Studies on antibiotic aerosols for inhalation in cystic fibrosis
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Effect of nebulised colistin sulfate and colistin sulfomethate on lung function in patients with cystic fibrosis: a pilot study


Summary

Pulmonary administration of colistin is one of the antimicrobial treatments used in cystic fibrosis (CF) patients chronically infected with *Pseudomonas aeruginosa*. Dry powder inhalation of colistin may be an attractive alternative to nebulisation of colistin. However, nebulised colistin can cause airway narrowing in CF patients. Therefore, in the progress of developing a dry powder formula, the choice of the inhaler and its contents should be guided by optimal efficacy and the least possible side effects. To investigate the side effects, a study was initiated to compare the tolerability of colistin sulfate to colistimethate sodium (colistin sulfomethate) per nebulisation in CF-patients.

Nine CF-patients chronically infected with *Pseudomonas aeruginosa* participated in a double blind, randomised cross over study. On two visits to the outpatient clinic, patients were submit- ted to either nebulised colistin sulfate or colistimethate sodium solution. Lung function tests were performed immediately before and 15 and 30 min after nebulisation.

Nebulisation of colistin sulfate caused a significant larger mean decrease in lung function compared to nebulised colistimethate sodium. A significant decrease in mean changes (SD) in FEV₁ at 30 min and FVC at 15 and 30 min after nebulisation compared to baseline of -7.3% (8.6%), -5.7% (7.3%) and -8.4% (7.5%) respectively was seen after colistin sulfate nebulisation compared to colistimethate sodium (P<0.05). Seven patients were not able to complete the nebulisation of colistin sulfate because of throat irritation and severe cough.

Based on these results it was concluded that inhalation with nebulised colistin sulfate is not suitable for treatment of CF patients chronically infected with *Pseudomonas aeruginosa*. Colistimethate sodium is the drug of choice for pulmonary administration of colistin.
Introduction

Nebulised colistin is one of the antimicrobial agents recommended for use in patients with cystic fibrosis (CF) chronically infected with Pseudomonas aeruginosa (Döring et al., 2000). For this therapy, commercially available vials for intravenous administration, containing colistimethate sodium (colistin sulfomethate), are generally used. As nebulisation of drugs in general is a time consuming activity, influencing daily life of patients, an alternative method of pulmonary delivery of colistin would be welcome. Therefore, dry powder inhalation of colistin may be an attractive alternative to nebulisation of colistin in CF-patients (Le Brun et al., 2002).

In vivo, colistimethate sodium is transformed into colistin sulfate, which is thought to have a more potent antibacterial effect than the parent compound (Shawar 1999). Therefore, we initially considered colistin sulfate as the compound of choice in the development of a colistin dry powder for inhalation. In a previous pilot study, the feasibility of colistin sulfate as a dry powder inhalation was investigated both in healthy volunteers and in patients (Le Brun 2002). This newly developed dry powder inhalation system was highly appreciated by the patients and provided a pulmonary deposition comparable to the deposition observed after nebulisation of colistimethate sodium solution. However, as reported, a decrease in pulmonary function and the occurrence of non productive cough after dry powder inhalation of colistin sulfate was observed in a number of patients, whereas no such effects were seen in the volunteer group. Furthermore, no such side effects were observed in CF-patients after nebulisation of colistin as sulfomethate. The origin of the side effects after colistin sulfate administration was not clear and it was concluded that further research was necessary. Either a suboptimal particle size distribution of the dry powder or the chemical properties of colistin sulfate were held responsible for these effects.

Improvement of particle size distribution is within reach. However, if the side effects were provoked by the physical chemical properties of colistin sulfate, colistimethate sodium would be the appropriate chemical form for further development of a dry powder inhalation system. To investigate the latter hypothesis while excluding the first, both colistin salts should be tested in a dissolved form. Therefore, the aim of this study was to compare the tolerability of colistin sulfate to colistimethate sodium per nebulisation in cystic fibrosis patients.

