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PHARMACOKINETICS OF RIBOSTAMYCIN IN HEALTHY VOLUNTEERS
AND PATIENTS WITH IMPAIRED RENAL FUNCTION

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Ribostamycin is an aminoglycoside antibiotic produced by Streptomyces ribosidificus, and extracted and isolated by NIIDA et al. 1,2) It has been used widely clinically with its charac-teristic of low ototoxicity.
UMEMURA et al. studied the pharmacokinetics of this antibiotic in animals and reported that it has a similar pharmacokinetic behavior in vivo to kanamycin. 3)
In the present studies, the pharmacokinetic behavior of ribostamycin was studied in 5 healthy adult volunteers receiving different doses (0.5g,1.0gand1.5g) by intramuscular injection, and 0.5 g by intravenous drip infusion.In addition, a similar study was conducted with11patients with varying degrees of renal dysfunction in order to study the application of ribostamycin in such patients.

Materials and Methods

Healthy volunteers
Five healthy adult volunteers were selected. They were 26-30-year-old males, weighing

Table1.Background of healthy volunteers

Table2.Background of patients with renal disease

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57.5•`70 kg (Table1). The laboratory examinations on the blood and the urine of the volunte-
ers were carried out 3 weeks before the studies, concerning the following items in order to
check for abnormalities: Red blood cell counts, hemoglobin, hematocrit, white blood cell

counts, hemogram, BUN,serum creatinine, S-GOT, S-GPT, Al-P, bilirubin , urinary protein,
sugar, urobilinogen and blood casts.

Patients with impaired renal function
Eleven hospitalized patients with impaired renal function were selected. They had varying
rate of creatinine clearance ranging from 144 to 0 ml/min which was being treated with hemo-
dialysis (Table2).
Administration of ribostamycin
The healthy volunteers were given, in a crossover study,ribostamycin as follows: a single intramuscular in jection of 1 g and 1.5 g; repeated intramuscular injection of 0.5 g 4 times every 8hours; and an intravenous drip infusion of 0.5 g at a constant rate for one hour, dissolving in 250 ml of saline solution. The rate of infusion was controlled by means of Debimatic G (Mei ji Seika), an automatic transfusion controlling device. The intervals between the 4 studies were one week or more. Patients with impaired renal function were administered 0.5 g in a single intramuscular injection.
Sample protocol of blood and urine

In case of a single intramuscular injection, the blood was taken before the injection, and
0.25, 0.5, 1, 2, 4 and 6 hours after injection; in the case of intravenous infusion, it was taken
before infusion, 0.25, 0.5, 1, 1.5, 2, 4 and 6 hours after initiation of the infusion;and in the
case of repeated intramuscular in jection, sampling was conducted after the first injection and
fourth in jection with the same sampling time as in the case of a single injection. Collection
of the urine was carried out 1, 2, 4 and 6 hours after administration in all cases . In the case
of repeated administration of 0.5 g creatinine clearance was determined.
In the patient group, blood samples were collected 5-7 times during the period of one to
48 hours after the administration, depending on the rate of creatinine clearance

.

Serum separated from the blood samples and the urine samples,after determination of the
volume, of each subject were kept at -20•Ž in a freezer for assay

.

Method of assay

Ribostamycin concentrations in the serum and the urine were assayed by the thin-layer cup method using Bacillus subtilis ATCC 6633 as the test organism with a Bacto Antibiotic Medium (pH8.0,Difco).
For assay of serum concentrations, the serum from the healthy volunteers collected before
drug administration was used as the diluent for preparation of the standard solution.
For assay of ribostamycin urinary concentrations, an 1/15 M phosphate buffer solution of

pH 7.8was used as the diluent for the standard solution. The urine samples were diluted
with the buffer mentioned above so that the assay level of ribostamycin fell within the range
of 1.25-100 mcg/ml.
Method of pharmacokinetic analysis

(1)Intramuscular injection
The data were analysed according to the
one-compartment model given in Fig.1(a).
The function of drug administration A(t) for the case of intramuscular administration is described in the following equation.

