SERUM CONCENTRATION AND PHARMACOKINETICS OF TOBRAMYCIN IN INTRAVENOUS DRIP INFUSION

—ADULTS AND NEONATES—

HIROSHI FUKUCHI, SATSUKI TSUKIAI and TERUAKI KITAURA
Department of Pharmaceutical Services, Hiroshima University Hospital

TAKASHI YOKOYAMA
Department of Surgery (I), Hiroshima University School of Medicine

YASUO HARADA
Department of Otorhinolaryngology, Hiroshima University School of Medicine

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For the purpose of studying the safe and effective administration dose of tobramycin, intravenous drip infusion of tobramycin was made on adults and neonates.

Multiple administration on adults (16～56 years of age) : Intravenous drip infusion of 40～120 mg of tobramycin was made two or three times daily for 30～150 min. Effective serum concentration (4 μg/ml or more) was observed in seven out of sixteen cases and in the seven cases the administration dose was 1.2 mg/kg or more. No accumulation due to multiple administration was observed.

Single administration on adults (22～63 years of age) : Intravenous drip infusion of 90 mg of tobramycin was made for one hour. Effective serum concentration was observed in nine out of ten cases and the administration dose was 1.5 mg/kg or more in all cases.

Neonates (4～29 days after birth) : When intravenous drip infusion of tobramycin of 2 mg/kg was made for one hour, effective serum concentration was observed in only one out of seven cases, in only one out of eleven cases when intravenous drip infusion of 3 mg/kg was made for one hour, and in only two out of five cases when intravenous drip infusion of 3 mg/kg was made for 30 minutes.

Biological half-life in neonates was more extended than in adults and the distribution volume and serum clearance in neonates were two or three times greater than in adults.

By intravenous drip infusion of tobramycin on neonates, a significant correlation was observed between elimination rate constant and distribution volume and between elimination rate constant and days after birth or body weight.

The biological half-life of neonates 4～7 days after birth was significantly extended when compared to that 9～29 days after birth.

Aminoglycoside antibiotics have a strong bactericidal effect against gram-negative organisms[1~3] and are extensively used when other types of antibiotics are ineffective and in the treatment of severe or intractable infectious diseases. The difference between effective blood concentration and toxic concentration is, however, small and it has been reported that the risk of ototoxicity and nephrotoxicity is high when the peak concentration of tobramycin and gentamicin continues to exceed 12 μg/ml or when their trough concentration immediately prior to the following administration continues to exceed 2 μg/ml[4~8]. In view of the foregoing, it is said that the safe and effective peak concentration of tobramycin and gentamicin is 4～10 μg/ml and that their trough concentration is less than 2.0 μg/ml[9].

The authors[10] have previously studied after intramuscular injection of tobramycin in healthy male adults the relation between administration dose and serum concentration of tobramycin from the stand-

points of efficacy and safety.

In the present study, intravenous drip infusion of tobramycin was made on adults and neonates and their serum concentrations were determined and the pharmacokinetic parameters were obtained for the study of the effective dose of tobramycin.

I. METHODS

Subjects. The following subjects were used in this study.

Adults: Adults without renal failure or hepatic disease who were administered tobramycin for treatment and prevention of infection.

Neonates: Neonates 4~29 days after birth having surgical diseases such as diaphragmatic hernia and congenital duodenal atresia whose postoperative circulatory dynamics were comparative stable.

Intravenous drip infusion. Multiple administration on adults: For the purpose of ascertaining the peak concentration and trough concentration of tobramycin by multiple administration, 40~120 mg of tobramycin (Eli Lilly and Co., Indianapolis, U. S. A., Shionogi & Co., Ltd., Osaka, Japan) was mixed with 100~500 ml of i. v. fluid and intravenous drip infusion for 30~150 min. was made two or three times a day. Immediately after completion of the 10 th intravenous drip infusion when the serum concentration is considered to have reached a sufficiently steady state and immediately before the 11 th administration, blood was drawn and both the peak concentration and trough concentration were measured.

Single administration on adults: For the purpose of ascertaining the changes over time of tobramycin concentration in the serum by single administration, 90 mg of tobramycin was mixed with 100 ml or 200 ml of i. v. fluid and intravenous drip infusion was made for one hour. Immediately after completion of intravenous drip infusion and 1, 3, 5, and 7 hours thereafter, blood was drawn to determine tobramycin concentration in the serum.

