EFFECT OF INFUSION TIME ON THE PHARMACOKINETICS OF DIBEKACIN IN RABBITS

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A study was made of the serum levels and of the pharmacokinetic parameters of dibekacin after administration by intravenous infusion at a dose of 2 mg/kg of the drug to rabbits using different infusion times. The peak serum level (C_{max}) was seen to decrease progressively on increasing infusion time. The maximum value of C_{max} was obtained after administration of the antibiotic by single bolus injection with an average value of 18.297 ± 9.694 μg/ml, while the minimum value was obtained after intravenous infusion over 1 hour, with an average value of 6.597 ± 1.250 μg/ml. A series of linear relationships was established between different pharmacokinetic parameters and the infusion time and a decrease was observed in the pharmacokinetic parameters α, K_{12}, K_{21} and K_{13} when the infusion time was increased. Changes were also observed in the distribution kinetics of dibekacin in the rabbit on varying the infusion conditions, suggesting alterations in the access and permanence of the antibiotic in tissues.

Parenteral administration of aminoglycoside antibiotics permits the use of several administration routes, the most frequently employed of which are intramuscular (im) injection and intravenous (iv) infusion[1]. Several workers have analyzed the relative advantages and disadvantages of the administration of such antibiotics by rapid and slow infusion rates in terms of clinical efficiency, toxicity, *etc.*...[2]. However, the literature contains few references to the possible alterations in the pharmacokinetic behavior of drugs as a consequence of the characteristics of the iv infusion employed for administration. Studies on the administration of aminoglycoside drugs, carried out on experimental animals and in clinical practice, reveal changes in the tissue levels of such antibiotics which are governed by the conditions of administration, implying possible alterations in their distribution kinetics.[2]

Dibekacin is a semisynthetic aminoglycoside antibiotic[3] with important relative advantages compared with the other drugs of its group in terms of a reduced appearance of resistances[4,5] and its high clinical efficiency against Gram-negative organisms of the *Pseudomonas* type[5,6].

Earlier kinetic studies carried out after iv infusion of this antibiotic have used different kinetic models to characterize the evolution of its serum levels when changes are made in the time of iv infusion[7,8] and it would seem justifiable to study the pharmacokinetic behavior of dibekacin in terms of distribution and elimination in circumstances where the infusion conditions are modified.

Materials and Methods

Antibiotic

The antibiotic used was dibekacin (Decabicin, Abelló, S.A., Madrid) in 100 mg vials.

Animals

The study was carried out on 28 healthy male NZ rabbits with a weight range of $1.3 \sim 2.9$ kg. All animals fasted for 24 hours prior to the start of the study, though water was provided "*ad libitum*".

The animals were divided into 5 groups for the study of dibekacin kinetics at different infusion times.

Group 1. Kinetic study of dibekacin after bolus iv administration (n=8).

Group 2. Kinetic study of dibekacin after iv infusion of 2 mg/kg over 5 minutes (n=5).

Group 3. Kinetic study of dibekacin after iv infusion of 2 mg/kg over 15 minutes (n=5).

Group 4. Kinetic study of dibekacin after iv infusion of 2 mg/kg over 30 minutes (n=5).

Group 5. Kinetic study of dibekacin after iv infusion of 2 mg/kg over 60 minutes (n=5).

Administration of the Antibiotic and Collection of Samples

All animals received a single iv dose of the drug; bolus type in the first group and by iv infusion of varying duration in the other four. For such infusion a Panlab-63L-607 infusion pump was used equipped with a 60-ml Plastipak syringe to contain the antibiotic. Administration of the antibiotic and sample collection was through marginal ear veins from the animals when conscious.

For all the animals studied, the collection of blood samples was carried out at the following times: 0, 5, 15, 30, 45 minutes and 1, 2, 4 and 6 hours after infusion had ended.

Serum was obtained by centrifuging the blood samples and was frozen at $-20°C$ prior to determination.

Analytic Technique

The determination of dibekacin in serum was carried out by an agar diffusion method with *Bacillus subtilis* (ATCC 6633) as the assay organism[9].

