THREE-COMPARTMENT OPEN MODEL ANALYSIS OF MICRONOMICIN IN MAN

MAKOTO WATANABE,* NOBUYOSHI KANENIWA,** MITSUO MATSUMOTO*** AND KEIMEI MASHIMO****

School of Pharmaceutical Sciences, Showa University,* ** 1-5-8 Hatanodai, Shinagawa-ku, Tokyo, 142, Japan, Showa College of Pharmaceutical Sciences,*** 5-1-8 Turumaki-cho, Setagaya-ku, Tokyo, 154, Japan
Department of Internal Medicine,**** and Department of Pharmacy, * Tokyo Kosei Nenkin Hospital, 23 Tukudo-cho, Shinjuku-ku, Tokyo, Japan

(Received December 18, 1985)

The pharmacokinetics of micronomicin (MCR) as a model drug of aminoglycoside antibiotics (AGs) was studied in man by applying our results previously obtained in rats. Three-compartment open model analysis of combined serum and total body store (T.B.S.) data obtained from multiple dosing in man was done using a non-linear least-squares regression program MULTI. We found large individual variations of MCR disposition in man and these variations did not appear within the serum concentration range measurable with conventional assay methods. This finding suggests that the disposition of AGs, included MCR, cannot be estimated by only plasma or serum level analyses. We conclude that the therapeutic drug monitoring of AGs by using T.B.S. data analysis should be an effective method for controlling therapy with AGs in the clinical setting.

Keywords — micronomicin; aminoglycoside; pharmacokinetics; three-compartment open model; man; total body store; individual variation; therapeutic drug monitoring

INTRODUCTION

Aminoglycoside antibiotics (AGs) are effective for treating severe infections due to certain gram-negative bacilli, but these agents must be carefully monitored in clinical practice because of their nephro-, or ototoxicity.1) Most pharmacokinetic studies aimed at developing effective and safe dosage regimens for AGs have been based on plasma or serum levels.2) However, clinically, nephrotoxicity is sometimes observed during prolonged administration even when dosage schedules derived from plasma or serum level analysis are used.3)

We have already studied micronomicin (MCR)4) as a model drug of AGs in rats and reported the following results.5) It was concluded that the disposition of MCR in rats could be better described by the three-compartment open model than by the one- or two-compartment open model and the amount of drug in the deep compartment was proportional to the kidney concentration of MCR. This three-compartment open model analysis was easily performed by using the total body store (T.B.S.: dose minus urinary recovery) data.

In this study, we analyzed the disposition of MCR in man by applying the results obtained in rats.

TABLE I. Background of Healthy Volunteers

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Name</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Height (m)</th>
<th>Body weight (kg)</th>
<th>Body surface area (m²)</th>
<th>Creatinine clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T.Y.</td>
<td></td>
<td>23</td>
<td>1.84</td>
<td>62</td>
<td>1.81</td>
<td>87.6</td>
</tr>
<tr>
<td>2</td>
<td>K.W.</td>
<td></td>
<td>23</td>
<td>1.81</td>
<td>62</td>
<td>1.78</td>
<td>83.9</td>
</tr>
<tr>
<td>3</td>
<td>R.U.</td>
<td></td>
<td>20</td>
<td>1.62</td>
<td>55</td>
<td>1.56</td>
<td>100.0</td>
</tr>
<tr>
<td>4</td>
<td>M.S.</td>
<td></td>
<td>26</td>
<td>1.69</td>
<td>60</td>
<td>1.67</td>
<td>110.4</td>
</tr>
</tbody>
</table>
MATERIALS AND METHODS

Analysis Data — Data were taken from a report on an MCR phase I study with intravenous infusion. In the phase I study, four healthy volunteers (Table I), who gave their informed consent were given 60 mg of MCR by intravenous infusion for 1 h, twice daily (dosage interval: 12 h) for 5 d (total of 9 infusions) under a condition of hospitalization, and the concentrations of MCR in serum and urine were measured by using a high-performance liquid chromatographic method. The data used in this study were serum level and T.B.S.

Pharmacokinetic Analysis — Non-linear least-squares regression method (weight=1) was done by using the MULTI program adapted to a Casio personal computer, type FP-1100 (Casio computer Co. Ltd., Tokyo).

The curve fitting of all 5 days data was carried out simultaneously by applying the following Eqs 1 and 2.

For serum level data,

\[ C_N = \frac{3}{\sum_{t=1}^{3} A_l} \frac{1}{\lambda_l T} \left( 1 - e^{-\lambda_l T} \right) \left( 1 - e^{-\lambda_l \tau} \right) e^{-\lambda_l \tau'} \]

(1)

for T.B.S. data,

\[ T.B.S. = \sum_{l=1}^{3} A_l \frac{k^l e^{V_c}}{\lambda_l T} \frac{1}{\lambda_l T} \left( 1 - e^{-\lambda_l T} \right) \left( 1 - e^{-\lambda_l \tau} \right) e^{-\lambda_l \tau'} \]

(2)

where \( C_N \) and T.B.S. are serum concentration and T.B.S. at time \( t \), which is the time after the end of the \( N \)th infusion, \( A_l \) is the coefficients of two Eqs. 1 and 2, respectively and the exponent of model, dosage interval and infusion time are indicated by \( \lambda, \tau \) and \( T \). Eq. 1 was obtained from a multi-dosing equation of IV infusion (p. 130 in ref. 9) by substituting of \( A_l \) (Eq. 2.8 in ref. 9) and \( k_0 = k_0^l / T \) for \( R_l \) (\( R_l \): coefficient of equation in multiple-dosing, \( k_0^l \): infusion rate). Eq. 2 was obtained by rearrangement of the Eq. 1 using the sigma-minus method (pp. 56—59 in ref. 9). The pharmacokinetic constants and the apparent volume of the central compartment (\( V_c \)) were calculated by using the equations assuming a three-compartment model (pp. 92—97 in ref. 9) and the volume of distribution at steady-state (\( V_{ss} \)) was calculated by the equation 2.234 in ref. 9.

