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# Validation of a Simplified Netilmicin Dosage Regimen in Infants

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**The aim of this study was to validate a simplified high-dosage, extended-interval netilmicin dosage regimen for infants. A total of 129 infants receiving 163 treatment courses of netilmicin (6 mg/kg every 24 or 36 h depending on gestational age (GA), postnatal age and postmenstrual age) was analysed. Serum netilmicin concentrations were monitored before ($C_{min}$), 30 min ($C_{0.5h}$) after and 7.5 h ($C_{7.5h}$) after the third dose. In 110 patients during first week of life mean $C_{0.5h}$ was 10.5 mg/l. Mean $C_{0.5h}$ was significantly lower (9.0 mg/l) in 38 infants older than 1 week of age. 14 of 15 patients with $C_{min}$ levels $\geq 2$ mg/l receiving netilmicin every 36 h were $< 28$ weeks of gestation. In the first week of life significant correlations between GA and elimination half-life ($p < 0.001$) and between plasma creatinine and elevated $C_{min}$ ($p < 0.002$) were found, but no correlation between $C_{0.5h}$ and GA. In this high-dosage regimen a dosing interval of 48 h for GA $< 29$ weeks, 36 h for GA 29–36 weeks and 24 h for full term babies seems appropriate, during first week of life, to avoid the majority of elevated trough levels and still obtain maximal therapeutic efficacy.**

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## INTRODUCTION

Aminoglycosides, along with a beta-lactam agent, are widely used for treatment of neonatal sepsis (1). High-dosage, extended-interval regimens may decrease toxicity, improve efficacy and decrease costs (2, 3). In vitro studies have shown that aminoglycosides exhibit concentration-dependent bactericidal effect (3, 4) and concentration-dependent post-antibiotic effect (PAE) (5). Peak concentrations 8–10 times the minimal inhibitory concentration (MIC) for the specific pathogen are associated with improved therapeutic outcome in life threatening bacterial infections in adults (6, 7), and may minimize bacterial regrowth and emergence of resistance (8).

In infants a beneficial pharmacokinetic profile is reported with longer dosing intervals (2, 9–12). However, in preterm babies with immature renal function it is difficult to achieve sufficiently high peak concentrations combined with safe trough values without extending the dosing interval beyond 24 h (2, 13). There is concern that dosing intervals up to 48 h (14) might exceed the duration of the PAE followed by a prolonged period of subtherapeutic drug concentration (11, 15).

Most data on aminoglycoside treatment in infants using high-dosage, extended-interval regimens are on gentamicin (2, 9, 10, 12, 15, 16). Animal (17–19) and human studies (20–23) indicate that netilmicin is less ototoxic and probably less nephrotoxic than gentamicin. In addition, netilmicin has higher in vitro activity towards coagulase-negative staphylococci (CoNS), the most prevalent pathogen causing late onset sepsis in neonates (24, 25).

Modern aminoglycoside dosage regimens vary considerably and are often complicated (11, 14, 26, 27). This might lead to errors in both drug dosing and administration in a busy day-to-day practice. The aim of this study was to validate a simplified netilmicin dosage regimen used across a wide range of gestational age (GA) and postmenstrual age (PMA). Primary endpoints were the proportion of patients who achieved therapeutic peak serum netilmicin concentrations (SNC) and who avoided potentially toxic trough SNC. Secondarily, we attempted to evaluate pharmacokinetic data calculated from routinely collected SNC.

## PATIENTS AND METHODS

This open, prospective, non-comparative study was conducted in the neonatal intensive care unit (NICU), University Hospital of North Norway, from September 2000 to December 2002. The regional committee for medical research ethics gave approval for the study.

### *Study design and patients*

All infants below 3 months of age, who were prescribed netilmicin and received at least 3 doses, were eligible. Netilmicin was not administered to infants with a history of severe perinatal asphyxia, recognized renal anomalies or known renal impairment. 17 courses of netilmicin treatment were excluded from the study due to improper dosage and/or drug level determination.