A(t)=WKƒ¿ƒÃ-Kat...(1)

where W is the dose;Ka is the transport rate
constant of the drug from the administration
site into the blood;and t is the time after
administration.
In general,when the weighing function

Fig.1.Pharmacokinetic models

(a)One-compartment model

(b)Two-compartment model

*A(t):function of administration

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which indicates a correlation between A(t)and serum level B(t)is represented as G(t),their relationship is written as equation(2):

B(t)=∫toA(t-θ)G(θ)dθ …(2)

According to the one-compartment model,G1(t)can be written as follows:

G1(t)=ε-KeLt/Vd…(3)

where Vd is the volume of distribution,and Kel is the elimination constant.When equations
(1)and(3)are substituted in equation(2),the serum level can be written as follows:
B(t)=KaW/Vd(Ka-Ket)・(ε-Kelt-ε-Kat)...(4)

(2)Constant rate intravenous infusion
The data were analysed according to one-compartment model,or two-compartment model
shown in Fig.1(b).When the drug was infused during the period of time zero to T,the
following equation is obtained:

when t≦T A(t)=W/T...(5)
when t>T A(t)=0...(6)

and in the case of one-compartment model,from equations (5),(6),(3)and(2),B(t)is derived as follows:

whent=T
B(t)=W/TVdKel・(1-ε-Kelt)...(7)

when t>T
B(t)=W/TVdKel・(1-ε-KelT)・ ε-Kel(t-T)...(8)

In the case of two-compartment model,weighing function G2(t) can be written as follows:

G2(t)=1/V,(a-β)・{(α-K,)ε-αt+(K2-β)ε-βt}...(9)

where V1 is volume of serum component;K1,K,and K3 are rate constants of drug transport(K1:
serum to tissue,K2:tissues to serum,andK3:serum to out of system);α+βisK1+K2十K3;
andα βis K2K3(α>β).
As in the case of the one-compartment model,the equations(9),(5),(6)and(2)produce
the following two equations:
when t≦T
B(t)=W/TV1(α-β)・{(α-K2)(1-ε-at)/α
+(K2-β)(1-ε-βt)/β}…(10)
when t>T
B(t)=W/TV1(α-β)・{(α-K2)(1-ε-αT)ε-α(t-T)/α
+(K2-β)(1-ε-βT)ε-β(t-T)/β}...(11)

(3)Calculation of pharmacokinetic parameters
For intramuscular administration,serum levels determined (B(t))were substituted into
equation(4)to calculate Vd,Ka and Kel by means of the least squares method.With the
constant rate intravenous infusion,Vd and Kel were calculated by means of the least squares
method from equations(7)and(8)for one-compartment model,and V1,ƒÀ1,K2 and K3 from
equations(10)and(11)for two-compartment model.A HITAC-20computer was used for the
calculation,employing the programs developed in the Central Research Laboratories of Meiji
Seika Kaisha,Ltd.
The biological half-life T1/2 was calculated as follows:
in the case of one-compartment model
T1/2=0.693/Kel…(12)

in the case of two-compartment model
T1/2=0.693/β...(13)

Body clearance CB was obtained with the following equations:

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in the case of one-compartment model
CB=VdKel...(14)
in the case of two-compartment model
CB=V1K3...(15)
If E(t)represents renal excretion accumulated during the time t,renal clearance CR can be calculated with the following equation:

CR=E(t)/∫toB(t)dt…(16)

Results and Discussion

Serum Levels and Renal Recovery

(1)Healthy volunteers
The individual and mean serum levels in each administration group are shown in Table 3 (intramuscular dose of0.5g),Table4(intramuscular doses of 1g and1.5g)and Table 5 (constant intravenous infusion of0.5g).
In the cases of intramuscular administration,the serum levels rose rapidly after the administration and in general the peak levels occurred at one hour,falling gradually there-after.When a dose of0.5g was given every 8 hours,the level and patterns were very similar to those after a single injection,showing no ribostamycin accumulation in the body.
When one-hour constant rate intravenous infusion was applied,peak serum level occurred
at the end of infusion.The peak values were all higher than those obtained at one hour

Table3.Serum levels of ribostamycin in healthy volunteers after repeated intramuscular injections of0.5g four times at8-hour intervals(mcg/ml)

Table4.Serum levels of ribostamycin in healthy volunteers after a single intramuscular
injection of1.0g and1.5g(mcg/ml)

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after an intramuscular administration of the same dose,but serum levels after2hours in both cases showed no significant difference.

(2)Patients with impaired renal function
The results are given in Table6.In the patients whose Ccr lay within the normal range,

Table5.Serum levels of ribostamycin in healthy volunteers after constant rate intravenous
drip infusion of0.5g for one hour(mcg/ml)

Table6.Serum levels of ribostamycin after an intramuscular injection of0.5g in patients
with renal disease(mcg/ml,*Ccr:ml/min)

Table7.Cumulative urinary recovery of ribostamycin in each administration group

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serum level behavior was almost the same as that of healthy volunteers.In the patients whose rate of Ccr dropped,the high serum levels continued proportionally for a long time;in the patients whose Ccr were below20ml/min, the serum levels were all assayable till48hours after intramuscular injection of0.5g.
Table8.Pharmacokinetic parameters for intramuscular administration,calculated from
the serum level data shown in Tables3and4

Ka,Kel:hr-1,Vd:Liman,T1/2:hr.

