Optimal Tobramycin Dosage in Patients with Cystic Fibrosis – Evidence for Predictability Based on Previous Drug Monitoring

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Summary

A retrospective analysis of files of patients with cystic fibrosis and pulmonary exacerbations was performed to investigate whether an individual dosage of tobramycin once established by serum level determination allows a reliable prediction of the adequate dosage in a consecutive exacerbation. All patients hospitalized ≥ 2 times between May 1997 and September 1998 with pulmonary exacerbation due to *Pseudomonas aeruginosa* infection susceptible to tobramycin were included. The initial dosage to tobramycin was 5 mg/kg body weight every 12 h followed by drug level determinations to establish the optimal dose. In a consecutive exacerbation the same dosage per kg body weight was used again and drug level determinations were repeated. Sixteen patients (six female = 38%) with a mean age of 24 years (median: 26 years, range: 9–33) were hospitalized for 49 pulmonary exacerbations (2–6 per patient, mean: 3, median: 2.5). During the first episode of tobramycin treatment in the study period all trough levels were < 2 µg/ml (median: 0.6) and the peak levels were 7.1–16.9 µg/ml (median: 11.9). In four patients the peak level was > 12 µg/ml. In 28 consecutive episodes the dosage of tobramycin was chosen based on optimal results of previous drug level monitoring and in 27 instances (96%) the previously established optimal dose was confirmed. In five consecutive episodes the tobramycin dosage had been increased erroneously and this resulted in abnormally high peak levels in three cases. These findings suggest that a safe and therapeutic tobramycin dosage in an individual patient with cystic fibrosis is predictable based on a previously established optimal dosage.

Introduction

Patients with late stage cystic fibrosis repeatedly suffer from pulmonary exacerbations caused by *Pseudomonas aeruginosa* infection of the lungs. The standard treatment of these exacerbations is the i.v. application of aminoglycosides, such as tobramycin, and betalactam antibiotics effective against *P. aeruginosa* (e.g. ceftazidim, piperacillin). Because of the different pharmacodynamics of antibiotics in patients with cystic fibrosis as compared to healthy subjects (increased distribution volume per kg body weight and decreased serum half-life) high doses of antibiotics have to be administered for successful therapy [1]. Especially in the case of aminoglycosides, serum levels need to be monitored during therapy to guarantee correct dosage. Thus, lack of therapy due to underdosage and harmful side effects, such as nephrotoxicity and ototoxicity caused by overdosage, can be avoided [2]. With progressive lung disease intervals between single episodes of pulmonary exacerbation tend to decrease and aminoglycosides need to be administered frequently. We wondered, whether an individual dosage of tobramycin once established by serum level determination allows a reliable prediction of the adequate dosage in a consecutive exacerbation. A retrospective analysis of patients' files was performed to answer this question. The results are the subject of this report.

Patients and Methods

Patients

All patients with cystic fibrosis included in this analysis were hospitalized ≥ 1–2 times in our institution with pulmonary exacerbation associated with growth of *P. aeruginosa* susceptible to tobramycin in the sputum between May 1997 and September 1998. Each patient's body weight was determined on admission to the hospital. The initial dosage of tobramycin was 5 mg/kg body weight every 12 h unless the patient had received treatment with tobramycin previously and drug level determinations had established the optimal dosage. In this case the same dosage per kg body weight was used again.

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Table 1
Tobramycin dosage and drug level determinations in patients with abnormally high peak levels during the first episode of tobramycin treatment in this study.

Patient	Age (years)	Dosage 1 (mg/kg)	Trough level (µg/ml)	Peak level (µg/ml)	Dosage 2 (mg/kg)	Trough level (µg/ml)	Peak level (µg/ml)
1	27	2 x 4.5	0.6	16.9	2 x 4.1	0.7	14.2
2	25	2 x 3.8	0.4	16.1	2 x 3.3	0.5	5.0
3	28	2 x 3.6	0.6	13.3	2 x 3.2	0.9	9.0
4	30	2 x 5.1	0.4	14.4	2 x 4.6	n.d.	n.d.

n.d. = not done.

