Disposition kinetics of dibekacin in normal subjects and in patients with renal failure

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Abstract. Dibekacin pharmacokinetics was studied in ten healthy volunteers and six patients with renal failure presenting Cl_{cr} <10 ml·min^{-1} per 1.73 m^2 of body surface, given as a slow intravenous bolus to the volunteers and as a 30-minute intravenous infusion to the patients. The antibiotic was assayed in plasma and urine by means of a microbiological method using Bacillus subtilis. A two-compartment kinetic model was used to describe the bi-phasic decline of the plasma concentration thus establishing the different pharmacokinetic parameters. Elimination parameters β, k_{10} and total body clearance were markedly diminished in renal patients ($p < 0.001$): $t_{1/2}\beta$ was 2.0 h, k_{10} = 0.016 min^{-1} and Cl = 0.87 ml·min^{-1} kg body weight in normal subjects and $t_{1/2}\beta$ = 21.4 h, k_{10} = 0.0011 min^{-1} and Cl = 0.131 ml·min^{-1} per kg in the patients. Other kinetic parameters, as distribution (α) and transfer (k_{12}, k_{21}) constants were lower in patients than in volunteers. Also the different terms of volume of distribution of the two-compartment model (V_1, Vd_{ss}, Vd_{area}) were significantly higher in patients than in normal subjects ($p < 0.05$). A good correlation ($r = 0.987$) between patients' β constant and creatinine clearance was found. A similar relationship between serum creatinine levels and disposition half-life was found ($r = 0.955$). Urinary recovery at 24 h was 89.0% of the dose given to normals and 15.8% of the dose given to patients.

Key words: dibekacin – pharmacokinetics – renal failure – disposition

Introduction

An improved understanding of the mechanisms by which gram-negative bacteria develop resistance allowed the development of dibekacin – 3'4'-dideoxy-kanamycin B. Substitution of the hydroxyl groups by hydrogen atoms in positions 3' and 4' of kanamycin B, prevents the phosphorylation of the 3' hydroxyl group which modifies the aminoglycoside molecule and is described as one of the mechanisms of resistance [Umezawa 1971 and 1976, Yamasaku 1974].

The pharmacokinetic parameters of drugs may be modified by various pathologic states. Renal failure is probably the most outstanding of these. Patients presenting poor renal function may show important modifications in the disposition of drugs [Dettli 1974, Le Sher 1976, Arancibia 1984].

Like other aminoglycosides, dibekacin's principal route of elimination is the kidney, which implies that in patients with renal impairment the pharmacokinetics of the antibiotic are significantly modified, especially the parameters which define the elimination process.

The purpose of this study was to define the pharmacokinetic parameters of dibekacin in subjects with normal renal function and in patients with chronic renal insufficiency with a creatinine clearance less than 10 ml·min^{-1}/1.73 m^2.

Material and methods

Subjects

Ten healthy volunteers, seven males and three females, ranging in age from 20 to 26 years (mean, 24.5 ± 1.7 years) and in weight from 48 to 73 kg (mean, 63.5 ± 9.7 kg) participated in this study. Written informed consent was obtained, and medical history, physical examination, and various laboratory tests (hematocrit, serum alkaline phosphatase, serum glutamate pyruvate transaminase, serum glutamate oxalate transaminase, serum creatinine and urinalysis) were carried out prior to the start of this study. The results of these examinations were within normal limits for all volunteers.

Table 1 Characteristics and biochemical parameters of the patients with impaired renal function.

