PHARMACOKINETICS AND CLINICAL OUTCOMES OF TOBRAMYCIN IN ADULT CYSTIC FIBROSIS PATIENTS WITH ACUTE PULMONARY EXACERBATION

Daniel Thirion[1], Kevin Koloskoff[1], Jean-Alexandre Caissy[1], Elias Matouk[2], and Amélie Marsot[1]

[1]Universite de Montreal Faculte de Pharmacie
[2]Montreal Chest Institute

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Abstract

Background Acute pulmonary exacerbation (APE) in cystic fibrosis patients is frequent and associated with a decline in pulmonary function, quality of life and survival. Tobramycin is often used in regimens requiring activity against *Pseudomonas aeruginosa*, however, an important number of centers do not use official dosing recommendation. The current dosing strategy may be suboptimal. *Methods* This retrospective cohort analysis was performed on all adult cystic fibrosis patients that were admitted at a tertiary care facility for treatment of APE and with tobramycin between January 2015 and December 2019. The primary objective was to evaluate the predictive performance of previously published pharmacokinetic (PK) models and, secondly, to evaluate potential factors that impact clinical outcomes. Clinical outcomes were only evaluated in a sub-group of patients with cultures positive for *P. aeruginosa*. *Results* A total of 202 APEs from 51 patients were included in the PK analysis. Two population PK models were assessed and failed to fit our data. In all, 109 APEs from 32 patients were included in the clinical analysis. Factors that significantly impacted clinical outcome were the number of prior APE and concomitant antibiotics. Clinical success rate for regimens containing at least one active agent against *P. aeruginosa* according to its susceptibility was 67%. *Conclusion* Population PK models evaluated in this study cannot be used to perform simulations. A new model must be developed for our population. In patients positive for *P. aeruginosa*, Ceftazidime in combination to tobramycin may be a superior regimen. APE history remains predictive for outcomes in adult CF patients treated for an APE.

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Running title: ASSESSING TOBRAMYCIN IN CYSTIC FIBROSIS

Authors: Daniel J.G. Thirion, PharmD[1,2], Kevin Koloskoff, PharmD[1,3], Jean-Alexandre Caissy, BSc[1,3], Elias Matouk, MD[4], Amélie Marsot, PhD[1,3]

Affiliations: [1]Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada; [2]Pharmacy Department, Royal Victoria Hospital, McGill University Health Centre, Montreal, Quebec, Canada; [3]Laboratoire STP2, Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada;[4]Adult Cystic Fibrosis Clinic, Montreal Chest Institute, McGill University, Montreal, Quebec, Canada

Corresponding author:

Amelie Marsot: Faculty of Pharmacy, Université de Montréal, PO Box 6128, succ. Centre-ville, Montreal, Quebec, Canada H3C 3J7

E-mail: amelie.marsot@umontreal.ca

Telephone: 1-514-343-6111 ext. 5207

Fax: 1-514-343-6120

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Key points:

The evaluation of regimens through their predictive attainment of PK/PD targets remains the fastest way to evaluate a dosing strategy and its factors.

Clinically history of APEs is predictive of clinical outcomes.

CF-specific variability is likely to cause the current tobramycin dosing regimen to be sub-optimal, rigorous identification of additional factors is needed to account for this variability.

Abstract

Background

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Methods

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Conclusion

Population PK models evaluated in this study cannot be used to perform simulations. A new model must be developed for our population. In patients positive for *P. aeruginosa* , Ceftazidime in combination to tobramycin may be a superior regimen. APE history remains predictive for outcomes in adult CF patients treated for an APE.

Introduction

Cystic fibrosis (CF) is the most common fatal genetic disease affecting children and young adults in North America. Lung infections are common in patients with CF with and increasing predominance of*Pseudomonas aeruginosa* as the patient advances in age. Annually, 63% of patients over the age of 18 experience infections

and periodic worsening signs and symptoms of respiratory health, recognized as acute pulmonary exacerbations (APE) (1). APE are estimated to be responsible for about half of the long-term decline in $ppFEV_1$(2) and are associated with a significant decrease in survival(3, 4).

Published guidelines affirm lack of evidence on best treatment practices (5). Current Cystic Fibrosis Foundation (CFF) guidelines recommend treating APEs in CF with two antipseudomonal agents, such as a beta-lactam (BL) and an aminoglycoside (AG) (5). Tobramycin is the most commonly used AG (6). The CFF and European consensus guidelines recommend an intravenous (IV) regimen of 10 mg/kg/day to achieve needed serum concentrations (7). However, an important number of CF centers do not use the official CFF dosing recommendations(7).

