Inhaled mannitol in patients with cystic fibrosis: A randomised open-label dose response trial

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Abstract

Background: Cystic fibrosis (CF) is characterised by impaired mucociliary clearance (MCC), chronic inflammation and infection, and progressively deteriorating lung function. Inhaled mannitol (Bronchitol) has been shown to increase MCC and cough clearance and FEV1 in CF patients, contributing to better lung hygiene and consequently a slower decline in lung function. This study was designed to determine the dose relationship of mannitol treatment and improvement in FEV1 and FVC as well as safety.

Methods: This was a randomised, open-label, crossover, dose response study. Following a 2-week treatment with mannitol 400 mg b.i.d., 48 CF patients with a mean (SD) FEV1 % predicted of 64 (13.2), received a further 3 treatments with 40 mg, 120 mg or 240 mg b.i.d. for 2 weeks each, in random order.

Results: The study demonstrated a dose dependent increase in FEV1 and FVC. The 400 mg dose showed the greatest improvement and the 40 mg dose had no discernible effect. The mean percent change in FEV1 was −1.57%, 3.61%, 3.87% and 8.75% respectively for the 40 mg, 120 mg, 240 mg and 400 mg treatments. There was a statistically significant change in FEV1 for 400 mg compared to 40 mg (p < 0.0001) but the difference with 120 mg and 240 mg did not reach significance.

The mean % change in FVC was −0.90, 1.74, 3.07 and 8.14, for the 40 mg, 120 mg, 240 mg and 400 mg treatment arms, with p=0.0001, p=0.0037 and p=0.0304 respectively when compared to 400 mg. The highest tested dose of 400 mg had a similar safety profile to the other doses tested.

The change in FEV1 and FVC by dose in the paediatric age group (<18 years) was similar to the results in the adult population.

Conclusion: Based on these results the 400 mg b.i.d. dose has been further studied in phase III trials.

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Keywords: Cystic fibrosis; Mannitol; Mucoactive; Mucus clearance; Lung function; FEV1

1. Introduction

Lung disease is the most important manifestation in terms of symptoms and treatment required and is by far the most frequent cause of death in cystic fibrosis (CF). It is manifested by an impaired clearance of mucus, chronic inflammation and infection and airway damage [1]. Over many years the lung function progressively deteriorates until respiratory failure and a range of other complications develop. The aims in the treatment of CF are to alleviate symptoms, improve quality of life and to slow the decline in lung function. This is achieved by improving airway clearance, by eradicating or suppressing the growth of bacterial pathogens and attenuating airway inflammation.

A formulation of inhaled dry powder mannitol (Bronchitol) is believed to meet the criteria for a suitable agent for use in CF [2]. Inhaled mannitol creates a sustained osmotic gradient which is thought to increase the amount of water in the airway lumen which encourages the hydration and subsequent restoration of the periciliary fluid layer [3]. This leads to improved clearance of mucus by ciliary and cough function [3]. It improves mucus rheology by hydration and possibly by breaking internal hydrogen bonds between mucins [4], stimulates the release of
mediators that are capable of increasing ciliary beat frequency [5], increases the secretion and flow of fresh mucus to help remove unwanted debris and pathogens [6] and by stimulating a productive cough it acts as an expectorant [6] causing reduction of the mucus load quickly [7]. Inhaled mannitol has been shown to increase the clearance of airway mucus in patients with CF aged between 16 and 46 years [8] and an initial short term study of inhaled mannitol showed increase in FEV1 [2]. This study was designed to determine the optimum dose of mannitol required to demonstrate clinical improvement in lung function in patients with CF. Other study outcomes including safety and tolerability were also assessed.

2. Methods

2.1. Study patients

Patients with CF were recruited from 12 sites in two countries (Canada 7 and Argentina 5).

Patients with confirmed diagnosis of CF (sweat test or genotype), aged 7 years or older, able to perform acceptable-quality spirometry, with a baseline FEV1 between 40% and 90% of predicted were eligible to participate in the trial.

