Efficacy and safety of a single daily dose of gentamicin in hospitalized Indian children: a quasi-randomized trial

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Objectives: To compare the clinical efficacy, pharmacokinetic profiles and safety of once-daily dosing (ODD) and multiple daily dosing (MDD) of gentamicin in hospitalized Indian children.

Patients and methods: Four hundred children admitted to our hospital were studied prospectively. The patients were randomized to ODD or MDD groups alternately. The primary outcomes were: (i) a good clinical outcome, as defined; and (ii) occurrence of side effects, if any. Clinical efficacy was determined by comparing the proportion of patients with a favourable response between the two groups, while pharmacokinetic profile was assessed by comparing the peak and trough concentrations of the drug in a subgroup of patients. Safety of the two regimens was compared, besides recording any symptoms due to side effects of the drug, with the help of serum creatinine and brainstem-evoked response audiometry (in a subgroup of the patients).

Results: We found ODD of gentamicin in hospitalized Indian children to be efficacious and safe. A favourable clinical response was achieved in 167 of the 188 patients (89%) in the ODD group and in 161 of the 212 patients (76%) in the MDD group. Similarly, a higher number of patients in the ODD group showed favourable gentamicin peak concentrations as compared with the MDD group (100% versus 87%). The MDD group showed a higher number of trough concentrations in the undesirable range as compared with the ODD group (17% versus 0%).

Conclusions: The study supports extended-interval (single daily) dosing in hospitalized Indian children due to its efficacy and safety with the added advantage of needing fewer injections.

Keywords: paediatric, aminoglycosides, pharmacokinetics

Introduction

Aminoglycosides are a cornerstone in the therapy of serious Gram-negative infections, despite their potential toxicity. Gentamicin is one of the most commonly used members of this group, because of a broad spectrum of activity and low cost. There has been a long-standing debate regarding whether aminoglycosides should be administered in multiple doses per day or with extended-interval dosing. The conventional multiple daily dosing (MDD) needs to be administered intravenously (iv) and is feasible only in hospitalized patients. Also, periodic determination of the plasma concentration of the drug is recommended to ensure that the drug is in the desired concentration range.

A once-daily dosing (ODD) regimen could reduce the risk of side effects, with equal or even improved efficacy.1–4 Features such as concentration-dependent bactericidal activity, post-antibiotic effect (which allows continued efficacy even when serum concentrations fall below expected MICs), decreased risk of adaptive resistance and diminished accumulation in renal tubules and the inner ear make ODD an attractive alternative to MDD.5–9 ODD is also compatible with domiciliary treatment and is less costly, as has been reported in a few studies conducted on children outside India.10 However, no study has been published from India on local subjects, to the best of our knowledge. Recommendations regarding ODD of aminoglycosides for paediatric patients are not consistent in various paediatric drug reference manuals and major textbooks.11,12 A relatively low level of adoption of this practice for treating neonates (11%) and children (23%) suggests that this is not yet standard practice, and considerable uncertainty remains among clinicians regarding the merits and safety of ODD for children.13
Single daily dose of gentamicin in Indian children

ODD of gentamicin, if proved to be at least as efficacious and no more toxic than MDD, would make domiciliary treatment possible, thereby enabling us to discharge patients early and significantly reduce bed occupancy as well as the total cost of treatment. It would also reduce the workload of the staff by decreasing the number of injections to be given in a rotation or shift. These considerations prompted us to conduct a prospective, randomized open labelled controlled trial comparing the efficacy, safety and pharmacokinetics of ODD versus MDD iv administration of gentamicin.

Patients and methods

Hospital setting

The present study was conducted in a tertiary care hospital affiliated to the University of Delhi in New Delhi, India. The study ran from 1 May 2005 to 31 March 2006. The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards, and approval was obtained from the Ethics Committee of the institute. It was decided that children with severe sepsis (defined as the need for inotropic support) be excluded for ethical reasons. An informed consent was obtained from the parents in all cases, and the children gave their assent wherever applicable. As most parents/caregivers were illiterate or semi-literate, the consent was a verbal informed consent approved by the institutional Ethics Committee, which was read out and explained by one of the authors (S. T.).

