Does the Drug Exposure of Aminoglycosides in the Treatment of Tuberculosis relate to Efficacy and Toxicity?
Does the Drug Exposure of Aminoglycosides in the Treatment of Tuberculosis relate to Efficacy and Toxicity?

ABSTRACT

Tuberculosis is an ancient disease responsible for the death of 2 million patients each year. Multidrug resistant TB (MDR-TB), resistant to at least isoniazid and rifampin, is an emerging threat and requires intensive treatment. The aminoglycosides amikacin and kanamycin are the cornerstone of MDR-TB treatment, however, treatment comes with hearing loss and nephrotoxicity.

We performed a systematic review to assess the factors influencing efficacy and toxicity. In total, 2,105 studies were screened and 102 studies were included in this analysis. The efficacy in vivo of amikacin is overall higher than kanamycin or streptomycin. Several studies found that the administration of aminoglycosides correlates with poor outcome in humans. The reported toxicity of aminoglycosides varied strongly: studies with regular documented monitoring reported high rates of toxicity (11 – 62%), while studies without regular monitoring reported low toxicity rates (1 – 39%).

The relation between drug exposure and toxicity or efficacy is, unfortunately, difficult to prove. We have observed from the studied literature that amikacin might be the most effective aminoglycoside. In addition, we found that regular monitoring of hearing loss and nephrotoxicity results in the highest reported toxicity rates; urging the need for regular monitoring to control and prevent further toxicity. No studies were performed to assess the relation between pharmacokinetic parameters and the efficacy of the treatment. The relationship between exposure and toxicity is essential to perform therapeutic drug monitoring, which in turn might prevent aminoglycoside related toxicity.

BACKGROUND

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* and is responsible for approximately 2 million deaths each year. Resistance to several antimicrobial drugs is emerging and multidrug resistant TB (MDR-TB) is becoming a major health issue worldwide. MDR is caused by *M. tuberculosis* resistant to at least isoniazid (INH) and rifampicin (RIF). MDR-TB treatment requires the use of second-line drugs, on top of drugs for which the isolate is still susceptible. Fluoroquinolones and aminoglycosides are the most effective second-line drugs, and are, therefore, considered the cornerstone of MDR-TB treatment. The aminoglycosides amikacin (AMK), kanamycin (KAN) and streptomycin (STR) are frequently used in the treatment of MDR-TB. Following WHO recommendations, aminoglycosides should be used during the intensive phase for a minimum of six months in a dosage of 15 mg/kg. Unfortunately, the treatment with aminoglycosides has two major side effects: ototoxicity and nephrotoxicity. Ototoxicity is, in contrast to nephrotoxicity, irreversible and audiometric testing is often not feasible in low-income countries. The reported prevalence of ototoxicity is 21-37%. Observed in only 15-17% of all cases, nephrotoxicity is less common but still clinically relevant.

The three factors: 1) the role of the daily-administered dose, 2) the total treatment duration and 3) the peak and trough serum concentrations are all conceivably important to predict the efficacy on one hand, and the toxicity on the other hand. The relationships between the three parameters mentioned, and the outcome are however unclear. With TDM, blood levels are determined and the dose can be adjusted to reach concentrations within the therapeutic window. TDM has been shown to be useful in other infectious diseases to reduce the incidence of side effects of other aminoglycosides, while optimizing efficacy. TDM has been suggested to be useful in the pharmacotherapy of TB, yet it has not been implemented in daily practice, and neither in treatment guidelines.
Chapter 2

The effectiveness of a single drug in a multi drug treatment regimen for TB is difficult to determine but one could advocate that administration of each of the drugs should result in sufficient drug exposure to prevent the emergence of resistance. To be able to guide dosing of aminoglycosides in MDR-TB treatment, data on in vitro, in vivo and clinical studies should be integrated to assess the influence of different factors on the efficacy, toxicity and development of drug resistance.

Therefore the objective of this systematic review is to evaluate the available evidence on efficacy and toxicity of MDR-TB treatment with aminoglycosides. When possible, recommendations on the use of aminoglycosides in the therapy of MDR-TB will be provided.

