A DISCRIMINATORY STUDY OF A PHARMACOKINETIC MODEL FOR INTRAMUSCULAR GENTAMICIN IN SHEEP

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ABSTRACT

Errecalde, J.O. and Mariño, E.L., 1990. A discriminatory study of a pharmacokinetic model for intramuscular gentamicin in sheep. *Veterinary Research Communications*, 14 (1), 53–58

The resulting serum concentrations were measured in six ewes after intramuscular administration of 10 mg/kg of gentamicin. The model providing the best fit for the experimental data was determined both by linear regression analysis between the experimental and theoretical values and by means of the Minimum Akaike Information Criterion Estimation (MAICE) test.

Linear regression analysis showed certain differences favouring the monocompartmental model although the advantage was not conclusive. The MAICE test, however, permitted a clear discrimination in favour of the same model. When linear regression analysis is not conclusive, the MAICE test represents a good alternative.

Keywords: gentamicin, models, pharmacokinetics, sheep

INTRODUCTION

The pharmacokinetics of the aminoglycoside antibiotics have been widely studied. Although mono-, bi- and tricompartmental models have been used to describe their intravenous kinetic behaviour in man and some animals, in studies on extravascular routes of administration only monocompartmental models have been employed (Schentag *et al.*, 1977; Baggot, 1978; Pedersoli and Belmonte, 1980; Baggot *et al.*, 1981; Adelman *et al.*, 1982; Brown *et al.*, 1985). No details on model discrimination procedures are supplied in these papers.

Discrimination of the best fitting model for a data set is a major pharmacokinetic problem. The choice of the model providing the smallest residuals between the last data points and values estimated by means of mono-, bi-, tri- or tetra-exponential equations is one of the most popular methods of discrimination. The residual sum of squares provides another tool for discrimination, although its tendency is to favour complicated models; goodness of fit can be checked through analysis of variance. The F test has been proposed by Boxenbaum *et al.* (1974) to determine the number of parameters. Linear regression analysis between the experimental and theoretical concentrations obtained by using mono-, bi- or tricompartmental models at the different sampling times represents another approach. The Minimum Akaike Information Criterion Estimation (MAICE) test is a statistical approach which discriminates among models with similar sums of squares, picking out the one with

the smallest number of parameters, according to the 'principle of parsimony' (Yamahoka et al., 1978).

The aim of the present study was to determine the most representative model for the plasma concentration versus time curves obtained after administration of gentamicin by the intramuscular (i.m.) route in sheep and to use this for comparison of two different discrimination procedures.

MATERIALS AND METHODS

Six adult, healthy ewes weighing 43 ± 9 kg were used. Anthelmintic treatment was administered 20 days prior to the start of the trial.

A polyethylene catheter was placed in the right jugular vein and two blood samples were drawn from each sheep before starting the experiment. 10 mg/kg gentamicin was administered intramuscularly in the ischiotibial zone to each sheep. Subsequently, blood samples were drawn at the following times after injection: 10, 15, 20, 30 and 40 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10 and 12 h. The samples were allowed to coagulate at room temperature and the serum was separated and stored at −20°C until assay.

Gentamicin concentrations were determined microbiologically using a modified cylinder-plate diffusion method (Grove and Randall, 1955), the test organism being *Bacillus subtilis* ATCC 6633 and the culture medium being antibiotic medium no. 2 (Difco).

Discrimination between the models shown in Figure 1 was performed by using the Akaike Information Criterion (AIC) (Akaike, 1973a, 1973b, 1976) and its adaptation defined for model discrimination by Yamahoka et al. (1978) in the MAICE test. The Akaike criterion is defined by the following expression:

$$AIC = N \ln Re + 2p$$

where N is the number of data points, p is the number of parameters and $\ln Re$ is the natural logarithm of Re, the sum of squares of the residual values between the experimental and estimated concentrations, as expressed by

$$Re = \sum_{i=1}^{n} Wi \, (C \, est \, i - C \, exp \, i)^2$$

where $C \, est \, i$ is the estimated concentration, $C \, exp \, i$ is the experimental concentration and Wi is the weighting factor for each datum i.

