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Original Article

## Exploration of the relationship between cumulative exposure to tobramycin and ototoxicity in patients with cystic fibrosis

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### ABSTRACT

**Background:** Aminoglycosides (AGs), such as tobramycin, are essential antibiotics in the management of pulmonary infections in patients with cystic fibrosis (CF). They induce ototoxicity without the relationship being clearly described in the literature. Our aim is to propose a mathematical and statistical model describing the relationship between the estimated cumulative exposure (Area Under the Curve, AUC) to tobramycin and ototoxicity with audiogram interpretation in young patients with CF.

**Methods:** Cumulative AUCs were estimated for each course of tobramycin, for the 106 individuals with CF (between 4 and 22 years of age) enrolled in this retrospective study (35 who had received IV tobramycin, 71 controls). Mean hearing loss was calculated for each audiogram and a statistical model was developed to predict hearing loss.

**Results:** The model confirms a significant relationship between cumulative tobramycin exposure and changes in hearing acuity:

$$\text{Mean hearing loss} = 2.7 + (3 \times 10^{-5}) \times \text{AUC}_{\text{tobramycin}} + \text{individual\_susceptibility}$$

However, the ototoxic effect is not clinically perceptible (mean hearing loss: 3.8 dB). The impact of AUC on hearing loss is minor in these subjects who received a limited number of courses of tobramycin (median: 5 courses).

**Conclusion:** A significant relationship between cumulative exposure to tobramycin and ototoxicity was demonstrated. Individual treatment susceptibility should not be overlooked. As ototoxicity is not clinically perceptible in the study subjects, hearing tests should be continued during adulthood to provide individualized medical guidance and to obtain a lifetime analysis of the relationship between exposure and hearing loss.

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### 1. Introduction

Aminoglycosides (AGs) are a major class of medicinal products in the management of cystic fibrosis (CF) patients. Both the intra-

*Abbreviations:* AG, Aminoglycosides; AUC, Area Under the Curve; CF, Cystic Fibrosis; CFC, Cystic Fibrosis Center; C<sub>max</sub>, Peak concentration of antibiotics; dB, Decibel; Hz, Hertz; IV, Intravenous; MIC, Minimum Inhibitory Concentration; PK, Pharmacokinetics; PK-PD, Pharmacokinetics-Pharmacodynamics.

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venous (IV) and inhaled forms are used to treat lung infections caused by micro-organisms such as *Pseudomonas aeruginosa* [1]. They were among the first effective therapeutic agents in the treatment of infections caused by Gram-negative bacteria. They are IV-administered hydrophilic antibiotics with concentration-dependent bactericidal activity. After entering the bacteria, AGs act by inhibiting bacterial protein synthesis through irreversible binding to ribosomes (30S subunit of 16S ribosomal RNA), which leads to the synthesis of defective messenger RNAs and then defective proteins.

Aminoglycosides have a synergistic bactericidal effect with other antibiotics, such as  $\beta$ -lactams and vancomycin [2,3].

The Pharmacokinetics-Pharmacodynamics (PK-PD) criterion recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to characterize the efficacy of aminoglycosides is the AUC/MIC ratio, where AUC is the area under the aminoglycoside plasma concentration curve and MIC (Minimum Inhibitory Concentration) is the minimum concentration of antibiotic capable of inhibiting the bacterial growth. However, this PK-PD criterion is difficult to apply in clinical practice, as the measurement of AUC requires repeated blood sampling. Thus, the PK-PD criterion retained for aminoglycosides is a  $C_{max}/MIC$  ratio  $> 8 - 10 \times MIC$ .  $C_{max}$ , or peak concentration, is the concentration measured at the peak, approximately 30 min after parenteral administration of the aminoglycoside over a period of 30 min [4].

The main adverse effects of AG therapy are reversible and cumulative nephrotoxicity and irreversible ototoxicity, including cochleotoxicity (with symptoms such as hearing loss and tinnitus), and vestibulotoxicity causing vertigo [5].