METHODS

Search strategy and selection criteria

PubMed and Embase were searched for relevant articles. References of the included articles were screened and included if relevant. Only articles presenting original data concerning at least ten adults with culture-confirmed MDR-TB, using aminoglycosides, were included. Meta-analyses, (systematic) reviews, letters, meeting and poster abstracts and correspondence were excluded.

In vivo

Preclinical studies including only in vivo studies were searched in PubMed using the MeSH terms ‘aminoglycosides’ and ‘tuberculosis’ and ‘mice’. Embase was searched using ‘aminoglycosides’/exp AND ‘tuberculosis’/exp with the ‘nonhuman’ search filter. In vivo studies were included when aminoglycosides were tested and the number of colony-forming units on the spleen and/or lungs were quantified and reported. Studies reporting spleen weights were also included.

Treatment outcome

Studies were searched in PubMed using the MeSH terms ‘treatment outcome’ and ‘Tuberculosis, Multidrug-resistant’. In Embase, the search terms were compiled using Emtree resulting in the search term ”‘treatment outcome’/exp AND ‘multidrug resistant tuberculosis’/exp”.

To determine the efficacy of aminoglycosides in MDR-TB treatment, only studies assessing the additional value of aminoglycosides in the therapy of MDR-TB with appropriate statistical tests were included. Studies reporting side effects were also included. In vivo studies resulting from this search were included according to the in vivo inclusion criteria.

Toxicity

The occurrence of toxicity was evaluated using the following PubMed search: ‘(“Antitubercular Agents/adverse effects”[Mesh] OR “Antitubercular Agents/toxicity”[Mesh]) AND “Tuberculosis, Multidrug-Resistant”[Mesh]’. For Embase, the search term “tuberculostatic agent’/exp AND ‘toxicity’/exp AND ‘multidrug resistant tuberculosis’/exp’ was used. Again, only studies addressing MDR-TB patients were included.
Does the Drug Exposure of Aminoglycosides in the Treatment of Tuberculosis relate to Efficacy and Toxicity?

**Pharmacokinetics**

Pharmacokinetics were evaluated by searching PubMed for “Aminoglycosides/pharmacokinetics”[Mesh] AND “Tuberculosis”[Mesh]. Embase was searched using ‘aminoglycoside’/exp AND ‘pharmacokinetics’/exp AND ‘tuberculosis’/exp. All humane studies assessing this subject with more than 5 subjects were included.

**Early bactericidal activity**

To assess the early bactericidal activity, “early bactericidal activity” AND “tuberculosis”[Mesh] was searched in PubMed. For Embase, “early bactericidal activity” AND “tuberculosis”/exp was searched. All humane studies describing the early bactericidal activity of aminoglycosides in the treatment of tuberculosis were included.

The above-mentioned search was performed repeatedly between March 1, 2013 until the December 8, 2013. The PubMed search was repeated until August 2015 to include any additional studies.

**Data extraction**

We developed two Excel sheets (Microsoft, Redmond, WA, USA) to enter the in vivo data and the data from humane studies on toxicity and efficacy. From in vivo studies, year of publication, used strain and treatment regimen and treatment outcome, CFU or spleen weight was collected. From humane studies, the geographical area, number of patients, number of patients receiving aminoglycosides or injectables, mean age, mean BMI, HIV status, treatment duration with aminoglycosides, drug regimen, days in hospital, time to sputum/culture conversion, treatment outcome, method of ototoxicity determination and ototoxicity and nephrotoxicity rates were noted. When treatment data was not available or insufficiently described, treatment data were extracted from the method-section of the article, if available.

Data were analyzed using SPSS 20 (IBM Corp., NY, USA). Meta-analysis is done using OpenMetaAnalyst released at 11.11.13 (Brown University, RI, USA). The Binary Random-Effects model with the DerSimonian-Liard method was used to analyze the available data.

**Summary measures**

Concerning preclinical studies, the difference in efficacy between the tested aminoglycosides was reported. In the case of humane studies, ototoxicity and nephrotoxicity rates were assessed in this systematic review. Correlations reported by the included studies between treatment factors and side effects or treatment outcome were also reported in this systematic review.

