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Original Article

A Retrospective Analysis of Vancomycin Pharmacokinetics in Korean Neonates

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Background : Vancomycin is commonly used in neonatal intensive care units (NICU) for the treatment of gram-positive bacterial infections. The aims of this study were to determine the pharmacokinetic parameters of vancomycin in Korean neonates and to assess the percentage of neonates who reached a therapeutic level (trough concentrations of 10 to 20 mg/L) with empirical vancomycin dosing according to the Neofax®.

Methods : This retrospective study reviewed data from 81 neonates admitted to the NICU. The elimination rate constant (Ke), half-life ($T_{1/2}$), clearance (CL), and the extrapolated trough and peak levels were calculated using first-order pharmacokinetics and a one-compartment model.

Results : Only 21% of the patients achieved therapeutic trough levels (10 to 20 mg/L) with initial dosing according to the Neofax®. Vancomycin clearance was significantly correlated with postmenstrual age (PMA), postnatal age (PNA), weight, and serum creatinine (SCr) level. The recommended dosing regimen in neonates <27 weeks PMA was 10~15 mg/kg q12hr. For neonates in the 27 to 30 week PMA range, the recommended regimen was 15 mg/kg q12hr or 10 mg/kg q8hr for PNA 0~14 days, 10~13 mg/kg q8hr for PNA >14 days with SCr <0.6 mg/dL, and 10~15 mg/kg q12hr for PNA >14 days with SCr 0.6 to <1.5 mg/dL. For neonates in the 30 to 37 week PMA range, the recommended regimen was 10~13 mg/kg q8hr for PNA 0~14 days, 13 mg/kg q8hr or 10 mg/kg q6hr for PNA >14 days with SCr <0.6 mg/dL, and 15 mg/kg q12hr or 10 mg/kg q8hr for PNA >14 days with SCr 0.6 to <1.5 mg/dL. For neonates in the 37 to 44 week PMA range, the recommended regimen was 10~13 mg/kg q8hr for PNA 0~7 days, 13~15 mg/kg q6hr for PNA >7 days with SCr <0.6 mg/dL, and 13 mg/kg q8hr or 10 mg/kg q6hr for PNA >7 days with SCr 0.6 to <1.5 mg/dL. Sixty-three percent (51/81) of the neonates reached a therapeutic level with the new dosing regimen.

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Conclusions : The Neofax® vancomycin initial dosing regimen is insufficient for Korean neonates. Further studies are needed to validate the new dosing regimen suitable for achieving target therapeutic levels in Korean neonates.

[Key words] Vancomycin, Infant, Newborn, Pharmacokinetics

Vancomycin is a glycopeptide antibiotic and it is commonly used in neonatal intensive care unit (NICU) for treatment gram positive bacterial infection, especially methicillin-resistant Staphylococcus aureus (MRSA) infection.[1] Vancomycin is mainly eliminated by glomerular filtration. The clinical pharmacokinetics in neonates differ from adults, and glomerular filtration rate is immature but increases rapidly with growth and aging.[2] Therefore, when administering vancomycin to neonates, these pharmacokinetic properties should be considered.

In 2009, The American Society of Health-System Pharmacists (ASHP) recommended that trough vancomycin level be maintained above 10 mg/L to avoid development of resistance.[3] Recent neonatal studies have reported that existing neonatal vancomycin dosing guidelines' achievement rate of target level (trough level ≥10 mg/L) was low.[4-6]

There is a lack of Korean neonatal pharmacokinetic study, therefore there is no optimal vancomycin dosing guideline for Korean neonate. In NICU of the Seoul National University Children's Hospital (SNUCH), Neofax®[7] dosing regimen is used for initial vancomycin dosing before therapeutic dose monitoring (TDM). According to dosing regimen of Neofax®, initial dose of vancomycin is 10~15 mg/kg/dose and intervals of vancomycin are determined by the post-menstrual age (PMA) and postnatal age (PNA). The target trough level was changed 5~10 mg/L to 10~15 mg/L, however their dosing recommendations were not changed.

The aims of this study were to determine the pharmacokinetic parameters of vancomycin in Korean neonates, and assess the percentage of neonates who is reaching a therapeutic level (trough concentrations of 10~20 mg/L) with initial vancomycin dosing according to Neofax®.

