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ORIGINAL ARTICLE

Serum calcium values in term and late-preterm neonates receiving gentamicin

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Abstract Since noting an apparent increase in hypocalcemia in neonates receiving gentamicin every 24 h (q 24 h) for ≥4 days, we have prospectively monitored serum calcium (Ca) values in these patients receiving prolonged gentamicin therapy. This study is a retrospective analysis of those values measured during gentamicin treatment. The study included neonates with gestational age ≥35 weeks who received ≥4 days of gentamicin therapy and in whom at least one serum Ca value was measured ≥47 h after initiation of therapy. Hypocalcemia was defined as a serum Ca level <8 mg/dl (2 mmol/l). Data were analyzed by Student *t*-test, chi-square test, and Pearson product moment correlation. There were 1,624 neonates that met the study criteria. Ca was <8 mg/dl in 241 (15%). Ca <8 mg/dl was more likely in boys than in girls (16.4% vs 11.8%, $P=0.01$) and in neonates <37 weeks gestational age (GA) than in those ≥37 weeks GA (23.9% vs 14.1%, $P=0.01$). A second Ca value was obtained in 883 neonates (54%); 23.2% of neonates with initial Ca <8 mg/dl remained hypocalcemic, and 30% of these were receiving oral Ca supplementation. The second Ca value was <8 mg/dl in eight neonates in whom initial Ca was ≥8 mg/dl. Hypocalcemia is not uncommon in neonates receiving gentamicin therapy, and it may occur more frequently in boys and late-preterm infants. These data suggest that the monitoring of serum Ca levels should be considered when gentamicin is given ≥ 4 days.

Keywords Serum calcium · Gentamicin · Antibiotics · Renal function · Renal calcium excretion · Neonate

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Introduction

Gentamicin is used frequently in the treatment of suspected or confirmed neonatal sepsis and/or pneumonia. Although nephrotoxicity secondary to gentamicin has been described extensively, this complication appears to be uncommon in neonates when serum drug levels are monitored closely [1]. When gentamicin is given every 24 h (q 24 h) (4 mg/kg per dose), the range of reported peak values is higher, and the range of trough values lower, than those of gentamicin given every 12 h (q 12 h) (2.5 mg/kg per dose) [1–3]. When compared with q 12 h dosing, q 24 h dosing of gentamicin (a) produces a higher serum peak to bacterial minimum inhibitory concentration ratio, (b) achieves a prolonged post-antibiotic effect, and (c) avoids the development of adaptive resistance. All these effects have been stated to improved clinical response, decrease nephrotoxicity, and also reduce ototoxicity [1–4]. However, after implementation of q 24 h gentamicin dosing in our nursery, we noted an apparent increase in the number of neonates with symptoms of hypocalcemia, including seizures [5]. To our knowledge, no other studies of human neonates have been reported that describe an increased incidence of hypocalce-

mia in term and late-preterm neonates treated with q 24 h gentamicin.

Animal and human studies have demonstrated that gentamicin and other aminoglycosides impair calcium transport in the renal tubules and, in some instances, result in a significant increase in urinary calcium excretion [6–9]. Parsons et al. demonstrated in the rat that the effect of gentamicin on calcium transport in the renal tubules is dose-related [9]. In addition, an association between aminoglycoside therapy and hypomagnesemia due to urinary magnesium losses has been reported, and this effect may influence serum calcium values [10]. However, the cause(s) of hypocalcemia is still unclear.

Since our previous report [5], we have monitored serum levels of calcium (Ca) in neonates receiving q 24 h gentamicin for >48 h. The purpose of this study was to provide an analysis of trends for sequential Ca values in term and late-preterm neonates receiving prolonged q 24 h gentamicin therapy and to report variables that might be associated with alterations of these values.

Methods

Criteria for admission to the Parkland Memorial Hospital Newborn Nursery (NBN) during the study period were gestational age ≥35 weeks, birth weight ≥2,100 g, and no apparent cardio-respiratory instability observed in the delivery room. "Late-preterm" neonates refers to those with gestational ages between 35 weeks and 36 weeks 6 days, and "term" neonates are defined as those of gestational ages ≥ 37 weeks. Within the NBN, a level 2 nursery is available for those neonates who require an increased level of care but who do not require continuous cardio-respiratory monitoring. Common medical diagnoses of neonates in the level 2 nursery include pneumonia, suspected or proven sepsis, hypoglycemia, transient respiratory distress, and withdrawal from illicit drugs.