**RESULTS**

The search terms as mentioned earlier resulted in a total of 2,105 studies. After a screening for relevance, based on the title of each publication and, when available, the abstract, 619 full-text articles were considered eligible for this systematic review. All studies were evaluated using the in- and exclusion criteria. This resulted in 102 studies eligible for inclusion (identical papers that were included in two separate searches were counted twice).
Furthermore, all included studies were screened for references that could be eligible for inclusion. The search strategy is displayed in Table 1.

Table 1. Search strategy

<table>
<thead>
<tr>
<th></th>
<th>In vivo</th>
<th>Treatment outcome</th>
<th>Toxicity</th>
<th>Pharmacokinetics</th>
<th>Early bactericidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hits</td>
<td>207</td>
<td>1266</td>
<td>443</td>
<td>11</td>
<td>148</td>
</tr>
<tr>
<td>Screening</td>
<td>42</td>
<td>500</td>
<td>120</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Full text</td>
<td>30</td>
<td>453</td>
<td>103</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Second screening</td>
<td>15</td>
<td>58</td>
<td>35</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Duplicate removal</td>
<td>15</td>
<td>50</td>
<td>29</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>References</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Included</td>
<td>20</td>
<td>58</td>
<td>29</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

In vivo — Comparison of individual aminoglycosides

Amikacin (200 mg/kg) seems to be the most effective bactericidal agent with identical dosages in mice, while kanamycin (200 mg/kg) did not show any significant bactericidal activity. Iseeomycin (200 mg/kg) shows a bactericidal activity comparable to streptomycin, yet less effective than amikacin. The effectiveness of streptomycin was confirmed by Dutta et al., which showed a significant effect of streptomycin (200 mg/kg) in comparison with no treatment.

The in vivo superiority of amikacin was supported in older studies. In a study of Sanders et al., amikacin (5, 10 and 15 mg/kg/day) shows a higher activity with all dosages tested in comparison to streptomycin (10 mg/kg/day) and kanamycin (10 mg/kg/day). The effectiveness of streptomycin and kanamycin was less distinguishable, with kanamycin being more active in the first 60 days and streptomycin in the last 30 days.

Paromomycin (100 and 200 mg/kg) showed a significant effect in mice against normal sensitive and multidrug resistant tuberculosis. The activity of paromomycin is lower than isoniazid against fully susceptible strains. In multidrug resistant bacilli the effect was significant when compared with the untreated control group.

Apramycin shows in vivo efficacy comparable to amikacin in a *Mycobacterium tuberculosis* murine aerosol infection model. Apramycin reduced the CFU with a 2.4-log reduction in CFU after 9 days of treatment, which differed significantly from the control group. The difference between amikacin and apramycin was not significant.

The in vivo effect of sisomycin and gentamicin (25 mg/kg) was significant lower than streptomycin (25 mg/kg). Sisomycin seemed to be more effective the first 30 days than gentamicin and streptomycin, yet after 90 days the efficacy of gentamicin and sisomycin is comparable and lower than streptomycin. Another study supported the finding that streptomycin had an enhanced bactericidal activity compared to gentamicin (both 25 mg/kg).

Liposomal amikacin (40-160 mg/kg thrice weekly) was 2.7 – 2.9 times more active than amikacin and 3.7 – 5.6 times more active than streptomycin (both 80-160 mg/kg five times a week). Aerolized gentamicin (5 mg/kg) significantly reduced the bacterial load in the lungs of mice infected with *M. tuberculosis*. However, the effect of inhaled gentamicin was lower than the effect of oral isoniazid (15 mg/kg).

In another study, the effect of streptomycin (1-16 mg/kg) was studied in various intermittent regimens. The effect of streptomycin did not differ, regardless of the interval between doses (1, 2, 4 or 8 days). This indicates that streptomycin had a post-bactericidal effect.

Comparison of aminoglycoside containing regimens

In a study from 2000, several regimens were compared in the treatment of tuberculosis. Two of the regimens contained isoniazid, rifampin and pyrazinamide daily for 2 weeks, followed
by 7.5 months the same cocktail once weekly. One regimen additionally contained streptomycin (200 mg/kg), which improved culture conversion leading to the conclusion that the addition of streptomycin enhances overall bactericidal activity. Furthermore, the authors claimed that streptomycin prevented the selection of resistant mutants. The addition of streptomycin (200 mg/kg) to isoniazid in an intermittent regimen during the continuation phase resulted in a reduction of the amount of CFUs found in the lungs and spleen. Furthermore, this reduction was also observed when adding streptomycin to isoniazid in a daily regimen. This finding was in contrast with an older study, indicating no enhancing effect when adding streptomycin to isoniazid both intermittent in the continuation phase after six months of intensive therapy. However, when the intermittent treatment was started immediately after infection, a significant reduction in CFUs was observed with streptomycin compared to isoniazid alone.

