

Bronchial response to nebulized antibiotics in children with cystic fibrosis

H.L. Chua, G.G. Collis, P.N. Le Souëf

Bronchial response to nebulized antibiotics in children with cystic fibrosis.
H.L. Chua, G.G. Collis, P.N. Le Souëf.

ABSTRACT: Nebulized antibiotics are being used increasingly in children with cystic fibrosis. We assessed the effect of nebulized antibiotic solutions of varying tonicity on lung function in 12 children aged 5-15 yrs with cystic fibrosis. Baseline forced expiratory volume in one second and (FEV_1) was measured, followed by a single nebulization of normal saline ($272 \text{ mosmol}\cdot\text{kg}^{-1}$), tobramycin ($248 \text{ mosmol}\cdot\text{kg}^{-1}$), or ticarcillin ($3,080 \text{ mosmol}\cdot\text{kg}^{-1}$). All children received each of these, administered randomly, one per day. FEV_1 was remeasured 5, 15 and 30 min after completion of the nebulization. Ticarcillin (mean fall 10.7% (SD 8.9)) caused a larger fall in FEV_1 than normal saline (4.8% (4.3), $p < 0.05$). The fall in FEV_1 for ticarcillin was greater than for tobramycin (1.2% (2.0), $p < 0.05$). Normal saline did not result in a significantly larger fall in FEV_1 than tobramycin ($p > 0.05$). Bronchoconstriction to ticarcillin persisted at 30 min. We conclude that nebulized antibiotics can affect lung function in children with cystic fibrosis if the solutions are hypertonic.

Eur Respir J., 1990, 3, 1114-1116.

Dept of Respiratory Medicine, Princess Margaret Hospital for Children, Perth, Western Australia.

Correspondence: Dr H.L. Chua, Dept of Respiratory Medicine, Princess Margaret Hospital for Children, Box D184, GPO, Perth, Western Australia 6001.

Keywords: Bronchoconstriction; cystic fibrosis; hypertonic nebulized antibiotics.

Received: May 19, 1990; accepted for publication July 9, 1990.

The inhalation route for delivery of medications has been a fundamental part of therapy for cystic fibrosis since modern intensive treatment began over 30 yrs ago [1, 2]. Nebulized antibiotics are being used increasingly to prevent and treat progressive lung disease in cystic fibrosis. There are many advantages of nebulized antibiotics; therapy can be undertaken at home, thus avoiding the need for hospitalization for intravenous therapy, lessening disruption to family life and reducing costs. Other potential advantages of nebulized antibiotics include a smaller dose of active agent for the desired effect and a lower incidence of systemic side-effects.

However, the inhalation of hypertonic and hypotonic solutions can cause bronchoconstriction in individuals with hyperresponsive airways, such as asthmatics [3, 4]. Some of the nebulized antibiotic solutions used in the treatment of cystic fibrosis are hypertonic. Nebulized antibiotics have been used in various studies [5-8], but almost no information on the bronchial response to these inhaled medications is available. This knowledge may be clinically relevant, as it may be possible to avoid or minimize bronchoconstriction by using more isotonic solutions in appropriate children.

The aim of the current study, therefore, was to measure the effect of nebulized antibiotic solutions of varying tonicity on lung function in children with cystic fibrosis. We wished to test the hypothesis that hypertonic

nebulizations will cause bronchoconstriction in children with cystic fibrosis who have hyperresponsive airways but not in those with normal airway responsiveness.

Methods

Twelve children with cystic fibrosis were recruited from Princess Margaret Hospital for Children. The median age was 8.5 yrs (range 5-15 yrs). The male:female ratio was 2:1. Permission for the study was obtained from the Medical Ethics Committee of the hospital. Informed consent was obtained from the parents before the studies were undertaken. The study was performed in the Respiratory Function Laboratory at Princess Margaret Hospital for Children.

