In vitro drug susceptibility of *Mycobacterium tuberculosis* for amikacin and kanamycin

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1. Background

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, affects over 12M people and causes about 1.3 million deaths each year. The aminoglycosides amikacin and kanamycin are the cornerstone in the treatment of multidrug resistant tuberculosis (MDR-TB).

In daily practice, the drug susceptibility is usually tested using the following breakpoints: 1 mg/L for amikacin and 2.5 - 4 mg/L for kanamycin. This indicates that the susceptibility of *M. tuberculosis* might be higher for amikacin than for kanamycin.

However, the maximum blood concentration \((C_{\text{max}})\) divided by the mean inhibitory concentration \((C_{\text{max}}/\text{MIC})\) is the efficacy determining parameter in the aminoglycoside treatment. Therefore, we tested the *in vitro* susceptibility of amikacin and kanamycin against clinical non-MDR and MDR isolates of *M. tuberculosis*.

2. Materials and methods

The absolute concentration method was used to determine the minimum inhibitory concentration (MIC).

**Experiment 1**

Amikacin and kanamycin were separately added to 25-well plates (concentration range 0.25, 0.50, 1.00, 5.00 and 10.00 mg/L). On each 25-well plate, two control wells were inoculated with a diluted suspension of the clinical *M. tuberculosis* isolate. In total, we tested 24 MDR isolates, 7 mono-resistant isolates resistant to either rifampin or isoniazid, and 46 fully susceptible drugs.

**Experiment 2**

We repeated experiment 1 for kanamycin with 24 strains in a concentration range of 1.25 – 2.50 – 5.00 mg/L.

3. Results

**Experiment 1**

75 strains were viable and were tested for susceptibility to amikacin and kanamycin. The MIC distribution of amikacin and kanamycin is shown in figure 1. The MICs differed significantly differed between amikacin and kanamycin \((Z = -4.417 , p = 0.000, \text{Wilcoxon Signed Rank Test})\).

**Experiment 2**

To provide a more precise estimation of the difference between amikacin and kanamycin, a subset of 22 strains with a known susceptibility for amikacin of 1 mg/L was tested. The majority of the strains were susceptible to 2.5 mg/L kanamycin \((n = 16, 66.6\%)\), as shown in figure 2. One strain \((4.2\%)\) was susceptible to 1.25 mg/L and five strains \((20.8\%)\) were susceptible to 5 mg/L kanamycin.

4. Discussion and conclusion

The results of our study indicate that the MIC of amikacin is generally lower than that of kanamycin, using the absolute concentration method. As the efficacy of aminoglycosides is correlated with the \(C_{\text{max}}/\text{MIC}\)-ratio, this finding indicates the need for a further pharmacokinetic and pharmacodynamic evaluation.

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**Figure 1.** MIC distribution of all strains during experiment 1

**Figure 2.** MIC distribution of the subset of strains (experiment 2)

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