ELSEVIER
Journal of Cystic Fibrosis 3 (2004) 23–28
JOURNAL OF CYSTIC FIBROSIS
www.elsevier.com/locate/jcf

Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study

E.M. Westerman[a,*], P.P.H. Le Brun[a], D.J. Touw[a], H.W. Frijlink[b], H.G.M. Heijerman[c]

[a]*Central Hospital Pharmacy The Hague, The Hague, The Netherlands*
[b]*Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands*
[c]*Adult Cystic Fibrosis Center, Leyenburg Hospital, The Hague, The Netherlands*

Accepted 17 December 2003

Abstract

Background: 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 nebulization of colistin. However, nebulized colistin can cause bronchoconstriction 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 sulphate to colistin sulphomethate per nebulization in CF-patients. *Methods*: Nine CF-patients chronically infected with *P. aeruginosa* participated in a double blind, randomized cross over study. On two visits to the outpatient clinic, patients were submitted to either nebulized colistin sulphate or colistin sulphomethate solution. Lung function tests were performed immediately before and 15 and 30 min after nebulization. *Results*: Nebulization of colistin sulphate caused a significant larger mean decrease in lung function compared to nebulized colistin sulphomethate. A significant decrease in mean changes (SD) in FEV1 at 30 min and FVC at 15 and 30 min after nebulization compared to baseline of −7.3% (8.6%), −5.7% (7.3%) and −8.4% (7.5%) respectively was seen after colistin sulphate nebulization compared to colistin sulphomethate ($P<0.05$). Seven patients were not able to complete the nebulization of colistin sulphate because of throat irritation and severe cough. *Conclusion*: Based on these results it was concluded that inhalation with nebulized colistin sulphate is not suitable for treatment of CF patients chronically infected with *P. aeruginosa*. Colistin sulphomethate is the drug of choice for pulmonary administration of colistin.

Keywords: Adverse effects; Bronchoconstriction; Colistin; Dry powder inhalation

1. Introduction

Nebulized colistin is one of the antimicrobial agents recommended for use in patients with Cystic fibrosis (CF) chronically infected with *Pseudomonas aeruginosa* [1]. For this therapy, commercially available vials for intravenous administration, containing colistin as sulphomethate, are generally used. As nebulization 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 nebulization of colistin in CF-patients [3].

In vivo, colistin sulphomethate is transformed into colistin sulphate, which is thought to have a more potent antibacterial effect than the parent compound [2]. Therefore, we initially considered colistin sulphate as the compound of choice in the development of a colistin dry powder for inhalation.

In a previous pilot study, the feasibility of colistin sulphate as a dry powder inhalation was investigated both in healthy volunteers and in patients [3]. This newly developed dry powder inhalation system was highly appreciated by the patients and provided a pulmonary deposition comparable to the deposition observed after nebulization of colistin sulphomethate solution. However, as reported, a decrease in pulmonary function and the occurrence of non productive cough after dry powder inhalation of colistin sulphate was

*Corresponding author.
E-mail address: e.westerman@ahz.nl (E.M. Westerman).

1569-1993/04/$30.00
doi:10.1016/j.jcf.2003.12.005

Questionnaire

Question	Score
1. Do you experience adverse effects during or after nebulization?	1-2-3-4-5-6
2. When do these adverse effects occur?	0-10 min / 10-20 min / 20-30 min after nebulization
3. Do these adverse effects influence your daily life?	1-2-3-4-5-6
4. Do you use other (inhalation)drugs to decrease chest tightness after nebulization?	yes / no

1 = none, 2 = minor, 3 = moderate, 4 = tolerable, 5 = serious, 6 = severe

Fig. 1. Questionnaire.

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 nebulization of colistin as sulphomethate. The origin of the side effects after colistin sulphate 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 sulphate 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 sulphate, colistin sulphomethate 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 sulphate to colistin sulphomethate per nebulization in Cystic fibrosis patients.

2. Materials and methods

2.1. 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 *P. aeruginosa* and therefore on maintenance treatment with nebulized colistin sulfomethate. Exclusion criteria were exacerbation of pulmonary infection, colistin hypersensitivity, treatment with an investigational drug within a month prior to enrollment, 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.

2.2. 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 nebulize colistin or any other inhalation medication on the morning of the day of visit to the outpatient clinic. On the first visit, the patient nebulized a solution of either colistin sulphate or colistin sulphomethate and on the second visit vice versa. This was done in a randomly assigned doubleblind order. Blinding and randomisation was performed by the hospital pharmacy.

Lung function tests were performed just before and 15 and 30 min after nebulization was completed.

The patients were asked five questions concerning their daily use of colistin. The questionnaire and different scales used for scoring are given in Fig. 1.