Tobramycin has wide inter- and intraindividual variability in its pharmacokinetic (PK) behaviour(8). An empiric 10 mg/kg daily dose of tobramycin in CF patients achieves target serum concentrations of 20-30 mg/L in only 42% of patients (9). This supports a recommendation of a daily dose of 12 mg/kg. . Further investigations are needed to assess and confirm the optimal dosing strategy.

The objectives of the study are to establish optimal dosing recommendations by performing an external validation of previously published PK models using data from a tertiary care facility, and to describe clinical outcomes and identify potential risk factors.

Materials and Methods

Design and setting

This retrospective cohort study and population PK analysis study screened all adults with a medically confirmed diagnosis of CF that were admitted at the McGill University Health Centre (MUHC), a tertiary care facility, for the treatment of an APE between January 2015 and December 2019. Patients were included if they received IV tobramycin in the antibiotic regimen as treatment for their APE, inhaled tobramycin resulted in exclusion. This study was approved by MUHC ethics committee. Tobramycin dosing regimens vary according to patient characteristics and physician's personnel assessment of patient severity and risk of adverse events. All dosing regimens were included in this study. Patients who were switched from tobramycin to another aminoglycoside or vice-versa were also included, however, changing antibiotic was considered in the analysis.

Data collection

Baseline demographic data (i.e. date of birth, age, weight, height, body mass index (BMI), body surface area (BSA), cystic fibrosis transmembrane conductance regulator (CFTR) mutation type), APE data (i.e. date of hospital admission, diagnosis, severity, per cent predicted forced expiratory volume in one second ($ppFEV_1$), microbial reports, white blood cell count and c-reactive protein count) and antibiotic data (i.e. tobramycin treatment duration, dose, plasma levels of tobramycin and concomitant antibiotic treatment) were collected. Data regarding outcomes included APE recurrence, hospital length of stay, increased levels of creatinine and bacteremia duration. Severity of the APE was assessed using the Matouk Score (10), a modified version of the Huang score, because of its systematic use at our center. All data was collected by manual review of the local electronic database.

PK samples

CF patients received 7.5mg/kg of IV tobramycin every 24 hours for 14 days in their antibiotic regimen for treatment of an APE. Pharmacists adjusted the dose per standard practice with target peak of 15-25 mg/L and trough of less than 0.5 mg/L. In case of treatment failure, clinicians were free to make any modifications to the antibiotic regimen including dosing changes, extending the duration of treatment or changing any of the antibiotics. Tobramycin peaks and troughs (1 hour after and 30 minutes before administration respectively) were measured at Day3. Concentrations were determined with an automated and validated immunoenzyme method on an AU5800 chemistry analyzer (Beckman Coulter, Brea, CA). The linear range for this assay was 0.5-50.0 mg/L with the intraday and interday variability being lower than 10%.

Model

A literature review was performed to identify population PK models for intravenous tobramycin in CF adult patients. Models were included in this study if they were developed with NONMEM® software (Icon Development Solutions, Ellicott City, MD, USA) and if associated covariates were consistent with our collected data. Models were excluded if not enough data was provided to characterize the structural model.

Model evaluation

Previously published models were implemented on NONMEM® version 7.4.4. Visual evaluation of plots was conducted using R (version 3.5.1). An analysis of goodness of fit plot was performed to assess model validity. Indicators, according to the method of Varvel et al., were then calculated(11). The relative performance error (PE_{ij}[%] for the ith individual at the jth tobramycin concentration) was compared to the predicted concentration ($C_{pred\ ij}$) with the corresponding observations ($C_{obs\ ij}$) – Equation 1 :

Equation 1

$$PE_{ij}\ (\%) = \frac{C_{pred\ ij} - C_{obs\ ij}}{C_{obs\ ij}} \times 100$$

To evaluate bias (i.e. overestimation or underestimation of C_{pred} from the line of unity) of the model predictions, median prediction error (MDPE) was estimated with Equation 2 :

Equation 2

$$MDPE_i\ (\%) = median\ \{PE_{ij},\ j = 1, \ldots,\ N_i\}$$

To assess inaccuracy (i.e. size of the typical miss) median absolute prediction error (MDAPE) was determined with Equation 3.

Equation 3

$$MADPE_i(\%) = median\ \{|PE_{ij}|,\ j = 1, \ldots,\ N_i\}$$

To go further in the evaluation of these models, the predictive performance of Bayesian forecasting was assessed according to Broecker*et al.* (12). Calculations of MDPE and MDAPE enable the comparison of different model-predicted and observed concentrations.

