Beta$_2$-agonists and asthma in children

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Due to the growing prevalence and morbidity of asthma in children in the past few years, Canadian physicians have addressed several issues concerning the correct use of beta$_2$-agonists for the treatment of asthma. These issues include the optimum delivery systems for beta$_2$-agonists, their appropriate dosages in children, infants and toddlers, and whether tachyphylaxis occurs with their chronic use.

Key Words: *Asthma, Beta$_2$-agonists, Delivery systems, Pediatrics, Tachyphylaxis*

Les bêta$_2$-agonistes et l'asthme chez les enfants

RÉSUMÉ : L'augmentation de la prévalence et de la morbidité de l'asthme chez les enfants, ces dernières années, a entraîné les médecins canadiens à se pencher sur plusieurs questions concernant l'utilisation adéquate des bêta$_2$-agonistes pour le traitement de l'asthme. Ces questions portent notamment sur les systèmes optimums pour administrer les bêta$_2$-agonistes, les doses appropriées pour les enfants, les nourrissons et les bambins, et sur le développement possible d'une tachyphylaxie liée à l'utilisation chronique des bêta$_2$-agonistes.

THE PREVALENCE AND MORBIDITY OF ASTHMA, ESPECIALLY in young children, have clearly increased over the past two decades, not only in Canada but in most industrialized western countries. In children from the province of Manitoba, the average annual increase of asthma cases in the 1980s was reported to be between 20 and 25 per 10,000 (1). By analyzing the diagnostic reports from Canadian physicians available through Canadian health insurance programs, it is possible to determine the prevalence of asthma among various age groups in the pediatric population. The most recent available data from 1990 suggest that the highest occurrence is observed in boys between five and nine years old, with 532 cases per 10,000 (1). Rates of hospital admission for asthma has also risen steadily during the past decade in Canada, reflecting most probably a greater morbidity from the disease. Hospitalization for asthma was necessary for as many as 545 children younger than 15 years of age per 100,000 population in Canada during 1988 (2).

The number of prescriptions for beta$_2$-agonists in Canada reached 4.6 million in 1990. Due to the growing prevalence and morbidity of asthma in children in the past few years, Canadian physicians have addressed several issues concerning the correct use of beta$_2$-agonists for the treatment of asthma.

DELIVERY SYSTEMS

Although wet nebulization has been the preferred method of administrating beta$_2$-agonist medication for the treatment of acute asthma in emergency and hospital wards, for many years pediatricians tended to prescribe beta$_2$-agonists as an

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oral solution due to the ease of administration for children treated at home. This practice has stopped almost completely since spacers with face masks or mouthpieces became available and were shown to deliver very effectively aerosolized beta$_2$-agonist medication to the bronchial tree. More attention is now being paid to instructing parents in the proper use of spacers. More recently, several pediatric studies have demonstrated the equal efficacy of medication delivered via a metered dose inhaler (MDI) attached to a spacing device compared with conventional wet nebulization for severe acute asthma in both the emergency room and hospital wards (3,4).

The current trend in beta$_2$-agonist treatment for chronic asthma in children is in the form of dry powder inhalers (DPIs). The advantages of these delivery systems are that they are breath-activated and do not contain any additives such as surfactant and freons. The delivery of medication in DPI form is a well established method that has been shown to be as potent and efficacious as the MDI for chronic asthma treatment. The minimal inspiratory flow required for optimal particle deposition varies among the DPIs currently on the market, ranging from 30 to 200 L/min. Obviously, those requiring high flow rates would be inappropriate for younger children, especially during acute bronchospasm. Therefore, knowledge of the properties of each DPI device should be obtained before beta$_2$-agonists are prescribed in this form.

DOSAGE IN CHILDREN

Several authors have tried to define the ideal dose of beta$_2$-agonists in children during an acute exacerbation. The original dose of 0.01 mL/kg of 0.5% salbutamol (the most popular beta$_2$-agonist in Canada) as wet nebulization was subsequently increased to 0.03 mL/kg with greater bronchodilation and no significant side effects. The interval between treatments was further reduced to 20 mins for those children with severe asthma, and this was shown to improve significantly the recovery time of pulmonary function tests (5). With continuous inhalation of a low salbutamol dose, the therapeutic index was enhanced even further (6). Finally, some Australian studies point to a different regimen for salbutamol in children. Fixed doses of 0.5 to 1.0 mL of 0.5% respiratory solution are given to asthmatic children but with variable nebulization times relative to their age. The ideal dose response of salbutamol has not yet been determined with this new technique, and no controlled studies have demonstrated its superior efficacy.