Patient No.	Age (years)	Hematocrit %	Weight	Hemoglobin (g%)	Transaminase GPT (U.I.)	Transaminase GOT (U.I.)	Alkaline Phosphatase (U.I.)	BUN (mg/dl)	Serum creatinine (mg%)	Creatinine clearance* (ml/min/ 1.73 m^2)
1. – R.I.O.	27	24	58.1	–	–	25	27	180	20.0	4.6
2. – L.R.C.	28	27	57.5	8.8	5	17	130	116	16.5	5.4
3. – G.N.C.	19	28	49.0	8.4	20	23	219	73	9.6	8.6
4. – L.J.R.	29	16	59.4	5.2	6	17	152	130	15.5	5.9
5. – O.M.G.	23	20	44.0	7.1	7	15	122	82	14.1	5.1
6. – A.P.P.	44	23	61.5	8.0	11	15	185	76	9.1	9.0
Mean	28.3	23.0	54.9	7.5	9.8	18.7	139	109.5	14.1	6.4
± SD	8.5	4.5	6.8	1.4	6.1	4.3	65.7	41.6	4.2	1.9

* Calculated from serum creatinine.

Each subject received, after an overnight fast, a single intravenous dose of 2 mg per kg of dibekacin* as a bolus injection within five min. Two h after dosage the volunteers took a light breakfast and three h later a normal lunch. Blood samples were drawn before injection and at 5, 10, 15, 20, 30, 40, 50, 60, 80 and 100 min and 2, 3, 4, 5, 6, 7 and 8 h thereafter.

Urine was collected before the injection and at the following intervals: 0–2, 2–4, 4–6, 6–8, 8–10, 10–12 and 12–24 h.

Subjects with chronic renal insufficiency

Six patients, all males, with endogenous creatinine clearance, Cl_{cr} <10 ml · min^{-1}/1.73 m^2, ranging in age from 19 to 44 years (mean, 28.3 ± 8.5 years) and in weight from 44 to 61.5 kg (mean, 54.9 ± 6.8 kg), participated in the study. The same laboratory tests as in normal subjects were carried out, but in addition, hemoglobin and blood ureic nitrogen (BUN) were determined. The results are shown in Table 1.

Each patient was given a 2 mg · kg^{-1} dibekacin dose as a 30-min intravenous infusion. The other conditions were similar to those for the normal subjects. Blood samples were taken at 0, 5, 10, 15, 30, 45, 60, and 90 min and at 2, 4, 6, 8, 12 and 24 h after the end of the infusion. Urine was collected at the spontaneous miction intervals of each patient.

Bioassay

The analytic technique used to determine the plasma and urine concentrations of the antibiotic was the agar diffusion method [Bennett et al. 1966]. Blood samples were collected in sterile glass tubes containing heparin, and plasma was obtained by centrifugation. Urine was also collected by aseptic technique, and aliquots were stored for assay. Plasma and urine were frozen upon collection (−20° C) and assayed within 72 h after sampling. Bacillus subtilis (ATCC 6633) was employed as the test organism.

* DIBE-M, kindly supplied by Instituto Bioquímico Beta S.A., Santiago, Chile.

Pharmacokinetic analysis

The plasma concentrations of dibekacin given i.v. declined with time in a biexponential manner. The plasma concentrations of the antibiotic were analyzed according to a two-compartment open

Table 2 Average dibekacin plasma concentrations after a 2 mg/kg body weight dose administered intravenously as a bolus to ten healthy volunteers and as a 30-minute infusion to 6 patients with impaired renal function (Cl_{cr} <10 ml·min^{-1}/1.73 m^2).

Time	Concentration (mg·l^{-1}) Mean ± SD	
	Patients	Volunteers
0	16.5 ± 0.5	0.0
5	14.1 ± 1.9	29.3 ± 3.4
10	12.2 ± 1.6	22.9 ± 2.6
15	11.5 ± 1.7	21.1 ± 4.1
20	–	17.9 ± 3.2
30	10.8 ± 1.6	14.9 ± 3.1
40	–	12.6 ± 2.7
45	10.1 ± 1.5	–
50	–	10.8 ± 3.0
60	9.2 ± 1.8	9.8 ± 2.7
80	–	7.9 ± 2.4
90	8.9 ± 2.1	–
100	–	6.9 ± 2.0
120	8.2 ± 2.0	5.5 ± 1.6
150	–	4.7 ± 1.6
180	–	4.1 ± 1.2
240	7.4 ± 1.8	2.8 ± 1.1
300	–	2.1 ± 0.8
360	6.7 ± 1.6	1.5 ± 0.6
420	–	1.1 ± 0.5
480	6.2 ± 1.5	0.8 ± 0.4
720	5.4 ± 1.2	–
1440	3.7 ± 0.9	–