### *Data collection and laboratory methods*

Data collected included gender, GA determined by routine antenatal ultrasound examination, birth weight (BW), postnatal age (PA), PMA (GA+PA) and indomethacin treatment. A complete blood count, blood cultures and C-reactive protein (CRP) were part of sepsis work up in all patients. According to clinical and microbiological findings, we classified the patients into 3 categories: blood culture confirmed sepsis; clinical signs of sepsis and CRP > 40 mg/l; and no proven infection.

Blood cultures (Pedi-BacT®) were collected from all patients. Susceptibility testing of invasive isolates was performed using the

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paper disc method and MIC for netilmicin was determined by E-test (AB Biodisk, Solna, Sweden).

Plasma creatinine was obtained concomitant with SNC 7.5 h after completion of the third dose, thus earliest at postnatal age of 56 h in patients $\geq 34$ weeks and earliest at postnatal age of 80 h in patients $< 34$ weeks. Other creatinine values were monitored at the discretion of the attending physician. Hearing evaluations were performed using an otoacoustic emission test (OAE).

*Dosage regimen, drug monitoring and pharmacokinetics*

The new dosage regimen was derived from various sources (2, 13, 26, 27). Dosing interval was either 24 (q24h) or 36 h (q36h) depending on GA, PA and PMA (Tables I and II). Netilmicin 6 mg/kg was administered as an intravenous infusion over a period of 30 min. All patients received ampicillin (early onset sepsis) or cloxacillin (late onset sepsis) in addition to netilmicin.

Trough SNC ($C_{min}$) was drawn just before the third dose at 48 or 72 h. In addition, SNC was drawn 0.5 h ($C_{0.5h}$) and 7.5 h ($C_{7.5h}$) after end of infusion of the third dose. SNC at 48 or 72 h postnatal age were considered to reflect steady state. $C_{0.5h} > 8$ mg/l, $C_{7.5h}$ 1.5–5 mg/l and $C_{min} < 2$ mg/l were considered therapeutic and safe (6, 13, 26, 28, 29). The recommendations regarding the $C_{7.5h}$ value are taken from adult studies in once daily dosing regimens. For neonates no recommendations exist for the $C_{7.5h}$ value. However, we obtained $C_{7.5h}$ to assure that the SNC did not drop too rapidly and thus leave the patient with subtherapeutic drug concentration for a prolonged period of time. SNC were determined by fluorescence polarization immunoassay (TDx, Abbott Laboratories, Abbott Park, Illinois, USA).

The pharmacokinetics of netilmicin has been described using 1-, 2- and 3-compartment models. The latter model includes a distribution ($\alpha$) phase and two elimination phases; an early ($\beta$) phase from plasma and extracellular fluid, and a late ($\gamma$) phase from a deep tissue compartment (13, 30). The characteristics of the data in this study did not allow advanced pharmacokinetic modelling. Assuming a steady state condition, we thus used $C_{min}$ and $C_{7.5h}$ to calculate the elimination rate constant ($Ke = [\ln C_{7.5h} - \ln C_{min}]/$ time) and $t^{1/2}\beta\gamma$ in a 1-compartment first order model (31–33).

*Statistical analysis*

All baseline data are given as mean values with standard deviation (SD). Group differences are presented as mean values with standard error of the means (SEM). The Mann–Whitney *U*-test was used for intergroup comparison. A linear regression model was used to correlate $t^{1/2}$ and GA. SPSS (11.0 for Windows) was used for all data analysis. $p < 0.05$ was considered significant.

## RESULTS

A total of 129 patients receiving 163 courses of netilmicin were recruited. 25 patients were below 28 weeks of gestation and 40 patients had a BW below 1500 g. Table I shows the clinical characteristics and the allocation of treatment courses to the dosage regimen. Group D is heterogeneous, including a proportion of immature babies with long hospitalization and repeated suspect episodes of late onset sepsis, but also hospital-born and outborn infants admitted to the NICU after first week of life. In group D, 9 patients had 2 or more sets of SNC, and all these 9 patients are also included in group A.

