European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:2365–2369
https://doi.org/10.1007/s10096-019-03689-7

ORIGINAL ARTICLE

The evaluation of the appropriate gentamicin use for preterm infants

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Received: 30 June 2019 / Accepted: 26 August 2019 / Published online: 3 September 2019
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Abstract

Gentamicin (GM) is used for neonates as the initial treatment for neonatal bacterial infection. An association between high trough GM levels and the elevation of the serum creatinine (sCr) level and hearing loss has been reported, although there have been no reports investigating the serial changes in the sCr level in preterm neonates treated with GM. The present study evaluated the serial changes in the sCr level and the incidence of hearing loss in preterm neonates treated with GM. This study included 56 neonates born at a gestational age of 32–36 weeks. Fifteen (group 1) and 20 (group 2) neonates were treated with 2.5 mg/kg of GM every 12 h and 4 mg/kg of GM every 36 h, respectively. Group 3 included 21 neonates without GM therapy. Serum GM levels, serial changes in the sCr levels, and the incidence of hearing loss were then compared among the three groups. The serum trough GM level in group 2 was significantly lower than that in group 1 ($P < 0.001$), whereas the serum peak GM levels in these groups were almost the same. The ratio of the sCr level at birth to that at the 5th day of life in group 1 was the lowest among the 3 groups. No neonates had hearing loss. GM therapy worsened the sCr level in late preterm neonates, especially those with multiple doses per day. The appropriate use of GM is needed in order to prevent the occurrence of nephrotoxicity.

Keywords Gentamicin · Preterm infant · Nephrotoxicity · Ototoxicity

Introduction

The prediction of the development of severe bacterial infection (SBI) during the early neonatal period (within the first week of life) is difficult because neonates do not always become febrile and often show non-specific symptoms at the onset of SBI. Maternal factors, including chorioamnionitis, premature rupture of the membranes (PROM), and a maternal fever around delivery, are often responsible for the development of early-onset neonatal infection [1]. The Centers for Disease Control and Prevention (CDC) recommends that neonates born to mothers with suspected chorioamnionitis should undergo a limited diagnostic evaluation and receive antimicrobial agents while awaiting culture results [2]. Contrary to this strategy, some guidelines in other countries recommend close observation without antimicrobial agents for 48 h for asymptomatic neonates with risk factors for infection [3–5]. In clinical practice, neonates born to mothers with risk factors for neonatal infection are prone to being administrated antimicrobial agents immediately after birth [6]. In particular, bacterial infection is often more severe in preterm neonates than in term neonates, and the treatment for infectious diseases tends to be excessive for preterm neonates [7].

The combination of gentamicin (GM) and ampicillin (ABPC) is generally used as the initial treatment for suspected early-onset neonatal SBI, except for meningitis [3]. These antimicrobial agents are given to high-risk neonates until infection can be excluded. High serum trough GM levels and a prolonged duration of GM treatment can cause nephrotoxicity and ototoxicity [8]. Although the traditional dosing strategy of GM is to prescribe multiple doses per day, elevated trough GM levels have been observed in a substantial number of

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neonatal patients, and the dosing interval has been adjusted according to gestational age [9]. Some previous studies have investigated the association between high trough GM levels and the elevation of the serum creatinine (sCr) level and hearing loss [10–12], but no studies have yet evaluated the serial changes in the sCr level in preterm neonates treated by GM.

To determine the appropriate use of GM for preterm neonates during early neonatal period from the point of view of adverse drug reactions, we evaluated the serial changes in the sCr level and the incidence of hearing loss at different dosing intervals of GM. In addition, we compared these values between preterm neonates with and without GM therapy during the early neonatal period.

Materials and methods

Study design

In the neonatal intensive care unit (NICU) of our hospital, through 2014, 5 mg/kg of GM per day was administrated in 2 divided doses for preterm neonates born at gestational ages of 32 to 36 weeks during the early neonatal period. The administration of GM for preterm neonates was changed to 4 mg/kg every 36 h in January 2015 [13]. In the present prospective observational study performed from 2013 to 2017, serum trough and peak GM levels as well as serial changes in the sCr level and the incidence of hearing loss after GM therapy were compared between the preterm neonates treated with 2.5 mg/kg of GM every 12 h and those treated with 4 mg/kg of GM every 36 h. In addition, serial changes in the sCr level and the frequency of hearing loss were compared between the preterm neonates with and without GM therapy.

