Comparison of Sisomicin and Gentamicin in Bacteriuric Patients with Underlying Diseases of the Urinary Tract

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Sisomicin and gentamicin (2 mg/kg) were administered in a random fashion to patients with bacteriuria superimposed on abnormalities of the urinary tract. Cure was achieved in a similar number of patients in both groups, but superinfection and reinfection with resistant microorganisms was more frequent in patients receiving gentamicin. Untoward side effects were not frequent in this series, especially if the serious underlying urological disease of most patients is taken into consideration. The susceptibility of the causative pathogens to the antibiotic administered and the severity of the underlying disease were the most important factors in the outcome.

Sisomicin is a new aminoglycoside antibiotic produced by the growth of a species of Micromonospora, Micromonospora inyoenis. This antibiotic is produced substantially as a single component and resembles most closely gentamicin C14, a component of the gentamicin complex. From in vitro data and from preliminary clinical studies (4, 6, 8), no major difference is to be expected between gentamicin and sisomicin; however, cross-resistance between gentamicin and sisomicin does not always exist, and no comparative study has yet been published from the clinical point of view.

The present investigation was undertaken to compare the efficacy and the tolerance of gentamicin and sisomicin when used to eradicate bacteriuria in patients with underlying diseases of the urinary tract. An in vitro comparison of gentamicin and sisomicin performed on a large number of recently isolated microorganisms will be presented as well.

MATERIALS AND METHODS

Bacteriological studies. The bacteria tested were isolated from patients hospitalized at the Institut Jules Bordet, which is the clinical center for cancer therapy of Brussels University. Bacteria studied comparatively with sisomicin and gentamicin were isolated during the first semester of 1974. They included 250 Escherichia coli, 183 Klebsiella, 40 Enterobacter, 85 Proteus mirabilis, 20 indole-negative Proteus, and 140 Pseudomonas aeruginosa. Only one isolate of the same bacterial species per patient has been considered here. These bacteria were identified according to Edwards and Ewing's (3).

Minimum inhibitory concentrations (MIC) of sisomicin and gentamicin were determined by the inocula-replicating method (7) using Mueller-Hinton agar (BBL) and an overnight bacterial suspension in Trypticase soy broth (BBL) diluted to a final concentration of approximately 10^6 viable microorganisms/ml. For the evaluation of cross-resistance between sisomicin and gentamicin only differences greater than a single dilution were taken into consideration. A similar technique was used to determine the MIC of the bacteria isolated from the patients who were included in the clinical trial.

To determine the bactericidal activity of the sera and urines of the patients against the offending pathogen, a standard twofold tube-dilution technique was employed. Trypticase soy broth and a final inoculum containing 10^8 viable bacteria/ml were used throughout.

The level of sisomicin and gentamicin in the samples of serum and urine was determined by the disc plate method of Davis and Stout (12), using a suspension of spores of Bacillus subtilis (Difco) as the test organism. Nutrient agar (Difco) was used throughout, and plates were incubated at 30°C for 18 h. In most patients serum was obtained 1 h after the injection of the antibiotic on day 2 or 3 of therapy. On the same day, a 12-h collection of urine was obtained. The samples of urine and serum were stored at -20°C until used.

Clinical studies. A total of 50 patients with cancer, who were receiving radiation or cytostatic therapy, were included in the present study; however, in four patients who received gentamicin no adequate evaluation could be performed. One patient developed a severe rash that was attributed to gentamicin on day 2 of treatment and therapy with gentamicin was discontinued; another patient was treated with penicillin after 48 h on gentamicin because of superimposed pneumococcal pulmonary infection, and two patients died from causes unrelated to the infection before adequate control cultures could be obtained. All the
patients in this series had a significant bacteriuria as defined by two consecutive cultures containing more than 100,000 colony-forming units of the same microorganism. In most patients, the offending microorganism was resistant to ampicillin, cephalosporins, tetracycline, and cotrimoxazole, presumably due to multiple courses of therapy that had been previously given to many of them for recurrent urinary tract infection. Most of the patients had mild or moderate symptoms of urinary tract infection such as dysuria, frequency, and nocturia; pyuria, fever, and/or costovertebral tenderness could be found in approximately one-half of the patients. These signs and symptoms were found with similar frequency in both treatment groups; however, because of the presence of an underlying pathological condition of the urinary tract in all the patients, it was occasionally difficult to ascribe them to infection only.

