

# The effect of different concentrations of lactose powder on the airway function of adult asthmatics

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**Abstract** Lactose is widely used as a carrier of drugs in inhalation devices for asthmatic patients, but some clinicians have suspected that it may cause bronchoconstriction. Only a few studies have been done to examine this and the results are not uniform. This study was conducted to determine the effects of inhalation grade lactose delivered by Diskhaler™ on lung function and airway conductance in asthmatic subjects. The effect of five doses of lactose ranging from 6.25 mg to 100 mg and placebo were investigated using spirometry and constant volume plethysmography. Nineteen subjects (nine females) with stable asthma and a proven reversibility of at least 12% in forced expiratory volume in 1 sec (FEV<sub>1</sub>) (compared to baseline) in the last 6 months, were included in this single-centre, randomized, placebo-controlled, double-blind, cross-over study. The subjects received placebo plus five doses of lactose on one study day and six doses of placebo on another study day. Both doses and study days were assigned in a random order, and intervals of 1 h were allowed between each dose and at least 36 h between study days. Specific airways conductance (sG<sub>aw</sub>) and FEV<sub>1</sub> were measured periodically over the course of 1 h after each dose of lactose or placebo. Administration of lactose at four or eight times the concentration in the Diskus™ and Diskhaler™ dry powder inhalers did not result in any statistically significant changes in FEV<sub>1</sub>. sG<sub>aw</sub> also showed no statistical difference between lactose and placebo at 1 or 3 min post-dosing. Both placebo and lactose produced both dilatation and constriction of the airways in the same patients, with no consistency in direction and no dose–response relationship. No adverse effect of lactose on airways conductance or FEV<sub>1</sub> of stable asthmatic patients was found in this study when given at higher than normal clinical doses.

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**Keywords** lactose; Diskhaler™ inhaler; Diskus™; specific airways conductance; sG<sub>aw</sub>; plethysmography.

## INTRODUCTION

Dry powder inhalers (DPI) have been introduced to help overcome the co-ordination problems experienced by some patients using pressurized metered dose inhalers (MDIs). Most DPIs are breath-actuated devices which rely on the patient's inhalation to dispense a dose of drug, the efficiency of their delivery depending on the inhalation manoeuvre, the design of the inhaler and the formulation of the inhalation powder (1). Because the micronized drug particles in dry powders are very cohesive and have poor flow properties they are generally mixed with larger inert carrier particles, most com-

monly lactose, to make the powder blend less cohesive and more free-flowing (2). This helps to ensure accurate dosing as small amounts of drug can be measured into individual factory dispensed doses, and also improves the emptying of the micronized materials from the delivery system (3,4). During inhalation the drug particles are separated from the surface of the carrier particles by the energy of the inspired airflow.

Lactose fulfils many of the requirements of an ideal carrier, being readily available in a pharmaceutical grade, chemically and physically stable, and inert to most drug substances (5). Other carriers used include trehalose and manitol, which are sugar structures similar to lactose (6). Another important requirement for an ideal carrier is that it should be readily cleared from the airways and have no harmful effects on the respiratory tract: little is known about the effect of inhaled lactose on airways function, however. It has been suggested from *in vitro* data that lactose may cause inflammation and mucus

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discharge in the human nasal mucosa (7), and some patients have reported irritation and chest tightness after inhalation of dry powder (8). Data from two studies specifically to investigate the effects of inhaling lactose have shown conflicting results, however. One showed that inhalation of a total dose of 600 mg of lactose over 20 min showed little bronchoconstrictor or irritant effect on the airways of asthmatic subjects (9), while the other (uncontrolled) study found that 25 mg lactose caused a significant decrease in airways conductance 1–3 min post-dosing (8). This study was therefore designed to investigate the effect of different concentrations of lactose on pulmonary function in stable asthmatic subjects, in a double blind, placebo-controlled manner. Airway function was assessed by forced expiratory volume in 1 sec (FEV<sub>1</sub>) obtained by spirometry, and specific airways resistance and conductance measurements, obtained by constant volume plethysmography.

