Clinico-Pharmacological Studies of Sisomicin in Ill Children

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Sisomicin, at 4.5 mg/kg per day, was prescribed for the therapy of serious bacterial infections of hospitalized infants, children, and adolescents. Eleven children received full treatment courses, with 10 clinical and 9 bacteriological cures. Three patients with underlying disease (two cystic fibrosis and one aplastic anemia) accounted for the failures. Mean half-life was 98.3 min (range, 26.1 to 159.3), and peak serum concentrations 10 min after intravenous infusion were similar (5 to 6 μg/ml) on days 1, 3, and 5 of therapy. Mean urinary concentrations were 54.3 μg/ml; 31 to 47% of the drug was excreted within the 8-h dosage interval. The drug was tolerated well by all patients; however, one patient, receiving the longest duration of therapy (26 days), developed reversible nephrotoxicity.

The emergence of gentamicin-resistant bacteria in hospitalized patients has emphasized the importance of evaluating alternative antibiotics. Sisomicin is a new aminoglycoside antibiotic derived from the fermentation broth of Micro- monospora inyoensis that has many properties in common with gentamicin as well as the advantage of activity against selected gentamicin-resistant bacteria (4, 6, 9, 14). The purpose of this study was to examine some of the pharmacokinetic, clinical, and toxicological properties of sisomicin in the therapy of serious infections of children.

MATERIALS AND METHODS

Sisomicin was administered to 12 patients hospitalized at the Montreal Children's Hospital. These patients were selected by the attending physician as candidates for aminoglycoside therapy using standard clinical and laboratory criteria. Once a patient was selected to receive aminoglycosides, sisomicin was offered in lieu of gentamicin after carefully explaining the nature of the study and the differences between the two drugs to the parents and only after obtaining informed consent. Appropriate bacterial cultures and base-line laboratory studies were obtained in each case. When positive cultures were obtained before therapy, appropriate cultures were repeated during and after therapy as well. Sisomicin was administered in a dosage of 4.5 mg/kg per day intravenously (divided every 8 h) over 0.5 h, and the duration of treatment was determined by standard clinical and bacteriological criteria.

All patients were carefully examined for tolerance to the drug and for hematological, hepatic, and renal toxicities by the following tests: hemoglobin, hematocrit, white blood count and differential, platelets, serum glutamic oxaloacetic transaminase, bilirubin, alkaline phosphatase, urea nitrogen, creatinine, and urinalysis. These tests were carried out before, during, and after therapy.

Audiological evaluations were performed within 72 h of initiation of therapy, and again after completion of the course of sisomicin. School-age children were studied by standard pure-tone and standard speech audiometry and impedance testing, pre-school children and infants by behavioral observation, play, and conditioned orienting response audiometry, and impedance measurements when possible. Vestibular function was tested only by clinical assessment of gait and balance. Follow-up studies included audiometry and clinical examination 2 weeks and 6 months after completion of therapy. Clinical cure was defined as improvement of initial clinical signs and symptoms during therapy; bacteriological cure was defined as the eradication of the infecting bacteria. On days 1, 3, and 5 of therapy the bladder was emptied before the dose was administered; urine was collected and pooled for the 8-h period following drug administration. On day 1, blood samples were taken before drug administration and 10 min after completion of the infusion. On day 3, bloods were taken before drug and 10, 20, 30, and 90 min, 4 h, and 8 h after cessation of drug infusion. Bloods were obtained prior to drug and at 10 min and 6 h after completion of drug administration on day 5.

Sisomicin concentrations were determined in the serum and urine of each patient by an agar diffusion bioassay technique employing a serum-resistant Klebsiella with a minimal inhibitory concentration (MIC) of 0.039 μg/ml for sisomicin (1). This bacterium is resistant to beta-lactam antibiotics (penicillin, cephalosporins). Disc diffusion sensitivities and microtiter broth dilution MICs were determined for all significant bacterial isolates, and checkerboard titration microtiter synergy studies were carried out when combinations of antibiotics were prescribed (2).