Key exclusion criteria included haemoptysis of >60 mL in the previous 12 months, Burkholderia cepacia or MRSA colonisation, active asthma, pregnancy, breast feeding, heart attack or stroke in the last 3 months or the need for home oxygen. Active asthma has been defined as “current symptoms and signs of asthma”. Since inhaled mannitol may induce bronchospasm in susceptible patients, patients with active asthma are at risk of bronchoconstriction and is one reason patients are tested with a dose of mannitol (mannitol tolerance test [MTT]) prior to starting therapy.

The concurrent use of nebulised hypertonic saline and beta blocker medication was not allowed, and a 2-week washout period was required for patients using hypertonic saline solution or any new/changed antibiotics or oral steroids. In order to ensure observed changes in FEV1 and dose effects were due to inhaled mannitol alone, the concomitant use of rhDNase and hypertonic saline was avoided.

The protocol stipulated that antibiotic use was to be maintained throughout the study and that any new or changed antibiotic use was to be followed by a 2-week washout period before recommencing a treatment period. The patients were allowed to use their routine antibiotics as per their usual prophylactic treatment schedule.

2.2. Study design

This was a phase II, randomised, open-label, dose response crossover study, to determine the dose of inhaled mannitol required to generate clinical improvements in FEV1 in patients with confirmed CF. The study was conducted at 12 sites. Duration of the study was 13 weeks, including 4 treatment periods of 2 weeks with a 1-week washout between each treatment period.

At screening, patients were assessed against the exclusion and inclusion criteria, and eligible participants were assessed for airway hyperresponsiveness (AHR) using a MTT of increasing doses of mannitol. Prior to MTT the majority of patients were not pre-medicated with a bronchodilator.

Patients were excluded if their FEV1 fell by ≥15% before a cumulative dose of 475 mg had been administered and they were classified as MTT positive. MTT negative patients commenced a 2-week treatment with inhaled mannitol at 400 mg b.i.d.

Prior to inhalation of doses during the treatment period patients inhaled a short acting beta agonist. Salbutamol 400 μg was delivered via a spacer 15 min prior to mannitol administration during the study visits. A salbutamol inhaler was dispensed to all patients for use at home prior to study medication.

Following a 2-week treatment with 400 mg b.i.d., patients were given further three treatments with 40 mg, 120 mg or 240 mg b.i.d. for 2 weeks each in random order.

Inhaled mannitol (Bronchitol™, Pharmaxis Ltd., Frenchs Forest NSW, Australia) was blister packed in 40 mg capsules and administered via an inhaler device (RS01™, Monodose Inhaler Model 7, Plastiape, Italy). Capsules were loaded into the inhaler device, punctured, then mannitol inhaled in a deep controlled manner followed by a 5 s breath hold. The process was to be repeated until the required number of capsules had been inhaled.

Order of assessment and treatment was standardized for each visit, i.e. 1) vital signs measured; 2) spirometry measured (FEV1, forced vital capacity [FVC], index of airflow limitation [FEV1/FVC], average forced expired flow over the middle half of the FVC [FEF25-75], and peak expiratory flow [PEF]); 3) pre-medication with bronchodilator; 4) mannitol administration; 5) spirometry repeated; 6) vital signs measured; 7) physiotherapy and 8) sputum sample collected.

Repeated spirometry was performed twice at all clinic visits: 1) prior to premedication with salbutamol and 2) after the drug administration. Physiotherapy was performed after the drug administration and prior to sputum collection. Sputum was collected 1 h post treatment dose at the clinic. Although chest physiotherapy was not standardized across the study, the patients were to continue with their standard physiotherapy. However, it was important that patients adhered to the same routine of bronchodilator, mannitol and physiotherapy treatments on each study day visit.

Patients who performed exercise or chest physiotherapy for clearing mucus were requested to exercise or have their last physiotherapy/exercise treatment no closer than 4 h prior to their scheduled visit as physiotherapy was attended to at the clinic.