METHODS

1. Patient eligibility

This retrospective study reviewed data from neonates hospitalized to the NICU of SUNCH between July 2012 and June 2015. This study was approved by our institutional review board (IRB No. H-1508-141-697). Neonates were included if they received vancomycin intravenously and had TDM records. Patients were excluded if they had acute renal failure (24hr-urine output <1 mL/kg/hr or serum creatinine (SCr) >1.5 mg/dL), or receiving renal replacement therapy, or their blood samples for vancomycin concentrations were obtained before 3rd dose, or their vancomycin administration record is insufficient, or they have congenital malformation (coarctation of aorta, pulmonary stenosis, Ebstein's anomaly, fetal hydrops, chromosomal disorder, syndromic disease).

2. Data collection

The following data were collected from electronic medical records (EMR): the date of birth and admission to the NICU, gender, gestational age (GA), birth weight, PNA and PMA at the date of vancomycin initiation, weight at the date of vancomycin initiation, weight at the date of blood sampling for determination of vancomycin level, blood sampling time and date, vancomycin levels, vancomycin administration records (dose and time of administration), blood urea nitrogen (BUN) and SCr, 24-urine output (mL/kg/hr) at the time nearest to the time of vancomycin initiation and the time of blood sampling for determination of vancomycin level, concomitant drugs that may affect to their renal function (ibuprofen, furosemide, spironolactone, amphotericin B, gentamicin, amikacin); on the first course of vancomycin therapy.

3. Pharmacokinetic analysis

Trough levels were measured 30 minutes before the administration of vancomycin. Peak level were not obtained routinely. Therefore, the volume of distribution of vancomycin in neonates was regarded as 0.46 L/kg with reference to Korean newborn data.[8] The elimination rate constant (Ke), half-life ($T_{1/2}$), clearance (CL), and the extrapolated trough and peak level were calculated using 1st-order pharmacokinetics and 1-compartment model.

Trough serum concentrations between 10 and 20 mg/L were considered therapeutic level. Initial dose required to achieve steady state level of trough 10~15 mg/L was calculated using obtained mean pharmacokinetic parameters and pharmacokinetic equations.

4. Statistics

Statistical analysis was performed using IBM SPSS version 22. Pearson's correlation test was used to find significant ($p<0.05$) association between CL and variables.

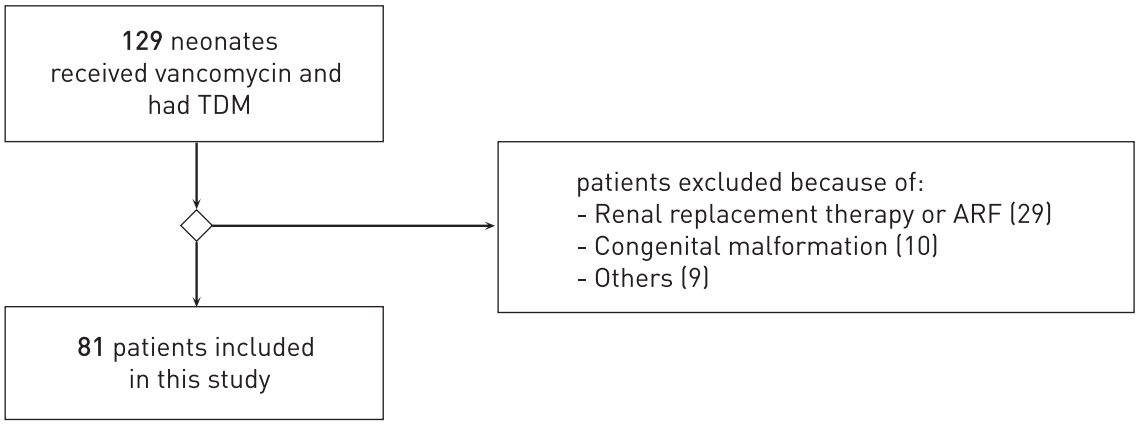
RESULTS

There were one-hundred-twenty-nine neonates who received vancomycin and had TDM records during the study period. Among them, twenty-nine had renal replacement therapy or ARF. And ten had congenital malformation, nine had insufficient data for study (e.g. inappropriate blood sampling time, initial vancomycin administration before hospital transfer). Therefore, eighty-one neonates were included in this study (Fig. 1). Patient demographics are presented in Table 1. Their mean PMA was 34.7±5.5 weeks (range 24.0~44.0) and premature neonates (GA < 37 weeks) were 58 (71.6%). Extremely low birth weight infants (ELBWI) were 37 (45.7%) of the patient. Their mean vancomycin dose was 10.9± 2.1 mg/kg/dose.

