IN VITRO ACTIVITY OF KITASAMYCIN AGAINST GRAM-POSITIVE COCCI

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Kitasamycin was tested in vitro against 214 clinical isolates of gram-positive cocci and its activity compared to minocycline, cephalothin, erythromycin, clindamycin and dicloxacillin. All isolates of Streptococcus pyogenes were inhibited by 0.39 μg/ml. At a concentration of 1.56 μg/ml, kitasamycin inhibited all isolates of Diplococcus pneumoniae. 98% of isolates of Staphylococcus aureus sensitive to penicillin G and 99% of isolates of Staphylococcus aureus resistant to penicillin G. Most of the other antibiotics were as active or more active than kitasamycin against gram-positive cocci.

In 1953, HATA, et al.3) reported the isolation of a new antibiotic complex known as kitasamycin (leucomycin). The organism producing this antibiotic complex was obtained from soil samples and named Streptomyces kitasatoensis HATA. In 1967, eight components were separated and their chemical structures determined10). Fig. 1 shows the chemical structure of kitasamycin which corresponds to leucomycin A6. Kitasamycin was found to be active against gram-positive and some gram-negative cocci, rickettsiae and large viruses. The antibiotic has been used in Japan for the treatment of acute infections for several years. It has been administered orally, intravenously and topically. Peak serum concentrations of 5.7 μg/ml have been obtained following oral administration9). Peak serum levels of 11.5 μg/ml have been obtained following intravenous administration. Kitasamycin has low toxicity and is effective against erythromycin-resistant and penicillin-resistant strains of Staphylococcus aureus6,8,7). Although this antibiotic was evaluated many years ago, it was felt of interest to determine its activity against recent isolates of gram-positive cocci. Consequently, the in vitro activity of kitasamycin was determined against 214 gram-positive cocci isolated from clinical specimens.

Materials and Methods

The activity of kitasamycin was determined against 214 clinical isolates of gram-positive cocci...
cocci, representing 3 genera and compared to the activity of 5 other antibiotics using a micro-
diluter4). Isolates of Diplococcus pneumoniae and Streptococcus pyogenes were inoculated into
Tryptose-phosphate broth containing 2% human blood. The isolates were incubated for 18
hours at 37°C. A 50 µl aliquot of a 10⁻³ dilution of this broth was added to wells containing
50 µl volumes of the antibiotics, resulting in a total of 100 µl in each well. The antibiotics
used were clindamycin (The Upjohn Co., Kalamazoo, Michigan), dicloxacillin (Beecham-
Massengill, Inc., Clifton, New Jersey), erythromycin (Abbott Laboratories, North Chicago,
Illinois), minocycline (Lederle Laboratories, Pearl River, New York), cephalothin (Eli Lilly and
Co., Indianapolis, Indiana) and kitasamycin tartrate (Ayerst Laboratories, New York, New
York). They were dissolved in MUELLER-HINTON broth and two-fold serial dilutions were
prepared, ranging in concentration from 25 µg/ml to 0.025 µg/ml. The minimum inhibitory
concentration (MIC) was determined after incubation at 37°C for 18 hours. All studies were
performed in triplicate. Disk sensitivity testing was performed according to the method of
BAUER et al3).

Seventeen isolates of Dipl. pneumoniae, 47 isolates of Str. pyogenes, and 150 isolates of
Staphylococcus aureus were tested. One hundred isolates of S. aureus were resistant to penicillin
G at a concentration of 50 µg/ml. The remaining 50 isolates were inhibited by less than 0.1
µg/ml penicillin G. Most of the organisms were isolated from cancer patients hospitalized at
this institution between August 1971 and January 1973.

Results

Tables 1 and 2 compare the activity of kitasamycin using the microdilutor and disk
sensitivity techniques. Fifty of the 150 isolates of S. aureus and 35 of the 47 isolates of Str.
pyogenes were selected for testing. All of the isolates of S. aureus which had an MIC of no
greater than 1.56 µg/ml produced zones of inhibition of at least 19 mm by the disk technique.
One isolate resistant to 25 µg/ml produced a zone less than 19 mm diameter. All of the isolates
of Str. pyogenes were inhibited by no greater than 1.56 µg/ml and all but one isolate produced
zones of inhibition of at least 19 mm diameter. The one isolate producing a smaller zone of
inhibition had an MIC of 0.20 µg/ml.

All of the isolates of Dipl. pneumoniae were inhibited by 0.39 µg/ml of kitasamycin. All
of the isolates of Str. pyogenes and 98% of the isolates of penicillin G sensitive S. aureus
were inhibited by 1.56 µg/ml of kitasamycin. The remaining 2% of penicillin G sensitive
S. aureus were resistant to 25 µg/ml. Among the 100 isolates of penicillin G resistant S. aureus,
92% had an MIC of no greater than 1.56 µg/ml and an additional 7% had an MIC of no greater

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Fig. 2. *In vitro* activity of six antibiotics against *Diplococcus pneumoniae*.