Materials and methods

Patients

Nine patients (five females) with CF, diagnosed by clinical history and confirmed by pathological sweat tests or DNA analysis, volunteered to participate in the study. Patients were clinically stable over the last 3 months, as determined by pulmonary function tests. All patients were
chronically infected with *Pseudomonas aeruginosa* and therefore on maintenance treatment with nebulised colistimethate sodium. Exclusion criteria were exacerbation of pulmonary infection, colistin hypersensitivity, treatment with an investigational drug within a month prior to enrolment, pregnancy, potentially pregnant or nursing women. The study was performed according to the Helsinki declaration and was approved by the medical ethical review board of the hospital. Patients were fully informed by the investigator and a written consent was obtained from every patient.

**Study protocol**

Patients were asked to visit the outpatient clinic two times, with an interval of at least 5 days. Patients were instructed not to nebulise colistimethate sodium or any other inhalation medication on the morning of the day of visit to the outpatient clinic. On the first visit, the patient nebulised a solution of either colistin sulfate or colistimethate sodium and on the second visit vice versa. This was done in a randomly assigned double-blind order. Blinding and randomisation was performed by the hospital pharmacy. Lung function tests were performed just before and 15 and 30 min after nebulisation was completed. The patients were asked five questions concerning their daily use of colistimethate sodium. The questionnaire and different scales used for scoring are given in Fig. 1.

**Materials**

Colistimethate sodium (Colistin parenteral®, Grünenthal GmbH, Aachen, Germany) and colistin sulfate (Ph. Eur. 1997, Duchefa, Haarlem, The Netherlands) were supplied by the hospital pharmacy. An amount of 160 mg colistimethate sodium or 100 mg colistin sulfate was dissolved in 6 ml 0.9% aqueous sodium chloride solution by the hospital pharmacy prior to the test. The solutions contained an equivalent amount of colistin (67 mg/6 ml). The pH of the colistimethate sodium solution was approximately 7.4; the osmolality 366 mOsm/kg. The pH and osmolality of the colistin sulfate solution were 5 and 306, respectively (pH meter Metrohm 713, Herisau, Switzerland; osmolality meter Knauer A 0300, Berlin, Germany). Nebulisation of the colistin solutions was done using a combination of a Porta-Neb® compressor and a Ventstream® jet nebuliser.
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(Medic Aid, Romedic, Meerssen, The Netherlands). The patients were instructed to operate the device until the complete dose was released. In case of adverse effects of any kind during nebulisation, participants were allowed to stop the inhalation of the aerosol temporarily.

**Pulmonary function**

Forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC) were measured using a calibrated Masterlab pneumotachograph (Jaeger, Würzburg, Germany). Lung function tests were performed following the guidelines of the European Respiratory Society (Quanjer et al., 1993). A fall in FEV$_1$ of 10% or more was considered as clinically significant. Percentage changes are relative to baseline, and not a percentage fall of predicted.

**Statistical analysis**

To compare the effects on lung function of the two colistin forms, the changes from baseline in the parameters FEV$_1$ and FVC, found after administration of colistin sulfate, were compared to the changes found after administration of colistimethate sodium using the paired Student’s t-test. A $p<0.05$ was considered to be significant.

**Results**

Nine patients participated in the study (five females). Mean age was 29 years (range 20–41). Mean baseline values (SD) of FEV$_1$ and FVC were 57.8% (11.9%) and 80.2% (9.5%), respectively (% predicted). After seven patients had been tested the severity of the adverse effects caused us to perform an interim analysis. However, the subsequent two patients were again studied under blinded conditions. The pulmonary function test results of the patients before and after nebulisation of either one of the colistin solutions are presented in Fig. 2.

**Colistin sulfate**

Two patients completed nebulisation without subjective adverse effects, despite a decrease in FEV$_{1,15-0}$ of 31.3% and 10.0%, respectively. The remaining seven patients were not able to complete nebulisation of colistin sulfate because of throat irritation and severe cough. In one of these seven patients a clinically significant fall in FEV$_1$ of 31.5% was seen 15 min after nebulisation. Five patients showed a fall in FEV$_1$ 15 and 30 min after nebulisation and in one patient no effect on FEV$_1$ was observed. FEV$_1$ values 30 min after nebulisation were not significantly altered compared to t=15 min. Chest tightness was noticed by those patients who were able to continue nebulisation for a longer period of time. Next to the two patients that completed nebulisation, two patients were able to nebulise at least 80% of the colistin sulfate solution. The chest tightness reported by these four patients lasted 2–3 days. In the seven patients that partially nebulised the solution, severe coughing was accompanied by perspiration and a sensation
of heat. The irritating effect of the solution was most pronounced in the throat. Some patients noticed an increased mucus production. All patients noted an unpleasant taste. One patient needed treatment with a bronchodilator drug after lung function tests were completed.