Table 2 shows the calculated vancomycin mean pharmacokinetic parameters (elimination rate constant, half-life, clearance). The mean (±SD) Ke was 0.16 (±0.07) hr^{-1} and the mean (±SD) $T_{1/2}$ was 5.6 (±3.3) hours. The mean (±SD) CL was largest in the 37~44 weeks' PMA 0.093 (0.035) L/hr/kg and smallest in the <27 weeks' PMA 0.042 (0.021) L/ hr/kg.

Among eighty-one patients, seventy-nine was administered vancomycin according to the Neofax® 2011 (Table 3). Among the seventy-nine extrapolated trough levels, therapeutic trough level (10~20 mg/L) was 17 (21.5%), sub-therapeutic level (<10 mg/L) was 55 (69.6%) (Fig. 2). Mean trough level was 9.7±8.7 mg/L.

Vancomycin CL was significantly correlated with PMA ($p<0.001$ and $R=0.488$), PNA ($p<0.001$



TDM, therapeutic drug monitoring; ARF, acute renal failure

Fig. 1 Flowchart of included patients

and R=0.533), weight ($p<0.001$ and R=0.361) and SCr ($p<0.001$ and R=−0.645) (Table 4, Fig. 3~4).

To calculate optimal dose and interval to reach therapeutic range, we put the obtained elimination constants of each PMA groups into the 1st-order pharmacokinetic equations. Table 5-1 and Table 5-2 present vancomycin dosing scale and recommended initial vancomycin dose and interval to achieve target level. It is based on weight, PMA, PNA and SCr. The recommended dosing regimen in <27 weeks' PMA was 10~15 mg/kg q12hr. Those in 27 to 30 weeks' PMA was 15 mg/kg q12hr or 10 mg/kg q8hr (PNA 0~14 days) and 10~13 mg/kg q8hr (PNA >14 days, SCr <0.6 mg/dL) and 10~15 mg/kg q12hr (PNA >14 days, SCr 0.6~<1.5 mg/dL) respectively. Those in 30 to 37 weeks's PMA was 10~13 mg/kg q8hr (PNA 0~14 days) and 13 mg/kg q8hr or 10 mg/kg q6hr (PNA >14 days, SCr <0.6 mg/dL) and 15 mg/kg q12hr or 10 mg/kg q8hr (PNA >14 days, SCr 0.6~<1.5 mg/dL). Those in 37 to 44 weeks' PMA was 10~13 mg/kg q8hr (PNA 0~7 days) and 13~15 mg/kg q6hr (PNA >7 days, SCr <0.6 mg/dL) and 13 mg/kg q8hr or 10 mg/kg q6hr (PNA >7 days, SCr 0.6~<1.5 mg/dL) res-pectively.

The predicted percentage of neonates who is reaching a therapeutic level with the recommended regimen was 63.0% (51/81) (Fig. 5).

With exclusion of outliers on 75% confidence interval of correlation between PMA and CL (Fig. 3), the predicted percentage of neonates achieving therapeutic level with the new regimen increased to 82.3% (51/62). Those of subtherapeutic trough level was 4.8% (3/62, range 7~9 mg/L), and supratherapeutic trough level was 12.9% (8/62, range 21~25 mg/L).

DISCUSSION

The purposes of this study were to find out the pharmacokinetic parameters of vancomycin in Korean neonates, and assess target level achievement rate of empirical vancomycin dosing according to Neofax®.

Our study shows low rate (21%) of target level achievement of initial vancomycin dosing. It is similar to those of a recent neonatal study.[9] It is

Table 1 Patient demographics (N=81)