On day 1, the histamine inhalation challenge technique of COCKCROFT *et al.* [9] was administered to the subjects. Standard criteria for the challenge were followed. The subjects had no history of respiratory tract infection for at least two weeks prior to testing. Routine medications were withheld as follows: bronchodilators for 8 h, theophyllines for 12 h, sodium cromoglycate for 24 h, antihistamines for 48 h and hydroxyzine for 96 h. The tests were performed only if baseline spirometry, which was measured with a Vitalograph (Vitalograph Ltd, England), was within the normal range with forced expiratory volume in one

second (FEV_1) >80% of predicted values. Baseline measurements were recorded before and after saline. Then, doubling concentrations of histamine from 0.125 mg·ml⁻¹ to a maximum concentration of 8 mg·ml⁻¹ were used. All solutions had an initial volume of 2 ml. The subject inhaled each dose *via* a mouthpiece during tidal breathing for two minutes. A noseclip was worn during the inhalation. FEV_1 was measured 30 and 90 s after inhalation. The doses were administered at five minute intervals. The challenge ceased when FEV_1 fell by >20%, or when a concentration of 8 mg·ml⁻¹ was reached. The concentration of histamine to cause a 20% fall in FEV_1 (PC_{20}) was obtained by linear interpolation.

On three subsequent days, physiotherapy was given by the parent before baseline FEV_1 was measured. This was followed by a 2 ml nebulization of ticarcillin, tobramycin or normal saline *via* a facemask until the nebulization was completed. All children received each of these solutions, which were administered randomly, one per day, for the three days. It was not feasible to perform a double-blind trial, as ticarcillin solution has a distinctive odour and takes longer to nebulize than the other solutions.

The Department of Clinical Chemistry at Princess Margaret Hospital for Children analysed the tonicity of the following solutions, which are as currently prescribed by our department for home use. Osmolality of normal (0.9%) saline was 272 mosmol·kg⁻¹. One ml of tobramycin (80 mg·2 ml⁻¹), made up to 2 ml with normal saline had an osmolality of 248 mosmol·kg⁻¹. Ticarcillin solution made up by adding 2.5 ml normal saline to 1g of powder had an osmolality of 3,080 mosmol·kg⁻¹. Two ml of the original solution was administered to each child.

FEV_1 was remeasured 5, 15 and 30 min after the nebulization was completed.

Statistical analysis was performed using analysis of variance (ANOVA). The significance of the differences between the nebulized solutions causing a fall in FEV_1 was analysed with the Student-Newman Keuls test.

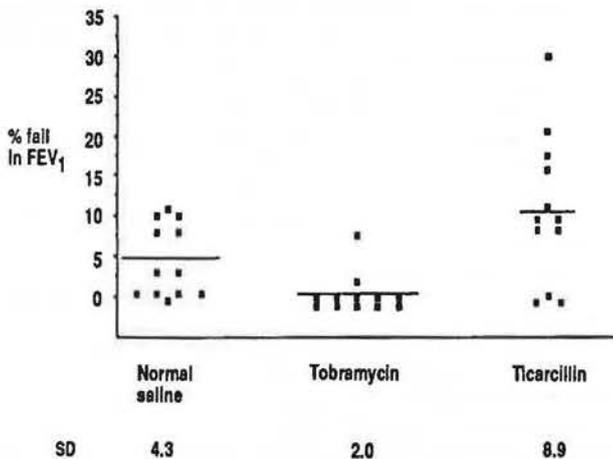


Fig. 1. - Change in FEV_1 following nebulized solution administered. Horizontal line depicts mean decrease in FEV_1 for each group. FEV_1 : forced expiratory volume in one second.