The efficacy of streptomycin and kanamycin (200 mg/kg) was studied by Lalande et al. Regimens containing sparfloxacin, pyrazinamide and streptomycin or kanamycin was evaluated. It appeared that the streptomycin containing regimen was significantly more efficacious. Streptomycin (200 mg/kg) on top of a rifampin and isoniazid containing regimen, however, showed no beneficial effect in mice infected with the H37Rv strain. The efficacy of oral nanoparticle-encapsulated streptomycin was compared with conventional streptomycin (200 mg/kg) and resulted in a comparable reduction in the CFU count in both lungs and spleen. The authors concluded therefore that nanoencapsulation might be a promising technique in developing oral aminoglycosides.

A regimen containing only ethionamide and streptomycin was highly efficient if given daily. Results were however mediocre when administered intermittently. Administration of isoniazid-streptomycin during 9-10 months did not result in a lasting sterilization. When given intermittently, results varied depending on the frequency of administration: twice weekly was more effective than once weekly.

### Efficacy

In a recent study, a hazard multivariable model is proposed to identify different hazards in MDR-TB patients in Latvia. Injectable drugs used were kanamycin and capreomycin. The statistical analysis was performed on 994 patients. A number of drugs reduced the chance of poor outcome, namely kanamycin, ofloxacin, prothionamide and cycloserine, all when administered for a minimum of three months. The hazard ratio of poor outcome with kanamycin was 0.60 (0.43 - 0.83, p = 0.002), indicating a significant reduction in poor outcome.
The efficacy of amikacin was debated by Ferrara et al. in a study assessing 127 MDR-TB patients. The statistical analysis done in this study indicated that the use of amikacin reduced the likelihood of a successful outcome. However, as indicated by the authors, this finding might be confounded since amikacin was only administered to severe cases (n = 28, 30%).

The same inverse association was found in another study with 583 patients, of which 385 (66%) used amikacin or kanamycin. The administration of both aminoglycosides was significantly associated with poor outcome. Yet, the authors indicated that only 7% of all patients were taking their medications without missing a dose. A study in 2014 showed that longer amikacin treatment duration (aOR 1.14, 95% CI 1.06 – 1.21) and higher dosages (aOR 1.90, 95% CI 1.79 – 3.00) correlated with a good outcome. Another study in the USA showed using multivariate analysis that the use of an injectable drug was significantly associated with a lower odd of dying of TB (odds ratio 0.017, 95% CI 0.002 – 0.176). However, after correcting for the use of a fluoroquinolones and a bacteriostatic drug, the effect of streptomycin, amikacin, kanamycin and capreomycin seems to diminish. This is further supported by another study, indicating that receiving amikacin or kanamycin correlates with poor outcome.

The recurrence of MDR-TB and XDR-TB and the factors influencing recurrence were also studied. The authors observed that the absence of an injectable drug had a negative impact on TB recurrence with a hazard ratio of 0.44 (0.23 - 0.84, p = 0.013) in comparison to no injectable drug. It should be noted that the effect of specific injectable drugs was not reported, so this finding might be influenced by the use of the peptide antibiotic capreomycin as well.

The use of streptomycin given for a minimum of 3 months did not reduce the time to initial sputum conversion (p = 0.124) compared to the patients not receiving streptomycin. This non-significance can be explained by the fact that only 6 patients received streptomycin. The use of kanamycin and amikacin did not have a significant effect (P > 0.20) on the time to initial sputum conversion.

Toxicity

The toxicity of TB treatment with aminoglycosides was evaluated in 49 studies. Unfortunately, not all studies published exact numbers of patients treated with aminoglycosides or injectables. All studies, except those, are displayed in figure 1.

