MMJ

Malta Medical Journal, 2024; 36(2)
http://mmsjournals.org/index.php/mmj/40

ORIGINAL ARTICLE

Gentamicin therapeutic drug monitoring in neonates: an observational study

Paul Torpiano, David Pace

Background

Gentamicin is important in the treatment of suspected neonatal sepsis, while also potentially oto- and nephrotoxic. Therapeutic drug monitoring of serum gentamicin levels (SGL) helps to prevent this. We present an investigation into the influence of birthweight, gestational age, and appropriateness-for-gestational age on the rates of high SGLs amongst neonates treated for suspected sepsis.

Methods

Case notes of neonates admitted to the neonatal and paediatric intensive care unit from 2013-2017 who received intravenous gentamicin treatment were reviewed. The dosing regimen, SGL, and demographic details were recorded. Trough SGLs ≥2mg/L before the 2nd gentamicin dose were taken as indicative of unsafe levels. Mean SGLs and percentage of safe SGLs were compared for each category (birthweight, gestational age, appropriateness-of-weight-for-gestational age) using odds ratios (Student's t-test), 'N-1' Chi squared test, and correlation coefficient.

Results

In total 170 neonatal gentamicin results were analysed. Nineteen (11.2%) of these were 32mg/L. Stratifying the results according to birthweight showed significantly higher mean gentamicin levels in neonates weighing <1.5kg (1.34mg/L; 95% CI: 1.16-1.53) and 1.5-3kg (1.33mg/L; 95% CI: 1.13-1.52), compared to those weighing >3kg (0.71mg/L; 95% CI 0.57-0.85). Premature neonates born at 28 weeks' gestation or less had significantly higher mean gentamicin levels (1.69mg/L; 95% CI: 1.33-2.04) than those born at term (0.84mg/L; 95% CI: 0.68-0.99mg/L).

Conclusions

While the current gentamicin dosing guidelines are safe, extremely premature neonates born under 28 weeks are at higher risk for high gentamicin trough levels and potential toxicity. Extended interval gentamicin dosing may have a role in mitigating for this.

Dr Paul Torpiano, MD,
Department of Child & Adolescent Health,
Mater Dei Hospital,
Msida, Malta

Prof David Pace, MD, PhD
Department of Child & Adolescent Health,
Mater Dei Hospital,
Msida, Malta

The initial empirical treatment of neonatal sepsis should include an aminoglycoside such as gentamicin.[1] This antimicrobial exhibits concentration-dependent bactericidal activity against gram-negative bacteria, as well as synergistic activity against important gram-positive organisms when combined with a penicillin.[2,3] This useful addition to the broad-spectrum coverage in treating neonatal sepsis comes at the risk of oto- and nephrotoxicity, both known adverse effects associated with aminoglycoside use.[4] Although toxicity studies in neonates are rare, there is no evidence that aminoglycoside toxicity should be different in neonates compared with adults, in whom toxicity has been extensively studied.[5] Therefore, in order to minimise toxicity, therapeutic drug monitoring (TDM) is recommended to guide gentamicin treatment that extends beyond 3 days.[6] Gentamicin trough levels of 2mg/l or more, taken 1 hour before the second dose, are associated with toxicity, while peak concentrations <5mg/L are associated with reduced efficacy.[7,8]

Dosing regimens for gentamicin in neonatal sepsis have changed considerably over the years, and there remains significant variation in aminoglycoside dosing and TDM guidelines across neonatal units worldwide.[9] Despite this, most dosing guidelines recommended a dose of 4-5mg/kg of gentamicin administered every 24-48 hours, with subsequent doses adjusted according to TDM.[5] Local guidelines implemented at the neonatal and paediatric intensive care unit at Mater Dei Hospital in Malta (the only neonatal unit locally) recommend a gentamicin dose of 5mg/kg, administered at 24-36 hour intervals in neonates born at a gestation of 32 weeks or more, and at 36-hourly intervals in neonates born at a gestation of under 32 weeks.[10] These follow the British National Formulary and National Institute of Clinical Excellence recommendations for dosing of gentamicin in neonatal sepsis.[11] The safety of this regimen is monitored using TDM of SGLs taken 1 hour before the second gentamicin dose.[12]

We present an investigation into the influence of birthweight, gestational age, and appropriateness-for-gestational age on the rates of high SGLs amongst neonates treated for suspected sepsis.

