Clinical Pharmacology of Sisomicin

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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 µg/ml and 4.0 µg/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 µg/ml. The levels gradually decreased and at 6 h was 0.6 µg/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 µg/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.

Sisomicin is a new aminoglycoside antibiotic isolated from the fermentation broth of *Micromonospora inyoensis* (4). The antibiotic most closely resembles gentamicin C_{1a}, 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. Antibiot., in press). Most strains of *Klebsiella* spp., *Escherichia coli*, *P. aeruginosa*, *Enterobacter* and *Proteus* spp. are inhibited at a concentration of 0.78 µg/ml (4; Stewart and Bodey, J. Antibiot., in press). Bacterial strains resistant to gentamicin are usually resistant to sisomicin (3; Stewart and Bodey, J. Antibiot., 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 who were not severely debilitated. Their ages ranged between 17 and 68 years. Their weights ranged between 40 and 82 kg. Seventeen patients were males. All 30 patients had normal blood urea nitrogen (<20 mg/100 ml), serum creatinine (<1.0 mg/100 ml), serum bilirubin (<1 mg/100 ml), serum glutamic oxaloacetic transaminases (<55 µm)

and alkaline phosphatases (<250 µm). Informed consent was obtained from all patients according with institutional policies.

Twelve patients received sisomicin (supplied by Schering Corp., Bloomfield, N.J.) intramuscularly on separate occasions at doses of 20 mg/m² and 40 mg/m² in a cross-over study. The same patients also received gentamicin sulfate by the intramuscular route in a dose of 40 mg/m². The dose of antibiotic was dissolved in 2 ml of distilled water and injected deep in the gluteal area. The administration of each dose of antibiotic was separated by at least a 2-day interval in each patient. Serum specimens were collected before administration and at 0.25, 0.5, 1, 2, 4, 6, and 8 h after administration of the antibiotic. Urine specimens were collected before initiation of the study and during the initial 6-h period.

Studies were also conducted in 10 patients who received sisomicin intravenously for therapy of infections. Each patient received a dose of 30 mg/m² dissolved in 50 ml of dextrose solution infused during 30 min every 6 h. Studies were conducted on day 1 after the initial dose and repeated on days 3 and 7 of therapy. Serum levels were determined at 0 (or 6 h after the preceding dose), 0.5, 1, 2, 3, 4 and 6 h after administration of the antibiotic.

Eight patients received 30 mg of sisomicin per m² in 50 ml of dextrose solution over 30 min, followed immediately by a dose of 30 mg/m² dissolved in 200 ml of dextrose solution given by constant infusion over 6 h. The dose by constant infusion was administered with an infusion pump (IVAC TH500, IVAC Corp., San Diego, Calif.) and repeated every 6 h. Serum levels were determined at 0, 0.5, 1, 2, 3, 4 and 6 h after the first dose was given.

The concentration of sisomicin in blood and urine specimens was determined by an agar well method using *Bacillus subtilis* ATCC 6633 as the test orga-

nism. The organism was incubated in brain heart infusion agar (BBL) for 1 week at 37 C, harvested, washed with normal saline, and heat 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 5×10^7 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 m^2 , the mean peak serum concentration occurred at 1 h and was 2.5 $\mu g/ml$. Mean serum concentrations greater than 1 $\mu g/ml$ were maintained for 4 h after the administration of sisomicin. Mean serum concentrations at 6 and 8 h were 0.5 $\mu g/ml$ and 0.3 $\mu g/ml$, respectively. The serum half-life was 120 min. After intramuscular administration of 40 mg/ m^2 of sisomicin, the mean peak level occurred at 1 h and was 4.0 $\mu g/ml$. The mean peak level of gentamicin after intramuscular administration of 40 mg/ m^2 occurred also at 1 h and was 3.7 $\mu g/ml$. Mean serum concentrations of sisomicin at 4, 6, and 8 h were 1.6 $\mu g/ml$, 1.0 $\mu g/ml$, and 0.7 $\mu g/ml$, respectively. Mean serum concentrations of

gentamicin were 1.6 $\mu g/ml$, 0.8 $\mu g/ml$, and 0.4 $\mu g/ml$ 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 m^2 over 30 min (Fig. 2). The serum level determined at 30 min on the first day of therapy was 5.1 $\mu g/ml$. At 4 and 6 h the mean serum concentrations were 1 $\mu g/ml$ and 0.6 $\mu g/ml$, 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 $\mu g/ml$, 1.2 $\mu g/ml$, and 0.8 $\mu g/ml$, 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 $\mu g/ml$, 1.2 $\mu g/ml$, and 0.8 $\mu g/ml$, 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 m^2 in 50 ml of dextrose solution over 30 min followed immediately by a dose of 30 mg/ m^2 as a constant infusion repeated every 6 h. The mean serum concentration at 30 min was 4 $\mu g/ml$ (Fig. 3). Mean serum levels greater than 1.4 $\mu g/ml$ 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/ m^2) and 61% of the high dose (40 mg/ m^2). The mean urinary excretion of gentamicin was 58% of the administered high dose (40 mg/ m^2).

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/ m^2 ; the upper curves correspond to doses of 40 mg/ m^2 .

FIG. 2. Serum concentration of sisomicin after intravenous administration of 30 mg/ m^2 .

TABLE 1. *Urinary excretion after administration of antibiotics*

Drug	Mean urinary excretion			Mean urinary concn ($\mu\text{g/ml}$)
	Dose (IM) ^a	(mg) ^b	(%)	
Sisomicin	20 mg/m ²	23.4 (13.8–35.0)	49 (48–88)	39.8 (17.0–72.0)
Sisomicin	40 mg/m ²	43.7 (15.5–67.5)	61 (28–87)	159.8 (38.6–480.0)
Gentamicin	40 mg/m ²	42.2 (16.8–76.3)	58 (22–100)	136.9 (25.5–500.0)

^a 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 $\mu\text{g/ml}$ or less of sisomicin (Stewart and Bodey, J. Antibiot., in press). Concentrations of 1.56 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ is obtained at 1 h and that mean serum concentrations >1.0 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$. Serum levels >1.0 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$ 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.

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