Paediatrica Indonesiana

VOLUME 55 July • 2015 NUMBER 4

Original Article

Effect of intravenous gentamicin on urinary calcium excretion in newborns

Kurniawan Tan, Adrian Umboh, Ari L. Runtunuwu

Abstract

Background Studies in newborns and animals have shown that gentamicin increases urinary calcium excretion. New recommendation for gentamicin in newborns is administered intravenously 36-48 hourly. Subsequent to this new recommendation, there have been no further studies on the effects of extended gentamicin dosage on urinary calcium excretion in newborns.

Objective To assess the effect of intravenous gentamicin on urinary calcium excretion in newborns.

Methods This pretest – posttest study was done in the Neonatology Division of Prof. Dr. R. D. Kandou Hospital, Manado, from August to November 2013**.** Subjects were full-term newborns who received intravenous gentamicin every 36 hours and whose parents provided informed consent. We excluded newborns with asphyxia and cardiovascular shock, also those who received diuretics or steroids. Urine spot collection was done before, after the first dose, and after the second dose of intravenous gentamicin. Urinary calcium and creatinine levels were measuerd. Urine calcium excretion was defined as the ratio of urinary calcium to creatinine level.

Results Of 28 newborns, there were 16 males and 12 females. The median of urine calcium creatinine ratio before intravenous gentamicin was 0.021 (range 0.004 to 0.071) mg/mg. After first dose of gentamicin, the median ratio was 0.043 (range 0.009 to 0.156) mg/mg, and after the second dose of gentamicin, the median ratio was 0.144 (range 0.015 to 1.160) mg/mg.

Conclusion There is a significant increase in urinary calcium excretion after the first and second doses of intravenous gentamicin. Furthermore, a cumulative effect of gentamicin on urinary calcium excretion is observed after the second dose. **[Paediatr Indones. 2015;55:185-8]**.

Keywords*: urinary calcium excretion, intravenous gentamicin, newborns*

Gentamicin is a common first-line antibiotic therapy for infections in newborns. Gentamicin accumulates in tissue, especially in the kidneys (almost 10% of the total dosage accumulates in the proximal tubules). Almost 70% of calcium filtered by the glomerulus is reabsorbed at the proximal tubule and 30% reabsorbed at other sites. Gentamicin can alter kidney and tubular function. One type of tubular dysfunction is electrolyte wasting. Electrolyte balance is very important for newborns, especially those with illness. Electrolyte disorders can further worsen the condition of a sick newborn. One of these important electrolytes is calcium.[1,2]

Some studies in newborns and animals have shown that gentamicin increases urinary calcium excretion.[11-15] Injection every 36-48 hours is a new recommendation for intravenous gentamicin treatment in newborns.[3] Following this new recommendation, there have been no further studies on the effects of extended gentamicin dosage on urinary calcium

From the Department of Child Health, Sam Ratulangi University Medical School/Prof. Dr. R.D. Kandou Hospital, Manado, Indonesia.

Reprint requests to: Kurniawan Tan, MD, Department of Child Health, Sam Ratulangi University Medical School/Prof. Dr. R.D. Kandou Hospital, Jalan Raya Tanawangko, Manado 95115, North Sulawesi, Indonesia. Tel. +62-431-865883, E-mail: kur_hwang@yahoo.com.

excretion in newborns. Hence, the aim of this study was to assess the effect of intravenous gentamicin on urinary calcium excretion in newborns.

Methods

We conducted a pretest – posttest study in the Neonatology Division of Prof. Dr. R.D. Kandou Hospital, Manado, from August to November 2013. Subjects were full-term newborns who received intravenous gentamicin every 36 hours and whose parents provided informed consent. We excluded newborns with asphyxia and cardiovascular shock, also those who received diuretics or steroids. Patients were included by consecutive sampling. The minimum required sample size was calculated to be 27 newborns, with a power of 90% and α 0.01. This study was approved by the Medical Faculty Ethics Committee for Research at the University of Sam Ratulangi.

Urine specimens were collected using urine collectors by medical personnel and then sent to *Prodia Laboratory* for urinary calcium and creatinine examinations. Urine spot collection was done before, after the first dose, and after the second dose of intravenous gentamicin. Urine calcium excretion was defined as the ratio of urinary calcium to creatinine level.

For the subjects' characteristics, data were analyzed by descriptive analysis. Wilcoxon signed-rank test was used to assess for a possible effect of intravenous gentamicin on urinary calcium excretion. Significance level used was $P \leq 0.01$. The data were processed with *SPSS for Windows version 21* software.