**Colistimethate sodium**

All patients completed nebulisation of colistimethate sodium. A clinically significant fall in FEV\(_1\) 15 min after nebulisation was observed in two patients. This effect ameliorated after 30 min. In one of these two patients, the fall in FEV\(_1\) was accompanied by a decrease in FVC. This
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A patient indicated that she also experienced chest tightness during daily colistimethate sodium nebulisation. No effects other than in daily use were noticed by the patients.

Comparison of colistin sulfate to colistimethate sodium

The results in Table 1 and Fig. 2 show that the decrease in lung function is more severe after administration of colistin sulfate than after administration of colistimethate sodium. A statistically significant difference in mean changes in FEV\textsubscript{1} from baseline after colistimethate sodium nebulisation compared to colistimethate sodium was observed. However, the difference in decrease in FEV\textsubscript{1} between the two colistin salts, observed 15 min after nebulisation, was not statistically significant.

**Table 1** Differences in effect on lung function between colistin sulfate and colistimethate sodium: mean changes in FEV\textsubscript{1} and FVC from baseline values after administration of colistin sulfate and after colistimethate sodium have been compared at t=15 and t=30 minutes.

<table>
<thead>
<tr>
<th></th>
<th>change in FEV\textsubscript{1} (S.D.) (15 min vs baseline)</th>
<th>change in FEV\textsubscript{1} (S.D.) (30 min vs baseline)</th>
<th>change in FVC (S.D.) (15 min vs baseline)</th>
<th>change in FVC (S.D.) (30 min vs baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>colistin sulfate</td>
<td>-11,3% (12,6%)</td>
<td>-10,2% (9,4%)</td>
<td>-10,4% (9,9%)</td>
<td>-10,5% (9,5%)</td>
</tr>
<tr>
<td>colistimethate sodium</td>
<td>-6,0% (7,0%)</td>
<td>-2,9% (3,3%)</td>
<td>-4,7% (8,1%)</td>
<td>-2,1% (4,9%)</td>
</tr>
<tr>
<td>results (difference)</td>
<td>-5,3% (12,2%)</td>
<td>-7,3% (8,6%)</td>
<td>-5,7% (7,3%)</td>
<td>-8,4% (7,5%)</td>
</tr>
</tbody>
</table>

\[ p = 0,225 \] \[ p = 0,034 \] \[ p = 0,047 \] \[ p = 0,010 \]

Change in ∆FEV\textsubscript{1} (S.D.): mean change in FEV\textsubscript{1} from baseline after colistin sulfate nebulisation minus mean change in FEV\textsubscript{1} from baseline after colistimethate sodium nebulisation. S.D. = standard deviation.

Change in ∆FVC (S.D.): mean change in FVC from baseline after colistin sulfate nebulisation minus mean change in FVC from baseline after colistimethate sodium nebulisation. S.D. = standard deviation.

The questionnaire was intended to give insight in the daily use of colistin (as sulfomethate) by the patients. Four patients experienced adverse effects during or after nebulisation (score 3), three patients scored 2 and two patients did not experience adverse effects at all (score 1). Adverse effects occurred at 0–10 min after starting nebulisation in eight patients and after 10–20 min in one patient. None of the patients indicated that the adverse effects influenced their daily life. All patients used inhalation medication daily. Six patients sometimes used a short acting β\textsubscript{2}-sympathicomimetic inhalation drug.

