POTENTIAL NEPHROTOXICITY OF BOTH CONVENTIONAL INTERVAL DOSING AND EXTENDED INTERVAL DOSING OF GENTAMYCIN IN PRETERM INFANTS

BY

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ABSTRACT

Few data exist for preterm infants < 34 weeks gestation concerning gentamycin dosage with only two studies using longer than 24 hours dosage interval in preterms ≤ 34 weeks gestation. The aim of this study is to compare potential renal toxicity of both conventional interval dosing (CID) and extended interval dosing (EID) of gentamycin in preterm infants < 34 weeks gestation. Forty infants < 34 weeks gestational age treated with ampicillin and gentamycin in the initial 24 hours of life were included. Infants were subdivided into two groups according to their birth weight: group I ---- birth weight ≤ 1500 gm, randomized to CID (2.5 mg/kg/dose given IV every 24 hours) or EID (5 mg/kg/dose given IV every 48 hours); group II ---- birth weight 1501-2000 gm, randomized to CID (2.5 mg/kg/dose given IV every 18 hours) or EID (4.5 mg/kg/dose given IV every 48 hours). The duration of therapy was 7 days in both groups. Gentamycin peak and trough levels, serum creatinine, urine output as well as volume of distribution and clearance of the drug were obtained. Both in group I and II, mean gentamycin peak levels were significantly higher and trough levels were significantly lower in EID compared with CID. Volume of distribution (Vd) in liters per kilogram was similar in CID and EID for both group I and in group II. Infants randomized to EID, however, had significantly higher clearance (in liters / hour / kilogram) than CID in both group I and II infants. Serum creatinine level at 7th day of gentamycin therapy increased by ≥25 % of its initial level in 20% (2/10) of group I “CID” patients and in 10% (1/10) of group I “EID” patients. While in group II patients, it increased in 40% (4/10) of CID patients and in 30% (3/10) of EID infants. However, this rise returned to normal at 12th day of study in all previous patients. Results suggest that EID of gentamycin in preterm infants appears safe and provides desirable peak and trough levels and less nephrotoxicity than in the CID schedule. Therapeutic monitoring, however, is still important in this population as a result of possible unpredictable inter-patient variability. It would be useful in the future to compare nephrotoxicity and clinical outcome of the dosing methods in a larger sample size.
INTRODUCTION

Infection is a significant cause of mortality and long-term morbidity in neonates. Antibiotics, thus, are among the most frequently used drugs in the neonatal period. Gentamycin provides synergistic coverage with ampicillin against the most common pathogens in the first month of life. Frequent use of therapeutic alternatives such as the third generation cephalosporins can result in rapid emergence of cephalosporin-resistant strains, especially enterobacter cloacae, klebsiella species, and serratia species in the neonatal intensive care unit (NICU) (American Academy of Pediatrics, 1997).

The side effects most frequently observed with gentamycin are ototoxicity and nephrotoxicity. The ototoxic reactions to aminoglycosides are a result of hair-cell destruction in the cochlear and vestibular apparatus.

Acute renal failure is a major complication of aminoglycoside antibiotics (Walker et al., 1999). Aminoglycoside nephrotoxicity typically presents initially as non-oliguric renal dysfunction. Serum creatinine and blood urea nitrogen concentrations increase as a result of a decreased glomerular filtration. There is also a decrease in the ability of the kidneys to concentrate urine as well as to eliminate aminoglycosides. Nephrotoxic reactions associated with gentamycin are almost always reversible upon discontinuation of the drug and appropriate medical management (Taylor and Finn, 1982). In humans, the occurrence of these signs may be followed by the development of overt renal failure characterized mainly by a nonoliguric and even often polyuric hypovolemic fall in creatinine clearance. Progression to oliguric or anuric renal failure is infrequent (Gilbert, 1995).

The risk factors that have been associated with aminoglycoside nephrotoxicity are total daily dose (mg/kg/day), duration of therapy, pre-existing renal dysfunction, sustained elevated trough levels (> 2 μg / ml), elevated peak levels (>12 to 15 μg / ml), concurrent administration of other nephrotoxic drugs such as cephalosporins or diuretics, prior aminoglycoside exposure and duration of treatment (Wiland and Szechinski, 2003).

A potential drawback to gentamycin therapy is the need to monitor serum drug levels (SDL) frequently to ensure achievement of concentrations which are effective and minimize the likelihood of renal and eighth nerve damage (McCormack and Jewesson, 1992).