Megaline-mediated endocytosis is primarily responsible for accumulation of AG in the renal proximal tubule, resulting in direct cellular injury and death [6]. However, this phenomenon can be saturated. Indeed, studies have shown that once-daily administration of aminoglycoside is less toxic than multiple daily doses [7]. As a direct clinical application, the dosing regimen of AG applied to date, regardless of the medical indication, is one dose per day.

The lack of ototoxicity markers that can easily be used *in vivo*/clinical practice, is a limiting factor in its evaluation [7,8]. However, clinical studies have highlighted the cumulative aspect of this toxicity. The incidence of ototoxicity was studied in a prospective study after the initial administration of tobramycin at a dose of 10 mg/kg/day for 10 days in patients with cystic fibrosis. The patients enrolled in the study performed various hearing tests (pure tone audiometry, distortion product otoacoustic emission, words in noise test, tinnitus functional index, and vertigo symptoms scale). This work shows that a course of IV tobramycin caused cochleotoxicity in 93% of the patients, according to American Academy of Audiology (AAA) and American-Speech-Language-Hearing-Association (ASHA) criteria. Other impairments reported by patients included the presence of tinnitus, the sensation of dizziness, and the inability to decipher certain words [5]. In a similar way, in a study assessing the effects of cumulative doses of intravenous aminoglycosides on the hearing status of cystic fibrosis patients, those who received a cumulative dose of 152–647 mg/kg (highest exposure quartile) had a 4.5-fold greater risk of cochleovestibular damage compared to those who received a cumulative dose of 16–52 mg/kg (middle exposure quartile) [9].

Based on data collected by The Paediatric Otorhinolaryngology Department and the Cystic Fibrosis Center (CFC) of the Toulouse University Hospital, our aim was to create a mathematical and statistical model to explain and predict the relationship between the estimated cumulative AUC of tobramycin and ototoxicity.

## 2. Patients and methods

This study is an observational, retrospective, single-center study that was approved by the Toulouse University Hospital review board (registration number: RnIPH 2022–119; CNIL number: 2206723 v 0).

All patients followed up at the CFC prior to reaching 18 years of age and who had audiometric tests during their follow-up (i.e., before and after tobramycin administration) were enrolled in the study. One hundred and six patients were retained. Of these, 35 had received intravenous tobramycin treatments, and 71 were not exposed to the medication.

The demographic and clinical data (age, gender, weight and height) of the patients during each course of IV tobramycin therapy were collected using Mucodomeos software. Pharmacological data related to IV tobramycin administration (dose received at each course, dates of the courses, duration of treatment) and concomitant prescriptions (oral azithromycin) were also collected using Mucodomeos. Biological data (plasma creatinine value during each course, expressed in  $\mu\text{mol/L}$ ) were collected from the OR-BIS computer system of Toulouse University Hospital. The Schwartz formula was used to calculate the Glomerular Filtration Rate (GFR) as shown below (with  $k$  being a constant that varies with age and sex) [10]:

$$GFR = \frac{k \times \text{height}}{\text{creatinine}}$$

Tone audiometry results for frequencies between 500 and 4000 Hertz (Hz) (corresponding to conversational frequencies) were used for the audiometry data in this study. Pure tone audiometry is a quantitative hearing analysis, which searches an audibility threshold. It can be determined using two methods, namely bone conduction, testing only the inner ear, and air conduction with headphones, testing the whole ear. The tonal audiogram obtained can differentiate between conductive and sensorineural hearing loss. In subjects with CF, both types of hearing loss exist but only sensorineural hearing loss is treatment related. Frequently bilateral and symmetrical, it tends to concern the high frequencies. Conductive deafness is related to the presence of serous otitis in these patients, and to nasosinus polyposis. Since the tonal audiogram distinguishes between both types of hearing loss, conductive hearing loss was not considered in this study, hence the model developed reviewed only AG-related ototoxicity.

