Effect of N-butyldeoxynojirimycin on chloride efflux from CF airway epithelial cells

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Using patch-clamp studies, the α-glucosidase inhibitor N-butyldeoxynojirimycin (miglustat) has been shown to restore CAMP-dependent chloride current in human nasal epithelial, tracheal gland serous, and pancreatic duct cell lines derived from AF508-homozygous CF-patients (Norecz et al., FEBS Letters 580, 2006, 2081-2086). In the present study we have determined the effect of N-butyldeoxynojirimycin on chloride efflux from human bronchial epithelial cells, using the fluorescent probe MQAE.

Non-CF (16HBE) and CF (CFBE) bronchial epithelial cells were cultured under standard conditions in M199 medium at 37°C. The cells were loaded with MQAE for 2 h, and subsequently exposed to 100 μM N-butyldeoxynojirimycin for 4 h. After that, chloride efflux was determined from the decrease of the MQAE fluorescence, when the cells were exposed to a solution in which all chloride was replaced by nitrate.

N-butyldeoxynojirimycin caused a 150% increase in chloride efflux from CFBE cells (p = 0.006), in the absence of CAMP-elevating agents. No significant effect of N-butyldeoxynojirimycin was observed in non-CF 16HBE cells, in which the chloride efflux in the absence of CAMP-elevating agents is about four times larger. These results confirm that N-butyldeoxynojirimycin can partially correct the defective chloride efflux in CF airway epithelial cells.

Flavonoides increase chloride conductance at the apical membrane of the respiratory epithelium in some CF-patients


Flavonoids (FL) interact directly with the nucleotide binding domain 2 to stabilize the open channel configuration of CFTR and improve in vitro and in vivo the permeability of CFTR dependent chloride channels in a part of the cystic fibrosis (CF) patients. We investigated the changes in chloride permeability during a therapy regimen. Safetyparameters are closely monitored throughout the study.

The initial values of the PD, as well as the PD under blocking the sodium channels and chloride-free solution were not significantly changed before and after systemic application of the FL. Under salbutamole superfusion after 6 and 12 months of FL there was seen a significant improvement in repolarization of the PD (p = 0.003/0.03). In 13 patients the PD increased >20%.

<table>
<thead>
<tr>
<th>month</th>
<th>repolarization after salbutamole(%)</th>
<th>standard-dev.</th>
<th>patients</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>9.16</td>
<td>5.78</td>
<td>n = 20</td>
<td>n.s</td>
</tr>
<tr>
<td>6</td>
<td>18.13</td>
<td>5.01</td>
<td>n = 14</td>
<td>0.003</td>
</tr>
<tr>
<td>12</td>
<td>16.53</td>
<td>8.37</td>
<td>n = 10</td>
<td>0.03</td>
</tr>
<tr>
<td>24</td>
<td>35.05</td>
<td>15.52</td>
<td>n = 6</td>
<td>n.s</td>
</tr>
</tbody>
</table>

Systemically given flavonoids affect CFTR dependent chloride channels in a part of the CF-patients positively and this effect seems to be stable over a period of 2 years.

Effective treatment of chronic Pseudomonas aeruginosa (Pa) infection with tobramycin inhalation powder in CF patients

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Rationale: This study assessed the efficacy and safety of a new formulation (inhaled powder) of tobramycin for treating chronic Pa infection in inhaled anti-Pa antibiotic naive CF patients.

Methods: Patients 6–21 years, >25% Pa predicted (%pred) were randomized 1:1 to double-blind treatment with tobramycin 112 mg bid (n=46) or placebo (n=49) administered for 1 cycle, followed by 2 open-label cycles of tobramycin (all patients). Cycles were 28 days on, 28 days off treatment. Primary endpoint was absolute change in FEV1%pred from baseline to Day 28 of Cycle 1. Other assessments included FVC and FEF25–75%pred respiratory-related hospitalizations, anti-Pa antibiotic use, sputum Pa density and safety.

Results: At Day 28 of Cycle 1, tobramycin significantly improved FEV1%pred vs placebo (difference 13.3, 95%CI 5.31; 21.28; p = 0.0016). In patients switching from PBO to tobramycin after Cycle 1, the relative change in FEV1%pred increases to and is maintained at the level observed with tobramycin in Cycle 1. FVC and FEF25–75 show similar results. Tobramycin decreases respiratory-related hospitalization and other anti-Pa antibiotic use vs PBO, and reduces sputum Pa density by about 2-log10 CFU from baseline at the end of dosing in each cycle. Most common AE’s reported were cough, pulmonary exacerbation and sore throat.

Conclusions: Tobramycin inhalation powder significantly improves lung function, decreases respiratory-related hospitalization and other anti-Pa antibiotic use vs PBO in CF patients with chronic Pa infection, and overall is well tolerated.

Pharmacokinetics of tobramycin (TOBI™) after 4 and 8 weeks of continuous once daily or twice daily inhalation

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Introduction: During the last years twice daily (b.i.d.) inhalation of TOBI™ (300 mg/5 mL) in a 28-day on/off-dosing regimen has proven its safety and efficacy for the treatment of Pseudomonas aeruginosa (Pa.) in CF subjects. As some patients do not tolerate off-phases continuous treatment with TOBI™ could provide an additional benefit.

Method: This multicenter, open label, two period cross-over study was designed to generate first interpretable pharmacokinetic (PK) data of 8 weeks continuous treatment with 1×300 mg/d and 2×300 mg/d TOBI™ inhaled with the PARI eFlow™ rapid. The study population does consist of 35 CF patients ≥6 years chronically infected with Pa.. After a screening period the patients are randomized to enter the first 8 weeks treatment period with either o.d. or b.i.d. inhalation. PK samples are taken after 4 and 8 weeks of inhalation. Following a 4 weeks wash-out period, the patients enter the second treatment period with the alternative inhalation regimen. Safety parameters are closely monitored throughout the study.

The key objectives of this study are to investigate the serum PK of tobramycin (AU C0−24h) of continuous daily dosing b.i.d. and o.d.. Further objectives are safety parameters, change of MIC of Pa., the effect on lung function and patient reported outcomes and the comparison of these parameters between subpopulations.

Conclusion: The data obtained from this study could generate valuable insights into PK and safety of continuous treatment with TOBI™ and will support planning of future studies on alternative treatment regimens.