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Original Article

Safety of inhaled (Tobi®) and intravenous tobramycin in young children with cystic fibrosis

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Abstract

Background: Use of inhaled tobramycin therapy for treatment of *Pseudomonas aeruginosa* infections in young children with cystic fibrosis (CF) is increasing. Safety data for pre-school children are sparse.
Methods: The aim of this study was to assess the safety of tobramycin solution for inhalation (TOBI®-TSI) administered twice daily for 2 months/course concurrently to intravenous (IV) tobramycin during *P. aeruginosa* eradication therapy in children (0–5 years). Audiological assessment and estimation of glomerular filtration rate (GFR) was measured prior to any exposure and end of the study.
Results: Data were available from 142 patients who were either never exposed to aminoglycosides (n = 39), exposed to IV aminoglycosides only (n = 36) or exposed to IV + TSI (n = 67). Median exposure to TSI was 113 days [59, 119]. Comparison of effects on audiometry results and GFR, showed no detectable difference between the groups.
Conclusions: Use of TSI and IV tobramycin in pre-school children with CF was not associated with detectable renal toxicity or ototoxicity.

Keywords: Aminoglycoside; Tobramycin solution for inhalation; Paediatrics; Cystic fibrosis; Adverse events

1. Background

Inhaled tobramycin has been a mainstay of treatment for those with cystic fibrosis (CF) for many years due to the excellent activity against *Pseudomonas aeruginosa* (*P. aeruginosa*) [1], the most common airway pathogen in CF. Tobramycin remains active after aeroionisation and is poorly absorbed across epithelial surfaces, thus achieving high concentrations in bronchial secretions with minimal systemic absorption [2]. Serum tobramycin concentrations after inhaled tobramycin are generally very low, with serum to sputum ratios of approximately 1% [3]. As a result, inhalation of tobramycin is anticipated to be associated with minimal systemic toxicity [4] in comparison to intravenous (IV) therapy which is known to be associated with increased risk of nephrotoxicity and ototoxicity [5–7].

Well recognised adverse events (AE) associated with aminoglycosides, and particularly tobramycin, include otovestibular and renal toxicity. Although precise mechanisms are unclear,

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it is likely that aminoglycoside-induced alteration of hair cell membrane permeability is integral to the ototoxic effects [7]. Similarly, nephrotoxicity is believed to occur as a result of retention of a portion of the administered dose in the cells of the proximal tubules of the nephrons [6]. Progression to renal failure is rare and recovery occurs upon discontinuation in most cases [8].

Treatment with tobramycin solution for inhalation (TSI), aimed at eradication of early *P. aeruginosa* infections is standard care in North America and frequently used in Europe and Australasia. There are few studies assessing the safety of TSI in young children. One small study using 300 mg TSI inhaled twice daily in 8 preschool children reported no AEs (changes in serum creatinine, audiometry and bronchospasm were assessed)[9]. A recent study including children aged 1–12 reported no AEs due to TSI although age of first exposure to TSI and methods for monitoring AEs were unclear [10]. Several studies have investigated inhaled tobramycin in older children and adults and reported very few treatment-related AEs. [1,11–13] The present study takes advantage of data from the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study which used TSI as part of the *P. aeruginosa* eradication protocol in preschool children [14]. Dosage and AE monitoring for IV tobramycin and TSI were protocol-driven over the entire 5 year study period, which allowed investigation of the safety profile of this medication.

2. Methods

2.1. Study and patients

The study design, protocol and other outcomes for ACFBAL study have previously been reported [14]. Briefly, the study which ended in December 2009, enrolled 170 infants diagnosed with CF across 8 sites in Australia and New Zealand and followed up until age 5 years.

Antibiotic treatment for *P. aeruginosa* infection included two weeks of IV therapy (once daily tobramycin commencing at a dose of 10 mg/kg, together with either 100 mg/kg ticarcillin–clavulanate three times a day or, 50 mg/kg ceftazidime three times a day). Tobramycin doses were adjusted by measuring 2 h and 6–14 h post-dose tobramycin concentrations and applying a linear regression method [15] aiming for an area under the concentration-time-curve of 100 mg/L.hr (with an acceptable AUC of 90 to 110 mg/L.h). Upon cessation of IV antibiotics, children received 56 days of TSI 300 mg (TOBI®) twice daily via a Pari LC Plus jet nebuliser with mask over a minimum of 15 min, or until nebulisation was complete. Concurrent oral ciprofloxacin (15 mg/kg twice daily) was administered for the first 28 days. As well as being used to treat proven infections with *P. aeruginosa*, IV antibiotics (including tobramycin) were administered to children who did not respond to outpatient treatment for a pulmonary exacerbation where *P. aeruginosa* was not detected upon microbiological culture. In these cases, the children did not receive follow-up treatment with TSI after completion of IV antibiotics.

For the present study all patients enrolled into the ACFBAL study with data available prior to any aminoglycoside exposure were included in order to compare the safety and toxicity between 3 distinct groups. The first group was designated 'never exposed' and children assigned to this group received neither IV aminoglycosides nor TSI during the 5 years. The second group; the 'IV only' group included children who received IV aminoglycosides treatment, predominantly tobramycin, but no TSI in the 5 years. Lastly, the third group, called the 'IV and TSI' group, as children assigned to this group received both IV aminoglycosides and inhaled TSI.

2.2. Safety assessment

Data collection included serum tobramycin concentration one hour after administration of TSI; renal function monitoring via estimation of glomerular filtration rate (GFR) and measurement of serum creatinine; audiometric function prior to and following exposure; and reported AEs. All comparisons were done between the first ever record and the closest to end of the study, unless specified otherwise.

2.2.1. Serum tobramycin concentration

The first dose of TSI was generally administered 24 h after cessation of IV tobramycin and normally after this first TSI dose tobramycin concentrations were measured 60 min. after the start of inhalation. Blood samples for tobramycin assay were collected via venipuncture or finger-prick depending on local practice. Investigations in April 2004 [16], demonstrated evidence for skin contamination with tobramycin after inhaled therapy affecting serum levels detected by finger prick. Consequently, samples taken via finger prick collections were analysed separately. The reported lower limit of quantification (LOQ) of tobramycin was 0.2 mg/L and thus any concentrations reported below LOQ were set to a value of LOQ/2.

2.2.2. Renal function

Cumulative renal toxicity over the study duration was assessed by comparing creatinine clearance at baseline (prior to aminoglycosides exposure) and creatinine clearance at the last measurement closest to end of study. These were summarised for each aminoglycoside group and mean differences compared. Creatinine clearance was assessed by estimating GFR using the Schwartz equation for pediatric patients[17].

To monitor the impact of an IV tobramycin course prior to TSI treatment on renal function, changes in serum creatinine concentrations measured within a patient during the same IV course were compared.

2.2.3. Audiometric function

Due to the age of the children in the study, the appropriate testing modality used at each audiometric assessment throughout the study was determined by the administering pediatric audiologists at each centre. Children were scheduled for screening audiometric assessments at baseline (<6 months of age prior to aminoglycoside exposure) and at 5 years at study completion. Those receiving inhaled TSI were scheduled for audiometry after