# Inhaled salbutamol for wheezy infants: a randomised controlled trial

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**Abstract**

***Background*—Salbutamol is frequently used as a bronchodilator for infants who wheeze. Many single dose studies have questioned its effectiveness.**

***Aims*—To investigate the response of wheezy infants to salbutamol over an extended time period in order to elucidate either symptomatic relief or a protective effect.**

***Methods*—Eighty infants under 1 year, with persistent or recurrent wheeze and a personal or family history of atopy, were recruited to a randomised, double blind, cross over, placebo controlled trial. Salbutamol (200 µg three times daily) or placebo were administered regularly over two consecutive treatment periods of four weeks via a spacer and mask. Symptoms of wheeze and cough were recorded in a diary. At the end of the study pulmonary function tests were performed before and after salbutamol (400 µg).**

***Results*—Forty eight infants completed the diary study; 40 infants underwent pulmonary function testing. No difference in mean daily symptom score was observed between the salbutamol and placebo periods. There was no difference in the number of symptom free days. Compliance and forced expiratory flows remained unchanged and resistance increased following salbutamol. There was no relation between the response measured by symptom score or pulmonary function in individual patients.**

***Conclusion*—In wheezy infants with an atopic background, there was no significant beneficial effect of salbutamol on either clinical symptoms or pulmonary function. Clinical effects could not be predicted from pulmonary function tests. Salbutamol cannot be recommended as the bronchodilator of choice in this age group.**

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The wheezy infant remains a conundrum for both primary care teams and hospital paediatricians. Treatment strategies vary from no treatment to regular treatment with inhaled bronchodilators and steroids. Many infants still receive antibiotics or multiple courses of oral steroids.

The ability to treat infants who wheeze depends on a medication that works, a suitable device to deliver the medication effectively, and adherence to treatment by the carers. The necessity to treat should be based on aetiology of the wheeze, effect on the infant, and predicted outcome of the disease process. Following the "lumping" of all wheezy infants to a diagnosis of asthma in the early 1980s, there is now clear evidence that there are different groups of wheezy infants and that treatment strategies should vary accordingly.[1]

The Tucson group suggest that the majority of infants who wheeze do so transiently, with only a minority (14.7%) progressing to symptoms in childhood.[2] The effect of wheezing in early life on long term lung function is still unclear. Therefore the need to treat all wheezy infants remains a questionable practice.

There have been numerous studies investigating the effectiveness of $\beta_2$ agonists for treating wheeze in infants as they are seen to be the most effective drugs in the treatment of variable airways obstruction in adults and children. $\beta_2$ Agonists remain the most commonly prescribed medications for treating wheeze in infancy by respiratory paediatricians and general paediatricians alike.[3] However the evidence from the literature does not necessarily support this practice.

The majority of the studies have tested the response to a single dose of bronchodilator or used a heterogeneous group of patients and a variety of outcome measures. Many studies include patients with acute bronchiolitis.[4–6] Documented adverse responses to a single dose of salbutamol include hypoxaemia,[7 8] increased airways resistance,[9 10] and a decline in forced expiratory flow.[6 11 12] The most repeatable beneficial effect of salbutamol has been to abolish or reduce the bronchoconstrictor response to histamine[13] or water.[14] One problem of single dose studies is that the infant is often asymptomatic on the day of testing, which may mask any response. Only two studies, to our knowledge, have examined the response to salbutamol taken regularly over an extended period. Both these studies also included the use of steroids and examined the period around an acute episode.[15 16]

We attempted to select a group of infants at high risk of progression to asthma in childhood. The best predictor of subsequent childhood asthma remains a personal or family history of atopy.[2] Study periods of four weeks were chosen to maximise the probability of the infant having at least one episode of upper respiratory tract infection during each treatment period. Infants were also enrolled for pulmonary function testing to investigate whether a measured response in the laboratory could be

extrapolated to a clinical response, and hence potentially be used as a predictive test.