Results

Of 28 newborns participated in this study, 16 were male and 12 were female. The characteristics of subjects are shown in **Table 1**.

The urinary calcium excretion data were not distributed normally, hence, we used Wilcoxon signed-rank test for analysis. After the first dose of intravenous gentamicin, urinary calcium excretion increase [median 0.043 (range 0.009 to 0.156) mg/mg] compared to that before intravenous gentamicin was given [median 0.021 (range 0.004 to 0.071) mg/mg; P=0.001]. Similar results were also observed after the second dose of intravenous gentamicin [median 0.144 (range 0.015 to 1.160) mg/mg] compared to before intravenous gentamicin, and after the first dose of intravenous gentamicin (P=0.001) (**Figure 1**).

Table 1. Characteristics of study subjects

Characteristics	Newborns (N=28)
Gender, n	
Male	16
Female	12
Mode of delivery, n	
Normal	21
C-section	7
Mean gestational age (SD), weeks	38.64 (0.99)
Mean birth weight (SD), grams	2,892.86 (309.33)
Mean birth length (SD), cm	48.07 (1.98)
Median APGAR score (range)	
1st minute	6 (4 to 8)
5th minute	8 (6 to 10)

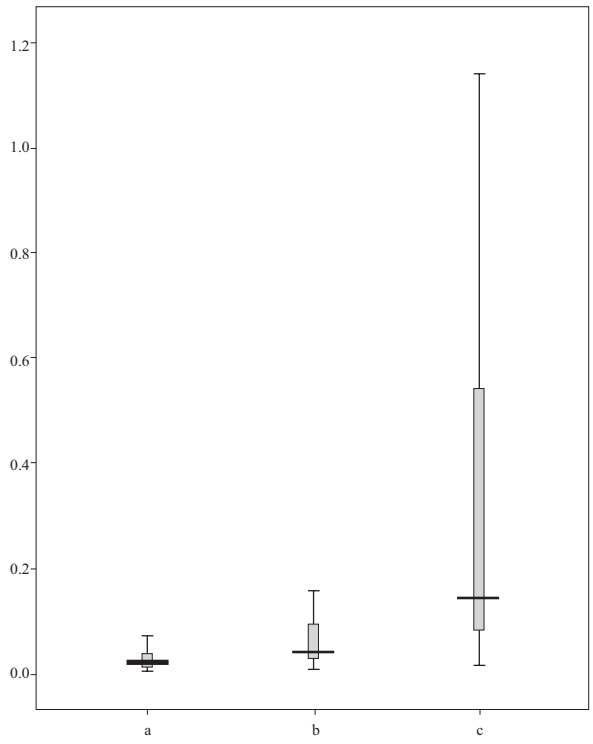

Figure 1. Urine calcium excretion (a) before intravenous gentamicin, (b) after the first dose of intravenous gentamicin, (c) after the second dose of intravenous gentamicin

= SD = upper range = lower range

Discussion

The results of this study demonstrate an effect of gentamicin on renal calcium excretion. The mechanism of gentamicin-mediated changes in urinary calcium excretion remains unexplained.[4] Gentamicin filteres freely through the glomerulus without being metabolized, and around 10% of it accumulates in the kidney cortex, especially at the proximal tubules.[4,5] Ward *et al*. hypothesized that sodium-potassium-chloride co-transporter (NKCC2) level decreases after injection of gentamicin into mice, hence, decreasing the lumen positive voltage and increasing urinary calcium excretion, even in the therapeutic range of gentamicin.[5] Gentamicin accumulates in the kidney cortex through a specific transport mechanism that involves megalin binding to gentamicin.[6] Gentamicin increases cytosolic calcium concentrations through an inositol triphosphate-mediated mechanism and activates the calcium-sensing receptor (CaR). This receptor (CaR) is found on the basolateral membrane of tubules.[7] Activation of CaR inhibits reabsorption of calcium in the tubules.[8,9]

Several studies have shown an increase in fraction excretion of calcium after gentamicin infusion in term and preterm newborns, and this effect continued even after gentamicin infusion stopped. There was also increased incidence of hypocalcemia after starting single daily dose of gentamicin infusions, which peaked on third day of treatment. These studies suggest that kidney does not adapt by decreasing urine calcium excretion. Indeed, a cumulative effect of gentamicin was observed.[10-12]

