NECESSITY OF TOBRAMYCIN TROUGH LEVELS IN ONCE DAILY IV-TREATMENT IN PATIENTS WITH CYSTIC FIBROSIS

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Abstract:

Background: Once daily intravenous (iv) treatment with tobramycin for Pseudomonas aeruginosa infection in patients with cystic fibrosis (CF) is usually monitored by measuring tobramycin trough levels. Although the necessity of these trough levels is recently questioned in CF patients without renal impairment, no study has evaluated this so far. The aim of this observational study was to evaluate the frequency of increased tobramycin trough levels in 278 courses of iv tobramycin in CF children and adolescents.

Methods: Patient records of all consecutive once daily iv tobramycin courses in 35 CF patients between 07/2009 and 07/2019 were analyzed for tobramycin level, renal function, co-medication and comorbidity.

Results: Eight elevated tobramycin levels (2.9% of 278 courses) were recorded in four patients, two with normal renal function. One of these did resolve without adjustment of tobramycin dosages suggesting laboratory error. In the other patient elevated tobramycin levels occurred after recently being started on lumacaftor/ivacaftor and decreased after dosage adjustment. Six of the elevated levels occurred in two patients with chronic renal failure. In 15 other patients with reduced glomerular filtration rate (GFR) (36 courses) no case of an elevated tobramycin trough level was detected. Cumulative tobramycin dosages were neither a risk factor for elevated trough levels nor were diabetes or nutritional status.

Conclusion: In CF patients with normal GFR (GFR >100 ml/min) and in absence of additional risk factors (e.g. recently started CFTR modulator therapy) a monitoring of the once daily iv treatment by tobramycin trough levels seems not to be necessary.

1. Background:

Aminoglycosides have been part of standard treatment for Pseudomonas aeruginosa infection in patients with cystic fibrosis for decades[1]. In addition to inhaled tobramycin intravenous treatment with aminoglycosides, predominantly tobramycin, is widely used. The frequency of per day application has been changed from thrice daily to once daily because of improved bactericidal activity of peak levels against Pseudomonas aeruginosa[2]. The most common side effects of the iv application include ototoxicity but also dose dependent acute and chronic nephrotoxicity[1, 3,4]. Therefore, monitoring of tobramycin trough levels and subsequent adjustment of dosages has been recommended during the decades of three-times daily application, and is still recommended in once daily iv treatment[5,6].

The relevance of measuring tobramycin levels in once daily iv application is generally questioned in CF patients with normal renal function and without additional risk factors, but the recommendation to monitor levels is still valid and carried out in most CF centers. In our experience elevated tobramycin trough levels are exceedingly rare except in patients with underlying renal insufficiency, and regular testing may therefore not be indicated. Measurement of iv tobramycin trough levels on day three of therapy poses some logistical obstacles as a lot of iv therapies are nowadays received at patient ´s home with the hospital staff to perform the blood test or to react to the result is not in direct reach.

2. Materials and Methods:

We conducted a single centre, observational cohort study, retrospectively collecting clinical data. Patients were recruited from the CF-centre of the pediatric hospital of the Ruhr University Hospital of Bochum. Source data were electronic patient files.

2.1. Patients:

All patients with genetically confirmed CF who received once daily iv tobramycin courses between 07/2009 and 07/2019 were included in the study. A once daily instead of thrice daily application of iv tobramycin therapy had been adopted into clinical routine in the early 2000s. Tobramycin trough levels were measured on a routine basis before the third dose. There were no exclusion criteria. The Ethics Committee of the Ruhr University Bochum approved the study (No. 19-6798-BR).

2.2. Analysis of clinical parameters:

Patient data was pseudonymized and analyzed for tobramycin trough levels and dosage, age, weight, renal function, cumulative tobramycin exposure, co-medication and comorbidities. Trough levels were considered within range if the concentration was < 1mg/ml. GFR was calculated using the Schwarz formula for patients < 18 years of age and the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) for adult patients.

2.3. Statistical analysis:

Descriptive statistics were used to characterize the population.

Risk factors for elevated tobramycin levels were analyzed using parametric and non-parametric tests as indicated.

3. Results:

35 CF-patients (17 male, 18 female; 14,5 years (SD 4,8; 0,3-34,3)) with 352 iv tobramycin courses, each over a period of 14 days, were included in the study. 85% (299 of 352) of these courses were done in patients below 18 years. Table 1 summarizes the characteristics of the included CF-patients.

Patients were treated with a medium dosage of 10mg/kg tobramycin once daily over 14 days. Dosage was adjusted to renal function according to official recommendations. Patients received on average 9 (SD 8; range 1-34) courses of iv tobramycin treatment during the 10 years observation period (table 2).

In 62% of 352 tobramycin courses the second medication was ceftazidime and in 25% meropenem. In 25% of the 352 tobramycin courses a third antimicrobial medication, and in 2% a fourth antimicrobial medication was used. During the observation period all patients had at least a period with additional inhalative therapy with tobramycin or colistin.