The deafness criteria used in the study are those of the International Bureau for Audiophonology. Mean hearing loss was calculated, from the loss in dB for right and left ear together, at the frequencies of 500 Hz (F500), 1000 Hz (F1000), 2000 Hz (F2000) and 4000 Hz (F4000), with the following equation: [11]

$$\text{Mean hearing loss} = \frac{F500 + F1000 + \frac{F2000 + F4000}{2}}{4}$$

The R software was used to estimate the AUC of tobramycin plasma concentrations based on a Population Pharmacokinetics model from the literature [12]. This pharmacokinetic model is described in the equation below:

$$Y_{ij} = f(t_{ij}, \Psi_i) + f(t_{ij}, \Psi_i)\varepsilon_{ij}$$

$$\Psi_i = g(x_i, \theta) + \eta_i$$

- $Y_{ij}$ :  $j$ th concentration measured in the  $i$ th individual, at the  $t_{ij}$  instant
- $\Psi_i$ : pharmacokinetic parameters of the  $i$ th individual
- $\varepsilon_{ij}$ : standard Gaussian random variables
- $X_i$ : covariates explaining the variation of  $\Psi_i$  from one individual to another

For each patient, based both on this model and the patient's covariates value (creatinine level, weight, height), tobramycin exposure was estimated after each administration, allowing to obtain the cumulative AUC to be obtained at the end of one treatment and then over subsequent treatments. Tobramycin inhalation treatments were not taken into account in the model for two main reasons:

- Its systemic passage is low, and generates a negligible exposure compared to the exposure observed during intravenous treatments [13]

**Table 1**

Demographic, biological and clinical characteristics of the patients enrolled in the study.

Number of patients		106
Age (years)	Minimal	4
	Median	10
	Maximum	22
Weight (kg)	Median	30
Height (cm)	Median	137.8
Creatinine ( $\mu\text{mol/L}$ )	Median	43

**Table 2**

Pharmacological and audiometric characteristics of the patients enrolled in the study.

Number of courses	Minimal	0
	Median	5
	Maximum	17
Cumulative dose of tobramycin (mg)	Mean	5411
Area under the curve of plasma tobramycin concentrations versus time (mg.h/L)	Minimal	0
	Mean	1943
	Maximum	28,651
Mean hearing loss (left+right ear) (dB)	Minimal	0
	Mean	3.83
	Maximum	15.64

- The systemic passage of Tobramycin by inhalation is very variable according to the patients, probably due to the nebulization techniques and to the variable pulmonary involvement in the patients [14]

A multiple regression model was used to assess the relationship between tobramycin exposure and hearing impairment. This is a linear mixed model taking into account the effect of age, oral azithromycin intake, cumulative AUC representing the patients' exposure to tobramycin at the time of each hearing test, and an individual factor.

A statistical model was developed to predict hearing loss: the following equation was used to establish the relationship between cumulative tobramycin exposure and hearing impairment:

$$\text{Mean hearing loss} = \mu + \text{Ind}_i + \alpha \times \text{AUC}_{ij} + \beta \times \text{age}_{ij} + \varepsilon_i$$

Where  $\mu$  is the average hearing loss over the losses measured at frequencies at 500, 1000, 2000, and 4000 Hz,  $\text{Ind}_i$  is the individual factor that impacts the mean value  $\mu$ ,  $\alpha$  represents the influence of AUC on hearing loss,  $\beta$  represents the influence of age, and  $\varepsilon$  is an uncontrollable variability factor commonly referred to as the "residual error."

### 3. Results

The patients' demographic, clinical and biological data are summarised in Table 1. The pharmacological and tone audiometry data are presented in Table 2.

The linear multiple regression model highlighted the significant effect of AUC, age, and an individual factor on the mean hearing loss.

Given the limited number of hearing tests performed, it was not possible to differentiate between the effect of age and exposure (AUC) on the hearing loss. Consequently, age appears to be a confounding factor in the model and was not retained in favor of the cumulative AUC of tobramycin.

