Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis

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Abstract

***Objective*—To compare once daily with thrice daily tobramycin for treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis.**

***Design*—22 patients with cystic fibrosis, mean (SD) age 11 (3.4) years (range 5.6–19.3), with pulmonary pseudomonas exacerbations were randomly assigned to receive a 14 day course of tobramycin (15 mg/kg/day) either in three infusions (group A) (n = 10) or a single daily infusion (group B) (n = 12), combined with ceftazidime (200 mg/kg/day as three intravenous injections). Efficacy was assessed by comparison of pulmonary, nutritional, and inflammatory indices on days 1 and 14. Cochlear and renal tolerance were assessed on days 1 and 14. Tobramycin concentration was measured in serum and sputum 1, 2, 3, 4, 8, and 24 hours after the start of the infusion. Analysis was by non-parametric Wilcoxon test.**

***Results*—Variables improving ($p < 0.05$) in both groups A and B were, respectively: weight/height (+4% and +3.1%), plasma prealbumin (+66 and +63 mg/l), forced vital capacity (FVC) (+14% and +11%), forced expiratory volume in one second (+15% and +14%), and forced expiratory flow between 25% and 75% of FVC (+13% and +21%). Improvement was not significantly different between groups. Renal and cochlear indices remained within the normal range. Serum peak concentration of tobramycin on day 1 was 13.2 (7.1) mg/l in group A and 42.5 (11.2) mg/l in group B ($p < 0.001$); serum trough was 1.1 (0.8) mg/l in group A and 0.3 (0.2) mg/l in group B ($p < 0.01$). Tobramycin concentrations in sputum were two to three times higher in group B than group A.**

***Conclusions*—Once daily tobramycin combined with three injections of ceftazidime is safe and effective for the treatment of pseudomonas exacerbations in cystic fibrosis patients.**

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Keywords: cystic fibrosis; antibiotics; aminoglycosides; *Pseudomonas aeruginosa*

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Pulmonary exacerbations in patients with cystic fibrosis colonised with *Pseudomonas aeruginosa* lead to frequent antibiotic courses.[1] A β lactam antibiotic and an aminoglycoside are usually given in three daily infusions for a period of two to three weeks.[2–4] Home antibiotic treatment has been instituted by most cystic fibrosis centres and allows improved quality of life for patients and their families.[5 6] Nevertheless, home treatment is time consuming, with a nurse spending 30 to 60 minutes in the home three times a day during the antibiotic infusions.

Recent studies strongly suggest that once daily administration of the total daily dose of aminoglycoside every 24 hours may be less ototoxic and nephrotoxic and even more effective than the conventional regimen.[7–10] We previously showed in an open study that 35 mg/kg amikacin given as a once daily infusion, combined with 200 mg/kg/day of ceftazidime in three daily injections, was a well tolerated and effective treatment of *Ps aeruginosa* exacerbations in cystic fibrosis.[11] This study aimed to compare efficacy, tolerance, and serum and sputum pharmacokinetics of once daily versus thrice daily tobramycin, combined with ceftazidime, in a population of young cystic fibrosis patients.

Methods

POPULATION

The study was approved by the Lille University Hospital ethics committee. Written consent of the patient or parents, or both, was required before enrolment in the study. Twenty two cystic fibrosis patients were enrolled. The diagnosis of cystic fibrosis was confirmed by at least two abnormal sweat tests (sweat chloride > 60 mmol/l). All patients had chronic pulmonary colonisation by *Ps aeruginosa*, defined by at least three positive bacteriological examinations of sputum over a period of at least six months. All strains of *Ps aeruginosa* were sensitive to ceftazidime and tobramycin. Sputum was free from colonisation by *Burkholderia cepacia* and *Stenotrophomonas maltophilia*. Patients had no known deafness or renal insufficiency. They needed antibiotics because of signs of pulmonary exacerbation—change in volume, appearance, or colour of the sputum, increased respiratory rate or dyspnoea, increased cough, deterioration of spirometric variables, decreased appetite, loss of weight, anorexia, or fever.[2 12–14] No patient had received either parenteral antibiotics or nephrotoxic or ototoxic drugs during the two months before the study. No patient was treated with oral ciprofloxacin or aerosolised antibiotics during the two months before the study or during the study period.

