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Is Salbutamol Useful in Babies with Wheezing?

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Abstract

Wheezing is one of the most common respiratory causes for seeking medical consultation for children up to one year of age, which has proven negative health, social and economic effects. Moreover, wheezing in patients of the mentioned age group is characterised by clinical heterogeneity, a broad spectrum of etiological causes and complex pathogenesis which make it difficult to choose the right therapeutic approach. In spite of this, Salbutamol remains to be the first medication of choice for treating wheezing in infants.

The aim of this review is to analyse the effectiveness of Salbutamol in the treatment of wheezing in infants in terms of the specific anatomical and physiological features of their respiratory system, as well as in terms of its etiological, pathogenic and clinical diversity.

Introduction

Wheezing is one of the most common respiratory causes for seeking medical consultation and for hospital admissions during the first year of life. It is estimated that worldwide approximately 25-45% of the infants up to one year of age suffer at least one episode of wheezing with differences among these rates depending on the country, study design and year. On the other hand, recurrent wheezing, which is defined as three or more episodes within a year, occurs in 12-22% of cases of the mentioned age group [9].

There is a diversity of disorders connected to wheezing in infancy-infections, recurrent aspirations/ Gastro Esophageal Reflux Disease (GERD), asthma, congenital anomalies, neonatal lung damage and hereditary diseases (cystic fibrosis, cilliary dyskinesia, etc.). Furthermore, it has a complex pathophysiology with multiple factors (anatomical, genetic, environmental and immunological) that alone or in interaction with each other can impair the patency of the lower airways [2,18].

Short-acting β2-agonists are the most common medication used in wheezy infants although their effectiveness is controversial and depends on the cause of wheezing [2]. Still widely discussed and without a definitive answer remains the question of whether infants have functional pulmonary β2-receptors.

All this makes it difficult for clinicians to make decisions about the proper diagnostic and therapeutic approach in managing wheezy infants, which is of great importance because it is estimated that wheezing can cause significant morbidity, decrease in quality of life, and increase in frequency of use of health care services and in economic costs [2,4].

Characteristics of bronchial obstruction in infants

No matter what the cause is, infants' airways are more prone to wheezing due to some specific anatomic and physiological characteristics of the respiratory system. The dimensions of the airways are smaller, which makes them easy to be obstructed. Furthermore, small caliber peripheral airways can contribute up to 50% of the total airway resistance, which appears to be a

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preconditon for wheezing in bronchiolitis. Smooth muscle tissue in the wall of the airways is disproportionately small (except from bronchioles where it is relatively well presented) and the cartilage rigidity is less, which together with the less rigid chest wall enables the inward pressure during expiration to close the airways early even in tindal breathing. A well-known physiological dependency is that resistance to airflow through the airway is inversely related to the radius of the tube to the fourth power, so even a small amount of additional narrowing of the airway can cause further flow limitation and a subsequent wheeze. The airways have highly vascularised mucosa and higher production of mucus which makes them prone to obstruction as well [2,15,18].

Salbutamol and β-adrenoceptors

The β-adrenoceptor is a cell membrane-spanning receptor, with at least three subtypes. β_1-adrenoceptors are largely cardiac, whereas β_2 receptors are found in the lungs, liver, vascular tissue and uterine muscles. Within the lung, β_2-adrenoceptors are largely located on airway smooth muscle, but are also located on type II pneumocytes, epithelial and endothelial cells, and mast cells [20].

Salbutamol is a synthetic sympathomimetic amine that selectively stimulates β-adrenoceptors. It is short-acting and stimulates the production of cyclic AMP through activation of adenylate cyclase. Cyclic AMP enhances the activity of cyclic AMP-dependent protein kinase and inhibits the calcium release from intracellular stores which prevents the mast cells release in the airways and leads to smooth muscle relaxation. As a result, following inhalation or oral administration, Salbutamol causes bronchodilation. Despite being rather selective, it still has an effect on β1-receptors in the heart resulting in tachycardia [14,20].