We altered the dose and dosing schedule of gentamicin from 2.5 mg/kg per dose q 12 h to 4 mg/kg per dose q 24 h on 1 June 2000. Shortly afterwards, we noted an apparent increased incidence of hypocalcemia [5], and prospective monitoring of serum Ca in neonates receiving gentamicin for >48 h was initiated on 1 April 2001. This report summarizes a retrospective analysis of the data collected prospectively from 1 April 2001 to 31 January 2007 (70 months). Measurement of serum Ca values was not a routine aspect of care for other neonates in the level 2 nursery (except for those receiving prolonged gentamicin therapy), unless they exhibited symptoms of suspected hypocalcemia.

The study included neonates who had received gentamicin ≥4 days and had had at least one serum Ca value measured ≥47 h after the start of gentamicin therapy. In addition to gentamicin, the antibiotic regimen typically included ampicillin 50 mg/kg given q 8 h.

Hypocalcemia was defined as an initial serum Ca value < 8 mg/dl (2 mmol/l) [11]. Criteria for the treatment of hypocalcemia were: (a) serum Ca <7 mg/dl (1.8 mmol/l) or (b) symptoms consistent with hypocalcemia and with serum Ca levels between 7 mg/dl and 8 mg/dl (1.8 mmol/l and 2.0 mmol/l). If serum Ca was <6.5 mg/dl (1.6 mmol/l), the neonate was transferred to the neonatal intensive care unit (NICU) for further treatment. Neonates treated with calcium and/or magnesium supplementation while on gentamicin therapy were not excluded, so that the number requiring treatment and their response to therapy could be determined.

Blood was collected for serum Ca measurement on approximately day 3 or day 4 after initiation of gentamicin. If the neonate received gentamicin > 5 days, serum Ca measurement was repeated on day 6. Serum inorganic phosphorus (iP) and magnesium (Mg) levels also were determined when adequate samples were available. Serum Ca, iP, and Mg levels were measured with an Olympus AU640 analyzer (Olympus America Inc, Center Valley, PA, USA). Gentamicin peak and trough levels were typically obtained after 49 h (after the third dose) and 71 h (before the fourth dose) of therapy, respectively. Gentamicin levels were determined by fluorescence polarization immunoassay using AxSYM (Abbott Laboratories, Abbott Park, IL, USA). Statistical analysis included chi-square test, Student *t*-test, and Pearson product moment correlation. The Institutional Review Board at the University of Texas Southwestern Medical Center approved this study; written consent was not required, since laboratory studies were performed for clinical monitoring following our earlier study [5].

Results

During the study period, 87,307 neonates were admitted to the NBN, and 5,295 (6%) were admitted to the level 2 nursery. Routine monitoring of serum Ca values was performed in 1,809 neonates receiving > 48 h of gentamicin therapy. Of 1,809 neonates, 1,624 (90%) received ≥4 days of gentamicin therapy and also had at least one available serum Ca value measured ≥47 h after initiation of gentamicin, and thus met our criteria for data analysis. Birth weight was 3,666±606 g (mean ± SD) and gestational age (GA) was 39.4±1.7 weeks; 65.5% were male, and 83% were Hispanic. Table 1 shows the characteristics of the study population.

Gentamicin was started at 0.6 (0.1–6.4) days [median (range)] postnatal age, and initial Ca level was measured at

Table 1 Characteristics of the study population

Characteristics (n = 1,624)	
Gestational age (weeks)	40 (35–43)[a]
Birth weight (g)	3,670 (2,100–5,635)[a]
Ethnicity (%)	
Hispanic	83
Black	12
White	2
Asian	2
Other	3
Male (%)	65.5
Female (%)	34.5
Maternal diabetes, n (%)	8 (0.5)
Maternal gentamicin during labor, n	343
Diagnoses (%)	
Pneumonia	89
Sepsis	11 (2)[b]

[a] Median (range)
[b] Presumed (confirmed)

3.8 (2–9) days postnatal age. The mean and median values for the initial Ca were 8.9±0.9 mg/dl (2.2±0.2 mmol/l) and 9 (6.0–11.4) mg/dl [2.2 (1.5–2.8) mmol/l], respectively. Fig. 1 depicts the distribution of serum Ca values in the study population. In 241/1,624 (14.8%), the initial serum Ca value was <8 mg/dl (2 mmol/l), and in 47/241 (19.5%) of these neonates, serum Ca was <7 mg/dl (1.7 mmol/l). None of the neonates received intravenous calcium supplementation; however, 69/241 (28.6%) received oral calcium supplementation; of these 69 neonates, 16 (23%) received oral magnesium supplementation for hypomagnesemia. Although none of those with Ca values <8 mg/dl (2 mmol/l) required transfer to the NICU for hypocalcemia, 7/241 (2.9%) had symptoms suggestive of hypocalcemia; most of these neonates had neuromuscular irritability, but none had seizures.