## METHODS

### Patients

Nineteen subjects aged 18–57 years with a history of asthma were randomized from 20 subjects screened. At screening all patients had to either have a documented history of reversibility  $\geq 12\%$  in FEV<sub>1</sub> [or  $\geq 20\%$  peak expiratory flow (PEF)] within the previous 6 months, or demonstrate similar reversibility to 800  $\mu\text{g}$  of salbutamol after withholding bronchodilator for  $\geq 6$  h. Patients who were receiving short-acting  $\beta_2$ -agonists as required and were able to use the Diskhaler™ correctly were included. All study subjects were symptom-free at the pre-study visit: one had wheezing on forced expiration. Patients who had experienced an exacerbation of asthma and required a change in their usual asthma medication, required either oral steroids or antibiotics, or had been hospitalized for their respiratory disease within 4 weeks of the screening visit, were excluded. Also excluded were patients who had used long-acting  $\beta_2$ -agonists within 2 weeks of the screening visit, who smoked  $> 20$  cigarettes a day regularly or had a smoking history of 20 pack-years, were pregnant or lactating, had known intolerance to lactose, or had clinical or laboratory evidence of serious uncontrolled systemic disease.

### Study design

This was a single-centre, randomized, double-blind, placebo-controlled, cross-over study. There were three study visits: a pre-study visit to assess eligibility and two study days on which treatments were administered. On one study day patients received lactose or placebo (empty blisters) on six occasions, while on the other they received six doses of placebo. The order of the study days was randomized and, to avoid any carry-over effect, they

were separated by at least 36 h. The doses of lactose administered were 6.25 mg, 12.5 mg, 25 mg, 50 mg and 100 mg, representing doses up to eight times that used clinically in a Diskus™\*, or four times that in a Diskhaler™\*. We think these doses represent the highest likely to be taken at one time by patients in a clinical situation, and they are equivalent to the maximum dose deliverable from one four-place Rotadisk™\*. Each study dose was separated by 1 h from the previous one and the order of doses was randomized.

On a study day, each patient was given a treatment pack consisting of six four-place Diskhalers™ pre-loaded with Rotadisks™ containing different doses of lactose or placebo. There was no more than 25 mg inhalation grade lactose powder in each blister (the dose present in commercial Rotadisk™ blisters). The six different Rotadisks™ were as follows:

- Four placebo (empty) blisters;
- One lactose 6.25 mg blister and three placebo blisters;
- One lactose 12.5 mg blister and three placebo blisters;
- One lactose 25 mg blister and three placebo blisters;
- Two lactose 25 mg blisters and two placebo blisters;
- Four lactose 25 mg blisters.

Doses were administered by taking all four blisters of a Rotadisk™ in quick succession, the timing of the lung function assessments being measured from the point that the last blister was inhaled. On the placebo day all Diskhalers™ were loaded with placebo Rotadisks™ (empty blisters); this was included to control for any effect due to non-lactose factors such as bronchoconstriction due to rapid inspiration of ambient air. Patients were asked to avoid caffeine during study days and for at least 6 h beforehand. The use of short acting  $\beta_2$ -agonists within 6 h before a visit was also not permitted.

### Ethics

Ethics Committee and Regulatory Authority approvals were both obtained prior to commencement of the study, and all patients gave their written informed consent to participate in the study before entry.

### Measurement of lung function

Airway calibre was assessed by measuring specific airways conductance ( $sG_{aw}$ ) in a constant volume whole body plethysmograph ('body box') (Master Lab Body, Erich Jaeger GMBH, Hoechberg, Germany). Patients remained in the plethysmograph for each set of  $sG_{aw}$  readings but were then allowed to leave it and relax until shortly before the next dosing occasion. Following baseline assessment ( $t = 0$ ), patients inhaled lactose powder

\*Diskus™, Diskhaler™ and Rotadisk™ are trademarks of the GlaxoSmithKline group of companies.

or placebo and measurements were taken at 1, 3, 5, 10 and 15 min afterwards. FEV<sub>1</sub> was measured outside of the body box at 10 min before the first dose, and at 20 and 50 min after each dose for all doses (the 50 min measurement acting as the –10 measurement for the next dose). Three FEV<sub>1</sub> measurements were taken at each time point and the highest recorded.

### Safety assessments

These comprised the recording of clinical adverse events throughout the study, and of baseline pulmonary auscultation and vital signs (pulse rate and blood pressure) at visit 1 to assess suitability for the study. Patients were asked how they felt and have their lung function monitored throughout the two study days. Patients with a known hypersensitivity to lactose were excluded from the study.

### Statistical methods

#### Sample size

There was insufficient published data to allow a proper sample size calculation to be made. Our previous study (8) had demonstrated significant findings with 15 patients, so the sample size in this study was based on practical rather than statistical considerations, with the aim of recruiting 20 patients to get 18 randomized.