MATERIAL AND METHODS

All neonates admitted to the neonatal and paediatric intensive care unit (NPICU) at Mater Dei Hospital in Malta from 2013 to 2017 and treated with at least 2 doses of intravenous gentamicin for suspected neonatal sepsis, and for whom TDM of trough serum gentamicin levels was done 1 hour before the second gentamicin dose, were included. In these cases, the gentamicin dosing regimen used was 5mg/kg every 36 hours in neonates born at under 32 weeks' gestation, while those born at 32 weeks' gestation or above were treated with 5mg/kg gentamicin every 24 hours. Clinical case notes for each of these patients were consulted, including the dedicated gentamicin treatment chart currently in use in the NPICU, and the following details documented: gender, date of birth, gestation in weeks, birthweight in kilograms, risk factors for gentamicin toxicity, antibiotic regimen used, age at start of gentamicin treatment, gentamicin start date, duration of treatment, and date of completion, date, timing, and result of trough serum gentamicin level, date, timing, and dose of previous gentamicin dose, the effect of TDM on subsequent gentamicin dosing, and documented potential reason for an inappropriately raised serum gentamicin level of >2mg/l. SGLs taken in neonates who received inappropriate doses of gentamicin, or that were sampled at inappropriate times in relation to the gentamicin dose, were excluded from subsequent analysis. Factors considered to increase the risk of gentamicin toxicity were clinical dehydration, diarrhoea or persistent vomiting, renal impairment (reduced urine output of <1ml/kg/hour; raised serum creatinine >120µmol/L in preterm neonates and >90µmol/l in term neonates), poor cardiac output, sepsis requiring inotropic support, a history of perinatal asphyxia, and concomitant medications (cephalosporins such as cefotaxime, vancomycin, amphotericin, furosemide, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors).[10] World Health Organisation standardised centile charts were consulted to identify the patients' centile for weight, and categorise the patients as small-for-gestational age, appropriate-for-gestational age, and large-for-gestational age. Serum samples taken for therapeutic drug monitoring were transported immediately to the laboratory, and stored at 4°C for up to 12 hours. Serum gentamicin levels were obtained using a gentamicin enzyme immunoassay (Emit 2000 Gentamicin Plus Assay, Beckman Coulter, CA, USA). Serum gentamicin levels equal to or above 2mg/l were taken as abnormally high. Ethical approval for this research was sought and obtained from the Faculty Research Ethics Committee at the University of Malta (FRECMDS_1920_196).

Mean, median and range were used to describe continuous variables, including gestation and trough serum gentamicin level, while percentages were used for categorical variables. 95% confidence intervals were calculated on Statistical Package for Social Sciences using binomial exact method. Odds ratios for mean gentamicin levels and gestations were calculated using Student's t-test, while proportions were compared using 'N-1' Chi squared test. p values of less than 0.05 were taken to indicate statistical

significance. Correlation coefficients were used to compare the relationship between birthweight, gestation, and serum gentamicin level.