Characteristic	
Gender, Male:Female	1.13:1
Gestational age [weeks, Mean±SD (range)]	31.5±5.7 (23.1~41.1)
Premature (<37 weeks) [n (%)]	58 (71.6)
Birth weight [kg, Mean±SD (range)]	1.64±1.10 (0.39~3.80)
ELBWI (<1 kg) [n (%)]	37 (45.7)
PMA [weeks, Mean±SD (range)]	34.7±5.5 (24.0~44.0)
PMA [n (%)]	
<27 weeks	8 (9.9)
≥27 and <30 weeks	13 (16.0)
≥30 and <37 weeks	24 (29.6)
≥37 and ≤44 weeks	36 (44.4)
Postnatal age [days, Mean±SD (range)]	23.7±23.0 (2~114)
Body weight [kg, Mean±SD (range)]	1.88±1.11 (0.37~3.87)
Baseline SCr [mg/dL, Mean±SD (range)]	0.52±0.31 (0.07~1.42)
Baseline SCr [n (%)]	
<0.6 mg/dL	52 (64.2)
≥0.6 and <1.0 mg/dL	22 (27.2)
≥1.0 and <1.5 mg/dL	7 (8.6)
Urine output [mL/kg/hr, Mean±SD (range)]	3.7±0.8 (2.3~6.3)
Vancomycin dose [mg/kg, Mean±SD (range)]	10.9±2.1 (8.9~20.2)
Vancomycin daily dose [mg/kg/day, Mean±SD (range)]	26.8±9.6 (9.7~60.5)
Concommitant drugs [n (%)]	
Aminoglycosides	40 (49.4)
Diuretics	29 (35.8)
Amphothericin B liposomal	2 (2.5)
Multiple birth [n (%)]	28 (34.6)
Oligohydramnios [n (%)]	11 (13.6)

ELBWI, extremely low birth weight infants; SCr, serum creatinine; PMA, postmenstrual age

suggested that vancomycin initial dosing regimen of Neofax® is inappropriate also in Korean neonates. According to the new vancomycin dosing regimen, the daily dosage requirements in each PMA group were higher than those of the Neofax®. It is recommended to consider that

Table 2 Vancomycin mean pharmacokinetic parameters (N=81)

Parameter	Mean±SD	Range
K_e (hr^{-1})	0.16±0.07	0.03~0.42
$T_{1/2}$ (hr)	5.6±3.3	1.7~23.5
CL (L/hr/kg)	0.07±0.034	0.01~0.19
PMA <27 weeks	0.042±0.021	0.027~0.091
PMA 27~<30 weeks	0.062±0.019	0.032~0.097
PMA 30~<37 weeks	0.055±0.021	0.014~0.098
PMA 37~44 weeks	0.093±0.035	0.033~0.191

PMA, postmenstrual age

Table 3 Vancomycin initial dosing guideline by Neofax® Initial Dose: 10 to 15 mg/kg/dose

PMA	PNA	Interval
29 weeks of less	0 to 14 days	18 hours
	Older than 14 days	12 hours
30 to 36 weeks	0 to 14 days	12 hours
	Older than 14 days	8 hours
37 to 44 weeks	0 to 7 days	12 hours
	Older than 7 days	8 hours
45 weeks or more	ALL	6 hours

PMA, postmenstrual age; PNA, postnatal age

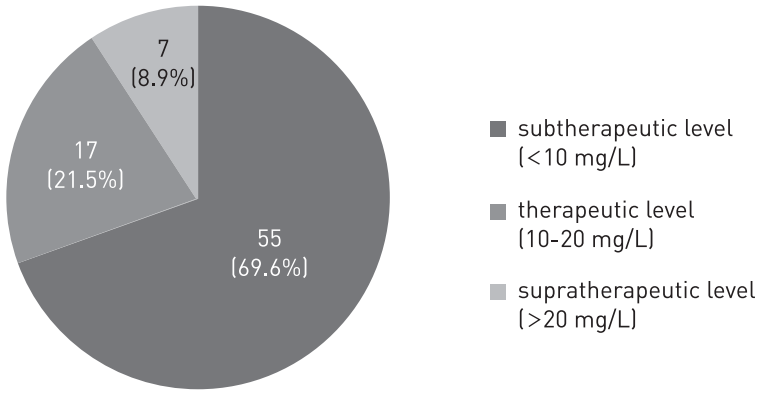


Fig. 2 Extrapolated trough level at steady state (N=79)

Table 4 Correlation between vancomycin clearance and variables

Variable	Vancomycin clearance	
	R	P value
Gender	−0.175	0.119
GA (weeks)	0.169	0.131
PMA (weeks)	0.488	<0.001
PNA (days)	0.533	<0.001
Birth weight (kg)	0.185	0.097
Body weight (kg)	0.361	<0.001
24hours-urine output (mL/kg/hr)	0.145	0.197
Baseline serum creatinine (mg/dL)	−0.645	<0.001
Drugs		
Aminoglycoside	−0.020	0.861
Diuretics	−0.133	0.238
Amphotericin B liposomal	−0.156	0.165
Oligohydramnios	−0.114	0.310
Multiple birth	−0.143	0.202