The underlying pathological conditions of the urinary tract present in our patients were repeated urinary manipulations (cystoscopy and/or catheterization for therapeutic and diagnostic purposes) for 14 patients scheduled to receive sisomicin and for 10 patients of the other group; the other patients had more serious diseases of the urinary tract, including prostatic and bladder tumors, compression of the bladder by uterine or rectal neoplasms, severe neurogenic bladder disease, and urinary diversion. When possible, all these patients received surgical attention to relieve the obstruction of the urinary tract and achieve better drainage. However, as could be expected, major anatomic alterations resulting from tumors or extensive previous surgery could not always be corrected.

Gentamicin or sisomicin was administered to the eligible patients at random, using a table of random numbers chosen by one nurse so that the investigators did not know the type of antibiotic that was given to the patients until analysis of all the results had been completed. Gentamicin or sisomicin was given intramuscularly at a total daily dose of 2.0 mg/kg administered in two equal doses (1 mg/kg twice a day). No other antimicrobials were given within 5 days of the onset of therapy; during the treatment with gentamicin or sisomicin no other antimicrobial therapy was administered. Cure was considered to have been achieved in the patient in whom negative cultures of the urine were obtained during the treatment and during the follow-up period. Failure was indicated by the persistence of the causative pathogen and superinfection by the presence of a new infecting organism during therapy.

Relapse was defined as the elimination of the pathogen followed by its reappearance in the follow-up cultures; if a new pathogen was isolated during the follow-up period, 12.0 and 13.5 days, respectively, for gentamicin- and sisomicin-treated patients, the patient was considered to have presented a cure with reinfection.

Cultures of urine and examination of the urinary sediment were performed every 3rd or 4th day during therapy and follow-up. A complete hematologic evaluation and determination of blood urea nitrogen, creatinine, alcaline phosphatase, bilirubin, and glutamic-oxaloacetic and glutamic-pyruvic transaminases were performed before, during, and after therapy.

Creatinine clearances were obtained in most patients. Surveillance of the auditory and vestibular function was accomplished by daily questioning of the patient on hearing, vertigo, dizziness, and headache. Romberg's test, Rinne's test, and the watch test were carried out in most patients. Audiograms were obtained in many patients before, during, and after therapy.

**RESULTS**

Bacteriological results are indicated in Tables 1 and 2. It can be seen that the MICs adequate to inhibit 50% (MIC 50%) and 90% (MIC 90%) of the strains tested are lower when the bacteria are tested with sisomicin as compared to the data obtained with gentamicin. This observation was confirmed by the percentage of strains with MIC for sisomicin equal to or greater than the MIC for gentamicin.

**Table 1. MICs adequate to inhibit 50% and 90% of the strains tested by the inocula-replicating technique**

<table>
<thead>
<tr>
<th>Organism (no. of strains)</th>
<th>MIC 50%</th>
<th>MIC 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>Sisomicin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td><strong>E. coli (250)</strong></td>
<td>0.15</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Klebsiella (183)</strong></td>
<td>0.15</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Enterobacter (40)</strong></td>
<td>6.0</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>Proteus (indole negative) (85)</strong></td>
<td>0.15</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Proteus (indole positive) (20)</strong></td>
<td>0.15</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa (140)</strong></td>
<td>0.30</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**Table 2. Percentages of strains for which the MIC for sisomicin was equal to, greater, or less than the MIC for gentamicin**

<table>
<thead>
<tr>
<th>Organism (no. of strains)</th>
<th>MIC for sisomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli (250)</strong></td>
<td>77.8</td>
</tr>
<tr>
<td><strong>Klebsiella (185)</strong></td>
<td>69.7</td>
</tr>
<tr>
<td><strong>Enterobacter (40)</strong></td>
<td>66.0</td>
</tr>
<tr>
<td><strong>Proteus (indole negative) (85)</strong></td>
<td>67.0</td>
</tr>
<tr>
<td><strong>Proteus (indole positive) (20)</strong></td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa (140)</strong></td>
<td>29.5</td>
</tr>
</tbody>
</table>

* Only differences equal to or higher than twofold dilutions were taken into consideration.
tion could be made for all the bacterial species
tested here, but was more striking for Klebsiella,
Enterobacter, and Pseudomonas aeruginosa
than for E. coli and Proteus sp.