Study population

To have a power of 0.80 and an α error of 0.05 for an equivalence study (less than 10% estimated difference in the proportion of subjects having a favourable outcome between two groups), a sample size of 200 patients in each arm of the study was considered adequate. However, because of a lack of kits for pharmacokinetic studies, only the clinical efficacy part of our study has the adequate statistical size.14

The present study was a prospective study conducted in a tertiary care hospital for children between 0 and 12 years of age.

Inclusion criteria. The study ran from May 2005 to March 2006 and enrolled all infants and children admitted to a paediatric unit with suspected or confirmed infections considered suitable for gentamicin therapy [viz. (i) suspected or proven Gram-negative sepsis, (ii) Gram-negative or staphylococcal infections like pneumonia and septic arthritis, and (iii) urinary tract infection (UTI) caused by Gram-negative bacteria]. The decision to start gentamicin therapy was taken by the admitting paediatricians who were not directly involved in the study or interested in the outcome of the study.

Exclusion criteria. Children with persistently abnormal renal function, children already diagnosed with impaired internal ear function, severely ill children (those requiring vasopressor/ventilator support or ICU care) or those with life-threatening infections, neonates <48 h old or <34 weeks of gestational age and children >12 years of age, were excluded from the study, as were those already on aminoglycoside antibiotic treatment.

Study design and intervention

In total, 400 consecutive cases were enrolled in this open labelled, quasi-randomized controlled trial. These patients were allocated to one of the two groups by the first author (S. T.) – those admitted on even days of the month (2, 4, 6, …) received a single daily dose of 6 mg/kg gentamicin15,16 (rounded off to the nearest whole number), while those admitted on odd days of the month (1, 3, 5, …) received the same total dose in two or three divided doses. All patients enrolled for the study were allocated to their respective groups as soon as the decision to start gentamicin was taken by the treating pediatrician. The decisions regarding companion antibiotic and duration of antibiotic therapy was dictated by the standard treatment policies and practices of the unit. Any change to another antibiotic due to clinical or bacteriological failure was totally at the discretion of the treating consultant, who was aware of the group the patient was assigned to, but was not a part of the study team and was not concerned with its outcome. In none of the cases was any patient shifted from the ODD group to the MDD group or vice versa.

Due to resource constraints, we could assess the serum gentamicin concentrations (SGCs) of a convenient subsample only. The serum samples were taken after 48 h of starting gentamicin therapy and stored at −80°C. All the samples were processed together at the end of the study. In the MDD group, a pre-dose sample (for trough concentration) was taken as close as possible to, but before, the next dose and the post-dose sample (for peak concentration) was taken 30 min after the end of gentamicin administration. For the ODD regimen the pre-dose sampling (trough concentration) was done 18 h after gentamicin injection and the post-dose sample was taken 30 min after the administration. For the ODD group, however, the trough concentrations were taken deliberately at 18 h to confirm the hypothesis that ODD maintains the trough concentrations below the threshold of toxicity for a much longer duration, thereby reducing the risk of adverse effects. The SGCs were measured using an Emit 2000 Gentamicin Plus Assay Kit (provided by Dade Behring Ltd, Milton Keynes, UK) by a technician who was blinded to the group allocation of the patient.

Outcome parameters

The primary outcome measure was the clinical efficacy of gentamicin. Clinical efficacy was defined as ‘favourable’ if gentamicin therapy led to a clinical improvement with resolution of symptoms of infection, return to normal body temperature (<37.9°C) for at least 48 h and normalization or a decrease (>15%) in the white blood cell count. All other responses were ‘unfavourable’. These parameters were monitored daily until discharge, death or replacement of gentamicin by another antibiotic.

Serum creatinine was measured at admission, 48–72 h later and at discharge. A rise in serum creatinine of 0.5 mg/dL or more during the study period was considered a sign of probable nephrotoxicity. The caregivers were also interviewed every day to assess the urine output. They were asked for any perceived change in the frequency or volume of urine in the previous 24 h.

All the patients were observed for signs and symptoms of otoxicity. Due to resource and technical constraints, brainstem-evoked response audiometry (BERA) screening for subclinical hearing impairment could be performed in 20 patients only.

Baseline assessment

Upon admission, demographic details, clinical examination and relevant radiological, biochemical and microbiological (where feasible) investigations were done for all those who were enrolled in the study.