RESULTS

A total of 183 neonatal trough serum gentamicin levels were recorded, of which 20 were above the safe threshold of ≥2mg/l (10.9%; 95% C.I. 6.8-16.4%). Six gentamicin levels were excluded from subsequent analysis as they were taken from patients receiving inappropriate doses of gentamicin (less or more than 5mg/kg), while a further 7 levels were excluded as the timing of the trough serum gentamicin level was deemed inappropriate. Of the 170 levels included in the final analysis, the mean and median gestation were 34.6 (95% C.I. 33.9-35.4) and 36 weeks respectively (range: 24-45.1 weeks), with a M:F ratio of 1.6:1. Birthweights ranged from 0.47kg to 5.18kg, with a mean and median of 2.32kg (95% C.I. 2.16-2.49kg) and 2.49kg respectively. Eight patients were commenced on gentamicin therapy beyond the age of 7 days (range: 7-26 days), while the majority (n=117; 68.8%, 95% C.I. 61.3-75.7%) were commenced on the first day of life. Nineteen of 170 results included in the final analysis were above or equal to 2mg/l (11.2%; 95% C.I. 6.9-16.9%), ranging from 2mg/l to 4.4mg/l. Amongst the raised serum gentamicin levels, the mean level was 2.51mg/l (95% C.I. 2.21-2.81mg/l). The serum gentamicin levels showed a negative correlation with both birthweight (R=-0.38; p<0.0001) and gestation (R=-0.4, p<0.0001).

The results were stratified according to 3 main categories: birthweight, gestation, and appropriateness for gestational age (Table 1). There was a significantly lower rate of safe SGLs in the neonates born under 28 weeks compared to both term neonates born >37 weeks (57.9% vs 95.9%, p<0.0001) and the overall cohort (57.9% vs 88.8%,

Table 1 Trough serum gentamicin levels in the study group stratified according to birthweight, gestation, and appropriateness for gestational age. (SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age; brackets = 95% confidence intervals)

Patient category	Safe trough levels (n, %) (95% CI)	Mean gestation (weeks) (95% CI)	Median gestation (weeks)	Mean gentamicin level (mg/l) (95% CI)	Range gentamicin level (mg/l)	Mean high gentamicin level (mg/l) (95% C.I.)	Range high gentamicin level (mg/l)
a. All (n=170)							
	151, 88.8% (83.1-93.1)	34.6 (33.9-35.4)	36	1.13 (1.02-1.23)	0-4.4	2.5 (2.21-2.81)	2-4.4
b. Birthweight							
<1.5kg (n=56)	46, 82.1% (69.6-91.1)	29.1 (28.4-29.9)	29.1	1.34 (1.16-1.53)	0-3.64	2.49 (2.13-2.84)	2.1-3.64
1.5-3kg (n=57)	49, 86% (74.2-93.7)	35.7 (35-36.5)	36	1.33 (1.14-1.52)	0-4.4	2.57 (1.89-3.25)	2-4.4
>3kg (n=57)	56, 98.2% (90.6-100)	38.9 (38.6-39.4)	38.9	0.71 (0.57-0.85)	0-2.8	2.2	2.2
c. Gestation							
<28 weeks (n=19)	11, 57.9% (33.5-79.7)	26.1 (25.6-26.6)	26	1.69 (1.33-2.04)	0.47-3.1	2.4 (2.14-2.65)	2.15-3.1
28-32 weeks (n=29)	28, 96.6% (82.2-99.9)	29.8 (29.3-30.2)	30	1.17 (0.94-1.4)	0-3.64	3.64	3.64
32-37 weeks (n=48)	41, 85.4% (72.2-93.9)	34.2 (33.7-34.6)	34	1.32 (1.14-1.5)	0-2.9	2.34 (2.01-2.67)	2.05-2.9
>37 weeks (n=74)	71, 95.9% (88.6-99.2)	39 (38.7-39.4)	38.9	0.84 (0.68-0.99)	0-4.4	2.83 (0-6.21)	2-4.4
d. Appropriateness for gestational age							
SGA (n=39)	34, 87.2% (72.7-95.7)	33.2 (31.5-34.9)	33	1.24 (0.95-1.53)	0-4.4	3.05 (1.85-4.24)	2.1-4.4
AGA (n=118)	105, 89% (81.9-94)	34.9 (34.1-35.8)	36.6	1.11 (0.99-1.23)	0-3.1	2.32 (2.12-2.52)	2-3.1
LGA (n=13)	12, 92.3% (64-99.8)	36.4 (34.5-38.2)	36.9	0.91 (0.53-1.29)	0-2.2	2.2	2.2