Table II shows the pharmacokinetic data in the different treatment groups. In group A, 15 of 35 (43%) $C_{min}$ levels were $\geq 2$ mg/l. 14 of these patients were immature with GA 24–27 weeks and 6 of 15 had creatinine values $> 90$ µmol/l. In group B, 11 of 75 (15%) patients had elevated $C_{min}$ levels, and 6 of these were of GA between 34 and 37 weeks. Mean $C_{0.5h}$ was 10.5 (2.0) mg/l for all patients during first week of life and no correlation was found between $C_{0.5h}$ and GA ($p = 0.51$). Mean $C_{0.5h}$ in patients below 1 week of age (group A–B) was compared with patients older than 1 week of age (group C–D). This comparison was made in 3 steps due to the statistical problem of dependent observations. First, only patients in group C–D not concomitantly included in group A–B, ($n = 20$, mean $C_{0.5h}$ 9.0 mg/l) were compared with group A–B. Secondly, all patients in group C–D were compared with group A–B, but only including the first treatment episode of those 9 patients with repeated measurements ($n = 37$, mean $C_{0.5h}$ 8.9 mg/l). Finally, all treatment episodes in group C–D ($n = 53$, mean $C_{0.5h}$ 9.1 mg/l) were

Table I. *Netilmicin (6 mg/kg) dosing regimen and baseline patient characteristics*

| | Group A PA 0-7 d and GA < 34 weeks | Group B PA 0-7 d and GA ≥ 34 weeks | Group C PA > 7 d, but PMA < 28 weeks | Group D PA > 7 d and PMA ≥ 28 weeks |
|---|---|---|---|---|
| Netilmicin dosing interval | Every 36 h | Every 24 h | Every 36 h | Every 24 h |
| Number of treatment episodes | 35 | 75 | 2 | 51 |
| Number of patients | 35 | 75 | 2 | 36 |
| Gestational age at birth (weeks) | 27.6 (2.5) | 39.1 (2.3) | 25.0 (1.4) | 28.7 (5.0) |
| Postmenstrual age (weeks) | | | 26.5 (0.7) | 33.4 (5.0) |
| Birth weight (g) | 1044 (375) | 3510 (832) | 840 (127) | 1416 (1189) |
| Number of netilmicin doses per treatment episode | 4.3 (1.4) | 5.3 (1.5) | 4.0 (1.4) | 6.5 (3.0) |
| Infection | | | | |
| Blood culture positive sepsis | 0 | 3 | 0 | 10 |
| Clinical sepsis+CRP > 40 mg/l | 1 | 24 | 0 | 21 |
| No proven infection | 34 | 48 | 2 | 20 |
| CRP maximum (mg/l) | 18 (18) | 50 (45) | 22 (17) | 89 (89) |
| P-creatinine (µmol/l) | 78 (19) | 56 (16) | 76 (4) | 51 (21) |

Data expressed as mean (SD).
Postnatal age (PA), gestational age (GA), postmenstrual age (PMA).

Table II. *Serum netilmicin concentration (SNC) and elimination half-life*

| Variable | Group A (q36h) | Group B (q24h) | Group C (q36h) | Group D (q24h) |
|---|---|---|---|---|
| $C_{0.5h}$ | 10.4 (2.0) | 10.6 (2.0) | 8.0 (0.8) | 8.9 (2.5) |
| $C_{7.5h}$ | 4.8 (1.1) | 3.5 (1.1) | 5.1 (0) | 2.9 (1.2) |
| $C_{min}$ | 1.7 (0.8) | 1.3 (0.8) | 1.5 (0.5) | 0.9 (0.5) |
| Estimated $C_{min}$ (q36h) | | 0.6 (0.6) | | 0.4 (0.4) |
| Estimated $C_{min}$ (q48h) | 1.0 (0.6) | | | |
| $T^{1/2}$ (h) | 17.8 (5.8) | 11.2 (5.8) | | 11.0 (6.0) |
| $C_{min} \geq 2$ mg/l n (%) | 15/35 (43%) | 11/75 (15%) | 0/2 (0%) | 3/51 (6%) |
| $C_{min} < 0.5$ mg/l n (%) | 2/35 (6%) | 4/75 (5%) | 0/2 (0%) | 8/51 (16%) |
| $C_{0.5h} < 8$ mg/l n (%) | 0/35 (0%) | 5/75 (7%) | 1/2 (50%) | 11/51 (22%) |