Neonates : A volume of 2 mg/kg and 3 mg/kg of tobramycin was mixed with i. v. fluid (2~8 ml/kg) and intravenous drip infusion was made for 30 minutes and one hour. Immediately after completion of intravenous drip infusion and 1, 2, 3, and 5 hours thereafter, blood was drawn to determine tobramycin concentration in the serum.

Determination of tobramycin concentration in the serum. Tobramycin concentration in the serum was determined by enzyme multiplied immunoassay technique (EMIT ; Syva Co., Palo Alto, California). The determination procedure described in the instruction sheet was followed.

Table 1 Peak concentration and trough concentration in adults given intravenous drip infusion of tobramycin

Subject	Sex	Age (yr)	Weight (kg)	Dose (mg)	Dose (mg/kg)	Inf. time (min)	Serum concn. (μg/ml) Peak[a]	Serum concn. (μg/ml) Trough[b]
EK	F	43	46.0	40	0.9	30	2.6	0
SY	F	23	44.0	40	0.9	55	2.1	0
HT	M	16	45.0	60	1.3	30	2.6	0.1
MM	M	35	68.0	60	0.9	30	3.2	0
KI	M	53	60.0	60	1.0	30	3.3	0.2
KK	F	56	43.0	60	1.4	30	4.4	1.3
YH	M	16	57.0	60	1.1	40	3.2	0.7
SY	F	23	44.0	60	1.4	55	4.4	0
YS	M	45	60.0	60	1.0	60	2.1	ND[c]
YT	M	56	52.0	60	1.2	75	5.1	0
KD	M	35	70.0	60	0.9	100	0.7	0
RF	F	52	49.0	60	1.2	120	4.2	0
TN	M	21	50.0	60	1.2	150	1.3	0
KT	M	17	45.0	120	2.7	60	4.4	0
HT	M	16	45.0	120	2.7	60	6.3	0
ZH	M	55	51.0	120	2.4	90	5.0	0

a. Immediately after 10th administration

b. Immediately before 11th administration

c. ND=Determination could not be made

Effective tobramycin concentration in the serum. The effective tobramycin concentration in the serum should be determined taking into account the contact time with the microorganisms[11,12], but in the present study it was assumed to be that when the peak concentration was 4 μg/ml or more in accordance with the hypothesis of JACKSON[9].

II. RESULTS AND DISCUSSION

1. Adults

Multiple administration : Table 1 showed the peak concentration determined immediately after the completion of the 10 th intravenous drip infusion and the trough concentration immediately before the 11 th intravenous drip infusion.

In the two cases given intravenous drip infusion of 40 mg, the administered dose was 0.9 mg/kg and in both cases effective serum concentration was not obtained. In four out of eleven cases given intravenous drip infusion of 60 mg, effective serum concentration was observed and in all the four cases the administered dose exceeded 1.2 mg/kg. In five out of seven cases in which effective serum concentration was not obtained, the administered dose was less than 1.1 mg/kg. In the three cases given intravenous drip infusion of 120 mg, effective serum concentration was observed and in all cases the administered dose exceeded 2.4 mg/kg. The trough concentration was less than 2.0 μg/ml in all cases and accumulation due to multiple administration was not observed.

The foregoing results suggest that an administered dose of more than 1.2 mg/kg is necessary to attain an effective tobramycin concentration in the serum. According to Physicians' Desk Reference (PDR)[13] in the case of serious infection with normal renal function, 3 mg/kg/day should be given in three equal doses every eight hours and in case of life-threatening infection, 5 mg/kg/day should be administered in three or four equal doses, but the present findings suggest that there is room to increase the dose to exceed 3 mg/kg/day.

Single administration : Table 2 showed tobramycin concentration in the serum over time of the ten adults given intravenous drip infusion of 90 mg of tobramycin.

The administered dose in all cases exceeded 1.5 mg/kg and in nine out of ten cases effective serum concentration was observed. Six hours after commencement of intravenous drip infusion, the serum concentration was less than 2.0 μg/ml in all cases.

Pharmacokinetic parameters : The tobramycin concentration in the serum of each case shown in Table 2 was applied to one-compartment open model and two-compartment open model and then analyzed[14]. The pharmacokinetic parameters thus obtained were shown in Table 3.