Standard curves of dibekacin were prepared in rabbit serum with concentrations ranging between $0.25 \sim 50$ μg/ml. The detection limit of the method was 0.1 μg/ml and the intragroup variation coefficient was less than 5%.

Pharmacokinetic Analysis

After iv infusion of dibekacin the concentrations of the drug in serum evolve according to the behavior shown by monoexponential and biexponential drugs as a function of the infusion time.

In groups $1 \sim 3$ the biexponential model was used for the analysis of the experimental results, while in the others (groups 4 and 5), the monoexponential model was used.

The pharmacokinetic analyses of the serum dibekacin levels in all cases employed a non-linear regression program based on the iterative method of GAUSS-NEWTON, using HARTLEY's modification[10]. The calculations were carried out on a Hewlett-Packard-85 computer.

The pharmacokinetic parameters corresponding to both models were calculated using the equations described elsewhere[11,12,13]. In the rabbits in which the monoexponential model was used, the following pharmacokinetic parameters were calculated: C_{max}, peak serum level at the end of infusion; K_e, the elimination constant; $t_{1/2}$, serum half-life; Cl_s, serum clearance and Vd_{area}, apparent distribution volume. For the biexponential model the following parameters were calculated; α, the rapid disposition constant; β, the slow disposition constant; $t_{1/2}\beta$, serum half-life of the slow disposition phase; K_{12}, distribution constant between the central and peripheral compartments; K_{21}, distribution constant between the peripheral and central compartments; K_{13}, the elimination constant; Vd_{area}, the apparent distribution volume; Vd_{ss}, the apparent distribution volume at steady-state; AUC, the area under the curve of serum levels and Cl_s, serum clearance.

The maximum concentration in serum reached for each infusion time was predicted from the average pharmacokinetic parameters obtained by single iv injection on the basis of the following equation[14]:

$$C_{max}=\frac{A_0}{\alpha \cdot T}(1-e^{-\alpha \cdot T})+\frac{B_0}{\beta \cdot T}(1-e^{-\beta \cdot T}) \quad (1)$$

where A_0 and B_0 are the coefficients of the biexponential equation defining the variation in the serum concentrations of dibekacin after administration by single injection in the rabbit and T represents the infusion time employed in each case.

The statistical analysis of the results was obtained using Student's "t" test[15].

Results

Figs. 1 and 2 show the mean serum level curves of dibekacin obtained in the 5 groups of rabbits studied. The corresponding average pharmacokinetic parameters obtained by applying the monoexponential and biexponential models are shown in Table 1.

The results reveal a decrease in the biexponential nature of the serum level curves which parallels the increase in infusion time (T) with a monoexponential plot in the descending part of the serum curves when infusion time is equal to or greater than 30 minutes.

The elimination capacity of dibekacin expressed as the half-life undergoes certain variations in the various groups studied, and there is no correlation between this pharmacokinetic parameter and infusion time. After administration by bolus injection, the $t_{1/2}\beta$ of dibekacin was seen to have an

Fig. 1. Average serum concentrations of dibekacin in groups 1~3 at a dose of 2 mg/kg.
Mean $\bar{X}$ ±SD; group 1, n=8; group 2 and 3, n=5.