Methods

As part of our standard procedures, tobramycin was administered over 30 min intravenously (doses < 80 mg in 50 ml 0.9% NaCl; doses ≥ 80 mg in 100 ml 0.9% NaCl) at 12 h intervals and trough and peak drug levels were measured on day 3 of treatment before and after the sixth dose, respectively (TDx-Analyzer, Abbott Diagnostics, Wiesbaden, Germany). In addition to tobramycin, other antibiotics were given depending on the results of sputum cultures and bacterial resistance patterns; the interval between application of two different antibiotics was at least 2 h. On admittance to the hospital, serum creatinine and urea levels were determined in addition to a number of other routine tests, including full blood count, c-reactive protein levels and others. These laboratory tests were repeated two to three times per week for the duration of therapy. Blood for tobramycin trough level determination was taken before administration of the sixth dose and blood for determination of the peak level was collected 30–60 min after the end of the infusion of the sixth dose. According to the manufacturer's instruction, a tobramycin trough level of < 2 µg/ml and a peak level of 5–12 µg/ml were considered optimal (variation coefficient of the method: < 6%).

Data analysis

For each patient each individual exacerbation during the study period was analyzed for dosage of tobramycin per kg body weight, trough and peak drug level determinations and time differences between consecutive exacerbations. If an individual dosage resulted in optimal peak and trough levels, as defined above, and the same dosage of tobramycin (per kg body weight) was used again for treatment of the next exacerbation, again resulting in optimal drug levels, the patient's individual dosage was considered "reliable." Bravais-Pearson correlation coefficient was used for 2-tailed correlation analysis between tobramycin dosage and patient's weight.

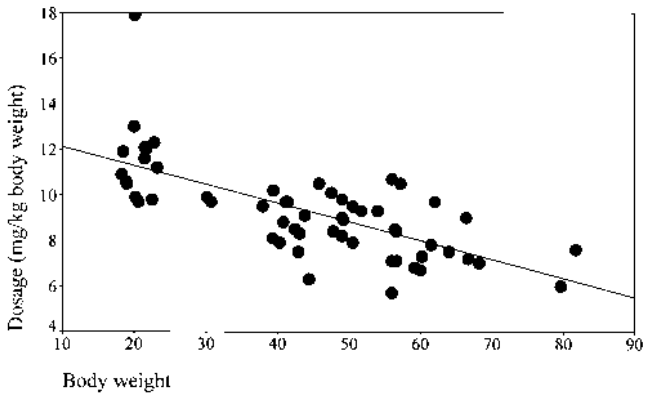

Figure 1
Correlation of body weight (kilogram) and dosage of tobramycin (in mg per kg body weight/24 h) in patients with cystic fibrosis and pulmonary exacerbation.

Results

Between May 1, 1997, and September 30, 1998, a total of 16 (six female = 38%) patients fulfilled the inclusion criteria. Their mean age was 24 years (median: 26 years, range: 9–33). There were 49 episodes of pulmonary exacerbation (2–6 per patient, mean: 3, median: 2.5) for analysis. The interval between two consecutive exacerbations in a patient varied from 1–17 months (median: 6 months).

The dosage of tobramycin used for treatment of an exacerbation varied between 2 × 3.0 mg/kg body weight/day and 2 × 9.0 mg/kg body weight/day (median: 2 × 4.7). There was no clinical evidence of serious side effects during treatment of any episode nor was there an increase of creatinine or urea serum levels noted at any time. Furthermore, trough levels of tobramycin were always below 2 µg/ml.

In Figure 1 the correlation between total body weight and tobramycin dosage (in mg/kg body weight) is demonstrated. For this specific analysis data from patients who were hospitalized only once during the study period were included to increase the power. As can be seen, there was an inverse correlation between body weight and individual tobramycin dosage ($r = -0.69$; $p < 0.001$).

When the first episode of tobramycin treatment in the 16 patients was analyzed, the following results were obtained: All trough levels were < 2 µg/ml (median: 0.6). The peak levels were 7.1–16.9 µg/ml (median: 11.9) and in four patients (25%) the peak level was > 12 µg/ml, leading to a dose reduction followed by another drug level determination with the sixth dose after the change in three of four patients (Table 1).

An analysis of 33 consecutive episodes in these 16 patients revealed the following findings: All trough levels were < 2 µg/ml (median: 0.4). The peak levels were 5.6–15.0 µg/ml (median: 11.5) and in four episodes (12%) the peak level was >12 µg/ml, leading to a dose reduction followed by another

Table 2
Tobramycin dosage and drug level determinations in patients with abnormally high peak levels during a consecutive episode of tobramycin treatment in this study.