Simulation was made using the parameters obtained from each case and with the two-compartment open model the predicted values corresponded to the measured values. However, with the one-compartment open model, the predicted values

Table 2 Serum concentration in adults given intravenous drip infusion of 90 mg of tobramycin for one hour

Subject	Sex	Age (yr)	Weight (kg)	Dose (mg/kg)	Serum concn. (μg/ml)				
					1 hr.[a]	2 hr.	4 hr.	6 hr.	8 hr.
NO	F	22	56.0	1.6	4.5	2.2	1.1	0.5	0.3
MY	F	33	50.0	1.8	7.1	2.4	1.1	0.5	ND[b]
EM	F	35	50.0	1.8	6.3	2.8	1.0	0.7	ND
KS	M	38	50.0	1.8	8.4	3.4	1.8	1.0	0.6
KK	F	50	49.5	1.8	8.3	3.7	1.7	1.0	ND
YT	F	51	57.0	1.6	7.9	3.2	1.4	0.9	ND
TF	M	56	43.0	2.1	8.6	4.6	2.3	1.2	ND
HS	M	58	60.0	1.5	3.3	ND	0.8	0.5	ND
YO	F	60	47.5	1.9	6.6	2.7	1.3	0.4	ND
KO	M	63	55.0	1.6	5.1	2.8	1.2	0.7	0.4
Mean ±S.D.		46.6 ±13.7	51.8 ± 5.1	1.75 ±0.17	6.6 ±1.8	3.1 ±0.8	1.4 ±0.4	0.7 ±0.3	0.4 ±0.2

a. Time after commencement of intravenous drip infusion

b. ND=Determination could not be made

Table 3 Pharmacokinetic parameters[a] in adults given intravenous drip infusion of 90 mg of tobramycin for one hour

〔One-compartment open model〕

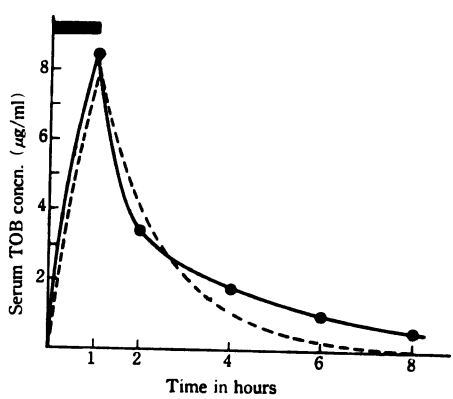
K (hr^{-1})	$t_{1/2}$ (hr)	V (1/kg)	Cl (1/kg/hr)
0.629 ± 0.149	1.17 ± 0.28	0.219 ± 0.071	0.131 ± 0.026

〔Two-compartment open model〕

K_{12} (hr^{-1})	K_{21} (hr^{-1})	K_{10} (hr^{-1})	α (hr^{-1})	β (hr^{-1})	$t_{1/2,\beta}$ (hr)	V_c (1/kg)	V_β (1/kg)	Cl (1/kg/hr)
0.705 ± 0.324	1.100 ± 0.277	0.712 ± 0.165	2.164 ± 0.336	0.354 ± 0.069	2.02 ± 0.35	0.174 ± 0.076	0.327 ± 0.052	0.116 ± 0.031

a. All data were shown as mean ± S.D. (n =10)

Fig. 1 Simulated serum concentration in subject KS given intravenous drip infusion of 90 mg of tobramycin for one hour



····· ; One-compartment open model (K=0. 695 hr^{-1}, V=0. 158 l/kg).

—— ; Two-compartment open model (K_{12}=1. 164 hr^{-1}, K_{21}=0. 899 hr^{-1}, K_{10}=0. 796 hr^{-1}, α= 2. 582 hr^{-1}, β=0. 277 hr^{-1}, V_C=0. 107 l/kg).

tended to be alienated from the measured values in all cases. As for the reason why it fitted the two-compartment open model, within the one hour intravenous drip infusion time tobramycin could not adequately reach the tissue and for this reason it was assumed that the depression of serum concentration showed a biphasic pattern.

An example of simulation was shown in Fig. 1.

2. Neonates

Table 4 showed the serum concentration by intravenous drip infusion of tobramycin in neonates 4~29 days after birth.

