Antibiotic blood concentrations in patients successfully treated with tobramycin

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Summary
Thirty-nine patients with severe Gram-negative infections were treated with parenteral tobramycin. Thirty-one (79%) were cured of their infection. Tobramycin was most effective in the therapy of patients with urinary tract infections, arthritis and skin and soft tissue infections and relatively less effective in patients with sepsicaemia, pneumonia, and osteomyelitis. The infection was cured more frequently in patients who achieved a high ratio between the peak serum concentration of tobramycin and the minimal inhibitory concentration of tobramycin against the pathogenic organism (so-called therapeutic ratio). The ratio was ≥4.0 in 11 of 13 (85%) assays performed in 12 cured patients, whereas this ratio was achieved in only 3 of 10 (30%) instances in 5 patients in whom the therapy failed (P < 0.05). The latter group also included a greater proportion of patients with an ultimately fatal illness, such as lung cancer and uraemia, compared to the former successfully treated group. Adverse effects of tobramycin on renal function were transitory. No significant effect of tobramycin on the hearing was observed.

Introduction
Tobramycin has been found to be an effective drug in the treatment of Gram-negative infections, even when these are resistant to gentamicin (Moellering, Wennersten and Kunz, 1974). It has greater in vitro activity than gentamicin against Pseudomonas aeruginosa (Britt et al., 1972; Burger, Sanford and Zweighaft, 1973; Hyams, Sinerkoff and Rahal, 1973; Yourassowsky, Schunent and Vanderlinden, 1973) and possibly in vivo (Burch et al., 1973). The pharmacology of tobramycin (Becholt and Black 1975; Christopher et al., 1974; Jaffe, Meyers and Hirschman, 1974a; Regamey, Gordon and Kirby, 1973), the in vitro susceptibilities of Gram-negative organisms (Geddes et al., 1974; Waterworth, 1972) and its clinical effectiveness (Blair et al., 1975; Carmalt, Cortez and Rosenblatt 1976; Jaffe et al., 1974b; Klastersky, et al., 1974; Schoutens, Vanderlinden and Yourassowsky, 1973) are well documented. The authors have evaluated the results of tobramycin therapy with respect to each patient’s underlying illness, type of infection, and a ratio of peak serum concentration and the minimal inhibitory concentration (MIC) of tobramycin against the patient’s own pathogen (so-called therapeutic ratio).

Patients and methods
The study included patients with severe aerobic Gram-negative infections with or without an anaerobic component treated in 1975 and 1976 at the Martin Luther King Jr General Hospital. Thirty-nine patients were treated with tobramycin. Of these, 2.6% had a rapidly fatal illness, 33.3% had an ultimately fatal illness, and 64% had a non-fatal illness as defined by McCabe and Jackson (1962). The mean age was 47.9 years. Twenty-four patients were male and 15 were female. The relationship of antibiotic levels, MICs of bacterial pathogens and the results of therapy were analysed in only 17 of these patients since the remainder lacked the pharmacological data. Nephrotoxicity and auditory toxicity were evaluated in 23 of these patients.

In patients with normal renal function, the initial recommended dosage of tobramycin or gentamicin was 1.66 mg/kg administered either i.v. (over a 15–30 min interval) or i.m. every 8 hr. In patients with reduced renal function, the calculation of the dose was based on the creatinine level (Becholt and Black, 1975) and the dose was adjusted according to measured serum concentrations of tobramycin. Some patients also received either carbenicillin for synergistic effect against Pseudomonas; clindamycin, chloramphenicol, or ticarcillin for anaerobic infections; or a cephalosporin for Klebsiella. The patient was considered cured when clinical signs and laboratory findings indicative of infection (fever, swelling, drainage, leucocytosis, abnormal chest X-ray, abnormal urinalysis and urine culture and abnormal cerebrospinal fluid) returned to normal during the therapy or shortly thereafter. Bacteriological cure or failure was determined on the basis of eradication or persistence of a pathogenic micro-organism respectively at the site of infection at the completion of surgery.