Another discutable aspect concerning wheezing and its therapy in infants is whether they have functional pulmonary β-adrenoceptors and it has caused confusion since the discovery of Salbutamol in 1969 [20].

At birth, intraalveolar fluid is rapidly displaced by air, and excessive interstitial fluid is absorbed into the vascular system. This removal of fluid, as well as, surfactant release are presumed to be linked to pulmonary β-adrenergic stimulation. Administration of β-blockers to fetal animal models has shown to abolish the increase in surfactant release that normally accompanies labour and delivery [11].

Similar observations have been reported in functional studies in human babies, although the ontogeny of human pulmonary receptors remains largely unknown. Infants born by caesarean section are more prone to respiratory difficulties suggesting lack of catecholamines induced by labour [11].

In the 1980s O'Callaghan et al. performed pulmonary function tests before and after nebulisation of water in a group of ten infants. They reported an increase in the mean airway resistance (indicating bronchoconstriction) over a period of five minutes post nebulisation. After return to baseline and administration of Salbutamol, further administration of water had no impact upon airways resistance or specific conductance, indicating that Salbutamol prevented bronchoconstriction. Thus, the authors demonstrated that administration of Salbutamol prevents chemically induced bronchoconstriction, providing indirect evidence for pulmonary β-receptor functionality [16].

Henderson et al. administered histamine to 40 infants, and randomly allocated infants to receive either Salbutamol or saline. The authors reported that Salbutamol induced a more rapid recovery of maximal flow rates, in contrast with saline controls. These studies therefore demonstrate that β_2-adrenoceptors are functional in the infant lung [12].

Role of salbutamol in treatment of acute bronchiolitis

Acute bronchiolitis is one of the most common viral respiratory tract infections. Although the term bronchiolitis refers to inflammation of the bronchioles, the diagnosis is based primarily on anamnesis and clinical findings. This causes a controversy and a unified definition is still lacking. In most publications, the diagnosis refers to a constellation of signs and symptoms including children under the age of two years old and prodromal symptoms of acute viral infection of the upper airways followed by wheezing and respiratory effort. Crackles can be registered on auscultation, as well [17]. The most common cause of viral bronchiolitis appears to be Respiratory Syncytial Virus (RSV), followed by Rhinovirus which is linked to a higher risk of recurrent wheezing and asthma [19].

Nebulized Salbutamol is reported to cause short-term clinical improvement in infants with acute bronchiolitis, but it has no significant effect on hospitalisation rates, length of stay, oxygen saturation and days to recover [19].

In 2014, a Cohrane report was published concerning the effect of bronchodilators on acute bronchiolitis which included 30 randomised controlled trials with 1992 infants suffering from acute bronchiolitis. The results did not show any significant improvement in oxygen saturation, hospitalization rates and length of stay. The high cost and adverse effects such as tachycardia and tremor were found to outweigh the short-term clinical improvement caused by the product [8]. Kellner et al. again report short-term improvement of clinical scores, but do not support the routine use of Salbutamol in infants with their first wheezing episode because it is not comparable to the costs [13].

In its first published guidelines concerning the management of acute bronchiolitis the American Association of Pediatrics (AAP) did not recommend the routine use of Salbutamol but justified its trial in cases with positive clinical response, registered through objective methods. However, given the greater strength of the evidence demonstrating no benefit, and that there is no well-established way to determine an objective method of response to bronchodilators in bronchiolitis, this option was removed afterwards [17].

As a reason for the lack of effect of Salbutamol in infants with acute bronchiolitis, many authors mention the main pathogenic mechanism of wheezing - the accumulation of debris, containing epithelial and inflammatory cells, mucus and fibrin and the submucosal edema rather than bronchial constriction [1].

Role of salbutamol in treatment of recurrent wheezing

Three and more episodes of wheezing for a period of one year is defined as recurrent wheezing, which is found in one-third of the children [2].

Due to the clinical heterogeneity of wheezing in the age group up to one year, determined by various etiological and risk factors, and thus with different outcomes, attempts have been made to classify phenotypes of recurrent wheezing with common characteristics [2].