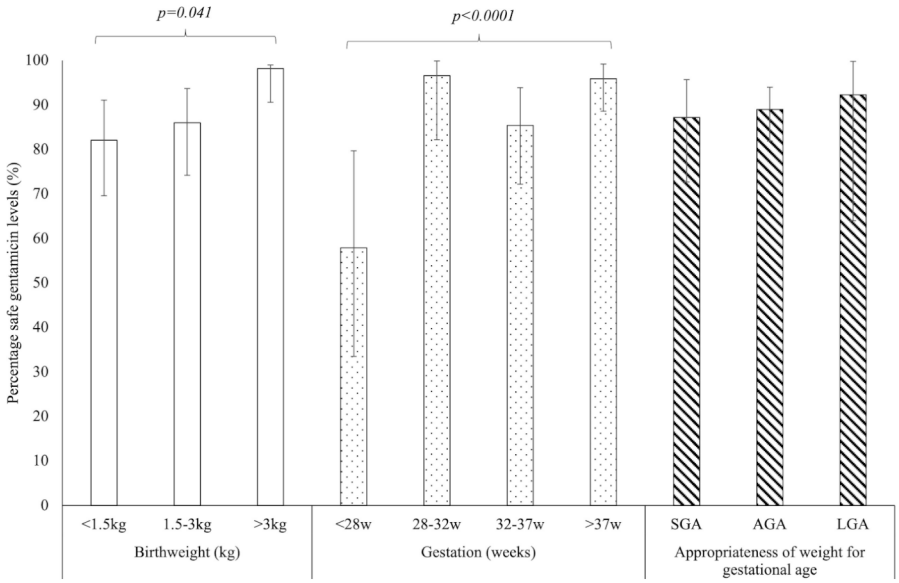

Figure 1 Percentage safe trough serum gentamicin levels amongst neonates in different birthweight, gestation, and appropriateness of weight-for-age categories.

p=0.0003). This was also seen when comparing neonates born weighing <1.5kg with those born over 3kg (82.1% vs 98.2%, p=0.0041). These differences were not seen when comparing the rates of safe SGLs amongst small for gestational age (SGA) with appropriate for gestational age (AGA) and large for gestational age (LGA) neonates. Focusing on the mean trough SGL, the mean SGL of neonates born at under 28 weeks' gestation was significantly higher than that of the overall cohort (1.69mg/l vs 1.13mg/l, p<0.0014) and of neonates born beyond 37 weeks' gestation (1.69mg/l vs 0.84mg/l, p<0.0001). Again, this is paralleled to a lesser extent in a comparison between neonates born <1.5kg and those 1.5kg and above (1.34mg/l vs 1.02mg/l, p=0.047), but not seen in the comparison of mean SGL in SGA with LGA or AGA infants (1.24mg/l vs 1.09mg/l, p=0.265).

While neonates born weighing <1.5kg were more likely to have unsafe SGLs than those >3kg (OR = 12.17 [95% C.I. 1.5-98.6]; p=0.019), they were not at a higher risk for unsafe SGLs than neonates weighing 1.5kg or more overall (OR=2.54 [95% C.I. 0.97-6.66]; p=0.059). Neonates born under 28 weeks were more likely than those born at >28 weeks (OR = 9.26 [95% C.I. 3.09-27.76]; p=0.0001), 28-32 weeks (OR = 20.37 [95% C.I. 2.27-182.46]; p=0.0071), 32-37 weeks (OR = 4.26 [95% C.I. 1.27-14.33]; p=0.0192), >32 weeks (OR = 8.15 [95% C.I. 2.67-24.9]; p=0.0002), and >37 weeks (OR = 17.21 [95% C.I. 3.95-74.94]; p=0.0001) to have unsafe trough SGLs. This contrasts with SGA infants who were not found to be at increased risk for unsafe SGLs compared with the AGA and LGA groups combined (OR = 1.23 [95% C.I. 0.41-3.66]; p=0.71) (Figure 1).