The model confirms a relationship between cumulative exposure to IV tobramycin and a change in hearing acuity in the patients enrolled in the study, based on the following equation:

$$\text{Mean hearing loss} = 2.7 + (3 \times 10^{-5}) \times \text{AUC}_{\text{tobramycin}} + \text{individual\_susceptibility}$$

In this equation, the term "individual" represents the patient's individual susceptibility factor to AG therapy, which is significant and cannot be anticipated. Azithromycin had no significant effect on the change in hearing acuity.

Prior to administering any tobramycin therapy (i.e., for an AUC of 0 mg.h/L), the mean threshold for frequency detection is 2.7 dB, which may be higher or lower depending on the term "individual" in the model. Thus, this term reflects inter-individual variability in frequency detection before any treatment. When tobramycin courses begin, the hearing loss increases by  $3 \times 10^{-5}$  for an AUC increase of 1 mg.h/L. For example, in patients with the highest cumulative exposures (cumulative AUC of approximately 28,000 mg.h/L), the impact on hearing loss is very small and of the order of 0.9 dB. In the study population, most patients received fewer than 10 courses of tobramycin, except for two patients who received 14 and 17 courses, respectively. Thus, the patients did not have any discernible hearing impairment according to the International Bureau for Audiophonology definition (mean hearing loss > 20 dB).

Azithromycin was evaluated in this study and did not have a significant effect on the ototoxicity triggered in these patients. The administration of tobramycin via the inhaled route was not considered because of its low systemic passage [13].

### 4. Discussion

A significant relationship between cumulative exposure to intravenous tobramycin and a change in hearing acuity was demonstrated. Age was identified as a confounding factor in this model and was excluded from the analysis. Data from the Cystic Fibrosis Patient Registry (Cystic Fibrosis Foundation, 2018) suggest that the prevalence of hearing loss in cystic fibrosis patients is low, estimated at 2.4% overall and 1.3% in patients under 18 years of age. Deafness may well not be related to the natural evolution of the condition in these patients [15].

The completeness of the database proved to be a limiting factor in the data analysis, underlining the importance of exhaustive data collection from patients throughout their lives.

Over time, patients receive an increasing number of courses of IV tobramycin therapy because of more frequent respiratory infections associated with the progression of cystic fibrosis. In a study, children who received more than 10 courses had a higher risk of ototoxicity [16]. In another study, the mean age associated with hearing loss was 33 years [17]. Patients in our pediatric study cohort may not have reached a sufficient cumulative AUC level to generate clinically quantifiable ototoxicity.

Our hypothesis is that the mathematical model describing the relationship between ototoxicity and the tobramycin AUCs presents an inflection point beyond the study population, probably in the adult population, making the multiple linear model obsolete beyond a certain number of courses of treatment (i.e., beyond a certain age) in favor of a sigmoidal model.

As cumulative exposure to AGs is correlated with hearing loss, strategies to adapt AG doses to *Pseudomonas aeruginosa*'s MIC should be enhanced, all the more in children recently colonized with a germ likely to have a lower MIC [18]. Thus, a Therapeutic Drug Monitoring (TDM) coupled with bacteria's MIC determination to achieve  $C_{\text{max}}/\text{MIC}$  ratio > 8 to 10 x MIC seems essential in young patients.

One limitation of this work concerns the date on which the audiometric tests were performed. The tests were sometimes conducted independently of tobramycin administration. However, as reliable treatment-related data were collected for the patients eli-

gible for analysis, the tobramycin AUCs were considered unchanged and were compared with the hearing test. Conversely, hearing tests were sometimes performed early post-treatment, i.e. within a few days, but ototoxicity onset could take weeks or months [19]. Moreover, ototoxicity is a complication that fluctuates over time and is sometimes asymmetric [17]. The mean hearing loss measured in the right and left ears was considered in this instance. Indeed, overall hearing loss could be underestimated if one side was more affected than the other. Each frequency was tested separately and it was found that there was little significant difference in the low frequencies (500 and 1000 Hz). However, the frequency at 2000 Hz showed a clear and strong impact of the injected tobramycin. As the structure of the population could have a strong influence on the results, the average of the frequencies was preferred to be used when presenting the results.