Pharmacokinetic parameters were derived from the analysis of individual serum data according to the one-compartment open model with zero-order infusion and
first-order drug elimination (15). During the infusion, concentrations \((C)\) as a function of time \((t)\) are described by equation (1):

\[
C = \frac{k_a/(k_e \cdot V_d)}{1 - \exp(-k_e t)}
\]

(1)

where \(k_e\) is the elimination rate constant, \(V_d\) the apparent volume of distribution, and \(k_a\) the rate of infusion. At the end of any infusion period, the concentration \(C_T\) is given by equation (1) if \(t = T\) = duration of infusion. Rearrangement of equation (1) at time \(T\) provides an estimate of the volume of distribution. Elimination rate constants \(k_e\) are calculated from the slope of log terminal serum concentrations versus time in the post-infusion phase from proper transformation of the following equation:

\[
C = C_e \{\exp[-k_e (t - T)]\}
\]

(2)

where \(C_e\) is the extrapolated concentration at time \(T\).

Theoretical maximum and minimum concentrations, \((C_w)_{\text{max}}\) and \((C_w)_{\text{min}}\), respectively, after an infinite number of infusions, are calculated using the following equations:

\[
(C_w)_{\text{max}} = \frac{(C_e)_{\text{max}}}{[1 - \exp(-k_r t)]}
\]

(3)

\[
(C_w)_{\text{min}} = \frac{(C_e)_{\text{min}}}{[1 - \exp(-k_r t)]}
\]

(4)

where \((C_e)_{\text{max}}\) and \((C_e)_{\text{min}}\), respectively, represent the maximum and minimum concentration after the first dose, and \(r\) is the length of dosage interval (8 h in all patients). \((C_w)_{\text{max}}\) was calculated for each subject using equation (2) and setting the time \(t\) to 8 h. Finally, serum clearances are calculated as the product \(k_e \cdot V_d\).

RESULTS

Twelve patients were enrolled in the study; complete studies were obtained in 11. The patient dropped from the study was a 3-week-old with group B streptococcal bacteremia and meningitis, where therapy was changed to penicillin in place of ampicillin and sisomicin.

The average age of the patients treated was 9 years, with a range of 2 weeks to 18 years. Characteristics of the patients studied are presented in Table 1. The outcome of therapy was usually influenced by a combination of the underlying disease and the in vitro susceptibility of the infecting bacteria. Two of the three bacteriological failures had cystic fibrosis, and the third had aplastic anemia. *Pseudomonas aeruginosa* relatively resistant to sisomicin was cultured from one of the cystic patients (MIC, 6.25 μg/ml) and from the child with aplastic anemia (MIC, 3.12 μg/ml); in neither case was the bacteria completely eradicated by therapy. Although bacteremia cleared in the patient with aplastic anemia, otitis media persisted, and *Pseudomonas* was not eradicated from this site.

Two patients were treated with sisomicin alone; in nine, sisomicin was prescribed in combination with ampicillin, carbencillin, cloxacillin, or penicillin. Bacteria from patients receiving either carbencillin or ampicillin combined with sisomicin were tested in vitro for susceptibility to the antibiotics used. Combinations of carbencillin and sisomicin were synergistic against *Pseudomonas* in all cases; however, ampicillin and sisomicin were antagonistic against *Proteus morganii*. This patient had a urinary tract infection which responded well to therapy despite these in vitro observations.

Complete pharmacological evaluation was performed in 10 of the 11 patients. Collections were incomplete in patient no. 5, a 2-week-old, and half-life \((t_{1/2})\) and excretion could not be ascertained. Mean sisomicin serum concentrations as a function of time after cessation of infusion are shown in Fig. 1. As revealed by the large standard deviations, concentrations immediately following infusion cut-off varied widely between subjects, as did the rate of serum disappearance. This is exemplified in Fig. 2. In some subjects, there was an indication that the elimination pattern followed two-compartment open model kinetics, but the limited number of data points did not allow for accurate determination of the \(\alpha\)-phase and related distribution constants. The mean \(t_{1/2}\) was 93.3 min (Table 2). There was no evidence of a change in \(t_{1/2}\) with time except in subjects 11 and 12, where \(t_{1/2}\) increased from 129 and 150 min on day 3 of therapy to 264 and 258 min, respectively, on day 5.

Volumes of distribution \((V_d)\) are shown in Table 2, both in absolute values and in percent of body weight. Although the method of calculation slightly overestimates the true value of this parameter, the values shown correspond approximately to extracellular space, as has been shown from two-compartment analysis after intravenous administration in normal volunteers (10). In two infants (subjects 1 and 6), the volume of distribution was expectedly higher. Similarly, these two infants had a much lower serum clearance than older children (Table 2).