We found an increase in urinary calcium excretion after the first dose of gentamicin, and an even higher increase after the second dose of gentamicin. A previous study showed that serum calcium levels were lowest on third day of gentamicin.[13] Another study found that in mice, gentamicin increased urine calcium excretion, but after day 3 and onwards, the effect decreased.[14] This three days observation may due to adaptation of the tubules to conserve transient receptor potential vanilloid-5 (TRPV5) and calbindin-D28k, thus improving urine calcium reabsorption. Tugay *et al*. showed gentamicin administration in preterm newborns increase urine calcium excretion from day 3 onwards.[15]

This study was the first of its type to be conducted in Manado, Indonesia and was the first to use extended doses of gentamicin (5 mg/kg body weight every 36 hours) to assess the effect on urinary calcium excretion. The results could provide new insights for scientists and health practitioners, particularly in pediatrics, and also the community. This study adds to our understanding of gentamicin and urinary calcium excretion, hence, we could recommend calcium supplements for newborns who receive gentamicin infusions at the every 36-hour dosage regimen.

A limitation of this study was the use of urine spot collection rather than 24-hour urine collection to determine urine calcium levels. Also, subjects were not followed until the end of therapy, and serum calcium level was not measured.

In conclusion, urinary calcium excretion increase after gentamicin infusion. A cumulative effect of gentamicin treatment on urinary calcium excretion is also observed following the second dose.

Conflict of interest

None declared.

References

1. Pacifici GM. Clinical pharmacokinetics of aminoglycosides in the neonate: a review. Eur J Clin Pharmacol. 2009;65:419–27.
2. Koo WWK, Tsang RC. Calcium and magnesium homeostasis. In: MacDonald MG, Seshia MMK, Mullet MD, editors. Avery's neonatology: pathophysiology and management of the newborn. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 848-75.
3. Fary R, Smith R. Neonatal pharmacopoeia. Melbourne: Royal Womens Hospital; 2005. p. 48-9.
4. Nagai J, Takano M. Molecular aspects of renal handling of aminoglycosides and strategies for preventing the nephrotoxicity. Drug Metab Pharmacokinetics. 2004;19:159–70.
5. Ward DT, Maldonado-Perez D, Hollins L, Riccardi D. Aminoglycosides induce acute cell signaling and chronic cell death in renal cells that express the calcium-sensing receptor. J Am Soc Nephrol. 2005;16:1236–44.
6. Nagai J, Saito M, Adachi Y, Yumoto R, Takano M. Inhibition of gentamicin binding to rat renal brush-border membrane

by megalin ligands and basic peptides. J Control Release. 2006;112;43–50.
7. Kwak JO, Kwak J, Kim HW, Oh KJ, Kim YT, Jung SM, *et al.* The extracellular calcium sensing receptor is expressed in mouse mesangial cells and modulates cell proliferation. Exp Mol Med. 2005;37:457–65.
8. Alexandridis G, Liberopoulos E, Elisaf M. Aminoglycoside-induced reversible tubular dysfunction. Pharmacology. 2003;67:118–20.
9. McLarnon S, Holden D, Ward D, Jones M, Elliot A, Ricardi D. Aminoglycoside antibiotics induce pH-sensitive activation of the calcium-sensing receptor. Biochem Biophys Res Commun. 2002;297:71–7.
10. Giapros VI, Cholevas VI, Andronikou SK. Acute effects of gentamicin on urinary electrolyte excretion in neonates. Pediatr Nephrol. 2004;19:322–5.
11. Chiruvolu A, Engle WD, Sendelbach D, Manning MD, Jackson GL. Serum calcium values in term and late-preterm neonates receiving gentamicin. Pediatr Nephrol. 2008;23:569–74.
12. Giapros VI, Andronikou SK, Cholevas VI, Papadopoulou ZL. Renal function and effect of aminoglycoside therapy during the first ten days of life. Pediatr Nephrol. 2003;18:46–52.
13. Jackson GL, Sendelbach MD, Stehel EK, Baum M, Manning WB, Engle WD. Association of hypocalcemia with a change in gentamicin administration in neonates. Pediatr Nephrol. 2003;18:653–6.
14. Lee CT, Chen HC, Ng HY, Lai LW, Lien YH. Renal adaptation to gentamicin-induced mineral loss. Am J Nephrol. 2012;35:279–86.
15. Tugay S, Bircan Z, Caglayan C, Arisoy AE, Gokalp AS. Acute effects of gentamicin on glomerular and tubular functions in preterm neonates. Pediatr Nephrol. 2006;21:1389-92.