Population pharmacokinetics of tobramycin administered thrice daily and once daily in children and adults with cystic fibrosis

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Abstract

Background: Tobramycin pharmacokinetics have not been evaluated previously in a large series of data collected in children and adults with CF receiving once (OD) or three times daily (TD) tobramycin.

Methods: Therapeutic drug monitoring data in children and adults with CF who participated in a randomised clinical trial evaluating efficacy and toxicity of OD versus TD tobramycin (TOPIC study) were analysed retrospectively. Population pharmacokinetic models stratified to treatment schedule were created, and individual pharmacokinetic parameters were calculated.

Results: In paediatric patients, volume of distribution per kg body weight (V1) was greater with OD treatment compared to TD (0.401 ± 0.092 versus 0.354 ± 0.041, p = 0.003). Elimination rate was reduced in all patients receiving OD tobramycin compared to TD (children: 0.00197 ± 0.00027 versus 0.00291 ± 0.00041, p < 0.001, adults: 0.00252 ± 0.00008 versus 0.00322 ± 0.00050, p < 0.001). Tobramycin V1 decreased with increasing age (R² = 0.3, p < 0.001).

Conclusions: The reduced elimination rate in OD may either be caused by circadian pharmacokinetic behaviour of tobramycin or indicates early renal damage caused by high tobramycin doses not detected by biochemical measurements. However, results of our previous work suggest that OD tobramycin may be less nephrotoxic. The higher V1 in children implies that a relative higher tobramycin dose in these patients is needed for the same target peak serum concentration.

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1. Introduction

A cornerstone of the antimicrobial treatment of patients with cystic fibrosis (CF) is the intravenous administration of tobramycin [1]. Despite more than 50 years of experience with aminoglycosides, there is still debate on the optimal way to administer these drugs. Serious drawbacks for aminoglycoside use are nephro- and ototoxicity. However, aminoglycosides, particularly tobramycin, are highly active against the most important cystic fibrosis pathogen, Pseudomonas aeruginosa, and so these drugs are likely to retain an important role in the management of pulmonary infection in cystic fibrosis.

Since the introduction of aminoglycosides, initiatives have been taken to optimise their management, thereby increasing efficacy, minimising toxicity and reducing the development of resistance. In vitro research has provided evidence that once daily dosing (better named as extended interval dosing) may be at least as effective and less toxic as multiple daily dosing. In other diseases than CF, the use of extended interval dosing is widespread and recently the TOPIC study has added important clinical evidence to support this approach in patients with CF [2]. Another important initiative is the use of therapeutic drug monitoring (TDM) aimed at early optimisation of serum levels to...
increase efficacy and limit toxicity. Evidence suggests that early TDM may have beneficial effects on patients’ outcomes and toxicity [3]. For optimal guidance of tobramycin therapy in patients with CF, reliable population pharmacokinetic models are necessary; on the one hand to develop dosing schemes and on the other hand for TDM [4].

The TOPIC study is by far the largest study conducted in CF where pharmacokinetic data have been obtained in a structured way in adults and in children with cystic fibrosis. The TOPIC study can be seen as 4 cohorts of patients; children and adults receiving three times daily 3.3 mg/kg tobramycin, and children and adults receiving once daily 10 mg/kg tobramycin. The purpose of this post-hoc analysis was 1) to build pharmacokinetic models in children and in adults for tobramycin either administered three times daily 3.3 mg/kg body weight or once daily 10 mg/kg body weight to be utilised for TDM and dosage adjustment of tobramycin in children and adults with cystic fibrosis and 2) to compare these models with each other and with published data.