There was no evidence of accumulation of the antibiotic over repeated infusions. This can readily be seen from inspection of Table 2, where maximum concentrations do not differ appreciably on days 1, 3, and 5. There were only two discrepancies (subjects 11 and 12), and these were due, as mentioned above, to an unexplained increase in \(t_{1/2}\) with time. In all subjects, minimum concentrations at 4 h in the day 3 dosage interval were below 2.0 μg/ml. On day 5, all subjects had serum concentrations below 2.25 μg/ml, and most were below the method’s detection limits.

Table 2 also shows theoretical maximum and minimum concentrations after an infinite num-
Table 1. Clinical and laboratory features of 11 children treated with sisomicin

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Bacteria</th>
<th>Sisomicin MICa</th>
<th>Duration of sisomicin treatment (days)</th>
<th>Added β-lactam antibiotics</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Urinary tract infection</td>
<td>5 mo.</td>
<td><em>Escherichia coli</em></td>
<td>0.39</td>
<td>10</td>
<td>Ampicillin (10) 3.12</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Bacteria, pyelonephritis, nephrolithiasis</td>
<td>18 yr.</td>
<td><em>Proteus morganii</em></td>
<td>0.78</td>
<td>9</td>
<td>Carbenicillin (5) 100</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Pneumonia, cystic fibrosis</td>
<td>10 yr.</td>
<td><em>Staphylococcus aureus</em></td>
<td>0.02</td>
<td>5</td>
<td>(Klebsiella, Enterobacter) 500 (Enterococcus)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Pneumonia, prematurity, respiratory distress syndrome</td>
<td>2 wk.</td>
<td><em>P. aeruginosa</em></td>
<td>12.5</td>
<td>5</td>
<td>Carbenicillin (6) 62.5</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Balanitis, inguinal abscesses</td>
<td>6 mo.</td>
<td><em>Enterobacter</em></td>
<td>0.09</td>
<td>7</td>
<td>Cloxacillin (7) 31.2 (Enterococcus)</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Otitis media, bacteremia, aplastic anemia</td>
<td>16 yr.</td>
<td><em>P. aeruginosa</em></td>
<td>3.12</td>
<td>6</td>
<td>(Klebsiella)</td>
<td>Blood, yes</td>
</tr>
<tr>
<td>8</td>
<td>Fever, leukemia</td>
<td>8 yr.</td>
<td>None</td>
<td>3.12</td>
<td>9</td>
<td>Yes</td>
<td>Ear, no</td>
</tr>
<tr>
<td>9</td>
<td>Osteomyelitis</td>
<td>12 yr.</td>
<td><em>P. aeruginosa</em></td>
<td>0.19</td>
<td>26</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Pneumonia, cystic fibrosis</td>
<td>12 yr.</td>
<td><em>P. aeruginosa</em></td>
<td>0.39</td>
<td>8</td>
<td>Carbenicillin (8) 31.2</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Urinary tract infection</td>
<td>8 yr.</td>
<td><em>P. aeruginosa</em></td>
<td>1.56</td>
<td>10</td>
<td>Carbenicillin (2) 125</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>Osteomyelitis</td>
<td>13 yr.</td>
<td><em>P. aeruginosa</em></td>
<td>1.56</td>
<td>7</td>
<td>Cloxacillin (7) Penicillin (4) &gt;100</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*a MIC, Minimal inhibitory concentration (µg/ml).
Mean and one standard deviation of serum concentrations of sisomicin determined on day 3 of therapy in 11 children.

Fig. 2. Variations in t1/2 and serum concentrations in three children who received 1.5 mg of sisomicin per kg by infusion over 30 min.