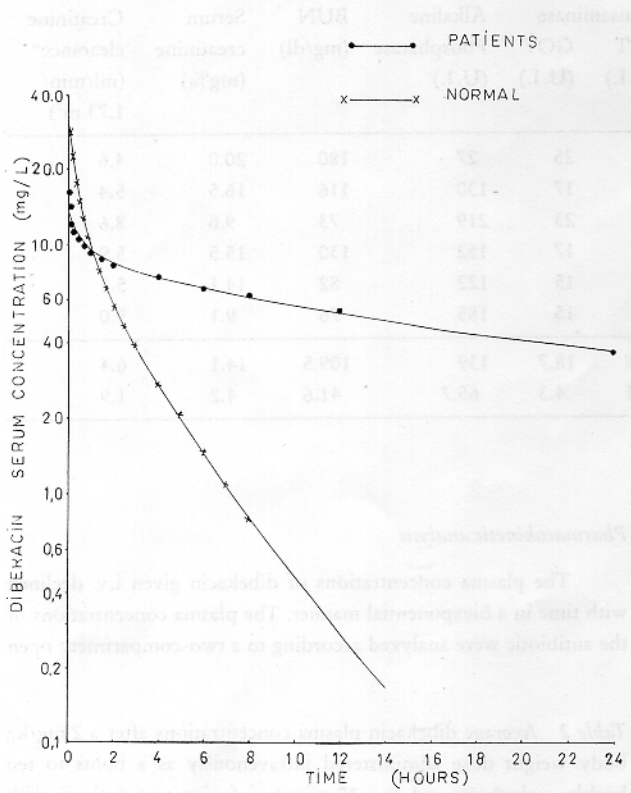

Fig. 1 Mean dibekacin serum concentration vs time profiles following a 2 mg·kg^{-1} dose as a bolus to 10 normal subjects and as a 30-minute i.v. infusion to 6 patients with renal failure (Cl_{cr} <10 ml·min^{-1}/1.73 m^2).

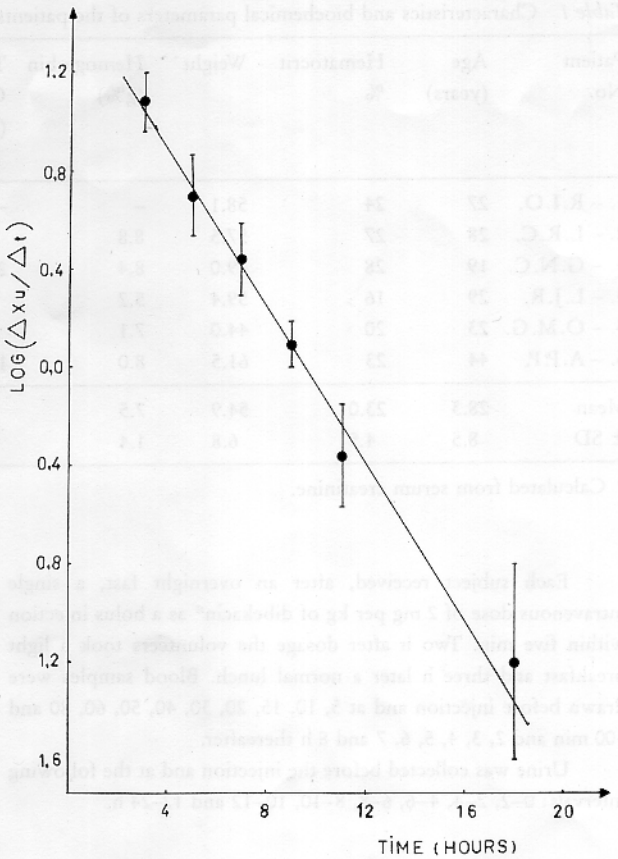

Fig. 2 Mean excretion rate vs time profiles of dibekacin in 10 normal subjects following a 2 mg·kg^{-1} i.v. bolus injection.