2.3. Study objectives

The primary objective was to determine the optimum dose of mannitol required to obtain clinical improvement in lung function by comparing the change in FEV1 and FVC at different doses of mannitol during 2 weeks of treatment.

The secondary objectives were to determine: (1) the effect on other measures of lung function, i.e. mean change in FEV1/FVC, FEF25-75, and PEF (before and after treatment periods), (2) the presence of acquired bacteria in sputum, (3) changes in...
quality of life (QoL), treatment effect scores and respiratory symptoms scores, (4) expectorated sputum volume post treatment and (5) the frequency and type of adverse events.

2.4. Lung function measurements

At all visits, pulmonary function testing was conducted according to ATS Guidelines [9] by suitably qualified and trained staff. Sites were supplied with a SpiroCard Diagnostic Spirometer, consisting of Z-7000-0030 SpiroCard PC Card Spirometer (CE 0086) and laptop computer with Windows 2000/XP Office Medic SWR with network ready database. Spirometers were calibrated before each patient visit and the results recorded for quality assurance.

2.5. Sputum microbiology and weight

Sputum samples were collected at screening and post treatment dose in the clinic at each study visit. The sputum was collected after spirometry and physiotherapy as a single sample over one-hour period. Salivary contamination was to be avoided. When the patients could not easily produce sputum, sputum was collected after a postural drainage for up to 30 min. Sputum samples were weighed at each participating clinic using their own balance and pre-weighed collection jars. Samples were analysed by the institutional laboratory for microbiology, using their standard laboratory procedures. The presence of pathogens was reported in terms of clinical significance by the study physician.

2.6. Quality of life (QoL)

Health-related QoL was measured using the Revised Cystic Fibrosis Questionnaire (CFQ-R) [10] which was administered at the beginning of the study prior to the first 2-week treatment and completion of each dosing period.

2.7. Respiratory symptoms

At Visits 2, 3, 5, 7 and 9 patients were asked standardized questions regarding respiratory symptoms over the past 2 weeks (e.g. breathlessness, cough, sputum production, congestion, fatigue, and discomfort) [2]. Responses were also obtained for sinus and nasal symptoms (such as postnasal drip, sore throat, sinus headache and pressure, nasal itch, nasal blockage, loss of smell, and mucus colour and production). A reduction in score indicated an improvement in symptoms.

2.8. Safety

Adverse event assessment, brief physical assessment, vital signs and spirometry were performed before and after the MTT, before and after initial administration of each mannitol treatment and at each follow-up visit. A brief physical examination included the following measurements: temperature, oxygen saturation, pulse rate and chest sounds.

2.9. Statistical analyses

Sequential treatment dose differences in the change in FEV1 and FVC values from baseline to post intervention were estimated. A linear mixed-effects model with orthogonal contrasts was used to compare mean % differences in FEV1 or FVC improvements at doses of mannitol 40 mg, 120 mg, and 240 mg relative to the reference dose of 400 mg mannitol. For each of the three comparisons the true mean difference was estimated using a 95% confidence interval. For each statistical test, a two-sided p value below 5% was considered as statistically significant. Baseline values at the start of the subsequent treatment periods were compared to the baseline values of the first treatment period in order to identify possible carry-over effects.

2.10. Determination of sample size

Thirty six patients were required to meet the precision of ±2% for detecting a difference between doses with a power of 0.80 and an alpha of 0.05 using a two-sided test.

2.11. Ethics

The relevant Research Ethics Boards (REB) in Canada and the National Administration of Products, Foods and Medical Technology (ANMAT) in Argentina approved the protocol, including any amendments, and the Informed Consent Document(s) before the study was initiated at each site. Documentation of this approval was provided to the sponsor or the sponsor’s designee.

3. Results

The study was conducted from November 2005 to June 2008.

3.1. Patient demographics and disposition

Overall 85 patients with mild to moderate CF aged 19.9 years ± 12.98 (range between 7 and 68 years), with baseline FEV1 63% ± 15 were enrolled in the study and included in the safety populations. Patients who did not meet eligibility criteria, were MTT positive or withdrew from the study prior to the treatment were excluded from continuing with the study (Fig. 1).