Table9.Pharmacokinetic parameters for the constant rate intravenous drip infusion

,

calculated from the serum level data shown in Table5

Kel,K1,K2,K3,ƒ¿,ƒÀ:hr-1,T1/2,T1/2(ƒ¿),T1/2(ƒÀ):hr.,Vd,V1,V2:L/man

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Fig.2.Simulated serum levels calculated from
the parameters obtained from mean serum
levels in each administration group

Fig.3.Correlation between dose and peak level
after intramuscular injection(peak levels
calculated from the parameters obtained from the individual serum levels)

Y=A•~+B
A=29.5708+2.7376
B=7.2787+2.9569
r=0.9486
P<0.01

Table7 shows the cumulative urinary recovery of ribostamycin in each administration

group of healthy volunteers.

Pharmacokinetic Parameters

(1)Healthy volunteers
Table8gives the pharmacokinetic parameters for intramuscular administration groups,

calculated from the serum level data shown in Tables3and4.The averages of all the para-

meters in the case of intramuscular administration were Ka=2.22•}1.13(hr-1),Kel=0.46•}0.11

Fig.4.Correlation between dose and duration of
serum levels maintained over12.5mcg/ml

Fig.5.Correlation between duration of serum
levels maintained over12.5mcg/ml with
the dose of0.5g and of those maintained
over25mcg/ml with the dose of1.0g

Y=A•~+B
A=2.9904•}0.2861
B=1.0639•}0.3090
r=0.9453
P<0.01

y=0.859•~+0.662
r=0.919
P0.01

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Fig.6.Correlation between duration of serum
levels maintained over12.5mcg/ml with
the dose of0.5g and of those maintained over 37.5mcg/ml with the dose of1.5g

Y=A•~+B
A=1.2624•}0.3904
B=-0.2801•}0.8375
r =0.8815
P<0.01

Fig.7.Simulated serum level calculated from the parameters obtained from the mean serum level after the first injection,and determined values after the first and the fourth injection of0.5g of ribostamycin every8hours

(hr-1),and Vd=16.89•}3.72(L).The

transport constant Ka(from the administra-

tion site into the blood)differed between

individuals and between administration

groups,but the variations in the elimination constant Kel,the biological half-life T1/2,
and the volume of distribution Vd between

the individuals were relatively small,with

little deviation from average among the

administration groups.These results prove

that ribostamycin's behavior is almost the

Table10.Body clearance(CB)and renal clearance

(CR)of ribostamycin in healthy volunteers in
each administration group

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Fig.8.Simulated serum levels when0.5g was
intravenously infused over different periods
of time

same with different doses and administration
method used in these studies.

The parameters for the constant intravenous
infusion are given in Table9.Fig.2gives the simulated serum levels calculated from the

parameters obtained from the mean serum levels
in each administration group.When a dose of
0.5g was intravenously infused for one hour at
a constant rate,the peak serum level one hour
after the start of infusion was about1.5times
that when the same dose was given intra-
muscularly.After one hour,however,the level
fell rapidly in the a phase,but in the,ƒÀ phase,
2hours after the start of infusion,the patterns
of decreasing serum levels were almost the same
as those with intramuscular administration.

Figs.3and4 indicate the correlation between the dose of ribostamycin and the peak levels calculated from the parameters obtained from the individual serum levels,and between the dose
and the duration of serum level maintained over12.5mcg/ml.Correlations were statistically
significant at p<0.01in both cases.Figs.5and6 show the correlations between the duration
of serum levels maintained over12.5mcg/ml with the dose of0.5g and of those maintained over 25mcg/ml with the dose of1g, and of those maintained over 37.5mcg/ml with the dose of1.5g. Correlations with the former were statistically significant at p<0.01,and the latter at p<0.01, indicating the close relationship between dose and serum level.
With the repeated intramuscular administration of0.5g the values determined after the 4th injection were virtually in agreement with the simulation curve calculated from the parameters obtained from the mean serum level after the first injection(Fig.7).
Fig.8 indicates the simulated serum levels when0.5g was intravenously infused over different periods of time.These levels were calculated using the parameters of the two-com-partment model obtained from the mean serum level when the same dose was intravenously