## Patients and methods

Eighty infants were recruited from outpatient clinics, from those admitted to the ward with wheezing, and from referral by general practitioners following mail shots. Infants were recruited to the study if they were aged between 3 months and 1 year, had a history of persistent wheeze or night cough, or recurrent wheeze, and they had a tendency towards atopy. Persistent symptoms were defined as those occurring on more than three days/nights per week for at least six weeks. Recurrent symptoms were defined as those occurring on at least three occasions over the previous three months. A tendency towards atopy was defined as either eczema in the infants themselves, or a parent or sibling with asthma, allergic rhinitis, or eczema. Infants who were recruited from the ward with an acute wheezing episode only entered the study a minimum of two weeks after the episode had resolved.

Infants were not considered for inclusion if they had a history of preterm birth below 34 weeks, an episode of mechanical ventilation, a major congenital malformation, or other form of chronic lung disease. Infants who were already using inhaled corticosteroids were also excluded. Infants who had received a course of oral steroid were not excluded, but recruitment was deferred until one month after the treatment course if they still fulfilled the recruitment criteria.

Infants were withdrawn from the study if they had an exacerbation of symptoms that required: admission to hospital; a course of oral steroids; or commencement on regular inhaled steroids as judged by the clinical team responsible for their treatment. Infants were also withdrawn from the study if their parents were unable to administer the medication effectively and regularly, following the protocol.

The study was a double blind, randomised, placebo controlled, crossover trial, with each patient acting as their own control. At recruitment each subject had a history taken and was fully examined, including weight and height (RC, YBL, HR). A written information sheet was given to the parents and written consent to participate was obtained. This study formed the first part of a two part study: the second part assessed the response to inhaled corticosteroids and will be reported separately. Approval for the study was obtained from the Brighton Area Ethics Committee.

The parents were asked to record symptoms in a diary, twice each day (morning and evening) over the total period of eight weeks while giving the prescribed inhalers. A score was recorded between 0 to 3 for symptoms of both cough and wheeze for the preceding time (night and day).[17] This gave a daily score out of a maximum of 12 points equating to maximum symptoms.

The study was split into two consecutive four week periods. The subject was reviewed at the beginning and end of each period. At the beginning of each treatment period the patient was prescribed, in random order, an inhaler containing either salbutamol (100 μg per activation) or placebo. Both inhalers appeared identical (supplied by Glaxo Wellcome) and were unmarked. The medication was delivered using a Babyhaler (small volume spacer and mask, Glaxo Wellcome). Parents were both taught and given written instructions on how to use the device optimally (RC, YBL, HR). They were instructed to give three doses of two activations of the inhaler every day with the option of giving a fourth dose at night if their infant was symptomatic.

At each review the infant was examined and the parents were asked "Did the inhaler help?". The diary cards were reviewed, complications recorded, and inhaler technique reassessed. At the end of the study the parents were asked "Which inhaler did you think was the more effective?".

At the end of the second treatment period the parents were invited to bring their child for pulmonary function testing. Separate consent was obtained for this part of the study.

### PULMONARY FUNCTION TESTING

The tests were performed within two weeks of completing the diary study. The parents were invited to attend at a time when the child was well and were asked not to give any medication on the morning of the tests.

The infants were examined and weighed. They were sedated with triclofos (100 mg/kg). When asleep the infant was placed supine on a cot with a neck roll in place to keep the head and neck in a neutral position. Continuous oxygen saturation monitoring was used throughout the time the infant was asleep. A facemask was placed over the infant's mouth and nose using therapeutic putty (Carters, Wiltshire) to ensure an airtight seal. A pneumotachograph (Hans Rudolph 3500 series) was attached to the mask. Flow and mouth pressure were measured using the pneumotachograph and Validyne transducers (MP45), and these analogue data were digitised and recorded using RASP software (PhysioLogic Ltd, Newbury, Berks. UK). The flow signal was digitally integrated to give volume.