Statistical analysis

Efficacies of the dosing regimens in the two groups (MDD and ODD) were compared by χ2 test, using SPSS 10.0 software.
The SGCs in the two groups were compared by Mann–Whitney U-test using GraphPad Prism software, while the mean duration of gentamicin therapy was compared by unpaired t-test using GraphPad Prism software.

**Results**

**Patient characteristics**

During the study 412 children met the inclusion criteria for the study and were evaluated prospectively. Twelve patients, who left against medical advice after initiation of treatment but before reaching the primary endpoint, were excluded from the data analysis, leaving a total of 400 patients (MDD, 212; ODD, 188) in the study. The flow of patients through the trial is shown in Figure 1. Children in both the groups were comparable with respect to age, sex, mean body temperature and percentage of patients in the neonatal age group (Table 1). Gentamicin was usually given in combination with at least one broad-spectrum antibiotic, and the choice of the accompanying antibiotic was also comparable between the two groups. The mean duration of gentamicin therapy was also similar in the two groups (8.3 days versus 8.13 days in the MDD and ODD groups, respectively; \( P = 0.552 \)).

**Infections and microorganisms**

The sites of infection in the two groups were also comparable (Table 1). Microbiological evaluation was done in 138 (65%) patients in the MDD group and 130 (69%) patients in the ODD group. Fifty-three patients in the MDD group and 64 patients in the ODD group had one or more microorganisms isolated. The majority of microorganisms isolated were Gram-negative bacilli; 44 out of 61 isolates (72%) and 55 out of 74 isolates (74%) in the MDD and ODD groups, respectively. The proportion of patients with positive blood and/or other cultures was 53 (25%) and 64 (34%) in the MDD and ODD groups, respectively. The number of polymicrobial infections was five in each group. The MICs of the drugs used for the isolates were not available due to lack of facilities.

SGCs and clinical efficacy

The mean peak and trough SGCs are shown in Table 2. The peak as well as trough concentrations were statistically different between the two groups. The mean peak concentrations in the ODD group were much higher than for the MDD group and the mean trough concentrations were lower in the ODD group. A favourable clinical response was achieved in 167 of the 188 patients (89%) in the ODD group and in 161 of the 212 patients (76%) in the MDD group, the difference being statistically significant (\( P = 0.0001 \)). On intention to treat analysis, the ODD group had a significantly more favourable clinical outcome (z value 2.56, \( P < 0.01 \)). Unfavourable response included all patients in whom gentamicin was stopped either due to non-improvement (ODD, 19 patients; MDD, 49 patients) or due to ototoxicity (ODD, 2 patients; MDD, 2 patients).

**Toxicity**

The change in serum creatinine did not differ between the two groups, and no child had either oliguria or polyuria. The mean serum creatinine at baseline and on the discontinuation day was 0.5 mg/dL and 0.8 mg/dL, and 0.6 mg/dL and 0.8 mg/dL in the ODD and MDD groups, respectively.

BERA evaluation for ototoxicity was feasible only in 20 patients (10 from each group). As most patients were too ill for BERA evaluations within the first 72 h of therapy, it was carried out only at the time of stoppage of gentamicin therapy for most of these patients. In addition, the mothers of some patients refused a second audiogram. Due to logistical constraints, BERA was feasible in the ideal fashion, i.e. both before and after treatment, only in four patients (two in each group). The baseline variables of the subsets who underwent BERA in the two groups were comparable. The cut-off of normal latency for wave V was taken at 6 ms. The mean latency of wave V was 5.8 ms and 6.1 ms in the ODD and MDD groups, respectively. Two patients in each group showed a significant hearing loss on BERA, involving both ears in all four patients. The ODD [2 out of 188 (1.06%)] and the MDD [2 out of 212 (0.94%)] groups developed ototoxicity in a similar proportion of patients.

None of the parents/patients reported any clinical symptoms of ocular or vestibular toxicity. However, upon prompting, four ODD patients and five MDD patients reported transient headache, dizziness and/or tinnitus. These symptoms, however, could not be directly attributed to ototoxicity.