About two-thirds of the strains tested here
were equally susceptible to sisomicin and to
gentamicin, as tested by the inocula-replicating
method (Table 2). The other one-third was
more susceptible to sisomicin than to gentami-
cin, the difference being equal to or exceeding a
twofold dilution.

Age and sex distribution was similar in the
patients who received sisomicin or gentamicin,
as was the duration of treatment (mean dura-
tion, 7.0 and 7.1 days, respectively) and the
follow-up period (mean duration, 13.5 and 12.0
days, respectively). Serious local complicating
factors, as defined earlier, were found in 11
(44%) patients who received sisomicin and in 11
(52%) patients of the other group. The presence
of severe uropathy was associated with a lower
rate of cure in both groups (Table 3). All three
unfavorable responses in the sisomicin-treated
group occurred in patients with important local
abnormalities of the urinary tract, and the same
observation could be made for five out of eight
of the unfavorable outcomes in gentamicin-
treated patients. It can also be seen that failure
and relapse occurred in two out of three sisomi-
cin-treated patients and in both gentamicin-
treated patients when the offending microorga-

nism was relatively resistant (MIC < 3 μg/ml)
to the antibiotics. Superinfection and cure with
reinfection occurred only in gentamicin-treated
patients.

Cure was thus observed in 22 (88%) of the
sisomicin-treated patients and in 13 (61%)
of the gentamicin-treated patients. The difference
between those overall results is statistically
significant at the 0.05 level (χ² = 4.69; P <
0.05).

In the sisomicin-treated group, two failures
and one relapse were observed; one failure
occurred in a patient with ileal bladder and
infection due to a resistant Klebsiella (MIC, 50
μg/ml), and the relapse occurred in a patient
with carcinoma of the bladder and an infection
cased by a Providencia strain (MIC, 25 μg/ml).

In both cases the bactericidal activity of the
urine was lower than 1:2. No explanation could
be found for the other failure, which occurred
in a patient with carcinoma of the vagina but
normal upper urinary tract as shown by pyel-
graphy. The offending organism was an E. coli
(MIC, 0.3 μg/ml), and the bactericidal activity
of the urine was lower than 1:2 in spite of a level
of sisomicin equal to 44.5 μg/ml in the urine.

In the gentamicin-treated patients, two fail-
ures were observed; one was encountered in a
Pseudomonas aeruginosa (MIC, 3 μg/ml) infec-
tion and the other in an E. coli (MIC, 25 μg/ml)
infection. The bactericidal activity of the urine
in those two patients was 1.2 and less than 1.2
respectively. Reinfection by an Enterococcus
(MIC > 50 μg/ml) occurred, after a cure, in two
other patients, one of whom had a mild obstruc-
tive uropathy superimposed on prostatic carci-
noma. Superinfection occurred in four patients,
three of whom had some kind of obstructive
uroopathy. The microorganisms responsible for
superinfection were Pseudomonas aeruginosa
(MIC, 25 μg/ml), E. coli (MIC, 50 μg/ml), a
Herellea sp. (MIC > 50 μg/ml), and Candida
albicans.

No significant relationship could be found
between the response to therapy and the age or
sex of the patient or the nature of the offending
pathogen. Neither could a relationship between

**Table 3. Clinical response and its relationship to characteristics of the underlying urological disease and those of the offending microorganism**

<table>
<thead>
<tr>
<th>Underlying disease and offending bacteria</th>
<th>Sisomicin*</th>
<th>Gentamicin*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total F</td>
<td>R</td>
</tr>
<tr>
<td>All the patients</td>
<td>25 2 1 0 0</td>
<td>22 (88%)</td>
</tr>
<tr>
<td>Severe uropathy</td>
<td>11 2 1 0 0</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Mild uropathy</td>
<td>14 0 0 0 0</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>MIC &gt; 3 μg/ml</td>
<td>6 1 1 0 0</td>
<td>4 (66%)</td>
</tr>
<tr>
<td>E. coli</td>
<td>13 1 0 0 0</td>
<td>12 (92%)</td>
</tr>
<tr>
<td>Proteus-Providencia sp.</td>
<td>5 0 0 0 0</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Klebsiella-Enterobacter sp.</td>
<td>5 1 0 0 0</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2 0 0 0 0</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>

