



A pilot study of inhaled dry-powder mannitol during cystic fibrosis-related pulmonary exacerbation

To the Editor:

Pulmonary exacerbation treatment aims to eradicate increased respiratory symptoms and recover acute loss in lung function. Current treatment strategies remain suboptimal, with conventional intravenous antibiotics and intensive physiotherapy failing to achieve this in 25% of patients [1]. Despite this worrying statistic, optimising recovery from acute pulmonary exacerbations has not been a focus of recent cystic fibrosis (CF) research efforts. There is a lack of adjunct evidence-based therapies for use in this setting [2] and strategies to optimise airway clearance with physiotherapy have been largely overlooked, despite common use in the outpatient setting [3, 4]. Inhaled dry-powder mannitol (IDPM), a mucoactive agent, improves mucociliary clearance [5], mucus rheology, and hydration and surface properties of mucus [6]. In the CF outpatient setting, IDPM treatment improves lung function, both in the short (>2 weeks) and long (>12 months) term [3, 7]. Its utility in in-patient pulmonary exacerbation care is unclear. In this pilot study, we investigated feasibility and safety of IDPM as an adjunct therapy to standard in-patient hospital care for children with pulmonary exacerbation. Efficacy was also explored using both conventional respiratory function outcomes and additional sensitive measures of peripheral airway function.

A double-blind, randomised, placebo-controlled pilot study was conducted of twice daily IDPM (10 × 40 mg) or very low dose IDPM (10 × 5 mg nonrespirable mannitol, termed “control” hereafter) administered for 12 consecutive days. Eligibility criteria for recruitment were age ≥ 6 years, admission to hospital for an infective pulmonary exacerbation (defined using Fuchs’ criteria [4]) and baseline forced expiratory volume in 1 s (FEV₁) ≥ 40% predicted (Global Lungs Initiative reference equations). Exclusion criteria included concurrent haemoptysis, hypertension, supplemental oxygen, oral corticosteroids, surgery or recent commencement of a mucolytic agent (within 3 months of admission). During hospital admission, subjects received combination *i.v.* antibiotic therapy (typically an aminoglycoside plus a β-lactam), daily airway clearance sessions and CF multidisciplinary team input, as clinically indicated.

Outcome parameters were assessed at admission, on day 7, on day 14 (discharge) and 1 month after discharge. Clinical status outcomes were the Cystic Fibrosis Clinical Score [8] and Revised CF Questionnaire quality of life [9]. Lung function outcomes were performed in the following order, in the morning, prior to inhalation of the study drug and airway clearance: multiple-breath nitrogen washout, using the VIASYS Vmax system (Sensormedics Corp., Yorba Linda, CA, USA) as previously described [10]; the forced oscillation technique (FOT), using custom-built equipment as previously described [11], reporting mean respiratory system resistance and reactance at 6 Hz, processed using breath-by-breath analysis [11]; spirometry and plethysmography, using the VIASYS Vmax system according to American Thoracic Society/European Respiratory Society standards [12]; and cardiopulmonary exercise testing (CPET) using the VIASYS Vmax system and a Bruce treadmill protocol as previously described [10], and reporting peak oxygen consumption ($V'O_2$) and measures of ventilation efficiency at peak exercise (minute ventilation ($V'E$)/ $V'O_2$ and $V'E$ /carbon dioxide production ($V'CO_2$)).

Blinded randomisation was performed (ratio 1/1, random number generation without stratification) to IDPM or control (both manufactured by Pharmaxis Ltd, Frenchs Forest, Australia). A study-drug tolerance test (SDTT) was deemed acceptable if baseline FEV₁ decreased by <50% immediately or <20% 15 min after the test dose, or if oxygen saturation remained >89%. The study drug was administered twice daily, immediately prior to individually tailored airway clearance sessions supervised by a physiotherapist. Mean treatment difference between groups, with 95% confidence intervals, was computed by linear regression using the group unstandardised beta coefficient after adjusting for baseline value (SPSS version 19.0; IBM, Armonk, NY, USA). This study was approved by the local Ethics Committee (EC no. 130; Children’s Hospital at Westmead, Westmead, Australia) and registered with the Australian and New Zealand Clinical Trials Network (ACTRN 12612001167853). Written, informed consent was obtained from all participants.

