Clinical Pharmacology of Sisomicin

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Sisomicin is a new aminoglycoside antibiotic isolated from the fermentation broth of Micromonopora inyoensis (4). The antibiotic most closely resembles gentamicin C12, a component of the gentamicin complex. In vitro, sisomicin has a spectrum of antimicrobial activity similar to that of gentamicin (1, 3, 4). However, it is more active against strains of Pseudomonas aeruginosa and indole-positive Proteus (D. Stewart and B. P. Bodey, J. Antibi.., in press). Most strains of Klebsiella spp., Escherichia coli, P. aeruginosa, Enterobacter and Proteus spp. are inhibited at a concentration of 0.78 \(\mu\)g/ml (4; Stewart and Bodey, J. Antibi., in press). Bacterial strains resistant to gentamicin are usually resistant to sisomicin (3; Stewart and Bodey, J. Antibi., in press). In vivo, mouse protection studies have shown that sisomicin is 2 to 4 times more effective than gentamicin. In the rat and cat, it appears to be slightly more nephrotoxic.

We conducted clinical pharmacological studies with sisomicin. The results indicate that the pharmacology of sisomicin is similar to gentamicin.

MATERIALS AND METHODS

Studies were conducted in 30 patients with neoplastic diseases. Twelve patients received sisomicin intramuscularly at doses of 20 mg/m² and 40 mg/m². The mean peak serum concentration occurred at 1 h and was 2.5 \(\mu\)g/ml and 4.0 \(\mu\)g/ml, respectively. Ten patients received intravenous sisomicin at doses of 30 mg/m² during 30-min infusion. Mean peak serum level determined at 30 min was 5.1 \(\mu\)g/ml. The levels gradually decreased and at 6 h was 0.6 \(\mu\)g/ml. The serum half-life was 160 min. Serum levels determined in eight patients who received sisomicin by continuous infusion at doses of 30 mg/m² every 6 h were greater than 1.4 \(\mu\)g/ml during the 6-h period. The urinary excretion of sisomicin during the 6-h period after intramuscular administration of 20 mg/m² and 40 mg/m² was 49 and 61%, respectively. The pharmacology of sisomicin is similar to gentamicin.

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nism. The organism was incubated in brain heart infusion agar (BBL) for 1 week at 37 C, harvested, washed with normal saline, and heated shocked at 65 C for 30 min to release the spores. The spores were washed and suspended in normal saline so that there were approximately $5 \times 10^9$ viable spores per ml. A 1.5-ml portion of this suspension was added to 1 liter of antibiotic medium no. 2, the pH was adjusted to 7.8 with phosphate buffer, and petri dishes were filled with 14-ml portions. Wells (0.75 mm in diameter and 0.4 mm in depth) were cut into the agar and filled with 0.05 ml of each specimen. The plates were incubated at 37 C for 18 h. Zones of inhibition were measured and compared to a standard curve. Assays were performed in triplicate.

The standard error of the mean was calculated according to the method of Mantel (2). The 95% confidence limits were determined as twice the standard error of the mean. Statistical analyses of the differences in serum concentrations were performed with Student's t test.

RESULTS

Serum concentrations after intramuscular administration of sisomicin and gentamicin are shown in Fig. 1. After administration of 20 mg of sisomicin per m², the mean peak serum concentration occurred at 1 h and was 2.5 µg/ml. Mean serum concentrations greater than 1 µg/ml were maintained for 4 h after the administration of sisomicin. Mean serum concentrations at 6 and 8 h were 0.5 µg/ml and 0.3 µg/ml, respectively. The serum half-life was 120 min. After intramuscular administration of 40 mg/m² of sisomicin, the mean peak level occurred at 1 h and was 4.0 µg/ml. The mean peak level of gentamicin after intramuscular administration of 40 mg/m² occurred also at 1 h and was 3.7 µg/ml. Mean serum concentrations of sisomicin at 4, 6, and 8 h were 1.6 µg/ml, 1.0 µg/ml, and 0.7 µg/ml, respectively. Mean serum concentrations of gentamicin were 1.6 µg/ml, 0.8 µg/ml, and 0.4 µg/ml at 4, 6, and 8 h, respectively.

Serum concentrations of sisomicin were determined in 10 patients after intravenous administration of 30 mg of sisomicin per m² over 30 min (Fig. 2). The serum level determined at 30 min on the first day of therapy was 5.1 µg/ml. At 4 and 6 h the mean serum concentrations were 1 µg/ml and 0.6 µg/ml, respectively. The serum half-life was 160 min. On the 3rd day of therapy, the study was repeated in the same patients. The mean serum concentrations at 0.5, 4, and 6 h were 4.7 µg/ml, 1.2 µg/ml, and 0.8 µg/ml, respectively. On day 7, the study was repeated in five patients. The mean serum concentrations at 0.5, 4, and 6 h were 5.3 µg/ml, 1.2 µg/ml, and 0.8 µg/ml, respectively.