* F. Failure; R, relapse; S, superinfection; C+R, cure plus reinfection.
* Caused by Pseudomonas aeruginosa (MIC, 25 μg/ml), E. coli (MIC, 50 μg/ml), a Herellea sp. (MIC, 50 μg/ml), and C. albicans.
* Caused by enterococci.
the type of urinary tract disease (asymptomatic bacteriuria, cystitis, pyelonephritis) and the outcome be found. Table 3 indicates the type of microorganisms that were encountered here. *E. coli* was responsible for 13 infections in the sisomicin group and for nine in the gentamicin group; the rate of favorable response was similar in both groups. The number of patients in the other subgroups was too small to allow any valid conclusion about the relationship between the nature of the pathogen and the outcome of the treatment. As already mentioned, a factor which seemed important for the outcome of the therapy was resistance of the causative pathogen to the given antibiotic; two of the unfavorable responses to sisomicin occurred in six infections caused by microorganisms resistant to 3 \( \mu g/ml \), whereas only one such unfavorable response occurred among the 19 other patients. In the gentamicin-treated group, none of the patients whose infection was caused by a microorganism resistant to 3 \( \mu g/ml \) responded adequately. The role of the susceptibility of the causative pathogen is also suggested by the observation that all patients with failure or relapse had an inadequate bactericidal activity in their urine against the offending pathogen (1:2 or lower than 1:2) in spite of adequate urine levels of antibiotics.

The mean MIC of the offending pathogens was very similar in both groups: 0.74 and 0.80 \( \mu g/ml \), respectively, for sisomicin- and gentamicin-treated infections. No significant differences could be found between the serum and urine levels of sisomicin and gentamicin, although the mean values for the latter drug were higher (Table 4). The mean bactericidal activity in the sera of sisomicin- and gentamicin-treated patients was 1:4 and the bactericidal activity of the urine was 1:32 and 1:64, respectively. With the exception of the patients whose infection was caused by highly resistant microorganisms (MIC > 25 \( \mu g/ml \)) the bactericidal activity of the urine almost always exceeded the 1:8 level.

Untoward reactions observed during therapy, and possibly related to it, were evaluated only in those patients for whom an initial examination or test was normal and for whom an adequate follow-up during and after therapy could be obtained. Hematuria, cylindruria, and albuminuria were observed with approximately the same frequency in sisomicin-treated and gentamicin-treated patients and ranged from 4.5 to 11.1% (Table 5). In only one patient in each series did hematuria, cylindruria, and albuminuria occur together during therapy. All these abnormalities were mild, and considering the underlying urological problems of the patients studied here it is not possible to ascribe the changes only to the use of the antibiotics. Rise of blood urea above normal values occurred in four out of 25 (16%) patients who received sisomicin and in four out of 21 (19%) patients who received gentamicin. In two of the patients in the sisomicin group, the rise of blood

**Table 4. Susceptibility of pathogens, levels of antibiotics, and antimicrobial activity in serum and urine**

<table>
<thead>
<tr>
<th>Determination*</th>
<th>Sisomicin</th>
<th>Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC of the causative pathogen (( \mu g/ml ))</td>
<td>0.74</td>
<td>0.80</td>
</tr>
<tr>
<td>Serum level of antibiotic (( \mu g/ml ))</td>
<td>2.35</td>
<td>4.08</td>
</tr>
<tr>
<td>Urine level of antibiotic (( \mu g/ml ))</td>
<td>42.4</td>
<td>65.0</td>
</tr>
<tr>
<td>Serum MBD* (reciprocal)</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Urine MBD (reciprocal)</td>
<td>32.0</td>
<td>128.0</td>
</tr>
</tbody>
</table>

*The number of pathogens with a MIC > 25 \( \mu g/ml \) was two for sisomicin and one for gentamicin.

*MBD, Maximal bactericidal dilution.
urea was associated with a decrease of the creatinine clearance; in one of them the level of serum creatinine rose from 1.4 to 2.4 mg\% during therapy, and in the other two patients the serum creatinine level and the creatinine clearance remained normal. In the other group, a decrease of the creatinine clearance was associated with the elevation of blood urea in two out of the four patients; in all these four patients, the serum creatinine level remained normal.

