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The assessment of pharmacokinetic parameters of teicoplanin in burns comparing the methods of nonlinear curve fitting and quantified maximum entropy

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Abstract

The pharmacokinetics of teicoplanin in patients with severe burns has been assessed using two different numerical methods: a nonlinear curve fitting procedure and quantified maximum entropy. On the whole nonlinear curve fitting and quantified maximum entropy provided different pharmacokinetic parameter estimates for the same sets of data. With respect to correctness and reliability of the values, quantified maximum entropy appears to be the better approach. However, its full success depends on the data available. The data material need to be comprehensive to assure a maximum information content to be extracted. The nonlinear curve fitting approach requires less sophisticated mathematical modelling which is possible on common hardware, and produces results faster than quantified maximum entropy. Thus, nonlinear curve fitting is the method of choice if a rapid assessment of the data is required, whereas quantified maximum entropy should be the method of choice in research and development, where the required accuracy of the estimates is more important than time.

Keywords: Teicoplanin; Burns; Pharmacokinetics

1. Introduction

Teicoplanin is a glycopeptide antibiotic, produced by the fermentation of *Actinoplanes teichomyceticus*. It is active against most Gram positive bacteria. Species usually sensitive include *Staphylococcus aureus* and coagulase negative staphylococci (sensitive or resistant to methicillin), streptococci, enterococci, *Listeria monocytogenes*, micrococci, group JK corynebacteria and Gram positive anaerobes including *Clostridium perfringens* and peptostreptococci. Bacterial synergy has

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been demonstrated in vitro with aminoglycosides against group D streptococci and staphylococci (Somma et al., 1984).

Teicoplanin as yet has not been shown cross resistance with other classes of antibiotics. There are concerns regarding toxicity, and because of the therapeutic drug monitoring thought to be required with vancomycin (chromatographically purified) in the intensive care unit, teicoplanin may supersede vancomycin (Murphy and Pinney, 1995).

Teicoplanin is indicated in potentially serious Gram positive infections including those resistant to treatment with other antibiotics such as penicillins or cephalosporins. The effectiveness of teicoplanin has been documented in the following infections (Brogden and Peters, 1994):

- lower respiratory tract;
- joint and bone;
- septicaemia;
- endocarditis;
- peritonitis related to chronic ambulatory peritoneal dialysis.

The pharmacokinetics of teicoplanin has been studied many times, both in healthy volunteers and especially in patients with renal dysfunction. The mean apparent volume of distribution after intravenous administration ranges from 0.8 to 1.6 l/kg (Outman et al., 1990; Brogden and Peters, 1994), but individual variations can double this value (Antony et al., 1991). The total clearance of the drug is about 10–15 ml/h/kg, whereas the renal clearance was reported to be between 6 and 12 ml/h/kg (Wise et al., 1986; Ripa et al., 1988). This suggests that the elimination of teicoplanin from the body is mainly a function of its renal clearance. The corresponding elimination half life was found to be 155–168 h and 182 h for intravenous and intramuscular administration, respectively (Falcoz et al., 1987; Crane and Garabedian-Ruffalo, 1992). Both the renal and the total clearance rate correlated with the creatinine clearance, and thus the clearance rates were lower in patients with impaired renal function. The mean total and renal clearance rate was more variable, if the patients had a history of intravenous drug abuse.

In terms of disposition of the drug, it appears that it can reach deep tissues such as bones (Wilson et al., 1988; Shah, 1991). The blood levels could be successfully fitted onto a two- (Wise et al., 1986; Antony et al., 1991) or three-compartment model (Ripa et al., 1988; Carver et al., 1989; Novelli et al., 1989; Danese et al., 1991), indicating that the disposition depends on the conditions of the patients or volunteers studied, and on the formulation.

According to Boucher et al. (1992), an adjustment of antibiotic dosing might be required for patients that suffered thermal injuries. For teicoplanin, the consequences in treatment due to changes in pharmacokinetics in burn patients have been discussed in detail by Potel et al. (1990).

The aim of the following study was to assess the pharmacokinetics of teicoplanin in patients with severe burns. Two mathematical approaches have been compared: nonlinear curve fitting, and quantified maximum entropy (Charter, 1992; Podczeck et al., 1995). The comparison assessed, in addition to the actual pharmacokinetic parameters, the reliability of the estimated values, the relationship between correctness/reliability of the estimated values and patient history and recovery process, the ease of obtaining the pharmacokinetic parameters, and the relation between the correctness/reliability of the estimated values and quantity of data available. The last point appears to be especially critical from an ethical point of view, i.e. if the additional load put on the patients due to blood sampling is considered.

2. Materials and methods

2.1. Experimental

This study was approved by the University College London Hospital ethical committee and informed consent was obtained for each participant. Adults with burns over 15% total body surface area (TBSA) and children older than 2 months with burns over 10% TBSA were eligible for inclusion. The results of the original study have been published by Steer et al. (1996), and the

Table 1
Summary of demographic data and history of burned patients

No.	Gender	Age (years)	Weight (kg)	Dose (i.v.) (mg)	TBSA (%)
1	M[DA]	23	55	660	15
2	F	82	60	733	22
3	F	65	60	733	60
4	M	41	104	1248	33
5	C (M)	3	16	200	24
6	M	64	86	1066	15
7	F	40	50	600	37
8	F	29	60	735	47
9	F	25	58	700	15
10	M	23	75	900	30
11	F	62	66	800	15
12	M	77	83	1000	60
13	M	21	71	850	20
14	M	32	66	800	23
15	M	40	84	1011	30
16	C (M)	0.8	10	133	12
17	M	42	100	1200	40
18	C (F)	8	27	325	15
19	C (F)	10	39	468	30
20	C (M)	3	16	185	11

M, male; F, female; C, child; TBSA, total burn surface area; DA, i.v. drug abuser.

details of the study are summarized in the following.

