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Personal practice

Bronchodilators for wheezy infants?

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The problem

The following scene is regularly enacted in hospitals throughout Britain. A 10 month old infant with a history of recurrent wheeze since early infancy arrives in the accident and emergency department with another distressing attack of airways obstruction. Despite being told by his well-read seniors that bronchodilators are of no value, the paediatric house officer prescribes the current favourite, to be given by nebuliser and facemask. Five minutes later, after a struggle, the infant, still wheezing loudly, is sitting up and playing with coloured bricks. Are we to believe objective clinical science or subjective clinical observation? There are several components to this question. Before a clear recommendation can be made concerning the use of bronchodilators in infancy, the answers to each should be available.

Airways function and dysfunction

Whatever the final trigger, there are anatomical reasons why infants may be more prone than older children to symptomatic airways obstruction. The absolute dimensions of the airways, from the trachea to the respiratory bronchioles, are all less in infancy than in later childhood, rendering them more easily obstructed.[1] In addition, the less rigid chest wall of young infants provides little passive support to the lungs, so that even during normal tidal breathing, some airways probably close off towards the end of expiration. The rigidity of the cartilage supported walls of segmental bronchi and trachea may be less in infancy, allowing the airways to collapse more readily during expiratory effort (the effect known as dynamic airway closure) producing audible wheeze and increasing the work of breathing during acute airways obstruction.

The quantity of smooth muscle in bronchioles is said to be disproportionately small in infancy[2] and little is known about its control or about the control of other important airways functions such as mucus secretion and clearance. None of the many tests of bronchial responsiveness have been adapted and applied to infants, although interestingly Milner's group have inadvertently given several groups of wheezy infants nebulised water by facemask.[3 4] This is now known to produce notable airways obstruction in older asthmatics.[5] In the infants no change in respiratory resistance was noted, implying a difference in airways responsiveness between infant wheezers and older subjects. Preliminary data suggests that β adrenoceptors are present and functional in airway preparations of infant mammals.[6] Information on human infant bronchi is not yet available.

Clinical patterns of infant wheeze

Although the list of disorders associated with wheeze in infancy is long, including congenital lung anomalies, neonatal lung damage, recurrent aspiration, and hereditary disease such as cystic fibrosis and ciliary dyskinesia, the group of disorders variously labelled bronchiolitis, wheezy bronchitis, or asthma is our main concern in relation to bronchodilator treatment. Is the mechanism of airways obstruction in an infant suffering his first attack of bronchiolitis different from that of an older infant with a history of recurrent or persistent wheeze? The physical signs are of little help in drawing a distinction between smooth muscle spasm, airway oedema, or mucus plugging—leaving aside the additional variable of upper airways (nasal) obstruction. Examination of the lungs from fatal cases of infantile bronchiolitis shows acute inflammation of the bronchiolar epithelium with widespread small airways obstruction, while children dying after chronic airways disease may have notable mucus gland hypertrophy.[2] On the face of it, this does not seem a fruitful scene for bronchodilator treatment.

The evidence that viral bronchiolitis is one of the manifestations of an asthmatic predisposition[7 8] has

been disputed recently,[9] although wheeze may persist for years after an attack.[10 11] In non-asthmatic adults, viral infections of the respiratory tract may produce asymptomatic minor degrees of both airways obstruction and increased bronchial responsiveness that may last for several weeks after the acute illness has passed. Such changes in infancy may be expected more commonly to lead to symptomatic airways obstruction.

Recurrent wheeze in infancy may represent the waning after-effects of viral bronchiolitis or the earliest symptoms of asthma. Viral infections are again the most important trigger for severe attacks.[12] A family or personal history of atopic disease may suggest that the recurrent wheeze be classified as asthma, but that does not give any useful clue to the likelihood of response to a bronchodilator. For the group of infants (often obese or with eczema) who have persistent wheeze there is even less information on reponse to treatment.

It is clear that we have insufficient understanding of normal airways function in infancy and little more knowledge of the pathophysiology of recurrent airways obstruction to either classify patients into discrete clinical syndromes or to provide a basis for rational treatment.

Measuring severity of airways obstruction and response to treatment

Although a wide range of physiological measurements may be made on infants with chronic wheeze or during recovery from an acute attack, few techniques are applicable during an acute attack. All direct measurements of airways function require some sort of mouthpiece or facemask and are therefore out of the question in unsedated, acutely ill infants. Measurements of thoracic and abdominal motion by inductance vest[13] or the Milner jacket,[14] can provide indirect values for tidal volume, but there are many methodological problems associated with dynamic measurements of lung mechanics from body surface measurements. Recent work has shown the jacket method to give acceptably reproducible results during quiet sleep in infants with acute bronchiolitis.[15] Perhaps the most useful overall measurement of the severity of acute airways obstruction is the Po_2 measured by radial artery sampling or from arterialised capillary blood, although the techniques upset the patients and their reproducibility must be poor. The accuracy of transcutaneous measurements has recently come under increasing question.[16]

Where infants can be studied during sleep or sedation (which is almost always needed for lung function tests after the first 3 months of age) reproducible measurements of respiratory resistance or of lung volume and airways resistance in a plethysmograph can be made. In general, measurements of resistance are not sensitive to small airways function, and when combined with lung volume measurements, errors begin to build up. All values of resistance, or work of breathing, include a major contribution (up to 50% even in normal infants) from the upper airways and are therefore very sensitive to nasal obstruction, a common accompaniment of acute wheeze. An exception may be the intriguing study of forced expiratory flows in infancy[17] which could give much needed sensitivity to tests of lower airways function in this age group.