2. Materials and methods

2.1. Patients and treatment schedule

TOPIC study: Patients were enrolled from 21 cystic fibrosis centres in the UK (15 paediatric and 6 adult centres). The study was approved by Trent multicentre research ethics committee and by local ethics committees in all centres. Written informed consent was obtained from adult patients and from parents of children under 18 years (with the child or young person giving assent). All participants had a diagnosis of cystic fibrosis (i.e., sweat chloride>60 mmol/l or a genotype known to cause the disease). Patients were eligible if aged over 5 years and able to participate in pulmonary-function tests reliably. Patients were excluded if they had pre-existing hearing impairment or renal impairment (serum creatinine concentrations outside the reference range for the enrolling centre). Nebulised antibiotics were discontinued on study entry. Patients were randomly assigned to once or three times daily tobramycin, given as a 30-min infusion in 0.9% saline (31 ml for children, 65 ml for adults). Patients allocated to the once daily regimen also received two infusions of 0.9% saline per day, which was the same volume as the active infusions to preserve the double blind study protocol. Total daily doses equivalent to those previously received by patients during routine treatment were used. If a patient had not previously had tobramycin, a dose of 10 mg/kg/day was prescribed up to a maximum of 660 mg/day. Tobramycin concentrations were measured immediately before the fourth infusion and 30 min after the end of the fourth infusion. All samples were thus drawn at the same times. Target concentrations of tobramycin for the once daily regimen were 1 mg/l or less (trough) and 20–30 mg/l (peak); for the three times daily regimen, these values were 2 mg/l or less and 5–12 mg/l, respectively. If the trough concentration was higher than the target range, the patient was withdrawn from the study. If the peak concentration was outside the target range, an appropriate 10% increase or 10% reduction in dose was made as appropriate. In every case, patients previously had tobramycin, a dose of 10 mg/kg/day was prescribed up to a maximum of 660 mg/day. Tobramycin concentrations were measured immediately before the fourth infusion and 30 min after the end of the fourth infusion.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Three times daily tobramycin</th>
<th>Once daily tobramycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric patients (N)</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Male/female</td>
<td>28/15</td>
<td>25/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.0±3.0 (5–15)</td>
<td>9.8±3.4 (5–15)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>34±15 (15–78)</td>
<td>32±12 (16–60)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>80±25 (30–131)</td>
<td>70±24 (35–128)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>124±35 (77–229)</td>
<td>110±24 (49–157)</td>
</tr>
<tr>
<td>Tobramycin peak (mg/l)</td>
<td>8.1±1.3</td>
<td>22.7±4.0</td>
</tr>
<tr>
<td>Tobramycin trough (mg/l)</td>
<td>0.73±0.33</td>
<td>0.045±0.102</td>
</tr>
<tr>
<td>Adult patients (N)</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/12</td>
<td>14/15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22±6.3 (16–40)</td>
<td>24±8.4 (16–50)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>57.4±9.3 (43–82)</td>
<td>55.1±10.0 (31–80)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>93±18 (62–125)</td>
<td>92±20 (60–148)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>98±21 (63–147)</td>
<td>100±18 (72–150)</td>
</tr>
<tr>
<td>Tobramycin peak (mg/l)</td>
<td>7.9±1.4</td>
<td>22.6±4.6</td>
</tr>
<tr>
<td>Tobramycin trough (mg/l)</td>
<td>0.88±0.38</td>
<td>0.035±0.042</td>
</tr>
</tbody>
</table>

Numbers represent mean values±s.d. and range (between brackets).
2.2. Analytical technique

Samples were analysed in the participating study centres using fluorescence polarisation immuno-assays [5]. Since different assays were used in the different participating laboratories an overall assay error of $s.d. = 0.25 + 0.15 C$ (where $C$ is the concentration measured) was used in the population pharmacokinetic analysis. Because the assay error was taken into account, also levels that should have been reported as below the limit of quantitation were evaluated in the pharmacokinetic analysis.