TABLE 2. Sisomicin pharmacokinetic data during repeated administration to ill children

<table>
<thead>
<tr>
<th>Subject</th>
<th>Vd</th>
<th>Percent Vd/kg</th>
<th>t1/2 (min)</th>
<th>Serum clearance (ml/min)</th>
<th>Cmax (µg/ml) Day 1</th>
<th>Cmax (µg/ml) Day 3</th>
<th>Cmax (µg/ml) Day 5</th>
<th>(Cmin)max (µg/ml)</th>
<th>(Cmin)min (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>10.26</td>
<td>16.34</td>
<td>111.5</td>
<td>74.8</td>
<td>8.0</td>
<td>8.0</td>
<td>10.0</td>
<td>8.4</td>
<td>0.43</td>
</tr>
<tr>
<td>4</td>
<td>7.86</td>
<td>29.34</td>
<td>26.1</td>
<td>117.1</td>
<td>2.2</td>
<td>3.5</td>
<td>4.2</td>
<td>3.5</td>
<td>0.01</td>
</tr>
<tr>
<td>7</td>
<td>12.20</td>
<td>25.48</td>
<td>159.3</td>
<td>95.5</td>
<td>12.5</td>
<td>5.6</td>
<td>5.5</td>
<td>6.4</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>6.94</td>
<td>12.33</td>
<td>36.4</td>
<td>89.0</td>
<td>2.3</td>
<td>5.5</td>
<td>4.5</td>
<td>5.5</td>
<td>1.57</td>
</tr>
<tr>
<td>9</td>
<td>7.42</td>
<td>12.46</td>
<td>52.2</td>
<td>101.8</td>
<td>6.7</td>
<td>10.0</td>
<td>8.0</td>
<td>10.0</td>
<td>0.02</td>
</tr>
<tr>
<td>10</td>
<td>6.91</td>
<td>27.62</td>
<td>36.4</td>
<td>105.7</td>
<td>4.4</td>
<td>4.4</td>
<td>5.8</td>
<td>4.4</td>
<td>0.01</td>
</tr>
<tr>
<td>11</td>
<td>6.55</td>
<td>25.61</td>
<td>149.9</td>
<td>45.8</td>
<td>6.3</td>
<td>5.0</td>
<td>15.0</td>
<td>5.6</td>
<td>0.46</td>
</tr>
<tr>
<td>12</td>
<td>20.50</td>
<td>28.71</td>
<td>129.0</td>
<td>128.4</td>
<td>5.7</td>
<td>4.5</td>
<td>8.6</td>
<td>4.9</td>
<td>0.37</td>
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<tr>
<td>1</td>
<td>1.91</td>
<td>61.61</td>
<td>149.9</td>
<td>10.5</td>
<td>2.2</td>
<td>2.2</td>
<td>2.0</td>
<td>2.5</td>
<td>0.26</td>
</tr>
<tr>
<td>6</td>
<td>2.78</td>
<td>31.90</td>
<td>131.9</td>
<td>15.5</td>
<td>5.5</td>
<td>4.0</td>
<td>3.1</td>
<td>4.3</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*a Cmax, Serum concentration 10 min after infusion cut-off.
*b Vd, Volumes of distribution.
*c (Cmin)max calculated according to equation (3).
*d (Cmin)min calculated according to equation (4).
renal function was already detected at this time) when a dosage error (one-half daily dose given instead of one-third) was followed by a peak serum concentration of 15 μg/ml and a trough of 3.6 μg/ml. The drug was then discontinued. No concomitant nephrotoxic drugs were being administered. One patient with previously abnormal hearing was treated with sisomicin with no untoward effects noted. Careful audiometric examination was necessary in this patient, as bilateral otitis media with perforations due to P. aeruginosa was part of her complicated clinical condition. No other toxicities were noted.

Follow-up of patients has indicated no further toxicities or intolerances to the drug and no relapses of clinical disease other than in the two patients with cystic fibrosis and the one with aplastic anemia.

**DISCUSSION**

The present study has evaluated the use of a new aminoglycoside, sisomicin, in the therapy of serious infections of hospitalized children. In vitro studies support the use of this agent for the treatment of selected infections due to gentamicin-resistant bacteria (4, 6, 9, 14). Preliminary in vitro studies in our laboratory indicated activity for sisomicin against some gentamicin-resistant P. aeruginosa as well as synergism between carbenicillin and sisomicin (5, 6). Application of these findings to clinical infections in the present study resulted in excellent clinical and bacteriological therapeutic responses. Other clinical studies demonstrated a similar favorable outcome in human infections treated with this drug (3, 4). Because cross-resistance between gentamicin and sisomicin is common, in vitro susceptibility studies are necessary to guide aminoglycoside therapy in these situations.

