Endotracheal Gentamicin in Bronchial Infections in Patients with Tracheostomy*

Jean Klastersky, M.D.; Christiane Geuning, M.D.;** Emile Mouawad, M.D.;** and Didier Daneau

Tracheotomized patients, with severe underlying illnesses and serious tracheobronchial infections due to gram-negative bacilli were treated at random with intramuscularly or endotracheally administered gentamicin (240 mg daily). Clinical improvement occurred in all seven patients treated by the endotracheal route and in two out of eight who received gentamicin intramuscularly. No gentamicin (less than 0.5 μg/ml) was detected in the respiratory secretions after intramuscular administration, while endotracheal injection resulted in measurable levels in all seven patients; five of them had more than 20 μg/ml of gentamicin in the respiratory secretions.

The incidence of infections of the respiratory tract caused by gram-negative bacilli is increasing. Although some are primary, most of these infections arise within the hospital as complications of various medical or surgical procedures. In particular, the respiratory tract of patients with tracheostomy often becomes infected with these organisms; in some cases this appears to have no pathologic effect, but in many other patients such an infection represents a major hazard of tracheostomy.

Gentamicin, an aminoglycoside antibiotic which is structurally related to kanamycin and neomycin and which presents an unusually broad bactericidal gram-negative spectrum including a majority of strains of the family Enterobacteriaceae and of the genus Pseudomonas, has been recommended and used in the treatment of severe respiratory infections caused by gram-negative rods. Since many patients with tracheostomy have infection confined to the trachea and to the bronchi, endotracheal administration of antibiotics in these cases might prove itself a valuable approach to the treatment of severe respiratory infections. This mode of therapy has already been employed in patients presenting chronic bronchitis.

Therefore, the following study compares the effectiveness of intratracheally and intramuscularly administered gentamicin in severely ill, tracheotomized patients, who present a serious tracheobronchial infection caused by gram-negative rods. It will be shown that the intratracheal route of administration is more effective than the intramuscular one.

**M**aterials and Methods

**Patients**

All the 15 tracheotomized patients studied here presented a serious underlying illness: they had either a disseminated malignant disease or had undergone intracranial surgery. Therefore these patients represented a fairly homogenous group with respect to the underlying disease, of which the importance for the outcome of serious gram-negative infections has been stressed. They were treated at the Institut Jules Bordet on the medical or on the neurosurgical wards during a period of three months (July-September 1970). In all of them respiratory tract infection was present as indicated by fever, purulent sputum and an elevated white cell count; in some of them auscultatory and radiologic evidence of pulmonary infection was also present. In these patients the sputum contained prior to therapy with gentamicin numerous leukocytes and gram-negative rods on gram-stained smears of the tracheal aspirate and gram-negative rods were cultured as the sole or predominant pathogen from at least two consecutive such specimens prior to therapy.

Gentamicin either by endotracheal or intramuscular route as indicated by prior randomization was administered to these patients. Intramuscular injections were given three times daily as 80 mg of gentamicin in a volume of 2 ml. Intratracheal instillation was performed with a plastic catheter, introduced deeply into the trachea; 1 ml of solution containing 40 mg of gentamicin was injected six times daily.
Table 1—Susceptibility to Gentamicin of Recently Isolated Pathogens: Cumulative Percentages of Strains Inhibited at Various Concentrations of Gentamicin.

<table>
<thead>
<tr>
<th>Minimum inhibitory concentrations* (µg/ml)</th>
<th>Staphylococcus aureus</th>
<th>Citrobacter species</th>
<th>Pseudomonas aeruginosa</th>
<th>Proteus mirabilis (indole +)</th>
<th>Proteus mirabilis</th>
<th>Escherichia coli</th>
<th>Klebsiella</th>
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<tbody>
<tr>
<td>&gt;50</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<td>100</td>
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<td>99</td>
</tr>
<tr>
<td>12.5</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>98</td>
<td>100</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>6.2</td>
<td>100</td>
<td>90</td>
<td>97</td>
<td>98</td>
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<td>3.1</td>
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<td>98</td>
<td>100</td>
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<td>100</td>
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<td>95</td>
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<td>94</td>
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<td>93</td>
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<tr>
<td>0.3</td>
<td>78</td>
<td>55</td>
<td>52</td>
<td>84</td>
<td>86</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>&lt;0.3</td>
<td>78</td>
<td>56</td>
<td>52</td>
<td>84</td>
<td>86</td>
<td>86</td>
<td>83</td>
</tr>
</tbody>
</table>

*Inoculum-replicating method on Muller-Hinton (Difco); inoculum: 0.001-0.003 ml of a suspension containing 10^4-10^5 microorganisms per milliliter.