The ototoxicity rates reported varied strongly. In the studies without documented monitoring, ototoxicity occurred in 1-38.9% of all cases. With irregular monitoring, this increased to 3-67%. Regular monitoring resulted in the overall highest ototoxicity rates: 11-62%. A retrospective study established a relationship between hearing loss, prolonged amikacin treatment duration (aOR 1.13 (95% CI: 1.06 – 1.21)) and higher amikacin dosages (aOR 1.90 (95% CI: 1.12 – 2.99)).

One study found a significant association between creatinine increase and ototoxicity and the use of amikacin and older age. Another study reported no statistically significant correlations between the occurrence of ototoxicity and several other factors. All other studies did not describe any statistical analysis on the occurrence of ototoxicity in relation to other therapeutic factors.

Out of all studies included, nine studies reported both aminoglycoside use and nephrotoxicity. All studies are shown in figure 2. Rates reported varied from 0-30. Overall, rates varied from 0.6-21.0%, neglecting possible confounding by the percentage of aminoglycoside users. One retrospective study showed significant correlations between the occurrence of nephrotoxicity and the duration of treatment with aminoglycosides and the cumulative dose.
Does the Drug Exposure of Aminoglycosides in the Treatment of Tuberculosis relate to Efficacy and Toxicity?

Figure 1. Ototoxicity

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Ev/Tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yew WW</td>
<td>0.036 (0.000, 0.081)</td>
<td>2/58</td>
</tr>
<tr>
<td>Tahaqqui K</td>
<td>0.012 (0.000, 0.030)</td>
<td>2/158</td>
</tr>
<tr>
<td>Chan ED</td>
<td>0.007 (0.000, 0.063)</td>
<td>2/75</td>
</tr>
<tr>
<td>Ullsd ML</td>
<td>0.608 (0.060, 0.018)</td>
<td>4/445</td>
</tr>
<tr>
<td>Keshavjee S</td>
<td>0.000 (0.000, 0.089)</td>
<td>1/33</td>
</tr>
<tr>
<td>Van der Walt M.</td>
<td>0.001 (0.000, 0.030)</td>
<td>1/190</td>
</tr>
<tr>
<td>Jiang R-H</td>
<td>0.002 (0.025, 0.095)</td>
<td>6/75</td>
</tr>
<tr>
<td>Mpegeo S.G.</td>
<td>0.066 (0.003, 0.128)</td>
<td>6/61</td>
</tr>
<tr>
<td>Jacobs T.O.</td>
<td>0.029 (0.011, 0.048)</td>
<td>6/1040</td>
</tr>
<tr>
<td>Palackis E.</td>
<td>0.154 (0.056, 0.252)</td>
<td>8/52</td>
</tr>
<tr>
<td>Gobie M</td>
<td>0.045 (0.016, 0.076)</td>
<td>9/398</td>
</tr>
<tr>
<td>Torun T</td>
<td>0.008 (0.000, 0.030)</td>
<td>2/258</td>
</tr>
<tr>
<td>Miller A.C.</td>
<td>0.000 (0.000, 0.049)</td>
<td>1/395</td>
</tr>
<tr>
<td>Shin S.S.</td>
<td>0.000 (0.000, 0.049)</td>
<td>3/47</td>
</tr>
<tr>
<td>Furr J.J.</td>
<td>0.002 (0.000, 0.048)</td>
<td>3/137</td>
</tr>
<tr>
<td>Bagthe P.</td>
<td>0.068 (0.016, 0.128)</td>
<td>7/79</td>
</tr>
<tr>
<td>de Jager P.</td>
<td>0.000 (0.000, 0.000)</td>
<td>18/61</td>
</tr>
</tbody>
</table>