Teicoplanin 12 mg/kg was injected intravenously as a bolus dose. The antibiotic was supplied by Marion Merrell Dow, Winnersh, Berks. as a powder for reconstitution, and made up to a concentration of 100 mg/ml with sterile water for injection. Blood was drawn immediately prior to administration of teicoplanin, and at 5, 10, 15, 20, 30 min; 1, 2, 3, 4, 6, 8, 12, 24 h; 2, 3, 4, 5 days, and then every 2–3 days thereafter, or until serum levels fell below the limit of detection, up to a maximum of 3 weeks.

Patient samples were stored at 4°C until separation of the serum by centrifugation and then at −70°C until assayed. Teicoplanin concentrations were determined by the agar diffusion method (Patton et al., 1987), using *Bacillus subtilis* NCTC 10400, ATCC 6633 (Difco, Michigan, USA) as indicator organism. In the presence of β-lactam antibiotics, samples were treated with β-lactamase (Genzyme Biochemicals, Suffolk, UK). A multiresistant *Staphylococcus aureus* was employed as indicator organism when antibiotics other than β-lactams were given concomitantly with teicoplanin. The limit of sensitivity using *Bacillus subtilis* was 0.5 mg/l, and was 1.0 mg/l using *Staphylococcus aureus*. The coefficients of variation at the high (40 mg/l), median (8 mg/l) and lower end (1 mg/l) of sensitivity were 5.38, 5.84 and 7.82%, respectively.

2.2. Mathematical analysis

Nonlinear curve fitting of different exponential equations to the blood concentration-time profiles was undertaken with the program 'MW/Pharm, version 3.03' (MEDI/WARE B.V., Groningen, Netherlands). The model was optimized for each blood concentration-time profile by variation of the number of exponential terms (2–4) and initial estimates. The final model was chosen on the basis of residual analysis. In this respect the 'root-mean-square' deviation (RMS) of the experimental and predicted blood concentrations was used. However, due to the blood concentrations dropping to very low values at later measuring times, the single differences between predicted and ex-

Table 2
Progress of the patients during treatment

No.	outcome	D	CD0	CD3	Further comments
1	Survived		77	73	None
2	Died	8	138	102	Multiple organ failure, renal failure after day 3
3	Died	3	186	–	Renal and respiratory failure from day 0
4	Died	2	94	–	Renal failure from day 0
5	Survived		56	39	None
6	Survived		93	85	Mild renal impairment after day 6
7	Survived		118	107	Creatinine normal throughout the study
8	Survived		51	78	Septic shock (day 5), additional Teicoplanin dose
9	Survived		45	42	Respiratory infection (day 5)
10	Survived		102	96	Creatinine normal throughout
11	Survived		86	86	Creatinine normal throughout
12	Died	15	118	115	Pneumonia and cardiac failure
13	Survived		85	74	Creatinine 61 (day 17)
14	Survived		104	81	Cellulitis leg (day 3 onwards)
15	Survived		77	95	Creatinine not measured after day 3
16	Survived		–	–	Baby, no suggestion of organ failure
17	Survived		107	120	Creatinine: 142 (day 6), 144 (day 7), 113 (day 8), 102 (day 9), afterwards normal
18	Survived		46	41	None
19	Survived		50	47	none
20	Survived		51	43	None

D, days from study to death; CD0, creatinine concentration (μmol/l) before beginning of the treatment; CD3, creatinine concentration (μmol/l) on day 3 of the treatment.

perimental values were also inspected. For models with higher numbers of exponents, the last four to five predicted blood concentrations sometimes were zero, and although the RMS value was reduced, such model was rejected.

Quantified maximum entropy is a more complex approach, which has been described in detail in terms of the mathematical background (Podczeck et al., 1995). The following information, however, appears useful to be summarized: quantified maximum entropy uses Bayesian inference, combined with an entropic prior. Due to Bayesian analysis being used throughout, uncertainties in the results, caused by experimental errors in the data, are fully quantified. The disposition kinetics are constructed as posterior probability density function (the result), which provides an idea of an average performance and the variability of pharmacokinetic parameters. The disposition kinetics are based on a continuous distribution of peripheral volumes (g ($\ln k$)) as a function of the return rate constants k of the drug, thus describing the rate of the return of the drug from the associated peripheral fluid or tissue. In this way, a defined specification of the number of exponential terms or compartments in the disposition model can be avoided. The disposition kinetics is assumed to be linear and time-invariant.

In this study, the blood levels were treated using commercial software (MADAME, version 2.01, 1993, Maximum Entropy Data Consultants Ltd., Cambridge).

3. Results and discussion

Table 1 provides a summary of the 20 patients' data and history, whereas Table 2 summarizes the progress of the patients during treatment. The teicoplanin doses given are equivalent to 12.1 ± 0.1 mg/kg. Four patients died during the observation period, due to organic failure. For one patient, a 10 month old baby, the creatinine concentration in the blood was not determined.