In 278 of 352 iv tobramycin courses (79%) a tobramycin trough level was available. Only 8 trough levels were elevated (>1 mg/l) (2,9% of 278) in 4 patients. Two of these 4 patients had a chronic kidney disease (chronic renal failure in one and IgA nephritis in the other patient) (table 3).

The other two elevated levels were detected in two patients with normal renal function and normal tobramycin dosages (9 mg/kg and 10 mg/kg). One did resolve without adjustment of tobramycin dosages suggesting a laboratory error. Control tobramycin trough level without dosage adjustment was normal. The other patient had just been started on lumacaftor/ivacaftor and levels normalized after adjustment of dosages.

In patients with elevated tobramycin trough levels creatinine levels were more frequently elevated than in patients with normal tobramycin trough level (OR 80,4, CI 10,9; 591,7,

p< 0,01), the glomerular filtration rate (GFR) was more often reduced (OR 6,5, CI 1,6; 27,2, p< 0,01), (table 4).

No elevated tobramycin levels were detected in 36 out of 278 courses of iv tobramycin treatment in 15 patients with preliminary reduced GFR. The correlation between GFR and tobramycin trough level is shown in figure 1: In cases with elevated tobramycin levels, the GFR was more likely below 100 ml/min/1,73m^2.

The cumulative dosage of tobramycin was 1,1g/kg/patient (SD 1,0; 0,13-4,6). There was no relation between the level of cumulative tobramycin dosage and the incidence of elevated tobramycin trough level. The majority of patients with a very high cumulative dosage did neither develop elevated tobramycin levels nor signs of kidney damage or ototoxicity.

Further statistical analysis did not reveal any significant differences between the patients with elevated and normal tobramycin trough levels (e.g. CF related diabetes, nutritional status and other nephrotoxic medication, for example previous iv colistin).

50 % of the elevated tobramycin trough levels were measured in one adult CF patient with severe CF lung disease including chronic Pseudomonas aeruginosa infection and chronic renal failure. Since 2013 this patient`s GFR was below 100 ml/min/1,73m2. Although the dosage was not consistently adjusted to renal function, tobramycin trough level only started increasing in 2017 (figure 2).

4. Discussion:

The primary aim of this study was to evaluate the impact of monitoring tobramycin trough levels in order to prevent nephrotoxicity which is described as a frequent side effect of iv tobramycin therapy, especially in CF patients[7]. Compared to the literature in our population the rate of renal failure was moderate. Only 16% of our analyzed cases receiving iv treatment with tobramycin had a reduced GFR < 100ml/min1,73m^2 in comparison to other cohorts stating 31-42%[8], and only two adult patients (5,7%) had a chronic renal failure whereas Santoro et al. reported 14%, Berg et al. 11%[9,10]. In parallel to that, only few tobramycin trough levels in patients with iv tobramycin therapy were elevated. The vast majority, namely 75% of these elevated tobramycin trough levels were measured in patients with developing renal failure (GFR below 100 ml/min/1,73m^2). To regard renal insufficiency as a major risk for having elevated tobramycin trough levels is also supported by Bertenshaw 2007[11] where 9 out of 24 CF patients with renal failure were found to have elevated tobramycin trough levels. In line with this our patients with elevated tobramycin trough levels also showed a significantly more severe renal impairment (elevated creatinine and decreased GFR) than patients with normal tobramycin level and renal failure.

Similar to the observations made by Wilcock et al.[4] cumulative exposure/dosage of tobramycin did not turn out to be a risk factor for toxic tobramycin levels in those patients. Furthermore, neither other potentially nephrotoxic drugs (like iv colistin) as described by Smyth et al.[3] nor comorbidities such as diabetes or nutritional failure proved to be independent risk factors for elevated tobramycin trough levels. Acute dehydration as an additional risk factor for elevated creatinine or reduced GFR did not occur in our cohort. Dosage adjustment was only necessary once in one patients with elevated trough level and normal renal function.

There are, however, limitations to the retrospective study design: we could not include information on tobramycin courses before 2009 so the cumulative dosage of some patients might be even higher than stated. In addition to this, we did neither perform more detailed pharmacokinetics in the analysis (e.g. area under the curve) or more sensitive markers of renal failure (cystatine C) and therefore might miss additional risk factors. Nevertheless, the number of patients showing elevated tobramycin trough levels is exceedingly small and restricted to adult patients with chronic renal failure.
In conclusion we recommend stopping routine tobramycin trough levels in CF patients on once daily iv tobramycin treatment and restrict it to patients with underlying renal impairment (GFR below 100 ml/min/1,73m^2) or specific risk factors such as recently started CFTR modulator therapy. In those patients close monitoring of renal function is also indicated.

Conflict of interest statement: All authors have nothing to disclose.

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