The mean fall in FEV1 following the MTT in the 27 patients who were positive was 17.6% (±3.8) and the mean dose at which FEV1 fell by 15% was 215.6 mg (±164 mg). It is of note that 22 out of 27 positive patients were not pre-medicated with salbutamol prior to MTT. There were no demographic indicators predictive of a positive MTT.

Fifty patients out of 85 screened patients were randomised to treatment. However, two patients withdrew from the study prior to receiving any treatment apart from the MTT. One of the patients was diagnosed with growth of Pseudomonas aeruginosa and was hospitalized for treatment. The second patient, although negative to MTT decided to withdraw from the study.
Forty eight of 50 randomised patients (29 paediatric patients between 7 and 17 years of age and 19 adult patients aged ≥18 years, overall mean age 19±13 years, with baseline FEV₁ 64%±13 [range between 43% and 89% predicted]) commenced on the 400 mg treatment arm and were included in the intent to treat (ITT) population (Table 1). Four patients withdrew after the initial treatment period due to their own decision; however, none of them withdrew due to adverse events.

Mean compliance in all treatment arms was similar at 92.08%, 96.09%, 96.06% and 93.95% for the 400 mg, 40 mg, 120 mg and 240 mg doses respectively.

3.2 Lung function

Pre-dose spirometry variables were analysed to measure the effectiveness of the washout period and no significant differences were detected for the start arm values for any variable confirming effective washout [Table 2]. However, there was a trend for slightly higher values to appear at the start of the second treatment period as compared to baseline, suggesting a slight carry-over effect from the first treatment arm which was 400 mg. b.i.d. Subsequent arms were randomised to minimise the impact on overall evaluation of each dose and the levels returned to baseline.

The effects of different mannitol dosages on lung function parameters are summarised in Table 3.

The mean percent change in FVC for the 400 mg treatment arm was 8.14% (183 mL), while it was −0.90% (−0.037 mL) for the 120 mg treatment arm, 1.74% (20 mL) for the 120 mg treatment arm and 3.07% (72 mL) for the 240 mg treatment arm. Significant
differences were noted for all three treatment arms compared to the 400 mg arm (p<0.0001, p<0.01 and p<0.05 respectively [Table 3]). Additionally the changes with the 120 mg and 240 mg doses were not significantly different to that with the 40 mg dose (Table 3).

When comparing the change in PEF a significant difference was noted between the 400 mg and 40 mg treatment arms (6.93% vs. 0.10%, p=0.0337), but not for the 120 mg or 240 mg treatment arms (p=0.12 and p=0.34, respectively).

In addition to the overall population, results were studied by age group. In particular, the change in FEV1 by dose in the paediatric age group (<18 years) was similar to the results in the adult population (Fig. 2) with a statistically significant increase in FEV1 for the 400 mg dose compared with the 40 mg dose (p=0.013 in 6–17 years old patients and p=0.0016 in patients 18 years and above). Significant differences in FVC were also noted for the 400 mg dose compared with the 40 mg dose in 6–17 years and 18+ years age groups (p=0.0038 and p=0.0069, respectively) as illustrated in Fig. 3.

### 3.3. Sputum microbiology and weight

The most common bacteria grown were *P. aeruginosa* (both mucoid and non-mucoid) in 56.3% of patients, *Staphylococcus aureus* (29.2%), and ‘Other’, (20.8%). No apparent reduction or increase in sputum microbiological growth occurred as a result of treatment. There was a negative relationship between mannitol