23 subjects were recruited. One control-group subject failed the SDTT due to vomiting, and 22 (96%, 11 each in the IDPM and control groups) completed the study. The study drug was well tolerated. Two adverse

TABLE 1 Relative change in clinical status and cardiopulmonary function in the inhaled dry-powder mannitol (IDPM) and control groups at discharge (day 14) and 1 month after discharge (follow-up), compared with admission values

	Baseline			Discharge			Follow-up			
	Control	IDPM	p-value	Control	IDPM	Mean difference (95% CI)	Control	IDPM	Mean difference (95% CI)	p-value
Clinical status										
CFCS total score	26.4 ± 2.6	26.7 ± 4.2	0.17	17.4 ± 1.8	18.6 ± 2.5	1.1 (-0.5-2.8)	19.6 ± 3.8	20.7 ± 3.1	-1.0 (-4.1-2.1)	0.5
CFQ-R respiratory domain	63.6 ± 19.9	55.6 ± 22.4	0.83	75.6 ± 14.6	73.5 ± 15.6	1.3 (-10.5-13.0)	75.0 ± 20.4	68.9 ± 11.4	3.5 (-10.7-17.7)	0.61
Spirometry										
FEV ₁ % pred	58.0 ± 13.0	73.1 ± 15.6	0.26	71.4 ± 11.2	88.8 ± 17.4	4.6 (-3.8-13.0)	70.8 ± 9.8	80.2 ± 20.7	5.4 (-2.8-13.5)	0.18
FEF _{25-75%} % pred	33.3 ± 15.9	48.9 ± 21.1	0.11	50.1 ± 17.6	82.9 ± 36.9	12.8 (-3.3-28.9)	47.7 ± 16.3	60.6 ± 31.2	3.9 (-10.7-18.5)	0.58
FVC (% predicted)	75.0 ± 13.0	87.1 ± 16.5	0.36	83.9 ± 12.3	95.4 ± 12.4	2.8 (-3.5-9.2)	84.2 ± 10.2	92.2 ± 15.6	1.7 (-4.1-7.5)	0.55
Plethysmography										
RV/TLC	36.4 ± 7.2	31.5 ± 6.6	0.08	33.9 ± 7.0	25.9 ± 5.5	-4.8 (-10.3-0.7)	31.3 ± 6.8	29.8 ± 7.5	-2.1 (-8.4-4.3)	0.49
MBNW										
LCI lung turnovers	9.2 ± 1.6	9.5 ± 1.7	0.06	8.1 ± 1.4	7.0 ± 1.4	-1.1 (-2.2-0.1)	8.2 ± 1.5	7.8 ± 1.9	0.2 (-1.6-2.0)	0.84
FOT										
R _{rs6} cmH ₂ O·L ⁻¹ ·s ⁻¹	6.1 ± 1.5	5.3 ± 1.2	0.37	5.6 ± 1.1	4.5 ± 1.4	-0.6 (-1.9-0.7)	5.9 ± 1.2	5.1 ± 1.8	0.3 (-1.5-2.1)	0.72
X _{rs6} cmH ₂ O·L ⁻¹ ·s ⁻¹	-2.8 ± 1.2	-2.3 ± 1.0	0.54	-2.1 ± 0.8	-1.6 ± 0.7	0.2 (-0.5-0.8)	-2.1 ± 0.9	-2.1 ± 1.3	0.2 (-1.0-1.3)	0.78
CPET										
V _{O2} mL·kg ⁻¹ ·min ⁻¹	1.5 ± 0.2	1.4 ± 0.4	0.41	1.6 ± 0.2	1.6 ± 0.7	0.1 (-0.2-0.4)	1.5 ± 0.3	1.7 ± 0.7	-0.2 (-0.5-0.0)	0.06
V _E /V _{CO2}	30.4 ± 2.8	31.1 ± 4.7	0.02	31.1 ± 3.1	26.7 ± 3.4	-4.5 (-7.9-1.0)*	31.5 ± 2.3	30.3 ± 2.4	1.4 (-1.0-3.8)	0.23
V _E /V _{O2}	33.4 ± 2.4	32.3 ± 6.5	0.14	34.6 ± 7.0	29.8 ± 5.0	-5.2 (-12.2-1.8)	35.8 ± 4.8	32.5 ± 2.4	2.5 (-1.7-6.6)	0.23

Data are presented as mean ± SD unless otherwise stated. Mean difference for IDPM minus control group at follow-up adjusted for baseline measure. All age reference equations used to calculate spirometric % predicted values have been shown to be applicable to Australian cohorts [13]. Complete lung clearance index (LCI), forced oscillation technique (FOT) and cardiopulmonary exercise testing (CPET) data were collected from 17 (77%) out of 22 subjects, and 15 (68%) out of 22 for plethysmography. CFCS: Cystic Fibrosis Clinical Score; CFQ-R: Revised CF Questionnaire; FEV₁: forced expiratory volume in 1 s; FEF_{25-75%}: forced expiratory flow at 25-75% of forced vital capacity; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; MBNW: multiple-breath nitrogen washout; R_{rs6}: resistance of the respiratory system at 6 Hz; X_{rs6}: reactance of the respiratory system at 6 Hz; V_{O2}: oxygen consumption; V_E: minute ventilation; V_E/V_{CO2}: carbon dioxide production. *: p<0.05.