Serum levels were determined in eight patients who received continuous infusion of sisomicin for therapy of infections. Each patient received an initial dose of 30 mg of sisomicin per m² in 50 ml of dextrose solution over 30 min followed immediately by a dose of 30 mg/m² as a constant infusion repeated every 6 h. The mean serum concentration at 30 min was 4 µg/ml (Fig. 3). Mean serum levels greater than 1.4 µg/ml were maintained during the 6-h period of constant infusion.

Urinary concentrations of sisomicin and gentamicin were measured in the patients who received the antibiotic intramuscularly (Table 1). The mean urinary excretion of sisomicin at 6 h was 49% of the administered low dose (20 mg/m²) and 61% of the high dose (40 mg/m²). The mean urinary excretion of gentamicin was 58% of the administered high dose (40 mg/m²). No acute side effects were seen in the patients of this study and the antibiotic was well tolerated by all of them.

![Fig. 1. Serum concentration of sisomicin and gentamicin. The lower curve corresponds to a dose of 20 mg/m²; the upper curves correspond to doses of 40 mg/m².](image1)

![Fig. 2. Serum concentration of sisomicin after intravenous administration of 30 mg/m².](image2)
Table 1. Urinary excretion after administration of antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean urinary excretion</th>
<th>Mean urinary concn (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (IM)*</td>
<td>(mg)*</td>
</tr>
<tr>
<td>Sisomicin</td>
<td>20 mg/m²</td>
<td>23.4</td>
</tr>
<tr>
<td>Sisomicin</td>
<td>40 mg/m²</td>
<td>43.7</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>40 mg/m²</td>
<td>42.2</td>
</tr>
</tbody>
</table>

* IM indicates intramuscular.
\(^{b}\) Numbers in parentheses indicate ranges.

Fig. 3. Serum concentration of sisomicin after continuous intravenous administration of 30 mg/m².

**DISCUSSION**

Sisomicin is a new aminoglycoside antibiotic whose spectrum of activity is similar to gentamicin (1, 3, 4). However, most strains of Klebsiella spp., E. coli, P. aeruginosa and Enterobacter are inhibited at concentrations of 0.78 μg/ml or less of sisomicin (Stewart and Bodey, J. Antibiot., in press). Concentrations of 1.56 μg/ml of gentamicin are necessary to produce similar inhibition in the same strains of organisms in vitro (Stewart and Bodey, J. Antibiot., in press). Our study demonstrates that after intramuscular administration of 40 mg of sisomicin per m² a mean peak level of 4.0 μg/ml is obtained at 1 h and that mean serum concentrations >1.0 μg/ml are maintained during the 4-h period after the intramuscular administration of the antibiotic. A similar dose of gentamicin administered to the patients yielded a mean peak level of 3.7 μg/ml. Serum levels >1.0 μg/ml were also maintained during the 4-h period after the administration of gentamicin.

Intravenous therapy of infections is desirable in compromised hosts who are frequently thrombocytopenic. We determined serum levels in cancer patients who received the drug intravenously for therapy of infections. After a dose of 30 mg/m² administered during 30 min, the highest mean peak of 5.0 μg/ml was determined at 30 min. However, the serum concentration gradually fell thereafter and beyond the initial 4-h period the serum concentrations were <1.0 μg/ml. Similar determinations were made on days 3 and 7 of therapy and no significant accumulation of the drug was determined.

In an attempt to maintain constant adequate serum levels during therapy, sisomicin was also administered intravenously by continuous infusion. Serum levels were determined in eight patients; mean serum concentrations >1.4 μg/ml were maintained at all times during the infusion.

Sisomicin appears to be excreted in the urine-like gentamicin. The urinary excretion of sisomicin during the 6-h period after intramuscular administration of 20 and 40 mg/m² was 49 and 61%, respectively. The urinary excretion of gentamicin after the high dose (40 mg/m²) administration was also 58%.

The administration of sisomicin was well tolerated by the patients of this study and no untoward immediate effect was elicited.

Our study indicates that the serum concentrations of sisomicin are similar to those obtained with gentamicin; the serum half-life is also similar. However, because the in vitro studies with sisomicin indicate superiority of this drug against P. aeruginosa and Proteus spp., there exist the possibility of better therapeutic effects with sisomicin. Studies are in progress to determine its efficacy in the therapy of infections in cancer patients.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**