*Neonatal and pediatric intensive care*

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# Once daily dosing of netilmicin in neonatal and pediatric intensive care

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**Abstract.** *Objective:* To examine a once daily dosing regimen of netilmicin in critically ill neonates and children. *Design and setting:* Open, prospective study on 81 antibiotic courses in 77 critically ill neonates and children, hospitalized in a multidisciplinary pediatric/neonatal intensive care unit. For combined empiric therapy (aminoglycoside and beta-lactam), netilmicin was given intravenously over 5 min once every 24 h. The dose ranged from 3.5–6 mg/kg, mainly depending upon gestational and postnatal age. Peak levels were determined by immunoassay 30 min after the second dose and trough levels 1 h before the third and fifth dose or after adaptation of dosing.
*Results:* All peak levels ($n = 28$) were clearly above 12 μmol/l (mean 22, range 13–41 μmol/l). Eighty-nine trough levels were within desired limits (<4 μmol/l) and 11 (11%) above 4 μmol/l, mostly in conjunction with impaired renal function.
*Conclusions:* Optimal peak and trough levels of netilmicin can be achieved by once daily dosing, adapted to gestational/postnatal age and renal function.

**Key words:** Netilmicin – Once daily dosing – Neonatal/pediatric intensive medicine – pharmacokinetics

Despite the availability of new, highly active antimicrobial agents, the aminoglycosides continue to play a major role in the treatment of critically ill neonates and children. The newly introduced once dialy dosing regimen of aminoglycosides is an attractive concept because it may improve efficacy and decrease toxicity. Increased efficacy is to be expected, since aminoglycosides exhibit concentration-dependent killing of bacteria [1], followed by prolonged post-antibiotic effect, especially when combined with beta-lactams [2]. Several authors have been able to demonstrate the excellent bactericidal effect of the once daily dosing regimen in experimental and clinical studies [3–5]. Compared to continuous infusion or repeated small dosing, intermittent exposure to high aminoglycoside levels has shown to decrease the uptake of the drug by renal and cochlear tissues in saturating the uptake mechanism, and therefore to diminish toxicity [5, 6].

In addition, large interindividual variability in aminoglycoside clearance and volume of distribution are found in neonates and children [7]. We therefore decided to perform an open, noncomparative study in order to establish a once daily dosing schedule.

## Materials and methods

All patients admitted to our 12-bed pediatric and neonatal multidisciplinary intensive care unit (PICU/NICU) and the 8-bed neonatal intermediate care unit were eligible for study, if there was indication for empiric antibiotic treatment. Netilmicin was used in combination with amoxicillin, cefuroxime (nosocomial infection) or amoxicillin clavulanate (nosocomial or anaerobic infection). Treatment lasted 10 days for culture-proven sepsis, 7–10 days for severe culture-proven local infection, and 2–3 days for the rule-out sepsis/infection situation. Netilmicin was given as a slow bolus injection over 5 min once every 24 h. The dose was chosen according to body weight, gestational and postnatal age resulting in five dosing regimens (group A–E, see Table 1). This dosing schedule was based upon the studies done by Fattinger et al. [7]. In renal insufficiency, adaption of dosage was performed either by extension of dosing interval to 36–72 h and/or reduction of dose to 2.5–3.0 mg/kg. Renal function was carefully monitored (urine output, serum creatinine), nephrotoxic agents (furosemide, acyclovir) were avoided around injection time, and renal perfusion pressure was agressively maintained.

Blood for determination of peak levels was drawn 30 min after the second dose in those patients with indwelling arterial catheters. Blood for determination of trough levels was obtained 1 h before the third and the fifth dose (or the subsequent dose after dosage-adaption). Netilmicin serum levels were determined by fluorescence polarization immunoassay. Peak levels over 12 μmol/l and trough levels less than 4 μmol/l were considered to be optimal [8]. Acute renal failure was defined as oliguria/anuria (less than 0.2 ml/kg/h) and/or 100% increase over normal range of serum creatinine. This included newborns with initially high creatinine levels with a lack of subsequent fall in creatinine over the first 2–4 days of life [9].

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**Table 1.** Once daily dosing regimen for netilmicin

| Group | Gestational (GA) and postnatal (PA) age (weeks, days) | Dose (mg/kg/day) | No. of treatment courses | Body weight[a] (kg) | Gestational age[a] (weeks) | Postnatal age[a] |
|---|---|---|---|---|---|---|
| A | post-conceptional age (GA+PA) >44 weeks | 6 | 10 | 20 (3.4–70) | – | 4.6 years (0.1–15.5) |
| B | PA≥4 days/ GA≥34 weeks | 5 | 9 | 3 (1.7–4.3) | 39 (36–39) | 9 days (4–24) |
| C | PA≥4 days/ GA<34 weeks | 4.5 | 5 | 1.7 (1.2–2.1) | 30 (28–33) | 13 days (4–26) |
| D | PA<4 days/ GA≥34 weeks | 4 | 43 | 3.2 (1.8–4.9) | 39 (34–43) | 2 days (1–3) |
| E | PA<4 days/ GA<34 weeks | 3.5 | 13 | 1.7 (1.1–2.9) | 31 (29–33) | 1 day (1–3) |

[a] Mean values and ranges (in brackets) are indicated

The study protocol was reviewed and approved by an institutional research committee, and informed parental consent was obtained.