Effective serum concentration was observed in only one case out of seven cases by intravenous drip infusion of 2 mg/kg of tobramycin for one hour, in only one case out of eleven cases by intravenous drip infusion of 3 mg/kg for one hour and in two cases out of five cases by intravenous drip infusion of 3 mg/kg for 30 minutes. Serum concentration 5. 5 hours or 6 hours after commencement of intravenous drip infusion was less than 2. 0 μg/ml in all cases. According to PDR[13] administration up to 4 mg/kg/day in two equal doses every 12 hours should be made to premature or full-term neonates one week of age or less and 6~7. 5 mg/kg/day in three or four equally divided doses to children. In the present study by single administration of 2 mg/kg, therapeutic level was not attained and six hours after commencement of intravenous drip infusion the concentration decreased to less than 2. 0 μg/ml. It was therefore considered that there might be room to increase the administration dose depending on the condition of the disease. TOYONAGA et al[15] have also reported that a dose of 3 mg/kg is possible in neonates.

Pharmacokinetic parameters : Tobramycin concentration in the serum of individual subjects was analyzed based on the one-compartment open model and the two-compartment open model[14]. The data

Table 4 Serum concentration in neonates given intravenous drip infusion of tobramycin

(1) 2 mg/kg 1 hr. i.v.d.

Subject	Sex	Age (day)	Weight (kg)	Serum concn. (μg/ml)				
				1 hr.[a]	2 hr.	3 hr.	4 hr.	6 hr.
IU	F	4	2.3	2.3	1.4	1.4	1.1	0.9
IH	F	6	1.8	1.7	1.4	1.1	1.0	0.7
KS	M	10	2.5	1.8	1.1	0.8	0.3	0.2
KY	F	14	3.1	2.5	1.2	1.3	0.6	0.3
MT	F	15	3.1	4.3	3.2	1.8	ND[b]	ND
HI	M	20	2.4	1.3	1.2	1.0	0.8	0.3
KN	M	21	3.2	1.7	0.9	0.8	0.6	0.5
Mean		12.9	2.6	2.2	1.5	1.2	0.7	0.5
±S.D.		±6.5	±0.5	±1.0	±0.8	±0.4	±0.3	±0.3

(2) 3 mg/kg 1 hr. i.v.d.

Subject	Sex	Age (day)	Weight (kg)	Serum concn. (μg/ml)				
				1 hr.[a]	2 hr.	3 hr.	4 hr.	6 hr.
KO	M	4	2.5	2.0	1.9	1.8	ND	0.9
KN	F	4	2.7	2.0	1.6	1.2	0.8	0.4
MH	F	4	3.1	2.1	1.5	1.4	1.0	0.6
KK	M	4	3.1	2.8	2.3	2.1	1.3	1.2
FS	M	7	2.9	3.1	2.9	2.3	2.0	1.6
KI	F	7	2.9	2.5	2.1	2.0	1.6	1.0
KS	F	13	3.1	5.9	4.0	2.9	2.1	1.5
MY	F	16	2.0	1.9	1.8	1.6	1.3	0.9
SO	F	25	3.0	2.8	1.9	1.2	0.9	0.4
YM	M	27	4.0	2.6	2.5	ND	1.1	ND
BM	M	29	4.0	2.7	2.2	ND	1.0	0.2
Mean		12.7	3.0	2.8	2.2	1.8	1.3	0.9
±S.D.		±10.0	±0.6	±1.1	±0.7	±0.6	±0.4	±0.5

(3) 3 mg/kg 30min. i.v.d.

Subject	Sex	Age (day)	Weight (kg)	Serum concn. (μg/ml)				
				0.5hr.[a]	1.5hr.	2.5hr.	3.5hr.	5.5hr.
TF	M	6	3.3	4.9	4.2	3.1	2.5	1.5
KO	M	9	2.5	3.2	2.3	1.6	1.2	0.6
EO	F	10	2.5	4.4	3.9	3.2	2.8	2.0
HE	M	10	3.2	2.5	1.9	1.3	1.1	0.8
BO	F	14	2.5	3.3	2.4	1.8	1.5	1.0
Mean		9.8	2.8	3.7	2.9	2.2	1.8	1.2
±S.D.		±2.9	±0.4	±1.0	±1.0	±0.9	±0.8	±0.6

a. Time after commencement of intravenous drip infusion

b. ND=Determination could not be made

Table 5 Pharmacokinetic parameters[a] in neonates given intravenous drip infusion of tobramycin

Dose	K (hr^{-1})	$t_{1/2}$ (hr)	V (1/kg)	Cl (1/kg/hr)
2 mg/kg	0.312	2.59	0.927	0.269
1 hr. i.v.d.	±	±	±	±
(n = 7)	0.124	1.06	0.316	0.100
3 mg/kg	0.262	3.11	1.008	0.249
1 hr. i.v.d.	±	±	±	±
(n = 11)	0.117	1.21	0.265	0.092
3 mg/kg	0.239	3.08	0.844	0.206
30min. i.v.d.	±	±	±	±
(n = 5)	0.063	0.83	0.258	0.084

a. All data were shown as mean ± S.D.