Subjects

A total of 56 preterm neonates born at gestational ages between 32 and 36 weeks whose parents consented to participate in this study were enrolled. Neonates with respiratory distress syndrome, severe asphyxia, shock, seizures, anomalies of kidney or ear, major congenital anomalies, and neuromuscular disorder were excluded. Of these neonates, 35 received ABPC and GM immediately after birth because of suspected SBI, chorioamnionitis, or PROM. Fifteen (group 1) and 20 (group 2) patients who were admitted to our NICU from 2013 to 2014 (group 1) and 2015 to 2017 (group 2) were treated with 2.5 mg/kg of GM every 12 h and 4 mg/kg of GM every 36 h, respectively. Neonates with a body weight of ≤ 2 kg ($n = 16$) and > 2 kg ($n = 19$) were treated with 100 mg/kg of ABPC every 12 h and with 150 mg/kg of ABPC every 8 h, respectively. The remaining 21 preterm neonates without antimicrobial therapy served as normal controls (group 3).

The measurement of the serum GM level

GM was administered intravenously for 60 min. All peripheral blood samples were obtained by venipuncture. A trough sample was taken within 60 min prior to the third dose, and a peak sample was taken 60 min after the end of the infusion of GM. The target GM levels were 5–12 μg/mL for the peak and < 2 μg/mL for the trough.

The measurement of the sCr level

We measured the sCr level at birth (sCr_0) and 5th day of life (sCr_5). All peripheral blood samples were obtained by venipuncture. The ratio of sCr_0 to sCr_5 (sCr_0/sCr_5) was calculated in all eligible neonates.

The evaluation of the hearing ability

All eligible neonates were examined for hearing loss before their discharge from the NICU. The auditory brain stem response (ABR) was used for the evaluation.

Statistical analyses

The results were analyzed using the GraphPad Prism 6 statistics software package (GraphPad Software, San Diego, CA, USA). In analyses of demographic and clinical characteristics, the Mann-Whitney *U* test was used to compare the quantitative values, and the chi-squared test and Fisher's exact test were used to compare the qualitative values. The GM concentrations were compared by the Mann-Whitney *U* test. *P* values < 0.05 were considered statistically significant. In the analysis of sCr_0/sCr_5, the Kruskal-Wallis test was used for comparisons among the three groups. If the values were considered to be statistically significant ($P < 0.05$), the comparison between 2 of the 3 groups was performed by the Mann-Whitney *U* test with Bonferroni's correction, with *P* values < 0.017 being considered statistically significant.

Ethical approval

Our study was approved by the Institutional Review Board of the University of Occupational and Environmental Health, Japan.

Results

The demographic characteristics of the three groups are shown in Table 1. Among the three groups, there was a significant difference in the birth weight but not in the gestational age. The birth weight of group 2 was heavier than other groups ($P = 0.02$). The duration of antimicrobial therapy in group 1