2.3. Materials

Colistin sulphomethate (Colistin parenteral®, Grünenthal GmbH, Aachen, Germany) and colistin sulphate (Ph. Eur. 1997, Duchefa, Haarlem, The Netherlands) were supplied by the hospital pharmacy.

An amount of 160 mg colistin sulphomethate or 100 mg colistin sulphate 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 colistin sulphomethate solution was approximately 7.4; the osmolality 366 mOsm/kg. The pH and osmolality of the colistin sulphate solution were 5 and 306, respectively (pH meter Metrohm 713, Herisau, Switzerland; osmolality meter Knauer A 0300, Berlin, Germany).

Nebulization of the colistin solutions was done using a combination of a Porta-Neb® compressor and a Ventstream® jet nebulizer (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 nebulization, participants were allowed to stop the inhalation of the aerosol temporarily.

2.4. Pulmonary function

Forced expiratory volume in one second (FEV1) 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 [4]. A fall in FEV1 of 10% or more was considered as clinically significant. Percentage changes are relative to baseline, and not a percentage fall of predicted.

2.5. Statistical analysis

To compare the effects on lung function of the two colistin forms, the changes from baseline in the parameters FEV1 and FVC, found after administration of colistin sulphate, were compared to the changes found after administration of colistin sulphomethate using the paired Student's *t*-test. A $P<0.05$ was considered to be significant.

3. Results

Nine patients participated in the study (five females). Mean age was 29 years (range 20–41). Mean baseline values (SD) of FEV1 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 nebulization of either one of the colistin solutions are presented in Fig. 2.

3.1. Colistin sulphate

Two patients completed nebulization without subjective adverse effects, despite a decrease in $FEV1_{15\text{-}0}$ of 31.3% and 10.0%, respectively. The remaining seven patients were not able to complete nebulization of colistin sulphate because of throat irritation and severe cough. In one of these seven patients a clinically significant fall in FEV1 of 31.5% was seen 15 min after nebulization. Five patients showed a fall in FEV1 15 and 30 min after nebulization and in one patient no effect on FEV1 was observed. FEV1 values 30 min after nebulization were not significantly altered compared to $t=15$ min. Chest tightness was noticed by those patients who were able to continue nebulization for a longer period of time. Next to the two patients that completed nebulization, two patients were able to nebulize at least 80% of the colistin sulphate solution. The chest tightness reported by these four patients lasted 2–3 days.

In the seven patients that partially nebulized 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.

3.2. Colistin sulphomethate

All patients completed nebulization of colistin sulphomethate. A clinically significant fall in FEV1 15 min after nebulization was observed in two patients. This effect ameliorated after 30 min. In one of these two patients, the fall in FEV1 was accompanied by a decrease in FVC. This patient indicated that she also experienced chest tightness during daily colistin nebulization. No effects other than in daily use were noticed by the patients.

3.3. Comparison of colistin sulphate to colistin sulphomethate

The results in Table 1 and Fig. 2 show that the decrease in lung function is more severe after administration of the colistin sulphate than after administration of colistin sulphomethate. A statistically significant difference in mean changes in $FEV1_{30\text{-}0}$, $FVC_{15\text{-}0}$ and $FVC_{30\text{-}0}$ after colistin sulphate nebulization compared to colistin sulphomethate was observed. However, the difference in decrease in FEV1 between the two colistin salts, observed 15 min after nebulization, was not statistically significant.

3.4. Questionnaire

The questionnaire was intended to give insight in the daily use of colistin (as sulphomethate) by the patients. Four patients experienced adverse effects during or after nebulization (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 nebulization 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 β2-sympathicomimetic inhalation drug.

4. 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 nebulization of two different chemical entities of colis-