The effect of the treatment on the respiratory flora was assessed by biweekly cultures of the tracheal aspirates. Serum and blood samples were obtained biweekly for the determination of the white cell count and urea and creatinine levels. Urine was cultured biweekly and a chest x-ray film was obtained in all patients before and after therapy. Besides the respiratory-tract infection the patients were managed routinely; frequent aspirations of bronchial secretions were performed in all of them, and none received other antibiotics with gentamicin.

Bacteriology

The identification of all microorganisms isolated in this study was performed by standard routine methods. Minimum inhibitory concentrations of gentamicin were determined by the inoculum-replicating method using an inoculum which contained 10^4-10^5 viable microorganisms per ml. Muller-Hinton medium (Difco) was utilized throughout.

Samples of bronchial secretions, serum and urine for the determination of the concentration of gentamicin were collected on the second day of therapy, just one hour after an administration of gentamicin. The sputum samples were prepared for assay by adding a volume of saline equal to one-third the volume of the specimen. The mixture was ultrasonicated for one minute and centrifuged at 1,500 rpm for 10 minutes. The supernatant, samples of serum and urine were kept at -20°C until used. The concentration of gentamicin in serum, sputum and urine was measured by the paper-disc method described by Sabath and associates, using Staphylococcus aureus (ATCC 12228) as the test organism. Levels

Table 2—Bacteriologic and Clinical Outcome in Gentamicin-Treated Patients.

<table>
<thead>
<tr>
<th>No.</th>
<th>Microorganism</th>
<th>Duration of Therapy (days)</th>
<th>Fever*</th>
<th>WCC**</th>
<th>Purulence of Sputum</th>
<th>Culture of Sputum</th>
<th>Death††</th>
<th>X-ray §</th>
<th>Auscultation¶</th>
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<td>Intramuscular</td>
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<tr>
<td>1</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
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<td>8</td>
<td>-</td>
<td>-</td>
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<td>(+)</td>
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<td>-</td>
<td>+</td>
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<tr>
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<td>-</td>
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<tr>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
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<td>6</td>
<td>+</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>10</td>
<td>E coli</td>
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<td>+</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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</tbody>
</table>

*Fever: + = defervescence, - = no defervescence.
**WCC: white cell count: + = decreased to normal values, - = remained increased.
††Purulence of the sputum: + = decreased, - = unchanged, (+) = the patient became severely leukopenic as a result of cytostatic therapy.
†††Death: yes = as a result of the infection, partly at least, no = unrelated to the infection.
§X-ray infiltrate (when present): - = unchanged, + = disappeared.
¶Auscultatory signs and amount of sputum: + = improved, - = unchanged.
of gentamicin comprised between 0.5 \( \mu g/ml \) and 20 \( \mu g/ml \) could be adequately determined using this technique. All the determinations of the concentration of gentamicin were done in triplicate. Serum and sputum samples were held for 30 minutes at 56\(^\circ\)C to destroy nonspecific bacteriostatic activity, before the assay.

**RESULTS**

The rationale for the use of gentamicin in the treatment of severe infections caused by gram-negative bacilli stems from the outstanding antimicrobial activity of this agent against most Enterobacteriaceae. To illustrate this point, the susceptibility to gentamicin of 611 pathogens recently isolated in this hospital, has been determined. The results are shown in Table 1. It can be seen that gentamicin is a highly effective antibiotic in vitro against *Staphylococcus aureus*, Enterobacteriaceae and *Pseudomonas aeruginosa* strains. For all these organisms the median MIC is inferior to 0.3 \( \mu g/ml \), a concentration that is readily attainable in the blood and in various body fluids. Actually, gentamicin appears in our hospital as the most active agent in vitro against staphylococci and Gram-negative rods.