Gentamycin dosing in the neonates continues to be a challenge, in view of rapidly changing and variable pharmacokinetic parameters in this group of patients, with
the addition of clinical problems (Thomson et al., 1988). The pharmacokinetics of
drugs in the premature neonate are unique and greatly influenced by gestational age and weight. The distribution of a drug within the body is influenced by several factors such as composition of body fluids, pH, and organ blood flow.
The premature neonate has a large volume of distribution (Vd) secondary to an increased volume of extracellular fluid compartment (Prober et al., 1990; Reed and Besunder, 1989). As such, a higher mg/kg dose is required to overcome this increased Vd and attain a target peak. Premature neonates also have a low glomerular filtration rate that results in slow renal clearance of drugs (Skopnik et al., 1992; Hayani et al., 1997; Murphy et al., 1998).

Aminoglycosides display concentration-dependent killing (Andes and Craig, 1998) and a post-antibiotic effect (the length of which is proportional to the peak concentration) (Rotschafer et al., 1992), and pathogens develop adaptive resistance (Karadowsky et al., 1997). Therefore, to maximize clinical efficacy, higher peak concentrations should result in improved bacterial killing and a longer post-antibiotic effect, while a “drug-free” period should occur in each dosing interval to allow the reversal of adaptive resistance (Stickland et al., 2001).

Aminoglycoside-induced nephrotoxicity may be reduced by limiting the total exposure per dosing interval to acceptable levels (Begg et al., 1995), and by ensuring a low concentration or drug-free period in each dosing interval to allow redistribution of the aminoglycoside out of the proximal renal tubules where it is known to concentrate (Laurent et al., 1990).

The desire to consistently obtain therapeutic and relatively safe gentamicin SDL in a dynamic and diverse population has led to implementation of complicated dosing schemes for NICU patients, with recommended dosing intervals ranging from every 36 hours to every 8 hours based on gestational age, postnatal age, and/or weight (Lundergan et al., 1999). Although the extended-interval dosing for the aminoglycoside, gentamicin, is recommended in NEOFAX (Young and Mangum, 2005), few data exist for preterm infants < 34 weeks gestation to support this recommendation (Mercado et al., 2004; Bartal et al., 2003).

The aim of this study is to compare the potential renal toxicity of both conventional interval dosing (CID) and extended interval dosing (EID) of gentamicin in preterm infants < 34 weeks gestation as well as to determine the impact on the frequency of monitoring of serum drug level in these subjects.
PATIENTS AND METHODS

This study was conducted in the Neonatal Care Unit of Mansoura University Children's Hospital. Forty infants < 34 weeks gestational age treated with ampicillin and gentamycin in the initial 24 hours of life for early onset sepsis were included. Infants with conditions that potentially affected renal function were excluded: (1) history of asphyxia and shock; (2) treatment with vasopressors or diuretics; (3) congenital or chromosomal abnormalities; (4) hemodynamically significant patent ductus arteriosus requiring indomethacin treatment; (5) infants whose mothers received drugs affecting renal function.

Infants were subdivided into two groups according to their birth weight: group I —— birth weight ≤ 1500 g, randomized to CID (2.5 mg/kg/dose given IV every 24 hours) or EID (5 mg/kg/dose given IV every 48 hours); group II —— birth weight 1501-2000 g, randomized to CID (2.5 mg/kg/dose given IV every 18 hours) or EID (4.5 mg/kg/dose given IV every 48 hours) (Lundergan et al., 1999; Mercado et al., 2004). All infants were treated with the antibiotics for 7 days.

Gentamycin levels were measured using the TD (Abbott Laboratories, Abbott Park, IL 60064) System which uses Fluorescence Polarization Immunoassay (FPIA) technology (Jolly, 1981). Levels were drawn at the second dose for EID and at the third dose for CID. Gentamycin trough levels were drawn 30 minutes prior to the scheduled dose and the gentamycin peak levels were drawn 30 minutes after completion of the 30-minutes dose infusion. Our target serum levels were peak concentrations of gentamycin between 5-12 µg/ml and trough levels of ≤ 2 µg/ml (Mercado et al., 2004). Urine output was recorded daily as ml/kg/h during the study period.

Serum creatinine levels were measured on days 1 (prior to gentamycin administration) and at day 7 of treatment then 5 days after gentamycin treatment was completed (day 12). Volume of distribution and clearance were calculated using standard pharmacokinetic equations (Bryson and Bryson, 1996). An informed consent was obtained from parents of infants included in this study.

