

Systemic absorption of nasally administered tobramycin and colistin in patients with cystic fibrosis

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Objectives: In cystic fibrosis (CF) patients the paranasal sinuses can constitute a niche for bacteria, which can migrate to the lungs. Nasal administration of antibiotics may be effective, but safety of this treatment has to be established first. The objective of this study was to investigate the systemic absorption of nasally administered tobramycin, colistin (administered as colistin sulfomethate sodium; CMS) and a combination of both drugs using systemic absorption as surrogate for safety. In addition, tolerability of the nasal irrigations was examined.

Methods: Ten adult CF patients performed three different nasal irrigations: 300 mg of tobramycin; 160 mg of CMS; and 300 mg of tobramycin combined with 160 mg of CMS. Serum concentrations of tobramycin and colistin A and B (the main components of colistin) were analysed. Tolerability was measured using a visual analogue scale. Dutch Trial Register: NTR 4008.

Results: Following the tobramycin and the combined irrigation, only two patients had detectable tobramycin serum levels, with the highest being 0.054 mg/L. Serum levels of colistin A and B were not detectable. All three nasal irrigation solutions were well tolerated with a higher tolerability for CMS compared with tobramycin.

Conclusions: Nasal irrigations with tobramycin, CMS and a combination of tobramycin and CMS resulted in safe serum levels and were well tolerated.

Keywords: nasal administration, antibiotics, pharmacokinetics

Introduction

Cystic fibrosis (CF) is a genetic disorder affecting multiple organs. The most important cause of morbidity and mortality in CF patients is infection of the respiratory tract.¹ Treatment of CF patients focuses mainly on preventing or controlling lung infections with intravenous and inhaled antibiotics.²

Similar microorganisms have been cultured from the upper and the lower airways.^{3,4} Previous research has shown that *Pseudomonas aeruginosa* was cultured from the upper airways in 48%–57% of CF patients.^{3,5} Infections in the paranasal sinuses can result in rhinosinusitis accompanied by complaints such as headache, blocked nose and loss of smell.⁶ These complaints often compromise a patient's quality of life. Even more important, recent studies have shown that the paranasal sinuses can constitute a niche for *P. aeruginosa*, which can intermittently spread to

the lungs and initiate or facilitate chronic lung infection.^{7–9} Unfortunately, accurate treatment against pathogens in the upper airways is not available yet.

Tobramycin and colistin are the most frequently used antipseudomonal antibiotics for lung infection in patients with CF and therefore seem good candidates for local treatment of *P. aeruginosa* in the upper airways. Also, combining tobramycin and colistin might be better than single drug therapy.¹⁰ Herrmann *et al.*¹¹ have shown that inhalation of this combination was more efficient than single tobramycin or colistin inhalation therapy in killing *P. aeruginosa* in biofilms *in vitro* and it also reduced *P. aeruginosa* cell counts significantly in rats and CF patients.

The present study is the first study to examine the safety of nasally administered tobramycin and colistin sulfomethate sodium (CMS). In addition, the tolerability of nasal irrigation with antibiotics was examined.

Methods

The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee South-West Holland. Informed consent was obtained from all subjects. From June 2013 to January 2014, adult patients (≥ 18 years) treated in the Cystic Fibrosis Centre of Haga Teaching Hospital, The Netherlands with a diagnosis of CF, based on a positive sweat test and/or genotype, were considered eligible for this study. Impaired renal (estimated glomerular filtration rate < 50 mL/min) and liver (aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transferase, lactate dehydrogenase and/or alkaline phosphatase $\geq 3 \times$ normal value) function, acute pulmonary exacerbation,¹² allergy or intolerance for aminoglycosides or polymyxins, recurrent epistaxis, ear/nose/sinus surgery 3 months prior to study entry and/or participation in another clinical trial 30 days prior to study entry were exclusion criteria.

Dutch Trial Register: NTR 4008.

Investigational drugs

In the present study, the investigational drugs were tobramycin (TOBI[®], Novartis) and CMS (Colistin[®], Forest Laboratories). Tobramycin peak serum concentrations > 30 mg/L and trough levels > 0.5 mg/L must be avoided.¹³ For colistin, toxic levels are not known.

