Temporal Variation in the Pharmacokinetics of Gentamicin in Man

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Objective : Aminoglycoside antibiotics such as gentamicin have unique characteristics such as a strong bactericidal effect especially against gram-negative bacilli, synergistic effects when in used combination with β -lactam antibiotics, and a postantibiotic effect (PAE). Therefore they are still widely used for the treatment of serious infection. As the therapeutic range of gentamicin is narrow, therapeutic drug monitoring (TDM) is recommended to avoid adverse effects such as nephrotoxicity and ototoxicity. Gentamicin is eliminated through the kidney in an unchanged form. It is reported that creatinine clearance depends on the time-of-day in man. Although chronopharmacokinetic findings of the drug have been reported in rodents, it is not known at present whether this is also the case in man or not. The purpose of this study was to clarify the effects of the time-of-day of drug administration on the pharmacokinetics of gentamicin in man.

Methods : Nine healthy male volunteers were administered gentamicin, 80 mg/body, intramuscularly at three different times of day with a washout period of more than three days (morning ; 8 : 00, evening ; 16 : 00, night ; 0 : 00). The subjects were randomized using Latin square design to receive the drug at the three different times of day. Pharmacokinetic parameters were calculated using the one compartment model with first order absorption.

Results : Although no difference was found in C_{max} and t_{max} of the drug among the three dosing times, clearance of the drug at midnight was significantly lower compared with the other two dosing times (morning : 4.71 ± 0.25 L/hr, evening : 4.60 ± 0.12 L/hr, night : 4.26 ± 0.16 L/hr, mean $\pm$ S. E. $p < 0.05$). In accordance with the lower clearance at night, the half life of the drug at night was significantly longer (morning : 1.49 ± 0.08 hr, evening : 1.52 ± 0.11 hr, night : 1.75 ± 0.10 hr, mean $\pm$ S. E. $p < 0.05$).

Conclusions : Clearance of gentamicin depends on the time-of-day of drug administration, showing a lower clearance at night in man. This temporal variation in the pharmacokinetics of gentamicin might be clinically important in patients with some clinical situations such as renal impairment.

Key words : antibiotics, gentamicin, chronopharmacokinetics, chronotoxicity, human

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Introduction

Gentamicin, an aminoglycoside antibiotic, was developed in 1963. Thereafter, numerous antibiotics including new quinolones and new generation cephalosporins have appeared. However gentamicin is still widely used in medical practice, because gentamicin has a reliable activity against a variety of virulent organisms causing severe infectious diseases, including *Pseudomonas aeruginosa*, and it also shows a synergistic effect in combination with β -lactam antibiotics. In clinical practice, therapeutic drug monitoring (TDM) is invaluable for ensuring appropriate dosing because the therapeutic range for gentamicin is narrow and there is a linear relationship between plasma drug levels and bactericidal activity and side effects such as nephrotoxicity and ototoxicity.

There have been many studies on numerous drugs which show administration time of day influences on pharmacokinetics and/or pharmacodynamics. In terms of antibiotics, few human studies have shown that administration time of day affects the drug concentration in plasma¹⁻³⁾, although many papers have been published in rodents. The circadian rhythm of susceptibility to gentamicin was first reported in mice by our group⁴⁾. Gentamicin is generally administered intramuscularly or intravenously two to three times a day. It has been reported that gentamicin has a postantibiotic effect (PAE)⁵⁾. Accordingly, a new method of administration to give a total daily dose once a day instead of a divided dosing schedule has been introduced. When administered intramuscularly, the absorption of gentamicin is complete and most is eliminated renally in an unchanged form. There are studies which have shown a lower creatinine clearance at night time, the

resting period, in comparison with that in the daytime, the active period, in man^{6,7)}, suggesting that the administration of gentamicin during the night time could show lower renal drug excretion. It is essentially important to determine when in the day that gentamicin should be administered, when we chose the once daily dosing schedule. The purpose of this study was to elucidate the influence of the administration time of day on the pharmacokinetics of gentamicin in man.

Subjects and Methods

Nine healthy male volunteers (age 23.4 ± 2.0 years, weight 61.4 ± 6.9 kg : mean $\pm$ S. D.) participated in the study. A written informed consent for the study was obtained from each subject. This study was approved by the Ethical Committee for Clinical Research of Ehime University School of Medicine where author, S. N., was previously working. Gentamicin, 80 mg, was administered intramuscularly at three different times of day, 8 : 00 (morning), 16 : 00 (evening), or 0 : 00 (night). Blood samples, 5 ml each, were drawn before and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after drug administration for the pharmacokinetic analysis. The subjects were randomized using Latin square design for the three administration times of day. Each subject was told to keep his life style of regular activity in the daytime and to rest at night.