Table 3
Teicoplanin blood level concentrations

Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8		Patient 9		Patient 10	
t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c
0.08	122.1	0.08	110.4	0.08	209.9	0.08	238.4	0.08	73.2	0.08	199.3	0.15	109.2	0.08	133.0	0.08	215.4	0.12	92.6
0.17	122.9	0.17	90.0	0.18	147.5	0.17	147.2	0.17	67.6	0.18	132.9	0.18	112.3	0.17	100.0	0.17	201.7	0.17	102.5
0.27	83.7	0.25	104.2	0.27	64.0	0.27	149.6	0.28	37.2	0.25	112.4	0.25	98.7	0.25	68.4	0.27	168.3	0.25	84.8
0.50	60.6	0.50	74.4	0.50	82.8	0.50	108.2	0.50	42.5	0.53	68.4	0.63	79.1	0.50	74.1	0.50	84.8	0.57	49.6
1.00	52.7	1.02	55.2	1.03	53.9	1.02	81.5	1.00	32.5	1.00	47.1	1.02	49.6	1.02	56.7	1.02	55.3	1.07	39.5
2.08	38.2	2.03	29.0	2.03	31.5	2.03	50.2	2.03	29.5	2.00	28.1	2.05	34.3	2.02	42.4	2.17	44.1	2.07	40.0
3.00	26.4	3.13	20.6	3.12	22.1	3.20	35.1	3.00	19.4	3.12	19.8	3.00	28.5	3.35	25.3	3.17	19.5	3.05	26.1
4.10	24.3	4.00	18.6	4.05	23.4	4.23	29.6	4.02	15.3	4.18	18.0	4.03	23.6	3.98	23.5	4.08	16.0	4.10	25.1
6.23	13.1	6.00	15.5	6.05	18.9	6.03	28.1	6.00	15.5	6.00	14.0	6.00	18.6	6.05	28.0	6.28	11.4	6.07	19.3
8.05	13.3	8.03	14.9	8.02	13.8	7.98	26.3	8.00	11.1	8.07	11.9	8.33	14.9	8.02	22.2	8.17	9.5	8.00	19.3
12.10	9.0	12.03	27.1	11.88	13.2	12.05	13.4	11.83	7.1	12.00	9.7	12.42	11.5	14.63	12.3	12.17	9.7	12.00	12.6
25.22	5.5	25.10	7.8	24.18	8.3	23.73	8.5	25.47	4.2	24.83	7.3	19.50	11.9	23.88	12.1	25.00	4.6	24.25	11.4
46.93	3.5	50.68	5.1	46.97	8.1			49.75	1.8	51.83	5.0	41.50	6.9	48.90	8.9	98.75	1.0	49.00	4.8
72.50	2.3	74.07	4.5					74.98	0.8	72.83	4.1	71.75	4.9	75.32	7.7			75.43	2.4
96.10	1.4	97.50	4.8					98.00	0.5	99.33	3.3	95.00	4.0	97.55	1.0			98.75	2.1
119.83	1.3	120.03	3.6							126.17	2.9	118.75	2.8					122.25	1.8
143.83	1.0	145.00	3.6							173.60	2.3	139.50	2.8					145.50	1.5
										213.90	2.0	166.92	2.4					194.00	0.8
										286.15	1.4	210.75	1.0					217.50	0.8
										340.90	1.4							290.00	0.6
										385.98	1.1							316.5	0.5

Patient 11		Patient 12		Patient 13		Patient 14		Patient 15		Patient 16		Patient 17		Patient 18		Patient 19		Patient 20	
t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c
0.08	223.9	0.08	230.5	0.08	238.8	0.08	84.4	0.08	170.7	0.08	166.6	0.08	248.4	0.08	246.2	0.08	143.5	0.08	112.3
0.17	171.6	0.18	163.1	0.17	200.0	0.17	79.7	0.17	121.1	0.15	162.0	0.17	202.7	0.17	189.6	0.17	199.0	0.17	84.4
0.25	154.8	0.25	133.0	0.25	176.3	0.25	80.8	0.25	109.0	0.23	202.8	0.25	98.4	0.25	97.6	0.25	117.5	0.25	78.9
0.58	101.2	0.50	117.7	0.50	156.4	0.52	80.4	0.50	70.9	0.50	47.1	0.75	68.5	0.53	75.4	0.50	58.3	0.05	53.2
1.00	54.1	1.00	52.5	1.00	43.9	1.02	30.4	1.00	63.8	1.02	43.1	1.31	45.3	1.07	50.8	1.00	57.5	1.00	35.4
2.00	37.0	2.00	30.5	2.10	27.5	2.00	18.9	2.00	38.4	2.07	26.0	2.00	42.0	1.92	28.7	2.00	47.8	2.08	28.9
3.00	31.0	3.03	27.7	3.30	33.9	3.02	18.7	3.00	28.3	3.07	18.6	3.00	39.0	3.03	23.1	3.08	27.5	3.05	17.9
4.00	21.0	3.95	27.7	4.00	32.4	4.02	14.4	4.00	23.1	4.00	13.4	4.08	19.6	4.03	18.3	4.08	29.6	4.00	17.2
6.00	15.2	6.05	16.5	6.08	25.3	5.00	12.4	6.00	14.2	6.27	11.6	6.00	18.4	6.00	15.7	6.00	19.1	5.97	14.3
11.88	12.7	8.03	15.0	7.92	19.2	6.05	14.2	8.00	16.4	7.98	10.7	7.92	12.0	8.13	13.0	7.92	11.8	8.50	11.3
24.00	8.8	11.92	13.3	12.00	14.8	8.03	13.8	11.92	12.8	11.90	6.6	12.15	12.8	12.25	9.8	11.92	10.8	12.25	7.6
46.70	4.4	24.00	9.4	24.08	6.6	12.40	9.0	25.58	7.4	23.90	5.7	23.65	6.4	23.58	6.0	24.50	4.7	67.58	2.0
69.92	2.8	43.50	9.0	47.00	3.8	24.08	10.9	48.33	3.9	47.82	3.2	36.25	6.4	49.25	3.1	49.66	2.2	187.67	0.5
96.42	1.7	67.50	5.9	70.50	2.9	50.50	5.1	72.25	3.6	72.65	1.7	66.58	3.6	122.33	1.3	70.75	1.6		