Overall (I²=90%, P=0.006) 0.041 (0.028, 0.055) 187/4947

Figure 2. Nephrotoxicity

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Ev/Tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yew WW</td>
<td>0.155 (0.042, 0.260)</td>
<td>9/58</td>
</tr>
<tr>
<td>Tahaqqui K</td>
<td>0.315 (0.238, 0.391)</td>
<td>45/143</td>
</tr>
<tr>
<td>Yew WW (G)</td>
<td>0.160 (0.077, 0.263)</td>
<td>12/75</td>
</tr>
<tr>
<td>Chan ED</td>
<td>0.128 (0.091, 0.166)</td>
<td>39/304</td>
</tr>
<tr>
<td>Ullsd ML</td>
<td>0.061 (0.021, 0.142)</td>
<td>2/35</td>
</tr>
<tr>
<td>Kim H.R</td>
<td>0.045 (0.015, 0.076)</td>
<td>8/177</td>
</tr>
<tr>
<td>Prasad R</td>
<td>0.087 (0.006, 0.168)</td>
<td>4/46</td>
</tr>
<tr>
<td>Keshavjee S</td>
<td>0.318 (0.260, 0.377)</td>
<td>78/245</td>
</tr>
<tr>
<td>Singla R</td>
<td>0.040 (0.006, 0.074)</td>
<td>9/126</td>
</tr>
<tr>
<td>Malla P</td>
<td>0.069 (0.031, 0.106)</td>
<td>12/175</td>
</tr>
<tr>
<td>Van Deur A</td>
<td>0.044 (0.025, 0.064)</td>
<td>19/427</td>
</tr>
<tr>
<td>Van der Walt M.</td>
<td>0.030 (0.021, 0.049)</td>
<td>42/1390</td>
</tr>
<tr>
<td>Jiang R-H</td>
<td>0.690 (0.352, 0.627)</td>
<td>26/51</td>
</tr>
<tr>
<td>Jacobs T.Q.</td>
<td>0.271 (0.225, 0.318)</td>
<td>95/350</td>
</tr>
<tr>
<td>Palackis E.</td>
<td>0.211 (0.081, 0.340)</td>
<td>8/38</td>
</tr>
<tr>
<td>Satered W</td>
<td>0.032 (0.005, 0.061)</td>
<td>5/153</td>
</tr>
<tr>
<td>Rao N.A.</td>
<td>0.011 (0.003, 0.029)</td>
<td>7/623</td>
</tr>
<tr>
<td>Singla R (G)</td>
<td>0.059 (0.026, 0.131)</td>
<td>1/17</td>
</tr>
<tr>
<td>Gobie M</td>
<td>0.317 (0.086, 0.256)</td>
<td>13/76</td>
</tr>
<tr>
<td>Burgos M</td>
<td>0.045 (0.005, 0.103)</td>
<td>3/61</td>
</tr>
<tr>
<td>Tucat EF</td>
<td>0.237 (0.165, 0.309)</td>
<td>22/125</td>
</tr>
</tbody>
</table>

Subgroup I (I²=95%, P=0.006) 0.128 (0.090, 0.158) 846/4712

Overall (I²=95%, P=0.006) 0.179 (0.148, 0.210) 841/6096
Pharmacokinetics

Pharmacokinetic parameters of STR intramuscularly (n = 11) and intravenously (n = 19) were studied in 30 individuals. Median dosages of 1000 mg intramuscularly and 800 mg intravenously were applied. The median Cmax was 42.6 and 43.6 mg/L, respectively.

In another study, serum concentrations of 10 patients using kanamycin (15 mg/kg) intramuscularly were measured. A Cmax of 30.94 ± 7.72 mg/L was achieved after 1.50 ± 0.53 hours. The estimated elimination halftime was 3.7 hours.

Early bactericidal activity

In total, 5 studies assessing the early bactericidal activity were included. Table 2 lists all the study parameters.

The EBA of streptomycin was dose related, yet rather low in comparison with INH (comparative agent) and paromomycin. Another study described the EBA of streptomycin in several different regimens. In multiple regression analysis of days 2 to 14 after starting the regimen streptomycin showed a significant effect on the amount of CFUs (p = 0.006).

Amikacin did not show significant EBA when compared with untreated controls. However, the patients receiving no drug showed the highest EBA effect ever recorded by the authors. When the effect of amikacin was compared to zero EBA, the difference was significant indicating minimal activity. The EBA of liposomal amikacin was not significant.

