Is mixing of tobramycin and colistimethate-sodium containing inhalation solutions a good idea?

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Objective: Patients suffering from bacterial infections of the lungs are frequently treated by alternating or combining the inhaled antibiotics tobramycin (aminoglycoside) and colistimethate-sodium (CMS, i.e. polymyxin E). Therefore, patients might feel encouraged to mix solutions of both antibiotics in order to inhale the mixture in one single inhalation session. As the effects of preparing such a mixture on physical and chemical stability of the solution are not known, an evaluation was triggered.

Methods: Vials of tobramycin solution (170 mg/1.7 ml) were mixed with reconstituted CMS (2 Mio. IU CMS dissolved in 4 ml of 0.9% saline) and physico-chemically characterized with respect to osmolality, viscosity, surface tension and pH. Additionally, the tobramycin content and possible tobramycin related impurities were assayed by HPLC.

Results and Conclusion: Mixtures of the antibiotics did not show obvious signs of physicochemical incompatibilities. However, the measured content of tobramycin in the mixture decreased to 70–75% of the initial amount within about 12 hours. Already 10 minutes after mixing a marked decrease of tobramycin content (approx. ~7%) was observed indicating a fairly rapid reaction or decomposition immediately after preparation and during treatment. Therefore, mixing of tobramycin containing solutions with CMS prior to inhalation cannot be recommended.

The effectiveness of nebulised tobramycin over a 3 year period

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Background: Although guidelines recommend that all CF patients chronically infected with Pseudomonas aeruginosa are offered prophylactic nebulised antibiotics (including high dose tobramycin, HDNT) to limit exacerbations and slow the rate of decline in lung function, their use has only been evaluated in a clinically stable population. However, HDNT is expensive and in the UK is often used as second line therapy, when patients are unstable or deteriorating on other treatments. We wished to determine whether HDNT is still effective in this patient group.

Method: We looked at the effect of HDNT in 54 patients in our adult clinic who were prescribed this as a second line treatment, comparing pre-treatment clinical parameters with those for the subsequent 3 years. Forty were also taking nebulised colomycin in the month off HDNT.

Results: The results are expressed as median (inter-quartile range) in the table. There was an improvement in FEV1, and FVC and a reduction in iv days at 2 years following commencement of HDNT.

Conclusion: This study demonstrates that HDNT is still effective when used as a second line agent in unstable deteriorating patients.

Table: Effect of nebulised tobramycin [median [IQ range]]

<table>
<thead>
<tr>
<th></th>
<th>FEV1%</th>
<th>FVC %</th>
<th>iv days (Inpatient)</th>
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</thead>
<tbody>
<tr>
<td>Pre-commencement</td>
<td>49 (43–62)</td>
<td>77 (65–88)</td>
<td>22 (14–41)</td>
</tr>
<tr>
<td>1 year post</td>
<td>49 (40–68)</td>
<td>76 (64–89)</td>
<td>28 (11–61)</td>
</tr>
<tr>
<td>2 years post</td>
<td>54 (42–72)</td>
<td>83 (65–92)</td>
<td>20 (0–41)</td>
</tr>
<tr>
<td>3 years post</td>
<td>49 (42–68)</td>
<td>80 (63–87)</td>
<td>25 (14–46)</td>
</tr>
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Efficacy of tobramycin inhalation powder (TIP) versus other inhaled antibiotics in cystic fibrosis (CF) patients with chronic P. aeruginosa infection: a network meta-analysis

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Objective: Inhaled antibiotics prescribed to treat CF patients with chronic P. aeruginosa infection have been shown to improve lung function. The relative efficacy of inhaled antibiotics is not known, as few comparative studies are available. The efficacy of tobramycin inhalation powder capsules (TIP), tobramycin inhalation solutions (TIS-T and TIS-B), colistimethate sodium (Colistin) and aztreonam lysine for inhalation (AZLI) was compared.

Methods: A systematic search found seven relevant randomised controlled trials in CF patients with moderate to severe lung function impairment. Percent change from baseline in FEV1% predicted at 4 weeks of treatment was analysed using network meta-analysis techniques, combining direct and indirect treatment evidence. Several covariates including prior exposure to active drug, considered as a potential treatment effect modifier, were included in the analysis.

Results: Two studies had patients with mean age <18 and five with mean age >18 years. Two studies had patients previously exposed to active drug, and five had naive to study drug patients. Mean baseline FEV1% predicted was between 50% and 64%. TIP TIS-T and TIS-B had comparable efficacy in improving FEV1% predicted at 4 weeks. TIP was comparable to all treatments, although point estimates may suggest a trend for better efficacy than Colistin and AZLI for this endpoint: TIP versus Colistin: ~5.8 (Crl: ~12.8; 1.2) and TIP versus AZLI: ~3.6 (Crl: ~8.3; 1.0).

Conclusion: The analysis suggests that TIP is at least as efficacious as other inhaled antibiotics for lung function improvement at 4 weeks of treatment.