Table3 continued.

Patient 11		Patient 12		Patient 13		Patient 14		Patient 15		Patient 16		Patient 17		Patient 18		Patient 19		Patient 20	
t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c	t	c
113.17	1.9	103.00	6.9	98.42	2.5	84.25	4.3	107.50	2.8	96.40	1.1	97.50	2.5	151.25	0.7	97.63	0.9		
136.92	1.7	139.83	4.9	119.00	1.2	107.00	3.3	130.50	1.2	120.30	0.9	114.00	1.8	193.33	0.5	167.08	0.5		
162.25	1.3	165.25	5.1	143.00	0.8	124.25	2.4	148.50	1.4	176.30	0.5	137.85	1.7						
214.92	1.2	236.00	3.8	167.75	0.7	144.75	2.4	193.50	1.0			162.58	1.6						
258.59	1.2	307.00	3.9	192.08	0.5	206.50	2.4					181.92	1.0						
331.09	1.0					271.25	1.3					236.18	0.7						
385.25	0.8					315.92	1.6					257.25	0.7						
						385.00	0.5					281.08	0.6						
												305.25	0.5						

t, time (h); c, concentration (mg/l).

Table 3 lists the teicoplanin blood levels. It can be seen that there are differences in the duration of observation in terms of incomplete drug clearance for four patients at the end of the observation period. This is due to an increasing morbidity or mortality of the patients. Thus, for patients 2–4 and 12, the estimation of the elimination process of the drug and the disposition parameters may be less reliable. Sometimes, larger gaps between single blood sampling times occurred, especially for patients 12 and 18–20. This may have affected the estimation of the disposition kinetics.

Table 4 compares the parameters 'area under the curve' (AUC) and 'mean residence time' (MRT) of the nonlinear curve fitting procedure (model approach *a*) with those derived using the quantified maximum entropy approach (model approach *b*). The data were given separately for male, female and infant patients. The parameters were always estimated up to the time of the last blood sampling, and not up to infinity. This was necessary, because there are considerable differences in the approximate time where the blood levels of teicoplanin had theoretically fallen to zero, if both model approaches were compared. This consequently alters especially the MRT-values and thus their direct comparison would not be possible.

After nonlinear curve fitting, the AUC was calculated from the coefficients and exponents of the derived polyexponential equation, which is equivalent to an integration of the estimated blood concentration-time curve assuming infinite small time intervals. The model equations derived using quantified maximum entropy are much more complex, and thus the AUC was calculated from the estimated blood concentration-time curve with a time interval of 1 min using the classical trapezoidal rule. Due to the extremely small time interval, it can be assumed that there is no detectable difference between the AUC derived in this way or derived from the quantified maximum entropy model equation. In seven cases (patients 2, 7, 11, 12, 16, 18, 20) there are major differences between the AUC-values obtained from the two different numerical approaches. In

proportion to the total number of cases per gender, the majority of these cases are female patients or children. For patients 2 and 12, the maximum deviation between measured and estimated blood concentrations in the first 2 h is higher for quantified maximum entropy than for nonlinear curve fitting (see Table 6), but in the other cases it is lower. However, with the original set of data for patient 2 (see Table 3), nonlinear curve fitting failed to provide a result, and the blood concentration value at 12.03 h had to be removed to obtain a model function. Quantified maximum entropy classified this data as noisy, but still derived a result based on all measuring points available. Therefore, the AUC must be larger using Quantified Maximum Entropy. Thus, for patient 12 only it appears that quantified maximum entropy provided a less successful model, probably because there is a lack of data in the middle of the observation period (see Table 3), but in the other six cases its accuracy in modelling the data superseded the nonlinear curve fitting approach, because the maximum deviation between measured and estimated blood concentrations up to 2 h was lower. (A deviation at high blood concentrations alters the AUC significantly, whereas deviations at low blood concentrations are numerically less important). It can therefore be concluded, that quantified maximum entropy provided to 95% a satisfactory AUC-value, whereas the use of the nonlinear curve fitting approach resulted in only 70% of the cases studied in a satisfactory AUC-value.