Tobramycin serum concentrations were assayed by...
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an agar-well diffusion assay based upon that for gentamicin (Riff and Jackson, 1971; Winters, Litwack and Hewitt, 1971) using a strain of Klebsiella (derived from K. pneumoniae ATCC 277799) resistant to commonly used antibiotics except tobramycin and gentamicin. The susceptibilities to tobramycin, gentamicin and amikacin of 242 clinical isolates (including the pathogenic bacteria isolated from the patients in the study) of Gram-negative bacteria were assayed by the International Collaborative Study agar-dilution technique (Washington and Barry, 1974). Escherichia coli, Klebsiella, Enterobacter, and Serratia strains were in general more susceptible to gentamicin, whereas Pseudomonas strains were more sensitive to tobramycin. On the weight basis, amikacin was less active than either tobramycin or gentamicin.

Results

Treatment with tobramycin resulted in the cure of 31 of 39 (79%) patients (Table 1). Patients with septicaemia, pneumonia, or osteomyelitis, had a less favourable outcome than the rest. Patients with pseudomonal infection were, on the average, younger than the rest, since this group included a large portion of young heroin addicts.

Seventeen patients were evaluated prospectively regarding serum concentrations of the drug and MICs of their pathogens (Table 2). All of these patients had Gram-negative pathogen(s), Pseudomonas being the most common and, in addition, some had anaerobic pathogens or Enterococcus. The dosage on body weight basis differed among the patients since some patients with severe infections were treated using a low dose of approximately 3 mg/kg/day despite the recommendation to use a high dose of tobramycin.

The patients who received tobramycin (by i.v. or i.m. routines) at a dose of 4.3 - 5.0 mg/kg/day achieved peak serum concentrations of 4.6 - 7.6 μg/ml (mean 6.0 μg/ml) and those who received 2.9 - 3.5 mg/kg/day had peak concentrations of 2.2 - 2.5 μg/ml (mean 2.4 μg/ml). Twelve patients were cured, and in 5 patients the treatment failed or was only partially effective. Only 2 of the 12 cured patients had a low therapeutic ratio (less than 4:0), whereas 4 of the 5 patients who failed the therapy had such a low ratio. Bacteria isolated from patients not responding to therapy were more resistant to tobramycin than those from patients responding to treatment. Thus, Pseudomonas strains isolated from the former patients had an average MIC of 3.3 μg/ml. Carbenicillin was used concurrently with tobramycin in one of 4 patients with Pseudomonas infection who failed to respond and in 3 of 8 patients who responded to the therapy. One patient in the group of patients responding to therapy and 2 in the group failing the therapy had an ultimately fatal illness; the majority had a non-fatal underlying disorder such as heroin addiction, diabetes, sickle-cell disease and trauma. The mean age of patients responding to the treatment included one case of lung infection, 4 cases of arthritis and one case of infection from the gastrointestinal tract. The other group comprised 2 cases of lung infection and one case of arthritis. Each group included a comparable proportion of sepsis (25% and 20%) and of urinary tract infection (17% and 20%).

Effect of tobramycin on renal and auditory functions

Renal function was evaluated by serial determinations of serum creatinine in 23 patients on tobramycin and in 18 patients on gentamicin therapy. In the

<table>
<thead>
<tr>
<th>Type of infection or underlying illness</th>
<th>No. (%)</th>
<th>Mean age</th>
<th>Clinical and bacteriological cures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septicaemia</td>
<td>5 (13)</td>
<td>47.5</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (15)</td>
<td>42.2</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Lung infection</td>
<td>15 (38)</td>
<td>48.8</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>5 (13)</td>
<td>63.2</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3 (8)</td>
<td>34.6</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>5 (13)</td>
<td>44.6</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Pseudomonas sp.</td>
<td>23 (59)</td>
<td>42.5</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>4 (10)</td>
<td>51.2</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Klebsiella-Enterobacter</td>
<td>8 (20)</td>
<td>57.6</td>
<td>7 (87)</td>
</tr>
<tr>
<td>Proteus sp.</td>
<td>3 (8)</td>
<td>63.7</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Serratia</td>
<td>1 (3)</td>
<td>58.0</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Rapidly fatal</td>
<td>1 (3)</td>
<td>86.0</td>
<td>0</td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>13 (33)</td>
<td>56.7</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Non-fatal</td>
<td>25 (64)</td>
<td>46.3</td>
<td>21 (84)</td>
</tr>
<tr>
<td>All patients</td>
<td>39 (100)</td>
<td>47.8</td>
<td>31 (79)</td>
</tr>
</tbody>
</table>
tobramycin group, serum creatinine rose in 7 (30%) patients by an average of 2-5 mg/dl, but it returned to normal in at least 2 patients, following the therapy. In the gentamicin group, creatinine rose in 6 (48%) patients, all with pre-existent renal damage, by an average of 1-0 mg/dl. Cochlear function was followed by serial audiograms at frequencies of 125 to 8000 Hz in 8 patients who had a prolonged course of tobramycin therapy (range 13 – 47 days, average 25-1 days). Changes were minimal and were observed predominantly in the high-frequency range (6000 Hz). Five patients had a loss of 10 – 20 dB and three patients had a gain of 10 – 20 dB during the therapy.