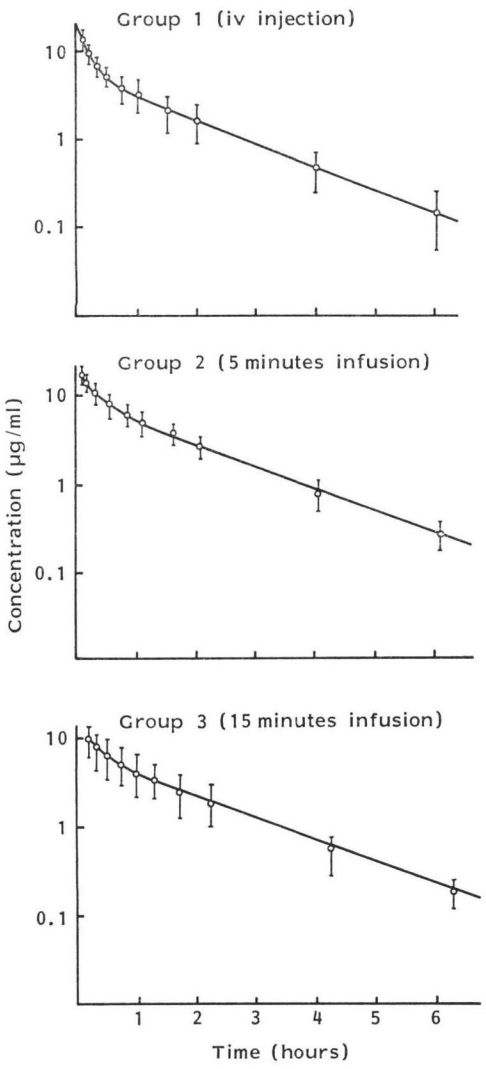


Fig. 2. Average serum concentrations of dibekacin in groups 4 and 5 at a dose of 2 mg/kg.
Mean $\bar{X}$±SD; n=5.

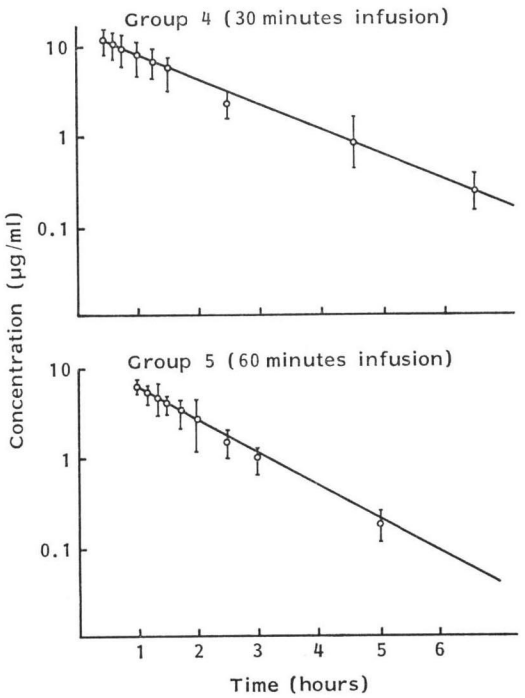


Fig. 3. Linear relationship established between the rapid disposition constant (α) and the infusion time (T).

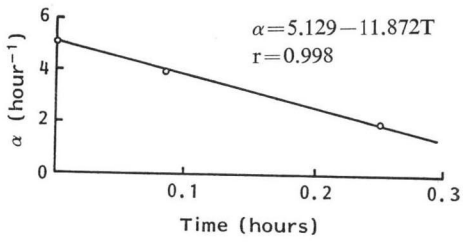


Table 1. Average pharmacokinetic parameters of dibekacin obtained in the five groups of rabbits studied.

	Group 1	Group 2	Group 3
C_{max} (μg/ml)	18.297±9.694	16.799±2.716	9.969±4.618
α (hour^{-1})	5.192±2.987	4.049±1.976	2.193±1.850
β (hour^{-1})	0.659±0.126	0.547±0.134	0.434±0.101
$t_{1/2}\beta$ (hour)	1.083±0.203	1.354±0.454	1.663±0.377
K_{12} (hour^{-1})	2.086±1.082	1.415±0.952	0.331±0.250
K_{21} (hour^{-1})	1.980±1.082	2.071±1.082	1.390±1.824
K_{13} (hour^{-1})	1.785±0.890	1.109±0.243	0.905±0.212
Vd_{ss} (l)	0.403±0.083	0.292±0.031	0.602±0.244
Vd_{area} (l)	0.547±0.205	0.384±0.107	0.989±0.553
Cl_s (l/hour)	0.359±0.112	0.202±0.039	0.387±0.156
(AUC) hour (μg/ml)	10.568±3.174	18.956±4.368	13.104±6.480
	Group 4	Group 5	
C_{max} (μg/ml)	12.611±5.336	6.597±1.230	
K_e (hour^{-1})	0.639±0.139	0.876±0.073	
$t_{1/2}$ (hour)	1.163±0.341	0.795±0.066	
Vd_{area} (l)	0.345±0.168	0.411±0.189	
Cl_s (l/hour)	0.203±0.047	0.361±0.171	
(AUC) hour (μg/ml)	20.267±5.201	10.798±3.101	