**Discussion**

The aim of this study was to assess the tolerability, defined as a possible clinically relevant difference in pulmonary function and adverse effects, during and after nebulisation of two different chemical entities of colistin. The results of this study show that nebulisation of colistin sulfate is not tolerated by CF-patients in contrast to nebulisation of colistimethate sodium. A
relationship between adverse effects and adherence to treatment by CF-patients has been established; airway narrowing may be a reason for poor and discontinuing the therapy (Abbott et al., 1994; Maddison et al., 1994). Therefore, colistin sulfate should not be considered as the chemical entity of choice in treatment of CF patients chronically infected with *Pseudomonas aeruginosa*.

The patients in this study were used to daily nebulisation of colistimethate sodium. Although some decrease in lung function was observed in all patients and in two patients a clinically significant decrease in FEV$_1$ was observed 15 min after nebulisation, only one patient noticed airway narrowing. In contrast, serious side effects (cough and irritation) and deterioration of lung function were observed after administration of colistin sulfate. In three patients, a reduction in FEV$_1$ of 10% or more was observed.

The adverse effects found after administration of the nebulised colistin sulfate solution appeared to be more serious compared to the adverse effects after dry powder inhalation, observed by Le Brun et al., 2002. Airway narrowing after inhalation of antibiotics in CF patients is quite common. Airway narrowing and chest tightness after nebulisation of colistimethate sodium has been reported in literature (Maddison et al., 1994; Cunningham et al., 2001). Cunningham et al. reported a decrease in FEV$_1$ of more than 10% in 20 out of 58 children (34%) immediately and 15 min after nebulisation. In 9% of these children, this decrease still persisted at 30 min after nebulisation. Maximal airway narrowing was measured immediately after nebulisation in 13 patients, after 15 min in five patients and after 30 min in two patients. Thirty-five of 46 patients (76%) in a study by Maddison et al. developed bronchoconstriction after nebulisation of colistin. No definition of clinically significant bronchoconstriction was reported by the authors. Maximal bronchoconstriction was observed immediately after nebulisation in 30 patients, after 15 min in three patients and after 30 min in two patients. No change in FEV$_1$ was reported in seven patients.

Recent published data concerning bronchial reactions to the inhalation of several tobramycin preparations, including high-dose tobramycin, in 12 CF-patients with moderate disease show a significant bronchial obstruction (10% decrease in mean FEV$_1$) shortly after nebulisation. Bronchoconstriction was most severe after nebulisation of high-dose tobramycin. After 10 min of inhalation lung function tests had normalised. These results support the suggestion that lung function tests generally normalise within 10 min after nebulisation (Nikolaizik et al., 2002). Our results show a decrease in FEV$_1$ similar as described by Maddison et al., 1994 and Cunningham et al., 2001. A statistically significant change in mean FEV$_1$, 30 min after nebulisation compared to baseline, between colistin sulfate and colistimethate sodium was observed. However, no significant difference in FEV$_1$ at t=15 min between the two colistin salts was seen. These observations show the lasting effect of colistin sulfate compared to the relatively rapid recovery of lung function after colistimethate sodium nebulisation. If the results of Cunningham et al. and Maddison et al. would be applicable to our patient group, maximal airway narrowing could have occurred immediately after cessation of nebulisation. Additionally, the decrease in forced
vital capacity at 15 and 30 min compared to baseline, seen after colistin sulfate nebulisation, was significantly lower compared to nebulised colistimethate sodium.

To our knowledge no earlier data concerning the effect of nebulised colistin sulfate in CF-patients have been published. The observed effects during and after colistin sulfate nebulisation are caused by a yet unknown mechanism. Whether the tonicity or pH of both solutions were of any influence on the results, remains unclear. Although adverse effects, related to nebulisation of colistimethate sodium, were reported in the questionnaire, none of the patients indicated that it influences their daily life. Apparently, lung function parameters improve within 30 min after completing nebulisation in most patients, as proven by our data.

**Conclusion**

This study showed that airway narrowing after nebulisation of colistin sulfate was significantly more severe than after nebulisation of colistimethate sodium. Most patients were forced to stop nebulising colistin sulfate because of throat irritation and (severe) cough. The mechanism causing the observed effects is not elucidated. As most patients experienced serious side effects, it is concluded that nebulised colistin as sulfate is not suitable for treatment of CF patients chronically infected with *Pseudomonas aeruginosa*. Future research towards the development of a colistin dry powder inhalation will focus on the use of colistimethate sodium.

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