DISCUSSION

Despite the known risk of oto- and nephrotoxicity, aminoglycosides remain an important part of the treatment of neonatal sepsis in association with a penicillin and, incases of suspected Gram-negative meningitis, a third generation cephalosporin.[1] Fortunately, since efficacy and toxicity of aminoglycosides show a strong correlation with serum concentrations, TDM has proven helpful in monitoring therapy with this class of antimicrobials.[5] A dosing interval of 36 to 48 h in neonates is generally able to maintain safe trough SGLs of ≤2 mg/L..[6] Nonetheless, unexpectedly high SGLs can still occur, and the long-term effects of such high serum concentrations remain uncertain [13] The overall rate of safe trough SGLs of 88.8% (95% C.I. 83.1-93.1%) taken in our centre compares favourably with similar studies elsewhere, with Rocha et al Krishnamoorthy et al and Vervelde et alreporting safe levels in 59%, 67% and 95% of neonates respectively.[14–16]

Dosing recommendations for gentamicin in neonatal sepsis have changed considerably over the years: gentamicin was previously administered in doses of 2.5mg/kg/12h, before evidence showed once daily dosing at 4-5mg/kg/day to provide higher peak and

lower trough SGLs [17–19]. Most recently, extending the dose interval to 36-48 hours with a dose of 5mg/kg has been recommended, particularly in very low birthweight (VLBW) or extremely premature neonates [20–23]. Tailoring the dose according to gestation and birthweight is another recent advancement in the field, with recommendations for a gentamicin dose of 5mg/kg/48h in neonates with a gestational age of ≤29 weeks, a dose of 4.5mg/kg/36h in neonates with a gestational age of 30 to 34 weeks, and a dose of 4mg/kg/day when the gestational age is ≥35 weeks.[24] While extending the gentamicin dosing interval to 48 hours in neonates born ≤29 weeks has been adopted in some centres, this is not yet reflected in the British National Formulary gentamicin dosing recommendations, upon which local gentamicin dosing guidelines are based. This reflects concerns around a potential risk for suboptimally-treated neonatal sepsis in patients treated with gentamicin administered every 48 hours rather than every 36 hours. Future revisions of the local gentamicin dosing guidelines could consider this practice, however, as a means to mitigate for the increased risk of high SGLs reported here in those born ≤29 weeks. Stratifying for birthweight, Begg et alshowed that neonates of a birthweight of <1.5kg, 1-2.49kg and ≥2.5kg could be optimally treated with doses administered at intervals of 48h, 36h, and 24h respectively.[25] These data suggest that amending the local guidelines to include specific dosing recommendations for VLBW or extremely-premature neonates may result in safer gentamicin administration. Consistent with findings in this study, Krishnamoorthy et alreported lower rates of safe SGLs in neonates born weighing under 2.5kg in Singapore.[15]

Despite evidence for the safety and efficacy of extending interval doses to 48 hours in specific neonatal subgroups, there remains considerable variation across dosing guidelines on how to do this, with doses varying from 4-6mg/kg/dose, dosing intervals ranging from 24-48 hours, and total daily doses ranging from 2.5-6mg/kg/day.[6,20,22,26] Complicating matters further, aminoglycoside pharmacokinetic studies also vary in the recommended acceptable threshold for SGL, varying from 0.5mg/L to 2mg/L.[5] Furthermore, there is evidence that making dosing guidelines more complex may increase the incidence of dosing errors related to prescription, dilution, manipulation and administration, and showing that underdosing with aminoglycosides in the neonatal intensive care setting is common.[27,28] Future research should focus on whether the variations in SGLs we have shown correlate in practice with a higher rate of long-term oto- and nephrotoxicity, and identifying a more unified approach to gentamicin dosing that can be easily applied in clinical practice without increasing dosing errors, and that caters for specific patient subgroups such as VLBW and extremely premature neonates.

