194 Clinical impact of inhaled mannitol in an adult cystic fibrosis population

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Inhaled mannitol (IM) was approved for use in Australia in August 2012.
Objectives: to evaluate the clinical impact of IM in suitable patients.
Methods: Patients' responses to the Initiation Dose (ID) of 400 mg of IM powder via a small inhaler device were evaluated to exclude hyperresponsiveness using the lung function database. Concurrent use of Dornase Alpha (DA) & hypertonic saline (HS) using the hospital pharmacy dispensing database and breathing technique were evaluated.
Results: Twenty-six adults (15 women) 35.4 years (7.8, 21–50) – mean (SD, range) were referred for the Initiation Dose. Baseline FEV1 2.19 (1.15, 0.79–5.04) after-bronchodilator FEV1 2.25 (1.16) and post IM ID FEV1 2.06 (1.19) L. The post IM ID change was −9.23 (10.2, −27 to +7)%. Eight patients had no drop or an increase in FEV1, six patients did not qualify for use of IM with >20% drop in FEV1. Twenty patients have continued to use IM as a mucolytic agent adjunctive to airway clearance therapy, 8 use IM and DA on a daily basis; 11 use IM and HS, and 5 use IM and DA and HS. The correct breathing technique (slow and deep inspiration with an inspiratory flow of around 30 L per minute) is crucial in preventing unnecessary coughing & bronchospasm. Patients report the benefits of IM being easy to use, no equipment cleaning, effective and time efficient (5 minutes for inhalation of 10 capsules am and pm). Four patients report a transient feeling of chest tightness after using IM. IM has not been available for long enough to evaluate longer term lung function outcomes.
Conclusion: IM has been enthusiastically welcomed by patients with CF as a stand alone mucolytic agent or in combination with DA and or HS.

195 Efficacy of inhaled amiloride solution versus hypertonic saline, prospective open label single center study in children with cystic fibrosis

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Objectives: The aim of the study was to compare efficacy of inhaled amiloride solution against standard therapy of hypertonic saline in children with CF.
Methods: Prospective open label single center study. Group of 45 children with CF from our centre were randomised in 1:2 ratio. 30 children were assigned to amiloride (A) arm and 15 children in 5% hypertonic saline (HS) control arm. Amiloride was prepared in water solution of amiloride chlorate. The dose was 0.6 mg twice daily administered via pari boy. Both groups were similar in mean age, sex, CFTR mutations, sweat chloride, pancreatic insuficiency, rDNAse, and chronic *P. aeruginosa* infection. Patients were observed in week 0, 12, 24 and 36. The differences in FEV1, exacerbations (modified Fuchs et al.), sputum cultivations, growth, weight, lung CT, hospital admission and drug tolerance were evaluated.
Results: Groups did not differ significantly in change of FEV1 (A +0.36%; HS −3.5%), number of exacerbations (A 1.6±1.4; HS 1.4±1.2), weeks to 1st exacerbation (A 20±13; HS 26±11), progression in lung CT (A 30%; HS 36%) number of positive sputum cultivations per patient (A 4.1; HS 3.8) rate of new *P. aeruginosa* cultivation (A 16%; HS 13%), weight gain (A +1.6 kg; HS +1.2 kg), growth (A +3.2 cm; HS +2.5 cm).
Significant difference was found in rate of hospital admission (A 13%; HS 33%, $p = 0.09$), in drug tolerance (A 100%; HS 80%, $p = 0.04$).
Conclusion: Inhaled amiloride solution was found less irritating and led to less hospital admissions then hypertonic saline, the other differences were not significant.
Further crossover study follows in 2014 to add more power to results.
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196 Airway surface liquid concentrations of aztreonam lysine for inhalation in children with cystic fibrosis: A modelling study

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Objectives: Deposition of inhaled antibiotics (IA) is higher in well preserved lung areas compared to obstructed airway regions. This may result in areas with concentration below minimal inhibitory concentration (MIC) causing under-treated lung parts. A computational model may be used to gain knowledge about antibiotic concentrations throughout the lung, possibly resulting in optimization of inhaled therapy. We aim to develop a patient-specific assessment tool, using computational fluid dynamics (CFD), that provides local depositions and concentrations of aztreonam lysine for inhalation (AZLI).
Methods: In- and expiratory CT-scans of children with CF (5–18 yr) are scored (CF-CT score), segmented and reconstructed into 3D airway models. We performed CFD simulations, using patient-specific lobar flow distribution, nebulisation of 75 mg AZLI through PARI eFlow® with reported MMAD range and thickness range of Airway Surface Liquid (ASL). Percentage of total airway area with AZLI concentration $<10\times MIC_{90}$ (1280 µg/ml) for *P. aeruginosa* are computed.
Results: 40 CT-scan sets from 31 patients (65% female) were selected, median [range] age 10.5 [5–17] years, bronchiectasis score 4.3 [0.0–26.7] % of max. CF-CT score, FEV_1 91.5 [69.4–113.4] %pred. Preliminary results of 19 patients (Table 1) show % of under-dosed areas. Simulations are on-going. We will study associations with age and disease severity, which will be reported at the conference.
Conclusion: Considerable parts of the CF-lung can receive IA concentrations $<10\times MIC_{90}$, depending on disease severity.
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MMAD and ASL values vs % under-dosed area

MMAD (µm)/ ASL (µm)	min (2.9)/ min (3)	max (4.35)/ min (3)	med (3.18)/ mean (5)	min (2.9)/ max (7)	max (4.35)/ max (7)
Airway area $<10\times MIC_{90}$	1%	42%	17%	10%	72%

197 Influence of inhalation mode on aerosol lung deposition in patients with cystic fibrosis PART 1: Pharmacokinetic data as representative of lung deposition

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Objectives: To investigate the impact of two different inhalation flow maneuvers (TIM = slow and deep inhalation and TBM = normal tidal breathing) on aerosol lung deposition in patients with CF using pharmacokinetic parameters as a representation of lung deposition.
Methods: Randomized, open-label, cross-over study. The study group consisted of 18 adult patients with a confirmed diagnosis of CF (genetic analysis). Each patient inhaled a tobramycin solution twice during separate study visits: once in TIM and the other time in TBM mode. Blood samples were collected in order to model tobramycin pharmacokinetics.
Outcome measurements: Relative bioavailability (F_{rel}) of tobramycin is defined as the ratio of AUC_{TIM} to AUC_{TBM}, in which the AUC represents the plasma concentration area under the curves. A ratio greater than 1 indicates higher lung deposition for TIM compared to TBM. Individual pharmacokinetic parameters were calculated and assimilated with patient tobramycin serum values using a computerized CF-based Bayesian population model (MW-Pharm, Mediware).
Results: F_{rel} was 1 or greater for all patients (mean = 1.55, sd = 0.39, 95%CI = 1.37–1.73). In addition, mean F_{rel} was significant higher than the value of 1 (mean difference = 0.55, $p < 0.001$, 95%CI = 0.36–0.74). Mean maximum serum levels (C_{max}) were also significantly increased for TIM compared to TBM. Differences in elimination half-life and time to maximum serum level were not statistically significant.
Conclusion: Slow and deep inhalation of aerosolized tobramycin results in higher lung deposition compared to normal tidal breathing, represented by a relative bioavailability greater than 1 and increased mean maximum serum levels.