Pediatric Pharmacotherapy

A Monthly Review for Health Care Professionals of the Children's Medical Center

Volume 2, Number 5, May 1996

Albuterol: A Review of its Use in Children with Asthma

Pharmacology Literature Reviews

Formularly Update

It has been estimated that five to ten percent of the population of the United States has asthma; most of those affected are children. This disease is a significant source of childhood morbidity. Asthma exacerbations have been estimated to result in more than 10 million missed school days each year.[1]

In the past decade, several attempts have been made to standardize the treatment approach for the asthmatic patient. Guidelines have been proposed by the American Academy of Pediatrics, the National Heart, Lung, and Blood Institute (in conjunction with the World Health Organization), and the American Academy of Allergy, Asthma, and Immunology.[2-4] All of these guidelines recommend inhaled $beta_2$-adrenergic agonists, such as albuterol, as single-agent therapy in patients with mild to moderate asthma and as an adjunct to inhaled corticosteroids and other therapies in patients with moderate to severe asthma.

Mechanism of Action

Albuterol, like other $beta_2$-adrenergic agonists, inhibits the effects of the early phase of an asthmatic response. This is achieved by stimulation of adenyl cyclase, the enzyme which catalyzes the conversion of adenosine triposphate (ATP) to cyclic-3'5' adenosine monophosphate (cyclic AMP).[5] Increasing cyclic AMP results in bronchodilation and relief of bronchospasm through relaxation of bronchial smooth muscle. Evidence supporting this mechanism has come from recent genetic research. The ability to clone and sequence the gene encoding the $beta_2$-adrenergic receptor has led to investigations which suggest an inherited dysfunction in these receptors in some patients with asthma.[6]
$Beta_2$-adrenergic agents also inhibit release of histamine from mast cells and increase ciliary transport. While the benefits of $beta_2$-adrenergic agonists are clear, it should be remembered that asthma is also an inflammatory disease and these agents have little or no effect on the late-phase asthmatic response. This secondary reaction is characterized by infiltration of eosinophils and inflammatory cells into the airways. In fact, frequent administration of $beta_2$-adrenergic agonists over prolonged periods can lead to aggravation of the inflammatory process and hyperresponsiveness of the airways.[5]

Administration

Albuterol can be administered orally or by inhalation. Either route is effective in the management of asthma, but the latter is usually preferred since it targets the site of action and minimizes systemic exposure.[7]
Inhalation therapy may be delivered with metered-dose inhalers (MDIs) or by nebulization. For home and school use, MDIs are the most convenient dosage form; however, patients must fully understand the proper technique for optimal drug delivery. The addition of a spacer device (such as an Aerochamber®) can alleviate some of the need to coordinate breaths with actuation of the MDI and has been demonstrated to provide a more consistent delivery of medication to the lungs.
Nebulization offers the benefit of providing a greater percentage of a given dose directly into the lungs, with less drug being swallowed. Nebulizer therapy is the preferred method for administering albuterol to children unable to activate an MDI, such as infants and young children.[8] The usual dosage of albuterol by this method is 0.15 mg/kg/dose. The primary disadvantages of nebulizer treatment are cost and the need to have specialized equipment.
The choice of technique should depend on factors such as patient age, frequency of use, cost, and ability to successfully administer a given albuterol dose. In two recent studies conducted in large, urban pediatric emergency departments, no significant differences in efficacy or tolerability were found between these two administration techniques.[9,10]
Albuterol is administered on an "as needed" basis, when the patient is symptomatic or prior to exercise. Families should be counseled about the maximum number of doses the patient should receive prior to seeking medical

attention. As a general rule, the need to use a nebulizer treatment or MDI more than four times in one day or more frequently than every four hours should alert the family of the need to contact their child's physician or an emergency department. For clinicians, the American Academy of Pediatrics has published practice guidelines for the office-based management of acute exacerbations in children. Specific recommendations for the administration of albuterol in the office are included.[11]

For children experiencing a severe exacerbation, continuous nebulization of albuterol has been found to be an effective therapy.[12-14] Patients treated with this method typically receive dosages of 0.05 to 0.4 mg/kg/hr. Several clinical trials have demonstrated the utility of continuous nebulization to improve clinical asthma scores, arterial blood gas values, and oxygen saturation. This method has also been associated with a reduction in the need for supplemental oxygen and length of hospital stay. Close monitoring is recommended, although continuous nebulization has not been associated with a significantly greater risk of adverse effects than intermittent use.[13-15]

Patient Monitoring

As described above, the efficacy of albuterol therapy may be assessed by a variety of methods. Outcomes such as the ability of the child to maintain normal levels of activity and school function as well as the need for hospitalization are the most significant measures. Objective indicators such as pulmonary function testing and clinical asthma scores are also used to assess the benefit of treatment. In the hospital setting, the need for ventilatory support and monitoring with arterial blood gases or oxygen saturation are used to determine efficacy.[16]

Albuterol is generally well tolerated by children. The most significant adverse reactions reported from clinical trials include muscle tremors, alterations in serum electrolytes, and cardiovascular changes. The presence of muscle tremor is typically a dose-related phenomenon and can be alleviated by a reduction in dose or frequency of administration. Decreases in serum potassium, magnesium, and phosphate are also known to occur in patients receiving frequent doses of albuterol by nebulization.[17] The long-term clinical significance of these electrolyte changes has not been established.