Statistical analysis:

Data were analysed using SPSS for Windows Statistical Package (SPSS Inc., Chicago, IL, U.S.A.). Summary statistics of data were expressed as mean ± SD, median and 25th - 75th percentiles (interquartile range). The Kolmogrov-Smirnov test was performed to check normal distribution of data. Non-parametric data were assessed by the X² test and the Mann Whitney U
test for continuous variables. T-test was used for comparing means of parametric data. A p value < 0.05 was considered statistically significant.

RESULTS

Forty infants were enrolled between January 2005 and January 2006. Twenty infants were in group I (750 to 1500 gm); 10 in CID and 10 in EID. Twenty infants were in group II (1501-2000 gm); 10 in CID and 10 in EID. Patients' clinical characteristics are summarized in table (1). No significant difference was found among CID and EID patients in either group I or II as regards sex, gestational age, birth weight or appropriateness for gestational age.

Tables (2 and 3) demonstrate peak and trough gentamycin levels in the studied groups. In group I, mean gentamycin peak levels were significantly higher and trough levels were significantly lower in EID compared with CID (p 0.0001 in both comparisons). Similarly, in group II, mean gentamycin peak levels were significantly higher and trough levels were significantly lower in EID compared with CID (p 0.0001 in both comparisons). None of the infants in CID or EID had subtherapeutic peak levels (<5 μg/ml) or peak levels exceeding the upper limit (12 μg/ml) necessitating dosage adjustment. Five infants in CID had a trough level slightly exceeding the upper limit (2 μg/ml) compared to only one infant in EID. Figures (1 and 2) demonstrate peak and trough gentamycin levels in CID and EID of group I and II.

Data are expressed as mean ± SD except clearance which is expressed as median (IQR).

Volume of distribution (Vd) in liters per kilogram was similar in CID and EID for both group I (CID 0.4 ± 0.04 versus EID 0.52 ± 0.03; p = 0.23) as shown in table (2) and in group II (CID 0.43 ± 0.08 versus EID 0.53 ± 0.12; p=0.8) as shown in table (3). Infants randomized to EID, however, had significantly higher clearance (in liters / hour / kilogram) than CID in both group I and II infants (p 0.001 and 0.003 respectively) as demonstrated in tables (2 and 3).

We considered renal toxicity if serum creatinine level following start of gentamycin showed an increase of ≥ 25 % of its level prior to the start of gentamycin infusion or if serum creatinine level following start of gentamycin was ≥ 1.4 mg/dl. All infants had normal serum creatinine levels (< 1 mg/dl) prior to gentamycin administration. Serum creatinine level at 7th day of gentamycin therapy increased by ≥ 25 % of its initial level in 20% (2/10) of group I "CID" patients and in 10% (1/10) of group I "EID" patients. While in group II patients, it increased in 40% (4/10) of CID patients and in 30% (3/10) of EID in-
fants. However, this rise returned to normal at 12th day of study in all previous patients.

All infants had a urine output (1 to 5 ml / kg/ hr ) throughout the 12-day study period except two patients in group II "CID" who exhibited urine output above 5 ml/ kg/hr in at least one occasion during the 12-day study period, those patients were among the 4 cases of group II "CID" who showed increased serum creatinine level at 7th day of treatment and they showed a decrease in urine output to ≤ 4 ml / kg / day in the rest of the study period.

**DISCUSSION**

In contrast to the traditional dosing method of gentamicin in neonates, the extended interval dosing method enables concentrations to approach the desired profile of high peak and low trough gentamicin levels. This should be associated with increased antibacterial killing and reduced toxicity, as has been suggested in meta-analyses of once-daily dosing (Barelay et al., 1999).

The desire to consistently obtain therapeutic and relatively safe gentamicin SDL in prematures which are considered a dynamic and diverse population has led to implementation of complicated dosing schemes for NICU patients (Nestaas et al., 2005). Few data exist for preterm infants < 34 weeks gestation with only two studies using > 24 hours dosage interval in preterms ≤ 34 weeks gestation; Gooding et al (2002) used a 24 hour traditional dosage (TD) interval and 36 hour EID dosage interval, and Mercado et al (2004) compared 24 hours in the TD group with 48 hours in the EID group.

This study shows that gentamycin EID in preterm infants provides higher peaks (therapeutic target of 5-12 μg/ml) and lower troughs (normal target < 2 μg/ml) than CID, a finding consistent with previous reports (Nestaas et al., 2005; Mercado et al., 2004; Glover et al., 2001). Nestaas et al. (2005) reported that the summary risk ratios for therapeutic serum drug concentrations (SDCs) were significantly in favour of the EID for both peak and trough SDCs.