Paromomycin showed a significant EBA in a dosage of 15 mg/kg (p = 0.023). This effect was not observed at a dosage of 7.5 mg/kg. The authors propose therefore that, based on this experimental data, streptomycin should be replaced with paromomycin to increase efficacy.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Value</th>
<th>Drug (dose)</th>
<th>N*</th>
<th>Period (days)</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6</td>
<td></td>
<td>STR (1g)</td>
<td>100 (4)</td>
<td>0-2, 2-14</td>
<td>Yes (2 to 14 days)</td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td>STR (7.5-30 mg/kg)</td>
<td>43 (10)</td>
<td>0-3</td>
<td>Yes (30 mg/kg)</td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td>AMK (5-15 mg/kg)</td>
<td>40 (40)</td>
<td>0-3</td>
<td>Yes (all dosages together)</td>
</tr>
<tr>
<td>B4</td>
<td></td>
<td>Liposomal AMK (30 mg/kg)</td>
<td>7</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>B5</td>
<td></td>
<td>PAR (7.5-15)</td>
<td>22 (15)</td>
<td>1-3</td>
<td>Yes (15 mg/kg)</td>
</tr>
</tbody>
</table>

STR: streptomycin, AMK: amikacin, PAR: paromomycin

* displayed as total patients (number of patients using the drug and dosage with significant effect)

DISCUSSION

This is the first systematic review on the efficacy and toxicity of different aminoglycosides and their therapeutic potential in the treatment of MDR-TB. Amikacin is in vivo the most potent aminoglycoside tested. The difference in activity between streptomycin and kanamycin is less clear. Kanamycin possesses no bactericidal activity according one study, while the efficacy is comparable between streptomycin and kanamycin according to an earlier study. It should be noted that the dosages used by Sanders et al. (10 mg/kg/day) are low, while it is common practice these days to use higher doses in mice to correct for the enhanced metabolism. Lounis et al. applied a dosage of 200 mg/kg six times weekly, which is more representative. According to the evaluation of monotherapy in vivo, the activity of amikacin is the highest, with streptomycin being second and kanamycin being the weakest aminoglycoside used today in the treatment of tuberculosis.

However, one could advocate preferring kanamycin above amikacin, since isolates acquiring resistance to kanamycin might be amikacin and capreomycin sensitive. Most isolates
with acquired resistance to amikacin are likely to develop cross-resistance to kanamycin and capreomycin at the same time.  Therefore, to prevent resistance to all injectables, treatment with kanamycin seems advantageous. The likelihood of resistance development should be taken into account when deciding which aminoglycoside to use.

Alternative aminoglycosides tested, such as isepamicin and gentamicin, did not show an enhanced bactericidal activity in comparison to amikacin or streptomycin. Furthermore, cross-resistance of these alternative aminoglycosides and amikacin, kanamycin or streptomycin is likely, giving no additional benefit to cases with aminoglycoside resistant tuberculosis. These other aminoglycosides should, therefore, not play a role in MDR-TB treatment.

Other methods of administration could have a potential benefit considering the burdensome intramuscular injections or intravenous infusions. The use of poly-lactide-o-glycolide nanoparticles encapsulating streptomycin showed an identical effect in comparison with free streptomycin with less nephrotoxicity. A disadvantage of this method could be the slightly lower $C_{\text{max}}$ and a larger AUC. This larger AUC seems however to increase ototoxicity, since literature suggests a relationship between the AUC and the occurrence of ototoxicity.

The additive effect of mainly streptomycin to certain regimens is tested in several in vivo studies. In short, it can be concluded that the addition of streptomycin lead to a significant improvement in long and/or spleen CFUs or weights. The effect of streptomycin in the continuation phase is however unclear, since no significant improvement was found. In a regimen containing sparfloxacin and pyrazinamide, streptomycin was significant more efficacious than kanamycin (P < 0.05) in reducing the spleen and lung CFU count. This supports the hypothesis, as described above, that kanamycin is in vivo significantly less active than streptomycin.

The EBA results were contradictory to the in vivo results. A dose dependent EBA of streptomycin and paromomycin was observed. The EBA of amikacin was not significant when compared to untreated controls. This while in vivo results suggested that amikacin exposures a higher activity than streptomycin. The exact reason for this difference is unclear. However, due to the working mechanism of aminoglycosides in combination with the slow proliferation of mycobacteria, a late onset of the effect is to be expected. In addition, other well established anti TB drugs, such as pyrazinamide, show no EBA while having a proven efficacy. We are therefore uncertain if the EBA model is suitable to estimate the bactericidal activity of aminoglycosides after only four days.

