143 Experience of inhaled tobramycin: impact in microbiological and clinical parameters in patients with cystic fibrosis

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Introduction of inhaled tobramycin (IT) for treatment of pulmonary *Pseudomonas aeruginosa* (PA) chronic infection in Cystic Fibrosis (CF) patients (pts), urged the need to acknowledge the outcome in our Center.
Objectives: Determination of microbiological and clinical evolution after IT.
Methods: Retrospective analysis of CF pts receiving IT (TOBI®) on the last 10 years. Microbiological patterns and clinical parameters were studied 2 years before and after IT. Chronicity was defined as positivity⩾3 isolates/6 months and intermittent as positivity⩾1 isolate/year.
Results: 49 pts were studied. PA isolates and chronic infection rates evolution are shown in Table 1. After 2 years, 7 pts became negative and 2 intermittent. Resistant PA increased: tobramycin (1 to 11.7%), gentamycin (3.7 to 35.7%), amycacin (1.6% to 28.5%), ceftazidime (0.5% to 4.1%) and ciprofloxacin (4.2% to 16.7%). *Staphylococcus aureus* chronic infection and MRSA rates increased: 51.4% to 73.5% and 11.5% to 22.7%, respectively. *Burkholderia cepacia* rates diminished (16.7% to 8.2%), chronicity increased (60% to 75%) but diminished later (33%). *Aspergillus flavus* emerged and *Aspergillus fumigatus* increased (0.5% to 9.8%). Median BMI-percentile, FVC, FEV1 and FEF25–75 transiently improved after IT. 4 pts died on the 2nd year.
Conclusions: We need to be aware of microbiological patterns changes and increased resistance of CF patients under IT.
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Table 1. Evolution of PA isolates and chronic infection rates

	2 years before	1 year before	1 year after	2 years after
Isolates	95.7% (n=43)	100% (n=49)	81.6% (n=38)	78.7% (n=36)
Chronic PA	65.1%	81.3%	84.2%	77.8%

144 Single daily administration of tobramycin (TO) after repeated multiple-dose treatment: oto- and nephrotoxicity and drug serum levels

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In the past multiple-dose antibiotic treatment has been used to treat pulmonary exacerbations in cystic fibrosis (CF) patients, even though single daily dosing of TO has been shown to be as efficacious as multiple doses, with less risk of side effects. It is advisable to monitor serum levels to try to reduce undesirable effects of the drug.
Objectives: To evaluate in patients treated with single daily dose of TO:
– mean yearly quantity of intravenous (iv) TO used previously
– serum levels
– the prevalence of oto-and nephrotoxicity
Methods: Retrospective study carried out in CF patients chronically infected by *P. aeruginosa* and undergoing therapy with iv TO. Cochlear damage was evaluated using audiometry and renal damage with creatinine clearance. TO serum concentrations were measured before the fifth infusion (baseline ⩽1 mg/L) and 30 min after (peak 20–30 mg/L).
Results: 35 patients (19 M, 16 F) (mean age 21.02±10.53) undergoing single-dose therapy for *P. aeruginosa* infection were evaluated. The mean yearly quantity of TO prescribed in previous years was 9431 mg (± 2987) and mean daily quantity was 343.71 mg (± 106.93). One patient (2.8%) had baseline TO levels out of range, 10 (28.5%) had peak values from 20–30 mg/L, 22 (62.8%) <20 mg/L and 2 (5.7%) >30 mg/L. Audiometry was given to 22 (62.8%) of 35 patients (11 M, 11 F) and creatinine clearance was measured in 14 (40%) of 35 patients (4 M, 10 F). Abnormal audiometric pattern was found in 2 (8.6%) patients and abnormal creatinine clearance in one (6.6%).
Conclusions: Since out of range TO serum levels were found in 2 patients (5.7%), even those treated with single-dose i.v. TO should be carefully monitored to minimize untoward effects.

145 Ototoxicity following once daily aminoglycoside administration in adults with CF

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The incidence of ototoxicity secondary to aminoglycoside use is reported to be similar for multiple dose (MD) or once daily (OD) administration. Following the introduction of OD aminoglycoside administration at the Royal Brompton Hospital an increase in patients presenting with ototoxicity (primarily vestibular toxicity) was noted.
Aim: To identify risk factors for developing ototoxicity with OD aminoglycoside administration.
Method: Case notes of all patients receiving OD IV aminoglycosides (10 mg/kg) between December 2005 and June 2006 were reviewed. The CF database was used to identify patients with ototoxicity in the 5 years before the introduction of the OD regimen. Factors that may increase the risk of ototoxicity were recorded.
Results: 11 cases were found in the five years before OD dosing was introduced (average 2 cases/year). 12/139 patients developed ototoxicity (11 predominantly vestibular toxicity) following OD aminoglycoside administration. There was no difference in age, sex, lung function, BMI or aminoglycoside dose between the ototoxic and asymptomatic groups. The ototoxic group had a higher proportion of individuals homozygous for ΔF508 ($p=0.002$), more IV aminoglycoside days in the year preceding OD dosing [47.5 vs 28 days ($p=0.038$)] and had received more courses of aminoglycosides in adulthood [16 vs 6 courses ($p<0.001$)]. The OD dose of aminoglycoside was significantly higher than the total MD dose: 595 mg vs 240 mg ($p=0.001$).
Conclusion: The higher incidence of ototoxicity in patients receiving OD aminoglycosides is probably due to both the significantly higher dosing schedule used and to repeated courses of IV aminoglycosides over a lifetime. We recommend caution with high dose (10 mg/kg) OD dosing in patients who have received repeated courses of aminoglycosides.

146 The effect of long term use of rhDNAse on pulmonary colonisation in children with cystic fibrosis

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rhDNAse has been shown to improve lung function and reduce exacerbation rates in children with mildly to moderately severe cystic fibrosis. Recent research hypothesised that this beneficial effect was partly caused by a decrease in bronchial colonisation. We performed a retrospective case control study to evaluate if this hypothesised effect of rhDNAse is seen in daily practice.
Methods: From the CF database of the CF centre Utrecht 32 children who used rhDNAse 2.5 mg on a daily base during at least 1.5 years and for each patient a control CF patient with the same age and not using rhDNAse, were selected.
Primary effect parameter was change in bacterial colonisation during the treatment period. Therefore the last 3 cultures before starting of rhDNAse and all cultures during treatment were analysed. Secondary effect parameters were changes in lungfunction, anthropometry, exacerbations and antibiotic courses before and during treatment.
Results: At the begining of the study period there were no significant differences between both groups in anthropometry, sex, age and bacterial colonisation, but the rhDNAse group had significantly worse lungfunction (FEV1%pred 78.3 vs 97.7%, $p<0.05$). During 1.5 years treatment there were no significant changes in bacterial colonisation with most important bacteria, but there was a significant increase in the % of patients with *Pseudomonas*+ cultures within the rhDNAse group (+23%, $p<0.05$) also versus this change in controls. Non significant improvements of lungfunction and exacerbation rates were seen in the rhDNAse group and no differences in exacerbation rates and anthropometry, compared to controls.
Conclusion: In this retrospective study rhDNAse treatment did not decrease bacterial colonisation in CF patients