Evaluation of target concentration intervention strategy of gentamicin therapy in a malnourished patient population of south India

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Background & objectives: Aminoglycoside antibiotics, especially gentamicin, are widely used in suspected Gram-negative infections in India. Therapeutic drug monitoring is not commonly used for this drug in our population. We evaluated the target concentration intervention (TCI) strategy of gentamicin therapy in a predominantly malnourished patient population with lower respiratory tract infection in south India.

Methods: Patients who were prescribed gentamicin for suspected lower respiratory tract infection were randomized to any of the three groups, viz., control (CG), once daily dosing (ODD), and pharmacokinetic dosing (TCI) groups. Diagnosis was initially done by clinical evaluation and confirmed radiologically. Patients in CG received 80 mg gentamicin twice daily, ODD group received 160 mg once daily, and TCI groups received 160 mg once daily initially followed by dose revision based on serum drug levels. Blood samples were collected at peak and trough levels and assayed for gentamicin concentration. Dose adjustment was done in TCI group whereas the other groups received standard doses. Efficacy and safety were evaluated as outcome measures.

Results: Of the 52 patients included initially in the study, 43 (CG 20, ODD 12, TCI 11) completed the study. The doses administered to the study subjects were less than those prescribed in standard textbooks and guidelines. Patients in TCI group had their gentamicin doses revised upwardly to a dose of 4.3 ± 0.6 mg/kg to achieve a peak gentamicin concentration of 12 to 15 µg/ml. Both ODD and TCI groups showed significant improvements in outcomes studied over the control group.

Interpretation & conclusion: The results of our study indicated that once daily dosing of gentamycin was superior to multiple daily dosing in treating the lower respiratory tract infection in the study population. All patients in the ODD and TCI groups achieved satisfactory serum drug concentrations at administered doses (160 mg/day for ODD and ≤ 200 mg/day for TCI group). In our study, target concentration intervention did not significantly improve the therapy outcomes. Since the study sample is small further research may be needed.

Key words Aminoglycosides - gentamicin - multiple daily dosing - once daily dosing - pharmacokinetic dosing
Rational therapy is based on observations that have been evaluated critically. Traditional approach in drug therapy has been to adjust the dose of the drug in the individual within the accepted therapeutic range. The common approach is an individualized approach in which the clinician evaluates the magnitude of each patient's individual need for the drug in question, and selects an estimated risk of toxicity which is felt on clinical grounds to be justified by the patient's need. However, in India, even the traditional approach of therapeutic drug monitoring (TDM) is not popular.

Aminoglycosides have been widely used in the treatment of infections by aerobic Gram-negative bacilli, including serious infections. They have great effectiveness, low likelihood of inducing resistance, and are less expensive. Though newer antibiotics have been developed and marketed, aminoglycosides are still prescribed frequently all over the world, and especially in India where resistance to antibiotics is common. Aminoglycoside antibiotics are known to carry the risk of renal and otovestibular toxicity, which limits their use in daily practice.

Peak concentrations 4-8 times the minimum inhibitory concentration (MIC) are necessary for adequate therapy. The long post-antibiotic effect (PAE) of aminoglycosides supports the use of longer dosage intervals. Duration of PAE is also shown to be positively correlated with the aminoglycoside concentration.

In many Indian hospitals, multiple daily dosing of gentamicin has been practiced. This is despite the availability of clear evidence showing the superiority of once daily dosing over multiple daily dosing. Also, the doses used seem to be less than the doses recommended by the standard textbooks and guidelines. We therefore undertook this study to evaluate the three different strategies in gentamicin dosing, viz., conventional multidose regimen, once daily dosing, and target concentration intervention (TCI) in lower respiratory tract infections (LRI) in a predominantly malnourished patient population in a hospital in south India.

Material & Methods

The study was conducted in Government Head Quarters Hospital, Udhagamandalam, Tamil Nadu, India for a period of eight months (June to January) in 2003-2004. Study protocol was approved by the Institutional Ethical Committee. Adult and geriatric patients who were admitted to medical wards with suspected lower respiratory tract infections, and have not taken antibiotics prior to the admission, were consecutively included into the study. Informed consent was obtained from the patients. Patients were excluded if (i) the pathogen isolated was not sensitive to gentamicin; (ii) the infection was severe enough to prevent patient from participating in audiogram assessment; (iii) the patients had mixed infections (systemic/organ) requiring multiple antibiotic therapy; (iv) the patients had rapidly deteriorating renal function or the baseline glomerular filtration rate (GFR) was < 70 ml/min; (v) patients who, in physician’s opinion, needed combination therapy with a beta-lactam antibiotic (ampicillin/amoxycillin) whereby its administration could not be delayed until the trough level blood collection was done; (vi) pregnant; (vii) the patient had a known history of allergy or hypersensitivity to aminoglycosides; and (viii) neutropenic.

