

A simple high-dose gentamicin regimen showed no side effects among neonates

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ABSTRACT

INTRODUCTION: Treatment of infections in neonates with gentamicin is a balance between optimising bactericidal effect and minimising adverse effects. Previously, at the Neonatal Intensive Care Unit (NICU) at Kolding Hospital, Denmark, neonates suspected of having infections were treated daily with gentamicin 5 mg/kg for the first three days, thus exposing the smallest neonates to double gentamicin amounts compared with those used in most Danish NICUs. We aimed to evaluate if this regimen increased the trough values and oto- and nephrotoxicity.

METHODS: Neonates admitted to the NICU between 2008 and 2012 and treated with gentamicin were included retrospectively in the study. Neonates with trough serum (S)-gentamicin level ≥ 2.0 mg/l before the third dose were reviewed in detail.

RESULTS: In total, S-gentamicin level was measured in 253 treated neonates of whom 7% displayed elevated trough values. Neonates < 32 weeks of age had a slightly higher incidence of S-gentamicin level ≥ 2.0 mg/l compared with less premature and mature infants (16%, 13%, and 2%, respectively). No oto- or nephrotoxicity was found despite the high-dose gentamicin regimen.

CONCLUSIONS: The incidence of elevated S-gentamicin trough levels was increased among very premature neonates. However, no evidence of oto- or nephrotoxicity was observed. This simple regimen of gentamicin 5 mg/kg for the first three days should be considered for all neonates as it potentially minimises the risk of dosing errors and bacterial breakthrough infection.

FUNDING: none.

TRIAL REGISTRATION: Danish Data Protection Agency (2008-58-0035).

Gentamicin, an aminoglycoside antibiotic, is extensively used to treat serious bacterial infections in neonates and older infants [1]. Gentamicin is a bactericidal antibiotic that is effective against most gram-negative bacteria, *Staphylococcus aureus* and other bacteria [2]. Although the efficacy of gentamicin is related to the peak serum concentration, continually elevated trough levels could cause toxicity due to gentamicin accumulation in the inner ears and kidneys [3, 4].

In adults and older infants, ototoxicity correlates



ABBREVIATIONS

GA = gestational age at birth
NICU = neonatal intensive care unit
PMA = postmenstrual age

with the duration of treatment, cumulative dose and number of treatments [5]; the effect on the cochlea and vestibule seems non-reversible [6]. Renal toxicity, however, which is associated with renal function and cumulative dose, is often reversible at the end of treatment [6]. In comparison to older infants and adults, gentamicin toxicity is believed to be lower in neonates when administered in controlled therapeutic doses [7, 8]. This may be attributed to a larger volume of distribution [2]. Nevertheless, most studies recommend maintaining a trough level < 2 mg/l in neonates due to the risk of toxicity [2, 4, 9].

There are numerous different dosing regimens for the administration of gentamicin in neonates, often involving multiple daily doses administered at short intervals [10, 11]. Previously, several studies have attempted to determine the optimal dosing regimen by optimising the bactericidal effect while minimising the risk of oto- and nephrotoxicity [5, 12], which has led to several seemingly contradictory recommendations. One proposed a single daily dose [10], while others suggested adjusting the interval 24-48 h according to gestational age (GA) [4] or weight [2, 9]. A study from 2012 [11] advocated adjusting the interval between doses based on serum gentamicin (S-gentamicin) measured 22 h after the first dose. In daily clinical practice, however, some of these regimens are difficult to follow which may increase the risk of dosing errors [13]. Furthermore, two recent cases highlighted the risk of breakthrough of ampicillin-resistant infections when gentamicin is administered at long intervals [14].

Until 2013, in the Neonatal Intensive Care Unit (NICU) at Kolding Hospital, Denmark, neonates suspected of sepsis were treated with a dose of 5 mg/kg gentamicin, once every 24 h, for the first three days of treatment independently of GA at birth, postmenstrual age (PMA) at the start of treatment, and weight. This

ORIGINAL ARTICLE

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Dan Med J
2017;64(6):A5387

recommendation was simple to follow, and the risk of breakthrough infection may be lower than with longer dosing intervals [14]. However, compared with more recent recommendations, the youngest neonates received considerably larger, cumulative doses of gentamicin under this regimen [15-17].