The estimations of the kinetic parameters, of the residual sum of squares and of the theoretical concentrations at the different sampling times according to the different models were performed by non-linear regression analysis using a specially designed parameter identification program, which uses the differential equation belonging to each model and the 'simplex' method of direct search (D'Argenio and Schumitzky, 1979).
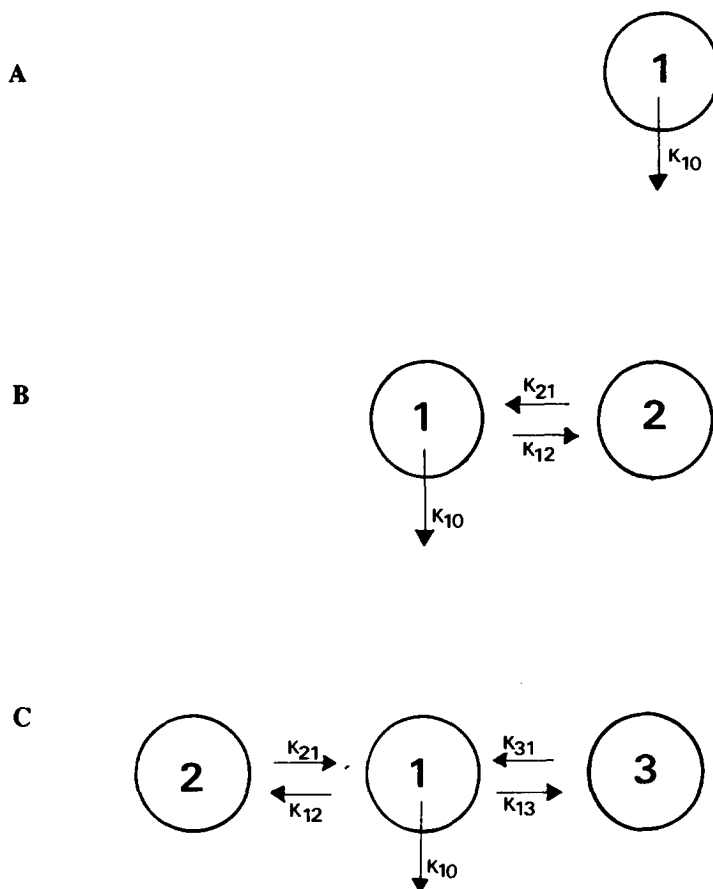
Figure 1. Representation of the monocompartmental (A), bicompartmental (B) and tricompartmental (C) pharmacokinetic models. In A, 1 is the unique compartment in which the drug distributes homogeneously. In B, 1 is the central compartment and 2 is the peripheral compartment. In C, 1 is the central compartment, 2 is a shallow peripheral compartment (rapid rate of exchange with 1) and 3 is a deep peripheral compartment (slow rate of exchange with 1). Intercompartmental flows and elimination flows are represented by their microconstants (K_{12}, K_{21}, K_{13}, K_{31} and K_{10}).

Another discrimination was performed by linear regression analysis between the experimental and theoretical concentrations obtained using mono-, bi- or tricompartmental models at the different sampling times. In this way, values for the correlation coefficient (r), y intercept term and slope were obtained for any model. The model which yielded an r value nearest to 1, a y intercept nearest to 0 and a slope nearest to 1 was regarded as the most representative. Differences between models were checked by analysis of variance (ANOVA) (Clarke, 1980).

RESULTS

The mean values and their standard deviations for the pharmacokinetic micro-constants are given in Table I. AIC values obtained by using mono-, bi- and tricompartmental models are presented in Table II. The results of the linear regression analysis, the y intercepts, slopes and standard errors of the estimates of the mean values are displayed in Table III.

TABLE I
Pharmacokinetic microconstants obtained by non-linear regression analysis using mono- (1), bi- (2) and triexponential (3) expressions

Parameter	1	2	3
K_{ab}	4.01 ± 1.11	3.49 ± 1.09	3.51 ± 1.36
K_{12}	–	0.21 ± 0.37	0.38 ± 0.57
K_{21}	–	0.16 ± 0.32	0.33 ± 0.42
K_{13}	–	–	0.04 ± 0.08
K_{31}	–	–	0.01 ± 0.01
K_{10}	0.30 ± 0.08	0.30 ± 0.12	0.33 ± 0.13

TABLE II
Values of Akaike Information Criterion (AIC) obtained by applying the MAICE test. 1: monocompartmental model; 2: bicompartmental model; 3: tricompartmental model

Animal No.	1	2	3
1	97.42	101.43	105.43
2	68.04	92.74	76.06
3	96.33	99.35	97.19
4	116.32	119.08	121.08
5	122.27	126.27	130.28
6	102.04	105.83	109.91

TABLE III

Slopes and y intercepts after regression analysis between experimental and theoretical values obtained by using mono- (A), bi- (B) and triexponential (C) equations

Animal No.	Slope			y intercept		
	A	B	C	A	B	C
1	1.00	1.00	1.00	−0.03	−0.04	−0.04
2	1.03	1.03	1.03	−0.44	−0.44	−0.45
3	1.00	1.03	1.04	−0.06	−0.34	−0.53
4	1.04	1.08	1.08	−0.79	−1.51	−1.51
5	1.19	1.19	1.19	−2.85	−2.87	−2.85
6	1.03	1.04	1.04	−0.79	−1.00	−0.86
$\bar{x}$	1.05	1.06	1.06	−0.83	−1.03	−1.04
SEE	0.029	0.028	0.027	0.43	0.43	0.41

$\bar{x}$: mean; SEE: standard error of the estimated mean. Analysis of variance demonstrated that the differences between slopes and between intersections were not significant.

DISCUSSION

The application of the MAICE test clearly discriminates a monocompartmental model (Table II). Correlation coefficients are acceptable in all cases. The intercepts on the y axis calculated from monoexponential data are the nearest to zero value with the exceptions of animals 2 and 5, where the y intercepts calculated from biexponentially and triexponentially obtained data respectively yielded values similar to those obtained monoexponentially (see Table III). The values of the slopes were similar in animals 1, 2 and 5, but were nearer to 1 when monoexponentially obtained data was used in animals 3, 4 and 6.

The conclusion drawn was that the results from the MAICE test and those from linear regression analysis both indicated that the kinetics of i.m. gentamicin should be described monoexponentially. The differences shown by linear regression were, however, inconclusive because ANOVA did not demonstrate any statistical significance among them. When the MAICE test was applied, the monocompartmental model was clearly preferred. Thus, when linear regression analysis does not discriminate adequately between such models, the MAICE test presents a useful additional procedure.

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