According to 2022 GINA Report, Global Strategy for Asthma Management and Prevention a large proportion of wheezing episodes in young children is virally induced. Bronchiolitis should be taken into account, as well as highly probable. They summarise the wheezing phenotypes, as well, but outline that allocating children in those groups is difficult in "real-life" clinical situations and their usefulness is still to be investigated [10]. They are presented in Table 1.

Table 1: Classification of wheezing phenotypes.

Symptom-based classification	1. Episodic wheezing (wheezing during discrete time periods, often associated with LRTI, symptoms absent between episodes) 2. Multi-factor wheezing-(episodes of wheezing with symptoms between them, during sleep triggers may be physical activity)
Time trend- based classification	1. Transient wheeze-symptoms became and ended before three years of age 2. Persistent wheeze-symptoms started before three years of age and continued after six years of age 3. Late-onset wheeze-symptoms began after three years of age

LRTI: low respiratory tract infection

Chavasee et al. investigated the response to inhalatory Salbutamol of 80 infants up to one year of age with history of wheezing more than three days/nights per week for at least six weeks and tendency to atopy. The trial was randomised, double blind, cross over, placebo controlled. The response was measured by scoring system answered by the parents for a period of eight weeks and respiratory function tests, performed two weeks after the recording of the scoring diary. There was no significant change in either the total score or in the individual components of the score. There was no significant difference between the number of symptom-free days on either treatment. There was no difference in mean daily scores between the first four week period and the second, indicating no time effect. Concerning the respiratory function tests there was a tendency towards a decrease in respiratory rate and increase in compliance but these were not statistically significant. There was a small but statistically significant increase in resistance of the respiratory system following Salbutamol [5].

In spite of the mentioned results, some authors suggest a therapeutic trial of inhalatory Salbutamol in infants with a family history of asthma and/or athopy and it should not be repeated if there is no clinical improvement (decrease in respiratory rate and respiratory effort) after 15-30 minutes of the first application [3].

In 2002, a Cohrane report revewed eight randomised controlled trials comparing the effect of β2-agonists against placebo in 229 children under two years of age who had two or more previous episodes of wheeze, not related to another form of chronic lung disease. The main outcome measure was a change in respiratory rate and symptom scores. Improvement in respiratory rate, symptom score and oxygen saturation were noted in one study in the emergency department following two Salbutamol nebulisers but this had no impact on hospital admissions. There was a reduction in bronchial reactivity following Salbutamol. There was no significant benefit from taking regular inhaled Salbutamol on symptome scores recorded at home. The authors concluded no benefit of using Salbutamol for wheezing in the mentioned age group [6].

However, Grenville et al. document benefits from oral Salbutamol in 59 infants, aged between 3 and 15 months, with an acute episode of wheezing lasting for more than 48 h and at least one previous similar episode. Improvement after treatment with oral Salbutamol was documented only in terms of a smaller number of treatment failures, but not in the scoring systems or the length of hospital stay [7].

Conclusion

Bronchial obstruction in infants up to one year of age is characterised by clinical heterogeneity, a broad spectrum of etiological causes and complex pathogenesis. Salbutamol, a selective β2-adrenoceptor agonist, remains the most common medication of choice in wheezy infants although its effect is controversial and most authors decline its benefits. One of the reasons is the pathogenesis of wheezing – most of the authors failed to prove benefits from the use of Salbutamol in infants with acute bronchiolitis, which is one of the most common causes of wheezing in the mentioned age group, and the guidelines do not recommend it at the present moment.

Concerning the cases of recurrent wheezing, which have different etiology and pathogenesis from those of acute bronchiolitis, no significant improvement of symptoms, hospitalisation rates and length of stay has been reported. One of the reasons mentioned for a long period of time has been the lack of functional β-adrenoceptors in infants' respiratory system, but there is indirect evidence rejecting that statement. Despite the fact that many authors connect the impossibility to prove benefits from Salbutamol to the studies being performed on infants at times of complete health, the routine use of Salbutamol has not been recommended yet.

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