equation:

$$Q = \frac{k}{k_N} = Q_0 + \frac{1 - Q_0}{Cl_{crN}} Cl_{cr} \tag{8}$$

It is evident that Eq. (8), which allows one to estimate the individual elimination rate fraction, $\hat{Q}$, in any patient with renal disease, is defined by one single parameter, Q_0, calculated from data determined in the plasma. On the other hand, as indicated by Eq. (6), the minimal elimination rate fraction, Q_0, is identical with the *normal extrarenal dose fraction*, f_{nrN}, and may therefore be calculated from the fraction of the dose eliminated unchanged in the urine of patients with normal renal function, f_{rN}, because

$$Q_0^U = \frac{k_{nr}}{k_N} = f_{nrN} = 1 - f_{rN} \tag{9}$$

By generalizing this relationship we demonstrated recently that Q_0^U may be calculated from the renal dose fraction, f_r', determined in *any* patient with normal or with impaired renal function [6]. The relationship reads as follows:

$$Q_0^U = \frac{Cl_{cr}'/Cl_{crN}}{Cl_{cr}'/Cl_{crN} + \dfrac{f_r'}{1 - f_r'}} \tag{10}$$

Finally Q_0^{UP} may be calculated combining plasma *and* urine data measured in any patient with normal or with impaired kidney function [6]. By dividing the first term of Eq. (4) through k_N one obtains:

$$Q_0^{UP} = \frac{k'(1-f_r')}{k_N} \tag{11}$$

Methods

Experimental subjects. Sixteen subjects aged 37–89 years (one healthy volunteer, eleven patients with chronic stable renal disease and four patients without kidney disease) were used in the experiments. In all patients there was an indication for the administration of a tetracycline.

The pharmacokinetic experiment. 200 or 300 mg MC were administered via an antecubital vein by a short (60 min) intravenous infusion. During the following 48–96 hours 7–12 blood samples were obtained from the contralateral antecubital vein. Concomitantly the urine was collected during up to 62 hours in such a way that the collection periods coincided with time periods between the venipunctures. Plasma and urine samples were stored at −20°C until assayed.

After completion of the one-dose experiment a comparative multiple-dose trial was performed in nine of our experimental subjects (patients nr. 8–16). After fasting overnight the patients received 200 mg MC every 24 hours during 8–12 days. For reasons of practicability all doses but the last one were administered orally[2]). The concentration measurements described above were repeated in the urine collected during 24 hours and in 7–10 blood samples obtained during 72–96 hours after the last dose.

Assay methods. All MC concentrations in plasma and urine were determined threefold by a conventional disc agar diffusion method with *Bacillus cereus varatio mycoides* APCC 9634 as the test organism. Standard solutions of MC were prepared from a powder containing 83.8% minocycline base. Creatinine was determined by the auto-analyser method.

Pharmacokinetic analysis. After the end of the drug infusion period the plasma concentration of MC decreased according to first-order kinetics. The overall elimination rate constant, k', was calculated by linear regression analysis. The following equation describes the amount of MC eliminated in the urine, m, as a function of time:

$$dm/dt = k_r \cdot M \tag{12}$$

where M and k_r represent the amount of MC in the organism and the renal elimination rate constant of the drug, respectively. On the other hand, M will decrease in the following way:

$$dM/dt = -k \cdot M \tag{13}$$

In its integrated form with $M_0 = D$, Eq. (13) reads

$$M_t = D \cdot e^{-k \cdot t} \tag{14}$$

[2]) 'Minocin'® (coated tablets) and 'Minocin intravenös'® (vials) containing minocycline HCl equivalent to 100 mg minocycline base were generously supplied by Lederle Arzneimittel, Munich, Federal Republic of Germany.

