Comparison of pierced versus broken capsules on delivered fine particle dose for the colistimethate dry powder inhaler

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Background: Colistimethate sodium is indicated for the management of chronic pulmonary infections with P. aeruginosa in patients ≥6 years of age who have cystic fibrosis. A 24-week, phase 3 trial has shown that a dry powder inhaler (DPI) formulation using pierced capsules has better patient acceptability than an earlier nebulized formulation.

Objectives: To look at possible variations in the delivered dose, we sought to determine if there is a difference in the fine particle dose and particle size of a colistimethate capsule that has been previously broken versus pierced by the dry powder inhaler.

Methods: Capsules were either deliberately broken in the inhaler or pierced by the inhaler and individually tested using an Andersen Cascade Impactor with high flow conversion kit (pressure drop of 4kPa and flow ~70L/min). The fine particle dose and mass median aerodynamic diameter (MMAD) were determined.

Results: A total of 20 capsules were either broken in (n=10) or pierced by (n=10) the inhaler. Following cascade impaction, the fine particle dose for broken vs pierced capsules were comparable (range [RU] 169666–315994 and 181785–363570, respectively). Additionally, the MMAD was similar between the two groups, with a range of 4.29–4.66 μm for broken capsules and 4.35–5.21 μm for pierced capsules.

Conclusion: Results for the fine particle dose and MMAD for broken colistimethate capsules were consistent with those found for capsules that were pierced by the inhaler. These results indicate that the delivered dose of colistimethate may not vary based on whether the capsule has been broken or pierced by the inhaler prior to inhalation.

Long-term safety of tobramycin powder for inhalation in patients with cystic fibrosis: ETOILES study

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Objective: To assess long-term safety (48 weeks) of tobramycin powder for inhalation (TIP™) by treatment emergent adverse events and supportive efficacy endpoints in CF patients.

Design: This is a multinational, single-arm, open-label study of 6 cycles of TIP in CF patients (≥6 years) with confirmed Pseudomonas aeruginosa (Pa) presence and a FEV1 % predicted ≥25–75%.

Methods and Baseline characteristics: The study enrolled 157 CF patients and assessed safety, tolerability, spirometry, change in spumum Pa density and Pa tobramycin minimum inhibitory concentration. Preliminary baseline demographics showed over 80% of study population were adults (>18 years) with 62% males. The mean (±SD) age of patients was 27.8 years (10.82); mean (±SD) BMI was 20.53 kg/m2 (3.35) and mean (range) FEV1 % predicted at baseline was 51.1% (22.5–85.6%). Pre-enrolment medication history (12 months) showed 72% of patients had exposure to inhaled tobramycin and >6% to other inhaled antibiotics. Concomitant macrolide use (started at pre-enrollment) was ~18%. The majority of patients had at least 1 exacerbation in the previous year leading to systemic antibiotic treatment and/or hospitalisation. The most frequently used anti-Pa antibiotic for exacerbations was ciprofloxacin (40%).

Conclusion: This long-term safety study has a unique population from prior TIP studies, predominantly consisting of adult patients with low macrolides use and more severe airflow obstruction. This study complements the long-term data of the ETOILES trials and its two extensions with younger patients (<21 years). Results will be presented at the congress.

Intravenous colistin and neurotoxicity: recommendations for optimal use in cystic fibrosis (CF) patients

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Background: Intravenous (i.v.) colistin is increasingly in CF patients. The most commonly reported adverse events are neuro- and nephrotoxicity. A protocol for high dosing of i.v. colistin in adult CF patients (9 MIU Colistin methanesulfonate [CMS] loading dose followed 24 hours later by 2 MIU CMS q6h – 30-minute infusions) evoked two cases of adverse events (paresthesias, bad taste) immediately after start of infusion.

Objectives: In order to understand the cause of the side effects and to design additional precautions for colistin use in CF patients, we explored the administration technique, drug interactions and renal function.

Results: No drug interaction were detected in our patients, renal impairment was excluded. In literature, doses between approximately 2 MIU and 4.5 MIU were given over 9 to 180 minutes and mostly as a 15–60-minute infusion. Toxicity can be overcome by dose reduction. Only one case report mentioned the influence of infusion time on a neurotoxic event. Side effects were overcome by a 1-hour instead of 30-minute infusion.

We re-adapted the protocol to an infusion rate of 1.5 hours instead of 30 minutes for the loading dose of 9 MIU. There were no further neurotoxic adverse events since.

Conclusion: Recommendations for optimal administration of i.v. colistin in CF patients are scarce. As higher doses are used more often, neurotoxicity might become increasingly important. We recommend to administer the i.v. CMS loading dose of 9 MIU over 1.5 hours instead of 30 minutes. For all subsequent doses of 2 MIU q6h we recommend a 30-minute infusion in the absence of toxicity and in case of neurotoxicity over 1.5 hours.

Therapeutic drug monitoring of piperacillin/tazobactam, given as continuous infusion to patients with cystic fibrosis

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Objectives: Patients with Cystic Fibrosis (CF) are often colonized with multidrug-resistant microorganisms, which increases the risk of suboptimal plasma concentrations of antibiotics. In pharmacokinetic studies continuous infusion of beta-lactam antibiotics optimizes the time above the minimum inhibitory concentration (T MIC) compared to intermittent infusion. Continuous infusion with piperacillin/tazobactam (Pip/Tazo) for a period of 2 weeks has been used at our department for several years in patients with CF. It is used as an outpatient treatment and the patients are given 16 g of Pip/Tazo per 24 hours through portable elastometric infusion pumps. To assess the efficacy and quality of the treatment, a blood test every 3rd day is obtained to determine the plasma concentration of Piperaclillin, in order to evaluate whether monitoring should be performed as a routine during treatment or not. The concentration is compared to the MIC for the bacteria found in a tracheal secretion sample.

Methods: Samples are drawn one hour before changing the infusion bags. Plasma Piperacillin is quantified with ultra high performance liquid chromatography.

Results: 4 patients have had their plasma concentration of Pip/Tazo monitored so far. One patient had a steadily increasing concentration over time whereas the other three showed an initial increment followed by a decrement. 2 out of 4 patients maintained a concentration above the MIC.

Conclusion: Monitoring the plasma concentration is helpful in assessing the quality of outpatient treatment. The decline in concentration with time from starting therapy might be related to problems with compliance. Further studies in this area are needed.