Results of clinical studies

Objective data on the use of bronchodilators in acute attacks of airways obstruction in infancy must be reviewed in the light of the problems outlined above. During the acute phase of bronchiolitis and during the recovery phase of acute bronchiolitis, wheezy bronchitis, or infantile asthma measurements of respiratory resistance, pulmonary resistance, and airways resistance or work of breathing have failed to show any immediate benefit from single doses of nebulised sympathomimetics (isoprenaline, adrenaline, or salbutamol), although a very few individual infants may have responded.[3 4 15 18 19 20] Tachycardia is reported, suggesting that adequate doses were given. In one study of a selected group of infants beyond the age of infantile bronchiolitis and with a strong personal and family history of atopy, no infant of less than 18 months responded to nebulised salbutamol.[20]

The folly of basing clinical judgements on single dose studies has recently been illustrated with a drug that is not usually classified as a bronchodilator—ipratropium bromide, an anticholinergic agent. About half of a group of wheezy infants aged under 18 months seemed to respond to a single nebulised dose of this drug by a reduction in the work of breathing.[21] The same authors have gone on to carry out a double blind clinical trial of nebulised ipratropium bromide on 66 children with acute viral bronchiolitis, showing no benefit from the drug.[22]

There are surprisingly few satisfactory clinical trials of bronchodilator treatment in acutely wheezy infants. In a recent partially blind study, 32 infants were randomly assigned to dexamethasone or placebo and within each of these two groups, to salbutamol or placebo.[23] The combination of salbutamol with dexamethasone (but neither drug alone)

significantly shortened the duration of the acute illness.

A large number of studies of theophyllines and their pharmacokinetics have been reported in infancy, but only one (retrospective) trial, showing no benefit, has been carried out.[24]

If the information on acute attacks in hospital is sparse, it is non-existent for chronic infantile wheeze outside hospital. The design of a clinical trial to evaluate a drug that may be given by several different routes in a group of wheezy infants whose disease is poorly characterised and extremely variable, using techniques of assessment that are of necessity subjective, would be a daunting task. For one specific group of wheezy infants, those with clinical airways disease resulting from neonatal mechanical ventilation, bronchodilator treatment has been shown to be completely ineffective.[25]

While it would be indefensibly bold to draw negative conclusions from small single dose studies using measurement criteria that are often of poor reproducibility and in which only limited types of wheezy infants have been studied, from the evidence available single doses of nebulised bronchodilators for acute attacks of wheeze have not been shown to be significantly better than placebo. Neither for chronic wheeze, nor for multiple dose treatment of acute attacks is adequate information available.

Practical recommendations

With the paucity of clinical science, practical recommendations must be largely based on personal practice. For children under 6 months, who are suffering from their first attack of wheeze and who seem to have acute viral bronchiolitis, with or without a family or personal history of atopic disease, I do not use bronchodilator treatment (or any other treatment normally associated with acute asthma in later childhood). At the other extreme, when a child aged over 6 months who has recurrent attacks of wheeze is admitted to hospital with acute airways obstruction, I use 4 hourly nebulised β_2 sympathomimetic drugs (salbutamol 2·5 mg or terbutaline 5 mg in 2·0–2·5 ml saline) given with a loose facemask, or by directing the nebulised mist over the infant's face. As oxygen treatment is often required (and should not be forgotten), it seems sensible to use oxygen as the carrier gas in the nebuliser. When an infant fails to respond to the bronchodilator, additional treatment with intravenous hydrocortisone and aminophylline or with oral prednisolone has then to be considered: the older the infant, the more likely I am to start this additional treatment early in the course of treatment.

Between the two extremes the decision is less clear. If in doubt I prefer to give a nebulised bronchodilator; the benefits may be dramatic and the hazards are negligible. After the initial dose, clinical judgement aided occasionally by serial arterial blood gas measurements, will indicate whether repeated doses of bronchodilator at 3–4 hourly intervals are necessary or whether a trial of an alternative agent such as ipratropium bromide is indicated.

Some precautions need to be observed. The diagnosis should have been established before resorting to bronchodilator treatment since, unlike older children, failure to respond in infants does not necessarily imply an alternative diagnosis. Extreme tachycardia (over 190/min) and prior exposure to large doses of bronchodilators are contraindications to further treatment.

Since more general practitioners now carry nebulisers for the emergency administration of β_2 sympathomimetic drugs, how should they be advised to cope with an acutely ill infant wheezer? I would suggest that in this age group, the need for an emergency dose of a nebulised bronchodilator implies the need for an emergency admission to hospital. Again, if in doubt, I would advise that the nebuliser is administered before leaving for hospital, according to the suggestions above.