GA, gestational age; PMA, postmenstrual age; PNA, postnatal age

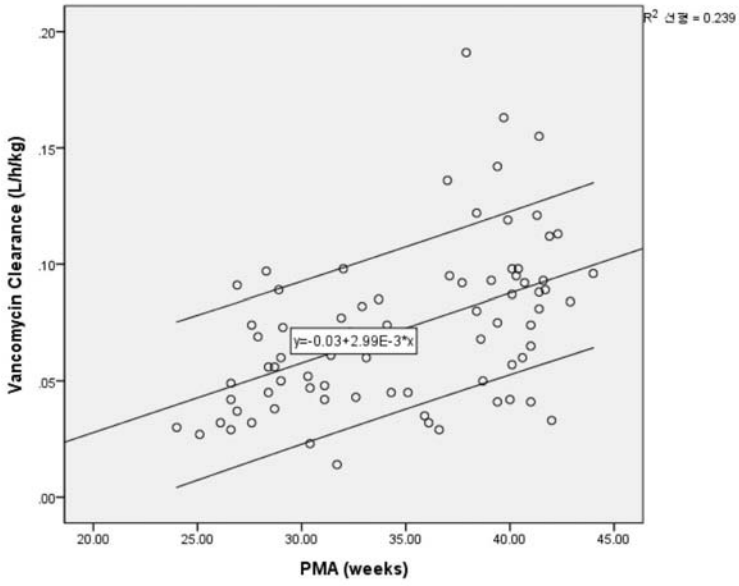


Fig. 3 Correlation between vancomycin clearance and postmenstrual age with 75% confidence interval

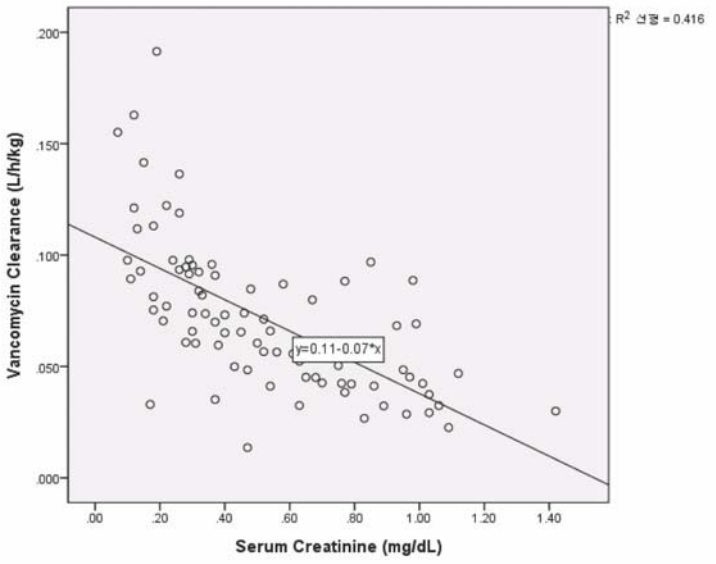


Fig. 4 Correlation between vancomycin clearance and serum creatinine level

Table 5-1 Vancomycin dosing scale

Scale	Dose (mg/kg)	Interval (hr)	Daily dose (mg/kg/day)
1	10	12	20
2	15	12	30
3	10	8	30
4	13	8	39
5	10	6	40
6	13	6	52
7	15	6	60

raised initial dosage would be needed to achieve target level.

There is a lack of published data of Korean neonatal vancomycin pharmacokinetic parameters. One Korean study in 1996, based on vancomycin serum levels obtained from 39 neonates, reported that the mean CL, Vd, $T_{1/2}$ was 0.13±0.08 L/hr, 0.46±0.12 L/kg, 5.6±2.13 hours.[8] In our study, when we calculated mean pharmacokinetic parameters (Ke, CL, $T_{1/2}$), Vd was regarded as 0.46 L/kg which is reported as mean Vd in the previous Korean study, because peak serum concentration were unavailable. On the other hand, the Vd was different from the results of another study in Korea, which included fewer numbers (PMA ≤30: Vd 0.79±0.11 L/kg, PMA 31~36: Vd 0.55±0.06 L/kg, PMA ≥ 37: Vd 0.56±0.19 L/kg)[10] or a published western data (PMA 27~30: Vd 0.55±0.02 L/kg, PMA 31~36: Vd 0.56±0.02 L/kg, PMA >37: Vd 0.57± 0.02 L/kg).[11] The actual Vd of our study group might be higher than 0.46 L/kg and therefore the actual $T_{1/2}$ might be slightly longer than that of this study accordingly. The mean clearance was similar to those of published western data.[11]