kinetic model. These concentrations (C) versus time (t) were fitted to equation 1:

$$C = A\,e^{-\alpha t} + B\,e^{-\beta t} \quad (1)$$

The SAS nonlinear computer program was used to obtain the best estimates of equation 1 [Cary 1982]. Beta half-life ($t_{1/2}\,\beta$), body clearance (Cl_B), volume of the central compartment (V_1), apparent volume of distribution (Vd_{area}), distribution rate constants (k_{12} and k_{21}) and the area under the plasma concentration-time curve (AUC) were determined by classical pharmacokinetic techniques [Gibaldi 1975]. The time at which the amount of dibekacin in the peripheral compartment reached a maximum (t_{max}) was also calculated, using equation 2.

$$t_{max} = \frac{1\,n\,(\alpha-\beta)}{(\alpha/\beta)} \quad (2)$$

When dibekacin was administered to patients by an i.v. infusion the method of Loo and Riegelman [1970] was employed to calculate the disposition parameters.

Statistical analysis

The Student's t-test was employed to assess the differences of the various parameters between normal subjects and patients.

Table 3 Pharmacokinetic parameters for dibekacin in healthy volunteers and patients with impaired renal function.

Parameters	Volunteers n = 10	Patients n = 6	p Value
$\alpha \times 10^2$ (min^{-1})	6.32 ± 3.18	2.57 ± 0.65	NS
$t_{1/2}\,\alpha$ (min)	14.10 ± 7.50	29.0 ± 10.1	NS
$\beta \times 10^3$ (min^{-1})	6.05 ± 1.40	0.56 ± 0.10	≪0.001
$t_{1/2}\,\beta$ (h)	1.99 ± 0.39	21.4 ± 3.6	≪0.001
$k_{12} \times 10^2$ (min^{-1})	2.74 ± 1.64	11.9 ± 5.2	<0.01
$k_{21} \times 10^2$ (min^{-1})	2.63 ± 1.60	1.3 ± 0.39	<0.05
$k_{10} \times 10^2$ (min^{-1})	1.55 ± 0.49	0.11 ± 0.04	≪0.001
t_{max} (min)	48.20 ± 19.90	139 ± 20	≪0.001
Vd_{area} (l·kg^{-1})	0.148 ± 0.045	0.238 ± 0.068	<0.005
V_1 (l·kg^{-1})	0.058 ± 0.009	0.119 ± 0.008	≪0.001
V_2 (l·kg^{-1})	0.068 ± 0.026	0.113 ± 0.066	<0.05
Vd_{ss} (l·kg^{-1})	0.111 ± 0.037	0.232 ± 0.064	≪0.001
Vd_{ext} (l·kg^{-1})	0.202 ± 0.106	0.243 ± 0.073	
Cl_b (ml × min^{-1}·kg)	0.87 ± 0.24	0.131 ± 0.04	≪0.001
Cl_r (ml × min^{-1}·kg)	0.77 ± 0.21	0.031 ± 0.02	≪0.001
Urinary recovery (%) in 24 h	89.0 ± 0.02	15.8 ± 2.5	≪0.001