2.3. Population pharmacokinetic analysis

At first, a single compartment open population pharmacokinetic model was made from all evaluable patient data. Population modelling was performed using the MW/Pharm pharmacokinetic software package version 3.60 [6]. In brief: data on the patients’ gender, age, weight, height, serum creatinine concentration, tobramycin dosages and tobramycin serum concentrations were recorded in the program. The pharmacokinetic equations used for the description of tobramycin pharmacokinetics were:

$$V = V_1 \times BW$$
$$TBC = V_1 \times BW \times Kel$$
$$Kel = Kelm + Kelr \times ClCr$$

where:

- $V$: volume of distribution (l)
- $V_1$: volume of distribution per kg body weight (l/kg)
- $BW$: body weight (kg)
- $TBC$: total body clearance (l/h)
- $Kel$: elimination rate constant (h$^{-1}$)
- $Kelm$: non-renal elimination rate constant (h$^{-1}$)
- $Kelr$: renal elimination rate constant per ml/min creatinine clearance (h$^{-1}$/ml/min/1.73 m$^2$)
- $ClCr$: estimated creatinine clearance

Creatinine clearance values were estimated using the formula of Schwartz [7] for paediatric patients and the formula proposed by Jelliffe [8] for adult patients. A model previously derived from a population of CF patients was used as starting (or prior) model [9]. Because there were no patients included in the TOPIC study with a poor renal function, population analysis would provide no information on non-renal or metabolic elimination rate constant ($Kelm$). Therefore, $Kelm$ was fixed at a value of 0.01 h$^{-1}$, corresponding with a tobramycin terminal half-life of 70 h, a value obtained from literature [9,10].

The continuous covariates that were analysed were age, body weight and serum creatinine concentration.

The values of the population pharmacokinetic parameters $V_1$ and $Kel$, the intersubject variability in each parameter and the residual error that describe the differences between the measured and the predicted concentrations were estimated using iterative two-stage Bayesian regression.

<table>
<thead>
<tr>
<th>Three times daily</th>
<th>Once daily</th>
<th>$p$</th>
</tr>
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<tbody>
<tr>
<td>(N=43)</td>
<td>(N=42)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Paediatric patients receiving tobramycin</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$ (l/kg)</td>
<td>0.354±0.041</td>
<td>0.401±0.092</td>
<td>0.003</td>
</tr>
<tr>
<td>$Kelm$ (hr$^{-1}$)</td>
<td>0.01*</td>
<td>0.01*</td>
<td>–</td>
</tr>
<tr>
<td>$Kelr$ (hr$^{-1}$/ml/min/1.73 m$^2$)</td>
<td>0.00291±0.00041</td>
<td>0.00197±0.00027</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adult patients receiving tobramycin</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$ (l/kg)</td>
<td>0.295±0.060</td>
<td>0.365±0.050</td>
<td>0.16</td>
</tr>
<tr>
<td>$Kelm$ (hr$^{-1}$)</td>
<td>0.01*</td>
<td>0.01*</td>
<td>–</td>
</tr>
<tr>
<td>$Kelr$ (hr$^{-1}$/ml/min/1.73 m$^2$)</td>
<td>0.00322±0.00050</td>
<td>0.00252±0.00008</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$V_1$: volume of distribution per kg body weight; $Kelm$: metabolic elimination rate; $Kelr$: renal elimination rate per ml/min/1.73 m$^2$ creatinine clearance; *: value fixed to 0.01 because of lack of data (for explanation: see text).
The criteria used to accept the model included the difference in objective functions ($p < 0.0001$ being considered to represent a significant improvement in fit), inspection of the parameter value distribution in each cohort of patients, convergence plots of parameter estimates and the log-likelihood (sum of all patients analysed).

The overall pharmacokinetic model so obtained was again used as prior model to make two new a priori models, one for children and one for adult patients. The derived model for the children was further used to build a model for the subpopulation of paediatric patients receiving tobramycin three times daily and a separate model for the subpopulation of paediatric patients receiving tobramycin once daily. The same was done for adults using the adult model as prior.

The mean parameter values for each cohort of patients were used to compare the pharmacokinetic parameters of all 4 cohorts of patients and with values from the published literature.