Diagnosis was made on the basis of X-ray findings and clinical features. Patients were classified as malnourished if the body mass index (BMI) was ≤18.5 kg/m². Serum creatinine was estimated by kinetic method using an autoanalyser TransAsia ERBA CHEM 5+ (Asian Labs, Chennai). Glomerular filtration rate (GFR) was calculated based on Cockcroft and Gault equation. Identification of the pathogens from sputum culture and their sensitivity to gentamicin were done by standard methods. Patients were assigned to control, once daily dosing and target concentration intervention groups in the ratio of 2:1:1 by block randomization technique. Control group (CG) patients received standard twice daily dosing of gentamicin (80 mg) according to the general practice of the hospital. Once daily dosing (ODD) group patients received once daily dosing of gentamicin, the dose of which was 160 mg or as fixed by the physician. Target concentration intervention (TCI) group patients received once daily dosing of...
gentamicin, the dose of which was 160 mg or as fixed by the physician initially, followed by adjustment of dose based on the TDM report, microbiological report and other factors, such as weight, age and renal functions of patient. Severity of the disease was not included as a factor since patients having LRI of moderate severity only were included in the study. Target serum concentration was fixed in consultation with the clinician based on the MIC\textsuperscript{14} of the pathogen identified and the patient’s need. In the TCI group, the target peak levels were 12 to 15 µg/ml and target trough levels were <2 µg/ml. Dose adjustment was performed immediately based on the serum drug concentration data generated for each patient.

Administered gentamicin doses in the study population were compared with standard text-books and guidelines\textsuperscript{9,10}. According to the guidelines\textsuperscript{10}, the starting doses of gentamicin for patients with normal renal function are as follows: Age 10-29 yr: 6 mg/kg/day; 30-60 yr: 5 mg/kg/day; >60 yr: 4 mg/kg/day.

**Blood collection and assay:** Gentamicin was diluted with 100 ml of normal saline in the intravenous fluid (iv) bottle and administered by infusion over a period of 30 min; 30 ml of normal saline was used to flush the drug solution from the iv drip set so as to avoid retention of gentamicin in the drip set. The entire infusion was programmed for 30 min delivery.

Two samples were collected from each patient. From the control group, peak concentration sample was collected 30 min after the iv administration of gentamicin and trough sample was collected 12 h post-dose (just before the next administration). From the ODD and TCI groups, peak concentration sample was collected 30 min after the 30 min intravenous infusion of gentamicin and trough sample was collected 20 h post-dose (just before the next administration). Patient details were collected including, age, height, body weight, and baseline serum creatinine. Ideal body weight and body mass index were calculated.

Serum gentamicin concentrations were determined using a multiple drug resistant *Staphylococcus epidermidis* (ATCC 12228) obtained from National Chemical Laboratories, Pune, India following the method described in Indian Pharmacopoeia (1996) (Indian Pharmacopoeia 1996; New Delhi: The Controller of Publications, Government of India, Ministry of Health and Family Welfare; 1996; vol. II, p. A100-7) with slight modification where a disk diffusion technique, instead of cylinder plate or cup plate method was used\textsuperscript{15}. The organism was sensitive to gentamicin (MIC 0.06 µg/ml against a standard inoculum consisting of 10\textsuperscript{5} cfu/ml). All samples obtained from the TCI group were immediately assayed whereas the samples obtained from the other groups were stored at -20°C until use, in order to accumulate sufficient number of samples for assay.

**Outcomes assessment:** Clinical efficacy was defined as cure, improvement or failure. Nephrotoxicity was defined as an increase in serum creatinine concentration of at least 25 per cent during the study period\textsuperscript{16,17}. Audiogram was administered using Arphi Clinical Diagnostic Audiometer Model 700 Mark – IV (Arphi Electronics (P) Ltd., Mumbai, India). Clinical auditory toxicity included any report of tinnitus, reduced hearing or deafness whereas auditory toxicity required an increase of more than 15 dB in two or more frequencies in the 0.5 to 8 MHz range measured by audiometry. Other drug related adverse effects were evaluated based on the causality assessment using Naranjo scale by a panel of three doctors including the treating physician\textsuperscript{18}.