Fractionated databases were created to assess the impact of observed tobramycin concentrations on the predictive performance: (a) complete database, (b) removal of all observed peaks, (c) removal of all residuals, (d) removal of all dosages after Day3, (e) removal of all observed concentration (*a priori* prediction). (c) and (d) were applied only for patients with more than 2 doses.

An MDPE between –20% and 20% and an MDAPE [?] 30% are considered acceptable criteria for bias and inaccuracy (13).

The predictive performance was further evaluated by simulating 500 tobramycin concentrations per time point using model PK parameters as fix and the $SIM of NONMEM®. To assess the forecasting error between the observed and the simulated dataset, the 5th, 50th and 95th percentile of the simulated data over the time dose (Predicted Corrected Visual Predictive Check [pcVPC]) was plotted. With the same simulated dataset, the distribution of the Normalized Prediction Distribution Error (NDPE) was also plotted. Normal distribution of NPDEs were checked visually by using the histogram of NPDEs frequency.

Outcomes

Clinical outcomes were evaluated retrospectively and only in patients with positive cultures for *P. aeruginosa* . This allows for a normalization of the cohort. Patients with polymicrobial culture results and antibiotic combinations were included in the analysis.

Treatment failures were categorized as: 1) early repeated exacerbation (defined as recurrent APE occurring within 45 days (10); 2) requirement of antibiotic regimen change or addition of antibiotics to the regimen during therapy due to ineffectiveness.

The clinical outcomes were incorporated into a composite criterion which included the 2 categories of treatment failures as its criteria. A negative to all 2 criteria was necessary to achieve a positive treatment outcome while a positive to 1 or more criteria resulted in a negative treatment outcome.

Nephrotoxicity was defined as an increase in serum creatinine at therapeutic drug monitoring over a preceding measurement within 48h as per the Kidney Disease Improving Global Outcomes (14, 15).

Statistical analysis

The study cohort was categorized into those who achieved a positive treatment outcome and those who did not; these two groups were compared using a Chi-square test or a Student's t-test, as appropriate, with regards to demographic and APE variables. Levene's test was used to determine if equality of variance was to be assumed for continuous variables. A 2-sided α of 0.05 and/or a 95% confidence interval (CI) was used in all analysis. Doses were converted from mg to mg/kg to account for weight differences between patients. Antibiotic combinations administered in concomitance to tobramycin were given their own category if they were used in 5% or more cases, otherwise, they were included in the « other » category. A multivariable logistic regression analysis was performed for determination of risk factors for therapeutic failure. All variables of clinical interest that differed between groups were forced into the model to account for variability. Microorganism susceptibility was also included. The Matouk Score was the only variable assessing the severity of the APE included in the analysis. All statistical analyses were performed on SPSS version 27.

Results

82 patients with a total of 235 APEs were treated with IV tobramycin between January 2015 and December 2019. Of these, 31 were excluded due to missing tobramycin serum concentration (n=28), for not being a confirmed APE (n=1) or because treatment was initiated at another hospital than the MUHC (n=2). In all, 51 patients with a total of 202 APEs were included.

Model

Two models were included in the study(16, 17). Both studies used a fluorescence polarization immunoassay method to determined tobramycin concentrations. Both models described data with 2 structural compartments. Parameters in the model developed by Alganhem *et al.* (model 1) (16) were Cl=4.65 L/h, V_1=13.3 L, Q=0.452 L/h and V_2=6.62 L. Height and creatinine clearance (Clcr) were set as covariates on Cl and height was set as covariate on V_1. Between Subject Variability (BSV) were estimated only on Cl and V1. In the model of L. Crass *et al.* (model 2) (17), parameters used were Cl=4.90 L/h, V_1=15.4L, Q=0.34 L/h and V_2=5.56 L. Height and Clcr were set as covariates on Cl and height was set as covariate on V_1. BSV were estimated on all parameters. For each model, inclusion of between occasion variability (BOV) on clearance achieved a further improvement of fit.

Model evaluation

The visual assessment of goodness of fit plot models showed that both models adequately described the observed tobramycin concentrations (Suppl. figure S1). Calculations of bias and inaccuracy indicated that the predictions of model 1 and 2 are slightly lower than the observed concentrations (Model 1: MDPE, 2.6 %; MDAPE, 12.2 % and model 2: MDPE, 0.9 %; MDAPE, 9.5 %). Bias and inaccuracy were reasonable and met the predetermined criteria.

Bias and inaccuracy were plotted as histograms in Fig.1A and 1B to compare model 1 and 2, respectively.