Resistance of the respiratory system ($R_{rs}$) and compliance ($C_{rs}$) were measured using the single breath occlusion technique (SBT). Up to 20 manual occlusions were performed to obtain at least five technically satisfactory measurements for analysis. Occlusions were deemed satisfactory if they met the criteria of Fletcher *et al*,[18] including a stable pressure plateau of at least 0.1 seconds and a linear portion ($r^2$ at least 0.995) extending over at least 40% of the expiratory flow–volume curve. The mean values from the five best occlusions were calculated.

A 30 second run of tidal breathing was recorded for analysis of tidal breathing parameters: respiratory rate (RR), time to peak tidal expiratory flow ($t_{PTEF}$), and ratio of $t_{PTEF}$ to expiratory time ($t_{PTEF}$:$t_E$).

Measurements of maximum flow at functional residual capacity ($V_{maxFRC}$) were made

*Table 1 Characteristics of infants enrolled in the study*

| | *Completed (n)* | *Withdrawn (n)* | *p value* |
|---|---|---|---|
| Number | 48 | 32 | |
| Sex (male) | 37 | 24 | 0.83 |
| Age at enrolment (days) | 221 | 234 | 0.47 |
| Eczema | 20 | 11 | 0.43 |
| Family history of: | | | |
| Asthma | 41 | 23 | 0.14 |
| Eczema | 33 | 21 | 0.77 |
| Hay ever | 37 | 24 | 0.83 |
| Smoking (either parent) | 19 | 20 | 0.05 |
| Presenting symptom: | | | |
| Persistent wheeze | 25 | 13 | 0.32 |
| Persistent night cough | 18 | 7 | 0.14 |
| Recurrent wheeze | 5 | 12 | 0.004 |
| Pets | 22 | 18 | 0.36 |

using the technique of rapid thoracoabdominal compression (RTC).[19] A soft plastic jacket with an inflatable compartment was wrapped around the chest and abdomen (arms outside). The jacket was inflated from a large, pressure controlled, reservoir of compressed air, in synchrony with the end of tidal inspiration, causing rapid exhalation. Respiratory flow and mouth pressure were recorded as above as was jacket pressure. A series of manoeuvres were performed using an increasing range of jacket pressures (30–100 cm $H_2O$) until flow limitation was achieved. Three to five technically satisfactory manoeuvres were then performed at this level.

A second series of measurements were recorded 15 minutes after a dose of 400 µg salbutamol administered via Babyhaler and mask.

### RANDOMISATION FOR DIARY STUDY

Sealed randomisation envelopes were generated by Glaxo Wellcome using a validated random number generation programme, PACT. Randomisation occurred in blocks of four.

### STATISTICAL ANALYSIS

Data were analysed by Minitab for Windows (v11.11 Minitab Inc., Philadelphia). Changes in diary score and lung function were compared by paired *t* test. Non-continuous data were compared by $2 \times 2$ table using either $\chi^2$ or Fisher's exact tests.

## Results

Eighty infants were recruited between October 1997 and February 1999. Of these, 48 successfully completed the diary study. Table 1 shows the characteristics of all the infants enrolled, comparing those who completed the diary study with those who withdrew. Forty infants underwent lung function testing; 29 infants successfully completed both diary study and pulmonary function tests.

Of the 32 infants who failed to complete the diary study, 10 dropped out because of deterioration in clinical condition. Seven parents reported extreme difficulty in giving the inhaler, which could not be resolved. Thirteen parents decided they no longer wished to take part or failed to attend follow up appointments. For the other two infants, one of the diaries was mislaid by the parents. Infants who withdrew were significantly more likely to have episodic symptoms rather than persistent and were significantly more likely to have a parent who smoked.

Overall 25 patients who withdrew did so during the first month. Sixty three per cent of patients who withdrew were in their placebo period, including seven of the 10 patients who withdrew because of a clinical deterioration. This slight excess of dropout in the placebo period did not reach statistical significance.

Lung function tests were not performed in 13 of the infants who completed the diary study. In six instances this was because of unavailability of a member of the lung function team. Five parents refused consent and two did not attend on the arranged day for personal reasons. In four infants inadequate sedation was achieved. Eleven infants who did not complete the diary study also had lung function tests performed before entering the steroid part of the trial.

