69 A randomised comparison of VANTOBRA and TOBI in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection for pharmacokinetic and therapeutic equivalence

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Objective: Inhalable tobramycin is an accepted therapy to treat chronic PA infection in CF. Efficacious twice daily inhalation is time-consuming for the affected patients. The aim was to evaluate the comparability of VANTOBRA/Tolero with TOBI/PARI LC PLUS regarding drug pharmacokinetics, clinical parameters, inhalation times and safety profile.
Methods: The drug/device combinations were compared in a randomised, two-period, multi-centre, cross-over 14-week study. 58 CF patients ⩾4 years with chronic PA infection were enrolled. Assessments included plasma/sputum AUC and C_{max}, reduction of PA CFU, FEV_1 % pred, inhalation time and adverse reactions.
Results: Plasma mean AUC was 4.2 (VANTOBRA) and 4.9 µg×h/ml (TOBI). Plasma mean C_{max} for both drugs was 1.3 µg/ml. Sputum mean C_{max} was 1.95 (VANTOBRA) and 1.42 mg/g (TOBI). A $\log_{10}$ CFU reduction of –1.77 vs. –1.70 was achieved with VANTOBRA and TOBI in treatment phase I and –1.30 vs. 0.12 in treatment phase II. FEV_1 % pred increased by 8.2% (VANTOBRA) and by 4.8% (TOBI), in treatment phase II by 2.40% vs. –0.44%. Mean time per inhalation was 4.4 min (VANTOBRA/Tolero) and 24.3 min (TOBI/PARI LC PLUS). No fatalities occurred. All 4 SAEs were not drug-related. Expected side effects (bronchospasms, tinnitus) were observed in each two VANTOBRA and TOBI patients.
Conclusion: Lower plasma AUC and higher sputum C_{max} values of VANTOBRA allowed a better control of PA infection and improved lung function without jeopardizing patient safety. The efficacy/safety profile and reduced inhalation time of VANTOBRA/Tolero may provide a significant therapeutic benefit for CF patients.

70 Use of an electronic monitoring system to generate objective information on patients' adherence to taking treatments of a novel inhaled tobramycin solution (VANTOBRA)

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Objective: Patient adherence to inhaled medications is important to interpret clinical trial results. Self-reported diaries have a high potential for manipulation. To provide a reliable tool to assess patient adherence to treatment, a monitoring feature was developed and incorporated into a specific eFlow technology nebulizer. VANTOBRA/Tolero was compared prospectively in a randomised study in cystic fibrosis patients with TOBI/PARI LC PLUS.
Methods: The configuration's key feature is an electronic chip card recording date, time and duration of each nebulization session and cause for termination. The nebulizer operates only by insertion of a valid chip card. Recorded data were processed using PARI's Patient Monitoring Software. Adherence is calculated as the ratio of actual/planned inhalations and shown graphically per study day or cumulatively.
Results: Data of 54/58 patients were analysed. Mean adherence was 99% for all evaluable patients, 98% in patients >13 years and 99% in patients of 7–13 years of age. The adherence rate was comparable in all treatment cycles, independent whether the patient was randomized to receive VANTOBRA as the first or second treatment cycle. As per patient diary, the compliance in the TOBI group was 99%. Mean time/inhalation was 4.4 min (VANTOBRA/Tolero) and 24.3 min (TOBI/PARI LC PLUS).
Conclusion: The eFlow technology nebulizer with patient monitoring function provides objective adherence data. The monitoring feature offers the potential to distinguish whether an observed treatment failure is based on lack of drug efficacy or non-adherence to the prescribed treatment regimen.

71 Pharmacokinetics of nasal administered tobramycin in patients with cystic fibrosis

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Recent studies showed that the paranasal sinuses can constitute a niche for bacteria. To date no effective treatment for these bacteria is available. Off label administration of nasal antibiotics may be an option. However, first safety of this treatment has to be established.
Objectives: With this pilot study in two patients the pharmacokinetic parameters of nasal administered tobramycin were investigated.
Methods: In two hospitalised CF-patients, treated with intravenous tobramycin, after a wash-out period, 320 mg of tobramycin, dissolved in 200 ml isotonic saline, was administered to the nose using nasal lavage. Eleven venous blood samples were collected and with a Liquid Chromatography Tandem Mass Spectometer (LC-MSMS) method, serum tobramycin concentrations were determined. Tobramycin pharmacokinetic parameters were calculated using the MW\Pharm software package. Systemic absorption was calculated by dividing AUC after nasal administration by AUC after intravenous administration corrected for the administered dose.
Results: In patient 1, a female of 32 years old, the maximum concentration (Cmax) of tobramycin was 0.027 mg/L. This Cmax was reached 30 minutes after the nasal lavage with tobramycin (tmax). In total 0.20% (0.62 mg) of the tobramycin was systemically absorbed. In patient 2, a male of 36 years old, the Cmax was 0.029 mg/L. The tmax was 45 minutes and in total 0.16% (0.51 mg) of tobramycin was absorbed.
Conclusion: Nasal lavage with 320 mg tobramycin did not result in toxic serum levels. The results of two patients showed a fast absorption of tobramycin and a slow elimination. Approximately 0.20% of the tobramycin was absorbed by the sinonasal mucosa.

72 Inspiratory flow characteristics of the T-326 dry powder inhaler (DPI) in CF patients

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Objectives: Successful use of a DPI rests on factors including adequate inspiratory flow and volume to disperse the drug and achieve deposition in the lower airways. We assessed inhalation profiles from CF patients over a wide range of age and disease severity, using the T-326 Inhaler (resistance = 0.079 cm $H_2O^{0.5}$ LPM^{-1}). We compared the results to a previous study of 96 CF patients who inhaled from an inspiratory trainer with various resistances. In that study averaged data from the 0.07 and 0.12 cm $H_2O^{0.5}$ LPM^{-1} resistances were considered representative of the T-326 Inhaler.
Methods: A diverse and clinically stable CF population (n = 38) was recruited according to age (6–11, 12–17 and ⩾18 years) and lung function (FEV_1 percent predicted high: >60%, medium: 40–60%, low: <40%). An Inhalation Profile Recorder measured 4 inhalation profiles/patient, from which inspiratory time and flows were derived.
Results: All but one patient achieved a peak inspiratory flow (PIF) >60 LPM. 87% patients achieved inhaled volumes ⩾1 L. The table presents means±SD.

Inhalation profile characteristics

	Total	6–11 yrs (n = 13)	12–17 yrs (n = 13)	⩾18 yrs (n = 12)
Inspiratory time, sec	1.6±0.6	1.2±0.3	1.6±0.5	2.1±0.6
Inhaled volume, L	1.6±0.7	1.1±0.3	1.5±0.5	2.2±0.7
PIF, LPM	82.8±14.1	83.5±13.3	76.1±10.7	89.2±16.0

Mean PIF and inhaled volume were comparable to averaged values seen with the simulated inhaler (inhaled volume 1.7±0.7 L; PIF 76.4±15.1 LPM).
Conclusion: CF patients ⩾ 6 years of age with a wide range of lung function can generate sufficient inspiratory volume and flow to effectively inhale the content of tobramycin capsules using the T-326 Inhaler.