**Statistical analysis:** Statistical analysis of data was done using GraphPad Instat\textsuperscript{®} (GraphPad Software Inc., CA, USA). Statistical comparisons were made with one way ANOVA followed by post hoc comparison using Student-Newman Keuls test (q value).

**Results**

A total of 52 patients were enrolled in the study (25 patients in CG, 15 in ODD and 12 in TCI). Three patients in the control group and two in the ODD group were dropped from the study as the isolates were not susceptible to gentamicin. Two patients in the control group and one patient each in ODD and TCI groups did not complete the discharge audiogram and hence were designated as ‘incomplete follow up’
and were not included in the analysis. Twenty patients in the control group, 12 in the ODD group and 11 in the TCI group completed the study. Age of the patients ranged from 23-65 yr in the control group, 18-65 yr in the ODD group and 18-70 yr in TCI group. One patient in the TCI group had actual body weight equal to the ideal body weight (IBW). All the other patients had their actual weight less than IBW. Eight patients in CG, three in ODD group and two in the TCI group marginally exceeded the cut-off limit of BMI for malnourished patients. The body mass index ranged from 14.5 to 20 with a mean of 18.1 ± 1.7 kg/m² in CG, 16 to 20 (17.38 ± 1.4 kg/m²) in ODD and 16 to 21 (18.1 ± 1.4 kg/m²) in the TCI group (Table I).

Klebsiella pneumonia was found to be the major infecting pathogen, affecting 67.4 per cent of the cases (Table II). Patients in the control group received a fixed dose of 80 mg twice daily, which ranged from 1.08 to 2.22 mg/kg with a mean of 1.67 ± 0.28 mg/kg; the peak serum concentration of gentamicin ranged from 3 to 6.72 µg/ml with a mean of 5.1 ± 1.1 µg/ml. The trough serum concentration of gentamicin in these patients ranged from 0.04 to 1.24 µg/ml with a mean of 0.6 ± 0.3 µg/ml (Table III).

Patients in the ODD group received a dose ranging from 3 to 4.7 mg/kg with a mean of 3.76 ± 0.53 mg/kg. The peak serum concentration of gentamicin in these patients ranged from 6.12 to 12.4 µg/ml with a mean of 9.4 ± 2.7 µg/ml. The trough serum concentration of gentamicin in these patients ranged from 0.48 to 0.82 µg/ml with a mean of 0.9 ± 0.4 µg/ml. Patients in the TCI group received a dose ranging from 2.8 to 4 mg/kg with a mean of 3.37 ± 0.4 mg/kg. The peak serum concentration of gentamicin in these patients ranged from 7.2 to 10 µg/ml with a mean of 8.5 ± 0.8 µg/ml. The trough serum concentration of gentamicin ranged from 0.1 to 1.6 µg/ml with a mean of 1 ± 0.4 µg/ml. Based on the recommended target peak serum concentration of 12 to 15 µg/ml, dose was altered in

### Table I. Demographic details of patients in the three study groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>Age (yr)</th>
<th>Sex (male : female)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>IBW (kg)</th>
<th>BMI (µg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n = 20)</td>
<td>44.4 ± 12.6</td>
<td>17:3</td>
<td>160.35 ± 5.1</td>
<td>47.9 ± 6.7</td>
<td>57 ± 5.2</td>
<td>18.1 ± 1.7</td>
</tr>
<tr>
<td>Once daily dosing group (n=12)</td>
<td>40.17 ± 20.63</td>
<td>10:2</td>
<td>158 ± 5.5</td>
<td>43.5 ± 6.1</td>
<td>55.5 ± 5.4</td>
<td>17.38 ± 1.4</td>
</tr>
<tr>
<td>Target concentration intervention group (n=11)</td>
<td>37.64 ± 16.4</td>
<td>8:3</td>
<td>161.1 ± 14.1</td>
<td>47.8 ± 8.3</td>
<td>58.97 ± 11.5</td>
<td>18.1 ± 1.4</td>
</tr>
</tbody>
</table>

BMI, Body mass index; IBW, ideal body weight

### Table II. Pathogens isolated from the patients in the three study groups

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of isolates</th>
<th>MIC&lt;sup&gt;1&lt;/sup&gt; (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella pneumoniae</td>
<td>14</td>
<td>0.06 - 1.0</td>
</tr>
<tr>
<td>Pseudomonas aureginosa</td>
<td>3</td>
<td>1.0 - 8.0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1</td>
<td>1.0 - 4.0</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>2</td>
<td>Moderate sensitivity</td>
</tr>
</tbody>
</table>

MIC, Minimum inhibitory concentration
patients, who received doses ranging from 3.5 to 5.3 mg/kg with a mean of 4.3 ± 0.6 mg/kg (Table III).