Table 2 shows the mean daily scores of the salbutamol and placebo periods (including mean difference between the two periods) and the breakdown of individual components of the score. There was no significant change in either the total score or any of the constituents. There was no significant difference between the number of symptom free days on either treatment. There were some individual patients who had lower mean daily scores during the salbutamol period ("responders") but as many with the opposite or no detectable response (fig 1). The subgroup of infants with a personal history of eczema were no more likely to respond to salbutamol than those without eczema.

The reported adherence to treatment was similar during both treatment periods, as was the number of additional doses of medication given. There was no difference in mean daily scores between the first four week period and the second, indicating no time effect.

*Table 2 Results of diary scores*

| | *Salbutamol period* | *Placebo period* | *Mean difference* | *p value* | *95% confidence interval* |
|---|---|---|---|---|---|
| Prescribed first | 27 | 21 | | | |
| Mean daily score | 3.78 (2.09) | 3.66 (2.07) | 0.12 | 0.62 | −0.37 to 0.61 |
| Symptom free days | 4.19 (6.33) | 4.71 (6.64) | −0.52 | 0.54 | −2.2 to 1.19 |
| Days with daily score greater than 6 | 5.17 (5.63) | 4.33 (4.68) | 0.83 | 0.32 | −0.84 to 2.51 |
| Mean night cough | 1.07 (0.61) | 0.94 (0.59) | 0.13 | 0.1 | −0.03 to 0.29 |
| Mean night wheeze | 0.65 (0.62) | 0.65 (0.63) | 0.003 | 0.97 | −0.14 to 0.14 |
| Mean day cough | 1.25 (0.58) | 1.18 (0.56) | 0.08 | 0.29 | −0.07 to 0.22 |
| Mean day wheeze | 0.86 (0.67) | 0.85 (0.69) | 0.02 | 0.79 | −0.11 to 0.14 |
| Number of treatments | 2.71 (0.59) | 2.83 (0.47) | −0.10 | 0.14 | −0.24 to 0.03 |
| Number of extra treatments | 0.16 (0.3) | 0.15 (0.3) | 0.02 | 0.54 | −0.04 to 0.07 |

Values for SD in brackets.

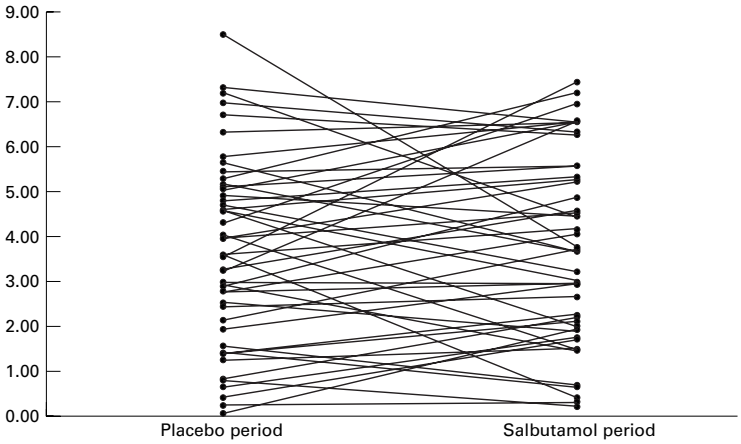


*Figure 1 Mean daily symptom score during placebo and salbutamol periods.*

*Table 3 Lung function results pre- and post-salbutamol for all patients studied*

| *Test* | *No.* | *Pre-salbutamol* | *Post-salbutamol* | *Mean change* | *p value* | *95% confidence interval* |
|---|---|---|---|---|---|---|
| Respiratory rate | 34 | 31.5 (5.2) | 30.6 (5.0) | −0.61 | 0.26 | −1.7 to 0.5 |
| $C_{rs}$ (ml/kPa) | 31 | 98.9 (18.8) | 103.8 (23.3) | 3.62 | 0.21 | −2.1 to 9.4 |
| $R_{rs}$ (kPa/Ls) | 31 | 4.25 (1.15) | 4.42 (0.93) | 0.36 | 0.03 | 0.04 to 0.68 |
| $V_{maxFRC}$ (ml/s) | 33 | 144.4 (72.4) | 135.0 (73.8) | −3.58 | 0.5 | −14.7 to 7.1 |
| $t_{PTEF}$:$t_E$ | 36 | 0.214 (0.06) | 0.212 (0.08) | 0.001 | 0.95 | −0.024 to 0.025 |

SD values in brackets.