Data expressed as mean (SD).

compared with group A–B. Mean $C_{0.5h}$ was significantly lower ($p < 0.003$) in all 3 comparisons. However, only 3 of 53 $C_{0.5h}$ levels after first week of life were below 6 mg/l. No significant differences in $C_{min}$ or $C_{0.5h}$ values between boys and girls were found. Table III summarizes clinical characteristics of patients with normal vs elevated trough levels in the first week of life.

Complete pharmacokinetic data were obtained from 156 treatment episodes; in 7 episodes $C_{7.5h}$ was missing. There was a significant negative correlation ($p < 0.001$, $r = -0.522$) between GA and $t_{\frac{1}{2}}\beta\gamma$ during first week of life (Fig. 1). Estimated negative regression coeffecient was 0.47 (0.32–0.62; 95% confidence interval). We estimated $C_{min}$ for each patient with a theoretically 12-h longer dosing interval (Table II). In a 48 h dosing interval, $C_{min}$ was between 0.8 and 2.1 mg/l for 20 of 22 patients with GA < 29 weeks. Applying a 48 h dosing interval to patients with GA 29–33 weeks resulted in 6 of 13 $C_{min} < 0.5$ mg/l. A subgroup analysis of babies between 29 and 36 weeks of GA in a 36 h dosing interval resulted in only 1 out of the 21 measured/estimated $C_{min} > 2$ mg/l.

Infection was highly suspected due to clinical symptoms and substantially increased CRP in 46 episodes and confirmed by positive blood cultures in 13 episodes (Table I). CoNS were the most frequent encountered pathogens ($n = 7$). The other 6 cultures were positive for Staphylococcus aureus ($n = 2$), Klebsiella oxytoca ($n = 2$) and group B streptococci ($n = 2$). One child with early onset klebsiella sepsis responded to the antibacterial treatment, but died due to trisomy 18. No other patient with highly suspected or confirmed infection died during or within 2 weeks after treatment with netilmicin. Susceptibility testing revealed that both strains of Klebsiella oxytoca and S. aureus respectively, and all CoNS strains, including 3 resistant to methicillin, were sensitive to netilmicin according to NCCLS breakpoint criteria (NCCLS: Performance standards for antimicrobial susceptibility testing; 12th informational supplement. M100-S12, Pennsylvania, USA, 2002).

All 11 patients with plasma creatinine measurement > 90 μmol/l during therapy had normal renal function parameters after therapy. Mean GA for this group was 28 weeks and only 1 was older than 34 weeks of gestation. This term born

Table III. *Patients with normal vs elevated $C_{min}$ in the first 7 d of life*

| | $C_{min} < 2$ mg/l | $C_{min} \geq 2$ mg/l | *p* |
|---|---|---|---|
| Number of patients | | | |
| Group A (GA < 34 weeks) | 20 | 15 | |
| Group B (GA ≥ 34 weeks) | 64 | 11 | |
| Gestational age (GA) | | | |
| Group A (GA < 34 weeks) | 29.0 ± 0.54 | 25.8 ± 0.33 | < 0.001 |
| Group B (GA ≥ 34 weeks) | 39.5 ± 0.25 | 36.9 ± 0.75 | < 0.003 |
| Birth weight (BW) | | | |
| Group A (GA < 34 weeks) | 1221 ± 90 | 810 ± 35 | < 0.003 |
| Group B (GA ≥ 34 weeks) | 3609 ± 96 | 2931 ± 292 | < 0.04 |
| P-creatinine value after third dose | | | |
| Group A (GA < 34 weeks) | 69 ± 3 | 91 ± 5 | < 0.002 |
| Group B (GA ≥ 34 weeks) | 53 ± 2 | 80 ± 8 | < 0.002 |
| CRP maximum | | | |
| Group A (GA < 34 weeks) | 15 ± 4 | 23 ± 5 | = 0.17 |
| Group B (GA ≥ 34 weeks) | 49 ± 5 | 59 ± 20 | = 0.92 |