#### Efficacy analysis

The FEV<sub>1</sub> recorded 10 min prior to dosing was taken as the baseline value for each dose, and the one at 20 min after dosing represented the post-dosing value. Results were summarized using summary statistics (*n*, mean, standard deviation, minimum and maximum) and the percentage change from baseline was calculated. The percentage change from baseline was analysed using analysis of covariance with the subject identifier, study day (1st or 2nd), dosing order from 1st to 6th dose and the baseline value included as covariates.

For sG<sub>aw</sub> the baseline was taken as the measurement immediately prior to dosing (*t*=0), and the measurements to be analysed were made at 1 and 3 min after dosing. The analysis was the same as for FEV<sub>1</sub>. Measurements after 3 min were not analysed statistically so as to minimize the number of comparisons and preserve the power of the study: our previous study (8) suggested that any changes in sG<sub>aw</sub> would be seen in the first 3 min. The data were, however, available to allow the duration of any effects to be determined.

All concentrations of lactose were compared to placebo. For the statistical comparison, the seven sets of placebo measurements for each subject (six from the placebo day and one from the lactose day) were all included in each analysis.

## RESULTS

Twenty patients were recruited into the study, of whom 19 fulfilled the inclusion criteria and were randomized, and received at least one dose of study medication. One patient was withdrawn after randomization due to an exacerbation of asthma after attending one study day (placebo only), otherwise all randomized patients completed all study procedures and assessments. Eight of the patients were current or ex-smokers, with a mean history of 5.1 pack-years (maximum 15 pack-years). The demographic details of the patients are shown in Table 1.

### Efficacy

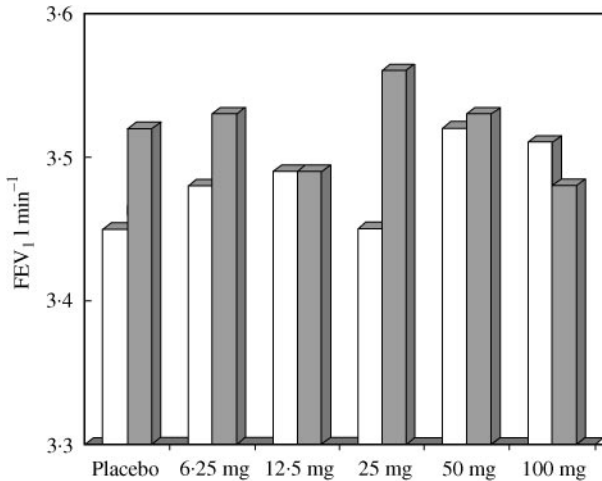
#### FEV<sub>1</sub>

Inhaling placebo resulted in an increase in FEV<sub>1</sub> of 2.22% at 20 min post-dosing compared to the pre-dosing value. By comparison, lactose at the lowest concentration (6.25 mg) resulted in a 1.95% increase in FEV<sub>1</sub> (Fig. 1; Table 2). Higher concentrations of lactose: 12.5 mg, 25 mg, 50 mg and 100 mg, resulted in changes in FEV<sub>1</sub> of 0.24%, 2.96%, 0.5% and –0.7%, respectively. There was no evidence of a trend in changes in FEV<sub>1</sub> with increasing lactose dose and there were no statistically significant differences between any dose of lactose and placebo (Table 2). The adjusted mean difference between lactose and placebo varied between –2.2% (100 mg dose) and +1.8% (25 mg dose), and there were no statistically significant differences between any dose of lactose and placebo.

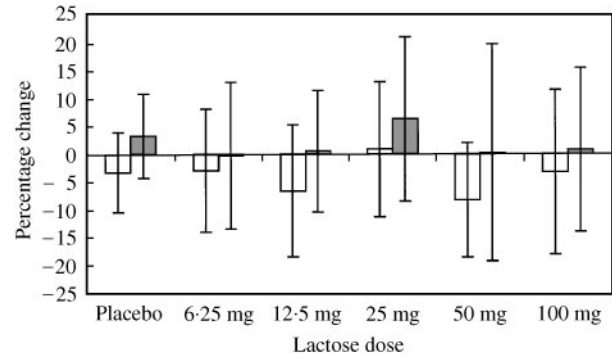
**TABLE 1.** Summary of demographic and clinical characteristics

		<i>n</i> (%)
Number of patients		19
Male: female		10:9
Age (years)	Mean (sd)	30.4 (9.9)
	Range	18–57
Duration of asthma	< 1 year	2 (10%)
	≥ 1–< 10 years	5 (27%)
	≥ 10 years	12 (63%)
Smoking status	Current smoker	1 (5%)
	Ex-smoker	7 (37%)
	Never smoked	11 (58%)
FEV <sub>1</sub> reversibility at pre-study visit (%) (12 patients)	Mean (sd)	18 (8%)
	Range	8–33

sd: standard deviation.