Results

The maximal percentage falls in FEV_1 following the nebulized solutions are plotted in figure 1. There was a significant difference between the nebulized solutions in terms of falls in FEV_1 ($p < 0.001$). Ticarcillin (mean fall 10.7% (sd 8.9)) caused a larger fall in FEV_1 than normal saline (4.8% (4.3), $p < 0.05$). The fall in FEV_1 for ticarcillin was also greater than for tobramycin (1.2% (2.0), $p < 0.05$). Normal saline did not result in a significantly larger fall in FEV_1 than tobramycin ($p > 0.05$). There were no clinically significant symptoms apparent in any subject.

The histamine responsiveness and maximal change in FEV_1 following the nebulized solutions are tabulated (table 1). There was no correlation between airway response to hypertonic solutions and airway response to histamine ($p = 0.12$).

Table 1. - Histamine responsiveness of the subjects and maximal change in FEV_1 (%) following nebulized solutions

Histamine PC_{20}	Maximal % fall in FEV_1		
	Normal saline	Tobramycin	Ticarcillin
>8	1	0	0
>8	11	0	1
5.10	3	1	9
3.20	1	1	9
2.80	10	1	30
2.30	8	1	17
2.30	3	1	15
1.46	1	2	11
0.49	1	0	20
0.48	8	0	8
0.41	0	0	0
0.05	10	7	8

FEV_1 : forced expiratory volume in one second; PC_{20} : provocative concentration (mg·ml⁻¹) producing a 20% fall in FEV_1 .

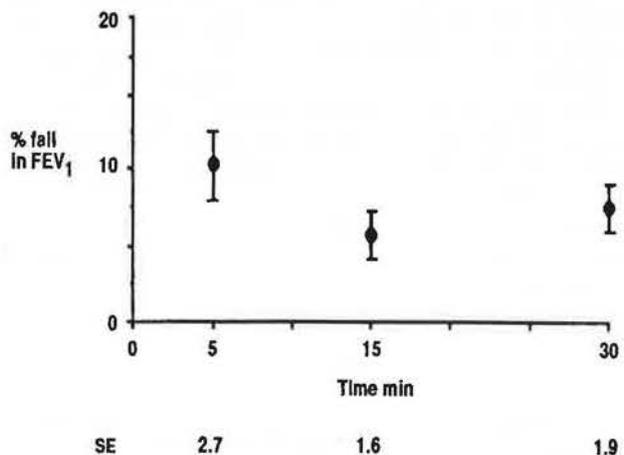


Fig. 2. - Change in FEV_1 with time for the group following nebulized ticarcillin. Means and standard errors are presented. FEV_1 : forced expiratory volume in one second.

There was no significant change in FEV₁ with time following nebulized ticarcillin (repeated measures ANOVA) (fig. 2). Therefore, bronchoconstriction persisted at 30 min.

Discussion

This study has found that nebulized antibiotic solutions can cause bronchoconstriction. This effect appears to be related to hypertonicity of the solution as it was observed in the subjects who received ticarcillin. Normal saline (which was isotonic) and tobramycin (which was mildly hypotonic) did not cause significant bronchoconstriction.

We did not find a relationship between the level of histamine responsiveness and the degree of bronchoconstriction following hypertonic nebulizations. BOULET *et al.* [10] also found no significant correlation between the airway response to hyperosmolar inhalation and the airway response to an inhaled agonist, but their subjects were asthmatics and methacholine was used rather than histamine. Therefore, bronchial responsiveness does not appear to be useful for predicting whether a child with cystic fibrosis will experience bronchoconstriction in response to hypertonic nebulizations.

The present study showed that nebulized antibiotic solutions can affect lung function in children with cystic fibrosis if the solutions are hypertonic. In most children, the bronchoconstriction is relatively mild but lasts at least 30 min. We should, therefore, consider tonicities when planning nebulized therapy and some children may need to avoid synthetic penicillins if they experience symptoms with hypertonic solutions.

Other possible causes for the bronchoconstriction following ticarcillin nebulization were considered. The pH of ticarcillin solution was 7.45, compared to 6.35 for normal saline and 5.65 for tobramycin; this small difference is unlikely to be significant. As the only component in ticarcillin solution is its disodium salt, there being no preservatives, other factors are not likely to be responsible for the bronchoconstriction.