The aim of the present study was to retrospectively evaluate if the daily administration of 5 mg/kg gentamicin for the first three days of treatment to all neonates, irrespective of GA and PMA at start of treatment, exposes the smallest neonates to increased gentamicin trough levels, thereby increasing the risk of oto- and nephrotoxicity.

METHODS

The present study retrospectively assessed all neonates admitted to the NICU at Kolding Hospital, Denmark over a five-year period (i.e. 2008-2012). The NICU is a 20-bed, level IIB/IIIA nursery. Until 2010 it cared for neonates born at GA 26 weeks or later and provided conventional mechanical ventilation for as long as needed. In 2010, owing to the new national guidelines, this was changed to GA 28 weeks and only short-term mechanical ventilation. All neonates with a PMA of less than 44 weeks are admitted to the NICU unless they are strongly suspected of having a contagious disease requiring isolation.

Antibiotic treatment with ampicillin and gentamicin was initiated if the neonate presented clinical or para-clinical signs of bacterial infection. The treatment was preceded by sepsis screening consisting of blood tests, including leukocytes, thrombocytes and C-reactive protein, as well as cultures from blood and tracheal secretion, and a lumbar puncture if required. Some neonates were treated prophylactically following unsterile invasive procedures or premature rupture of membranes. In all cases, the first three doses of gentamicin were ad-

ministered as 5 mg/kg every 24 h. The majority of neonates were treated only for three days or less, but neonates with positive bacterial cultures in blood or spinal fluid often received four or five days of gentamicin treatment. In order to adjust the fourth dose, S-gentamicin trough levels were measured just before the administration of the third dose, unless a short treatment (three days or less) had been planned. If the trough value was ≥ 2 mg/l, then the treatment was paused and the S-gentamicin level was measured again 24 h later. When the trough value was between 1.0 and 1.9 mg/l, the fourth dose was halved. Peak values were not measured routinely.

The neonates were identified through a clinical database: Neobase, and were eligible for this study if they had been treated with gentamicin and their S-gentamicin level had been measured before the third dose. Those transferred during treatment to other units with different dosing regimens were excluded. The medical and biochemical records of all neonates included in this study were reviewed extensively. Records belonging to neonates with S-gentamicin level ≥ 2.0 mg/l were reviewed in detail collecting data on GA at birth, PMA at start of treatment, the dose and duration of treatment, S-gentamicin trough levels, subsequent kidney function, information on positive bacterial cultures and hearing evaluation results. In Denmark, audiometric testing using transient otoacoustic emission or automatic auditory brainstem response is optional; however, neonates who stay at NICUs for more than 48 h should be tested using both techniques. While the majority of neonates included in this study underwent audiometric testing, some were evaluated clinically at the corrected ages of 12 and 24 months in the neonatal outpatient clinic, since they did not show up at audiometric testing despite several notices. The ten neonates who underwent a second treatment with gentamicin during the first month of life are described separately, but otherwise only included in relation to their first treatment.

Statistics: The very premature group of gentamicin-treated neonates was compared with the premature and mature groups using χ^2 -tests.

The study was approved by the Danish Data Protection Agency (2008-58-0035).

Trial registration: Danish Data Protection Agency (2008-58-0035).

RESULTS

During the five-year study period, 1,914 neonates were admitted to the NICU and 364 received gentamicin treatment. A total of 29 were excluded as they were transferred to other hospitals during their treatment, and 82 did not have a gentamicin measurement; in 73

TABLE 1

Characteristics of 253 neonates treated with gentamicin, stratified according to gestational age at birth. The values are n (%).