Individual pharmacokinetic parameter values were obtained by fitting the appropriate a priori model for the 4 cohorts of patients to the individual data points. Individual pharmacokinetic data points were plotted against age to investigate this relationship.

### 3. Results

The TOPIC study enrolled 244 patients who were randomised to three times daily or once daily tobramycin. Of these, 219 patients completed the study per protocol. More details on the results are published in the TOPIC paper [2]. After inspection of all data of these patients, 136 patients were eligible for inclusion in the post-hoc pharmacokinetic analysis (43 paediatric patients on three times daily tobramycin and 42 paediatric patients on once daily tobramycin, 22 adult patients on three times daily tobramycin and 29 adult patients on once daily tobramycin).

The characteristics of the patients included in the post-hoc analysis are shown in Table 1. Apart from an uneven distribution of male and female patients in the paediatric subpopulations, the groups were comparable.

Table 2 shows the models that were built for the population as a whole, the paediatric and adult subpopulations and Table 3 shows the models stratified to the treatment schedule and their statistics. Volume of distribution was significantly larger in the paediatric population receiving once daily tobramycin and Kelr was higher in the three times daily cohorts in both the paediatric and adult populations (Table 3).

The relationship between volume of distribution per kg body weight and age is shown in Fig. 1 which illustrates the significant trend, with lower values for V1 with increasing age (non-linear regression, $R^2 = 0.3$, $N = 136$, $p < 0.001$).

The relationship between elimination rate per ml/min/1.73 m$^2$ creatinine clearance and age is shown in Fig. 2.

### 4. Discussion

In this retrospective study we found that the volume of distribution was significantly greater with once daily treatment compared to three times daily in paediatric patients. The elimination rate of tobramycin, for once daily, was prolonged compared with three times daily dosing in both children and adults. Further, a significant trend for a smaller volume of distribution per kg body weight of tobramycin with increasing age was observed.

The main strength of the present study is the large population studied and the uniform protocol of drug administration and data analysis.

Our study stresses again the large intersubject variability in pharmacokinetic parameter values for tobramycin in patients with CF. Optimal efficacy of aminoglycosides is reached with a peak serum concentration/Minimal Inhibitory Concentration (peak/MIC) ratio of 10. With a good total body clearance of tobramycin, peak serum concentration largely depends on volume of distribution. Mean volume of distribution per kg body weight is 0.363 l/kg in paediatric patients compared to 0.294 in adult patients ($p < 0.001$). This means that for the same target peak serum concentration, paediatric patients need on average a 20% higher dose on a mg/kg body weight basis compared to adults. Moreover, the coefficient of variation of the volume of distribution per kg body weight is large (22% in the paediatric population and 15% in the adult population) further adding to the wide interindividual difference in tobramycin dosing range on a mg/kg basis to obtain comparable target peak serum concentration levels. Therefore, therapeutic drug monitoring is an important tool to optimise tobramycin dose.

Together with the publication of the initial report of the TOPIC study [2], there was debate about the correct use of a 1-compartment model for tobramycin [11,12]. It was argued that pharmacokinetics of tobramycin administered 10 mg/kg/day on a once daily basis is probably better described by a 2-compartment model than a 1-compartment model [13]. In the latter paper it was demonstrated that tobramycin volume of distribution of the central compartment tended to be smaller in the once daily group due to delayed distribution of the drug [13]. It was also argued that the peak level preferably be drawn 2 h after administration [13]. Bates [14] however, demonstrated that tobramycin distribution is completed 1 h after administration and based on these results a 1-h postdose peak level was chosen in the design of the TOPIC study. In our post-hoc pharmacokinetic analysis we found a small but significantly larger volume of distribution of tobramycin in the paediatric patients who received once daily tobramycin.

