UK-18892, a New Aminoglycoside: An In Vitro Study

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UK-18892 is a new aminoglycoside antibiotic, a derivative of kanamycin A structurally related to amikacin. It was found to be active against a wide range of pathogenic bacteria, including many gentamicin-resistant strains. The spectrum and degree of activity of UK-18892 were similar to those of amikacin, and differences were relatively minor. UK-18892 was about twice as active as amikacin against gentamicin-susceptible strains of Pseudomonas aeruginosa. Both amikacin and UK-18892 were equally active against gentamicin-resistant strains of P. aeruginosa. There were no appreciable differences in the activity of UK-18892 and amikacin against Enterobacteriaceae and Staphylococcus aureus. Cross-resistance between these two antimicrobials was also apparent.

The emergence of gentamicin resistance among a wide range of pathogenic bacteria has stimulated the search for drugs which show activity against such strains. Amikacin, 1-N-[(S)-4-amino-2-hydroxybutyryl] kanamycin A, is active against many such resistant strains (5–7). A number of derivatives of kanamycin A have been shown to possess poor antibacterial properties (2), but UK-18892, 1-N-[(S)-4-amino-2-hydroxybutyryl] kanamycin A (Fig. 1), has promising properties worthy of further investigation (4). In this study, the in vitro activity of UK-18892 was compared with that of gentamicin and amikacin against common clinical isolates.

MATERIALS AND METHODS

Known-potency antibiotic material was obtained from the following sources: UK-18892 from Pfizer Re-

Fig. 1. Structure of UK-18892 and amikacin.

The activity of the three compounds was compared against recent clinical isolates of *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* spp., indole-positive *Proteus* spp., *Proteus mirabilis*, *Enterobacter* spp., *Staphylococcus aureus*, and *Providencia stuartii*. Aminoglycoside-resistant strains of certain species were also tested.

An agar plate dilution technique was used, and Oxoid Isosensitest agar (pH 7.2) was employed throughout. The organisms were grown overnight in nutrient broth and then diluted to approximately $10^6$ colony-forming units per ml. A replicating device transferred 1 $\mu$l to the agar surface. The plates were incubated at 37°C overnight, and the minimum inhibitory concentration (MIC) was defined as that concentration of drug which gave a 99% reduction of the initial count, that is, less than 10 colonies remaining.

The protein binding of gentamicin, amikacin, and UK-18892 was tested in triplicate by an ultrafiltration technique with an Amicon Centriflo cone of 50,000-molecular-weight exclusion. The initial concentration of each drug was 50 $\mu$g/ml and was prepared in human serum. The ultrafiltrate was assayed by a large plate diffusion technique, with samples in triplicate applied randomly. The standards were prepared in phosphate-buffered saline made to the same pH as the ultrafiltrate. The 95% confidence limits of the assay were better than $\pm14\%$.

The ability of UK-18892 and amikacin to be acetylated at the 6'-amino position was studied as in the method described by Benveniste and Davies (1). An acetylating enzyme was prepared from *E. coli* R5/W677. Standards of each compound in human serum at 20, 10, 5, 2.5, and 1.25 $\mu$g/ml were used.

**RESULTS**

In Fig. 2 the activity of the three drugs against 21 unselected strains of *P. aeruginosa* is shown. UK-18892 (mode MIC, 2 $\mu$g/ml) was approximately twice as active as amikacin (mode MIC, 4 $\mu$g/ml) and half as active as gentamicin (mode MIC, 1 $\mu$g/ml). Against those strains of *P. aeruginosa* with gentamicin MICs of $\geq8$ $\mu$g/ml (Fig. 3), there was no appreciable difference between UK-18892 and amikacin, both drugs

![Fig. 2. Activity of UK-18892, amikacin, and gentamicin against 21 strains of *P. aeruginosa*.](http://aac.asm.org/Downloaded from http://aac.asm.org/)
Pseudomonas aeruginosa 15 strains resistant to gentamicin (>8 μg/ml)

Fig. 3. Activity of UK-18892, amikacin, and gentamicin against 15 strains of P. aeruginosa resistant to 8 μg or more of gentamicin per ml.
FIG. 4. Activity of UK-18892, amikacin, and gentamicin against 50 strains of E. coli.
inhibiting 53% of the strains at 16 μg/ml. Two strains of P. aeruginosa which were resistant to amikacin (MIC > 128 μg/ml) were equally resistant to UK-18892.