Introducing Eq. (14) in Eq. (12) and integration results in:

$$m_t = D \cdot \frac{k_r}{k} \cdot (1 - e^{-kt}) \tag{15}$$

with $t \to \infty$ one finds the renal dose fraction, $f_r = m_\infty/D$:

$$f_r = m_\infty/D = k_r/k \tag{16}$$

With $t < \infty$ Eq. (15) and Eq. (16) predict

$$f_r = \frac{m_t}{D \cdot (1 - e^{-kt})} \tag{17}$$

The *renal clearance* of the drug, Cl_r was calculated from the area under the time-plasma concentration curve, A_t, during the measuring interval and from the amount of drug eliminated in the urine, m_t:

$$Cl_r = \frac{m_t}{A_t} \tag{18}$$

From the fraction of the drug not bound to plasma proteins, f_f, one finds the *renal plasma water clearance*, Cl_{rw}.

$$Cl_{rw} = \frac{Cl_r}{f_f} \tag{19}$$

The total area under the time-concentration curve, A_∞, between $t = 0$ and $t = \infty$ was calculated as follows [16]:

$$A_\infty = A_t + \frac{c_t}{k} \tag{20}$$

where c_t is the drug plasma concentration at the end of the measuring interval. The *overall plasma clearance*, Cl_p, was calculated in the following way:

$$Cl_p = \frac{D}{A_\infty} = \frac{D}{A_t + \frac{c_t}{k}} \tag{21}$$

The absolute distribution volume, V_{abs}, was calculated based on the relationship $V_{abs} = Cl_p/k$. Dividing through the body weight, G, results in the relative distribution volume, $V_{rel} = V_{abs}/G$:

$$V_{rel} = \frac{Cl_p}{G \cdot k} \tag{22}$$

Assuming complete bio-availability the steady-state area under the plasma concentration curve during one dosage interval after repeated administration, A_{24}^n, should be equal to the area under the plasma concentration curve after the first dose extrapolated to infinity, A_∞^1. When the absorbed fraction of the dose is F one has to write

$$A_{24}^n = A_\infty^1 \cdot F \tag{23}$$

Since in our experiments the first dose, D^1, and the elimination rate constant during the first dosage interval, k^1, were different from the maintenance dose, D^n, and the elimination rate constant, k^n, during repeated administration Eq. (23) had to be modified in the following way:

$$A_{24}^n = A_\infty^1 \cdot F \cdot \frac{k^1}{k^n} \cdot \frac{D^n}{D^1} \tag{24}$$

Table 1

The one-dose experiment: Experimental results. D: dose; G: body weight; Cl_{cr}: endogenous creatinine clearance; c_0: apparent initial drug plasma concentration; m_t and A_t: amount of drug eliminated unchanged in the urine and area under the drug plasma concentration–time curve during the measuring interval t; c_t: drug plasma concentration at time t; A_∞: area extrapolated to $t = \infty$; k: overall elimination rate constant; f_r': renal dose fraction. Patients denoted by an asterisk participated in the multiple dose experiment (see Table 4).

Patient nr.	D (mg)	G (kg)	Cl_{cr} (ml/min)	c_0 (mg/l)	t (h)	c_t (mg/l)	m_t (mg)	A_t (h mg/l)	A_∞ (h mg/l)	k (h^{-1})	f_r'
1	200	69.0	50	1.843	24.02	1.065	4.800	35.11	83.87	0.02184	0.0793
2	200	61.6	46	1.718	24.00	0.727	7.250	33.43	54.21	0.03498	0.0776
3	200	53.6	34	2.418	25.02	0.912	4.139	35.42	59.47	0.03792	0.0346
4	200	92.6	43	1.135	36.00	0.434	6.603	24.56	40.60	0.02706	0.0705
5	200	58.5	50	3.150	47.99	0.308	7.642	62.74	69.20	0.04770	0.0278
6	200	61.0	12	2.315	48.00	0.363	2.046	53.82	63.27	0.03840	0.0125
7	200	63.0	130	2.167	47.97	0.323	10.217	51.10	57.61	0.04960	0.0633
8*	200	64.5	7	3.161	48.33	0.836	1.977	83.03	112.61	0.02826	0.0133
9*	200	62.0	71	5.794	47.98	0.425	15.712	87.34	94.93	0.05598	0.0981
10*	200	70.9	41	3.369	48.00	0.411	4.425	53.93	63.19	0.04440	0.0348
11*	200	43.5	6	3.839	47.98	0.327	0.804	72.37	78.53	0.05310	0.0044
12*	300	62.0	64	2.700	48.00	0.848	12.080	86.81	120.06	0.02550	0.0571
13*	200	69.5	148	2.350	47.91	0.241	11.961	49.33	54.40	0.04758	0.0651
14*	300	74.0	81	5.640	61.67	1.834	6.775	130.59	186.17	0.03300	0.0318
15*	200	81.0	101	3.222	48.02	0.646	14.026	131.25	150.37	0.03378	0.0872
16*	200	76.9	130	3.205	48.08	0.433	19.538	73.24	83.95	0.04044	0.1141
$\bar{x}$	212.5	65.85	63.4	3.002	43.69	0.633	8.125	66.50	85.78	0.03872	0.05447