Table11.Pharmacokinetic parameters calculated from serum level data,given in Table6, when0.5g was intramuscularly given to patients with renal diseases

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infused at a constant rate for1hour,and also indicates the duration of serum level maintained
over12.5mcg/ml.
When the drug was given by intravenous injection or by intravenous infusion with too short
infusion time,the peak serum level rose to undesirably high level.However,the infusion time
was one to2hours,the peak level was within the safe range.Therefore,this infusion time
was thought to be appropriate for clinical use with little difference in the duration of serum
level maintained over12.5mcg/ml.
The body clearance CB and renal clearance CB of ribostamycin are given in Table10 .The

correlation between them can be written as follows:
CR=(0.727•}0.150)CB+(11.715•}18.230)

where the correlation factor was0.709,being statistically significant at p<0 .01.

(2)Patients with impaired renal function

Table11shows the pharmacokinetic parameters calculated from serum level data when0 .5g

was intramuscularly given to patients with impaired renal function,given in Table6

.

The values of Ka in the majority of the patients were calculated as too high,because there
was a lack of the data during the phase where the serum level was increasing.The Kel and
body clearance CB decreased very much in relation to a reduction of Ccr,whereas the values
of T1/2increased.This indicates that renal function plays an important part in elimination of
the drug.

Renal Function and Pharmacokinetics

The serum level data after the first intramuscular injection of0.5g to healthy volunteers
and data from the patients with renal diseases were studied as follows.
They were classified into the following4groups:
Group I,Normal renal function group with Ccr•†100ml/min•cCases A to G
Group II,Moderate dysfunction group with 99>Ccr•†30•cCases H and I

Fig.9.Simulated serum levels in four groups classified by creatinine clearance

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Fig.10.Correlation between elimination constant
(Kel)of ribostamycin and creatinine clearance
(Ccr)

Y=A•~+B
A=0.003853•}0.000484
B=0.045651•}0.037609
r =0.9049
P0.01

Fig.11.Correlation between body clearance(CB)
of ribostamycin and creatinine clearance (Ccr)

Y =A•~+B
A=1.0149•}0.0611
B=3.9205•}4.7431
r=0.9756
P<0.01

Group III,Severe dysfunction group with30>Ccr•†10•cCases J to L
Group IV,Oliguria group with Ccr<10•cCases M to P
Fig.9 shows the serum level curves simulated from parameters calculated from mean serum
levels of each group after intramuscular injection of0.5g. The curves show clearly that as
the degree of renal dysfunction becomes more serious,so the serum level increases and the
duration of serum level maintenance become longer.
Between Kel(hr-1)and Ccr(ml/min),a correlation was found as shown in Fig.10,from
which the following linear regression equation was obtained:
Kel= (0.003853•}0.000484)Ccr+(0.045651•}0.037609)•c(17)
The correlation factor was0.9049,being statistically significant at p<0.01.Equation(17)
is very similar to the following equation(18)which GROSS,et a1.4),formulated when800mg
of ribostamycin was intramuscularly administered to16patients with different renal diseases.
Kel=0.0036.glomerular filtration rate+0.027•c(18)
Between the body clearance CB(ml/min)and the Ccr(ml/min),a correlation as shown in Fig.
11was found,and can be shown as follows:
CB=(1.0149•}0.0611)Ccr+(3.9205•}4.7431)•c(19)
The correlation factor was0.9756,being statistically significant at p<0.01.In equation(19)
the direction coefficient was close to one;the intercept,3.9205 was small in comparison with
the Ccr>100ml/min of a normal person and a high correlation was found,as shown above,
between the CB and Ccr of ribostamycin.It can therefore be considered that the body clearance
of ribostamycin is almost equal to creatinine clearance,except when there is a remarkable
decrease in renal function.

If CB=Ccr,equation(20)can be obtained from equation(14):
Kel=Ccr/Vd•c(20)
The mean Vd of all the tested individuals can be shown as follows:

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Vd=13.585•}3.600(L)
When this is put into equation(20)and the unit is changed, equation(21)is obtained: Kel(hr-1)=Ccr/(226.41•}60.00)•c(21)
The following equation leads from equations(12)and(21):
T1/2=(156.90•}41.58)/Ccr(hr)•c(22)
The values of T1/2were calculated by means of equation(22).These results compared with
the values obtained from the experiments are shown in Table12.If renal function decreases
critically and Ccr comes near to zero,the hypothesis CB=Ccr,mentioned above,does not hold.
Therefore,excepting cases N to P,over half of the values obtained from the remaining13
cases fell within the range calculated from the equation(22).
Administration of ribostamycin in patients with impaired renal function

Among the aminoglycoside antibiotics,ribostamycin and streptomycin have the lowest renal toxicity,so there are relatively few problems when administering them to patients with renal disorders.
In general,the methods of administration with these in patients with renal disorders are as
follows.
Method1:Prolonging the intervals between doses but using a dose the same as that given
to patients with normal kidney function.
Method2:Prolonging the intervals between doses and using an initial dose identical to
that given to normal patients but with the reduced maintenance dose.
Method3:Using with the same intervals between doses as in normal patients,but with
the reduced initial and maintenance doses.