PROCEDURES

Patients were randomly assigned to either thrice daily tobramycin (group A) or once daily tobramycin (group B).

Antibiotics

In all patients, ceftazidime was given intravenously three times daily over 5 to 10 minutes; total daily dose 200 mg/kg. Tobramycin was given in a daily dose of 15 mg/kg either in three divided 30 minute infusions (group A) or in a once daily 30 minute infusion (group B). Treatment was given for 14 days: the first day was spent in hospital, after which the patients were discharged. For the study, patients were readmitted for 24 hours on day 14. Adjuvant treatment remained unchanged during antibiotic treatment (physiotherapy, pancreatic enzymes, and vitamins). No specific dietetic recommendations were given. The patients did not receive parenteral or enteral nutritional support.

Efficacy

Efficacy was assessed by comparison of nutritional, respiratory, and inflammatory indices on days 1 and 14. The improvement of these variables was compared between group A and group B. Weight to height ratio was expressed as a percentage of the predicted value for age, sex, and height.[15] Serum prealbumin was determined. Heart and respiratory rates were measured after a 10 minute rest. Forced vital capacity, forced expiratory volume in one second, and forced expiratory flow between 25% and 75% of forced vital capacity were measured using a portable spirometer (Respiradyne II Plus, Model 5-7930 P; Sherwood Medical, St Louis, Missouri, USA). Results are expressed as a percentage of predicted values for age, sex, and height. White blood cells and polymorphonuclear neutrophil cells were counted in peripheral blood.

Tolerance

Tolerance of antibiotic treatment was assessed by comparison of renal and cochlear indices evaluated on day 1 (before the start of antibiotics) and on day 14 (the last day of antibiotics). Audiograms were performed with frequencies ranging from 100 to 8000 Hz. The following biological variables were measured: 24 hour proteinuria with electrophoresis, lysozymuria, β_2 microglobulinuria, and creatinine clearance.

Pharmacokinetics of tobramycin

Blood was drawn one hour after the start of the infusion (H1) and 2, 3, 4, 8, and 24 hours afterwards (H2, H3, H4, H8, H24) on days 1 and 14. Blood samples were kept at +4°C until measurement by fluorescent polarisation. Sputum samples were collected on day 1 at around the same time (when the patients were able to expectorate) and kept at +4°C. After ultrasonification and liquefaction by isotonic sodium chloride or acetylcysteine, tobramycin concentration in sputum was measured using the same assay as in serum. Concentrations in sputum were not measured on day 14 because most of the patients were no longer able to expectorate. Serum pharmacokinetic variables were analysed using a non-linear least square regression analysis computer program, assuming a two compartment pharmacokinetic model.

STATISTICAL ANALYSIS

The non-parametric Wilcoxon signed rank test for paired samples was used to compare data between days 1 and 14 in each group as well as to compare the data between the two groups.

Results

Twenty two patients were enrolled in the study (table 1): 10 in group A (six boys and four girls; mean (SD) age 10.7 (2.9) years, range 7.4–17.2), and 12 in group B (eight boys and four girls; mean (SD) age 11.4 (4.2) years, range 5.6–19.3). No statistical difference was observed on day 1 between the two groups for any of the variables studied.

EFFICACY OF ANTIBIOTIC TREATMENT

The outcome measures improved in all the patients in both groups (table 1). No statistical difference was observed between the groups.

TOLERANCE OF ANTIBIOTIC TREATMENT

Audiograms were performed on days 1 and 14 in nine patients from group A and 10 from group B; they were all normal. No patient experienced dizziness during or after the antibiotic treatment. Creatinine clearance was normal in both groups on day 1 and did not

Table 1 Characteristics of the 22 patients, changes in indices of efficacy from day 1 to day 14 in the two groups, and comparison of the improvement between the groups