Table 4
Comparison of the parameters AUC and MRT, estimated using nonlinear curve fitting (model approach *a*) and quantified maximum entropy (model approach *b*)

Gender	No.	AUC (h mg/l)		MRT (h)	
		a	*b*	*a*	*b*
Male	1	644	641	48.5	32.6
	4	594	581	12.0	7.1
	6	1423	1463	233.4	122.3
	10	1008	968	90.8	53.9
	12	1997	2113	296.0	107.4
	13	864	874	43.7	35.8
	14	1237	1251	147.6	101.3
	15	883	901	66.4	43.5
	17	981	1030	80.3	50.1
	Mean	1070	1091	113.2	61.6
	S.D.	434	471	94.9	39.3
Female	2	968	1137	255.7	46.4
	3	668	628	40.7	16.5
	7	886	1156	65.2	57.2
	8	1001	1051	34.1	29.3
	9	615	552	28.0	20.5
	11	1122	973	245.8	51.4
	Mean	877	916	111.6	36.9
	S.D.	198	262	108.6	17.1
Child	5	409	388	23.6	19.8
	16	626	384	41.2	6.5
	18	823	619	45.5	24.4
	19	644	621	34.6	22.9
	20	698	573	49.6	33.8
	Mean	640	517	38.9	21.5
	S.D.	150	121	10.2	9.9

Comparing the mean values between the different genders, the AUC decreases in the order male > female > child. However, the difference between 'male' and 'female' AUC values is statistically not significant. Also, the average AUC is similar for both mathematical models tested.

The MRT-values are calculated on the basis of the coefficients and exponents of the polyexponential equations, if the nonlinear curve fitting procedure has been used. In the case of quantified maximum entropy, the MRT is derived from the distribution of peripheral volumes as a function of the return rate constant k of the drug (Charter, 1992). For more than half of the values (see Table 4), the differences between the MRT-values of both models are pronounced. For patients 2, 3 and 12, the nonlinear curve fitting procedure provided MRT-values larger than or very close to the maximal assessment time. This indicates a major fault in the model equations, because the actual blood concentrations at the last sampling times are sufficient small to assume that the majority of drug has already been eliminated. In general, the MRT-values are larger using the nonlinear curve fitting approach. Major differences, however, appear to occur only, if the last five or more blood concentration values are very similar, and hence the remaining data points in the nonlinear curve fitting approach lack a sufficient slope, which is necessary for a good approximation of an exponential term. Also, in most of these cases, the

quantified maximum entropy results indicate rather a smaller number of compartments (see Table 6) to be used, which would provide more data points for the terminal exponential term and thus a sufficient slope of the data included in this term. It appears therefore that the values obtained from quantified maximum entropy are more suitable.

Using nonlinear curve fitting, the mean MRT values are similar for male and female patients, and the mean value for children is about one third of that of adults. The difference between the MRT values estimated by both mathematical models is largest for female patients. Using quantified maximum entropy, female patients and children have statistically similar MRTs, while in male patients an average MRT of nearly twice that of female patients was observed. Thus, the mathematical models lead to different conclusions about the MRT of teicoplanin.

Table 5 summarizes the values of total body clearance rate (Cl), volume of the sampling compartment (V_P) and volume in steady-state (V_{ss}), again separated into male, female and infant patients. The estimation of the Cl-values appears less affected by the choice of the numerical method. The mean values are similar, and only in four cases (patients 2, 3, 11, 16) larger differences in the estimates occur. Patient 3 died and hence a full set of samples could not be collected. Therefore, none of the two methods were able to estimate a correct Cl-value in this case, because the assessment time interval influences the estimation of this pharmacokinetic value significantly (Brogden and Peters, 1994). The differences found for patient 2 are due to the alteration of the data required for the use of the nonlinear curve fitting as discussed above. For patient 16, quantified maximum entropy indicates that the data are noisy, and thus has probably underestimated the data, whereas for patient 11 a comparably high misfit appears to occur using the nonlinear curve fitting approach, because the maximum deviation between estimated and measured blood concentrations in the first 2 h is nearly a threefold of that using the quantified maximum entropy approach. In terms of Cl, the reliability of both mathematical methods appears therefore to be similar, and no advantage can be observed using either of them. For the male and female patients, the average Cl when related to the body weight is 11.3 ml/h/kg, which is consistent with literature data (Antony et al., 1991; Brogden and Peters, 1994). However, for children this value exceeds the literature values (18.9 ml/h/kg and 21.7 ml/h/kg for nonlinear curve fitting and quantified maximum entropy approach, respectively).

With the exception of patient 13, the V_P-values (see Table 5) are always much larger if calculated using the nonlinear curve fitting approach, than using quantified maximum entropy. The estimation of this value depends in the case of the nonlinear curve fitting approach on the fictive concentration at time point zero ($V_P = \text{dose}/c_{p0}$),

Table 5
Comparison of the parameters Cl, V_P and V_{ss} estimated using nonlinear curve fitting (model approach a) and quantified maximum entropy (model approach *b*)