## Results

During the study period (October 1st, 1989 to May 6th, 1990) 77 patients had 81 courses of netilmicin treatment fulfilling the criteria as outlined above (total number of admissions 738). Twenty-four courses of netilmicin treatment had to be excluded because of improper dosage and/or drug level determination. These 81 courses included: sepsis with positive blood culture, 8; bacterial bronchopneumonia, 14; peritonitis, 1; surgical prophylaxis, 10; and rule-out sepsis situations, 48. Patient allocation to different dosage regimens, as well as patient characteristics (weight and postnatal age at onset of treatment, gestational age at birth) are given in Table 1. Peak levels were determined in 28 and trough levels in 100 instances. Duration of antibiotic treatment and measured serum concentrations of netilmicin are shown in Tables 2 and 3. All peak levels were clearly above 12 µmol/l (mean 22 µmol/l), the highest levels being observed in group A (6 mg/kg netilmicin). Eleven trough levels (11%) were above 4 µmol/l: 7 were taken in patients with sudden onset of renal impairment and 2 remained elevated despite dose/interval adaption. In 2 instances there was no measurable renal impairment, but both patients suffered from shock requiring volume replacement and vasopressors. Acute renal impairment occurred during 13 netilmicin treatments (see Table 3) and resolved in all nine survivors. In 11 cases, severe underlying disease was most likely the reason for renal failure: severe perinatal asphyxia, 5; sepsis and shock, 2; hyaline membrane disease and severe hypoxemia, 2; necrotising enterocolitis and shock, 1; coarctaion syndrome and ischemia, 1.

## Discussion

The principal goal of this study was to achieve high serum peak levels – associated with increased bactericidal and postantibiotic effect [1, 2] – and to keep trough levels in an acceptable range – leading to decreased cumulative toxicity [5, 6] – in a critically ill patient population with large variability of netilmicin clearance and volume of distribution. The once daily dosing regimen for netilmicin per kilogram of body weight was therefore adapted to gestational age and postnatal age (see Table 1).

Resulting peak levels in our series were clearly above 12 µmol/l in all cases and substantially higher than peak levels reported before under conventional multiple daily dosing of netilmicin: mean peak levels, 19 (Group C and E) versus 13 µmol/l [10]. Peak levels in group A (post-conceptional age>44 weeks, dose of netilmicin 6 mg/kg) were very high, similar to those achieved in adult studies using single daily dosing of the drug [4]. In contrast, study patients in groups E and D (postnatal age<4 days,

**Table 2.** Pharmacokinetic data: peak levels

| | Patient group | | | | | |
|---|---|---|---|---|---|---|
| | A | B | C | D | E | Total (A–E) |
| Duration of treatment | | | | | | |
| Mean (day) | 5 | 4 | 5 | 5 | 5 | 5 |
| Range (day) | 2–11 | 3–6 | 4–5 | 3–11 | 3–9 | 2–11 |
| Peak levels of netilmicin[a] | | | | | | |
| No. of determinations | 5 | 4 | 2 | 10 | 7 | 28 |
| Mean (µmol/l) | 33 | 23 | 26 | 19 | 17 | 22 |
| Range (µmol/l) | 23–41 | 18–26 | 16–35 | 14–23 | 13–25 | 13–41 |

[a] All peak levels drawn 30 min after full second dose

**Table 3.** Pharmacokinetic data: trough levels

| | Patient group | | | | | |
|---|---|---|---|---|---|---|
| | A | B | C | D | E | Total (A–E) |
| Trough levels of patients with normal renal functions[a] | | | | | | |
| *n* | 9 (11) | 8 (9) | 3 (4) | 37 (49) | 9 (11) | 66 (84) |
| Mean (μmol/l) | 1.3 | 1.9 | 1.0 | 2.3 | 3.0 | 2.2 |
| Range (μmol/l) | 0.2–3.2 | 1.1–3.0 | 0.7–1.3 | 0.7–4.2 | 1.3–5.2 | 0.2–5.2 |
| *n* of trough levels >4 μmol/l | – | – | – | 1 | 1 | 2 |
| Trough levels of patients with impaired renal functions[b] | | | | | | |
| *n* | – | 1 | 2 (3) | 6 (7) | 4 (5) | 13 (16) |
| Mean | | 2.6 | 4.8 | 5.1 | 3.6 | 4.4 |
| Range | | | 2.4–7.2 | 2.8–9.2 | 1.4–5.8 | 1.4–9.2 |
| *n* of trough levels >4 μmol/l | – | – | 1 (2) | 5 | 2 | 8 (9) |

[a] All trough levels drawn 1 h before third dose; ( ) include trough levels drawn 1 h before fifth dose
[b] 88% (7/8) of trough levels drawn during sudden onset of renal impairment were >4 μmol/l. All other trough levels are drawn after reduced dose and/or increased interval

dose of netilmicin 3.5 to 4.0 mg/kg) showed considerably lower peak levels. In those groups, one might consider larger netilmicin doses in order to ensure higher ratios between peak serum concentrations and minimal bactericidal concentrations of pathogens. However, in order to maintain trough levels below 4 μmol/l, dosing interval would have to exceed 24 h and might therefore outlast duration of the postantibiotic effect.

Despite relatively high peak levels, 89% of our trough levels were within the desired range of 0–4 μmol/l compared to only 50% of trough levels during multiple daily dosing regimens in preterm infants [10]. 65% of all observed elevated trough levels were in patients with acute onset of renal insufficiency during initial treatment and 86% of these patients belonged to group D and E, i.e. postnatal age was less than 4 days. Despite reports of poor correlation between serum creatinine and aminoglycoside pharmacokinetics [7], monitoring of renal function especially within the first 2–4 days of live (urine output and daily serum creatinine measurements) might help prevent high trough levels in a critically ill patient population.

In conclusion we have been able to show that with a once daily dosing of netilmicin, adapted to gestational/postnatal age and renal function, theoretically optimal peak and trough levels can be achieved. Further clinical studies are needed to prove increased efficacy and less toxicity by this regimen.

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