The values of gentamicin peak and trough levels were available for analysis in 1,003/1,624 (61.7%) neonates. When all values were analyzed, weak but significant negative correlations were observed between initial Ca and gentamicin peak and trough levels (r=−0.08, P<0.05 and r=−0.28, P<0.01, respectively). When the values for only those neonates with hypocalcemia were analyzed, a significant negative correlation was observed between the initial Ca and the gentamicin trough values (r=−0.15, P< 0.05); however, a weak positive correlation existed between initial Ca and the gentamicin peak values (r=0.16, P< 0.05).

Serum iP and Mg were available in 1,601 and 1,188 neonates, respectively. A negative correlation was observed (r=−0.37, P<0.01) between initial Ca and iP. The correlation between initial Ca and Mg was not significant (P=0.4). When the values of only those neonates with hypocalcemia were analyzed, significant negative correlation was observed between initial Ca and iP (r=−0.23, P<0.01); the correlation between initial Ca and Mg was not significant (P=0.26).

Although hypocalcemia was more likely to occur in late-preterm neonates than in term neonates (23.9% vs 14.1%, P=0.01), among the 241 hypocalcemic neonates, 219 (90.9%) were term. Hypocalcemia was more likely in boys than in girls (16.4% vs 11.8%, P=0.01), and 174/241 (72.5%) with hypocalcemia were male. Two of the eight neonates whose mothers had diabetes were hypocalcemic, but neither required supplemental calcium. Three hundred and forty-three neonates were born to mothers who had been treated with gentamicin during labor (generally for maternal chorioamnionitis); 59 (16.8%) were hypocalcemic, but the incidence of hypocalcemia in this group was not significantly different (P=0.19) from that of those neonates whose mothers did not receive gentamicin during labor.

A second Ca level was measured in 883/1,624 (54%) neonates on postnatal day 6 (3.0–12.5 days). The mean and median for second serum Ca values were 9.5±0.8 mg/dl (2.4±0.2 mmol/l) and 9.7 (6.1–12) mg/dl [2.4 (1.5–3) mmol/l], respectively. In 60/883 (6.8%) neonates, Ca was < 8 mg/dl (2 mmol/l) and in 8/883 (0.9%) Ca was <7 mg/dl (1.7 mmol/l). Of 241 neonates in whom the initial serum Ca value was <8 mg/dl, 224 (93%) had a second Ca level measured (Fig. 1), and 52 (23.2%) remained hypocalcemic. Among those, 21 (30%) were already receiving calcium supplementation. Of the 1,383 neonates with an initial Ca value ≥8 mg/dl, a second serum Ca value was measured in 659 (47.6%). The value was <8 mg/dl in 8/659 (1.2%) neonates, and none had a serum Ca value <7 mg/dl (1.7 mmol/l).

Discussion

Gentamicin, usually in conjunction with ampicillin, is administered frequently to neonates with suspected or confirmed sepsis and/or pneumonia. However, this drug is not benign, and 6–26% of adults treated with gentamicin develop some degree of impaired renal function. This effect is due to active reabsorption and incomplete exchange of the drug by the proximal tubules, leading to high drug concentration in the renal cortex [12]. Abnormalities such as increased urine calcium-to-creatinine (Cr) ratio and increased fractional excretion of sodium and magnesium have been reported in neonates treated with prolonged gentamicin therapy [6–8]. In those studies, the observed hypercalciuria was attributed to the well-known nephrotoxic effect of