Audiograms were normal and available initially in 20 of the sisomicin-treated and 20 of the gentamicin-treated patients. In one patient receiving sisomicin, a bilateral decrease of hearing could be found. This could be correlated to a clinical examination, which also indicated a partial loss of hearing. These abnormalities did not persist after discontinuation of therapy. Another patient receiving sisomicin complained of headache during therapy. No other signs of acoustic or vestibular dysfunction could be observed in this patient.

**DISCUSSION**

Patients with underlying urological problems might not be considered to be the optimal population to be investigated for efficacy and tolerance of drugs such as sisomicin and gentamicin. However, in most of our patients the causative pathogen was resistant to most common antibiotics, as frequently happens in this type of patient. Therefore the present trial provides an evaluation under conditions likely to be those of common clinical practice. Because of the underlying urological disease that was present in our patients, the emphasis has been placed on bacteriological results as far as the evaluation of treatment is concerned, since clinical signs and symptoms suggesting urinary tract infection could not always be attributed to the infection only. As far as eradication of the offending microorganism is concerned, sisomicin and gentamicin appeared similarly effective. However, sisomicin appeared to be associated with a higher overall rate of favorable results than gentamicin, owing chiefly to a greater number of superinfections by gentamicin-resistant microorganisms in the gentamicin-treated patients. Whether this reflects the presence in the hospital environment of a substantial number of gentamicin-resistant strains is difficult to assess. Nevertheless, the present in vitro studies have confirmed previous investigations (4, 6, 8), indicating that resistance to gentamicin among gram-negative rods isolated in hospitals was more common than that to sisomicin and that cross-resistance between the two drugs does not always exist. Of course, this situation might change when sisomicin is used more frequently.

On the other hand, serious urological problems were slightly more frequent in the gentamicin-treated patients and might explain the higher incidence of superinfection and reinfection in these patients. The major point to be stressed with regard to the evaluation of the efficacy of the newer compound sisomicin is that it proved to be at least as effective as the most potent antibiotic now available and resulted in 88% of bacteriological cures in patients with abnormalities of the urinary tract. This is in accordance with previous observations made in this hospital (6a).

Adverse reactions were not found frequently in the present series. Significant alteration of the urinary sediment occurred in one patient in each series but cannot be easily interpreted because of the underlying urological pathology. Azotemia, indicated by an elevation of the blood urea (and possibly serum creatinine level) and a decrease of the creatinine clearance occurred in two patients in each series, representing a frequency of 8.0 and 9.5% for sisomicin-treated and gentamicin-treated patients, respectively. Acoustic and vestibular functions were closely followed in the present study and objective alterations were found in only one patient who received sisomicin. It should be stressed here that nephrotoxicity and ototoxicity were mild in this series and did not persist after discontinuation of therapy.

Thus, sisomicin compares favorably with gentamicin for the treatment of urinary tract infections, and it should therefore be recommended for the therapy of infections caused by gentamicin-resistant organisms. The definition of resistance to gentamicin (or to sisomicin) of pathogens responsible for urinary tract infection is somewhat arbitrary. The levels of sisomicin and gentamicin obtained in the urine were in the range of 50 \( \mu \)g/ml; but among nine patients whose bacteriuria was caused by a microorganism of which the MIC was equal or superior to 3 \( \mu \)g/ml there were only four cures (44.4%), contrasting with 31 (83.8%) cures out of 37 patients with bacteriuria caused by more susceptible microorganisms. In the three cases where the offending bacteria had a MIC equal to or higher than 25 \( \mu \)g/ml, a failure to respond to the treatment was observed; in all of them, the bactericidal activity of the urine was inadequate. These observations suggest that the level of "clinical resistance" of microorganisms involved in complicated urinary infections might be set at a relatively low level.

The efficacy of sisomicin in extra-urinary infections remains to be further investigated. It
should, however, be pointed out that the bactericidal activity of the serum obtained with the dosages of sisomicin and gentamicin used here was rather low. Previous studies from this laboratory indicated that a bactericidal dilution of 1:8 of the serum is associated with optimal therapeutic results (5) and, therefore, the mode of therapy used here might prove to be inadequate in patients with renal tissue infections.

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LITERATURE CITED