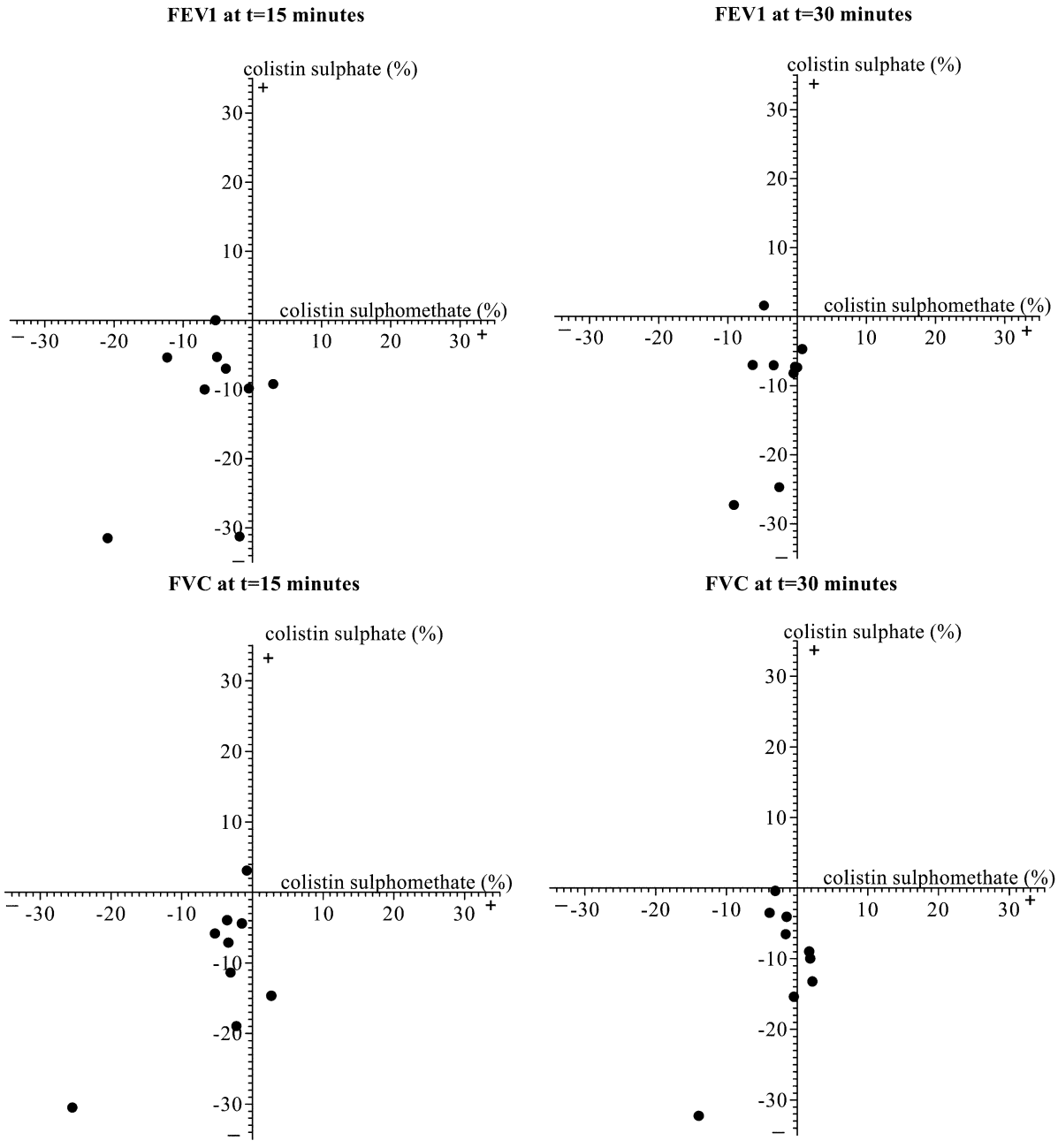

Fig. 2. Individual FEV1 and FVC-values (deviation from baseline in percentage), for nine patients, after nebulization of colistin sulphate and colistin sulphomethate respectively.

tin. The results of this study show that nebulization of colistin sulphate is not tolerated by CF-patients in contrast to nebulization of colistin sulphomethate.

A relationship between adverse effects and compliance with treatment by CF-patients has been established; bronchoconstriction may be a reason for poor compliance and discontinuing the therapy [6,7]. Therefore, colistin sulphate should not be considered as the chemical entity of choice in treatment of CF patients chronically infected with *P. aeruginosa*.

The patients in this study were used to daily nebulization of colistin sulphomethate. Although some decrease in lung function was observed in all patients and in two patients a clinically significant decrease in FEV1 was observed 15 min after nebulization, only one patient noticed bronchoconstriction.

In contrast, serious side effects (cough and irritation) and deterioration of lung function were observed after administration of colistin sulphate. In three patients, a reduction in FEV1 of 10% or more was observed.

Table 1
Differences in effect on lung function between colistin sulphate and colistin sulphomethate: mean changes in FEV1 and FVC from baseline values after administration of colistin sulphate and after colistin sulphomethate have been compared at $t=15$ and $t=30$ min

	Change in FEV1 (S.D.) (15 min vs. baseline)	Change in FEV1 (S.D.) (30 min vs. baseline)	Change in FVC (S.D.) (15 min vs. baseline)	Change in FVC (S.D.) (30 min vs. baseline)
Colistin sulphate	−11.3% (12.6%)	−10.2% (9.4%)	−10.4% (9.9%)	−10.5% (9.5%)
Colistin sulphomethate	−6.0% (7.0%)	−2.9% (3.3%)	−4.7% (8.1%)	−2.1% (4.9%)
Results (difference)	−5.3% (12.2%)	−7.3% (8.6%)	−5.7% (7.3%)	−8.4% (7.5%)
	$P=0.225$	$P=0.034$	$P=0.047$	$P=0.010$

Change in ΔFEV1 (S.D.): mean change in FEV1 from baseline after colistin sulphate nebulization minus mean change in FEV1 from baseline after colistin sulphomethate nebulization. SD = standard deviation.