According to Eq. (24) the absorbed fraction of the dose is

$$F = \frac{A_{24}^n \cdot k^n \cdot D^1}{A_\infty^1 \cdot k^1 \cdot D^n} \tag{25}$$

Results

The one-dose experiment. Based on Eq. (1) the following relation between k and Cl_{cr} was calculated from the data presented in Table 1:

$$k^P = 0.0355 + 0.000051 \cdot Cl_{cr} \tag{26}$$

According to Eq. (26), the elimination rate of MC is practically independent of kidney function (see Fig. 1).

Introducing $Cl_{crN} = 100$ in Eq. (26) results in $k_N = 0.0406$. With this value Eq. (8) predicts

$$Q^P = \frac{k}{k_N} = 0.87 + 0.0013 \cdot Cl_{cr} \tag{27}$$

On the other hand the renal and the plasma drug clearance and the estimating constants in Eqs. (2), (3), (10) and (11) were determined in each individual patient as presented in Table 2. The resulting mean values, the corresponding equations and the estimated drug elimination rates in anuric and normal patients are summarized in Table 3.

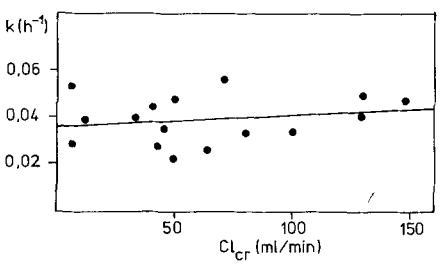

Figure 1
The relation between the overall elimination rate constant, k, of minocycline (ordinate) and the endogenous creatinine clearance, Cl_{cr} (abscissa), after the administration of a single dose in 16 subjects with normal and with impaired kidney function. The straight line corresponds to the estimating Eq. (26).

The renal clearance of the drug, Cl_r, calculated according to Eq. (18), depends linearly from the creatinine clearance, Cl_{cr}, according to the following equation:

$$Cl_r = 0.036 \cdot Cl_{cr} \tag{28}$$

In contrast, the overall plasma clearance of the drug according to Eq. (21) is independent of renal function with a mean value of $Cl_p = 46.9$ ml/min.

Table 2

The one-dose experiment: Kinetic parameters. Cl_r: renal drug plasma clearance; Cl_p: overall drug plasma clearance; V_{rel}: relative distribution volume; k_{nr}^{UP} and α^{UP}: estimating parameters of Eq. (1) determined by combined analysis of urine and plasma data according to Eqs. (2) and (3); Q_0^{UP} and Q_0^U: minimal elimination rate fractions determined from data in urine and plasma according to Eq. (11) and from urine data according to Eq. (10). Patients denoted by an asterisk participated in the multiple dose experiments. For further explanations see text.