Table12.Comparison of biological half-life of
ribostamycin estimated from creatinine
clearance and that obtained from determined
serum levels

Fig.12.Nomogram for calculation of initial
dose and maintenance dose based on creatinine clearance(Ccr)

*Initial dose based on Ccr for8hourly
administration

**Initial dose based on Ccr for12hourly
administration
***Maintenance dose based on Ccr for both8 and12hourly administration

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If aminoglycoside antibiotics are given normal doses to patients with severe renal dysfunc-

tion,the peak serum level becomes undesirably high.On the other hand,if the administration

interval is too much prolonged,the duration of low serum level may be prolonged,causing low

efficacy.For these reasons,Method1is unsuitable,but Methods2and3are recommended.

Concerning Method3,DETTLI et al.formed the following equation:

D =D•EKel/Kel•c(23)

where D=maintenance dose for a patient with impaired renal function.

D=a single dose for a patient with normal renal function.

Kel=elimination constant in a patient with impaired renal function.

Kel=elimination constant in a patient with normal•Erenal function.

The initial dose D*for a patient with impaired renal function can be obtained from equation(24).
D *=D/(1-ƒÃ-KelƒÑ)•c(24)

where ƒÑ=the administration interval.

A nomogram was prepared to calculate the maintenance dose in patients with impaired

renal function and initial dose D*by using relationship between Kel and Ccr,shown in Fig.10

and equation17.This is shown in Fig.12,where the solid line indicates the relationship

between Ccr and maintenance dose,D;the dotted line indicates the relationship between Ccr

and initial dose,D*,when administration interval,ƒÑ,is8hours,and the broken line indicates

that when the interval is12hours.

For example,the dose for a patient with Ccr50ml/min can be calculated from the nomogram

given Fig.12as follows:
Ex.1:for the dose which will give the same serum level as when500mg of ribostamycin
are administered every8hours to a patient with normal renal function,
Maintenance dose D=500mg•~0.55=275mg
Initial dose D*=500mg•~0.63=315mg
Ex.2:for the dose which will give the same serum level as when800mg of ribostamycin
are administered every12hours to a patient with normal renal function,
Maintenance dose D=800mg•~0.55=440mg
Initial dose D*=800mg•~0.58=464mg

As explained above,the dose of ribostamycin suitable for patients with impaired renal function

can be obtained using the nomogram shown in Fig.12.With this method,effective and safe

serum levels,comparable to those after administration of the same dose to patients with normal
renal function,can be obtained.

Summary

Five healthy adult volunteers,in a crossover study,were given ribostamycin in single doses

of1g and1.5g intramuscularly,in4repeated doses of0.5g given intramuscularly every8

hours,and in a one-hour intravenous infusion to determine the serum levels and recovery rates

in the urine. Also,eleven patients with various degrees of renal dysfunction were given a

single dose of0.5g intramuscularly to determine the serum levels .All the resulting data were

used for pharmacokinetic analysis.

The ribostamycin serum levels of the healthy volunteers were virtually in proportion to the

dose.In the case of intramuscular administration of0.5g every8hours,no accumulation of

ribostamycin in the blood was found.Though the transport rate constant Ka from the administra-

tion site into the blood showed relatively wide variance,the other pharmacokinetic parameters

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were similar regardless of the dose.The urinary recovery rate by6hours after administration
was more than70%,indicating significant correlation between the renal clearance and body
clearance of ribostamycin.
In patients with impaired renal function,biological half-life increased and body clearance
dropped in proportion to the degree of renal dysfunction.A significant linear correlation was
found between creatinine clearance and the elimination constant Kel,and between creatinine
clearance and body clearance.As a result,it is considered that the elimination of ribostamycin
from the body is mainly via the kidney.
Based on the results obtained from these studies,a nomogram has been prepared which is
applicable for calculating the appropriate dose of ribostamycin for administration to patients
with impaired renal function.
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