In response to the question "Which inhaler was the most effective?" the parents' answer more closely reflected the mean daily symptom score than the inhaler content. A total of 62.5% indicated that the "most effective" inhaler was given during the period which proved to have the lower mean daily score. However, only 45.8% indicated salbutamol as the "most effective" inhaler. There was no effect of the order in which the inhalers were prescribed (p = 0.577).

PULMONARY FUNCTION RESULTS

Table 3 shows the lung function data for the infants studied, including those who did not complete the diary section. There was a tendency towards a decrease in respiratory rate and increase in $C_{rs}$ but these were not statistically significant. There was a small but statistically significant increase in $R_{rs}$ following salbutamol.

Comparison of changes in infants who had paired diary score and lung function data (29 infants) was performed (fig 2). The difference in diary score between the salbutamol and placebo periods showed no significant relation with change in $V_{maxFRC}$ following salbutamol (p = 0.255).

## Discussion

We have investigated the effect of regular inhaled salbutamol in infants with both a history of wheezing and an atopic background. The effect was evaluated both by symptoms, in an eight week randomised crossover clinical trial, and by pulmonary function measurements. We could show no consistent effect, positive or negative, in response to salbutamol by either method and there was no correlation between responses measured by the two methods. Our study design (crossover) and size (48 patients completing) has adequate power to detect a change in daily symptom score of 0.8 with a power of 90% at a significance level of 0.05.

To our knowledge this is the only study measuring the response to regular salbutamol over a period of four weeks. Studies by Tal *et al*[15] and Fox *et al*[16] both extended follow up beyond a hospital admission but only to a maximum of a fortnight. Both studies also involved the use of steroids. We chose two treatment periods of four weeks to increase the likelihood of at least one viral infection occurring during each period and therefore be more representative of what usually happens. Fox *et al* found no difference in improvement in clinical score between treatment groups (placebo or oral salbutamol, with or without prednisolone) during the recovery phase of an acute illness. The only significant findings were an increase in readmission rate (treatment failure) in the placebo group. Slightly more infants who were

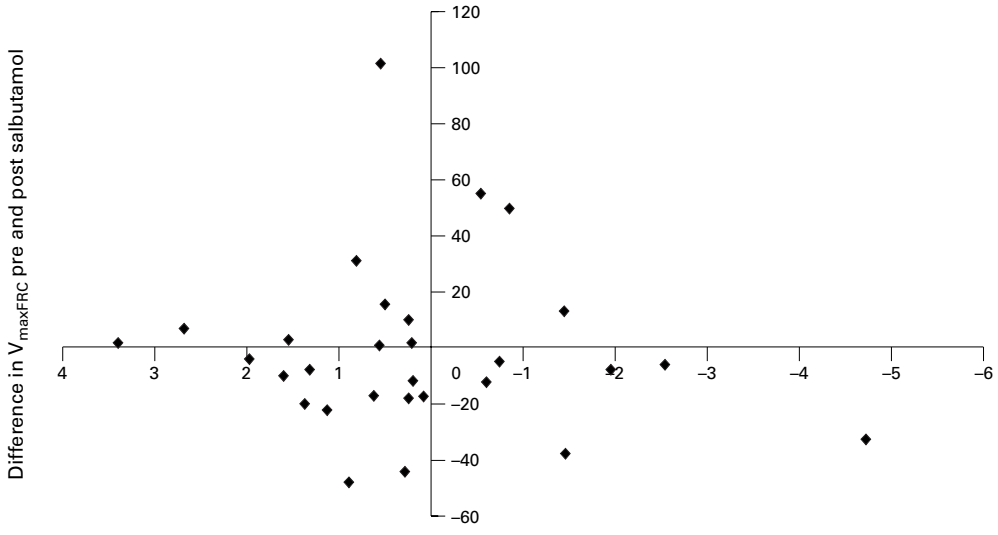


*Figure 2 Agreement between response to salbutamol measured by clinical score and lung function.*