### Table 3

Comparison of relative (%) and absolute (L) change in lung function measures across treatment groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>40 mg</th>
<th>120 mg</th>
<th>240 mg</th>
<th>400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>Mean±SD</td>
<td>(-1.57±9.03)</td>
<td>(3.61±10.84)</td>
<td>(3.87±12.79)</td>
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<tr>
<td>p value vs. 400 mg</td>
<td>p&lt;0.0001</td>
<td>p=0.079</td>
<td>p=0.1138</td>
<td>p=0.1138</td>
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<tr>
<td>p value vs. 40 mg</td>
<td>p=0.018</td>
<td>p=0.025</td>
<td>p=0.0001</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>FVC</td>
<td>Mean±SD</td>
<td>(-0.90±7.90)</td>
<td>(1.74±9.22)</td>
<td>(3.07±11.68)</td>
</tr>
<tr>
<td>p value vs. 400 mg</td>
<td>p&lt;0.0001</td>
<td>p=0.0037</td>
<td>p=0.0304</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>p value vs. 40 mg</td>
<td>p=0.157</td>
<td>p=0.069</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>Mean±SD</td>
<td>(-0.80±5.62)</td>
<td>(2.11±6.32)</td>
<td>(0.73±6.69)</td>
</tr>
<tr>
<td>p value vs. 400 mg</td>
<td>p&lt;0.0001</td>
<td>p=0.0037</td>
<td>p=0.0304</td>
<td>p=0.0304</td>
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<tr>
<td>p value vs. 40 mg</td>
<td>p=0.157</td>
<td>p=0.069</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>FEV25–75</td>
<td>Mean±SD</td>
<td>(0.23±21.33)</td>
<td>(11.26±24.86)</td>
<td>(6.92±23.66)</td>
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<tr>
<td>p value vs. 400 mg</td>
<td>p=0.157</td>
<td>p=0.069</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
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<tr>
<td>p value vs. 40 mg</td>
<td>p=0.157</td>
<td>p=0.069</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>PEF</td>
<td>Mean±SD</td>
<td>(0.10±11.16)</td>
<td>(1.62±12.26)</td>
<td>(2.94±12.79)</td>
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<td>p=0.0001</td>
<td>p=0.0001</td>
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<tr>
<td>p value vs. 40 mg</td>
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<td>p=0.0001</td>
<td>p=0.0001</td>
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</table>

\(^*\) Post hoc analysis: p value calculated for each dose level vs. 40 mg for FEV1 and FVC using unpaired t-test.
dose and the change in sputum weight when comparing before and after 2-week treatment, with larger doses resulting in a greater decrease in sputum weight. A mean decrease by 0.18 g, 0.24 g, 0.37 g and 0.86 g for 40 mg, 120 mg, 240 mg and 400 mg doses respectively was seen; however the difference between doses was not significant (Table 4). The reduction in sputum weight after 2 weeks of treatment may result from a reduction in sputum load after 2 weeks of increased clearance. It appeared also that the volume cleared during a single treatment was dose dependent.

3.4. Other study outcomes

The CFQ-R respiratory domain score had the highest change from pre-treatment with the mean (SD) of 13.95 (40.65) for the 400 mg treatment arm vs. 1.15 (43.15), 2.59 (33.29) and 0.97 (42.51) for the 40 mg, 120 mg and 240 mg arms but this did not achieve statistical significance.

Participants either reported no change or general improvement in respiratory symptoms such as breathlessness, coughing, sputum production, affected chest and complications associated with CF, in all treatment arms. Nasal and sinus symptoms were reported as improved or worse in an equal number of patients. Vital signs (blood pressure, heart rate, oxygen saturation, body temperature and weight) were similar at baseline and throughout the study and were not different between treatment arms. Most patients at all dose levels had no abnormal chest sounds on examination at either the pre- or post treatment measure.

3.5. Adverse events

The safety was assessed for the entire safety population (n = 85). In the safety population, throughout the study 19 (22.4%) patients had adverse events which were considered related to the study medication. Of these events the most common were bronchospasm occurring in 5 (5.9%) patients, and headache, cough and pharyngolaryngeal pain, each occurring in three (3.5%) patients. Only two (2.4%) events considered related to the study medication (diarrhoea and bronchospasm each occurring in one patient) were reported following the MTT challenge. Only one (1.2%) patient was withdrawn from the study due to an adverse event (bacteria sputum identified) and this was on the day of MTT.