The serum creatinine level was significantly correlated with vancomycin CL. Serum creatinine based dosing was suggested,[4] however for a first few days after birth, SCr would be inaccurate to estimate actual renal function.[12]

Table 5-2 Recommended vancomycin dosing regimen

PMA (weeks)	PNA (days)	SCr (mg/dL)	Dosing regimen (dosing scale)	Daily dose (mg/kg/day)
<27	-	-	10~15 mg/kg q12hr (1~2)	20~30
27~<30	0~14	-	15 mg/kg q12hr or 10 mg/kg q8hr (2~3)	30
	>14	<0.6	10~13 mg/kg q8hr (3~4)	30~39
		0.6~<1.5	10~15mg/kg q12hr (1~2)	20~30
30~<37	0~14	-	10~13 mg/kg q8hr (3~4)	30~39
		<0.6	13 mg/kg q8hr or 10 mg/kg q6hr (4~5)	39~40
		0.6~<1.5	15 mg/kg q12hr or 10 mg/kg q8hr (2~3)	30
37~44	0~7	-	10~13 mg/kg q6hr (5~6)	40~52
	>7	<0.6	13~15 mg/kg q6hr (6~7)	52~60
		0.6~<1.5	13 mg/kg q8hr or 10 mg/kg q6hr (4~5)	39~40

PMA, postmenstrual age; PNA, postnatal age; SCr, serum creatinine

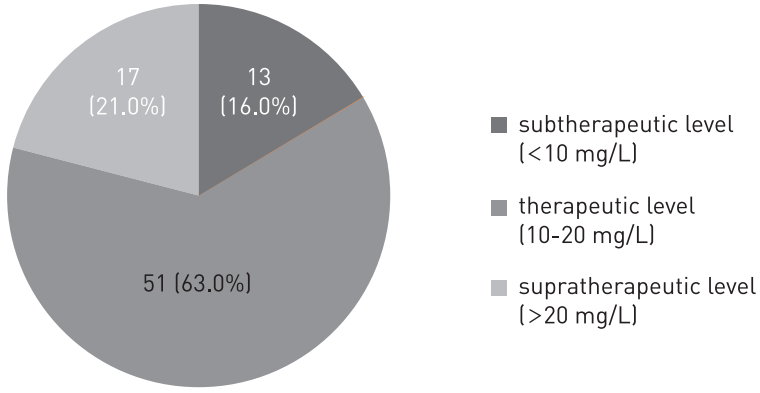


Fig. 5 The predicted trough level at steady state with the recommended vancomycin dosing regimen (N=81)

Therefore, we suggested the new dosing regimen to take into account SCr when PNA is longer than 7 or 14 days.

Among the 19 outliers on the 75% confidence interval of correlation between PMA and CL, 10 have bigger CL for the PMA and 9 have smaller CL for the PMA. 7 of 10 who have bigger CL for the PMA have PNA >30 days. In this regard, we should consider the possibility that neonates whose PNA longer than 30 days have bigger CL for their PMA. 5 of 9 who have smaller CL for the PMA have SCr ≥0.6 mg/dL. Therefore, it should be considered that neonates whose SCr is considerably higher than the average could have

lower CL than our study result.

The recent Korean study reported that only 15.8% (6 of 38) neonates achieved the therapeutic range with Neofax® vancomycin dosing.[13] They analyzed the characteristics of subtherapeutic level group and suggested that PMA, daily dose, dosing interval were major factors of achievement of the vancomycin therapeutic range. However, neither the pharmacokinetic data nor the adjusted dosage guideline was not suggested in their study.

In our study, we suggested new vancomycin dosage guideline for neonates targeting trough level 10~20 mg/L. Our study had the limitations of retrospective study. The post-dose serum levels were unavailable; therefore the volume of distribution was referenced for previous data. In addition, each PMA group's sample size was too small.

CONCLUSIONS

The vancomycin dosing according to Neofax® resulted in low achievement rate of the therapeutic trough level (10~20 mg/L). Therefore, this initial dosing regimen would be insufficient to the Korean neonates, and the dose is generally needed to be raised in normal renal function. Further studies are needed to validate the new dosing regimen suitable for Korean neonate to achieve target therapeutic level.

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