In large doses or with frequent use, $beta_2$-adrenergic agonists can produce hypokalemia, arrhythmias, such as tachycardia and AV block, and hypertension.[18] These latter two effects demonstrate the lack of $beta_2$-receptor specificity observed with larger doses. Management of toxicity typically consists of supportive measures. Administration of a beta-adrenergic antagonist (e.g. atenolol) may be useful, but can aggravate airway obstruction.

Hypersensitivity reactions to albuterol have been reported, but appear to be rare. Other adverse effects include: hyperactivity, headache, nausea, vomiting, dizziness, vertigo, fatigue, aggressive behavior, nasal congestion, changes in

sputum, epistaxis, hoarseness, altered appetite, bronchospasm, and muscle cramps.[18]

Summary

Albuterol is rapidly becoming the most frequently prescribed treatment for asthma. It has earned this status by providing effective management of acute exacerbations of asthma and preventing exercise-induced asthma, with minimal adverse effects. However, clinicians should remember that patient education regarding appropriate use is the key to optimal benefit from albuterol therapy.

References

1. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. New Engl J Med 1992;326:862-6.
2. American Academy of Pediatrics. Guidelines for the diagnosis and management of asthma. Washington, DC: US Department of Health and Human Services; 1994.
3. National Heart, Lung, and Blood Institute and World Health Organization. Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Bethesda, MD: National Heart, Lung, and Blood Institute; 1995.
4. American Academy of Allergy, Asthma, and Immunology. Practice parameters for diagnosis and treatment of bronchial asthma; 1993.
5. Ahrens RC, Smith GD. Albuterol: An adrenergic agent for use in the treatment of asthma: Pharmacology, pharmacokinetics and clinical use. Pharmacotherapy 1984;4:105-21.
6. Ohe M, Munakata M, Hizawa N et al. Beta$_2$ adrenergic receptor gene restriction fragment length polymorphism and bronchial asthma. Thorax 1995;50:353-9.
7. Bartfield JM, Boenau IB, Lozon J et al. Comparison of metered dose inhaler and oral administration of albuterol in the outpatient treatment of infants and children. Am J Emerg Med 1995;13:375-8.
8. Bentur L, Canny GJ, Shields MD et al. Controlled trial of nebulized albuterol in children younger than 2 years of age with acute asthma. Pediatrics 1992;89:133-7.
9. 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.
10. Chou KJ, Cunningham SJ, Crain EF. Metered-dose inhalers with spacers vs nebulizers for pediatric asthma. Arch Pediatr Adolesc Med 1995;149:201-5.
11. Provisional Committee on Quality Improvement, American Academy of Pediatrics. Practice parameter: The office management of acute exacerbations of asthma in children. Pediatrics 1994;93:119-26.
12. Buck ML. Administration of albuterol by continuous nebulization. AACN Clin Issue Crit Care Nurs 1995;6:279-86.

13. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmatic in children. Crit Care Med 1993;21:1479-86.
14. Singh M, Kumar L. Continuous nebulised salbutamol and oral once a day prednisolone in status asthmaticus. Arch Dis Child 1993;69:416-9.
15. Katz RW, Kelly HW, Crowley MR et al. Safety of continuous nebulized albuterol for bronchospasm in infants and children. Pediatrics 1993;92:666-9.
16. Holmgren D, Sixt R. Effects of salbutamol inhalations on transcutaneous blood gases in children during the acute asthmatic attack: From acute deterioration to recovery. Acta Paediatr 1994;83:515-9.
17. Bodenhamer J, Bergstrom R, Brown D et al. Frequently nebulized beta-agonists for asthma: effects on serum electrolytes. Ann Emerg Med 1992;21:1337-42.
18. Olin BR ed. Drug Facts and Comparisons. St. Louis: Facts and Comparisons, Inc. 1996:173a-175.

Pharmacology Literature Review

Intranasal Premedication

The efficacy and safety of intranasal midazolam and sufentanil were compared in a group of 60 children (ages 2 1/2 to 6 years) undergoing outpatient surgery. Midazolam was associated with nasal irritation in more patients (20/31 vs. none in the sufentanil group). More children cried after receiving midazolam than sufentanil (71% vs. 20%). Ability to separate the children from their parents, level of sedation, vital signs, and oxygen saturation did not differ between the groups. Two sufentanil patients experienced apneic episodes during induction. The response time following surgery was similar in the groups. After surgery, more patients in the sufentanil group developed nausea and/or vomiting (34% vs. 6% in the midazolam group). At follow-up 24 to 36 hours after surgery, parents reported similar incidences of GI effects and sleepiness. The authors concluded that both treatments were safe and effective in this population, with the appropriate monitoring for respiratory depression. Zedie N, Amory DW, Wagner BKJ et al. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. **Clin Pharmacol Ther 1996;59:341-8.**