Table 1 The demographic and clinical characteristics in the 3 groups

Characteristics	Group 1[*1] ($n = 15$)	Group 2[*2] ($n = 20$)	Group 3[*3] ($n = 21$)	P value[*4]
Gestational age, days, median (range)	240 (226–252)	239 (229–255)	243 (226–249)	0.43
Gender, %male	53.0%	55.0%	52.4%	0.99
Birth weight, g, median (range)	1896 (1402–2244)	2164 (1714–2754)	1938 (1346–2604)	0.02
Small for gestational age, n	1	0	6[+]	0.02
Peripheral white blood cell counts at birth, /μL, median (range)	11,500 (7200–29,200)	12,800 (8900–44,800)	10,600 (6500–16,200)	0.06
Serum C-reactive protein level at birth, mg/dL, median (range)	0 (0–0.90)	0.01 (0–0.62)	0 (0–0.05)	0.09
Duration of the antimicrobial therapy[*5], day, median (range)	3 (3–5)	3 (3–5)	N/A	0.22
Confirmed severe bacterial infection, n	0	0	0	N.D.
Neonates born to mothers with risk factors responsible for the development of neonatal infection			v	
Chorioamnionitis	5	10	0[#+]	< 0.01
Premature rupture	8	9	3[#]	0.03
Emergency caesarean section for prolapse of the umbilical cord	1	0	0	0.25
Without GBS screening	1	1	0	0.52
Serum creatinine level at birth, mg/dL, median (range)	0.54 (0.43–0.86)	0.53 (0.4–0.72)	0.62 (0.48–0.91) [+]	0.02
Serum creatine level at the 5th day of life, mg/dL, median (range)	0.61 (0.43–0.78)	0.55 (0.42–0.83)	0.55 (0.43–0.69)	0.19
Hearing loss at discharge, n	0	0	0	N.D.

[*1] Neonates treated by 2.5 mg/kg of gentamicin every 12 h

[*2] Neonates treated by 4.0 mg/kg of gentamicin every 36 h

[*3] Neonates without the antimicrobial therapy

[*4] P values indicate the result of comparison among the 3 groups by Kruskal-Wallis test. If the values was considered to be statistically significant ($P < 0.05$), the comparison between 2 of the 3 groups was performed by the chi-squared test or Mann-Whitney U test with the Bonferroni correction

[*5] Combination therapy of gentamicin and ampicillin

[#] $P < 0.017$ compared with group 1, [+] $P < 0.017$ compared with group 2

GBS group B Streptococcus, *N/A* not applicable, *N.D.* not done

(median, 3 days; range, 3–5 days) was almost the same as that in group 2 (median, 3 days; range, 3–5 days). There were no patients with confirmed SBI among the eligible neonates. The maternal characteristics did not differ markedly between groups 1 and 2.

There were no significant differences in the serum peak GM level between group 1 (median, 8.8 μg/mL; range, 5.1–10.7 μg/mL) and group 2 (median, 8.7 μg/mL; range, 3.2–11.3 μg/mL) (Fig. 1a). The serum peak GM level was ≥ 5 μg/mL in 100% and 90% of neonates in group 1 and group 2, respectively. The serum trough GM level in group 2 (median, 0.9 μg/mL; range, 0.4–1.4 μg/mL) was significantly lower than that in group 1 (median, 3.7 μg/mL; range, 2.1–5.3 μg/mL, $P < 0.001$) (Fig. 1b). The trough GM levels of all the neonates in group 2 were < 2 μg/mL, whereas those of all the neonates in group 1 were > 2 μg/mL.

The sCr_0 level in group 3 (median, 0.62 mg/dL; range, 0.48–0.91 mg/dL) was the highest among the 3 groups. The sCr_0 level in group 2 (median, 0.53 mg/dL; range, 0.40–0.72 mg/dL) was almost the same as that in group 1 (median, 0.54 mg/dL; range, 0.43–0.86 mg/dL) (Table 1). The sCr_5 levels in group 1 (median, 0.61 mg/dL; range, 0.43–0.78 mg/dL) were higher than those in the other 2 groups (group 2, median, 0.55 mg/dL; range, 0.42–0.83 mg/dL; group 3, median, 0.55 mg/dL; range, 0.43–0.69 mg/dL), although there was no significant difference (Table 1). The sCr_0/sCr_5 was < 1.0 in group 1 (median, 0.89; range, 0.62–1.51), indicating that the sCr_5 level tended to be higher than the sCr_0 level (Fig. 2). The sCr_0/sCr_5 in group 1 was significantly lower than that in group 3 (median, 1.16; range, 0.73–1.86) (Fig. 2). The ratio in group 2 (median, 1.0; range, 0.61–1.62) was lower than that in group 3 and higher than that in group 1, but the differences were not statistically significant.

All neonates were examined for hearing loss using ABR before discharge. No neonates developed hearing loss during the investigation period (Table 1).