In Fig.1A, bias was between -6.0% when only covariates remain (e) and 5.4% when only concentration at peak remain (c). Inaccuracies were between 12.2% and 24.8%. In Fig.1B, bias were between -40.6% when observed concentration are missing (e) and 0.9% in the complete database (a). Model 1 met the predefined criteria for each database whereas model 2 did not.

Concerning simulations-based diagnostics of model 1, the histogram of NPDEs frequency revealed that they were not normally distributed (Fig.2 and Suppl. figure S2). Visual inspection of pcVPC showed evidence of misspecification (Fig.3), particularly for early time after dose (Suppl. figure S3).

Clinical outcomes

Of 202 APEs in 51 patients, 109 had cultures positive for *P. aeruginosa* and were included in the clinical analysis, 74 and 35 in the positive and negative outcome groups, respectively. The average Matouk score was 46.5 and 40.8 in the positive and negative outcome group, respectively. Table 1 shows patient's characteristics and Table 2 shows APE-specific data. The negative outcome group was composed of 31 (88.6%) APEs with 1 criterion and 4 (11.4%) APEs with 2 criteria. Early APE reoccurrence was the leading criteria of treatment failure (71.4%) while antibiotic change was present in 40% of failures.

Of the 109 *P. aeruginosa* positive cultures, 97 were sensitive to at least one antibiotic administered while 12 were resistant to all antibiotics administered. A total of 65 (65.0%) susceptible strains and 6 (50%) resistant strains were in the positive outcome group.

Between outcome groups, only APE occurrence per patient, baseline ppFEV$_1$ and concomitant antibiotics significantly differed. APE occurrence per patients, severity, concomitant antibiotics and microorganism-specific data were included in the multivariable analysis. Baseline ppFEV$_1$ was excluded as to avoid confusion bias. The interaction between concomitant antibiotic and severity of the APE was not significant (p =0.695).

In relation to treatment outcome, APE occurrence per patients (p =0.004), ceftazidime and piperacillin/tazobactam as concomitant antibiotics (p <0.001 and p =0.047, respectively) were the only variables achieving significance (Table 3).

Of the 153 evaluated APEs, no cases of nephrotoxicity were identified. Nephrotoxicity could not be evaluated in 51 APEs as a result of missing data; 28 in the analyzed group, 15 (24.2%) and 13 (27.7%) APEs in the positive and negative outcome groups, respectively.

Discussion

Model evaluation

The external evaluation of the population PK models revealed that neither of the models assessed fitted our data. The model 2 was suboptimal when describing observed concentrations in our adult CF population when only covariates remained in the dataset. Furthermore, simulation based diagnostics revealed misspecification, especially for NPDEs, which were not normally distributed. Bias and inaccuracy of model 1 were compliant with the set criteria. Even if MDAPE exceed 20 % when only covariates remained in the model, indicating that residuals and peaks at Day3 are valuable data for the Bayesian forecasting. However, simulations-based diagnostic plots were not adequate to produce relevant Monte-Carlo simulations.

Several hypotheses can be put forward to explain the inability of the two models to fit our data. (i) Demographic and clinical differences in our populations and those used in evaluated models may have a significant impact on the results. Crass *et al.* used a mixed CF population composed of pediatric and adult patients, which can lead to bias in the estimated parameters. (ii) Also, height was set as covariate on clearance and V_1 for both investigated models. Even if height-based doses should be considered for patients with CF according to Alghanem *et al.* , further studies are required to understand the clinical relevance of this result (18). A weight-based tobramycin model for CF patients should have been investigated. (iii) The wide inter- and intra-individual variability in our population, especially for doses (ranging from 2.7 to 14.2 mg/kg) and dosing schedules (q12h, q24h, q36h, q48h and q72h) could explain the deviations observed in our results. The pcVPC, theoretically corrects this deviation by taking into account the dosing regimens of patients.

Moreover, NPDEs further correct this discrepancy, as each individual tobramycin concentration is compared to the simulated one, taking individual dosing and covariates into account. (iv) An unknown source of variability may not have been considered. It is known that the concomitant administration of a BL affects the PK of tobramycin (19). Set as covariate, the administration of a BL may explain this inter-individual discrepancy.

A new model must be developed for this adult CF population in order to make relevant Monte-Carlo simulations.