Five (5.9%) patients experienced serious adverse events (one during the MTT challenge, one on 40 mg and three on 120 mg) and five (5.9%) patients’ events were deemed severe (two patients each accounted for one serious adverse event listed also as severe). All serious adverse events were either exacerbation of CF, respiratory tract infection or infected sputum samples requiring hospitalization. One serious and severe CF pulmonary exacerbation was considered to be possibly related to the study medication in the 120 mg treatment arm group.

When only ITT population was considered, the number of adverse events which were judged related to the study medication was similar between the four different treatment arms (Table 5).

4. Discussion

The present study was designed to determine the optimal dose of mannitol required to demonstrate improvement in lung function in patients with CF as measured by FEV1 and FVC. FEV1 has been conventionally used as a primary outcome in CF clinical trials because it is objective, with less coefficient of variation and can be easily measured. In addition its decline predicts mortality and correlates with survival in CF [11,12]. In addition changes in FVC and other lung parameters are used to support this primary measure of lung function.

The trial was of an open-label, crossover design. This approach was taken to reduce the number of patients required because of the limited patient pool and also to minimise between patient variabilities. The results provide clear evidence of a dose response effect between doses of 40 and 400 mg and do not suggest that the

<table>
<thead>
<tr>
<th>Preferred terms</th>
<th>40 mg (n=44)</th>
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<th>240 mg (n=44)</th>
<th>400 mg (n=50)</th>
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design has either masked an effect or provided misleading dose information.

The reactivity to MTT was assessed in the absence of bronchodilator in most patients and this resulted in patients being excluded from subsequent treatment. However prior to treatment they did use bronchodilator so in future studies the use of bronchodilator before the MTT would be a more appropriate way to screen and result in more patients progressing to treatment.

The mannitol doses were randomised except for the first dose of 400 mg which was always administered first. This was done to reduce subsequent drop outs due to dose intolerance and maximise patient retention and thereby maximise the data from the limited patient pool available in CF studies. No significant carry-over effects were found, though some carry-over effect from the first treatment periods cannot be completely excluded. For the later treatment periods all the FEV1 and FVC values returned to pre-treatment baseline.

The treatment period of 2 weeks was chosen on the basis of previous studies with hypertonic saline [13] and rhDNase [14], and a previous phase II trial of inhaled mannitol [2] and was sufficient to show a dose response effect between doses of 40 mg and 400 mg but establishing whether this is the maximum achievable improvement at 400 mg will require a larger study. The interpretation of results in this study is therefore based only on the effect of different doses during a 2-week treatment period.

Although the highest possible dose has not been formally established, the use of more than 10 mannitol capsules for each dose may compromise compliance. The 400 mg dose b.i.d. appears to be a reasonable balance between acceptability and efficacy. The mean compliance to treatment in all treatment arms was good (>92%), though further studies are required to adequately assess long-term compliance. Most other therapeutics in this disease area experience similar compliance and several studies indicate a 30% to 70% therapeutic adherence in CF [15–19].

The present study achieved its primary end point of demonstrating a dose dependent improvement in lung function as measured by FEV1 and FVC following a 2-week treatment with inhaled mannitol in patients with CF. Each of the mannitol dose arms (40 mg, 120 mg, and 240 mg) was compared against the 400 mg dose arm. The 400 mg dose was the most effective achieving a statistically significant increase in both FEV1 and FVC (8.75% [150 mL] and 8.14% [183 mL], p<0.0001 respectively). These findings are in accordance with a previous study in which the dose of 420 mg bid for 2 weeks produced a similar increase in FEV1 [2].

In another phase II study the administration of 400 mg b.i.d. for 12 weeks resulted in a 7% increase in FEV1 [20].