**Fig. 1.** Mean FEV<sub>1</sub> pre- (□) and 20 min post-dosing (■).



**Fig. 2.** Mean percentage change ( $\pm$ SD) from pre-dosing in sG<sub>aw</sub> after 1 min (□) and 3 min (■).

**TABLE 2.** Summary of FEV<sub>1</sub> 20 min post-dosing

	Change from pre-dosing in FEV <sub>1</sub> (%)					
	Placebo	6.25 mg	12.5 mg	25 mg	50 mg	100 mg
Mean	2.22	1.95	0.24	2.96	0.5	-0.7
SD	2.78	4.68	2.82	5.73	3.2	2.62
Lactose vs. placebo*						
Adjusted mean difference		0.7	-1.0	1.8	-0.8	-2.2
SE		1.2	1.2	1.2	1.2	1.2
95% CI		-1.65, 3.04	-3.35, 1.34	-0.59, 4.10	-3.13, 1.55	-4.49, 0.19
P-value		0.561	0.398	0.141	0.508	0.072

\*ANCOVA on the % change from pre-dosing with covariates of patient, study day, time and baseline FEV<sub>1</sub> included.

**TABLE 3.** Summary of sG<sub>aw</sub> 1 min post-dosing

	% change from pre-dosing in sG <sub>aw</sub>					
	Placebo	6.25 mg	12.5 mg	25 mg	50 mg	100 mg
Mean	-3.24	-2.96	-6.65	0.87	-8.30	-3.31
SD	7.18	11.09	11.89	12.14	10.32	14.84
Lactose vs. placebo*						
Adjusted mean difference		0.6	-3.1	4.3	-5.0	0.0
SE		2.7	2.7	2.7	2.7	2.7
95% CI		-4.77, 6.04	-8.53, 2.28	-1.15, 9.66	-10.36, 0.45	-5.36, 5.45
P-value		0.818	0.255	0.122	0.072	0.988

\*ANCOVA on the % change from pre-dosing with covariates of patient, study day, time and baseline sG<sub>aw</sub> included.

sG<sub>aw</sub>

For sG<sub>aw</sub>, inhaling placebo resulted in a small, not clinically relevant, bronchoconstriction, reflected by a decrease of -3.24% at 1 min post-dosing compared to pre-dosing levels. Changes after lactose ranged between -8.30% (50 mg dose) and +0.87% (25 mg

dose) at this time point. There was no evidence of a trend in changes with increasing lactose dose, and there were no statistically significant differences between any dose of lactose and placebo (Fig. 2; Table 3). At 3 min post-dosing inhaling placebo resulted in an increase of 3.33% when compared to pre-dosing levels, and changes after lactose ranging between -0.25%

(6.25 mg dose) and +6.32% (25 mg dose) compared to pre-dosing. There was no evidence of any trend with increasing lactose dose and there were no statistically significant differences between any dose of lactose and placebo. The adjusted mean difference between lactose and placebo varied between  $-5.0\%$  (50 mg dose) and  $+4.3\%$  (25 mg dose) at 1 min post-dosing, and there were no statistically significant differences between any dose of lactose and placebo nor dose-related trend. The data at 3 min showed a similar lack of statistical significance and trend, and smaller differences than at 1 min.

## Safety

Only one adverse event was reported during the study: an exacerbation of asthma which occurred 5 days after the patient had attended their first study day and received placebo only. The event was assessed as not related to the study drug and the patient was subsequently withdrawn from the study. No serious adverse events were reported.

## DISCUSSION

There is little published data on the effect of lactose on airways function as opposed to its effects on patient preference or dosing perception. One study in 10 asthmatics with known bronchial hyper-responsiveness to methacholine (9) found little or no effect on FEV<sub>1</sub> of 600 mg lactose administered over 20 min with the authors concluding that the majority of the bronchoconstriction was due to the forced expiratory volume manoeuvre itself. In our previous study in 15 asthmatics with FEV<sub>1</sub> reversibility  $> 15\%$  (8), however, we found a significant reduction in specific airways conductance ( $sG_{aw}$ ) 1–3 min after 25 mg lactose and concluded that lactose could cause bronchoconstriction in asthmatics. Our previous study, though, was uncontrolled, and so we set out to examine both FEV<sub>1</sub> and  $sG_{aw}$  over a range of doses of lactose in a double-blind, placebo-controlled study.