Previous pharmacokinetic data of sisomicin in adult volunteers and patients are similar to those described herein for children (3, 8, 11, 12). Four subjects had extremely rapid t1/2 (<1 h), and this may indicate that age and/or health status have some influence on the elimination rate of this drug. Two of the three children with very short t1/2 had cystic fibrosis, a condition previously associated with increased excretion rates of dicloxacillin and methicillin (17). t1/2 values for the other subjects were in the range reported by others (4, 6, 12, 15, 16).

In most cases, postinfusion serum concentrations obtained in the subjects of this sample population agree with concentrations obtained after administering the drug at the dose of 1.0 mg/kg to volunteers (7) and elderly male patients suffering from urinary tract infections (16). Several patients had higher steady-state serum concentrations than predicted by our pharmacokinetic model. A two-compartment model may provide more accurate estimates of Cmax and Cmin for aminoglycoside antibiotics.

Sisomicin appears to behave like amikacin, of which it has been recently shown that body clearance and volume of distribution are, respectively, less and greater in infants than in adults (13). Very little accumulation of sisomicin was detected, which is expected when the dosage interval is much greater than the t1/2 of the drug. Steady-state serum concentrations are illustrated in Fig. 1. Wide individual variations in serum and urinary concentrations and percentage of dose excreted noted in our study have also been described in normal volunteers (7). There was no significant correlation between serum clearance or t1/2 and percentage of dose excreted within the three dosage intervals where urinary levels were measured. This indicates that in children, as well as in adults (16), there is a variable but significant contribution of infusion and excretion rates, as well as extravrenal

### Table 3. Urinary excretion data for three dosage intervals

<table>
<thead>
<tr>
<th>Subject</th>
<th>Day 1</th>
<th></th>
<th>Day 3</th>
<th></th>
<th>Day 5</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Excreted*</td>
<td>Urinary concn (μg/ml)</td>
<td>% Excreted</td>
<td>Urinary concn (μg/ml)</td>
<td>% Excreted</td>
<td>Urinary concn (μg/ml)</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>34</td>
<td>63</td>
<td>100</td>
<td>100</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>46</td>
<td>71.3</td>
<td>50</td>
<td>61</td>
<td>106</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>1.8</td>
<td>9.4</td>
<td>10</td>
<td>75.3</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>49.8</td>
<td>50</td>
<td>72</td>
<td>80</td>
<td>60.9</td>
<td>145</td>
</tr>
<tr>
<td>9</td>
<td>54.2</td>
<td>59.5</td>
<td>67.8</td>
<td>84</td>
<td>28</td>
<td>115</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>28</td>
<td>9.2</td>
<td>10</td>
<td>6.8</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>0.7</td>
<td>2</td>
<td>69.6</td>
<td>45</td>
<td>7.8</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>60</td>
<td>45.9</td>
<td>90</td>
<td>87</td>
<td>115</td>
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<tr>
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<td>33</td>
<td>15</td>
<td>13</td>
<td>10</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>ND</td>
<td>ND</td>
<td>21</td>
<td>36</td>
<td>17</td>
<td>36</td>
</tr>
</tbody>
</table>

* % Excreted, percentage of dose excreted within one 8-h dosage interval.

ND, Not determined.
distribution mechanisms (as yet undefined), to the total elimination profile.

Alterations in urinalysis and azotemia were reported in 5% of patients by Klastersky et al. (4). Sisomicin nephrotoxicity was noted in one of our patients. Serum concentrations and/or the duration of treatment may be responsible in this case. It is noteworthy that the renal toxicity was reversible and could be detected at an early stage by monitoring of the urinalysis, urea nitrogen, and creatinine. Although the small number of patients and wide age range studied preclude firm conclusions about the efficacy of therapy and about precise dosage recommendations for infants, the bulk of our in vitro and in vivo data would seem to support a useful clinical role for sisomicin in the therapy of selected infections of hospitalized children.

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LITERATURE CITED

7. Meunier-Carpentier, F., M. Staguet, and J. Klaster-
13. Sardemann, H., H. Colding, J. Hendel, J. P. Kamp-
mann, E. F. Hvidbert, and R. Vejlaagard. 1976. Kinetics and dose calculations of amikacin in the new-
ards Laboratory, Groese Pointe Park, Mich.
16. Welling, P. G., A. Mosegaard, and P. O. Madsen. 1974. Sisomicin treatment of complicated urinary tract infec-
macokinetics of methicillin in patients with cystic fibro-