Patient	Age (years)	Dosage 1 (mg/kg)	Trough level (µg/ml)	Peak level (µg/ml)	Dosage 2 (mg/kg)	Trough level (µg/ml)	Peak level (µg/ml)
3	28	2 x 4.2	0.5	15.5	2 x 2.9	0.3	13.0
4	30	2 x 5.3	0.4	15.0	2 x 4.4	n.d.	n.d.
5	31	2 x 5.1	1.2	14.1	2 x 4.4	1.0	8.5
6	23	2 x 4.9	0.4	14.8	2 x 4.4	0.6	6.7

n.d. = not done.

drug level determination with the sixth dose after the change in three of four patients (Table 2).

In these 29 consecutive episodes, where peak and trough level determinations had revealed "optimal dosage," the dose per kg body weight was identical to that used for treatment in 27 cases at the end of the previous episode. In two patients an unjustified change of dosage had been performed for treatment of the consecutive episode but the peak tobramycin level remained in the optimal range.

In contrast, in three of the four consecutive episodes with abnormally high peak levels (patients 3, 4 and 5 in Table 2), the tobramycin dosage had been increased for unknown reasons compared to the previous dosage considered to be optimal (patient 5) or to a previous drug level analysis which had already indicated that the dosage was too high (patients 3 and 4, Tables 1 and 2). In patient six an abnormally high peak level was measured, despite the fact that the same dosage had resulted in an optimal peak level 11 months before.

Overall, in 28 episodes of pulmonary exacerbation the dosage of tobramycin was chosen based on optimal results of previous drug level monitoring and in 27 instances (96%) determination of tobramycin trough and peak levels confirmed the previously established optimal dose.

Discussion

Aminoglycosides are an essential part of successful treatment of pulmonary exacerbations in patients with cystic fibrosis [3]. While short dosing intervals of tobramycin (every 6–8 h) had been recommended until approximately 10 years ago [4, 5], it has been shown that dosing intervals of 12 h or even 24 h are advantegous compared to traditional 8 h intervals [2, 6]: Lower trough levels and higher peak levels can be obtained with lower total amounts of tobramycin with prolonged dosing intervals compared to an 8 h dosing interval. To guarantee success of therapy and to avoid toxic side effects, the serum levels of aminoglycosides before (trough) and after (peak) application in the steady state phase are recommended. The goal is to achieve trough levels of tobramycin below 2 µg/ml and peak levels in the upper part of the recommended range (i.e. > 8 µg/ml) [7]. Although different ways to establish the optimal dosage of aminoglycosides in patients with cystic fibrosis have been suggested, including calculations based on body surface [5], lean body mass [8] and body weight [9], the general consensus has been that each new episode requires determination of trough and peak aminoglycoside levels.

The findings in the present study, however, suggest that a once established optimal dosage of tobramycin in an individual patient might be re-used for consecutive treatments up to 17 months later, thus saving time, effort and money involved with repeated drug level monitoring. As we demonstrated, in 27 of 28 later episodes monitoring of tobramycin trough and peak levels confirmed the findings obtained with the same dosage during the previous treatment. In the only instance where this was not the case (patient 6 in Table 2), reduction of the dosage resulted in an unusually prominent decrease of the peak level, suggesting an error during specimen sampling or in the laboratory process when the initial peak level was measured. In two patients (patients 3 and 4 in Tables 1 and 2), the abnormally high peak level measured during a consecutive course of tobramycin treatment was based on not taking a previous result of a tobramycin level assay into account, which had already indicated that the individual dosage was too high. It has recently been discussed that patients with cystic fibrosis and pulmonary colonization with *P. aeruginosa* be treated with i.v. antibiotics every 3–4 months regardless of signs of acute exacerbation ("aggressive therapy") [10]. Although this strategy has not yet been universally accepted (and not been practiced in our institution), in light of such a new tendency, our findings suggest that results from a previous tobramycin serum level determination can serve as a reliable dosage guideline during each new course of antibiotic treatment, provided that no major changes in medical conditions (e.g. renal function) have occured in the meantime. However, for the time being it is still wise to confirm the right dosage by drug level determination.

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