Data expressed as mean ± SEM.

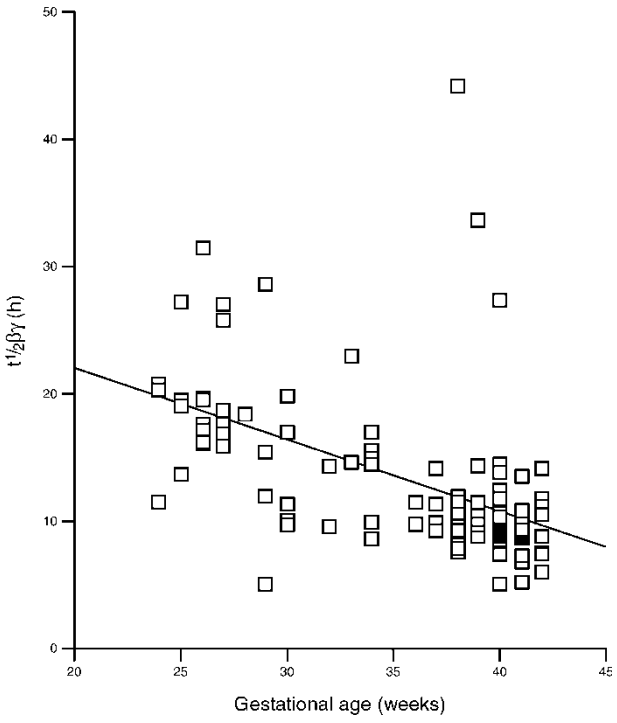


*Fig. 1.* Correlations between $t^{1/2}\beta\gamma$ and gestational age during 1st week of life.

patient had a severe asphyxia and according to our protocol aminoglycoside treatment should have been withheld. Only 2 patients were treated with indomethacin, and their $C_{min}$ and creatinine values were 1.9 mg/l–79 μmol/l and 3.5 mg/l–125 μmol/l, respectively.

Deafness was diagnosed on follow-up in a preterm girl (GA 31 weeks) who had a neonatal meningitis. Hearing impairment was later found in a preterm boy (GA 25 weeks) with severe periventricular leucomalacia. Their $C_{min}$ were 0.8 and 2.4 mg/l respectively.

## DISCUSSION

Administration of netilmicin 6 mg/kg to infants across a wide range of GA and PMA resulted in similar or mostly higher peak values than found in comparable studies (10, 13, 15, 16, 27, 34). We did not detect a correlation between $C_{0.5h}$ values and GA during the first week of life, despite the fact that GA correlates inversely to the volume of distribution. Different doses according to GA seem unnecessary in clinical practice, and complicate the dosing regimen. We therefore suggest a uniformly high dose for all neonates, regardless of GA, in the first week of life (13, 35), but we emphasize that trough levels should be obtained in preterm and very sick babies.

A significant correlation ($p < 0.001$) was found between the estimated $t^{1/2}\beta\gamma$ and GA in the first week of life (Table II and Fig. 1). The long $t^{1/2}\beta\gamma$ explains the unacceptably high proportion of children with potentially toxic $C_{min}$ levels among the youngest patients in both the q24h and q36h regimen in the first week of life. Aminoglycoside serum concentrations associated with nephro- and ototoxicity have been difficult to establish, but $C_{min}$ levels of $< 2$ mg/l are considered safe (10, 13). Extending the dosing interval by 12 h for certain subgroups in this study would theoretically minimize the number of potentially toxic $C_{min}$ values. However, for patients between 29 and 33 weeks of age a dosing interval of 48 h, as recommended in Neofax (14), might lead to prolonged periods of very low netilmicin concentrations.