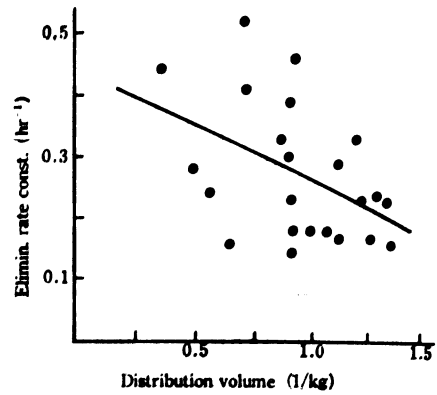
of all cases made a good fit with the one-compartment open model, but the data of most of the subjects did not fit the two-compartment open model. Pharmacokinetic parameters which were analysed based on the one-compartment open model were shown in Table 5.

In comparison with the adults, the neonates were characterized by a large standard deviation in the pharmacokinetic parameters.

The biological half-life ($t_{1/2,\beta}$) of tobramycin in adults was 2.02 ±0.35 hours, while that ($t_{1/2}$) in neonates was 2.59±1.06 hours in the group given intravenous drip infusion of 2 mg/kg for one hour, 3.11±1.21 hours in the group given intravenous drip infusion of 3 mg/kg for one hour, and 3.08± 0.83 hours in the group given intravenous drip infusion of 3 mg/kg for 30 minutes, demonstrating an extension. The distribution volume (V_β) in adults was 0.327±0.052 1/kg, while the distribution volume (V) in neonates was 0.927±0.316 1/kg, 1.008±0.265 1/kg, and 0.844±0.258 1/kg, respectively, showing values about threefold that of adults. Serum clearance (Cl) in adults was 0.116± 0.031 1/kg/hr, while in neonates it was 0.269± 0.100 1/kg/hr, 0.249±0.092 1/kg/hr and 0.206± 0.084 1/kg/hr, showing values almost twofold that of adults.

These findings coincide with the fact that in most of the administered cases in neonates effective serum concentration was not obtained. When the distribution volume and serum clearance are high, it is necessary to increase the administration dose in order to attain a given drug concentration in body fluid.

Fig. 2 Correlation between elimination rate constant and distribution volume of tobramycin in neonates



$y=-0.177x+0.440$, $\gamma=-0.444$, $P<0.05$ (n=23).

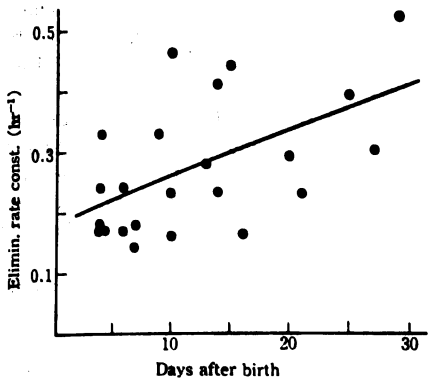
As for the speculated reason why intravenous drip infusion on neonates fitted the one-compartment open model, the distribution volume of the neonates was high in comparison with that of adults and also tissue transferability of drugs was also high and consequently within intravenous drip infusion of 30 minutes or one hour, the drugs rapidly spread within the body and α-phase could not be demonstrated.

Correlation between parameters : The correlation between elimination rate constant and distribution volume obtained from each subject was studied by least-squares regression analysis, which demonstrated a significant correlation between the two ($y=-0.177x+0.440$, $\gamma=-0.444$, n=23, $P<0.05$; Fig. 2).

The correlation of various parameters to days after birth and body weight was examined, which showed a significant correlation between elimination rate constant and days after birth and between elimination rate constant and body weight with $y=0.0075x+0.182$ ($\gamma=0.530$, n=23, $P<0.01$; Fig. 3) and $y=0.089x+0.019$ ($\gamma=0.437$, n=23, $P<0.05$; Fig. 4), respectively.