Current tobramycin regimen

Most decisions regarding antibiotic use are based on expert opinion with few high-quality studies to support what is done. This is reflected by the lack of consensus as a large variability dosing regimens exists between CF centers (7, 20, 21). A regimen of 8-10 mg/kg/day has been shown to achieve peak tobramycin concentrations of 20-30 mg/L (22, 23), a widely accepted PK/pharmacodynamics target in the treatment of APEs. However, this strategy is questioned by our results and some previously reported (9, 24). An average dosage of 7.8 mg/kg/day achieved an average C_{max} of 17.9 mg/L in our patients, still within the local target range of 15-25 mg/L, but lower than expected. Higher doses may increase concentration and effectiveness, however, they also increase toxicity (25). Furthermore, the PK of aminoglycosides is altered in patients with CF (26, 27), given the individual variability in the disease itself, CF patients may need a more personalized strategy when it comes to tobramycin dosing.

Concomitant antibiotics

The interaction between various intravenous medications for APE is considered important to ensure optimal treatment (28, 29). This was assessed retrospectively in 162 adult CF patients with continuous intravenous infusion of BL antibiotics, in combination with intravenous tobramycin (19). The BL clearance rate increased by nearly 21% while the tobramycin clearance rate decreased by 6.3% between admission and discharge (19). A specific combination of antibiotics appears to change the basic PK properties of tobramycin. This synergy introduces further variability when treating an APE and may be an important factor to consider when evaluating dosing strategies.

Tobramycin concomitant to ceftazidime and to piperacillin/tazobactam were the only combinations that significantly impacted the composite criterion in this study, increasing the probability of a positive outcome. Given their wide confidence interval, specific recommendations cannot be made. However, ceftazidime in combination with tobramycin has been previously shown effective in the treatment of an APE and our results support the superiority of this combination (30). Anaerobic organisms identified by non-culture methods appear prevalent in APEs (31), antibiotic treatment covering these organisms may be more effective.

The presence of microorganisms other than *P. aeruginosa* is rarely investigated and may need to be integrated in the rationale behind the treatment of an APE. Although not significant in our study, the presence of such organisms showed a trend towards impacting the clinical efficacy of current treatments, especially resistant organisms. Higher-powered studies are needed to evaluate the impact of these additional organisms and how to manage them.

APE occurrence per patients

Our results show that each subsequent APE significantly decreases the probability of achieving a positive outcome by 24% in individual patients. Such decrease may be the result of bacterial resistance. The prevalence of *P. aeruginosa* among CF patients increases with age. Approximately 20% of patients < 6 years of age are infected, compared to 70% of those who are 35 to 44 years of age (32). The incidence and complexity of *P. aeruginosa* resistance has been increasing over time (33), which can impact the effectiveness of tobramycin on subsequent APEs.

Our results support previous observations that intravenous antibiotic treated APEs are associated with subsequent decline in $ppFEV_1$ (34), effectively decreasing the probability of return to baseline. Furthermore,

it was shown that 1-2 exacerbations/year increases the risk of death 3-fold, and [?] 3 exacerbations/year increases the risk of death 4.5-fold (4). Subsequent APEs are also associated with lower long-term health-related quality of life (35).

Limiting the number of APEs per patient is paramount in achieving positive clinical outcomes. Antimicrobial prophylaxis has been shown to be effective in young children (36, 37), however its use in adults remains controversial. Optimizing dosing strategies may result in faster and more effective eradication of causative organisms, which may, in turn, decrease early recurrences of APE (38).

Limitations

The database collected prior to the evaluation of the models is a retrospective database, derived from pharmacological therapeutic monitoring data. Hospital staff may imprecisely document the time of collection and administration. This imprecision can be up to 30 minutes. Moreover, only population PK models developed on NONMEM(r) with covariates readily available to us were evaluated. This reduces the number of models that were assessed. This retrospective cohort study lacks randomization, however, efforts to minimize this bias through the addition multiple variables in the analysis were done. APEs were only identified as of 2015 and only when treated with IV tobramycin. APEs prior to 2015 or not treated with tobramycin were not included in the study and may underestimate the absolute number of APE occurrences per patient. MICs were not readily available and susceptibility was classified as sensitive or resistant, as per our center's microbiology reports. This prevents the ability to capture variability inside a susceptibility group, which is likely to underpower our ability to identify a significant trend. Also, the smaller sample size for clinical outcomes may further impede the likelihood of detecting trends.

Conclusion

This retrospective cohort analysis advances that CF-specific variability is likely to cause the current tobramycin dosing regimen to be sub-optimal. Rigorous identification of additional factors is needed to account for this variability. The evaluation of regimens through their predictive attainment of PK/PD targets remains the fastest way to evaluate a dosing strategy and its factors. Clinically history of APEs is predictive of clinical outcomes. Further population PK models must be developed in our population to optimize current treatment thus increasing clinical efficacy.

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