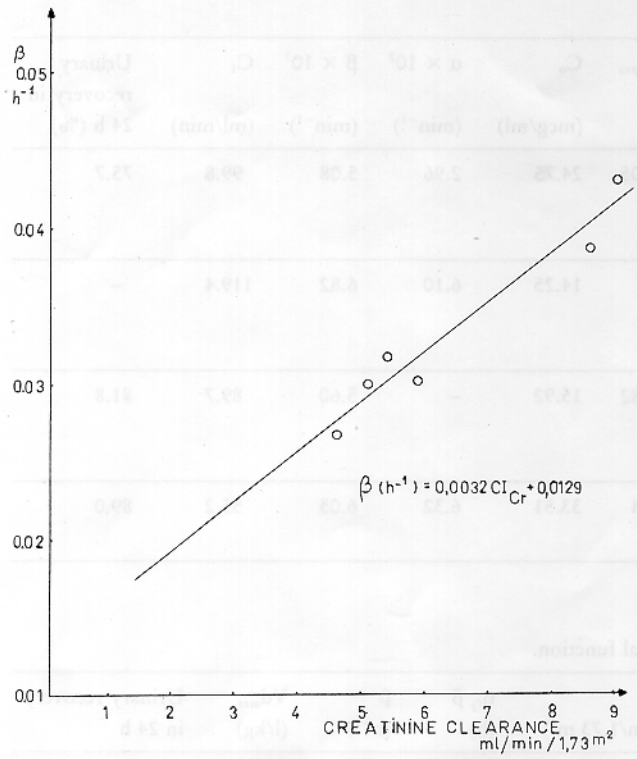

Fig. 3 Relationship between creatinine clearance and the disposition rate constant β of dibekacin.

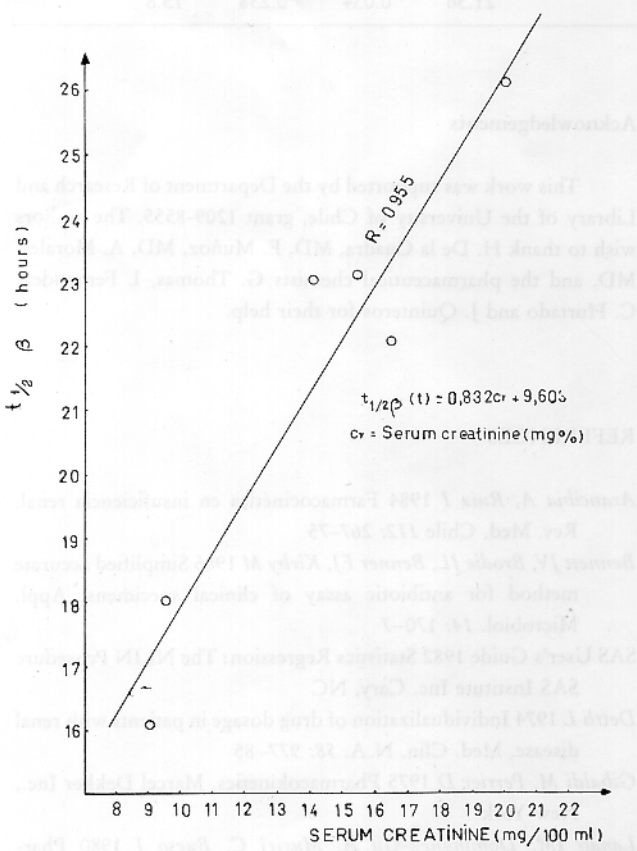

Fig. 4 Relationship between serum creatinine concentration and the beta half-life of dibekacin.

Results

Mean serum concentrations after i.v. dosage administered to both normal subjects and patients are shown in Table 2. Mean and individual serum concentration-time curves followed the biexponential pattern described by equation 1 (Figure 1). Mean values of the various pharmacokinetic parameters of the two-compartment model are listed in Table 3.

Normal subjects

Disposition is characterized by a rapid phase with a $t_{1/2}$ of 14.1 min, indicating a rather prompt distribution to the peripheral compartment reaching a maximum at 48.2 min. The $t_{1/2}\beta$ of 2.0 h along with a k_{10} of 0.93 h^{-1} indicates that dibekacin is eliminated from the body in a manner similar to other aminoglycosides. The volume of distribution Vd_{area} was 0.148 $l \cdot kg^{-1}$ and the other volumes calculated according to the two-compartment model V_1, V_2 and Vd_{ss} were 0.06, 0.07 and 0.111 $l \cdot kg^{-1}$, respectively.