average value of 1.083±0.203 hours. With respect to this group, statistically significant differences may be observed in the value of $t_{1/2}\beta$ obtained when infusion time was 15 minutes; ($t_{1/2}\beta$ 1.663±0.377 hours) ($P<0.01$) and when it was 1 hour; ($t_{1/2}\beta$=0.795±0.066) ($P<0.02$). The differences observed between groups 1 and 5 may be attributed to the kinetic model employed, while between groups 1 and 3 they may be accounted for by the statistical size of the populations studied.

In the group of rabbits where the distribution of the antibiotic is dealt with biexponentially, modifications may be observed in the various parameters parallel to the variation in infusion time.

The rapid disposition constant (α) which defines the initial variation in serum levels, due to transport to peripheral tissues, decreases progressively with the increase in infusion time (Fig. 3). The maximum value obtained for this constant was in group 1, comprised of rabbits receiving the drug by bolus iv injection, with an average value of 5.192±2.987 hour^{-1} and the minimum value when infusion lasted 15 minutes, with an average value of 2.193±1.850 hour^{-1}; the difference observed is statistically significant ($P<0.05$).

Similar variations were observed on increasing infusion time for other pharmacokinetic parameters.

Table 2 shows a series of linear relationships established between the mean value of different pharmacokinetic parameters for each of the groups studied and infusion time. These results show the existence of a progressive decrease of the different rate constants defining the biexponential kinetic model — when infusion conditions are modified.

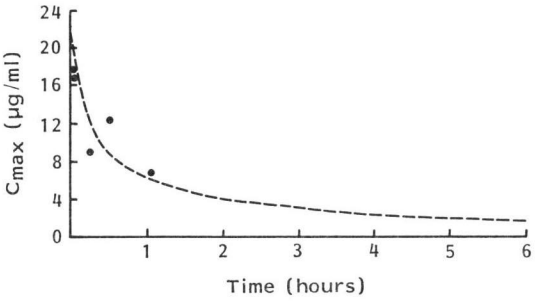
On the basis of the equation obtained for the rapid disposition constant (α), this becomes null for an infusion time (T) of 0.432 hour, implying that for infusion periods greater than this a loss of biexponentiallity should be observed in the serum level curve, thereby justifying the use of a monoexponential model for the kinetic analysis of the results. In our study, the results obtained when infusion time was 0.5 and 1.0 hour could not be fitted statistically to biexponential kinetics and therefore the monoexponential model was used.

Table 2. Linear relationship established between various pharmacokinetic parameters and infusion time.

α	(hour^{-1})=5.129−11.872T (hour)	r=0.998
K_{12}	(hour^{-1})=2.049− 6.943T (hour)	r=0.998
K_{21}	(hour^{-1})=2.103− 2.599T (hour)	r=0.898
K_{13}	(hour^{-1})=1.621− 3.189T (hour)	r=0.881

(n=3)

Fig. 4. Variation in the predicted peak serum levels (C_{max}) of dibekacin *versus* infusion time (dashed line) and mean peak serum levels obtained experimentally (black points).



Several authors appearing in the literature use a single model for the kinetic analysis of serum dibekacin concentrations when administered by infusion lasting more than 0.5 hour to humans[8] agreeing with the results obtained in this study.

The maximum serum concentration (C_{max}) undergoes a progressive decrease which parallels the increase in infusion time (T). Fig. 4 shows the variation in the values of C_{max} which are predictable from the pharmacokinetic constants obtained after a single iv injection of dibekacin by using equation (1), together with the mean values obtained experimentally in each group of rabbits studied. The highest C_{max} value obtained experimentally was in group 1, corresponding to the single iv bolus injection of the antibiotic, with an average value of 18.297±9.694 μg/ml and the lowest to group 5, with infusions of 1 hour and an average value of 6.597±1.230 μg/ml, implying a decrease of 63.9% in the value of this parameter.