Chronic wheezers seen in the outpatient clinic are dealt with in the same way as older asthmatics, by avoidance of recognisable provoking factors and by home based trials of treatment using daily record cards as a guide to success. When oral treatment fails, a home nebuliser should be obtained so that intermittent treatment or regular prophylaxis can be provided under medical supervision.

Conclusions

In the practice of clinical paediatrics and in our teaching of others who deal with children, we rely on a background of sound clinical research. It is clear that in the field of airways obstruction of infancy we have insufficient empirical or experimental data on the effects of drugs. Until the information is available, we will continue to prescribe bronchodilators to infants in a largely haphazard way.

References

[1] Polgar G, Weng TR. The functional development of the respiratory system. *Am Rev Respir Dis* 1979;**120**:625–95.

[2] Matsuba K, Thurlbeck WM. A morphometric study of bronchial and bronchiolar walls in children. *Am Rev Respir Dis* 1972;**105**:908–13.

[3] Rutter N, Milner AD, Hiller EJ. Effect of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezy bronchitis. *Arch Dis Child* 1975;**50**:719–22.
[4] Lenney W, Milner AD. Alpha and beta adrenergic stimulants in bronchiolitis and wheezy bronchitis in children under 18 months of age. *Arch Dis Child* 1978;**53**:707–9.
[5] 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**:1285–7.
[6] Duncan PG, Brink C, Douglas JS. β receptors during ageing in respiratory tissues. *Eur J Pharmacol* 1982;**78**:45–52.
[7] Rooney JC, Williams HE. The relationship between proved viral bronchiolitis and subsequent wheezing. *J Pediatr* 1971;**79**:744–7.
[8] Laing I, Riedel F, Yap PL, Simpson H. Atopy predisposing to acute bronchiolitis during an epidemic of respiratory syncytial virus. *Br Med J* 1982;**284**:1070–2.
[9] Sims DG, Gardner PS, Weightman D, Turner MW, Soothill JF. Atopy does not predispose to RSV bronchiolitis or postbronchiolitic wheezing. *Br Med J* 1981;**282**:2086–8.
[10] Pullan CR, Hey EN. Wheezing, asthma and pulmonary dysfunction ten years after infection with respiratory syncytial virus in infancy. *Br Med J* 1982;**284**:1665–9.
[11] Mok JYQ, Simpson H. Outcome of acute lower respiratory tract infection in infants: preliminary report of seven-year follow-up study. *Br Med J* 1982;**285**:333–7.
[12] Horn MEC, Brain EA, Gregg I, Ingils JM, Yealland SJ, Taylor P. Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* 1979;**34**:23–8.
[13] Dolfin T, Duffty P, Wilkes DL, Bryan MH. Calibration of respiratory induction plethysmography (Respitrace) in infants. *Am Rev Respir Dis* 1982;**126**:577–9.
[14] Stokes GM, Milner AD, Groggins RC. Work of breathing, intra-thoracic pressure and clinical findings in a group of babies with bronchiolitis. *Acta Paediatr Scand* 1981;**70**:689–94.
[15] Stokes GM, Milner AD, Hodges IGC, Henry RL, Elphick MC. Nebulised therapy in acute severe bronchiolitis in infancy. *Arch Dis Child* 1983;**58**:279–83.
[16] Department of Health and Social Security. *Evaluation of transcutaneous oxygen monitors.* DHSS Health Equipment Information No 97, 1981.
[17] Taussig LM, Landau LI, Godfrey S, Arad I. Determinants of forced expiratory flows in newborn infants. *J Appl Physiol* 1982;**53**:1220–7.
[18] Phelan PD, Williams HE. Studies of respiratory function in infants with recurrent asthmatic bronchitis. *Aust Paediatr J* 1969;**5**:187–96.
[19] Radford M. Effect of salbutamol in infants with wheezy bronchitis. *Arch Dis Child* 1975;**50**:535–8.
[20] Lenney W, Milner AD. At what age do bronchodilator drugs work? *Arch Dis Child* 1978;**53**:532–5.
[21] Hodges IGC, Groggins RC, Milner AD, Stokes GM. Bronchodilator effect of inhaled ipratropium bromide in wheezy toddlers. *Arch Dis Child* 1981;**56**:729–32.
[22] Henry RL, Milner AD, Stokes GM. Ineffectiveness of ipratropium bromide in acute bronchiolitis. *Arch Dis Child* 1983;**58**:925–6.
[23] Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moss SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics* 1983;**71**:13–8.
[24] Brooks CJ, Cropp GJA. Theophylline therapy in bronchiolitis. *Am J Dis Child* 1981;**135**:934–6.
[25] Tal A, Bar-Yishay E, Eyal F, Godfrey S. Lack of response to bronchodilator of airway obstruction after mechanical ventilation in the newborn. *Crit Care Med* 1982;**10**:361–2.

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