Nasal irrigation

Nasal irrigation of the drugs was performed using a plastic squeeze bottle (NeilMed[®] Sinus Rinse[™]).

Subjects had to bend forward above a sink and slightly tilt their head in one lateral direction. The bottle was placed against the most superior nasal passage and the subject had to hold their breath. The bottle was squeezed until the solution started draining from the opposite nasal passage. When half of the bottle was empty, the procedure was transferred to the other nasal passage. The irrigation time was ~ 1 min.

Three irrigation solutions were used: (i) 300 mg of tobramycin; (ii) 160 mg of CMS; and (iii) 300 mg of tobramycin plus 160 mg of CMS. Approximately 214 mL of isotonic saline was added to all three drug solutions.

Subjects who were on tobramycin or colistin inhalation therapy had to stop this therapy ≥ 120 h before nasal irrigation was applied. Intravenous

tobramycin or colistin therapy had to be terminated ≥ 48 h before nasal irrigation.

Subjects performed two irrigations with each solution with a time gap of 24 h between the two irrigations. One blood sample was taken just before the second irrigation and five more blood samples were taken at 0.5, 1, 2, 4 and 6 h after the second irrigation. The squeeze bottle was weighed before and after each irrigation to calculate the exact amount of solution that was administered to the nose.

Drug analysis

All tobramycin and colistin analyses were performed by the clinical pharmaceutical and toxicological laboratory of the Central Hospital Pharmacy, The Hague, The Netherlands. Drug serum concentrations were measured using validated HPLC–tandem mass spectrometry (MS/MS) assays.^{14,15}

For tobramycin, the lower limit of quantification (LLOQ) was 0.015 mg/L, the intra-assay coefficient of variation was 2.0% and the assay was linear from 0.25 to 5.00 mg/L. Colistin consists of multiple components, with the two main components colistin A (polymyxin E1) and colistin B (polymyxin E2) accounting for $> 75\%$ of the compound. Since colistin was administered as CMS, which is hydrolysed *in vivo* into colistin, colistin A and B serum concentrations were measured before and after hydrolysis and CMS was indirectly determined. The LLOQ was 0.010 mg/L for both components while the intra-assay coefficient of variation was 6.1% and 5.2% and the assay was linear from 0.010 to 0.46 mg/L and from 0.010 to 0.34 mg/L for colistin A and B, respectively.

Tolerability

Subjects' tolerability of nasal irrigation was measured using a visual analogue scale (VAS), in which a score of 0 stood for 'no inconvenience' and a score of 10 stood for 'as much inconvenience as I can imagine'.

Results

Ten patients were enrolled in the study with a mean age of 33.5 ± 9.4 years and 50% were male. Seven out of 10 subjects reported at least one sinus surgery in the past.

All patients completed the tobramycin irrigations. The mean administered dose of tobramycin was 280.65 ± 5.54 mg. Only

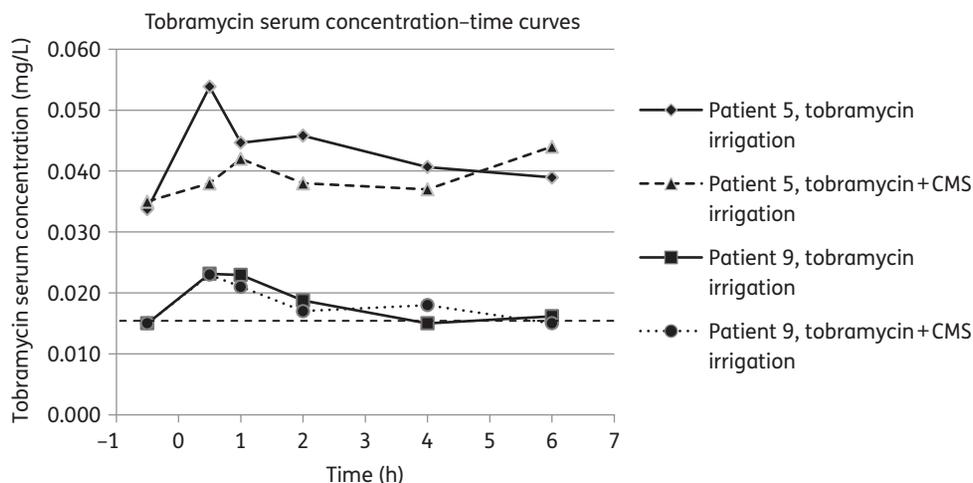


Figure 1. Tobramycin serum concentration–time curves for Patients 5 and 9 following nasal irrigation of 300 mg of tobramycin and 300 mg of tobramycin combined with 160 mg of CMS. The LLOQ was 0.015 mg/L for the tobramycin assay (broken horizontal line at 0.015 mg/L).