	Group A (n=10)				*Group B (n=12)*				
	Day 1	*Day 14*	*Difference between day 14 and day 1*	*p value*	*Day 1*	*Day 14*	*Difference between day 14 and day 1*	*p value*	*Group A v B p value**
W/H (%)	96.4 (11.6)	100.4 (11.5)	3.96 (2.63)	<0.001	93.2 (11.7)	96.3 (15)	3.14 (4.35)	<0.002	0.6
Prealb (mg/l)	194 (70)	260 (54)	65.8 (67)	<0.05	170 (45)	233 (60)	63.4 (51.4)	<0.002	0.09
WBC ($\times 10^9$/l)	11.3 (4.9)	7.9 (2.5)	3.44 (3.84)	<0.05	10.2 (4.4)	6.4 (1.4)	3.81 (3.38)	<0.004	0.8
PMN ($\times 10^9$/l)	7.3 (3.9)	4.2 (2.0)	3.05 (3.38)	<0.05	6.5 (3.6)	3.3 (1)	3.18 (3.10)	<0.01	0.9
FVC (%)	61 (18)	75 (28)	13.8 (15)	<0.05	72 (21)	83 (20)	10.5 (13)	<0.05	0.6
FEV_1 (%)	50 (19)	65 (29)	14.9 (16)	<0.05	61 (22)	75 (22)	14 (15.3)	<0.05	0.9
FEF 25–75 (%)	32 (16)	45 (27)	12.9 (14.8)	<0.05	38 (21)	59 (22)	21 (22)	<0.02	0.3
HR (beats/min)	100 (14)	86 (7)	−14 (9)	<0.001	91 (15)	77 (12)	−14 (19)	<0.05	0.9
RR (breaths/min)	30 (7)	24 (4)	−6 (4)	<0.003	33 (16)	21 (5)	−12 (14)	<0.05	0.2

Group A, thrice daily infusions of tobramycin; group B, once daily infusions of tobramycin. Values are mean (SD).
*Comparison of improvements between groups A and B.
FEF 25–75, forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HR, heart rate; PMN, polymorphonuclear neutrophil cells; Prealb, prealbumin; RR, respiratory rate; WBC, white blood cells; W/H, weight/height ratio; %, per cent of predicted values.

Table 2 Serum pharmacokinetic indices for tobramycin

	Group A	*Group B*	*p value*
Serum peak on day 1 (mg/l)	13.2 (7.1)	42.5 (11.2)	< 0.001
Serum peak on day 14 (mg/l)	12.4 (3.9)	39.4 (20)	< 0.001
Serum trough on day 1 (mg/l)	1.1 (0.8)	0.3 (0.2)	< 0.01
Serum trough on day 14 (mg/l)	0.9 (0.5)	0.4 (0.3)	< 0.01
Total clearance (ml/h/kg)	3.73 (1.37)	4.73 (2.43)	0.4
Volume of distribution (l/kg)	0.54 (0.88)	0.97 (0.44)	0.6
Area under the curve (mg.h/l)	121.5 (42)	98.6 (32.5)	0.6

Group A, thrice daily infusions of tobramycin; group B, once daily infusions of tobramycin. Values are mean (SD).

Table 3 Mean (SD) sputum concentrations of tobramycin (mg/l) on day 14

*Time**	*Group A*	*Group B*
H1	1.4 (0.9) (n = 6)	2.8 (1.4) (n = 4)
H2	1.9 (1.6) (n = 8)	3.2 (0.9) (n = 7)
H3†	1.7 (1.6) (n = 7)	4.9 (2.8) (n = 9)
H4†	1.3 (0.8) (n = 7)	3.5 (1.9) (n = 9)
H8	1.0 (0.7) (n = 6)	1.9 (0.7 (n = 5)

Group A, thrice daily infusions of tobramycin; group B, once daily infusions of tobramycin. n, number of measurements at each time.
*Hours after infusion; †p < 0.02 group A *v* group B.

change on day 14. Proteinuria was always < 0.14 g/24 h (upper normal limit) in the two groups on day 1 and did not increase during the treatment period. Lysozymuria on day 1 (normal < 1.5 mg/l) was 0.14 (0.1) mg/l in group A and 0.21 (0.2) mg/l in group B (NS). On day 14 it was 0.56 (1.0) mg/l in group A and 0.5 (0.8) mg/l in group B (NS). β_2 Microglobulinuria on day 1 was 0.4 (0.8) mg/l in group A and 0.2 (0.1) mg/l in group B (NS). On day 14, although it remained within the normal range in both groups, it was higher in group A than in group B: 0.87 (0.5) mg/l *v* 0.18 (0.2) mg/l (p < 0.01).