Current guidelines do not provide a threshold for clinically meaningful improvement in FEV1 in CF. The Phase 3 randomised trial with rhDNase [21], one of the most widely used mucolytic agents in CF [22] reported an improvement in FEV1 at 24 weeks of 5.80% for once daily and 5.60% for b.i.d. treatment. The change of 8.75% at week 2 with inhaled mannitol is comparable and considered to be clinically meaningful.

Short term clinical trials with hypertonic saline and rhDNase have showed similar improvements in FEV1. After 2 weeks of administration of ultrasonically nebulised hypertonic saline the mean change in FEV1 from baseline was an increase of 15.0%, values returning to baseline after a 2-week wash out period [13]. Ballman et al. [23] showed an improvement in FEV1 of 7.7% with hypertonic saline and 9.3% with rhDNase following a 3-week treatment period.

Although the difference in change in FEV1 was statistically significant for the 40 and 400 mg doses neither 120 nor 240 mg was statistically significantly different to the 400 mg dose. There was nevertheless a clear trend of dose dependency. However the increase in FVC was significantly greater with 400 mg compared with all other doses, and the most effective dose was based on the primary end point of change in both FEV1 and FVC. Thus 400 mg was determined to be the most efficacious dose.

The demographic characteristics of the study population reflect those of the anticipated patient population suited to treatment i.e. mild to moderate CF patients. More than 80% of the patients were using drugs for obstructive airways disease. Microbiological findings were also typical of a CF cohort with 56.3% of the patients demonstrating colonisation with P. aeruginosa. As rhDNase use is known to increase FEV1, it was avoided in order to ensure that the treatment effect of each mannitol dose alone could be measured.

The results in patients above and below 18 years of age both demonstrated a dose dependent improvement in lung function as measured by FEV1 and FVC with the highest efficacy at the 400 mg dose in both children and adults. It thus appears that this dose is applicable to both age groups.

The improvement in lung function was supported by positive trends in QoL changes. The respiratory domain score CFQ-R questionnaire showed a trend toward improvement on inhaled mannitol, with the highest mean change from pre-treatment of 13.95 for the 400 mg treatment arm, however, this did not achieve statistical significance due to large variability. A change of 4 points is considered to be clinically significant [24] and this improvement was reached for the 400 mg dose. It is likely that a 2-week treatment period is not long enough to document robust changes in QoL measures. In addition, there was also a trend to no change or general improvement in respiratory symptoms and effects of treatment on mucus clearance and cough as reported by the majority of patients at 400 mg.

No apparent overall change in sputum microbiological growth occurred as a result of treatment, showing no evidence of increased microbial growth from mannitol. However, longer and larger studies may be needed to confirm this.

The safety profile for inhaled mannitol over 2-week administration supports consideration of longer term administration, and no apparent dose related trends in AEs or vital signs were observed. The maximum dose did not appear to have any notable safety issues compared to lower doses. No serious adverse events emerged during the 400 mg treatment period. In a study by Minasian et al. [20] cough has been reported as a main reason for withdrawal in 6 patients, half of them having a chest exacerbation at the time of withdrawal, however in the present study cough did not appear to be a significant issue. The reason for this difference is not clear though factors may include the use of different devices and the different treatment periods (12 weeks vs. 2 weeks in the current study) as well as the recruitment of rhDNase users.
Overall, in the present study the adverse events seen were characteristic of a CF population.

5. Conclusions

The primary measures of both FEV₁ and FVC changes clearly show a dose dependent treatment effect for inhaled mannitol and show that a 400 mg dose was the most efficacious and a 40 mg dose had no discernible effect. The 400 mg dose appears to be the appropriate dose for longer term studies in CF patients including children. This dose showed the greatest improvement in spirometric measures and a similar benign safety profile to other doses. The 40 mg dose showed no evidence of efficacy and could as such be considered as a non-effective control dose in long-term studies.

Conflicts of interest

Ms Jaques is the Clinical Development Manager of and hold shares and stock options in Pharmaxis Ltd. Dr Charlton is the Medical Director of and holds share and stock options in Pharmaxis Ltd. Dr Teper is the Investigator in this trial and has nothing to disclose relevant to this manuscript.

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