Change in ΔFVC (S.D.): mean change in FVC from baseline after colistin sulphate nebulization minus mean change in FVC from baseline after colistin sulphomethate nebulization. SD = standard deviation.

The adverse effects found after administration of the nebulized colistin sulphate solution appeared to be more serious compared to the adverse effects after dry powder inhalation, observed by Le Brun et al. [3].

Bronchoconstriction after inhalation of antibiotics in CF patients is quite common. Chest tightness after nebulization of colistin sulphomethate has been reported in literature [5,6]. Cunningham et al. reported a decrease in FEV1 of more than 10% in 20 out of 58 children (34%) immediately and 15 min after nebulization. In 9% of these children, this decrease still persisted at 30 min after nebulization. Maximal bronchoconstriction was measured immediately after nebulization 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 nebulization of colistin. No definition of clinically significant bronchoconstriction was reported by the authors. Maximal bronchoconstriction was observed immediately after nebulization in 30 patients, after 15 min in three patients and after 30 min in two patients. No change in FEV1 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 FEV1) shortly after nebulization. Bronchoconstriction was most severe after nebulization 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 nebulization [8].

Our results show a decrease in FEV1 similar as described by Cunningham et al. and Maddison et al. [5,6]. A statistically significant change in mean FEV1, 30 min after nebulization compared to baseline, between colistin sulphate and colistin sulphomethate was observed. However, no significant difference in FEV1 at $t=15$ min between the two colistin salts was seen. These observations show the lasting effect of colistin sulphate compared to the relatively rapid recovery of lung function after colistin sulphomethate nebulization.

If the results of Cunningham et al. and Maddison et al. would be applicable to our patient group, maximal bronchoconstriction could have occurred immediately after cessation of nebulization. Additionally, the decrease in forced vital capacity at 15 and 30 min compared to baseline, seen after colistin sulphate nebulization, was significantly lower compared to nebulized colistin sulphomethate.

To our knowledge no earlier data concerning the effect of nebulized colistin sulphate in CF-patients have been published. The observed effects during and after colistin sulphate nebulization 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 nebulization of colistin sulfomethate, 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 nebulization in most patients, as proven by our data.

5. Conclusion

This study showed that bronchoconstriction after nebulization of colistin sulphate was significantly more severe than after nebulization of colistin sulphomethate. Most patients were forced to stop nebulizing colistin sulphate 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 nebulized colistin as sulphate is not suitable for treatment of CF patients chronically infected with *P. aeruginosa*. Future research towards the development of a colistin dry powder inhalation will focus on the use of colistin sulphomethate.

Acknowledgments

The authors wish to thank the pharmacy technicians (Central Hospital Pharmacy, The Hague, The Nether-

lands) for preparing the study medication and Mr G. van der Meyden (Adult Cystic Fibrosis Center, Leyenburg Hospital, The Hague, The Netherlands) for performing the pulmonary function tests.

References

[1] Döring G, Conway SP, Heijerman HGM, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. Eur Resp J 2000;16:749–67.
[2] Shawar R, Anderson S, Barker L, Nguyen L, VanDevanter DR, Tanaka SK. In vitro assessment of bactericidal activity and relevance to pharmacodynamics of aerosolized antibiotics. Neth J Med 1999;54(Suppl):S38–S39.
[3] Le Brun PPH, de Boer AH, Mannes GPM, et al. Dry powder inhalation of antibiotics in cystic fibrosis therapy: part 2. Inhalation of a novel colistin dry powder formulation: a feasibility study in healthy volunteers and patients. Eur J Pharm Biopharm 2002;54:25–32.
[4] Quanjer PhH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows – Standardization of lung function tests. Eur Respir J 1993;6(Suppl. 16):5–40.
[5] Cunningham S, Prasad A, Collyer L, Carr S, Lynn IB, Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child 2001;84(5):432–3.
[6] Maddison J, Dodd M, Webb AK. Nebulized colistin causes chest tightness in adults with cystic fibrosis. Respir Med 1994;88:145–7.
[7] Abbott J, Dodd M, Bilton D, Webb AK. Treatment compliance in young adults with cystic fibrosis. Thorax 1994;49:115–20.
[8] Nikolaizik WH, Trociewicz K, Ratjen F. Bronchial reactions to the inhalation of high-dose tobramycin in cystic fibrosis. Eur Respir J 2002;20:122–6.