**Discussion**

Gentamicin is inexpensive, widely available and a highly effective antibiotic for treating serious infection in young infants in developing countries.\textsuperscript{17} We felt there was a need to provide data to support ODD, if appropriate, to encourage clinicians from resource-poor countries to accept it. We do realize that without adequate data it is impossible to change a practice based on many years of experience with multi-dose gentamicin regimens.
A large number of our patients, in either group, were neo-
nates. In a review of 13 comparison studies conducted on pa-
ediatric patients, 8 involved the neonatal age group.18 However,
none of the studies in this analysis had a sample size as large as
our study. The authors concluded in their review that ODD was
more efficacious, with no higher toxicity at 48–96 h in neonates
and at 3–10 days of therapy in older infants and children. Our
results echo a similar finding. This is of significance because
ODD in resource-poor settings becomes all the more advan-
tageous in newborns as it obviates the need for more frequent
changes of iv cannula.

In routine practice, for MDD therapy in children up to
2 years of age, 2–2.5 mg/kg of gentamicin every 8 h has been
considered safe, while 5 mg/kg daily divided into two equally
spaced injections of gentamicin has been recommended for
neonates with severe infections.15 The target peak serum
concentration ranges between 4 and 12 mg/L with a trough con-
centration of 2 mg/L.16 Although gentamicin concentration
monitoring is recommended, it is not always practicable or
followed in developing countries due to the need for extra
serum sampling, limited laboratory facilities and the additional
cost.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>MDD (n = 212)</th>
<th>ODD (n = 188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>120 (56.6)</td>
<td>110 (58.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>92 (43.4)</td>
<td>78 (41.5)</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>11 months (2 days to 12 years)</td>
<td>14 months (2 days to 11.5 years)</td>
</tr>
<tr>
<td>Neonates, n (%)</td>
<td>93 (43.9)</td>
<td>88 (46.8)</td>
</tr>
<tr>
<td>Mean temperature (°C)</td>
<td>38.5</td>
<td>38.2</td>
</tr>
<tr>
<td>Mean duration of antibiotic therapy (days)</td>
<td>8.3</td>
<td>8.13</td>
</tr>
<tr>
<td>Antibiotics accompanying gentamicin, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ampicillin</td>
<td>149 (70.3)</td>
<td>140 (74.5)</td>
</tr>
<tr>
<td>cefotaxime</td>
<td>21 (9.9)</td>
<td>23 (12.2)</td>
</tr>
<tr>
<td>amoxicillin/clavulanate</td>
<td>13 (6.1)</td>
<td>7 (3.7)</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>4 (1.9)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>17 (8.0)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>others</td>
<td>8 (3.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infections, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>septicaemia/bacteraemia</td>
<td>97 (45.8)</td>
<td>101 (53.7)</td>
</tr>
<tr>
<td>bronchopneumonia</td>
<td>69 (32.5)</td>
<td>48 (25.5)</td>
</tr>
<tr>
<td>empyema</td>
<td>3 (1.4)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>UTI</td>
<td>11 (5.2)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>dysentery</td>
<td>13 (6.1)</td>
<td>8 (4.3)</td>
</tr>
<tr>
<td>septic arthritis</td>
<td>4 (1.9)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>pyogenic liver abscess</td>
<td>8 (3.8)</td>
<td>8 (4.3)</td>
</tr>
<tr>
<td>multiple infection sites</td>
<td>3 (1.4)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>unexplained fever</td>
<td>4 (1.9)</td>
<td>6 (3.2)</td>
</tr>
</tbody>
</table>

Table 2. Mean peak and trough SGCs

<table>
<thead>
<tr>
<th></th>
<th>MDD group (n=23)</th>
<th>ODD group (n=22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (mg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>6.65 ± 1.34</td>
<td>9.08 ± 1.38</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>range</td>
<td>5–11.9</td>
<td>6.3–11.7</td>
<td>—</td>
</tr>
<tr>
<td>no. of patients with SGC &gt;6 mg/L (%)</td>
<td>20 (87)</td>
<td>22 (100)</td>
<td>—</td>
</tr>
<tr>
<td>Trough (mg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>1.49 ± 0.64</td>
<td>1.08 ± 0.37</td>
<td>0.0337*</td>
</tr>
<tr>
<td>range</td>
<td>0.6–2.9</td>
<td>0.6–1.8</td>
<td>—</td>
</tr>
<tr>
<td>no. of patients with undesirably high trough concentrations (SGC &gt;2 mg/L) (%)</td>
<td>4 (17)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Significance value (P<0.05).
Though there have been suggestions that gentamicin should be administered as an infusion over 30–60 min, we administered it as a bolus over 2–3 min because bolus administration is more convenient, reduces the work load of nursing staff and is certainly cheaper, as has also been reported by Robinson et al.\textsuperscript{19} Moreover, no published support has been found that recommends each dose to be given as an iv infusion over 30–60 min. Abrupt neuromuscular blockade could theoretically occur after bolus administration, but has never actually been reported.\textsuperscript{19}