This underestimation of the hearing loss may be emphasized by the fact that ototoxicity often affects high frequencies (over 6 kHz) at the beginning [11]. High frequencies have been shown to be implicated in speech recognition, in noise and in sound localization [20,21]. The usual mean auditory tonal threshold performed in silent conditions appears insufficient to evaluate well cochlear ototoxicity as it is limited to frequencies from 0.5 kHz to 4 kHz. The use of high frequencies audiometry and/or speech in noise recognition tests might be better at detecting pauci-symptomatic hearing loss and have been proposed for platinum-based chemotherapy follow-up [22]. New statistical models utilizing these measures could be of great interest for future studies. This is something we may explore in the coming years. However, given the retrospective nature of our study, we have chosen to focus on the frequencies typically used in standard audiometry. Some of the patients recently included in our cohort have high frequency hearing data available.

We observed a large inter-individual variability that could be explained by factors unstudied in the model, such as the patients' exposure to other treatments including loop diuretics (hydrochlorothiazide), exposure to noise, and genetic factors [17]. A genetic predisposition to AG ototoxicity has been identified and was observed in 17 to 33% of hearing-impaired patients [1]. This is the A155G mutation in the mitochondrial genome [23]. The prevalence of the A155G mutation varies by ethnicity, with two UK studies indicating a prevalence of 0.19% and 0.26%, respectively [24]. A study conducted in adult CF patients highlighted a prevalence of 1.3% for this gene. Several polymorphisms of this mutation have been linked to hearing loss [25]. Published data regarding the influence of genetics on AG-induced ototoxicity are variable, and this genetic component is one of the limitations of our model, represented by the term "Individual" in the equation. Aminoglycoside ototoxicity would tend to increase in patients with this mutation. Since we are unable to identify this genetic factor in patients, it is even more important to exercise caution when AGs are used in subjects older than the current study cohort.

The CFTR modulator therapy Elexacaftor, Tezacaftor, Ivacaftor (ETI) appears to have revolutionised the management of cystic fibrosis patients and to limit the number of respiratory infections to considerable extent. Pediatric cohort subjects will perhaps not reflect an age-dependant increase in the number of courses of tobramycin therapy, as evidence in patients prior to the market launch of ETI. However, this treatment is not indicated for all cystic fibrosis patients, and the anticipation of clinically perceptible ototoxicity could be beneficial for patients not eligible for ETI treatment.

## 5. Conclusions

In conclusion, a significant relationship has been demonstrated between cumulative exposure to tobramycin and variation in mean

hearing loss measured by pure tone audiometry. It is likely that at the cumulative AUC of 28,000 mg.h/L, the auditory toxicity of AGs is not sufficient to be considered significant.

Azithromycin, which was supposed to be a concomitant ototoxic prescription for these children, did not exert a significant effect on hearing acuity in our analysis.

This study should be continued with the lifelong hearing follow-up of the patients enrolled in the study, the aim being to document hearing during adulthood. Once the cumulative AUC at which deafness occurs is identified, this will allow to define an optimal administration strategy to limit their ototoxicity. Therapeutic Drug Monitoring (TDM) also has a major role to play in assessing cumulative exposure in individuals. It should not be overlooked in children and it is essential for adults, in whom renal function may be impaired, possibly resulting in uncontrolled exposure to aminoglycosides.

## Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Justine Madaule:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Félix Valenzuela:** Conceptualization, Investigation. **Marie Mittaine:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Yohan Gallois:** Conceptualization, Methodology, Writing – review & editing. **Blandine Baladi:** Writing – review & editing. **Marlène Murriss:** Writing – review & editing. **Marie-Noelle Calmels:** Writing – review & editing. **Didier Concordet:** Methodology, Software, Formal analysis, Writing – original draft. **Peggy Gandia:** Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing.

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