For FEV<sub>1</sub> we found only small variations after inhaling empty blisters (placebo) or lactose, and no statistically significant differences between lactose and placebo. The changes we saw probably represent the natural variability of the measurement, therefore, and we concurred with the results of Shaw *et al.* (9) by failing to find any clinically relevant reduction in FEV<sub>1</sub>.

The plethysmography data supported the conclusions from the FEV<sub>1</sub> results.  $sG_{aw}$  at 1 and 3 min after inhaling again showed variable small changes not apparently related to lactose dose, and did not show any statistically significant differences between lactose and placebo.

Our previous study, where we found a significant effect of 25 mg lactose on  $sG_{aw}$  (8), was a smaller, open

label study using only a single dose of lactose and no empty blisters for control. In addition, the subjects had a reversibility  $> 15\%$  at baseline and were symptomatic, compared with a proven reversibility of  $> 12\%$  in the last 6 months and stable asthma for those in the current study. The decrease of  $sG_{aw}$  after lactose at 1 and 3 min in our previous study could simply have been a consequence of the inspiratory manoeuvre itself in those more symptomatic subjects or of being 'locked in' the body box, and hence unrelated to the presence of lactose. In the present study we controlled for these factors by administering placebo blisters, and did not detect any significant decrease from baseline at 1 or 3 min or differences between lactose and placebo. Further studies of this type would be needed to definitively exclude bronchoconstriction due to lactose powder in patients with unstable asthma. No increase in bronchoconstriction episodes was reported in a recent study of prednisone-dependent severe asthmatics whose oral steroid was replaced by a lactose-containing formulation (Diskus<sup>TM</sup>) of fluticasone propionate (14), however, and their FEV<sub>1</sub> improved after the change. It is probable therefore that in clinical situations lactose powder either exerts no effect on severe/unstable asthma, or an imperceptible one in relation to the effect of the drug given.

Concerns about the theoretical risks of lactose should be weighed against the benefits from its inclusion. Carriers such as lactose aid the flow and dispersion properties of dry powder formulations, helping the delivery of a high fine particle fraction of drug to the lung while the carrier remains in the upper airways. This has been shown for lactose formulations from the Diskus<sup>TM</sup> inhaler, for example, by consistent emission of drug in the fine particle range and consistency of dosing close to the label claim (10,11). Radiolabelling has shown that there is high oropharyngeal deposition of inhaled lactose with only a small percentage deposited in the lungs (12).

As well as aiding dispersion, lactose also helps patients to perceive that they have taken a dose, thus aiding treatment compliance (13). Indeed, some patients have complained when given DPIs that deliver drug without a lactose carrier that the devices are not working (13), whilst a small proportion do not appreciate the taste sensation. There are good reasons, therefore, for including a lactose carrier in an inhaled dry powder formulation so long as it is safe, and it is used in a number of different inhalers, for example Diskus<sup>TM</sup>, Diskhaler<sup>TM</sup>, Turbuhaler<sup>TM†</sup> and Easyhaler<sup>TM‡</sup>. To our knowledge the highest single dose of lactose delivered by these devices is 25 mg. Our study found that lactose powder, at doses at least four times higher than those used commercially in inhalers, produced no evidence of any clinically relevant changes in airway function in stable asth-

<sup>†</sup>Turbuhaler<sup>TM</sup> is a trademark of Astrazeneca.

<sup>‡</sup>Easyhaler<sup>TM</sup> is a trademark of Orion Pharma.

matics, and so is probably safe for use in this patient group.

In summary, this study showed that high concentrations of lactose were not associated with any clinically important changes in FEV<sub>1</sub> or airway conductance in stable asthmatic subjects. No statistically significant difference from placebo was observed. The small changes seen showed no consistency in direction and no dose–response relationship, and are likely to be attributable to the subject variation and measurement techniques. More work needs to be done to confirm its safety in other parameters. Lactose is therefore not only a useful additive in dry powder inhalers, with regards to FEV<sub>1</sub> and airways conductance, it is probably also a safe one.

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