Plasma gentamicin concentrations were determined by enzyme immunoassay (EMIT). The pharmacokinetic parameters were calculated with the plasma gentamicin concentrations. Individual plasma gentamicin concentration-time data points fitted to the one-compartment open model using the nonlinear least-squares method. The area under the time-concentration curve (AUC) from 0 to 8 hours after drug administration (AUC_{0-8}) was determined by

trapezoidal rule, and the AUC from 8 hours, the last sampling point, to infinity was determined by the concentration at 8 hour (C_p) and the elimination constant (K_e). Pharmacokinetic parameters were compared among three administration times of day by ANOVA for Latin square design. AP value of <0.05 was considered significant.

Results

The concentration-time curves after intramuscular administration of gentamicin (80 mg) to nine healthy volunteers at three different dosing times of day are shown in Fig. 1 and the pharmacokinetic parameters are given in Table 1. The pharmacokinetic parameters were calculated using the one-compartment open model with first order absorption. Although we tried to analyze data using the two-compartment open model, the fitting as evaluated using Akaike's Information Criterion (AIC) was better with the one-compartment model.

As shown in Fig. 1, gentamicin was rapidly absorbed and reached C_{max} within 30 minutes with all three administration times. Because there were no significant differences in C_{max}

and t_{max} , the absorption phase of gentamicin was considered not to be affected by administration time of day. But in the elimination phase, plasma concentrations were kept at slightly higher levels at night compared with

Fig. 1 Plasma concentrations of gentamicin after intramuscular administration, 80 mg, at three different times of day (—□— morning,▲..... evening, ----○---- night) (n=9, mean±S.D.)

Table 1 Pharmacokinetic Parameters of Gentamicin in Plasma after Intramuscular Administration, 80 mg, to Nine Healthy Volunteers at Three Different Times of Day

Pharmacokinetic parameters	Time of administration			Statistical significance (ANOVA)
	Morning	Evening	Night	
K_a (hr^{-1})	5.98 ± 1.08	4.42 ± 0.47	5.65 ± 0.77	N. S.
C_{max} ($\mu g/ml$)	6.84 ± 0.24	6.78 ± 0.44	6.58 ± 0.32	N. S.
t_{max} (hr)	0.37 ± 0.05	0.42 ± 0.03	0.39 ± 0.05	N. S.
AUC ($\mu g \cdot hr/ml$)	17.3 ± 0.8	15.5 ± 2.0	19.0 ± 0.7	$p < 0.05$
V_d (L)	9.97 ± 0.43	10.03 ± 0.59	10.58 ± 0.51	N. S.
K_e (hr^{-1})	0.477 ± 0.026	0.475 ± 0.037	0.408 ± 0.023	$0.05 < p < 0.10$
$t_{1/2}$ (hr)	1.49 ± 0.08	1.52 ± 0.11	1.75 ± 0.10	$p < 0.05$
CL (L/hr)	4.71 ± 0.25	4.60 ± 0.12	4.26 ± 0.16	$p < 0.05$

Administration time was as follows ; morning : 8 : 00, evening : 16 : 00, night : 0 : 00 (n=9, mean±S. E.)

Table 2 Duration Over Target Gentamicin Concentration in Plasma After Three Different Times of Day

Target concentration of gentamicin ($\mu\text{g/ml}$)	Time over target concentration			Statistical significance (ANOVA)
	Morning	Evening	Night	
3.0	2.2 ± 0.1	2.2 ± 0.1	2.4 ± 0.1	N. S.
2.0	3.2 ± 0.2	3.2 ± 0.1	3.5 ± 0.1	$p < 0.05$
1.0	4.7 ± 0.2	4.8 ± 0.2	5.3 ± 0.2	$p < 0.05$
0.5	6.2 ± 0.3	6.3 ± 0.3	7.0 ± 0.3	$p < 0.05$

Administration time was as follows ; morning : 8 : 00, evening : 16 : 00, night : 0 : 00 (n=9, mean $\pm$ S. E.)

morning and evening, the half-life at night was significantly longer than morning and evening (morning ; 1.49 ± 0.08 hr, evening ; 1.52 ± 0.01 hr, night ; 1.75 ± 0.10 hr, mean $\pm$ S. E. $p < 0.05$). As there were no significant differences in volume of distribution (V_d) among the three dosing times shown in Table 1, the longer $t_{1/2}$ at night was due to the significantly lower clearance of the drug at night (morning ; 4.71 ± 0.25 L/hr, evening ; 4.60 ± 0.12 L/hr, night ; 4.26 ± 0.16 L/hr, mean $\pm$ S. E. $p < 0.05$). According to this temporal variation of gentamicin clearance in night, AUC was increased about 10 ~20% compared that in the morning and evening.