Peak and trough SGCs were measured only 48 h after the start of gentamicin therapy. This was because of the suggestion that, unless renal function is poor, it takes three half-lives for plasma concentrations to stabilize once treatment is started.\textsuperscript{20} For the MDD group, the peak and trough concentrations were taken 30 min after and just before the iv bolus, respectively. For the ODD group, however, the trough concentrations were taken deliberately at 18 h to confirm the hypothesis that ODD maintains the trough concentrations below the threshold for toxicity for a much longer duration, thereby reducing the risk of adverse effects. Peak concentrations of the ODD group were taken 30 min after the iv bolus.

In our study, peak SGCs were significantly higher and trough SGCs significantly lower in the 6 mg/kg ODD group. It was confirmed that the peak SGC was >6 mg/L in 100% of children (22 patients) in the ODD group and in 87% (20 out of 23 patients) in the MDD group. No children among the ODD group had an undesirable trough concentration of >2 mg/L, while 17% (four patients) of children in the MDD group had a trough SGC of >2 mg/L.\textsuperscript{15}

The study also showed that more children on the ODD regimen had a favourable clinical outcome than those on the conventional MDD regimen. The improved clinical efficacy in terms of clinical outcome agrees with several other studies, both in adults and in children.

Recent research suggests that higher doses administered less frequently (ODD) may improve efficacy and reduce toxicity associated with gentamicin therapy.\textsuperscript{21,22} Because gentamicin exhibits concentration-dependent killing activity, a higher peak serum concentration to MIC ratio improves bacterial killing.\textsuperscript{9} Likewise, a longer dosing interval and lower trough concentration may prevent adaptive microbial resistance while also reducing toxicity.\textsuperscript{21,23} Our ODD group had significantly higher peaks and lower troughs than the MDD group (Table 2). These pharmacodynamic principles of gentamicin coupled with the children’s pharmacokinetic profile make the ODD regimen very appealing in paediatric patients.

No nephrotoxicity was observed in any of the patients in either of the study groups. Nephrotoxicity usually occurs after 10–14 days of therapy.\textsuperscript{24} The duration of antibiotic therapy, in most of the patients in either group was <10 days and therefore safe.

We found no difference in ototoxicity between the two study groups. The incidence of ototoxicity found in the two groups (1.06% in the ODD group and 0.9% in the MDD group) matched the prevalence of 1–2% reported by other workers.\textsuperscript{25} However, the disappearance rate of aminoglycosides from the inner ear compartments (perilymph and endolymph) is very slow,\textsuperscript{26} and it is possible that the ensuing very long exposure time of the sensory hair cells to the aminoglycosides makes the dosage regimen a less important factor in ototoxicity than in nephrotoxicity.

Being an unfunded study in a relatively resource-constrained setting, our study was open labelled and had limited assessment of the pharmacokinetics; in addition, BERA evaluation for ototoxicity was restricted to a subset of patients. This could have led to certain unintended bias in patient allocation and assessment. However, we believe that the pharmacokinetic advantage of ODD is well underlined by the numbers evaluated for gentamicin concentrations in our study. A detailed pharmacokinetic evaluation with more frequent measurements would have been desirable but was not feasible.

Conclusions

ODD of gentamicin, at a dose of 6 mg/kg, in children results in appropriate peak concentrations and lower troughs that are consistently in the desired range. The clinical efficacy and safety achieved in our patients supports the use of ODD of gentamicin in hospitalized Indian children. This will result in a lower workload and cost, especially desirable in resource-poor settings.

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Transparency declarations

None to declare.

Author contributions

S. T.: collection and analysis of data, preparation of initial drafts, and reviewing the manuscript. H. S. R.: collection and analysis of data, and reviewing the manuscript. J. C.: analysis of data, and reviewing the manuscript. V. S.: conceptualization of the study, study design, analytical framework, writing the manuscript, and review of the manuscript.

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