Discussion
In this study, tobramycin was remarkably effective in the therapy of Gram-negative infections of all types but relatively less so in infections of the lung, bone and in septicemia. Particularly pleasing was the favourable response to the combined tobramycin and carbenicillin regimen of infections due to Pseudomonas sp. The relatively less effective response to tobramycin in Gram-negative pneumonia may be related to the low concentration of tobramycin in the lung. In one patient dying with pseudomonal pneumonia, the post-mortem revealed consolidation and microabscesses in the whole lung. Since aminoglycosides administered systemically penetrate poorly into normal pulmonary secretions (Klastersky et al., 1974) in a consolidated lung, the concentration would be expected to be low. Recently, a patient with pseudomonal pneumonia, initially not responding to systemic therapy, was cured with simultaneous endotracheal nebulization of the drug and administration of up to 8 mg of tobramycin/kg/day which achieved a peak serum concentration of 12 μg/ml.

Most patients who failed the therapy had a low therapeutic ratio, usually as a result of a high MIC of the pathogenic organism rather than because of low peak serum concentration. The peak antibiotic serum concentration is a useful index, since it approximates the peak tissue concentration (Barza et al., 1974). Pharmacological reasons for the failure of gentamicin therapy were similarly advanced (Jackson and Riff, 1971). The group of patients failing the tobramycin therapy also included a greater proportion of lung infections and of lung cancer and uraemia as underlying illness compared to the successful group. Further experience is needed to determine whether raising the serum concentration of the drug might defeat (a) pathogens with a greater resistance; (b) infections in patients with severe underlying illnesses; (c) Gram-negative lung infections.

Although serum creatinine rose in 7 (30%) of 23 patients treated with tobramycin and in 6 (46%) of 13 treated with gentamicin, the rises appeared to be transitory on follow-up. No significant adverse effect on hearing was observed.

In vitro, tobramycin has been shown to be the most active aminoglycoside against P. aeruginosa. (Britt et al., 1972; Burger et al., 1973; Hyams et al., 1973; Waterworth, 1972). The present results confirm a greater susceptibility of Pseudomonas to
tobramycin and a greater susceptibility to gentamicin of *Esch. coli*, *Klebsiella*, *Enterobacter* and *Serratia* strains. Recently, amikacin has been proposed as an aminoglycoside of choice in the initial treatment of a compromised host with severe, presumable Gram-negative sepsis (Hewitt and Young, 1977). Amikacin has been shown to be effective in infections with gentamicin- and tobramycin-resistant organisms, including infections unsuccessfully managed with gentamicin (Bartlett, 1977). Although amikacin has the broadest antibacterial spectrum of all aminoglycosides, it is less active against *P. aeruginosa* than tobramycin (Moellering et al., 1974). Since the importance of bacterial species varies in different hospitals and frequently *P. aeruginosa* assumes a major role, in the authors’ opinion, the selection of an aminoglycoside antibiotic should be based on the knowledge of the locally important pathogens and their susceptibilities.

Additionally, in this trial, it was found that tobramycin causes nephrotoxicity less frequently than does gentamicin, very much like the result of Smith et al. (1980), following their double-blind comparison of nephrotoxicity of gentamicin and tobramycin.

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References


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