Further clinical studies are required in children with cystic fibrosis to determine whether routine, repeated use of hypertonic antibiotic solutions contributes to respiratory symptoms in some individuals by their acute effect on airway calibre. The possibility that longer-term use of hypertonic nebulizations could be deleterious to some patients should also be investigated.

References

1. Waring WW. – Current management of cystic fibrosis. *Advances in Paediatrics*, 1976, 23, 401–438.
2. Taussig LM. – Mists and aerosols: new studies, new thoughts. *J Pediatr*, 1974, 84, 619–622.
3. Schoeffel RE, Anderson SD, Altounyan REC. – Bronchial hyperreactivity in response to inhalation of ultrasonically nebulised solutions of distilled water and saline. *Br Med J*, 1981, 283, 1285–1287.
4. Cheney FW, Butler J. – The effects of ultrasonically-produced aerosols on airway resistance in man. *Anesthesiology*, 1968, 29, 1099–1106.
5. Wall MA, Terry AB, Eisenberg J, McNamara M, Cohen R. – Inhaled antibiotics in cystic fibrosis (letter). *Lancet*, 1983, i, 1325.
6. Stephens D, Garey N, Isles A, Levison H, Gold R. – Efficacy of inhaled tobramycin in the treatment of pulmonary exacerbations in children with cystic fibrosis. *Pediatric Infectious Disease*, 1983, 2, 209–211.
7. Kun P, Landau LI, Phelan PD. – Nebulized gentamicin in children and adolescents with cystic fibrosis. *Aust Paediatr J*, 1984, 20, 43–45.
8. Cooper DM, Harris M, Mitchell I. – Comparison of intravenous and inhalation antibiotic therapy in acute pulmonary deterioration in cystic fibrosis. *Am Rev Respir Dis*, 1985, Vol A242.
9. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. – Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy*, 1977, 7, 235–243.
10. Boulet L-P, Legris C, Thibault L, Turcotte H. – Comparative bronchial responses to hyperosmolar saline and methacholine in asthma. *Thorax*, 1987, 42, 953–958.

Réponse bronchique à des nébulisations d'antibiotiques, chez les patients atteints de fibrose kystique. H.L. Chua, G.G. Collis, P.N. Le Souëf.

RÉSUMÉ: L'on utilise de façon croissante des antibiotiques en aérosol chez les enfants atteints de fibrose kystique. Nous avons apprécié l'effet de solutions nébulisées d'antibiotiques, de tonicité variable, sur la fonction pulmonaire de 12 enfants âgés de 5 à 15 ans atteints de fibrose kystique. Le VEMS de base a été mesuré. Une nébulisation simple de solution saline isotonique (272 mosmol·kg⁻¹), de tobramycine (248 mosmol·kg⁻¹), ou de ticarcilline (3,080 mosmol·kg⁻¹), a été mesurée réalisée ensuite. Tous les enfants ont reçu une de ces nébulisations par jour dans un ordre randomisé. Le VEMS a été à nouveau 5, 15 et 30 minutes après la fin de la nébulisation. La ticarcilline a provoqué une chute du VEMS supérieure (valeur moyenne 10.7% (sd 8.9)) à celle provoquée par la solution saline (4.8% (sd 4.3), p<0.05). La chute du VEMS après ticarcilline fut plus importante qu'après tobramycine (1.2% (sd 2.0), p<0.05). La solution saline n'a pas entraîné une chute plus importante du VEMS que la tobramycine (p>0.05). La bronchoconstriction après ticarcilline persiste à 30 minutes. Nous concluons que les aérosols nébulisés peuvent altérer la fonction pulmonaire des enfants atteints de fibrose kystique lorsque les solutions sont hypertoniques. *Eur Respir J.*, 1990, 3, 1114–1116.