Risperidone Toxicity

The development of extrapyramidal symptoms following the accidental ingestion of risperidone by a 3 1/2 year old child is described. This is the first report of risperidone toxicity in a child. Risperidone is an oral antipsychotic agent with antagonist effects at both dopamine and serotonin receptor sites. The child in this case developed a bilateral upward eye gaze, jerky movements of his

extremities, and irritability after ingesting a single 4 mg tablet. Treatment consisted of diphenhydramine and gastric lavage with activated charcoal. Cardiac monitoring was performed for potential arrhythmias. He was discharged 33 hours after admission, with complete resolution of symptoms. Cheslik TA, Erramouspe J. Extrapyramidal symptoms following accidental ingestion of risperidone in a child. **Ann Pharmacother 1996;30:360-3.**

Tobramycin Pharmacokinetics in CF

The value of an equation based on weight to predict tobramycin dosing was evaluated in 26 adolescents and adults with cystic fibrosis (CF). The equation, dose (in mg to be given every 8 hours)= 90 + 2.13 x Lean Body Mass, was developed from a previous correlation analysis. The predictive performance of this equation was compared to a standardized initial dosing regimen of 3.3 mg/kg every 8 hours. The equation resulted in more patients with initial serum concentrations in the desired range, 9-11 mcg/ml. Touw DJ, Vinks AATMM, Heijerman JGM et al. Prospective evaluation of a dose prediction algorithm for intravenous tobramycin in adolescent and adult patients with cystic fibrosis. **Ther Drug Monit 1996;18:118-23.**

Warfarin-Fluconazole Interaction

This three-part series explores the inhibition of warfarin metabolism by fluconazole, an azole antifungal agent. In the first article, the authors report the results of an *in vitro* analysis of fluconazole's ability to inhibit warfarin metabolism in isolated human liver microsomes. Fluconazole was found to be a potent inhibitor of cytochrome P450-3A4 activity, resulting in increased concentrations of the more potent R-warfarin, but had little effect on the metabolism of S-warfarin via the P450-A2 pathway.
In the second article, the authors confirmed their results in six healthy volunteers. Clearance of R-warfarin via the major metabolic pathway was reduced by an average of 45%. In the final article, the authors make recommendations for adjusting therapy in clinical practice based on the results of their studies. They suggest a five-day stepped dose reduction of warfarin in those patients requiring treatment with fluconazole.
In addition to clearly identifying the source of this specific drug interaction, these articles provide a useful tool for understanding the utilization of *in vitro* models to predict drug-drug interactions. Kunze EL, Wienkers LC, Thummel KE et al. Inhibition of the human cytochrome P450-dependent metabolism of warfarin by fluconazole: *In vitro* studies. **Drug Metabol Disposit 1996;24:414-21**; Black DJ, Kunze EL, Wienkers LC et al. A metabolically based drug interaction: *In vivo* studies. **Drug Metabol Disposit 1996;24:422-8**; Kunze KL, Trager WF. A

rational approach to management of a metabolically based drug interaction. **Drug Metabol Disposit 1996;24:429-35**.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/19/96:

1. Both indinavir (Crixivan®) and ritonavir (Norvir®) were added to the formulary, but restricted to use by the Infectious Disease Division. These drugs are both used in the management of patients with AIDS.
2. Amphotericin B lipid complex (ABELCET®) was added to the formulary, but requires approval from the Infectious Disease Division prior to use. The use of the lipid complex reduces the adverse effects associated with amphotericin use and allows administration of larger doses. There are several reports of its use in pediatric patients in the medical literature. It has been used previously in UVA CMC patients under a compassionate use protocol.
3. Fluvoxamine (Luvox®) also was added to the formulary. This agent is one of the newer generation selective serotonin-reuptake inhibitors (SSRIs) indicated for the treatment of obsessive-compulsive disorders.
4. An intravenous form of amiodarone (Cordarone®) was added for use in the intensive care units. This Class III antiarrhythmic has been available in an oral formulation in the United States for several years. Although data in children are limited, a loading dose of 5 mg/kg followed by an infusion of 7-22 mg/kg/day has been used successfully (Am J Cardiol 1994;74:573-7).
5. Sulfisoxazole (Gantrisin®) was removed from the formulary due to lack of use. If this agent is required for a specific patient, it may be obtained through the pharmacy using the non-formulary request system. For more information, contact the Drug Information Center at 924-8034.

If you have comments, questions, suggestions, or would like to be included on our mailing list, please send a note to Marcia Buck, Pharm.D., Box 274-11 Children's Medical Center at the University of Virginia, Charlottesville, VA 22908 or e-mail to mlb3u@virginia.edu
Fax: 804-982-1682 Office: 804-982-0921

Return to the Children's Medical Center Home Page

Send comments to Witz@Virginia.edu

Revised: August 14, 1996