Nephrotoxicity in neonates assessed by increasing creatinine concentrations is relatively rare. It seldom occurs before 5 d of therapy and usually even later with extended-interval regimens due to lower daily accumulation rate of the drug in the renal cortex (21, 36–38). However, aminoglycosides are primarily tubulotoxic agents and affection of tubular function may occur earlier (22, 30). Our study was not designed to detect minor renal toxic effects and few patients were treated for long periods. It is unlikely that the elevated levels of creatinine, found in some of our patients, were the result of netilmicin therapy. Most of these patients were immature, and the elevated creatinine concentrations during first week of life can be explained by tubular reabsorption of creatinine (39). Nevertheless, we found a significant correlation between plasma creatinine values $> 90$ μmol/l and $C_{min} > 2$ mg/l among patients during first week of life, an observation not seen in other studies (26, 31). Monitoring of renal function during first week of life, especially in preterm babies, thus might help to prevent high trough levels (27). The risk for infants to develop clinically significant hearing problems after 3 to 7 d of aminoglycoside treatment is small (21). Among preterm babies the coexistence of different risk factors for hearing loss may be more important than the individual risk factors themselves (40). In our study only patients with severe comorbidities were found to have impaired hearing function on follow-up. Due to the small study population and study design, however, no definitive information can be given about the possible toxicity of this regimen.

Demczar et al. (32) found a significant longer distribution phase with a high (7 mg/kg) dose vs a traditional (2 mg/kg) gentamicin dose regimen in adults. In neonates the distribution phase inversely correlates with GA (30). In Moore's studies a strong association between maximal and mean $C_{max}$/MIC ratio and clinical response to aminoglycoside therapy was demonstrated (6, 7). However, these studies used traditional doses of aminoglycosides and $C_{max}$ was obtained 1 h after a 30 min infusion, most probably in the postdistribution phase. In our study the $C_{0.5h}$ value is most likely measured during the distribution phase. A direct comparison to Moore's results is thus not justified. Surprisingly, this fact is neither addressed in recent neonatal studies using a high-dosage, extended-interval regimen (15, 16, 34) nor in drug dosing recommendations (14).

The reported netilmicin elimination $t^{½}$ varies considerably, mainly as a result of difference in study design (13, 30, 31, 41, 42). Estimations of the total $t^{½}$ with aminoglycoside serum concentrations obtained only in the early elimination phase are inappropriate to predict trough values in a high-dosage, extended-interval regimen due to the longer $t^{½}$ in the late elimination phase (3, 35). Conversely, by using $C_{7.5h}$ and $C_{min}$, as in our study, one might overestimate the total $t^{½}$ due to a disproportional contribution of the late elimination phase. Another limitation with our pharmacokinetic data is the assumption that in a steady state situation $C_{min}$ is constant after each subsequent dose of netilmicin. We believe that in the clinical setting, where sampling is limited, a desire to predict future trough levels is best met if an early postdistributional value, i.e. $C_{2h}$, and a trough value are used for analysis in a 1-compartment model.

In conclusion, this dosage regimen results in high $C_{0.5h}$ values for the majority of patients across a wide range of GA and PMA. Acceptable $C_{min}$ values were found for most patients, except those with the lowest GA in the q24h and q36h regimen in the first week of life. To minimize the number of potential toxic trough values in this period a dosing interval of 48 h for GA < 29 weeks, 36 h for GA 29–36 weeks and 24 h for full term babies seems appropriate. For patients older than 7 d a dosing interval of 24 h is usually sufficient. Clearly this suggested modified dosage regimen has to be validated pharmacokinetically, and in terms of its clinical efficacy and potential toxicity.



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