If a 2-compartment model was appropriate for tobramycin then one would expect peak serum concentrations to be relatively higher in children and adults receiving tobramycin once daily than in the three times daily groups, as reflection of the smaller volume of distribution in the central compartment for the once daily group as found by Aminimanizani [13]. Our results, however, show similar...
values for tobramycin volume of distribution per kg body weight in the two adult groups and a small but significantly higher value in the paediatric patients receiving tobramycin once daily, contrary to what could be expected if a 2-compartment model would describe the pharmacokinetics. This means that at least in our population a 2-compartment model would have had no advantages over the 1-compartment model we used, providing further evidence in favour of the design of the TOPIC study.

A higher volume of distribution is generally seen in a younger population or may be associated with a poorer clinical state. Our demographics show that both paediatric populations did not differ with respect to age and body weight. As baseline FEV1 values in the paediatric patients receiving either once daily tobramycin or three times daily tobramycin were comparable [2], we have no straightforward explanation for the difference in volume of distribution.

Fig. 1 of V1 against age suggests the lowering trend for V1 with increasing age. This finding is not surprising. Tobramycin is like all other aminoglycosides a highly water soluble drug that distributes mainly into extracellular fluid. With increasing age, the relative amount of extracellular fluid tends to decrease. This trend of decreasing volume of distribution per kg body weight against age has also been described for gentamicin in a non-CF paediatric population [15].

We found significantly lower mean values for Kelr in both the paediatric and adult patient populations randomised to once daily administration compared with the three times daily administration. This is also depicted in Fig. 2. Kelr must be multiplied by CrCl to result in renal elimination constant. Creatinine clearance was estimated using the formula of Schwartz [7] for children and Jelliffe [8] for the adult population during the whole study and measurement of serum creatinine concentration did not change throughout the study. So our data suggest that the mean rate of elimination in our population is about 30% less in the populations who received tobramycin once daily. There are at least four possible explanations for the observation:

Firstly it is possible that patients receiving tobramycin once daily had more severely damaged kidneys than patients receiving tobramycin three times daily. We feel that this is unlikely as patients who entered the TOPIC study were randomly allocated to the once or three times daily administration regimen. There was no selection. Further, renal toxicity analysis in the TOPIC study demonstrated that at baseline mean renal function was comparable between the once and three times daily administration groups [2]. In our view, more renal damage in the patients randomised to once daily therefore can be excluded. Another possibility related to renal function is that once daily administration of 10 mg/kg body weight of tobramycin results in early renal damage that is not revealed by the usual biochemical tests. Aminoglycoside toxicity is related to dose and to the length of the therapy. After 10–14 days of therapy, measurable signs of nephrotoxicity appear. A rise of creatinine concentration as marker of nephrotoxicity has been demonstrated for adults in other diseases than CF [22,16]. However, in the TOPIC study children who received once daily tobramycin [2] actually had a fall in mean creatinine concentration after 14 days of treatment and so we feel that early renal damage is unlikely to explain the prolonged Kelr seen in our retrospective analysis.

Secondly it is possible that tobramycin clearance is saturable at higher dosages. Saturable pharmacokinetics of renally cleared drugs is not uncommon. This phenomenon has for example also been described for piperacillin in CF patients [17]. However, pharmacokinetic behaviour of piperacillin and tobramycin are different. Piperacillin is filtered by the glomerulus as well as actively excreted in the proximal tubule, whereas tobramycin is filtered by the glomerulus and actively reabsorbed in the tubule [18]. For amikacin, saturation of tubular reabsorption has been observed [18]. In other comparative studies to the pharmacokinetics of once daily versus multiple daily administration of tobramycin there has been no sign of saturable pharmacokinetics [13,19]. Moreover, if saturation of reabsorption should occur, an increase of clearance would have been observed at higher doses, which is not the case in our study. So in our view, the observed differences in Kelr cannot be ascribed to non-linear clearance.