Amikacin and UK-18892 had a similar degree of activity against E. coli (Fig. 4), both being about fourfold less active than gentamicin. P. mirabilis (Fig. 5) was equally susceptible to UK-18892 and amikacin, which were again fourfold less active than gentamicin. Similarly, against indole-positive Proteus spp. and Klebsiella spp., amikacin and UK-18892 were equally active (Table 1) against gentamicin. Two Klebsiella strains with gentamicin MICs of 8 μg/ml were susceptible to 1 μg of amikacin or UK-18892 per ml. Ten strains of Enterobacter spp. were equally susceptible to UK-18892 and amikacin. Both amikacin and UK-18892 were very active against the 16 strains of P. stuartii (Fig. 6) tested; they were 16-fold more active than gentamicin, to which all the strains were resistant (MIC > 4 μg/ml).

Gentamicin-susceptible strains of S. aureus were susceptible to both the other drugs. Amikacin was slightly more active than the other agents tested.

Two strains of S. aureus which were gentamicin resistant (MIC > 128 μg/ml) were also resistant to UK-18892 (MICs > 128 μg/ml), but the MICs of amikacin were 32 and 16 μg/ml.

Both amikacin and UK-18892 were acetylated by the enzyme preparation of R5/W677. In Table 2, the counts per minute obtained from each enzyme preparation are shown.

The protein binding of the three drugs was as follows: gentamicin, 14%; UK-18892, 16.1%; and amikacin, 21.8% bound.

**DISCUSSION**

Amikacin is active against many bacteria which are resistant to gentamicin by virtue of the fact that it is enzymatically inactivated at fewer sites than gentamicin (3). However, amikacin can be acetylated at the 6’-amino group. It would appear that UK-18892 has a spectrum of activity similar to that of amikacin and that an enzyme preparation will acetylate both drugs at the 6’-amino group. It is unlikely that the difference in counts obtained with the two drugs is significant.

**Table 2. Acetyltransferase enzyme activity against UK-18892 and amikacin**

<table>
<thead>
<tr>
<th>Antibiotic concn (μg/ml)</th>
<th>UK-18892 (cpm)</th>
<th>Amikacin (cpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>27,100</td>
<td>33,200</td>
</tr>
<tr>
<td>10</td>
<td>14,400</td>
<td>16,800</td>
</tr>
<tr>
<td>5</td>
<td>8,000</td>
<td>8,500</td>
</tr>
<tr>
<td>2.5</td>
<td>4,100</td>
<td>4,500</td>
</tr>
<tr>
<td>1.25</td>
<td>2,000</td>
<td>2,300</td>
</tr>
</tbody>
</table>

**Table 1. Mode MICs of UK-18892, amikacin and gentamicin against pathogenic organisms**

<table>
<thead>
<tr>
<th>Strain</th>
<th>No. of strains</th>
<th>Mode MIC (μg/ml) of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK-18892</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>10</td>
<td>2 (1-4)*</td>
</tr>
<tr>
<td>Indole-positive Proteus</td>
<td>10</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>10</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>10</td>
<td>1 (0.5-4)</td>
</tr>
</tbody>
</table>

* Figures in parentheses indicate the range of MICs.
UK-18892 appears to be about twice as active as amikacin against *P. aeruginosa*, but less difference was noted among those strains resistant to gentamicin. Amikacin and UK-18892 were more active than gentamicin against some of the gentamicin-resistant strains. It seems probable that the majority of these gentamicin-resistant strains are not resistant by virtue of the fact that they possess inactivating enzymes (which would be ineffective against amikacin and UK-18892) but rather because they possess a permeability barrier to all three aminoglycosides. There was little difference between amikacin and UK-18892 in the susceptibility of the other gram-negative organisms tested. Amikacin was no more active than UK-18892 against *S. aureus*.

Cross-resistance is apparent between amikacin and UK-18892 in the strains of *P. aeruginosa* and *S. aureus* tested.

UK-18892, therefore, shares many properties with amikacin. The pharmacology of the two antimicrobial agents would appear to be similar (M. Kendall and R. Wise, manuscript in preparation).

Acknowledgment

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LITERATURE CITED