Gender	No.	Cl (l/h)		V_P (l)		V_{ss} (l)	
		a	*b*	*a*	*b*	*a*	*b*
Male	1	0.94	0.96	4.2	2.3	45.5	43.6
	4	1.77	1.60	6.1	4.0	21.3	30.8
	6	0.65	0.70	6.0	1.6	152.4	90.0
	10	0.83	0.91	8.8	1.2	75.2	42.2
	12	0.32	0.36	4.1	1.8	95.8	71.7
	13	0.95	0.94	2.6	3.0	41.4	39.4
	14	0.58	0.60	7.7	1.8	86.2	69.3
	15	1.04	1.05	7.1	0.9	69.3	52.8
	17	1.17	1.14	2.8	0.4	93.9	44.4
	Mean	0.92	0.92	5.5	1.9	75.7	53.8
	S.D.	0.41	0.35	2.2	1.1	38.4	19.2
Female	2	0.36	0.52	6.2	5.1	92.1	42.7
	3	0.75	0.52	4.9	1.9	30.5	44.7
	7	0.51	0.47	4.5	2.9	33.4	36.4
	8	0.69	0.61	6.7	4.1	23.4	24.8
	9	1.07	1.12	3.7	2.1	30.0	32.1
	11	0.55	0.80	3.8	0.5	135.2	35.4
	Mean	0.66	0.67	5.0	2.8	57.4	36.0
	S.D.	0.24	0.25	1.2	1.6	45.7	7.2
Child	5	0.47	0.49	3.7	1.4	11.2	11.5
	16	0.21	0.34	0.9	0.4	8.5	1.7
	18	0.39	0.50	1.9	0.7	17.5	9.8
	19	0.70	0.74	4.2	0.4	24.3	14.8
	20	0.26	0.32	2.2	0.2	12.7	9.6
	Mean	0.41	0.48	2.6	0.6	14.8	9.5
	S.D.	0.19	0.17	1.4	0.5	6.2	4.8

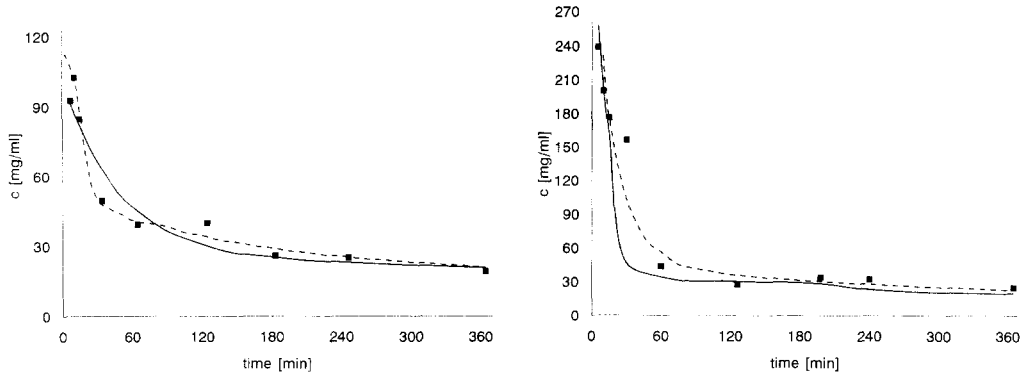

Fig. 1. Estimated blood concentration-time profiles in comparison to measured blood concentration values for patients 10 (lack of fit, a) and 13 (close fit, b) —— , nonlinear curve fitting approach; - - -, quantified maximum entropy approach; ■, measured values.

which will be extrapolated by means of the polyexponential model equation. In all cases the estimates for c_{p0} were too small, because the maximum deviation between the estimated and measured blood concentrations (estimated values usually smaller than measured ones, see Fig. 1(a, b)) always occurred within the first three measuring points, hence for data of the first 30 min of the study. Thus the values of V_P are all too large. Using quantified maximum entropy, V_P is obtained from the distribution of peripheral volumes as a function of the return rate constants (Charter, 1992). The fit of the data is closer to the measuring values (see Fig. 1(a, b)), and it can therefore be assumed, that this distribution function reflects the true drug distribution better. Hence, the estimates of V_P, which are directly obtainable from this distribution function, should also be closer to reality.

The numerical evaluation of V_{ss} involves in both approaches the exact knowledge of V_P, and hence the nonlinear curve fitting approach is at a disadvantage. Furthermore, in the nonlinear curve fitting approach, the calculation of V_{ss} also requires the knowledge of the distribution constants of the drug approaching and leaving different compartments, which are calculated from the coefficients and exponents of the polyexponential equations. Hence, the fit of the data by the model equations is the dominant factor in terms of an accurate estimate of V_{ss}. Using quantified maximum entropy, the calculation of V_{ss} is also based on the knowledge of V_P plus the total volume of the peripheral compartments, which again can be obtained from the distribution of peripheral volumes as a function of the return rate constants (Charter, 1992). The value estimates appear to be more reliable when determined using quantified maximum entropy due to the strong influence of V_P on their value. The ratio between the values for V_{ss} for male, female and infant patients is 1:0.75:0.2 using nonlinear curve fitting, and 1:0.66:0.2 using quantified maximum entropy. Hence, in this respect the results are comparable.