A third possibility is the issue of model misspecification. Our data were analysed by a 1-compartment model, but in theory a 2-compartment model could also apply (see the discussion above). On prolonged administration of tobramycin this will lead to tissue accumulation and redistribution from the tissues can contribute to higher trough concentrations particularly with once daily dosing where the trough levels are much lower (greater impact of tissue redistribution). However, most levels were drawn at the beginning of the tobramycin therapy when tissue accumulation does not yet contribute to trough levels and moreover our data were separately analysed using a 2-compartment model. This analysis also demonstrated a reduced value for Kelr in the once daily group, consistent with the results obtained from the 1-compartment analysis (data not shown). Therefore, in our view, model misspecification does not explain our findings.

Finally we considered whether the differences in clearance observed are due to a circadian rhythm of the clearance of the drug. This might have been influenced by the timing of administration. After inspection of the TOPIC data, 53 out of the 71 patients in the once daily group received their active dose between 16.00 and 20.00 h. This means that in most patients, most of the drug is in the body at resting time. It has been demonstrated in animal studies that clearance of aminoglycosides is significantly higher during night time, which is the period of activity of these animals, and toxicity is lower when these drugs are administered during the activity period. For healthy humans, a circadian rhythm of
glomerular filtration has been demonstrated [20]. However, patient data on a circadian rhythm of drug clearance are conflicting. In a prospective study no evidence was found for a circadian rhythm in gentamicin pharmacokinetics in severely ill patients [21]. Administration of the drug during resting time, however, did result in significantly more nephrotoxicity [21]. On the other hand, in endocarditis patients amikacin clearance was best described by a model taking circadian variation of creatinine clearance into account [22]. In CF patients who were treated with a continuous infusion of ceftazidime, a circadian rhythm for ceftazidime clearance was observed with a reduced clearance during resting hours [23]. Other investigators found a lower total body clearance for aminoglycosides during the resting period [24–26] or no difference [27]. These conflicting results may be caused by the nature of the patients studied. From animal studies it is clear that there are circadian differences related to night time and daytime, or, in other words, to activity and rest. In patient studies, night time and daytime are not always similar to rest and activity. Studies that included severely ill patients [21,27] found no differences in aminoglycoside pharmacokinetics between daytime and night time, whereas studies with CF patients [23] and freely ambulating patients [24] did. Since CF patients are encouraged to exercise during daytime and, if treated at home, to resume their normal life, there is considerable activity at daytime. Further, it is interesting to note that Bleyzac et al. [25], who used the same type of population analysis as we performed, found a difference in elimination rate in the same order of magnitude for evening dosing versus morning dosing as we observed for once daily versus three times daily dosing. Another factor of influence on aminoglycoside clearance may be the dietary intake of proteins [28]. Thus, our observation of a lower Kelr for both paediatric and adult once daily groups may be the result of a circadian rhythm in drug clearance caused by either activity and rest or dietary protein intake or both combined with the administration of the active dose in the once daily group in the early evening.

In conclusion, we observed a significant difference in elimination constant with a 30% lower value for patients receiving the active dose of tobramycin once daily in the evening. This observation may be the result of a circadian rhythm in drug clearance as observed in other studies. A further possibility (which is not supported by the data from the TOPIC study) is a previously unknown aspect of aminoglycoside toxicity, with early renal toxicity at high dosages, not revealed by routine biochemistry measurements. We hope to study this in a trial that randomises patients on once daily tobramycin to 0800 h, 1600 h or 2400 h administration and studies the Kelr, creatinine and NAG concentrations. Until these results are available we would suggest that once daily tobramycin be administered in the morning. Further, the population pharmacokinetic models, provided by our study can be used to develop dosing schemes for predetermined tobramycin target peak and trough concentrations in CF patients. Because of the wide interindividual range of volume of distribution and hence in required dose for predetermined optimal serum concentrations to avoid underdosing on the one hand and too high serum concentrations on the other hand, monitoring of serum concentrations remains necessary.

Acknowledgement

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