Bacteriologic cure, defined as the disappearance of the offending microorganisms from the bronchial secretions, occurred in two out of eight patients treated with intramuscular gentamicin and in four out of seven treated endotracheally, as shown in Table 2. In these patients, clinical improvement indicated by either defervescence, diminution of the leukocytosis or a decrease of the purulence of the sputum, occurred also but without clinical improvement in one out of seven patients treated with endotracheal gentamicin. All the colonizing organisms were relatively resistant to gentamicin in vitro against *Staphylococcus aureus*, Enterobacteriaceae and *Pseudomonas aeruginosa* strains. For all these organisms the median MIC is inferior to 0.3 \( \mu g/ml \), a concentration that is readily attainable in the blood and in various body fluids. Actually, gentamicin appears in our hospital as the most active agent in vitro against staphylococci and Gram-negative rods.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Cure</th>
<th>Colonization of the Respiratory Tract</th>
<th>Levels of Gentamicin (( \mu g/ml ))</th>
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<td>Intrapleural Gentamicin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Pseudomonas</td>
<td>No</td>
<td>No</td>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td>2 Klebsiella</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>3 Klebsiella</td>
<td>No</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>4 Proteus mirabilis</td>
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<td>No</td>
<td>Pseudomonas</td>
</tr>
<tr>
<td>5 Klebsiella</td>
<td>Yes</td>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td>6 Pseudomonas</td>
<td>Yes</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>7 Klebsiella</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>8 E. coli</td>
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<td>No</td>
<td>Yeasts, Pseudomonas</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Proteus mirabilis</td>
<td>Yes</td>
<td>Yes</td>
<td>1.7</td>
</tr>
<tr>
<td>2 E. coli</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>3 Pseudomonas</td>
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<td>Yes</td>
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<td>Yes</td>
<td>1.9</td>
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biotic endotracheally levels superior to 20 μg/ml were detected in five and concentrations of 8.0 and 7.5 μg/ml respectively were found in the other two patients, as shown in Table 3. Our results are similar to these reported by Pines and co-workers but after intramuscular injection we found lower levels of gentamicin within the respiratory secretions than these authors. After endotracheal instillation the levels found in the tracheal secretions in our study were higher than those reported in their patients. In all patients urine levels of gentamicin exceeded 20 μg/ml. Toxicity that could have been attributed to gentamicin was not found in this study, but special tests of auditory function were not done. In only one patient did the urea and creatinine serum level rise, but this patient developed acute renal failure following vasomotor collapse caused by gastrointestinal hemorrhage and died within 48 hours after this complication.

**DISCUSSION**

It has been decided to limit this comparative study to a small number of patients because our data strongly suggest a superiority of intratracheal administration of gentamicin over the intramuscular route. Two out of eight patients were cured by the intramuscular therapy and all seven patients who received gentamicin endotracheally were cured. The difference between these two groups is statistically significant (p < 0.011; Fischer's test). The more favorable results obtained by endotracheal administration correlated with high levels of gentamicin within the bronchial secretions, that could not be obtained by intramuscular injections.

Treatment of serious pulmonary infection caused by Gram-negative rods is usually disappointing, though the use of gentamicin probably represents an improvement over the therapy of such infections with colistin or polymyxin B. However, it might be possible that in patients whose infection is confined to the trachea or to the bronchi these antibiotics are prevented from reaching the microorganisms within the trachea or within the bronchi by fibrosis, thick layers of pus, relative avascularity and presence of bronchial abscesses.

As already mentioned we were not able to detect gentamicin in the bronchial secretions after intramuscular injection, with a technique sensitive enough to detect 0.5 μg/ml. Since the goal of antimicrobial therapy is to achieve optimal levels of antibiotic at the site of the infection it is suggested that gentamicin, if chosen for therapy, should be administered intratracheally rather than intramuscularly to patients with severe bronchial infections caused by gram-negative rods.

However, there is no complete evidence that patients such as those studied here should necessarily receive antibiotics when bronchial infection is suspected; frequent physiotherapy and careful bronchial toilet may be sufficient in these patients who have frequent infection confined to the trachea and the bronchi. Since endotracheal administration of gentamicin might result in a better bronchial toilet, it would be advisable to compare further endobronchial administration of both gentamicin and saline. This study is now being done in our hospital.

**ACKNOWLEDGMENTS:** The authors thank Prof. J. Brihaye (Dept of Neurosurgery) and Prof. J. Henry (Dept of Radiotherapy) for permission to use data on their patients. The technical assistance of Miss G. Swings and Miss L. Vandenborre is gratefully acknowledged.

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