The apparent distribution volume of dibekacin (Vd_{area}) obtained with different infusion rates showed statistically significant differences compared with the values obtained after bolus iv injection when infusion time was 5 minutes ($P<0.10$); 15 minutes ($P<0.05$) and 30 minutes ($P<0.05$) though no statistically significant differences were observed when infusion time was 1 hour ($P>0.20$).

Similarly, in the group of rabbits where a biexponential kinetic model was used, the apparent distribution volume at steady-state (Vd_{ss}) showed significant variations. Compared with group 1, the Vd_{ss} shows statistically significant differences when infusion time was 5 minutes ($P<0.02$) and 15 minutes ($P<0.05$).

For the two values of the apparent distribution volume, no type of correlation could be observed with infusion time in spite of the statistical variations observed.

Discussion

Frequently, aminoglycoside antibiotics are administered by iv infusion in order to maintain serum concentrations within the desired therapeutic interval, thereby obtaining maximum clinical efficiency and lowering the risk of toxic effects[1].

It is generally accepted that the controlled administration of a drug by intravenous infusion over a previously programmed period (T) permits us to predict the serum concentrations reached during infusion time[16]. The work described by MORGAN and RAYMOND[14] shows that in drugs which follow monoexponential kinetics the serum concentrations reached as well as the duration of the pharmacological effect for a given infusion time may be predicted with relative ease. In drugs with multi-exponential kinetics, however, it is difficult to predict such information owing to the intervention of many different factors, particularly the parameters defining the distribution of the drug.

In the case of dibekacin the results obtained after bolus iv administration show that the relationship α/β for this antibiotic is 7.878 and the relative contribution of the rapid disposition phase (A_0/α)

to the AUC of serum levels is 25% after administration by single injection. Consequently, and in agreement with MORGAN's postulate[17], the variation in the peak serum level of dibekacin in the rabbit when administered by iv infusion will depend not only on the relationship $T/t_{1/2}$ but also on the parameters A_0, α, B_0 and β, depending on the kinetic model used to determine the disappearance of the antibiotic.

If, in the case of dibekacin, we consider a progressive modification of the pharmacokinetic parameters with infusion time (T), in particular the constant α, it is likely that there will be a correlation, though poor, between the peak serum level (C_{max}) and infusion time (T), as shown in Fig. 4, obtained from the experimental determination of the values of C_{max} for different infusion times.

The variation in C_{max} as a function of the infusion time (T) is of considerable toxicological interest in drugs like dibekacin since, as one is dealing in this particular case with an aminoglycoside antibiotic, the maximum serum concentrations reached after each administration should be maintained at values lower than the maximum levels tolerated[2]. Furthermore, because dibekacin is an antibiotic, it is necessary to consider the importance of the relationship of the peak serum level (C_{max}) reached and the minimum inhibitory concentration (MIC) of the antibiotic (C_{max}/MIC) as described in a previous study[18]. The possible variation in such a relationship on modifying infusion time (T) could affect the therapeutic efficiency of the antibiotic when used in a clinical situation assuming that the changes in human kinetics are similar to those observed in the rabbit.

The variation observed in the parameters defining the distribution of the antibiotic as a function of T and, in particular, the apparent distribution volumes, implies changes in the access and permanence of dibekacin in several organs and tissues which in turn might be of therapeutic importance in terms of the use of this drug by infusion in hospital practice. The changes observed in the distribution kinetics of the antibiotic could be accounted for as a variation in tissular retention of the drug *versus* infusion time.

Various authors[19,20] have observed different toxicological effects after the administration of gentamicin and tobramycin by iv infusion compared with iv bolus injection. Considering the relationship between the toxicological effects and the tissue concentrations of aminoglycoside drugs, we may assume variations in these latter on modifying the infusion time.