Two hours after the injection, 53% of the dose was recovered in the urine corresponding to 57% of the total amount excreted at 24 h which was 89.0% of the given dose. Figure 2 is a graphic of the mean excretion rates of the ten normal subjects at different times. The straight line confirms the first-order elimination kinetic of the antibiotic. Mean $t_{1/2}\beta$ calculated using urinary data was 1.96 h which is close to the value obtained with plasma data. Renal clearance was 0.77 $ml \cdot min^{-1}$ kg.

Patients with renal failure

Mean concentration after finishing the infusion was 16.5 $mcg \cdot ml^{-1}$ and fell to 3.7 $mcg \cdot ml^{-1}$ at 24 h. $t_{1/2}\beta$ was 21.4 h which is 45 times larger than $t_{1/2}\alpha$ which was 0.48 h. The different terms of volume calculated according to the model employed V_1, V_2, Vd_{ss}, Vd_{area} and Vd_{ext}, were 0.12, 0.11, 0.23, 0.24 and 0.25 $l \cdot kg^{-1}$, respectively. Mean total amount of dibekacin excreted in the urine at 24 h was 15.8% of the administered dose.

Discussion

Most of the pharmacokinetic parameters found in our study are in good agreement with those reported previously as can be seen in Tables 4 and 5 where we have listed our values in comparison with those found in the literature [Leroy et al. 1978, Lanao et al. 1980, Thauvin et al. 1983, Viott et al. 1983]. However, the

Table 4 Pharmacokinetics of dibekacin in healthy subjects.

Authors	Route and dose	Number of subjects	$t_{1/2}\ \alpha$ (min)	$t_{1/2}\ \beta$ (h)	Vd_{ss} (l)	Vd_{area} (l)	C_o (mcg/ml)	$\alpha \times 10^2$ (min^{-1})	$\beta \times 10^3$ (min^{-1})	C_l (ml/min)	Urinary recovery in 24 h (%)
Leroy et al. [1980]	Bolus 1 $mg \cdot kg^{-1}$	5	–	2.30	8.31	14.05	24.75	2.96	5.08	99.8	75.7
Lanao et al. [1980]	Bolus 1.5 $mg \cdot kg^{-1}$	5	11.36	1.69	14.60	–	14.25	6.10	6.82	119.4	–
Thauvin et al. [1983]	Bolus 1 $mg \cdot kg^{-1}$	5	–	2.11	–	16.82	15.92	–	5.60	89.7	81.8
This work	Bolus $mg \cdot kg^{-1}$	10	14.1	1.99	7.0	9.4	33.51	6.32	6.05	55.2	89.0

Table 5 Pharmacokinetics of dibekacin in patients with impaired renal function.

Author	Route	Number of subjects	Dose (mg/kg)	Cl_{cr} (ml/min/1.73 m^2)	$t_{1/2}\ \beta$ (h)	β (h^{-1})	Vd_{area} (l/kg)	Urinary recovery in 24 h
Viott et al. [1983]	i.m.	6	1	15	24.50	0.030	0.346	23.0
Leroy et al. [1980]	i.m.	5	1	8.4	26.22	0.026	0.374	20.6
This work	Infusion	6	2	6.4	21.36	0.034	0.238	15.8

value of dibekacin clearance in healthy subjects found in our study was about 50% lower than the value reported in other studies. Since the values of β in our work are similar to that previously reported the differences noted in the total body clearance are the result of a lower volume of distribution. In fact, Vd_{area} and Vd_{ss} were also about 50% lower than the values reported by other authors. These differences in clearance and volume of distribution are also apparent in the results found in renal failure patients. Since a smaller volume of distribution determines higher plasma concentrations, this finding may be of interest if it corresponds to a characteristic of the population studied. The risk of aminoglycoside toxicity and adverse reactions would be higher in this population and a reduction of the usual dose might be necessary. Studies in a larger number of subjects are required to clarify this point.

Both β and $t_{1/2}\beta$ correlate well with creatinine clearance and serum creatinine respectively (Figures 3 and 4).

Transfer of dibekacin between compartment was slower in patients with impaired renal function than in normal subjects. However, k_{12}/k_{21} ratios were rather similar in both groups (1.0 for normal subjects and 0.9 for patients).

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