Patient nr.	Cl_r (ml/min)	Cl_p (ml/min)	V_{rel} (l/kg)	k_{nr}^{UP} (h^{-1})	α^{UP}	Q_0^{UP}	Q_0^U
1	2.279	39.74	1.58	0.02011	0.0000346	0.853	0.853
2	3.615	61.49	1.71	0.03227	0.0000590	0.845	0.845
3	1.948	56.05	1.66	0.03661	0.0000386	0.905	0.905
4	4.481	82.12	1.95	0.02515	0.0000444	0.850	0.850
5	2.030	48.18	1.04	0.04637	0.0000265	0.946	0.946
6	0.634	52.68	1.35	0.03792	0.0000400	0.905	0.905
7	3.332	57.86	1.11	0.04646	0.0000242	0.950	0.951
8*	0.397	29.60	0.97	0.02788	0.0000537	0.838	0.838
9*	2.998	35.11	0.61	0.05049	0.0000773	0.867	0.867
10*	1.368	52.75	1.01	0.04286	0.0000377	0.919	0.919
11*	0.185	42.45	1.10	0.05287	0.0000389	0.931	0.931
12*	2.319	41.65	1.58	0.02424	0.0000228	0.913	0.914
13*	4.041	61.27	1.11	0.04448	0.0000209	0.955	0.955
14*	0.865	26.86	0.66	0.03195	0.0000130	0.961	0.961
15*	1.781	22.17	0.49	0.03083	0.0000292	0.914	0.914
16*	4.446	39.71	0.77	0.03583	0.0000355	0.910	0.910
$\bar{x}$	2.295	46.86	1.17	0.03662	0.0000373	0.904	0.904
s	1.413	15.35	0.43	0.00988	0.0000160	0.041	0.041

The relative distribution volume exhibits considerable variation with a mean value $V_{rel} = 1.17$ l/kg. There is no indication that V_{rel} depends on renal function.

The multiple-dose experiment. The experimental data and kinetic parameters determined in patients nr. 8–16 after the administration of the last dose (see Table 4) resulted in the following estimating equation (see Fig. 2):

$$k^{nP} = 0.0271 + 0.000064 \cdot Cl_{cr} \quad (29)$$

With $k_N = 0.0335$ Eq. (8) yields

$$Q^{nP} = \frac{k}{k_N} = 0.81 + 0.0019 \cdot Cl_{cr} \quad (30)$$

In the same patients the corresponding estimating equations after the first dose read as follows:

$$k^{1P} = 0.0374 + 0.000059 \cdot Cl_{cr} \quad (31)$$

$$Q^{1P} = 0.86 + 0.0014 \cdot Cl_{cr} \quad (32)$$

It is apparent from Eq. (29) and Eq. (31) that the elimination rate of MC is again independent of renal function and decreases somewhat with repeated drug administration. The difference is statistically significant ($P < 0.05$).

Table 5 summarizes the estimated constants, equations and the characteristic elimination rate constants in anuric and in normal individuals after the first and after the last dose.

After the first dose the following linear relationship between the renal drug clearance, Cl_r^1, and Cl_{cr} was found (see Fig. 3):

$$Cl_r^1 = 0.028 \cdot Cl_{cr} \quad (33)$$

The difference between Eq. (33) and Eq. (28) is statistically not significant. In contrast, the relation

$$Cl_r^n = 0.019 \cdot Cl_{cr} \quad (34)$$

found after the last dose (see Fig. 3) is significantly different from both Eq. (33) and Eq. (28) ($p < 0.05$).

Calculation of the absorbed fraction of the dose after oral administration, F, from the data in Tables 2 and 4 according to Eq. (25) results in

$$F = 0.58 \quad (35)$$

In most patients the creatinine clearance was lower after the last than after the first dose (see Fig. 2 and Fig. 3). The difference is just below statistical significance ($0.05 > P < 0.01$). Creatinine and urea nitrogen concentrations in the plasma did not change significantly with

Table 3

The one-dose experiment: Kinetic parameters, characteristic rate constants and estimating equations. α: constant relating renal drug clearance to creatinine clearance; Q_0: minimal elimination rate fraction; k_{nr}: extrarenal elimination rate constant; $t_{1/2nr}$: half-life in anuric patients, k_N; $t_{1/2N}$: elimination rate constant and half-life in patients with normal kidney function.