Only 5 humane studies statistically assessed the value of aminoglycosides in the therapy of MDR-TB. Unfortunately, none of the studies retrieved were prospective controlled trials. Therefore, the results could be biased by the severity of the disease: the likelihood to receive aminoglycosides increased with the degree of burden of disease. This was also recognized by the authors of one of these papers mentioned this hypothesis in their discussion. However, one study found a positive relationship between the cure rate and the use of kanamycin. Another study found that the absence of an injectable, including the polypeptide capreomycin, has a significant negative impact on the recurrence of TB. This indicates that aminoglycosides are important in the eradication of all tuberculosis bacilli. The aminoglycoside was used only in the intensive phase, yet one could hypothesize that the aminoglycosides have an additive sterilizing effect on dormant tuberculosis bacilli resulting in a lower chance of recurrence. This effect is also described in an in vitro study. It should however be noted that these studies are potentially biased and definite conclusions cannot be made.

The side effects of aminoglycosides, and in particular ototoxicity and nephrotoxicity, are frequent. The meta-analysis with subgroup analysis as shown in this paper indicates that
monitoring of ototoxicity is an essential key in the treatment with aminoglycosides. Without monitoring, ototoxicity rates are significantly underestimated (12.8 vs. 26.2%). It is reasonable to assume that ototoxicity rates during treatment without monitoring are even higher than 20%, since no adjustments can be made to avoid further hearing loss. Regular audiometric tests should, therefore, be standard care in aminoglycoside treatment. Audiometric testing is, unfortunately, not recommended by current guidelines and is neither implemented in daily practice.\textsuperscript{93–95}

Nephrotoxicity is overall less common than ototoxicity. Nephrotoxicity is generally reversible.\textsuperscript{6} This can be caused by the finding that patients infected with TB are relatively young, making pre-existing renal dysfunction unlikely. However, monitoring renal function by measuring the serum creatinine is questionable, since TB patients are typically cachectic.\textsuperscript{96,97} A rise in muscle weight as a result of successful treatment could cause a rise in serum creatinine, and thereby masking the emergence of renal dysfunction.

The $C_{\text{max}}$ and the AUC of aminoglycosides in patients with TB are described in two studies and vary strongly. Moreover, the Cmax/MIC varies from 8 to 16 with kanamycin.\textsuperscript{81} With the $C_{\text{max}}$/MIC being the efficacy-predicting parameter,\textsuperscript{98} a large interindividual variation is to be expected in the efficacy of the aminoglycoside treatment. A method should be designed to identify patients with a risk of an insufficient pharmacokinetic profile and to change the dose accordingly.

The relationship between toxicity, efficacy and pharmacokinetic parameters is, however, difficult to prove. Although it is assumed that the efficacy of aminoglycosides is dependent on the $C_{\text{max}}$,\textsuperscript{98} none of the studies retrieved addressed the relationship between the $C_{\text{max}}$ or AUC and efficacy. In addition, none of the studies tested the correlation between $C_{\text{max}}$ or AUC and toxicity, while in vivo studies indicate that this relationship exists.\textsuperscript{99} These relationships are, however, essential in determining the added value of therapeutic drug monitoring of aminoglycosides in TB therapy. A hollow fiber model with aminoglycoside-containing regimens could possibly establish a relation between pharmacokinetics and efficacy.\textsuperscript{99} Furthermore, with this hollow fiber model, the added value of aminoglycosides can be evaluated. These regimens can afterwards be validated with in vivo models to evaluate the efficacy and can help to choose the most promising regimen.

**CONCLUSION**

In summary, amikacin seems to be the most effective aminoglycoside in vivo. Nephrotoxicity and especially ototoxicity are frequent side effects of the treatment with aminoglycosides. It is recommended to perform regular audiometric testing to identify and prevent hearing loss. Furthermore, a large interindividual pharmacokinetic variation was observed. Further research should clarify if therapeutic drug monitoring should play a role in the treatment of TB.
REFERENCES


34. Podewils LJ, Gler MT, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. *PLoS One* 2013; **8**(7): e70064.


Does the Drug Exposure of Aminoglycosides in the Treatment of Tuberculosis relate to Efficacy and Toxicity?


Does the Drug Exposure of Aminoglycosides in the Treatment of Tuberculosis relate to Efficacy and Toxicity?