The high peak is desirable because a high peak aminoglycoside concentration relative to the minimum inhibitory concentration of the organism is a major determinant of bacterial killing. The low trough achieved with EID is desirable because aminoglycosides exhibit a postantibiotic effect; longer durations of low or undetectable levels help avoid the rapid development of microbial resistance (Hayani et al., 1997).

The main benefits from giving gentam-
ycin in an extended interval are the achievement of desired gentamycin concentrations, a reduction in the frequency of blood sampling needed with associated cost savings in gentamycin assays.

Pharmacokinetic analysis in this study showed no difference between CID and EID with respect to Vd; however, EID had significantly higher clearance as compared with infants in CID. This should result in less aminoglycoside accumulation in the proximal renal tubules in EID group.

Increased serum creatinine level was observed at the 7th day of gentamycin therapy by ≥ 25% of its initial level in group I (in 20% of CID infants and 10% of EID ones) and in group II (in 40% of CID infants and 30% of EID ones). The lower incidence of increased serum creatinine level among EID patients compared to CID ones didn’t reach a statistically significant difference, but it could be the result of accurate peak and trough gentamycin concentrations in EID group which resulted in a lower incidence of nephrotoxicity (Taylor and Finn, 1982). This rise in serum creatinine was found to return to normal by the 12th day of the study in all previous patients corresponding to what was reported by Kahn et al. (1980); Taylor and Finn (1982) and Gilbert (1995) that nephrotoxic reactions associated with gentamycin are almost always reversible upon discontinuation of the drug and appropriate medical management. The absence of a significant difference in toxicity between traditional dose and EID groups was also concluded from Nestaas et al. (2005) meta-analysis.

From this study, we can conclude that the EID of gentamycin in preterm infants appears safe and provides desirable peak and trough levels than in the CID schedule. Therapeutic monitoring, however, is still important in this population as a result of possible unpredictable inter-patient variability. This also enables dose individualization to be made early in therapy. It would be useful in the future to compare outcomes of the dosing method using sensitive indices of nephrotoxicity and ototoxicity and clinical outcome in a larger sample size.
**Table (1):** Characteristics of study groups.

<table>
<thead>
<tr>
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<th>CID</th>
<th>EID</th>
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<tbody>
<tr>
<td><strong>Group I:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>30.8 ± 3.1</td>
<td>30.5 ± 1.5</td>
</tr>
<tr>
<td>Birth weight (gm)</td>
<td>1125 ± 217.8</td>
<td>1302 ± 200.8</td>
</tr>
<tr>
<td>Sex ( M/F )</td>
<td>5 / 5</td>
<td>4 / 6</td>
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<tr>
<td><strong>Group II:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>31.2 ± 1.8</td>
<td>31.7 ± 2.1</td>
</tr>
<tr>
<td>Birth weight (gm)</td>
<td>1542.6 ± 430</td>
<td>1539 ± 305.5</td>
</tr>
<tr>
<td>Sex ( M/F )</td>
<td>6 / 4</td>
<td>4 / 6</td>
</tr>
</tbody>
</table>

Gestational age and birth weight are expressed as mean ± SD

**Table (2):** Peak and trough concentrations and pharmacokinetic parameters of gentamycin in group I (CID and EID) patients.

<table>
<thead>
<tr>
<th></th>
<th>CID</th>
<th>EID</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak gentamycin level (µg/ml)</td>
<td>6.29 ± 0.6</td>
<td>9.68 ± 0.63</td>
<td>0.0001</td>
</tr>
<tr>
<td>Trough gentamycin level (µg/ml)</td>
<td>1.26 ± 0.37</td>
<td>0.63 ± 0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>0.4 ± 0.04</td>
<td>0.52 ± 0.03</td>
<td>0.23</td>
</tr>
<tr>
<td>Clearance (L/hr/kg)</td>
<td>0.04 (0.04–0.05)</td>
<td>0.06 (0.05–0.06)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD except clearance which is expressed as median (IQR).

**Table (3):** Peak and trough concentrations and pharmacokinetic parameters of gentamycin in group II (CID and EID) patients.