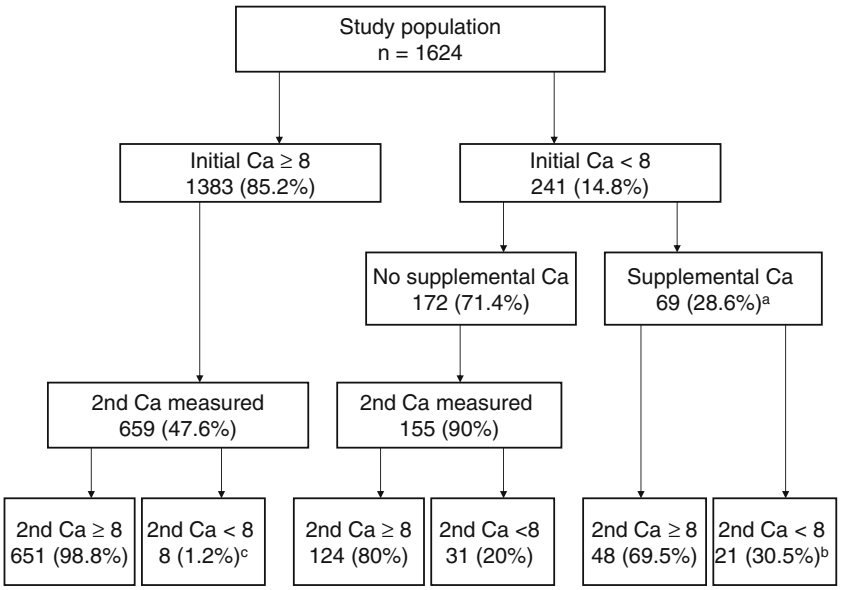

Fig. 1 Distribution of serum Ca values (mg/dl) in the study population. **a** Of the 69 who received supplemental Ca, 47 (68%) had an initial serum Ca value <7 mg/dl. **b** Among 21 neonates who remained hypocalcemic in spite of the treatment, five (23.8%) had a second serum Ca value <7 mg/dl. **c** Of the eight neonates who were hypocalcemic on the second serum Ca measurement, despite an initial serum Ca value ≥8 mg/dl, none had a value <7 mg/dl

gentamicin on proximal tubules, but, since the investigators had excluded neonates who had developed serum electrolyte abnormalities, the incidence of hypocalcemia was unknown. In contrast, in our study, measurement of urinary Ca excretion was not part of routine monitoring; however, serum Ca values in this population were examined. To the best of our knowledge, aside from our earlier study [5], serum Ca values have not been reported previously in neonates receiving prolonged aminoglycoside therapy.

The mechanism by which gentamicin causes alterations in urinary Ca and magnesium excretion is not well understood. Gentamicin may inhibit basilateral Ca transport in the proximal tubules, or it could displace Ca bound to the renal tubular brush border, leading to decreased absorption and increased urinary excretion [13]. Parsons et al. used precise locating techniques to demonstrate that the nephron site where gentamicin acts to reduce tubular Ca reabsorption is the early distal tubule [14]. Those results suggest that, in addition to the proximal tubular nephrotoxicity described above, a different mechanism for gentamicin-induced hypercalciuria may also play a role. Furthermore, hypomagnesemia due to renal Mg wasting can occur early in gentamicin therapy and may result in hypocalcemia through decreased parathyroid hormone (PTH) secretion and/or decreased PTH action on kidney and bone [10]. Another possible mechanism implicated in gentamicin-induced hypercalciuria and hypocalcemia includes alteration of the activity of the calcium-sensing receptor (CaR). The ability of the CaR to sense extracellular Ca is essential for the appropriate regulation of PTH secretion by the parathyroid glands [15]. McLarnon demonstrated that aminoglycosides evoked dose-dependent increases in intracellular Ca in CaR-transfected human embryonic kidney cells, but not in non-transfected cells [16]. Aminoglycosides increase CaR sensitivity to serum Ca, leading to PTH suppression that may result in hypercalciuria and hypocalcemia [17, 18].

We reported an apparent increased incidence of hypocalcemia in our NBN after the gentamicin dose and dosing schedule had been changed from 2.5 mg/kg per dose q 12 h to 4.0 mg/kg per dose q 24 h [5]. Although hypocalcemia has been defined by some as a serum total Ca level < 8.8 mg/dl (2.2 mmol/l) [19], for the purposes of our study we defined hypocalcemia as a total Ca value of <8 mg/dl (2 mmol/l). Among the neonates treated with ≥4 days of gentamicin therapy, 15% had initial Ca levels <8 mg/dl, measured, in most instances, following the expected postnatal nadir for serum Ca values [20]. These data support the importance of monitoring serum Ca in term and late-preterm neonates who have receive prolonged q 24 h gentamicin therapy. The absence of hypocalcemic seizures and fewer symptomatic study neonates, in contrast to our previous observation [5], suggest that the monitoring of serum Ca values in neonates receiving prolonged gentamicin therapy may have led to timely initiation of supplemental therapy in some instances. Possible risks associated with asymptomatic hypocalcemia are unclear at the present time. It also should be noted that multiple causes of hypocalcemia in the term neonate exist, and this retrospective analysis of prospectively collected data on neonates receiving prolonged gentamicin does not include other causes, such as unrecognized maternal, placental, fetal, or neonatal disorders.