Parameters, characteristic values and estimating equations calculated from drug concentrations in:

	Plasma	Eqs. nr.	Plasma and urine	Eqs. nr.	Urine	Eqs. nr.
k_{nr} (h^{-1})	0.0355	(1)	0.0366	(2)	–	
$t_{1/2nr}$ (h)	19.5	(1), (24)	18.9	(24), (2)	–	
α	0.000051	(1)	0.000037	(3)	–	
k_N (h^{-1})	0.0406	(1)	0.0403	(4)	–	
$t_{1/2N}$ (h)	17.1 hours	(1), (24)	17.2	(24), (4)	–	
Q_0	0.87	(1), (6)	0.91	(11), (4)	0.90	(10)
Estimating equations	$k^P = 0.0355 + 0.000051 \cdot Cl_{cr}$ $Q^P = 0.87 + 0.0013 \cdot Cl_{cr}$	(1) (1), (6), (8)	$k^{UP} = 0.0366 + 0.000037 \cdot Cl_{cr}$ $Q^{UP} = 0.91 + 0.0009 \cdot Cl_{cr}$	(4) (8), (6)	– $Q^U = 0.90 + 0.001 \cdot Cl_{cr}$	(8), (10)

repeated drug administration. No side effects were noted except for marked dizziness and nausea in two subjects.

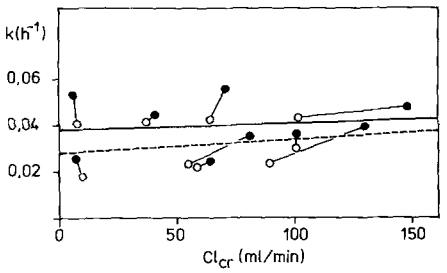

Figure 2
Relationship between the overall elimination rate constant, k, of minocycline (ordinate) and the endogenous creatinine clearance, Cl_{cr} (abscissa), after the administration of a single dose (solid symbols, uninterrupted line) and after repeated administration (light symbols, interrupted line) of the drug. The straight lines correspond to Eqs. (31) and (29).

Discussion

Our data demonstrate unequivocally that the elimination rate of MC is practically independent of kidney function. As can be seen from Table 3 the estimating parameters determined in the plasma and in the urine are in excellent agreement. For example, when Q_0 is determined from both urine and plasma data after the administration of one dose the resulting values are $Q_0^P = 0.87$ and $Q_0^{UP} = Q_0^U = 0.91$. This means on the one hand that in patients with normal kidney function only 9–13% of the dose are eliminated via the renal route, and on the other that in the anuric patient the elimination rate of MC is only 9–13% lower than normal. Accordingly the elimination rate constant determined in the plasma decreases only slightly from $k_N^P = 0.0406$ in normal subjects to $k_{nr} = 0.0355$ in the anuric patient. The corresponding half-lives are

Table 4

The multiple dose experiment: Experimental results and kinetic constants determined after the administration of the last dose. For the corresponding values after the first dose and for the explanation of the symbols see Tables 1 and 2.

Patient nr.	D (mg)	Cl_{cr} (ml/min)	c_0 (mg/l)	A_{24} (mg h/l)	m_{24} (mg)	Cl_r (ml/min)	k (h^{-1})
8	200	10	4.333	85.67	2.572	0.500	0.01746
9	200	64	3.619	72.93	5.804	1.326	0.03888
10	200	37	3.437	48.93	3.060	1.041	0.04086
11	200	8	4.699	85.47	1.107	0.216	0.03606
12	200	58	2.925	37.36	4.470	1.994	0.02280
13	200	102	3.434	61.77	5.970	1.611	0.03996
14	200	55	4.365	85.60	2.230	0.434	0.02298
15	200	101	5.495	94.69	8.450	1.487	0.03096
16	200	88	4.939	55.41	8.480	2.551	0.02610
$\bar{x}$	200	66.3	4.136	69.76	4.683	1.240	0.03139

Table 5

The multiple dose experiment: Kinetic parameters, characteristic rate constants and estimating equations after the first dose (left) and after the last dose (right) calculated from the experimental results presented in Table 2 (patients nr. 8–16) and Table 4. For explanation of the symbols see (Table 3.