The data collection in this research was dependent on proper in-hospital documentation, so that documentation errors or missing information may have influenced the analysis and results. Furthermore, the categorisation of infants according to appropriateness-for-gestational age was based on international centile charts, as similar charts tailored to the local population are unavailable. Therefore, normal variation in the local birthweight compared with that in other populations may have impacted the comparisons of raised SGLs in SGA, AGA, and LGA infants. The authors did not make any distinction between suspected and confirmed sepsis, the latter of which may itself influence gentamicin pharmacokinetics.[29] This research also makes no attempt at extending conclusions on raised SGLs to those on the long-term clinical impact on neonates, as data on subsequent rates of deafness or renal function are not presented. This type of analysis would require a much longer term surveillance period with follow up of patients into adulthood, but would be important since previous studies have questioned the relationship between SGLs and

SUMMARY BOX

What is already known about this subject

- Gentamicin is often used in the empirical treatment of suspected neonatal sepsis.
- Gentamicin therapy is potentially oto- and nephrotoxic.
- Therapeutic drug monitoring of trough serum gentamicin levels helps to prevent toxicity.

What are the new findings

- There is a negative correlation between birthweight, gestation, and trough serum gentamicin levels taken one hour before the next dose.
- Extremely premature neonates born under 28 weeks have a higher risk of raised gentamicin levels and potential toxicity than those born beyond 28 weeks when gentamicin is administered at 36-hourly intervals.

clinical toxicity, and shown neonates to have a lower risk of oto- and nephrotoxicity compared with adult patients.[4,30]

CONCLUSION

Gentamicin is important in the treatment of suspected neonatal sepsis, but is also potentially oto- and nephrotoxic. Therapeutic drug monitoring of gentamicin levels helps prevent this. This study confirms that while the current gentamicin dosing guidelines are safe, extremely premature neonates born under 28 weeks are at higher risk for higher gentamicin trough levels and potential toxicity. Extended interval gentamicin dosing for this gestational category has been adopted in some centres for this reason, and may have a role locally. The long-term effects of high SGLs remain uncertain, and should be a focus of future research.

ABBREVIATIONS

AGA	Appropriate for gestational age
LGA	Large for gestational age
NPICU	Neonatal & paediatric intensive care unit
SGA	Small for gestational age
SGL	Serum gentamicin level
TDM	Therapeutic drug monitoring
VLBW	Very low birthweight

ETHICS APPROVAL

Ethical approval for this research was sought and obtained from the Faculty Research Ethics Committee at the University of Malta (FRECMDS_1920_196). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its amendments.

REFERENCES

1. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017; 390:1770–1780
2. Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th ed. McGraw Hill: New York; 2006
3. Darmstadt GL, Miller-Bell M, Batra M, et al Extended-interval dosing of gentamicin for treatment of neonatal sepsis in developed and developing countries. J Health Popul Nutr 2008;26:163–82
4. Kent A, Turner MA, Sharland M, Heath PT. Aminoglycoside toxicity in neonates: Something to worry about? Expert Rev. Anti. Infect. Ther 2014;12:319–331
5. Touw DJ, Westerman EM, Sprij AJ. Therapeutic drug monitoring of aminoglycosides in neonates. Clin. Pharmacokinet 2009;48:71–88
6. Van Donge T, Pfister M, Bielicki J, et al Quantitative analysis of gentamicin exposure in neonates and infants calls into question its current dosing recommendations. Antimicrob Agents Chemother 2018; 62:(4) e02004-17.
7. Rougier F, Claude D, Maurin M, Maire P. Aminoglycoside nephrotoxicity. Curr. Drug Targets - Infect. Disord. 2004;4:153–162
8. Kovarik JM, Hoepelman IM, Verhoef J. Once-daily aminoglycoside administration: new strategies for an old drug. Eur J Clin Microbiol Infect Dis 1989;8:761–9.
9. Kadambari S, Heath PT, Sharland M, et al Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units. J Antimicrob Chemother 2011;66:2647–2650.
10. Pace D, Attard-Montalto S, Paracandalo R, et al Neonatal intravenous gentamicin dosing protocol, Department of Child and Adolescent Health, Mater Dei Hospital, Malta; 2013
11. Joint Formulary Committee. British National Formulary for Children, BNF 77. Pharmaceutical Press, London; 2019
12. NICE. Neonatal infection (early onset): antibiotics for prevention and treatment; 2020 https://www.nice.org.uk/guidance/cg149/chapter/1-Guidance. Accessed 14 Jun 2020