Discussion

A circadian rhythm in the acute toxicity of gentamicin in mice was first reported by our group⁴⁾, showing higher toxicity in light time, the resting period, and lower toxicity in dark time, the active period. In that study, the gentamicin-induced death could be attributed to respiratory insufficiency resulting from neuromuscular blockade, since neostigmine reduced the drug-induced mortality⁴⁾. The clearance of gentamicin given subcutaneously in midlight, rest period, was significantly lower compared with in middark, active period⁸⁾. The

gentamicin-induced mortality after repeated administration in mice well coincided with the circadian rhythm in the clearance of the drug. Exercise was reported to play an important role in drug absorption⁹⁾. To minimize this factor, in the present study all subjects were kept rested for 2 hours after administration and only nonstrenuous activity was allowed thereafter. The difference of absorption phase among three administration times could be small because there was no significant difference in K_a , t_{max} and C_{max} . The clearance of gentamicin at night was significantly lower compared with the other two administration times in man. This temporal variation in clearance could be due to the temporal change in the renal clearance of gentamicin which is primarily eliminated through the kidney. The reports that creatinine clearance is decreased in the night-resting period compared with in day-active period^{6,7)} support our results. It is interesting that the significant circadian rhythm in gentamicin kinetics showed lower clearance in the rest period and higher clearance in the active period, in both man and mice.

Early studies suggested that the incidence of ototoxicity increased when C_{max} values were more than $12 \mu\text{g/ml}$ and nephrotoxicity increased when C_{min} was more than $2 \mu\text{g/ml}$; the

recommended $C_{\min}$ was reported to be 1~2 $\mu\text{g/ml}$ ^{10~12). In the present study, no one showed a plasma concentration of gentamicin of more than 12 $\mu\text{g/ml}$ after a single muscular administration, and all concentrations at 8 hour after administration were less than 1 $\mu\text{g/ml}$. The duration over target gentamicin concentration was calculated using pharmacokinetic parameters of each subject (Table 2). Although no significant difference was observed with over 3 $\mu\text{g/ml}$ among three dosing times, the duration over 2 $\mu\text{g/ml}$ was significantly longer in night. The duration with over 1 $\mu\text{g/ml}$ was also significantly longer at night compared with morning and evening. There was a trend in that the duration over target concentration between night and the other two dosing times become longer according to the lower target concentration.}

Aminoglycoside antibiotics including gentamicin have a bactericidal effect depending on the concentration. In an *in vivo* study, it is reported that aminoglycoside antibiotics show much more of a bactericidal effect when administered in a total daily dose once a day compared with divided doses^{13). In animal studies, the advantage of the single daily dosing was shown in the reduced nephrotoxicity^{14,15). These phenomena may indicate that nephrotoxicity which is caused by the accumulation of aminoglycoside in the proximal renal tubular cells does not depend on the plasma concentration but rather on the duration of exposure of the kidneys to the drug. Furthermore, the duration of PAE was subsequently found to be related to aminoglycoside $C_{\max}$ values, showing that the higher the $C_{\max}$, the longer the PAE^{16,17). Therefore a single daily dosing schedule is recently recommended instead of multiple daily doses.}}}

Many clinical trials comparing aminoglyco-

side dosage regimens using the same total daily dose have been carried out. Although some studies have shown that there is no significant difference in nephrotoxicity or ototoxicity among dosage regimens^{18,19), some indicated that a single daily dosing schedule is better^{20~26). Similar findings have been reported using metaanalysis^{27~32). From those results, the strategy of administering a total daily dose once a day would be at least the same as or superior to a divided doses schedule. The difference in PAE could not be observed among the three different times of administration in the present study, because $C_{\max}$ was not different. However, the difference in duration over target concentration at night could be much longer compared with the other two different times of administration, if total daily dose with a once a day schedule is much more than 80 mg. The difference with over 1 $\mu\text{g/ml}$ could be about 1 hour by calculating using the pharmacokinetic parameters shown in Table 1 when 80 mg of the drug was used.}}}

As gentamicin is eliminated primarily through the kidney without any metabolism, there is a possibility that in renal impaired patients the time-of-day of drug administration may have a great influence on the time-concentration curve compared with those of normal volunteers. Since we found that the efficacy of aminoglycoside antibiotics such as amikacin against *Pseudomonas aeruginosa* depends on the time-of-day of administration in mice^{33), further studies are needed to clarify the clinical importance of this temporal variation in gentamicin kinetics.}

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