<table>
<thead>
<tr>
<th></th>
<th>CID</th>
<th>EID</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak gentamycin level (µg/ml)</td>
<td>6.21 ± 1.35</td>
<td>8.74 ± 1.36</td>
<td>0.0001</td>
</tr>
<tr>
<td>Trough gentamycin level (µg/ml)</td>
<td>1.65 ± 0.82</td>
<td>0.82 ± 0.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>0.43 ± 0.08</td>
<td>0.53 ± 0.12</td>
<td>0.8</td>
</tr>
<tr>
<td>Clearance (L/hr/kg)</td>
<td>0.05 (0.038–0.05)</td>
<td>0.06 (0.05–0.06)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD except clearance which is expressed as median (IQR).
Fig. 1: Peak gentamycin levels in CID and EID in group I and group II

Fig. 2: Trough gentamycin levels in CID and EID in group I and group II
REFERENCES


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السُمية الكلوية المحتملة لكل من إعطاء عقار الجنتاميسين للأطفال المبتسمرين بجرعة على فترات تقليدية وإعطائه لهم بجرعة على فترات أكثر تباعدًا

المثير في البحث

د. عصام مجدوع على ود. بسمه أسامة شومان

من أقسام الطب الشرعي والسوم الإكلينيكية وطب الأطفال ووحدة حديثي الولادة

كلية الطب - جامعة المصرية

هناك القليل من المعلومات التي تخص جرعة عقار الجنتاميسين للأطفال المبتسمرين ذوي العمر الرحمي أقل من 44 إسبوعًا حيث توجد دراسات فقط تم فيها إعطاء الجنتاميسين على فترات أطول من 24 ساعة لآلهة الأطفال. استشهدت هذه الدراسة المقترحة بسماة الكلوية المحتملة لكل من إعطاء الجنتاميسين بجرعة على فترات تقليدية وإعطائه على فترات أكثر تباعًا للأطفال المبتسمرين ذوي العمر الرحمي أقل من 44 إسبوعًا. قمت دراسة 40 طفلًا من الأطفال الذين قيل عمرهم الرحمي عن 44 إسبوعًا وذين كانوا يتطاولون الأميلسنين والجنتاميسين بدءًا من الرابع والعشرين ساعة الأولى من عمرهم للعلاج من العدوى البكتيرية.

تم تقسيم هؤلاء الأطفال إلى مجموعتين بناءً على وزنهم عند الولادة: المجموعة الأولى: وزنها 2-5 جرام وتم تقسيمها عشوائيًا إلى مجموعتين: مجموعتي تناول الجنتاميسين بجرعة تعادل 2.5 مجم/كمج/كم/ساعة بالوريد أو إلى تناول بجرعة تعادل 0.5 مجم/كمج/كم/ساعة. المجموعة الثانية: يترواح وزنها 5-10 جرام وتم تقسيمها عشوائيًا إلى مجموعتي تناول الجنتاميسين بجرعة تعادل 5 مجم/كمج/كم/ساعة بالوريد أو إلى تناول بجرعة تعادل 1 مجم/كمج/كم/ساعة واستمرت فترة العلاج في المجموعتين 7 أيام.

تم قياس مستوى الجنتاميسين بالدم عند الذروة في النقطة الدنيا كما تم قياس الكرياتينين في الدم وكمية البول وكذلك حجم تروع الجنينين في حمض الجسم. أظهرت الدراسة أنه في كلتا المجموعتين الأولى والثانية كان مستوى الجنتاميسين بالدم عند الذروة أعلى عند النقطة الدنيا أقل بدرجة ملحوظة بين الأطفال الذين تناولوا الجنتاميسين على فترات أكثر تباعًا مقابل في الذين تناولوا على فترات تقليدية.

لربط الإفراط في نسب الكرياتينين بالدم عند اليوم السابع للدراسة عن قبل إعطاء الجنتاميسين في 20% من المجموعة الأولى (جرعة تقليدية) و10% من المجموعة الأولى (جرعة متباينة) وفي 40% من المجموعة الثانية (جرعة تقليدية) و30% من المجموعة الثانية (جرعة متباينة).

إلا أن هذا الارتفاع عاد إلى المستوى الطبيعي في اليوم الثاني عشر من الدراسة.

من نغمة هذه الدراسة أن إعطاء الجنتاميسين بجرعات متباينة للأطفال المبتسمرين ذوي العمر الرحمي أقل من 44 إسبوعًا له سمية كلوية أقل ويريد إلى مستوى جنتاميسين بالأميروغ عند الذروة أعلى عند النقطة الدنيا أقل بدرجة ملحوظة عن عند إعطاء بجرعات تقليدية. إلا أنه لايزال من الأهمية متابعة مستوى العقار بالدم أثناء العلاج لاحثما وجود اختلافات بين الرحم. ونتصح بعمل دراسات مستقبلية تقارن السمية الكلوية لجرعات المختلفة في عينة أكبر من الأطفال المبتسمرين.