events occurred in the IDPM group (vomiting and dizziness/headache) *versus* three in the control group (vomiting, minor haemoptysis and blurred vision). Baseline characteristics were well matched apart from baseline FEV₁: mean \pm SD 58.0 \pm 13.0% *versus* 73.1 \pm 15.6% predicted in control and IDPM groups, respectively ($p \leq 0.05$). Dornase alfa and hypertonic saline were used regularly in 59% and 14% of the whole cohort, respectively.

Changes in outcome measures are summarised in table 1. No significant difference in improvement of conventional lung function outcomes or clinical status occurred between groups. A significant difference was detected in the magnitude of improvement in $V'_E/V'CO_2$: mean (95% CI) difference -4.5 (-7.9--1.0) ($p=0.02$), a decrease of 11% *versus* 3% from baseline in the IDPM *versus* control groups. The treatment effect for lung clearance index (LCI) was -1.1 (-2.2--0.1) lung turnovers ($p=0.06$), an improvement of 26% *versus* 13% from baseline, respectively. Improvements in other peripheral airway function measures were detected but not statistically significant (residual volume/total lung capacity ratio, $p=0.08$; forced expiratory flow at 25–75% of forced vital capacity, $p=0.11$). At 1 month post-discharge, previous described benefits were no longer present.

In this pilot study, improvements in outcomes reflecting peripheral airway function were observed with adjunctive IDPM treatment during a hospital admission for pulmonary exacerbation. Improvements were, however, temporary, suggesting no ongoing benefit once treatment was ceased. IDPM was well tolerated over 12 days with no serious adverse events and few non-serious adverse events.

This study incorporated additional sensitive outcome measures (CPET, LCI and FOT) reflecting peripheral airway function, which are feasible in this setting [10] and able to detect treatment effects despite small subject numbers (≥ 12 subjects per group) [14]. A significant treatment effect in $V'_E/V'CO_2$, and a trend towards significance in LCI ($p=0.06$) was detected, despite small study numbers. Comparable changes in $V'_E/V'CO_2$, to gas-mixing efficiency measures such as LCI, are not surprising given that $V'_E/V'CO_2$ reflects functional clearance of carbon dioxide during exercise. The results highlight the complementary information gained from incorporation of these novel tests, in addition to conventional lung function tests. Based on the findings in this study, we speculate that IDPM, used in conjunction with airway clearance techniques, is able to improve mucus clearance in peripheral airways, augmenting recovery of peripheral airway function. Previous work in bronchiectasis subjects using radioisotope scanning also demonstrated greatest benefit of IDPM in peripheral lung regions [15].

The limitations of our study included the relatively small sample size, preventing strong conclusions about clinical utility in this setting. Recruitment was challenged by current clinical practice of regular planned *i.v.* “tune-ups” limiting those fulfilling stringent criteria for pulmonary exacerbation at a single institution [4], and the commencement of a “hospital in the home” programme. Use of these criteria also accounts for the larger magnitude of improvement in the control group compared with a previous observational study at our institution [10]. Inability to show a significant change in more central airway measures, such as FEV₁, despite benefits described in larger outpatient-based studies over a similar time period [7], may be explained by inadequate power to detect differences, non-matched FEV₁ on admission across the two groups and, finally, the different phase of disease studied (*i.e.* pulmonary exacerbation *versus* outpatient setting during a period of stability). Attempts to match FEV₁ on admission may affect matching of other, more sensitive outcome measures used (*e.g.* $V'_E/V'CO_2$ or LCI), which, importantly, were comparable between the groups on admission. The effect of concurrent regular dornase alfa and hypertonic saline on the observed effect of adjunct IDPM also could not be examined within a cohort of this size.

In summary, IDPM is both safe and feasible as an adjunctive treatment in this setting, and offers potential to improve clinical outcomes from pulmonary exacerbation. The findings of our study support a larger, multicentre study examining the potential beneficial effect on clinical and lung function outcomes. Strategies to accelerate and maximise recovery from pulmonary exacerbations are highly desirable, given the occurrence and treatment of pulmonary exacerbations in CF are costly from the perspective of both healthcare provider and patient.



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Mannitol is a safe feasible treatment adjunct in cystic fibrosis acute exacerbation and may improve clinical outcomes <http://ow.ly/CrU1X>

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