Discussion

In the present study, we explored the appropriate use of GM for preterm infants during the early neonatal period in order to prevent adverse drug reactions. A few studies have compared the serial changes in the sCr level between preterm neonates treated with GM at different dosing intervals and those without GM therapy at all. With regard to nephrotoxicity, GM at

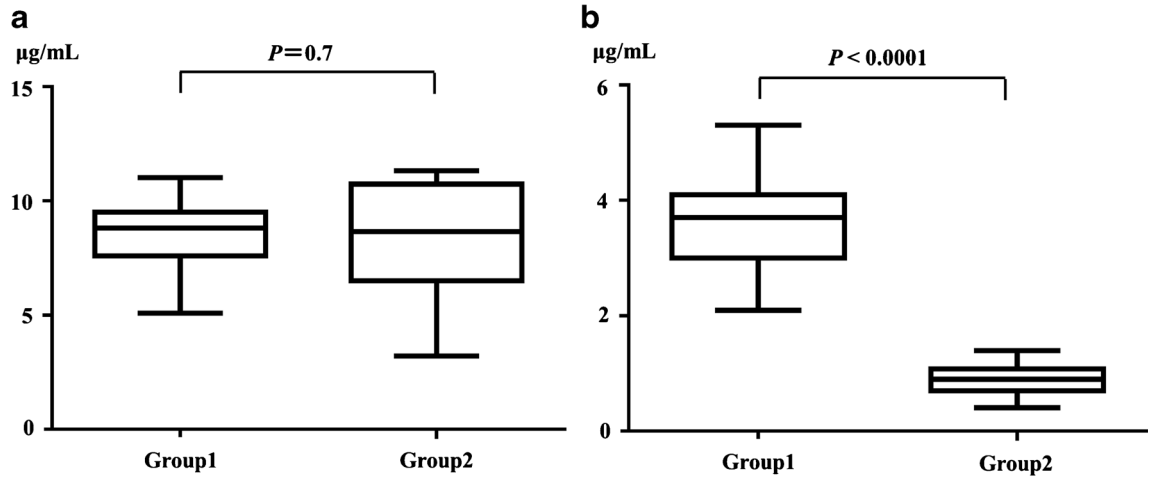

Fig. 1 Serum peak (**a**) and trough (**b**) gentamicin levels. Group 1 and group 2 indicated preterm neonates treated with 2.5 mg/kg of gentamicin every 12 h and 4 mg/kg of gentamicin every 36 h, respectively

4 mg/kg every 36 h seemed to be a more appropriate treatment for preterm neonates during the early neonatal period than a treatment with GM at 2.5 mg/kg every 12 h. Furthermore, the indications for antimicrobial therapy should be carefully considered, even in preterm neonates with maternal risk factors for neonatal infection.

With regard to aminoglycosides, the trough level is important to monitor in order to prevent adverse drug events [13]. Some previous studies have recommended the administration of GM at 4–5 mg/kg every 36 h for preterm neonates born at gestational ages of 32 to 36 weeks within the first week of life [12, 14]. In the present study, the serum peak GM levels in 90% of preterm neonates treated with GM at 4 mg/kg every 36 h was higher than the minimal effective blood concentration (5 μg/mL), and the serum trough GM level in all of the preterm neonates was within the safe range (< 2 μg/mL), suggesting that this dosing regimen was more appropriate for preterm neonates than a treatment with GM at 2.5 mg/kg every 12 h.