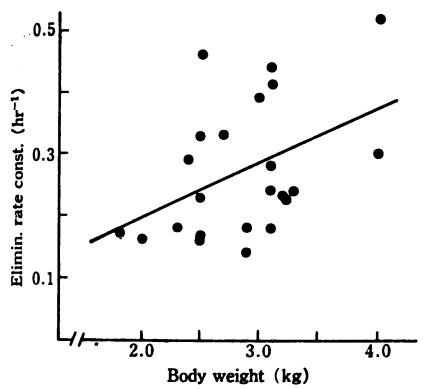
A total of 18 cases composed of a group given intravenous drip infusion of 2 mg/kg for one hour and a group given intravenous drip infusion of 3 mg/kg for one hour were stratified into a group 4~7 days after birth and a group 10~29 days after birth and the significant difference in pharmaco-

Fig. 3 Correlation between elimination rate constant of tobramycin and days after birth in neonates



$y=0.0075x+0.182$, $r=0.530$,
$P<0.01$ (n=23).

Fig. 4 Correlation between elimination rate constant of tobramycin and body weight in neonates



$y=0.089x+0.019$, $r=0.437$,
$P<0.05$ (n=23).

kinetic parameters of each group was tested by STUDENT's t-test (Table 6).

The elimination rate constant 4~7 days after birth was significantly smaller than that 10~29 days after birth ($P<0.005$) and also the biological half-life was significantly extended ($P<0.005$). Even when the test was repeated after adding five cases with a different intravenous drip infusion time, that is drip infusion of 3 mg/kg for 30 minutes, to make the total 23 cases, a significant difference was demonstrated in elimination rate constant ($P<0.02$) and in biological half-life ($P<0.02$). These suggest that a change has developed

Table 6 Pharmacokinetic parameters[a] of tobramycin by days after birth

Age (day)	K (hr^{-1})	$t_{1/2}$ (hr)	V (1/kg)	Cl (1/kg/hr)
4~7 (n=8)	0.199 ± 0.060	3.71 ± 0.86	1.098 ± 0.146	0.221 ± 0.085
10~29 (n=10)	0.348[b] ± 0.114	2.26[b] ± 0.94	0.880 ± 0.328	0.285 ± 0.092

a. All data were shown as mean ± S.D.
b. $P<0.005$

in the excretion function of neonates between less than seven days after birth and seven days or more after birth.

III. CONCLUSION

1. In order to attain an effective serum concentration by intravenous drip infusion of tobramycin on adults, it is considered that an administration dose in excess of at least 1.2 mg/kg is necessary.

2. By intravenous drip infusion of tobramycin on neonates, it was found that the biological half-life was extended more than that of adults and both the distribution volume and serum clearance were twofold or threefold greater that those of adults. These findings and the determined values of tobramycin concentration in the serum by intravenous drip infusion have suggested that there is room to increase the administration dose in excess of 3 mg/kg which was examined in the present study.

3. In the intravenous drip infusion of tobramycin in neonates, a significant correlation was observed between elimination rate constant and distribution volume and between elimination rate constant and days after birth or body weight.

4. The biological half-life at 4~7 days after birth was significantly extended over that 9~29 days after birth.

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Tobramycin 点滴静注時の血清中濃度とファルマコキネティクス

－成人と新生児－

福地 坦・突合 卓月・北浦 照明
広島大学医学部附属病院薬剤部

横山 隆
広島大学医学部第1外科学教室

原田 康夫
広島大学医学部耳鼻咽喉科学教室

Tobramycin の安全でより有効な投与量を検討する目的で，成人および新生児に tobramycin を点滴静注した。

成人（16～56 歳）への頻回投与：tobramycin 40～120 mg を1日2～3回，30～150 分で点滴静注した。16 例中7例が有効血清中濃度（4 μg/ml 以上）を示し，この7例はいずれも投与量 1.2 mg/kg 以上のものであった。頻回投与による蓄積は認められなかった。

成人（22～63 歳）への単回投与：tobramycin 90 mg を1時間で点滴静注した。10 例中9例が有効血清中濃度を示し，投与量は全例 1.5 mg/kg 以上であった。

新生児（生後4～29日）：tobramycinを点滴静注したが，2 mg/kg 1時間点滴群では7例中1例が，3 mg/kg 1時間点滴群では11例中1例が，また3 mg/kg 30分点滴群では5例中2例が有効血清中濃度を示したにすぎなかった。

生物学的半減期は成人よりも延長し，分布容積，血清クリアランスは成人の2～3倍大であった。

新生児におけるtobramycinの点滴静注で，消失速度定数と分布容積，消失速度定数と生後日数または体重との間に有意の相関性が認められた。

生後4～7日での生物学的半減期は生後9～29日のそれに比べて有意に延長していた。