PHARMACOKINETICS OF TOBRAMYCIN

Table 2 summarises serum pharmacokinetics. Serum peak was observed at H1 in the two groups. Serum tobramycin concentrations did not change between day 1 and day 14 in either group. Sputum tobramycin concentrations were measured in eight patients from group A and nine from group B (those who were able to expectorate). Not all patients were able to expectorate at the scheduled hours and some concentrations were not measured for technical reasons. Sputum concentrations of tobramycin were higher in group B than in group A (table 3). MIC_{50} of tobramycin for *Ps aeruginosa* (the minimum in vitro concentration of tobramycin that inhibits the growth of 50% of the strains of *Ps aeruginosa* isolated from the sputum of our cystic fibrosis patients) was 2 mg/l. The sputum tobramycin concentrations remained above this value during the first six hours after tobramycin infusion in group B, but did not reach this value in group A.

Discussion

Aminoglycosides are very important antibiotics in cystic fibrosis patients because of their efficacy against *Ps aeruginosa*. They are usually combined with a β lactam antibiotic in cases of pulmonary exacerbation caused by chronic colonisation with *Ps aeruginosa*.[2–4] Several studies in severely ill patients have shown that once daily administration of aminoglycosides is as effective and probably less toxic than conventional thrice daily administration. For these antibiotics, efficacy is closely correlated with serum peak concentration and the ratio of serum peak to minimum inhibitory concentration of the bacteria, whereas toxicity depends on the trough serum level.[7 16 17] Furthermore, the postantibiotic effect of aminoglycosides on Gram negative bacteria seems to be partly related to the serum peak value.[8] Administration once daily allows a high peak concentrations to be reached and enables the trough concentration to be as low as possible.

These conditions were clearly demonstrated in our study. Peak serum tobramycin was three times higher and the trough concentration three times lower with once daily than with thrice daily tobramycin. The serum pharmacokinetics of tobramycin did not change between day 1 and day 14, indicating that there was no accumulation of the drug during treatment. In contrast with our previous study with once daily amikacin,[11] we observed a large interindividual variation in serum peak tobramycin, not only in the thrice daily group but also in the once daily group. There was a high sputum concentration of tobramycin early after the end of the infusion. In the once daily regimen, tobramycin reached higher concentrations in sputum than in the thrice daily regimen. We also found this in our previous study with amikacin.[11]

Sputum concentration of aminoglycosides in people with or without cystic fibrosis depends on the unit dose of aminoglycoside and on the peak serum concentration. There are studies suggesting a close relation between concentrations of aminoglycosides in serum and bronchial secretions, with peak concentrations in serum reflected by higher concentrations in the sputum.[18]

Guglielmo *et al* recently performed a serum pharmacokinetic study of tobramycin in a once versus thrice daily regimen in five cystic fibrosis patients.[19] Neither the age nor the clinical condition of the patients were specified and no measurements of tobramycin were performed in bronchial secretions. These investigators showed that pharmacokinetic indices were identical with the two regimens and suggested that a once daily regimen, which allowed higher peak serum concentrations to be achieved, would lead to higher concentrations in sputum. This hypothesis was confirmed in our study. The treatment efficacy was the same in the two groups, with a significant improvement in nutritional, respiratory, and inflammatory indices in both groups. The changes observed in our study are comparable with those published in other studies.[11 14] Cochleovestibular tolerance was excellent in the two groups, while renal tolerance seemed slightly better with once daily than with thrice daily tobramycin, the difference reaching statistical significance for β_2 microglobulinuria on day 14. This could be explained by the higher trough concentration of tobramycin in the thrice daily regimen.[20]

CONCLUSION

Once daily administration of tobramycin combined with ceftazidime in three injections is safe and effective for treating pulmonary exacerbations in cystic fibrosis patients chronically colonised with *Ps aeruginosa*. This schedule of administration allows high sputum concentrations to be attained, and saves time during home intravenous antibiotic treatment.

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