forced to withdraw from our study because of clinical deterioration (treatment failure) were taking placebo at the time but the numbers were small and not statistically significant.

The previous studies investigating the response to salbutamol using a variety of pulmonary function tests have shown a mixed response. Many have primarily included children with acute bronchiolitis. We selected a group of infants with well documented persistent or recurrent wheeze rather than those recovering from acute bronchiolitis. It is possible that primary acute bronchiolitis causes wheeze by different mechanisms to other wheezing disorders and should therefore be considered separately. We were careful to define a group with persistent/recurrent, rather than transient wheezing, and an atopic background—that is, analogous to older children with asthma.

The most consistently reported beneficial effect of salbutamol has been protection against bronchoconstriction following a chemical challenge.[13 14 20 21] We could not show this benefit being carried over to protection against (probable) virus induced wheeze as our infants did not show any reduction in "exacerbations" (defined as days with high symptom score). This may indicate that the mechanisms behind naturally triggered wheeze in infancy are different from wheeze induced by chemical challenge.

We noted no improvement in $V_{maxFRC}$ which concurs with the findings of Prendiville *et al*[11] and Hughes *et al*.[22] We also noted a slight increase in resistance as did O'Callaghan *et al*[10] and Yuksel and Greenough.[23] In these latter studies they noted that the increase was transient and began to resolve by 15 minutes,[23] postulating that it was either temporary loss of airway muscle tone or a bronchoconstrictive effect caused by the osmolarity or acidity of the salbutamol inhalation. We made our post-bronchodilator measurements after 15 minutes and might therefore have missed a more clinically significant deterioration in resistance, which may have been more apparent had we performed an earlier series of recordings. We used a metered dose inhaler which should have circumvented the issue of osmolarity of nebulised solutions. The finding of a small increase in resistance despite this would suggest that this phenomenon is an effect of the drug itself rather than the preparation. However, this isolated finding is difficult to interpret in the context of no significant change in $V_{maxFRC}$, supposedly a more sensitive indicator of small airway obstruction. It may simply represent a type 1 error.

We performed our pulmonary function tests at a set time within the study protocol and, for ethical reasons, if the infant had moderate symptoms, the tests were postponed by a few days. This meant that most of the patients were symptom free or had only mild symptoms at the time of testing. This may have reduced the capability of individuals to respond to the bronchodilator; however many of the patients still had considerably reduced forced expiratory flows and an obstructive appearance to their flow volume loops. Despite being relatively symptom free, there was evidence of ongoing disease.

It is possible that the lack of response to salbutamol in this study was because of poor adherence to the treatment regime, rather than lack of efficacy. We asked parents to record drug administration, and this reported adherence (table 2) was similar to that reported in clinical studies in older children, and identical between the two treatment periods. We did not directly measure adherence, and it is likely that this was less good than that reported by the parents.[24] Nevertheless, in this group of well motivated parents of infants with troublesome symptoms, adherence is likely to have been at least as good as in normal clinical practice.

In summary, we were unable to show a positive response to salbutamol in this group of infants, either clinically or using pulmonary function tests. There seemed to be no relation between the two outcome measures. There was if anything a trend for most clinical markers to be worse in the salbutamol period, and for there to be a small but statistically significant increase in $R_{rs}$ following salbutamol.

On the basis of this trial, we would not recommend that salbutamol be used as the bronchodilator of choice in this age group. Any use of bronchodilator should be carefully monitored, and if there is no definite response, an alternative should be tried. Further evidence should be sought for the use of other bronchodilators in this age group.

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