	Gestational age, weeks + days		
	25 + 1-31 + 6	32 + 0-36 + 6	37+ 0-42 + 3
Neonates			
Boys	33 (66)	35 (65)	90 (60)
Girls	17 (34)	19 (35)	59 (40)
Total	50	54	149
Indication for treatment			
Prophylactic treatment	9 (18)	16 (30)	23 (15)
Sepsis suspicion	41 (82)	38 (70)	126 (85)
Positive bacterial cultures, total	32 (64)	12 (22)	34 (23)
S-gentamicin level < 2.0 mg/l	42 (84)	47 (87)	146 (98)
S-gentamicin level ≥ 2.0 mg/l	8 (16)	7 (13)	3 (2)



TABLE 2

Neonates exposed to S-gentamicin level ≥ 2.0 mg/l.

Gestational age at birth, weeks + days	Postmenstrual age at start of treatment, weeks + days	Indication for treatment	Bacterial culture	Doses of gentamicin, n	S-gentamicin level, mg/l	Last measured S-creatinine level, $\mu\text{mol/l}$: age at measurement	Hearing-evaluation
27 + 6	27 + 6	Prophylactic	Tracheal: <i>Enterobacter ludwigii</i>	4	2.1	52: 10 days ^c	Not performed ^c
28 + 2	28 + 2	Sepsis suspicion	No growth	3	2.0	26: 4 yrs	Normal ^a
28 + 3	28 + 3	Sepsis suspicion	No growth	3	3.9	36: 6 yrs	Normal ^a
28 + 3	28 + 3	Prophylactic	No growth	3	4.0	35: 6 yrs	Normal ^a
28 + 4	28 + 4	Prophylactic	No growth	2	2.6	31: 4 yrs	Normal ^a
28 + 4	28 + 4	Sepsis suspicion	No growth	2	6.4	89: 9 days ^d	Not performed ^d
30 + 6	30 + 6	Sepsis suspicion	Tracheal: <i>Escherichia coli</i>	3	2.0	13: 1 yr	Normal ^a
30 + 6	30 + 6	Prophylactic	Blood: <i>E. coli</i>	4	2.1	15: 1 yr	Normal ^a
32 + 2	32 + 2	Sepsis suspicion	No growth	3	2.1	37: 7 yrs	Normal ^a
32 + 2	32 + 2	Prophylactic	No growth	3	2.2	37: 4 days	Normal ^a
33 + 5	33 + 5	Sepsis suspicion	No growth	3	2.6	23: 2 yrs	Normal ^a
34 + 2	34 + 2	Sepsis suspicion	No growth	4	7.7 ^e	31: 6 yrs	Normal ^a
34 + 4	34 + 4	Sepsis suspicion	No growth	3	2.3	24: 4 mo.s	Normal ^a
34 + 5	34 + 5	Prophylactic	No growth	3	2.3	27: 1 yr	Normal ^a
35 + 3	35 + 3	Sepsis suspicion	No growth	2	3.0	89: 3 yrs ^f	Normal ^a
38 + 0	38 + 4	Sepsis suspicion	Spinal fluid: <i>Streptococcus</i> gr. B	3	9.2 ^e	21: 6 mo.s	Normal ^a
39 + 5	39 + 5	Prophylactic	No growth	3	2.7	85: 2 days	Normal ^a
40 + 2	40 + 2	Prophylactic	No growth	3	2.2	39: 2 wks	Normal ^a

a) Neonatal evaluation: transient evoked otoacoustic emission and automatic auditory brainstem response, pass/pass.

b) Clinical evaluation at the hospital during hospitalisation or at the outpatient clinic.

c) Died 11 days old from severe sepsis, S-creatinine level decreased from 92 $\mu\text{mol/l}$ on day 2.

d) Severe twin-twin transfusion syndrome, died 4 weeks old from multiple organ dysfunction, S-creatinine level decreased from 194 $\mu\text{mol/l}$ on day 4, the neonate only received 2 doses of gentamicin.

e) Most likely a measurement error (see text).

f) Born with polycystic kidneys and only received 2 doses of gentamicin, S-creatinine level decreased from 117 $\mu\text{mol/l}$ before treatment to 89 $\mu\text{mol/l}$ after treatment.

treatment was discontinued before S-gentamicin level was measured, and nine died before receiving the third dose. The causes of death were severe malformations ($n = 4$), metabolic disease ($n = 2$), cerebral bleeding ($n = 1$), severe asphyxia ($n = 1$) and necrotising enterocolitis ($n = 1$). The remaining 253 neonates were included in the present study. None of the neonates were treated concomitantly with nonsteroidal anti-inflammatory drugs, loop diuretics or vancomycin.