![Graphs showing curve fitting of Micrornomicin Level in 4 Volunteers Based on a Three-Compartment Open Model](image.png)

FIG. 1. Curve Fitting of Micrornomicin Level in 4 Volunteers Based on a Three-Compartment Open Model
— ○ —, serum level (μg/ml); — ● —, T.B.S. (mg).
RESULTS

Curve fitting of serum level and T.B.S. with a three-compartment open model coincided well with the observed data obtained from each volunteer (Fig. 1). Large individual variations in the terminal phase were found by comparing the disposition of MCR in 4 volunteers. However, these variations could not be found by serum level analysis alone, because they occur below the assay limit and could only be identified by

**FIG. 2.** Regular Plot of Serum and T.B.S. Data

●, mean ± S.D.

| TABLE II. MCR Pharmacokinetic Parameters<sup>a)</sup> in 4 Volunteers |
|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                    | \( A_1 \) (mg/l)    | \( A_2 \) (mg/l)    | \( A_3 \) (mg/l)    | \( \lambda_1 \) (h<sup>-1</sup>) | \( \lambda_2 \) (h<sup>-1</sup>) | \( \lambda_3 \) (h<sup>-1</sup>) | \( k'eV_c \) (l/h) |
| 1                   | 5.41               | 4.72               | 0.019              | 5.898               | 0.947               | 0.007               | 8.646               |
| 2                   | 5.27               | 4.84               | 0.184              | 3.970               | 1.074               | 0.024               | 6.549               |
| 3                   | 15.80              | 3.94               | 0.005              | 9.936               | 0.438               | 0.001               | 3.875               |
| 4                   | 0.71               | 5.06               | 0.037              | 3.657               | 0.694               | 0.011               | 6.580               |
| Mean                | 6.80               | 4.64               | 0.061              | 5.865               | 0.788               | 0.011               | 6.413               |
| S.D.                | 6.39               | 0.49               | 0.083              | 2.889               | 0.282               | 0.010               | 1.956               |
| \( k_{12} \) (h<sup>-1</sup>) | \( k_{21} \) (h<sup>-1</sup>) | \( k_{13} \) (h<sup>-1</sup>) | \( k_{31} \) (h<sup>-1</sup>) | \( k_{10} \) (h<sup>-1</sup>) | \( V_c \) (l/kg) | \( V_{ss} \) (l/kg) |
| 1                   | 1.875              | 3.258              | 0.560              | 0.010               | 1.150               | 0.09                | 5.66                |
| 2                   | 0.857              | 2.476              | 0.924              | 0.054               | 0.757               | 0.09                | 1.74                |
| 3                   | 6.178              | 2.335              | 0.457              | 0.002               | 1.403               | 0.06                | 14.00               |
| 4                   | 0.287              | 3.294              | 0.227              | 0.016               | 0.539               | 0.17                | 2.62                |
| Mean                | 2.299              | 2.841              | 0.542              | 0.021               | 0.962               | 0.10                | 6.01                |
| S.D.                | 2.668              | 0.506              | 0.290              | 0.023               | 0.388               | 0.05                | 5.59                |

<sup>a)</sup> \( k'e \) is the apparent first-order rate constant for renal excretion, and other parameters:

```
  \[ 2 \quad k_{12} \quad 1 \quad \quad 1 \quad k_{13} \quad 3 \quad k_{21} \quad \quad 1 \quad k_{31} \quad k_{10} \]
```
analysis of the combination of serum and T.B.S. data. Figure 2 shows the regular plot of serum and T.B.S. data (mean ± S.D.). In this figure, the plot of serum level suggested a steady-state with little individual variation. On the other hand, the plot of the T.B.S. data showed large individual variations and corresponded to the form of accumulation.

The pharmacokinetic parameters of MCR obtained from Eq. 1 and 2 are shown in Table II; the large variations are reflected in the standard deviations.

DISCUSSION
Aminoglycoside antibiotics, which offer high degrees of both benefit and risk, have been studied to determine a basis for rational use, and many dosage regimen methods and nomograms have been proposed. However, almost all the dosage regimen evaluations of AGs were based on a one-compartment open model. Matzke et al. showed that nephrotoxicity is sometimes observed during prolonged administration using dosage regimens derived from a one-compartment open model.

Schentag et al. carried out a two-compartment open model analysis of AGs by sampling plasma and urine for about 2 weeks after the end of dosing. They suggested that the nephrotoxicity of AGs is correlated with the tissue content of the drug. Unfortunately, those observations could not be applied clinically, because their analyses should have been done after the end of therapy.

In the previous report, we found that pharmacokinetic analysis of MCR with the three-compartment open model could be easily performed by applying a modification of the sigma minus analysis method to the T.B.S. data. The simulation of multiple dosing based on rat parameters suggested the feasibility of determination of the terminal exponent by analysis of the T.B.S. data combined with serum, plasma or urinary excretion rate data.

In the present study, we applied the three-compartment open model for analysis of MCR in man by using the serum and T.B.S. data during multiple dosing. We found large individual variations, which did not appear within the measurable serum concentration range using conventional assay methods. We consider that the disposition of AGs, including MCR, cannot be estimated only by plasma or serum data analyses.

We conclude that the therapeutic drug monitoring of AGs by using T.B.S. data analysis should be an effective method for controlling therapy with AGs in the clinical setting.

REFERENCES