DOSAGE IN INFANTS AND TODDLERS

As shown by the very high rates of hospitalization for asthma in young children, beta$_2$-agonists seem to be less effective in this age group. Using the forced oscillation technique on infants less than 18 months old, Lenney and Milner (7) could not find more than a 5% decrease in resistance after giving 0.5 mL of 0.5% salbutamol with a Pari nebulizer. Turner et al (8) were able to obtain reproducible results of forced expiratory volume in 1 s (FEV_1) in children between three and nine years old. After four nebulizations of 2.0 mL salbutamol 0.5% respiratory solution in 2 mL normal saline, over 1 min of tidal breathing at 15 min intervals, a fifth and final nebulization was delivered for 5 mins. Their results showed a significant positive relationship among maximal FEV_1 response and age. Similarly, Henderson et al (9) studied the bronchodilating effects of salbutamol on histamine-induced bronchoconstriction in 20 infants. Despite a large dose of inhaled salbutamol, only four of the 20 infants showed an immediate return to baseline values, with an average recuperation time only half as long as that after inhaled normal saline. Thus, beta$_2$-agonists appear to have less of an effect in the young child with asthma; however, the reasons for this remain unclear. To compensate for this relative risk of bronchodilating effect, physicians have attempted to increase the medical deposition into the airways of very young children by giving larger doses of beta$_2$-agonist aerosols.

Minimal doses for small infants, such as 0.25 mL of 0.5% salbutamol, are now becoming popular if not standard in some Canadian hospitals, but controlled studies are still lacking. Using nebulized racemic adrenaline in infants younger than one year of age during a first episode of wheezing, Sanchez et al (10) demonstrated a significant improvement in their clinical score and airway resistance, whereas the control group receiving salbutamol, 0.03 mL/kg of a 0.5% solution, failed to show any improvement. This study raises the issue of whether salbutamol or racemic adrenaline should be used in infants during acute bronchoconstriction. More studies should be undertaken to verify their findings.

TACHYPHYLAXIS

The long term use of beta$_2$-agonists in the treatment of chronic asthma has been the subject of many warning statements in a number of consensus reports from Australia, Canada, Great Britain and the United States, along with an international report. For the past several years there has also been an ongoing debate within the scientific community on the presence or absence of tachyphylaxis with the chronic use of beta$_2$-agonists. It was finally concluded that the acute bronchodilating effect of beta$_2$-agonists remained unabated, even after days, weeks or months of chronic use; however, results from two recent studies have rejuvenated this debate. After seven days of inhaled terbutaline taken four times a day, terbutaline taken immediately before a methacholine bronchial challenge test showed a significant tolerance phenomenon, resulting in a lesser protection against experimentally induced bronchoconstriction (11). Cheung et al (12) showed similar results with the continual use of salmeterol over a 28 day period, suggesting that it is a phenomenon to be observed not only with terbutaline but with probably all beta$_2$-agonists. These results further support the many warnings against using beta$_2$-agonists on a long term basis for the treatment of chronic asthma, but rather to rely on the use of effective anti-inflammatory agents.

CONCLUSION

Despite more than two decades of experience with beta$_2$-agonists in the treatment of acute asthma, new regimens are still being evaluated to reduce the growing morbidity of this

disease, especially in very young children. We hope that these studies will define the optimal strategies for using beta2-agonists or other adrenergic agents in the treatment of these children. However, Canadian physicians should respect the many warnings against the long term use of beta2-agonists in the treatment of chronic asthma, and should rather rely on the use of an effective anti-inflammatory medication.

REFERENCES

1. Mantreda J, Becker AB, Wang PZ, Roos LL, Anthonisen NR. Trends in physician-diagnosed asthma prevalence in Manitoba between 1980 and 1990. Chest 1993;103:151-7.
2. Wilkins K, Mao Y. Trends in rates of admission to hospital and death from asthma among children and young adults in Canada during the 1980s. Can Med Assoc J 1993;148:185-90.
3. Bâ M, Spier S, Lapierre G, Lamarre A. Wet nebulizer versus spacer and metered dose inhaler via tidal breathing. J Asthma 1989;26:355-8.
4. Kerem E, Levison H, Schuh S, et al. Efficacy of albuterol administered by nebulizer versus spacer device in children with acute asthma. J Pediatr 1993;123:313-7.
5. Robertson CFR, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. J Pediatr 1985;106:672-4.
6. Bâ M, Thivierge RL, Lapierre G, Gaudreault P, Spier S, Lamarre A. Effects of continuous inhalation of salbutamol in acute asthma. Am Rev Respir Dis 1987;135:326A.
7. Lenney W, Milner AD. At what age do bronchodilator drugs work? Arch Dis Child 1978;53:532-5.
8. Turner DJ, Landau LI, Le Souef PN. The effect of age on bronchodilator responsiveness. Pediatr Pulmonol 1993;15:98-104.
9. Henderson AJW, Young S, Stick SM, Landau LI, Le Souef PN. Effect of salbutamol on histamine induced bronchoconstriction in healthy infants. Thorax 1993;48:317-23.
10. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. J Pediatr 1993;122:145-51.
11. O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled B2 agonists in asthma. N Engl J Med 1992;327:1204-8.
12. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Longterm effects of a long-lasting B2-adrenoreceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. N Engl J Med 1992;327:1198-203.