Patients in the control, ODD and TCI groups had a hospital stay ranging from 6 to 13 days with a mean of 9.9 ± 1.5 days, 5 to 7 days with a mean of 5.92 ± 0.8 days and 5 to 7 days with a mean of 5.5 ± 0.7 days, respectively. The mean difference between the days of therapy for CG and ODD groups, and for CG and TCI groups was statistically significant (\( P<0.001 \)).

Three patients in the control group, one each in ODD and TCI groups had nephrotoxicity. One patient in the control group had ototoxicity. None of the patients in the other groups had ototoxicity. Two patients in the control group did not show clinical improvement and hence were prescribed other antibiotics.

**Discussion**

Trials evaluating the efficacy of once daily dosing regimens with conventional dosing regimens have shown varying results\(^9\). The lack of ability of these trials to show a clear difference has largely been attributed to the use of another, usually a beta-lactam antibiotic. In our study also, 8 (40%) patients in the control group, 6 (50%) in the ODD group and 5 (45.5%) in the TCI group were prescribed a beta-lactam antibiotic. However, we isolated the pathogen and tested its sensitivity to gentamicin. Only those patients in whom the infecting organism was sensitive to gentamicin were included in the study. Also, both the peak and trough samples were taken before the beta-lactam antibiotic was administered in order to prevent its influence in assay results. Our study revealed that once daily gentamicin dosing regimens in lower respiratory tract infections with suspected Gram-negative pathogens was more efficient than conventional twice daily dosing practiced at the hospital both in terms of increase in efficacy (as observed in the duration of therapy required) and reduction in toxicity. The efficacy of the once daily regimen could have resulted from the higher peak serum drug concentrations it produced, which led to enhanced tissue penetration and a longer post-antibiotic effect. This has been proved in earlier
In clinical trials, peak plasma concentrations of \(>5\ \mu g/ml\) of gentamicin attained early in therapy in patients with Gram-negative bacteraemia were associated with decreased mortality compared with patients with lower peaks\(^\text{22}\). In addition, patients with gentamicin concentrations of \(7\ \mu g/ml\) or more were more likely to have positive outcome in Gram-negative pneumonia than patients with lower concentrations\(^\text{22}\). In our study, all patients in the ODD and TCI groups achieved gentamicin concentrations of \(>5\ \mu g/ml\) and most of these patients (87\%) attained a serum concentration of \(>7\ \mu g/ml\). In the control group also, 55 per cent of patients attained serum gentamicin concentrations of \(>5\ \mu g/ml\). This is despite the fact that in all these patients the dose of aminoglycoside was below the standard doses of 5 to 7 mg/kg used in clinical trials\(^6\). Only TCI group received higher doses than the other groups. All patients in the TCI group had their doses revised upwardly, however, even these patients had a mean dose of \(4.3 \pm 0.6\ \text{mg/kg}\) only. This finding supported the practice of our clinicians in using lower doses of gentamicin for our patients.

Nephrotoxicity was reported to range from 3.8 to 21 per cent in various studies\(^6,\text{16},\text{23},\text{24}\). The probability of an incidence of nephrotoxicity seemed to increase with the duration of therapy. In our study, no patient in the ODD and TCI groups and 15 per cent of patients in the control group had nephrotoxicity. High rates of ototoxicity (10\%) has also been reported\(^25\) whereas in our study, one patient in the control group only had ototoxicity. This may be due to the short duration of treatment with gentamicin in our study population.

We did not find significant differences in patient outcomes in the ODD and TCI groups. The limitations of our study were that serum drug concentrations of gentamicin could not be measured after the dose adjustment because the patients also received a beta-lactam antibiotic after the initial peak and trough levels were drawn, and in the TCI group, intervention for dose adjustment could not be done immediately since microbiological assay was used. Pharmacokinetic monitoring may improve the safety and efficacy of once daily dosing of gentamicin, but in our study we could not show it with the small number of patients studied by us. Further studies need to be carried out to examine the efficacy and toxicity of once daily dosing of gentamicin with target concentration intervention monitoring in a large sample of population before a conclusion is drawn.

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References


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