Journal of Cystic Fibrosis 6 (2007) 327–333

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

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

D.J. Touw [a,*], A.J. Knox [b], A. Smyth [c]

[a] *Apotheek Haagse Ziekenhuizen and Haga Teaching Hospital, PO Box 43100, 2504 AC The Hague, Netherlands*
[b] *Centre for Respiratory Research, Clinical Sciences Building, Nottingham City Hospital, Nottingham, United Kingdom*
[c] *Paediatric Respiratory Medicine, Division of Child Health, University of Nottingham, Nottingham, United Kingdom*

Received 3 July 2006; received in revised form 4 December 2006; accepted 17 December 2006
Available online 1 February 2007

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 ($R^2=0.3$, $p<0.001$).
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.

Keywords: Tobramycin; Pharmacokinetics; Diurnal variation

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

* Corresponding author. Tel.: +31 70 3217180; fax: +31 70 3217156.
E-mail address: d.touw@ahz.nl (D.J. Touw).

1569-1993/$ - see front matter © 2007 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved
doi:10.1016/j.jcf.2006.12.007

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 received ceftazidime as the only additional intravenous antibiotic. Further details are given in the TOPIC paper [2].

Criteria for inclusion in the post-hoc pharmacokinetic analysis were complete and verifiable data on drug administration dates and times as well as accurate timings of blood sampling and availability of tobramycin concentration data.

Table 1
Overview of demographic characteristics and tobramycin levels of patients participating in the TOPIC study [2] and where a pharmacokinetic analysis could be carried out

	Three times daily tobramycin	Once daily tobramycin
Paediatric patients (*N*)	43	42
Male/female	28/15	25/17
Age (years)	10.0±3.0 (5–15)	9.8±3.4 (5–15)
Body weight (kg)	34±15 (15–78)	32±12 (16–60)
Creatinine clearance (ml/min)	80±25 (30–131)	70±24 (35–128)
Creatinine clearance (ml/min/1.73 m^2)	124±35 (77–229)	110±24 (49–157)
Tobramycin peak (mg/l)	8.1±1.3	22.7±4.0
Tobramycin trough (mg/l)	0.73±0.33	0.045±0.102
Adult patients (*N*)	22	29
Male/female	10/12	14/15
Age (years)	22±6.3 (16–40)	24±8.4 (16–50)
Body weight (kg)	57.4±9.3 (43–82)	55.1±10.0 (31–80)
Creatinine clearance (ml/min)	93±18 (62–125)	92±20 (60–148)
Creatinine clearance (ml/min/1.73 m^2)	98±21 (63–147)	100±18 (72–150)
Tobramycin peak (mg/l)	7.9±1.4	22.6±4.6
Tobramycin trough (mg/l)	0.88±0.38	0.035±0.042

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

Table 2
Overview of tobramycin pharmacokinetic models built from the patients participating in the TOPIC study

Parameter	Mean±s.d.
Overall pharmacokinetic model (N=136)	
V1 (l/kg)	0.335±0.055
Kelm (hr^{-1})	0.01*
Kelr (hr^{-1}/(ml/min/1.73 m^2))	0.00294±0.00028
All paediatric patients (N=85)	
V1 (l/kg)	0.363±0.081**
Kelm (hr^{-1})	0.01*
Kelr (hr^{-1}/(ml/min/1.73 m^2))	0.00281±0.00035
All adult patients (N=51)	
V1 (l/kg)	0.294±0.038**
Kelm	0.01*
Kelr (hr^{-1}/(ml/min/1.73 m^2))	0.00314±0.00029

V1: 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); **: significantly different ($p<0.001$).