Fig. 3. *In vitro* activity of six antibiotics against *Streptococcus pyogenes*.

Fig. 4. *In vitro* activity of six antibiotics against penicillin G sensitive *Staphylococcus aureus*.

Fig. 5. *In vitro* activity of six antibiotics against penicillin G resistant *Staphylococcus aureus*. 

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**Fig. 2**: A graph showing the in vitro activity of six antibiotics against *Diplococcus pneumoniae*. The x-axis represents the minimum inhibitory concentration (μg/ml) ranging from 0.025 to 25, and the y-axis shows the cumulative percent of isolates inhibited from 0% to 100%. The antibiotics tested are Clindamycin, Minocycline, Dicloxacillin, Cephalothin, Erythromycin, and Kitasamycin.

**Fig. 3**: A graph showing the in vitro activity of six antibiotics against *Streptococcus pyogenes*. The x-axis represents the minimum inhibitory concentration (μg/ml) ranging from 0.025 to 25, and the y-axis shows the cumulative percent of isolates inhibited from 0% to 100%. The antibiotics tested are Clindamycin, Minocycline, Dicloxacillin, Cephalothin, Erythromycin, and Kitasamycin.

**Fig. 4**: A graph showing the in vitro activity of six antibiotics against penicillin G sensitive *Staphylococcus aureus*. The x-axis represents the minimum inhibitory concentration (μg/ml) ranging from 0.025 to 25, and the y-axis shows the cumulative percent of isolates inhibited from 0% to 100%. The antibiotics tested are Clindamycin, Minocycline, Dicloxacillin, Cephalothin, Erythromycin, and Kitasamycin.

**Fig. 5**: A graph showing the in vitro activity of six antibiotics against penicillin G resistant *Staphylococcus aureus*. The x-axis represents the minimum inhibitory concentration (μg/ml) ranging from 0.025 to 25, and the y-axis shows the cumulative percent of isolates inhibited from 0% to 100%. The antibiotics tested are Clindamycin, Minocycline, Dicloxacillin, Cephalothin, Erythromycin, and Kitasamycin.
than 6.25 \( \mu g/ml \) of kitasamycin. The remaining 1% were resistant to 25 \( \mu g/ml \).

Erythromycin was the most active of the 6 antibiotics against *Dipl. pneumoniae* (Fig. 2). All of the isolates were inhibited by 0.05 \( \mu g/ml \). Although the other 5 antibiotics were comparable in activity, dicloxacillin was the least active. All of the 17 isolates of *Dipl. pneumoniae* were inhibited by 1.56 \( \mu g/ml \) of all 5 antibiotics.

Erythromycin was the most active antibiotic against *Str. pyogenes* (Fig. 3). All of the isolates were inhibited by 0.2 \( \mu g/ml \). Cephalothin and kitasamycin were the least active antibiotics against *Str. pyogenes*. At a concentration of 0.1 \( \mu g/ml \), erythromycin inhibited 95% of isolates, clindamycin inhibited 94%, dicloxacillin inhibited 92%, cephalexin inhibited 61% and kitasamycin inhibited 17%.

Cephalothin was the most active antibiotic against the 50 isolates of *S. aureus* sensitive to penicillin G (Fig. 4). All of the isolates were inhibited by 0.2 \( \mu g/ml \). Dicloxacillin and minocycline also inhibited all of the isolates, at a concentration of 0.78 \( \mu g/ml \). One isolate was resistant to 25 \( \mu g/ml \) of the other 3 antibiotics. Kitasamycin was substantially less active than the other antibiotics.

Clindamycin was the most active antibiotic against the 100 isolates of *S. aureus* resistant to penicillin G (Fig. 5). All of the isolates were inhibited by 0.1 \( \mu g/ml \). Minocycline and dicloxacillin also inhibited all of the isolates at higher concentrations. One isolate was resistant to kitasamycin and cephalexin and 13 isolates were resistant to erythromycin. Kitasamycin was the least active antibiotic against most of the isolates.

**Discussion**

Our results are comparable to those obtained by other investigators who tested kitasamycin against isolates of *Dipl. pneumoniae* and *Str. pyogenes*. In our study there was no difference in the activity of kitasamycin against staphylococci, regardless of their sensitivity to penicillin G. Only 1% of isolates of *S. aureus* which were resistant to penicillin G were resistant to kitasamycin. All of these isolates were sensitive to clindamycin, minocycline and dicloxacillin, but 13% were resistant to erythromycin. Kitasamycin has activity against the vast majority of clinical isolates of *S. aureus*, *Str. pyogenes* and *Dipl. pneumoniae*, but *in vitro* studies do not suggest that it has any advantages over currently available antibiotics, although it would be expected to be effective in clinical situations in which erythromycin is indicated.

**Bibliography**

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