The results obtained in the present study reveal alterations in the serum levels and in the parameters defining the distribution of dibekacin with respect to infusion time, making it difficult to predict the serum levels of the antibiotic on varying the conditions of infusion since one is dealing with a multicompartmental model.

This possibility, however, would require further studies on tissue distribution, since the modifications observed in the apparent distribution volumes may be related, at least partially, to interindividual alterations in the pharmacokinetic parameters.

Appendix

The choice of the kinetic model used in each case was based on statistical criteria according to AKAIKE's information criterion (AIC) which uses the minimum value of AIC when the concentration-time values are fitted to a different number of exponential terms[21].

Single Compartment Open Kinetic Model

The equations describing the evolution of the serum levels of dibekacin after iv infusion are the following:

$$C=\frac{(D/T)}{Vd\cdot K_e}(1-e^{-K_e\cdot t}) \quad \text{infusion period} \tag{1}$$

$$C=\frac{(D/T)}{Vd\cdot K_e}(1-e^{-K_e\cdot T})e^{-K_e\cdot t'} \quad \text{post infusion period} \tag{2}$$

Once the general equation for the curve had been characterized the pharmacokinetic parameters derived were calculated on the basis of the following equations:

$$t_{1/2}=\ln 2/K_e \tag{3}$$

$$Vd_{area}=\frac{Dosis}{AUC\cdot K_e} \tag{4}$$

$$Cl_s=Vd\cdot K_e \tag{5}$$

Two-compartment Open Kinetic Model

The equations characterizing the evolution of serum levels of dibekacin after iv administration are the following:

$$\text{iv injection: } C=A_0\cdot e^{-\alpha\cdot t}+B_0\cdot e^{-\beta\cdot t} \tag{6}$$

$$\text{iv infusion: } C=\frac{(D/T)}{V_c\cdot K_{13}}\left(1+\frac{\beta-K_{13}}{\alpha-\beta}e^{-\alpha\cdot t}+\frac{K_{13}-\alpha}{\alpha-\beta}e^{-\beta\cdot t}\right) \quad \text{infusion period} \tag{7}$$

$$C=Re^{-\alpha\cdot t'}+Se^{-\beta\cdot t'} \quad \text{post infusion period} \tag{8}$$

$$R=\frac{(D/T)(\alpha-\beta)(1-e^{-\beta\cdot T})}{V_c(\alpha-\beta)\alpha} \tag{9}$$

$$S=\frac{(D/T)(K_{21}-\beta)(1-e^{-\beta\cdot T})}{V_c(\alpha-\beta)\beta} \tag{10}$$

The coefficients R and S are related to A_0 and B_0 on the basis of the following equations:

$$A_0=\frac{R\cdot D\cdot\alpha}{(D/T)(1-e^{-\alpha\cdot T})} \tag{11}$$

$$B_0=\frac{S\cdot D\cdot\beta}{(D/T)(1-e^{-\beta\cdot T})} \tag{12}$$

In both kinds of administration the pharmacokinetic parameters A_0, B_0, α, and β were calculated by a non-linear regression program obtaining the pharmacokinetic parameters derived from the following equations:

$$t_{1/2}\beta=\frac{Ln\ 2}{\beta} \tag{13}$$

$$K_{12}=\frac{A_0\cdot B_0(\alpha-\beta)^2}{C_0(A_0\beta+B_0\alpha)} \tag{14}$$

$$K_{21}=\frac{A_0\beta+B_0\alpha}{C_0} \tag{15}$$

$$K_{13}=\frac{C_0\cdot\alpha\cdot\beta}{A_0\beta+B_0\alpha} \tag{16}$$

$$Vd_{ss}=V_c\frac{K_{12}+K_{21}}{K_{21}} \tag{17}$$

$$Vd_{area}=\frac{D}{\beta\cdot AUC} \tag{18}$$

$$Cl_s=V_c\cdot K_{13} \tag{19}$$

The area under the curve of the serum levels were calculated by the trapezoidal rule.

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