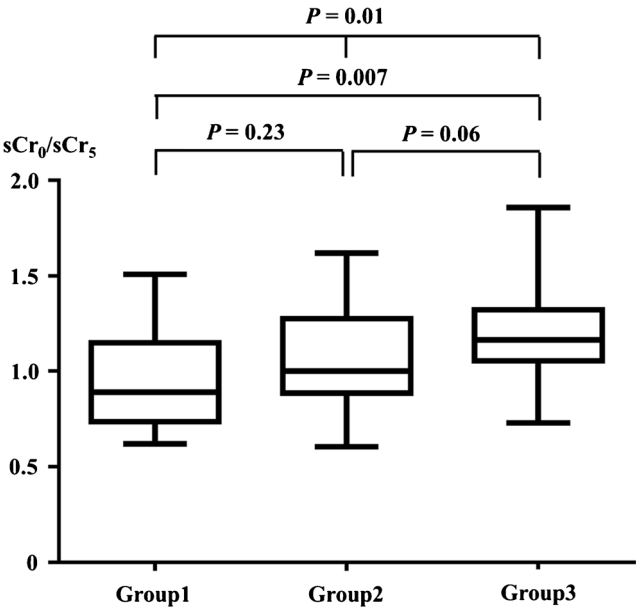

Fig. 2 Ratio serum creatinine levels at birth (sCr_0) to those at 5th day of life (sCr_5). Group 1 and group 2 indicate preterm neonates treated with 2.5 mg/kg of gentamicin every 12 h and 4 mg/kg of gentamicin every 36 h, respectively. Group 3 indicates preterm infants without gentamicin therapy. The Kruskal-Wallis test was used to compare among the 3 groups (the top of number). The comparison between 2 of the 3 groups was performed by Mann-Whitney *U* test (other number)

The blood creatinine level increases temporarily after birth and subsequently falls to steady state levels [15]. The more premature a neonate, the greater the rise in creatinine after birth and the later the fall in creatinine begins [15, 16]. The creatinine concentration in late preterm neonates falls steadily after peaking at around 15 h of age [16]. In the present study, the sCr_5 level was lower than the sCr_0 level in preterm neonates without GM therapy, whereas the opposite trend was observed in preterm neonates with GM, especially those treated with GM at 2.5 mg/kg every 12 h. The main risk factor for GM-associated nephrotoxicity was the duration of therapy [17]. However, the median duration of GM therapy was only 3 days in the present study, indicating that an increase in the sCr level could be induced even by a short duration of inappropriate GM therapy.

The association between the occurrence of hearing loss and the administration of GM is controversial in neonates. A previous report recommended evaluating the hearing ability of neonates receiving aminoglycoside for > 7 days [18]. However, El-barbary et al. found that the incidence of hearing loss did not increase in neonates receiving GM for ≥ 5 days compared with those who received GM for < 5 days or did not receive GM at all [19]. The present study indicated that a short duration of GM therapy did not markedly affect the hearing ability in preterm neonates.

Neonates with clinical signs of SBI should be treated with an empirical antimicrobial regimen as soon as possible. However, the prediction of the development of SBI during the neonatal period is difficult. Therefore, inappropriate or unnecessary

antimicrobial therapy is often performed for neonates [20]. Only 5% of preterm neonates receiving antimicrobial agents had culture-proven infection [21]. Of note, antimicrobial therapy for neonates born to mothers with chorioamnionitis is recommended in the USA [2]. The present study suggested that GM therapy was prone to inducing an increase in sCr levels even with a short duration of appropriate therapy, suggesting that strict antimicrobial stewardship was needed in order to minimize the administration of unnecessary therapy.

The present study has some limitations. First, the long-term evaluation of nephrotoxicity could not be performed in the eligible neonates. Second, the differences in the sCr levels may have been caused by other factors, including ABPC and maternal factors. Finally, the study population was relatively small, which may have affected the accuracy of the statistical analysis.

In conclusion, the sCr level in preterm neonates after GM therapy was higher than that in the neonates without GM therapy, and it increased even with only a short duration of therapy. In addition, the serum trough GM levels in neonates receiving traditional dosing of GM were higher than those in neonates treated with GM of 4 mg/kg every 36 h. From the point of view of nephrotoxicity, the administration of GM of 4 mg/kg every 36 h might be a more appropriate dosing regimen for late preterm neonates during the early neonatal period, and unnecessary antimicrobial therapy should be avoided in these neonates.

Acknowledgments We appreciate the help of Dr. Brian Quinn (Japan Medical Communication, Fukuoka, Japan) for editing the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Our prospective observational study was approved by the Institutional Review Board of University of Occupational and Environmental Health, Japan.

Informed consent Informed consent was obtained from all individual participants included in the study.

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