Table 6 compares the number of compartments proposed by model approach *a* with the number of peaks in the disposition kinetics estimated using model approach *b*. Quantified maximum entropy (model approach *b*) does not use a fixed number of compartments, because this would not reflect true physiological conditions. It is based on the idea that there exists an unlimited spectrum of tissues and fluids, connected with each other, but different in terms of their return rate constants, i.e. the speed with which a defined drug substance

Table 6
Comparison of the number of compartments proposed by model approaches *a* and *b*, and residual analysis

Gender	No.	PNC		Residual analysis			
		a	*b*:(NP co)	*a*:RMS (%)	*a*:MD (mg/l)	b:MD (mg/l)	*b*:DC
Male	1	3	2 (1 –)	13.80	16.2	8.9	—
	4	2	2 (1 us)	15.97	50.9	23.0	—
	6	3	2 (1 –)	14.12	41.4	39.0	Noisy
	10	3	3 (2 –)	15.89	15.0	6.4	—
	12	3	2 (1 –)	13.68	21.0	70.4	—
	13	3	3 (2 –)	14.67	19.0	57.0	—
	14	3	2 (1 us)	21.86	22.2	44.2	Noisy
	15	3	3 (2 –)	19.15	38.5	23.8	—
	17	3	2 (1 us)	21.07	37.2	15.0	Noisy
Female	2[a]	3	2 (1 us)	7.56	10.9	15.4	Noisy
	3	2	2 (1 –)	29.37	72.9	31.5	—
	7	3	2 (1 –)	8.18	7.9	7.2	—
	8	2	2 (1 us)	36.81	29.3	14.0	Noisy
	9	2	3 (2 –)	24.85	38.8	20.4	—
	11	3	2 (1 us)	13.71	32.6	11.3	—
Child	5	2	2 (1 us)	20.88	20.0	11.5	Noisy
	16	2	2 (1 us)	35.09	79.2	68.6	Noisy
	18	2	2 (1 –)	32.22	88.6	59.4	—
	19	2	2 (1 us)	35.73	94.8	33.0	Noisy
	20	2	2 (1 us)	27.57	30.0	28.6	—

PNC, proposed number of compartments; NP, number of peaks in the distribution of peripheral volumes; co, comment about the peaks; us, peak unsharp (could be two unseparated peaks); RMS, root mean square deviation between measured and calculated concentration values; MD, maximum deviation in the first 2 h; DC, data classification.
[a] For model approach *a*, the data point at 12.03 h had to be removed.

can be cleared from each of them (see Section 2). The likelihood of drug being distributed in such peripheral units is then reflected by the volume estimated for a tissue or fluid with a defined return rate constant, and the distribution of peripheral volumes as a function of the return rate constant indicates in which tissues or fluids the drug substance has been disposed. A distribution into a series of tissues or fluids of more or less similar return rate constants results in a peak. Hence it can be assumed that the occurrence of one or more peaks is equivalent to one or more peripheral compartments defined in classical pharmacokinetics, although this is not always correct, because broad peaks can be related to more than one compartment in the classical meaning, but the differentiation is difficult. Thus, one peak in the distribution of peripheral volumes will be treated as an indicator of a classical two-compartment model, and two peaks will be interpreted as a classical three-compartment model.

From Table 6 it can be seen that, if the peak(s) (see Fig. 2(a)) occurring in the distribution of peripheral volumes as a function of their return rate constants are used for suggesting classical compartments, in the majority of cases the use of only quantified maximum entropy would lead to a reduced number of compartments. However, in half of the blood levels evaluated, quantified maximum entropy could not separate clear single peaks (see Fig. 2(b)), suggesting that there should be at least one more compartment-equivalent peak seen. This demonstrates a major weak point of quantified maximum entropy: the full success of all features of the approach depends strongly on a sufficient number of data points. The occurrence of unsharp peaks can be related to a generally reduced number of data points (e.g. patients

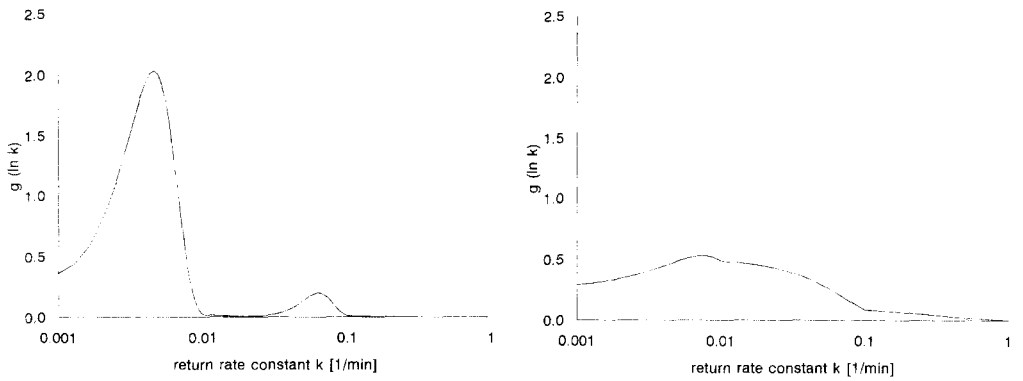

Fig. 2. Distribution of peripheral volumes as a function of their return rate constants of teicoplanin for patients 9 (a) and 8 (b).

5, 8, 16, 20), to an incomplete blood sampling (e.g. patients 2, 4), or to larger gaps between certain time points having generally a sufficient number of data points available (e.g. patients 19, 20).

Table 6 also provides values concerned with the residual analysis for both model approaches. These results have already been discussed in relation to the estimated pharmacokinetic parameters. (Note: data are classified as 'noisy', if the run-time parameter 'SCALE' exceeds a certain value, depending on the number of data. This parameter is software-specific).