Table 1 summarises the findings of the 253 neonates treated with gentamicin. A total of 18 neonates demonstrated an S-gentamicin level of 2 mg/l or above. When the results were stratified according to GA, the most premature group showed an increased risk of having an elevated S-gentamicin level compared with the mature group ($p = 0.02$, χ^2 -test). Additionally, significantly more neonates with a GA < 32 weeks had a positive bacterial culture compared with the mature group ($p < 0.001$, χ^2 -test). The less premature group did not differ significantly from the very premature and mature groups.

Table 2 summarises information about the 18 neonates who had an S-gentamicin level ≥ 2.0 mg/l, among whom 13 neonates (72%) had only a slight elevation be-

tween 2.0 and 3.0 mg/l, whereas three neonates displayed highly elevated values of 6.4, 7.7 and 9.2 mg/l, respectively. The two highest values are probably erroneous and were likely to have been measured after gentamicin dosing. In the first case, after receiving the next equivalent dose, the S-gentamicin level of the neonate decreased remarkably from 7.7 mg/l to 1.7 mg/l 24 h later. The second neonate with an S-gentamicin level of 9.2 mg/l received prolonged and repeated gentamicin treatment, but showed no elevated level of S-gentamicin again. The recorded value of 6.4 mg/l is most probably correct as this neonate was very sick and had an impaired renal function, and thus only received two doses of gentamicin.

It remains unknown how many neonates with normal S-gentamicin levels had a hearing test performed.

Table 3 shows details regarding the ten neonates who were treated with gentamicin twice during their first month of life.

DISCUSSION

Several different regimens have been proposed for the administration of gentamicin to neonates, the aim of which to optimise the bactericidal effects while minimis-

A nurse at the neonatal intensive care unit prepares gentamicin for administration.



ing the risk of oto- and nephrotoxicity [2, 4, 9, 10]. Consensus on the dose and dosing interval has not been established for gentamicin, and several complicated dosing regimens exist. At the NICU at Kolding Hospital, a single daily dose of gentamicin of 5 mg/kg was administered for the first three treatment days, irrespective of the GA or PMA at treatment initiation. The fourth dose, however, was corrected according to the S-gentamicin trough level. This recommendation was easy to follow and probably lowered the risk of dosing errors in comparison to other more complicated regimens where gentamicin was administered at extended or variable intervals [13, 17]. Since gentamicin is primarily cleared through the kidneys, the administration of an equivalent gentamicin dose to all neonates could increase the risk of elevated gentamicin trough levels among the smallest neonates who have the lowest renal clearance [18, 19]. For this reason, in 2013 the department changed the

dosing regimen according to the guideline of the Danish Paediatric Society regarding the empiric treatment of early neonatal group B streptococcal sepsis. Gentamicin dosing is now stratified into 5 mg/kg every 48 h to neonates with a GA < 32 weeks, and 4 mg/kg every 24 h as from GA 32 weeks [20]. After changing the gentamicin guideline at the unit, it was decided to retrospectively evaluate if the previous, more aggressive gentamicin regimen had exposed the smallest neonates to oto- or nephrotoxicity.

In total, with the previous gentamicin regimen, 7% of gentamicin-treated neonates had an elevated S-gentamicin trough level > 2.0 mg/l, whereas 93% of neonates had an acceptable level (< 2.0 mg/l). Neonates < 32 weeks had a slightly higher incidence (16%) of having S-gentamicin levels \geq 2.0 mg/l compared with the less premature (13%) and mature groups (2%). However, the increased risk of elevated S-gentamicin level for the youngest neonates was counterbalanced by an increased risk of having serious culture-positive bacterial infections compared with the group of mature neonates. These results corroborate previous studies, reporting elevated trough levels in 6.7% of neonates who were administered a daily gentamicin-dose of 4 mg/kg [8], while a regimen in which neonates weighing less than 1,250 g were administered gentamicin 4 mg/kg every 48 h while those above this weight who were administered by the same dose 24 hourly reported a slightly lower incidence (4.3%) [2]. Currently, the results cannot be compared to the outcome of using gentamicin administration following the national guideline, since this has not yet been evaluated.