As a group, the mean and median second serum Ca values increased, as expected, compared with the initial serum Ca values. Nevertheless, for neonates in whom a second Ca value was measured, 6.8% were hypocalcemic. These results suggest that it is important for a repeat serum Ca value to be measured toward the end of antibiotic therapy, especially if gentamicin is given for more than 5 days. Of the neonates receiving supplemental calcium, 30% remained hypocalcemic, further supporting the need for a repeat Ca measurement toward the end of gentamicin therapy. This suggests that some variable, such as an effect of gentamicin, might have played a role in this altered calcium homeostasis. This notion is supported by the observations of Andronikou et al., that elevation of the urine Ca/Cr ratio persisted up to 2 days following the end of therapy [6], and of Giapros et al., that there is progressive increase in the fractional excretion (FE) of sodium (Na) and of Mg, and an increased urine Ca/Cr ratio between days 1 and 7 of gentamicin therapy, possibly due to accumulation of gentamicin [8].

Both glomerular and tubular function increases with gestational age; nephrogenesis is usually completed by 34–36 weeks, a range that encompassed neonates in this study [21]. Our observation that hypocalcemia was more likely to occur in late-preterm neonates than in those born at term may be a reflection of this developmental immaturity. This also was observed by Giapros et al. [7, 8] in studies in which the electrolyte wasting and renal tubular disturbances were more pronounced in preterm than term neonates. To our knowledge, our observation that boys have significantly lower initial serum Ca values has not been previously reported, and this merits further study. It is noteworthy that gender differences indicating delayed maturation in boys has been well documented, particularly in pulmonary development [22, 23].

It is well known that serum peak and trough gentamicin levels vary considerably among individuals receiving similar dosing [24]. In studies of term and late-preterm neonates [8] and preterm neonates [25], a positive correlation was found between post-infusion Ca excretion and peak serum gentamicin concentrations. When the relationship between serum gentamicin levels and serum Ca was examined, the strongest relationship ($P<0.01$) was a negative correlation ($r=-0.28$) with trough gentamicin values in the entire study population. Overall, our results suggest only a weak relationship between serum Ca values and either peak or trough levels of gentamicin; this may indicate that the decision to obtain serum Ca values should not be based solely on gentamicin levels. In addition, a negative correlation was observed between initial serum Ca and iP values; one might speculate that CaR stimulation by gentamicin might suppress PTH, as noted above. No significant correlation was observed between initial serum Ca and Mg, which suggests that renal Mg depletion secondary to aminoglycoside administration might not play a role in observed hypocalcemia.

Although ionized calcium gives more physiologically relevant information, measurement of this ion is particularly important when one is evaluating the condition of sicker preterm neonates who have abnormally low levels of serum proteins, are receiving total parenteral nutrition, or who have acid–base or electrolyte disorders [11]. Ionized calcium was not routinely measured, since most of the subjects were late-preterm and term neonates in the NBN, whose condition was stable and who were assumed to have normal serum albumin concentrations. In addition, the measurement of ionized calcium levels in our institution requires a central venepuncture and is more expensive.

A limitation of our study is the lack of a control group, due to the practical and ethical dilemmas of our obtaining laboratory values for healthy neonates who are discharged before they are 60 h old. In addition, serum Ca is not typically measured in those neonates admitted to our level 2 nursery unless prolonged gentamicin therapy is administered. Furthermore, collection of urinary electrolyte values was not part of routine monitoring in neonates receiving prolonged treatment with gentamicin.

Based on the results in this large study population, the occurrence of hypocalcemia in gentamicin-treated neonates appears to exceed what might be expected in a normal population. Although gentamicin administered every 24 h may have clinical advantages over q 12 h dosing, our study suggests that the monitoring of late-preterm and term neonates receiving prolonged gentamicin therapy for hypocalcemia is advisable. A prospective randomized trial comparing gentamicin q 12 h with gentamicin q 24 h to study the effects of change in dose and dosing interval on renal and parathyroid function in term neonates is underway currently in our nursery.

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