				Eqs. nr.
k_{nr}^1 (h^{-1})	0.0374	k_{nr}^n (h^{-1})	0.0271	(1)
$t_{1/2nr}^1$ (h)	18.5	$t_{1/2nr}^n$ (h)	25.6	(1), (2), (4)
α^1	0.000059	α^n	0.000064	(1)
k_N^1 (h^{-1})	0.0433	k_N^n (h^{-1})	0.0335	(1)
$t_{1/2N}^1$ (h)	16.0	$t_{1/2N}^n$ (h)	20.7	(1), (24)
Q_0^1	0.86	Q_0^n	0.81	(1), (6)
Estimating equations	$k^{1P} = 0.0374 + 0.000059 \cdot Cl_{cr}$ $Q^{1P} = 0.86 + 0.0014 \cdot Cl_{cr}$	Estimating equations	$k^{nP} = 0.0271 + 0.000064 \cdot Cl_{cr}$ $Q^{nP} = 0.81 + 0.0016 \cdot Cl_{cr}$	(1) (1), (6), (8)

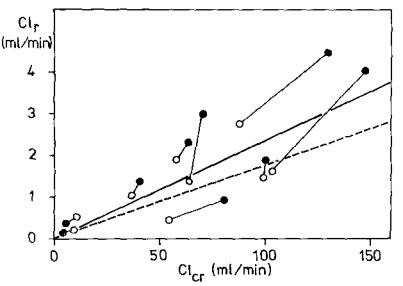

Figure 3
The linear relationship between the renal plasma clearance, Cl_r, of minocycline (ordinate) and the endogenous creatinine clearance, Cl_{cr} (abscissa), in nine subjects with normal and with impaired renal function after the administration of a single dose (solid symbols, uninterrupted line) and after repeated administration (light symbols, interrupted line) of the drug. The straight lines correspond to Eqs. (33) and (34).

$t^P_{1/2N} = 17.1$ and $t^P_{1/2nr} = 19.5$ hours (see Table 3). The high value of the distribution volume and the predominant extrarenal elimination of MC are consequences of the marked lipophilic properties of the agent. Since the fraction of MC not bound to the plasma proteins is $f_f = 0.24$ [11] Eq. (19) indicates that the renal plasma water clearance, Cl_{rw}, is only 12–15% of the glomerular filtration rate. This means that after glomerular filtration 85–88% of the drug undergoes tubular reabsorption. As a result, the renal plasma clearance of the drug is only about 3% of the creatinine clearance (see Eqs. (21) and (33)) and about 8% of its overall plasma clearance.

Practically identical results were obtained repeated administration of MC (see Table 5) except for the finding already described with other tetracyclines [8] that the overall elimination rate is somewhat lower: the half-life increases from $t^n_{1/2N} = 20.7$ hours in normal subjects to $t^n_{1/2nr} = 25.6$ hours in anuric patients. The reason why the renal drug clearance was smaller after repeated administration remains unclear and cannot explain the lower overall drug clearance because only a small fraction of the dose is eliminated unchanged in the urine. A more probable explanation is the existence of a 'slow' compartment in the organism.

The cumulative behaviour of the drug as characterized by the apparent initial concentration, c^n_0, and by the area under the plasma concentration curve, A^n_{24}, is consistent with the elimination rate constants determined under steady-state conditions and with a gastrointestinal bio-availability of about 60%.

It is evident that the small decrease in the elimination rate of MC with decreasing creatinine clearance is not of clinical significance even in patients with severe kidney disease. In this respect MC is similar to doxycycline [10, 12] and differs from older tetracycline derivatives whose elimination rates depend markedly on renal function [5]. From a kinetic point of view it must therefore be concluded that the usual dosage regimen of MC should be maintained in patients with renal disease because reducing the dose would result in subtherapeutic drug plasma concentrations. This is in contradiction to the following recommendation apparently accepted officially by most drug regulatory authorities: 'If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual doses are indicated' [2].

On the other hand it has been suggested that MC is contra-indicated in patients with renal disease because an increase in plasma urea concentration in uremic subjects was found after repeated administration of the drug [9]. In our experiments this anti-anabolic effect could not be detected. As far as renal toxicity of MC is concerned our results are inconclusive because the small decrease of the creatinine clearance after repeated drug administration remained below statistical significance.

Our finding of an incomplete gastrointestinal bioavailability of MC from the coated tablet preparation is in accordance with results reported by ALESTIC and LINDBERG [1].

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