13. Samiee-Zafarghandy S, Van Den Anker JN. Aminoglycosides and ototoxicity in neonates: Is there a relation with serum concentrations? Int. J. Clin. Pharmacol. Ther. 2013;51:993–994
14. Rocha MJ, Almeida AM, Afonso E, et al The Kinetic Profile of Gentamicin in Premature Neonates. J Pharm Pharmacol 2000;52:1091–1097.
15. Krishnamoorthy SS, Nair A, Furness J, Sanderson J. Gentamicin use in neonates: Should we have a change of practice? Scott Med J 2013;58:241–245.
16. Vervelde ML, Rademaker CMA, Krediet TG, et al Population pharmacokinetics of gentamicin in preterm neonates: Evaluation of a once-daily dosage regimen. Ther Drug Monit 1999;21:514–519.
17. Hindmarsh KW, Nation RL, Williams GL, et al Pharmacokinetics of gentamicin in very low birth weight preterm infants. Eur J Clin Pharmacol 1983;24:649–653.
18. Rao SC, Srinivasjois R, Moon K . One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst. Rev; 2016
19. Miron D. Once daily dosing of gentamicin in infants and children. Pediatr Infect Dis J 2001;20:1169–1173.
20. Rastogi A, Agarwal G, Pyati S, Pildes RS. Comparison of two gentamicin dosing schedules in very low birth weight infants. Pediatr Infect Dis J 2002;21:234–240.
21. Avent ML, Kinney JS, Istre GR, Whitfield JM. Gentamicin and tobramycin in neonates: comparison of a new extended dosing interval regimen with a traditional multiple daily dosing regimen. Am J Perinatol 2002;19:413–20.
22. Lanao JM, Calvo MV, Mesa JA, et al Pharmacokinetic basis for the use of extended interval dosage regimens of gentamicin in neonates. J Antimicrob Chemother 2004;54:193–198.
23. Mercado MCK, Brodsky NL, McGuire MK, Hurt H. Extended Interval Dosing of Gentamicin in Preterm Infants. Am J Perinatol 2004;21:73–77.
24. Young TE, Mangum B. The antibiotics. Neofax: a manual of drugs used in neonatal care, 20th ed. Thomson Healthcare, MOntvale, NJ, USA; 2007
25. Begg EJ, Vella-Brincat JWA, Robertshawe B, et al Eight years' experience of an extended-interval dosing protocol for gentamicin in neonates. J Antimicrob Chemother 2009;63:1043–1049.
26. Alshaikh B, Dersch-Mills D, Taylor R, et al Extended interval dosing of gentamicin in premature neonates ≤ 28-week gestation. Acta Paediatr Int J Paediatr 2012;101:1134–1139.
27. Allegaert K, Cossey V, van den Anker J. Dosing Guidelines of Aminoglycosides in Neonates: A Balance Between Physiology and Feasibility. Curr Pharm Des 2015;21:5699–5704.
28. Nunes BM, Xavier TC, Martins RR. Antimicrobial drug-related problems in a neonatal intensive care unit. Rev Bras Ter Intensiva 2017;29:331–336.
29. Lingvall M, Reith D, Broadbent R. The effect of sepsis upon gentamicin pharmacokinetics in neonates. Br. J. Clin. Pharmacol. 2005;59:54–61
30. Setiabudy R, Suwento R, Rundjan L, et al Lack of a relationship between the serum concentration of aminoglycosides and ototoxicity in neonates. Int J Clin Pharmacol Ther 2013; 51:401–406.