two patients, Patients 5 and 9, had detectable tobramycin serum levels (Figure 1). Peak and trough serum concentrations were 0.054 and 0.034 mg/L for Patient 5 and 0.023 and ≤ 0.015 mg/L for Patient 9, respectively. The mean VAS score of all 10 patients for the tobramycin irrigations was 2.1 ± 2.62 .

All patients completed the irrigations with CMS. For CMS, a mean of 151.20 ± 3.44 mg was administered. In all 10 patients the serum levels of colistin A as well as colistin B were below the LLOQ of 0.010 mg/L. The mean VAS score for nasal administration of CMS was 0.12 ± 0.13 .

One patient could not stop his colistin inhalation therapy because he was clinically unstable; therefore, we collected data from nine patients for the combined irrigation. The mean administered doses for these nine patients were 284.09 ± 15.61 mg of tobramycin and 154.40 ± 2.72 mg of CMS. In the same two patients as with the single tobramycin irrigation, serum levels of tobramycin were above the LLOQ following the combined irrigation (Figure 1). Tobramycin peak and trough serum concentrations were 0.044 and 0.035 mg/L for Patient 5 and 0.023 and ≤ 0.015 mg/L for Patient 9, respectively. The mean VAS score for irrigations with a combination of tobramycin and CMS was 0.50 ± 0.87 .

Discussion

To our knowledge, this is the first reported study in which the systemic absorption of tobramycin and colistin after nasal irrigations with tobramycin and CMS solutions was studied. Only 2 out of 10 patients had detectable, though very low, tobramycin serum levels, which were well below the toxic limits. Serum levels of colistin A and B, the two main components of colistin, were below the LLOQ for all patients.

Potential pathways of systemic absorption following nasal irrigation are absorption through the nasal mucosa, via the gastrointestinal tract after swallowing the irrigation solution or through the middle ear mucosa.¹⁶ However, tobramycin and colistin are not effectively absorbed by the gastrointestinal tract^{17,18} and research showed no nasal irrigation fluid in the middle ear, suggesting that the systemic uptake of the nasally administered antibiotics is through the nasal mucosa.¹⁹

The two patients with detectable tobramycin serum levels showed similar levels after irrigation with solely tobramycin and with the tobramycin/CMS combination. This suggests that no interaction in drug absorption between colistin and tobramycin exists, which is advantageous since combined administration might be more effective in killing *P. aeruginosa*.¹³

Tobramycin was less tolerated by the study population compared with CMS. However, this result could be limited because of the lack of a randomization scheme in the order of the different irrigations. Habituation to irrigation in general could lead to lower VAS scores as the study proceeds. However, the mean VAS score of the combination solution, which was administered last in the study, was higher (VAS=0.50) than the VAS score of the CMS solution (VAS=0.12).

In conclusion, systemic absorption of tobramycin was very low with non-detectable serum levels or levels well below the toxic or therapeutic levels. Nasal irrigation with CMS and with a combination of tobramycin and CMS resulted in non-detectable colistin A and B serum levels. Overall, nasal irrigations were well tolerated.

However, patients tolerated the CMS irrigations the best and the tobramycin irrigations the least. Further research into the effects of nasal antibiotic irrigations on bacteria in the sinonasal area, on the symptoms of sinonasal disease and on pulmonary disease in CF patients is needed.

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Transparency declarations

None to declare.

Author contributions

M. C. B., A. J. v. V., D. J. T. and H. G. M. H. contributed to the study design, data collection, data analysis and writing of the manuscript. B. M. d. K. was involved in the data collection and writing of the manuscript. W. J. F. contributed as otorhinolaryngologic consultant and participated in the writing of the manuscript.

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