The peak concentration of aminoglycoside is the

TABLE 3

Characteristics of the ten neonates treated with gentamicin twice.

Postmenstrual age at initiation of 1st treatment, weeks + days	Doses of gentamicin at 1st treatment, n	Elevated S-gentamicin level at 1st treatment, mg/l	Postmenstrual age at initiation of second treatment, weeks + days	Total doses of gentamicin, 1st and 2nd treatment, n	Elevated S-gentamicin level at 2nd treatment	Hearing-evaluation	Last measured S-creatinine, μ mol/l: age at measurement
28 + 2	4	No	32 + 4	9	No	Normal ^b	22: 1 mo.
28 + 2	3	2.0	31 + 2	6	No	Normal ^b	26: 4 yrs
28 + 3	3	3.9	29 + 4	6	No	Normal ^a	36: 6 yrs
28 + 4	2	2.6	29 + 6	6	No	Normal ^b	31: 4 yrs
29 + 2	5	No	30 + 3	10	No	Normal ^a	51: 10 days ^c
29 + 2	5	No	31 + 4	8	No	Normal ^a	24: 1 yr
32 + 2	3	No	35 + 4	5	No	Normal ^a	— ^d
33 + 0	3	No	34 + 1	6	No	Normal ^a	20: 2 mo.s
34 + 5	3	No	37 + 0	6	-	Normal ^b	29: 3 wks
35 + 0	4	No	37 + 1	7	No	Normal ^a	17: 1 mo.

a) Neonatal evaluation: transient evoked otoacoustic emission and automatic auditory brainstem response, pass/pass.

b) Evaluation at the outpatient clinic, typically at 1 and 2 yrs of age, 1 child evaluated at ear specialist.

c) S-creatinine level not measured later, blood urea nitrogen level 1.3 mmol/l at 2 mo.s of age.

d) Blood urea nitrogen level 1.1 mmol/l at 1 mo. of age.

single most important factor that correlates with the successful treatment of bacterial infections using aminoglycosides. Therefore, lower doses, used to avoid adverse effects, increased the risk of having a peak concentration below the recommended range, and thus consequently reduced bactericidal effect [2]. Likewise, extending dosing intervals could increase the risk of breakthrough infection. Remarkably, the department experienced two very serious infections in premature neonates caused by ampicillin-resistant *Escherichia coli* after the shift to the new regimen with longer dosing intervals. Both neonates improved initially after the first gentamicin dose, but deteriorated again before the second, delayed dose. One died [14]. The overall incidence of breakthrough infections caused by ampicillin-resistant gentamicin-sensitive microorganisms with different guidelines is currently unknown.

Other studies have indicated that gentamicin toxicity among neonates is lower than in adults [2, 7]. Still, the lack of oto- and nephrotoxicity, despite the high-dose gentamicin regimen, is an important finding of this study. Neither the neonates exposed to large, cumulative doses following repeated treatment, nor the neonates who developed an elevated S-gentamicin trough level, displayed signs of subsequent hearing loss or impaired renal function. However, the evaluation of this treatment regimen cannot necessarily be generalised to the most intensive neonatal settings, where gentamicin treatment may be combined with nonsteroidal anti-inflammatory drugs, loop-diuretics, or vancomycin.

The simple gentamicin treatment regimen consisting of a daily dose of 5 mg/kg has the potential advantage of minimising dosing errors and the risk of breakthrough infection. Although an increased risk of elevated gentamicin trough values was found among the very premature neonates, we observed no evidence of oto- or nephrotoxicity. The daily administration of gentamicin at a dose of 5 mg/kg for the first three days of treatment should be considered for use in level II NICUs. A prospective study evaluating the different aspects of the current national neonatal practice, however, would be of great value to recommend future antibiotic treatment regimens.

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ACCEPTED: 9 May 2017

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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