It can be concluded, that on the whole nonlinear curve fitting and quantified maximum entropy provided different pharmacokinetic parameter estimates for the same sets of data. With respect to correctness and reliability of the values, quantified maximum entropy appears to be the better approach. However, its full success depends on the comprehensiveness of the data. The approach is based on an extremely sophisticated mathematical model. However, there are a greater number of data points required to assure a maximum information content to be extracted. The nonlinear curve fitting approach requires less sophisticated mathematical modelling, which is possible on common hardware, and produces results much faster. Thus, nonlinear curve fitting is the method of choice for immediate clinical use to provide a fast answer about the data, whereas quantified maximum entropy should be the method of choice in research and development, where the required accuracy of the estimates is more important than time.

References

Antony, K.K., Lewis, E.W., Kenny, M.T., Dulworth, J.K., Brackman, M.B., Kuzma, R., Yuh, L., Eller, M.G. and Thompson, G.A., Pharmacokinetics and bioavailability of a new formulation of teicoplanin following intravenous and intramuscular administration to humans. *J. Pharm. Sci.*, 80 (1991) 605–607.

Boucher, B.A., Kuhl, D.A. and Hickerson, W.L., Pharmacokinetics of systematically administered antibiotics in patients with thermal injury. *Clin. Infect. Dis.*, 14 (1992) 458–463.

Brogden, R.N. and Peters, D.H., Teicoplanin-A reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*, 47 (1994) 823–854.

Carver, P.L., Nightingale, C.H. and Quintiliani, R., Pharmacokinetics of single- and multiple-dose teicoplanin in healthy volunteers. *Antimicrob. Agents Chemother.*, 33 (1989) 82–86.

Charter, M.K., Modelling drug behaviour in the body with MAXENT. In Smith, C.R. (Ed.), *Maximum Entropy and Bayesian Methods*, Kluwer Academic, Dordrecht, 1992, pp. 287–302.

Crane, V.S. and Garabedian-Ruffalo, S. M., Current treatment of Gram-positive infections: focus on efficacy, safety, and cost minimalization analysis of teicoplanin. *Hosp. Formular.*, 27 (1992) 1199–1210.

Danese, A., Bernareggi, A., Rosina, R. and Rowland, M., Model choice for teicoplanin kinetics in man. *Eur. J. Drug Metab. Pharmacokin.*, 3-special issues (1991) 250–255.

Falcoz, C., Ferry, N., Pozet, N., Cuisinaud, G., Zech, P.Y. and Sassard, J., Pharmacokinetics of teicoplanin in renal failure. *Antimicrob. Agents Chemother.*, 31 (1987) 1255–1262.

Murphy, S. and Pinney, R., Teicoplanin or vancomycin in the treatment of Gram-positive infections? *J. Clin. Pharm. Ther.*, 20 (1995) 5–11.

Novelli, A., Mazzei, T. and Reali, E.F., Clinical pharmacokinetics and tissue penetration of teicoplanin. *Int. J. Clin. Pharmacol. Res.*, 9 (1989) 233–237.

Outman, W.R., Nightingale, C.H., Sweeney, K.R. and Quintiliani, R., Teicoplanin pharmacokinetics in healthy volunteers after administration of intravenous loading and maintenance doses. *Antimicrob. Agents Chemother.*, 34 (1990) 2114–2117.

Patton, K.R., Beg, A., Felmingham, D., Ridgway, G.L. and Grüneberg, R.N., Determination of teicoplanin concentration in serum using a bioassay technique. *Drugs Exp. Res.*, 13 (1987) 547–525.

Podczeck, F., Charter, M.K., Newton, J.M. and Yuen, K.H., Calculation of the drug absorption rates of two sustained-release theophylline formulations using Quantified Maximum Entropy. *Eur. J. Pharm. Biopharm.*, 41 (1995) 254–261.

Potel, G., Moutet, J., Bernareggi, A., LeNormand, Y., Meigner, M. and Baron, D., Pharmacokinetics of teicoplanin in burn patients. *Scand. J. Infect. Dis.*, 72 (Suppl.) (1990) 29–34.

Ripa, S., Ferrante, L., Mignini, F. and Falcioni, E., Pharmacokinetics of teicoplanin. *Chemotherapy*, 34 (1988) 178–184.

Shah, P.M., Pharmakokinetik von teicoplanin. *Krankenhauspharmazie*, 12 (1991) 428–436.

Somma, S., Gastaldo, L. and Corti, A., Teicoplanin, a new antibiotic from Actinoplanes teicomyceticcus nov. sp. *Antimicrob. Agents Chemother.*, 26 (1984) 917–923.

Steer, J.A., Papini, R.P.G., Wilson, A.P.R., Dhillon, S., Hichens, M.F., McGrouther, D.A., Frame, J.D. and Parkhouse, N., Pharmacokinetics of a single dose of teicoplanin in burn patients. *J. Antimicrob. Chemother.*, 37 (1996) 545–553.

Wilson, A.P.R., Taylor, B. and Treasure, T., Antibiotic prophylaxis in cardiac surgery: serum and tissue levels of teicoplanin, flucloxacillin and tobramycin. *J. Antimicrob. Chemother.*, 21 (1988) 201–212.

Wise, R., Donovan, I.A. and McNulty, C.A.M., Teicoplanin, its pharmacokinetics, blister and peritoneal fluid penetration. *J. Hosp. Infect.*, 7 (1986) 47–55.